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Targeting the hallmarks of aging: preclinical evidence and molecular mechanisms underlying the therapeutic potential of *Centella asiatica* (L.) Urban

Nam Anh Nguyen Ngoc, Thanh Truc Pham Thi, Bao Chau Ngo Huynh, Anh Vu Tran, Anh Thu Do Thi, Huong Ha Ly Hong*
Faculty of Pharmacy, Hong Bang International University, 215 Dien Bien Phu street, Ho Chi Minh city, 700000, Vietnam
*Correspondence author: lyhonghuongha@gmail.com

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Abstract

As the global demographic shifts toward an aging population, the escalating prevalence of age-related pathologies necessitates the identification of geroscience-based interventions. *Centella asiatica* (L.) Urban has emerged as a potent candidate for healthspan extension due to its dense concentration of bioactive pentacyclic triterpenoids, specifically asiaticoside, madecassoside, asiatic acid, and madecassic acid. This review synthesizes preclinical evidence demonstrating the capacity of *C. asiatica* to pharmacologically modulate the fundamental hallmarks of aging. At the molecular level, its constituents have been shown to maintain genomic stability by enhancing DNA repair mechanisms and mitigating epigenetic drift through the regulation of histone modifications. Furthermore, the plant exerts profound effects on mitochondrial bioenergetics, restoring mitochondrial homeostasis to counteract age-related metabolic decline. Analysis of *in vitro* and *in vivo* models reveals that *C. asiatica* suppresses the senescence-associated phenotype and systemic "inflammaging". We further detail the plant's neuroprotective and tissue-regenerative properties, driven by the neutralization of reactive oxygen species (ROS) and the activation of antioxidant signaling. By systematically targeting these discrete cellular aging drivers, *C. asiatica* represents a potent, naturally-derived scaffold for the development of multi-target therapies aimed at extending biological healthspan. This review underscores the necessity of translating these preclinical mechanistic insights into targeted gerotherapeutic strategies.

Keywords: *Centella asiatica*, aging, neuroprotection, anti-inflammation, triterpenoids

1. Introduction

The aging of the global population has become a critical challenge in modern medicine. By 2050, individuals aged over 60 years are projected to reach two billion, representing 21% of the global population (United Nations, 2013). However, increased life expectancy is often marred by a period of late-life morbidity. Consequently, there is a profound gap between lifespan and healthspan, the period of life spent in good health, free from the chronic infirmities of age-related diseases (ARDs) (Shlisky *et al.*, 2017).

The burgeoning field of geroscience posits that aging itself is the primary risk factor for most chronic pathologies, including neurodegenerative, cardiovascular, and metabolic disorders (Niccoli and Partridge, 2012). Rather than treating these conditions in isolation, targeting the underlying biological drivers of aging offers a more holistic therapeutic approach. These drivers are categorized within the "Hallmarks of Aging" framework, which describes a complex interplay of molecular and cellular malfunctions (López-Otín *et al.*, 2023). These hallmarks are classified into (i) primary hallmarks, such as genomic instability, telomere attrition, epigenetic alterations, and loss of proteostasis, which represent the initial triggers of cellular damage; (ii) antagonistic hallmarks, including cellular senescence and mitochondrial dysfunction, which arise as compensatory or defensive responses to damage but ultimately become deleterious; and (iii) integrative hallmarks, like stem cell exhaustion and "inflammaging", a state of chronic, low-grade systemic inflammation which collectively result in the functional decline observed in aging phenotypes (López-Otín *et al.*, 2023). Understanding these interconnected mechanisms will shed light on strategies to extend healthspan (Schmauck-Medina *et al.*, 2022).

In the search for natural bioactive compounds capable of modulating these hallmarks, *Centella asiatica* (L.) Urban (CA), a medicinal herb with a long history in Ayurvedic and Traditional Medicine (Sun *et al.*, 2020), has gained significant attention. The therapeutic efficacy of CA is largely attributed to its unique profile of pentacyclic triterpenoids, most notably asiaticoside, madecassoside, asiatic acid, and madecassic acid (James and Dubery, 2009). While CA has been studied for its wound-healing and cognitive-enhancing properties, recent preclinical investigations have begun to unravel its deeper role as a multi-target gerotherapeutic. These studies suggest that CA does not merely mask symptoms but interferes with the aging process at the subcellular levels.

Despite the promising data, there is a critical need to distinguish between the efficacy of whole botanical extracts and isolated compounds, as well as the varying degrees of evidence provided by different experimental models. This review provides a comprehensive synthesis of the evidence supporting the use of *C. asiatica* in healthspan extension. We aim to interpret the molecular pathways through which CA modulates the hallmarks of aging and to identify the gaps remaining for future clinical translation.

Table 1. Summary of the multi-target mechanisms of triterpenoids of *C. asiatica* in regulating the hallmarks of aging. Evidence levels are categorized as "direct" (studies specifically focusing on aging models) or "indirect" (mechanistic studies in non-aging contexts).

Hallmarks – evidence level	**Mechanisms**	**Models**
Total extracts		
Proteostasis – indirect	Reducing amyloid-beta levels in Alzheimer's-related brain pathology (Dhanasekaran *et al.*, 2009)	*In vitro*
Others – direct	Enhancing learning performance and cognitive flexibility in aged mice (Hack *et al.*, 2025)	*In vivo*
Asiaticoside		
Genomic instability – indirect	Reducing radiation-induced DNA strand breaks (Shen *et al.*, 2020)	*In vitro,* *In vivo*
mitochondrial bioenergetics – indirect	Enhancing mitochondrial respiration and ATP production (Boondam *et al.*, 2025)	*In vitro, in vivo*
Cellular senescence – direct	Delaying senescence and decreases ROS generation by modulating the TGF- β1/Smad pathway (Jiang *et al.*, 2022).	*In vitro*

'Inflammaging' – indirect	Reducing IL-6, TNF-α and IL-1β via HO-1 upregulation, cAMP/PKA modulation and NF-κB inhibition, thereby attenuating inflammation and apoptosis across arthritis, diabetic and LPS-induced injury models (He *et al.*, 2024; Luo *et al.*, 2022; Zhang *et al.*, 2022).	*In vivo,* *In vitro*
Others – indirect	Predicted to regulate synaptic plasticity via TSC1 – Rheb – FMRP and the AKT/mTORC1 pathway (Ibrahim *et al.*, 2023).	*In silico*
Madecassoside		
Proteostasis – indirect	Restoring synaptic and circadian function in PIMT deficits (Ling *et al.*, 2024).	*In vivo*
Autophagy – indirect, direct	Activates AMPK/autophagy to reduce ER stress and fatty liver (Choi *et al.*, 2023).	*In vivo,* *In vitro*
	Enhancing autophagic flux and lysosomal function to limit protein aggregation and oxidative stress (Ling *et al.*, 2017).	*In vitro*
Mitochondrial bioenergetics – indirect	Inducing ROS-mediated apoptosis and G2/M arrest, suppressing proliferation and migration via MAPK and PI3K/AKT (Hou *et al.*, 2025).	*In vitro*
Senescence – indirect	Suppressing NF-κB signaling and decreases IL-6, TNF-α, and IL-1β secretion, alleviating chronic inflammation associated with SASP and cellular aging (Won *et al.*, 2010; Yun *et al.*, 2008).	*In vitro*
'Inflammaging' – indirect	Inhibiting inflammation in *Propionibacterium acnes* and UV models, improving hydration and reducing melanogenesis (Shen *et al.*, 2019).	*In vitro*
Intercellular communication – indirect	Inhibiting acetylcholinesterase, reducing neuroinflammation and oxidative stress while stabilizing neuronal communication (Li *et al.*, 2025).	*In vitro*
Antioxidant – indirect	PRDX2-mediated redox control limits neurodegeneration (Zhong *et al.*, 2025).	*In vivo*
	Improving skin aging parameters by antioxidant mechanisms, enhancing collagen elasticity, hydration, and dermal integrity (Haftek *et al.*, 2008)	*Clinical*
Asiatic Acid		
Proteostasis – direct, indirect	Maintaining proteostasis and delaying cellular aging (Wang, 2014).	*In vitro*
	Improves cognition via proteostasis and hippocampal neurogenesis (Umka Welbat et al., 2016). Modulating PI3K/Akt/mTOR, MAPK, and GSK3β signaling to promote cell survival (Nataraj *et al.*, 2017; Wei *et al.*, 2018).	*In vivo*
Autophagy – indirect	Enhancing mitophagy, glycophagy; preserving mitochondrial homeostasis; reducing ROS (Qiu *et al.*, 2022; Yi *et al.*, 2020; Zhu *et al.*, 2021). Promoting autophagy to clear protein aggregates and protects neurons from proteotoxic stress (Yi *et al.*, 2020).	*In vitro,* *In vivo*
Mitochondrial bioenergetics – indirect, direct	Maintaining mitochondrial function and bioenergetics (Hu *et al.*, 2020). Inhibiting ROS-mediated apoptosis via Bcl-2/Bax modulation, reducing cytochrome c release and caspase activation (Hu *et al.*, 2020). Suppressing ROS-dependent apoptosis via Bcl-2/Bax modulation, reduced cytochrome c release, and caspase suppression in non-malignant cells (Tang *et al.*, 2009).	*In vitro*

	Repressing p38/JNK MAPK signaling and modulates AKT-mediated survival pathways (Yi *et al.*, 2022). Inducing ΔΨm dissipation and ATP depletion via UCP/ANT involvement, triggering intrinsic apoptosis in cancer cells (Lu *et al.*, 2016).	
Senescence – indirect, direct	Delaying cellular senescence and reduces UV-induced ROS via modulation of the TGF-β1/Smad signaling pathway, contributing to protection against photoaging (Dang *et al.*, 2024; Yun *et al.*, 2008).	*In vitro*
'Inflammaging' – indirect	Suppressing neuroinflammation in BV2 microglial cells via modulation of the Sirt1/NF-κB signaling pathway (Qian *et al.*, 2018; Yuyun *et al.*, 2018).	*In vitro*
Intercellular communication – indirect	ERK activation drives osteogenic differentiation (Thamnium *et al.*, 2023).	*In vitro*
Antioxidant – direct, indirect	Protects mitochondria against rotenone-induced apoptosis (Nataraj *et al.*, 2017). Protecting HepG2 cells from oxidative stress and apoptosis Via AKT/ERK (Papaiahgari *et al.*, 2006; Qi *et al.*, 2017). Scavenging ROS and improving oocyte quality and embryo development (Hu *et al.*, 2020; Qi *et al.*, 2021).	*In vitro*
	Restoring redox balance, and reducing oxidative stress – induced neuronal apoptosis in Alzheimer's models (Gray *et al.*, 2017; Rather *et al.*, 2018).	*In vitro,* *In vivo*
Madecassic acid		
'Inflammaging' – indirect	Reducing SASP-related inflammatory cytokines through NF-κB inhibition (Gray *et al.*, 2017; Liu *et al.*, 2012; Rather *et al.*, 2018).	*In vitro,* *In vivo*
	Attenuating inflammatory mediator production and cartilage degradation in chondrocyte and osteoarthritis models (Fu *et al.*, 2022).	*In vitro,* *In vivo*
Intercellular communication – indirect	Activating PPARγ/AMPK/ACC1 signaling, restoring Th17/Treg balance and suppressing pro-inflammatory cytokine production (Xu *et al.*, 2017).	*In vivo*
	Inflammasome inhibition promotes repair and remyelination (Li *et al.*, 2025).	*In vitro,* *In vivo*
Other components		
Intercellular communication – indirect	**Araliadiol** promotes hair growth via p38/PPAR-γ signaling (Park *et al.*, 2024).	*In vitro*
Others – direct	**Caffeoylquinic acids** ameliorate age-related cognitive changes in aged mice (Hack *et al.*, 2025).	*In vivo*
Antioxidant – indirect	**Flavonoids** reduce ROS levels, and protect skin cells from oxidative stress (Kim *et al.*, 2023).	*In vitro*
Antioxidant – indirect	**Polyphenols** reduce oxidative stress via radical scavenging and metal reduction (Ponnusamy *et al.*, 2008).	*In vivo*

2. Literature Review Approach / Review Methodology

Literature Search Strategy

A comprehensive literature search was conducted to identify relevant preclinical studies. We searched three primary electronic databases, including PubMed, ScienceDirect, and SpringerLink, covering until 03/2026.

The search utilized combinations of the following Boolean operators and keywords:

"*Centella asiatica*" OR "Gotu Kola" AND "hallmarks of aging"
"*Centella asiatica*" OR "Gotu Kola" AND "genomic instability"
"*Centella asiatica*" OR "Gotu Kola" AND "safeguarding proteostasis"
"*Centella asiatica*" OR "Gotu Kola" AND "enhancing autophagy"
"Centella asiatica" OR "Gotu Kola" AND "cellular senescence"
"*Centella asiatica*" OR "Gotu Kola" AND "inflammaging"
"*Centella asiatica*" OR "Gotu Kola" AND "intercellular communication"
"*Centella asiatica*" OR "Gotu Kola" AND "antioxidant"

Inclusion and Exclusion Criteria

Inclusion was limited to:

(1) Peer-reviewed primary research articles.
(2) Studies specifically investigating the molecular pathways of its triterpenoids related to the nine hallmarks of aging.
(3) Articles published in the English language.

Exclusion criteria included clinical trial protocols without results, conference abstracts, and studies focusing solely on the botanical cultivation of the plant rather than its biological activity.

3. Centella asiatica and the Hallmarks of Aging

3.1. Primary hallmarks

The primary hallmarks of aging represent the foundational triggers of cellular damage, beginning with the loss of genomic stability. The genome is constantly exposed to exogenous and endogenous insults, including replication errors and oxidative stress, which cause mutations and chromosomal alterations. This leads to genomic mosaicism (López-Otín *et al.*, 2023; Vijg and Suh, 2013) and eventually contributes to aging and ARDs (Vijg & Dong, 2020). While endogenous DNA repair machinery such as base excision repair and nucleotide excision repair maintains genomic integrity, its functional efficacy diminishes significantly with age. This age-related attrition facilitates the accumulation of unrepaired lesions, driving genomic instability (Miller *et al.*, 2021). Closely linked to this genomic decay is the progressive attrition of telomeres. Telomere length declines with each division, triggering senescence or apoptosis at a critical threshold (Blackburn *et al.*, 2015; López-Otín *et al.*, 2023). As most somatic cells lack telomerase, telomeres undergo continuous attrition (Blasco, 2005; Chakravarti *et al.*, 2021). While this limits malignancy, excessive erosion impairs tissue regeneration and accelerates aging, marking it as a hallmark distinct from genomic instability (López-Otín *et al.*, 2023). Notably, telomerase reactivation can reverse aging phenotypes, identifying telomere dynamics as a key target for healthspan interventions (Jaskelioff *et al.*, 2011). Beyond the physical structure of the DNA sequence, epigenetic dysregulation further compounds cellular dysfunction. Shifts in DNA methylation patterns (the "epigenetic clock"), aberrant histone modifications, and the reactivation of transposable elements (retrotransposons) all contribute to the loss of cell identity and the progression of ARDs (Gorbunova *et al.*, 2021; López-Otín *et al.*, 2023).

The convergence of genomic instability, telomere attrition, and epigenetic dysregulation creates a molecular foundation for biological aging. However, the inherent plasticity of these primary hallmarks suggests that biological decline is not an unalterable trajectory, but rather a process susceptible to pharmacological attenuation. By enhancing the efficiency of DNA repair enzymes, stabilizing telomerase activity, and restoring histone acetylation/methylation patterns, geroscience-based interventions aim to preserve the structural and functional integrity of the cell. Preclinical evidence indicates that modulating these upstream drivers can effectively delay the transition from healthy aging to symptomatic disease. Consequently, targeting this triad of genetic and epigenetic integrity offers a potent strategy for extending healthspan, providing a molecular basis for the therapeutic application of multi-target botanicals like *C. asiatica* (Figure 1).

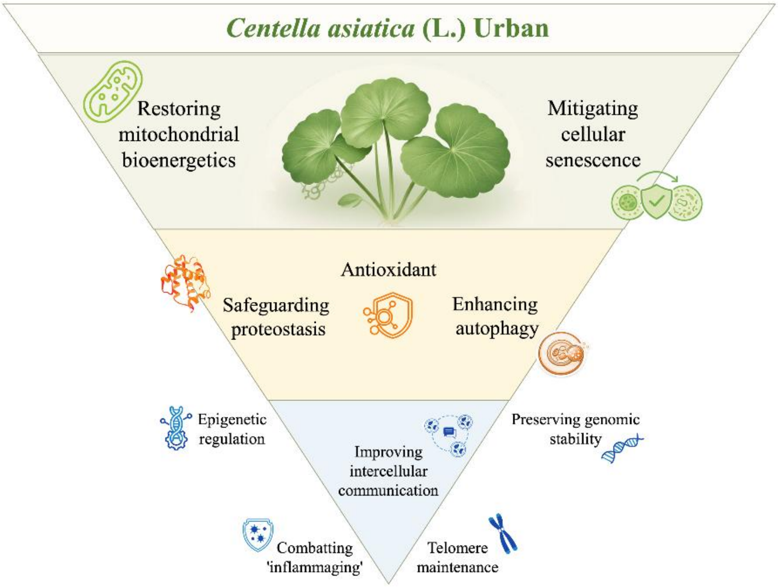

Figure 1. Multi-target effects of *Centella asiatica* on the hallmarks of aging. The hallmarks are organized hierarchically, with a top-to-bottom gradient representing the strength of evidence from direct aging-related studies. *C. asiatica* exerts prominent effects on mitochondrial function and cellular senescence, followed by antioxidant activity, proteostasis maintenance, and autophagy promotion. Direct evidence remains nascent for genomic stability, epigenetic regulation, intercellular communication, telomere maintenance, and aging-related chronic inflammation. Illustration created with Adobe Illustrator.

The anti-aging potential of *Centella asiatica* has been demonstrated across multiple experimental systems. A bioactive extract, DLBS1649, has been shown to preserve cellular replicative capacity by maintaining telomere length and modulating the expression of aging-associated genes, including telomerase reverse transcriptase (TERT), sirtuin 1 (SIRT1), and Klotho. In addition, the extract reduced lipid accumulation, suggesting a calorie restriction–mimetic effect. These cellular findings were further supported by in vivo studies in *Drosophila melanogaster*, where DLBS1649 treatment significantly extended lifespan, highlighting its potential to modulate physiological aging processes (Karsono *et al.*, 2021). These systemic impacts are further elucidated through epigenetic profiling. For instance, water extracts of *C. asiatica* have been shown to modulate peripheral blood DNA methylation in aged mice, specifically targeting genes linked to antioxidant responses, metabolic regulation, and circadian rhythms (Monestime *et al.*, 2025).

Complementing these systemic effects, specific compounds like asiaticoside provide targeted protection against genotoxic stress by significantly reducing radiation-induced DNA strand breaks and improving cellular resistance to damage (Joy *et al.*, 2015). This protective efficacy extends to specialized tissues like the skin, where *C. asiatica* works synergistically within multi-component botanical formulations. When combined with extracts of *Punica granatum*, *Glycyrrhiza glabra*, and *Cynara scolymus*, it targets the extracellular matrix by inhibiting elastase and collagenase, the primary enzymes responsible for structural protein degradation, while simultaneously stimulating type I collagen synthesis in human dermal fibroblasts (Quiles *et al.*, 2022).

In summary, *Centella asiatica* emerges as a potent multi-targeted agent in the field of geroscience, addressing several fundamental hallmarks of aging (Figure 1, Table 1). By integrating mechanisms that preserve genomic stability, modulate the epigenetic landscape, and maintain the integrity of the extracellular matrix, it offers a comprehensive approach to both systemic longevity and localized tissue regeneration. Whether through the regulation of longevity-related genes like SIRT1 or the direct stimulation of structural proteins, *C. asiatica* demonstrates a unique dual-action capability-protecting existing biological structures from environmental and chronological decay while actively promoting the synthesis of youthful cellular components.

3.2. Proteostasis and autophagy

Proteostasis disruption is a hallmark of accelerated aging and neurodegeneration, characterized by the intra- and extracellular accumulation of misfolded or damaged proteins (Gerashchenko *et al.*, 2021; Hipp *et al.*, 2019). This collapse is largely driven by the age-associated impairment of the unfolded protein response (Maruthiyodan *et al.*, 2026), ubiquitin-proteasome system (UPS), and autophagic-lysosomal pathways, all of which exacerbates systemic proteotoxic stress (Hetz *et al.*, 2020).

Meanwhile, autophagy, a highly conserved degradation pathway via lysosome, responsible for degrading damaged organelles and proteotoxic aggregates, is defined by the decreased expression of core autophagy-related genes (ATGs), such as ATG5, ATG7, ATG12, beclin 1 (BECN1), unc-51 like autophagy activating kinase 1 (ULK1), and microtubule-associated protein 1A/1B-light chain 3 (MAP1LC3) (Lipinski *et al.*, 2010). This genetic decline is compounded by the depletion of endogenous autophagy-inducing metabolites, such as spermidine, and the dysregulation of regulatory signaling pathways like E1A-binding Protein p300 (EP300) (Alsaleh *et al.*, 2020; Xu and Wan, 2023; Zhang *et al.*, 2019).

Regarding *in vitro* mechanisms, *C. asiatica* and its bioactive compounds safeguard proteostasis by modulating key autophagic and proteolytic pathways. Asiatic acid serves as a potent inhibitor of advanced glycation endproducts (AGEs) (Wang, 2014), normalizes dysregulated autophagy in cardiac models by regulating LC3-II, BECN1, and p62 (Franceschi *et al.*, 2018). Furthermore, it induces apoptosis in various cancer models via PI3K/Akt/mTOR inhibition (Hao *et al.*, 2018; Ren *et al.*, 2016). Similarly, asiaticoside and madecassoside function as potent mTOR inhibitors (Zulkipli *et al.*, 2020), which enhance the autophagic clearance of toxic α-synuclein aggregates through dual AMPK activation and mTOR suppression, thereby restoring lysosomal function (Limanaqi *et al.*, 2019).

In *in vivo* models, these proteostatic effects translate into broad neuroprotective and systemic benefits. Asiatic acid restores redox balance and promotes neuronal survival in Parkinson’s disease and myocardial injury models by modulating mitophagy- and glycophagy-based energy metabolism (Franceschi *et al.*, 2018; Nataraj *et al.*, 2017; Qiu *et al.*, 2022). Its systemic reach is evidenced by its ability to protect cognitive function in valproic acid-induced models

(Umka Welbat *et al.*, 2016), attenuates liver fibrosis through Bcl-2/Bax signaling (Wei *et al.*, 2018), and also improves diabetic nephropathy by restoring podocyte autophagy (Ni *et al.*, 2025). Madecassoside specifically alleviates deficits from protein-L-isoaspartate O-methyltransferase (PIMT) deficiency, restoring synaptic function disrupted by protein misrepair (Ling *et al.*, 2024). Furthermore, whole extracts, including water extracts and phytosomal preparations, seclectively decrease hippocampal β-amyloid levels (Dhanasekaran *et al.*, 2009; Matthews *et al.*, 2024), protect dopaminergic neurons by enhancing proteasome activity (Haleagrahara and Ponnusamy, 2010) and activate mTOR-S6 signaling to promote local protein synthesis and synaptic density (Gray *et al.*, 2018; Sbrini *et al.*, 2020). These actions address the continuum of age-related diseases by mitigating proteotoxicity and maintaining the integrity of the cellular proteome (Yi *et al.*, 2020).

Collectively, the bioactive constituents of *Centella asiatica*, specifically asiatic acid, asiaticoside, and madecassoside, act as sophisticated modulators of cellular quality control (Figure 1, Table 1). By simultaneously inhibiting harmful protein aggregation and enhancing the clearance mechanisms, such as autophagy and the proteasome, these compounds mitigate the accumulation of unwanted or damaged materials that characterize biological aging. Whether through neuroprotection in the brain or metabolic restoration in the liver and kidneys, *C. asiatica* demonstrates a profound ability to stabilize the proteome, offering a promising therapeutic avenue for delaying the onset of age-related physiological decline and neurodegenerative disease.

3.3. Mitochondrial dysfunction and cellular senescence

Mitochondrial dysfunction and cellular senescence are two fundamental, interconnected drivers of the aging process. Mitochondrial decline is marked by DNA mutations, respiratory complex instability, and impaired mitophagy, further exacerbated by the loss of mitochondrial-derived peptides like humanin and MOTS-c (Reynolds et al., 2021; Somasundaram *et al.*, 2024; Dominiak *et al.*, 2025). This failure in energy production often triggers cellular senescence, a state of permanent proliferative arrest driven by acute or chronic cellular stress (Gorgoulis *et al.*, 2019). Once cells become senescent, they employ a "pro-aging" secretory profile known as the senescence-associated secretory phenotype (SASP), spreading inflammation via cytokines like interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), which ultimately leads to chronic conditions like neurodegeneration and atherosclerosis (Birch and Gil, 2020; Xu *et al.*, 2022).

Strategic interventions to preserve mitochondrial integrity focus on optimizing metabolic efficiency and resilience. Key approaches include enhancing fatty acid oxidation via L-carnitine, such as beneficial low-level stress (mitohormesis) with metformin, and plastoquinonyl-decyl-triphenylphosphonium (SkQ1) to neutralize localized oxidative damage (Rattray *et al.*, 2019; Reid; Chee *et al.*, 2021;Thompson *et al.*, 2021). Consequently, safeguarding mitochondrial function has emerged as a primary strategy for extending healthspan and delaying physiological decline. Parallel to mitochondrial maintenance, current anti-aging therapeutics target the accumulation of senescent cells through two distinct pharmacological classes: senolytics, which selectively induce apoptosis in aberrant cells to eliminate them from tissues, and senomorphics, which modulate the cellular phenotype to suppress the SASP without causing cell death. By neutralizing the inflammatory output of these cells, senomorphics mitigate the hallmarks that drives systemic aging.

In cellular models of aging, *Centella asiatica* and its bioactive compounds exhibit pronounced senomorphic effects. Triterpenoids, including asiatic acid, madecassic acid, and madecassoside, attenuate oxidative stress and suppress pro-inflammatory signaling by inhibiting nuclear factor kappa B (NF-κB). This inhibition effectively reduces the secretion of SASP factors, such as IL-6, IL-1β, and TNF-α (IL-1β) (Yun *et al.*, 2008; Dang *et al.*, 2024). Asiaticoside further delays cellular senescence and reduces ROS levels in ultraviolet (UV)-induced fibroblast models via modulation of the transforming growth factor-β1/Smad pathway (Jiang et al., 2022). In addition, *C. asiatica* extracts protect dermal fibroblasts against hydrogen peroxide and UVB-induced senescence by modulating microRNA expression (Kim *et al.*, 2011; An *et al.*, 2012).

Beyond cellular systems, these anti-senescence effects are reflected in organismal models. Extracellular vesicles derived from *C. asiatica* promote skin repair in UVB-induced mouse models by enhancing keratinocyte proliferation and collagen deposition (Chang *et al.*, 2025). Furthermore, supplementation with *C. asiatica* has been shown to improve cognitive function while reducing systemic inflammation and oxidative stress markers in human studies (Phoemsapthawee *et al.*, 2022).

At the mitochondrial level, *C. asiatica* exerts context-dependent regulatory effects across different cellular models. In neuronal and oocyte systems, standardized extracts such as ECa 233 and asiatic acid enhance mitochondrial respiration, ATP generation, and membrane potential ($\Delta\Psi$m). These benefits are mediated through activation of the Nrf2/HO-1 signaling axis, which upregulates essential antioxidant enzymes, including superoxide dismutase (SOD) and glutathione peroxidase (GPx) (Shinomol and Muralidhara, 2008; Xu et al., 2012; Hu *et al.*, 2020).

Whole-organism studies further support these mitochondrial effects. *C. asiatica* attenuates oxidative stress and improve mitochondrial function in brain tissues exposed to neurotoxicity (Boondam *et al.*, 2025). In models of seizure and myocardial ischemia-reperfusion injury, asiatic acid preserves mitochondrial integrity by modulating Bcl-2/Bax balance and restoring key mitochondrial proteins such as sirtuin 3 (SIRT3) and ATP synthase (Lu *et al.*, 2021; Yi *et al.*, 2022). Moreover, in neurodegenerative and metabolic disease models, including amyloid-β toxicity and diabetes, C. asiatica alleviates mitochondrial dysfunction by enhancing oxidative respiration and upregulating antioxidant and mitochondrial genes via the Nrf2/HO-1 pathway (Gray *et al.*, 2015; Gray *et al.*, 2018; Giribabu *et al.*, 2020; Kundu *et al.*, 2023).

Overall, *C. asiatica* serves as a dual-action therapeutic agent that stabilizes mitochondrial bioenergetics while simultaneously mitigating the deleterious effects of cellular senescence (Figure 1, Table 1). By upregulating antioxidant defenses via the Nrf2 pathway and suppressing the pro-inflammatory SASP profile, it addresses both the internal metabolic failures and the external inflammatory signaling that characterize aging. This comprehensive ability to restore redox balance and preserve the cellular life cycle positions *C. asiatica* as a significant botanical intervention for extending healthspan and treating age-related pathologies.

3.4. Inflammaging

Inflammaging is defined as a state of chronic, sterile, low-grade systemic inflammation that develops during aging. It is characterized by elevated circulating levels of pro-inflammatory markers, including IL-6, TNF-α, and C-reactive protein (CRP) (Hirata *et al.*, 2020), which collectively contribute to the progression of ARDs such as atherosclerosis and neurodegeneration (Mcgeer & Mcgeer, 2004; López-Otín *et al.*, 2023). This phenomenon arises from a complex interplay of primary aging hallmarks, including genomic instability, the accumulation of the SASP, and impaired autophagy/proteostasis. Furthermore, overactivation of nutrient-sensing pathways, specifically the growth hormone (GH)/insulin-like growth factor 1 (IGF1)/mTORC1 axis, compounded by immune system decline, and gut barrier dysfunction (Miller *et al.*, 2021; Mittelbrunn and Kroemer, 2021; López-Otín *et al.*, 2023). Strategic interventions targeting these inflammatory cascades have demonstrated significant therapeutic potential, showing an ability to reduce systemic inflammation, enhance metabolic and cognitive function, and extend lifespan in various animal models (Gocmez *et al.*, 2020; Marín-Aguilar *et al.*, 2020; Sciorati *et al.*, 2020).

In *in vitro* inflammatory models, the anti-inflammatory effects of *Centella asiatica* and its triterpenoids are typically investigated using lipopolysaccharide (LPS)-induced cell systems.

In these models, macrophages, microglial cells (e.g., BV2), or endometrial epithelial cells are first treated with compounds such as asiatic acid or asiaticoside, followed by LPS stimulation to induce inflammatory responses (Qiu *et al.*, 2015; Cao *et al.*, 2018; Yuyun *et al.*, 2018; Xiao *et al.*, 2025). The activation of key signaling pathways, including NF-κB and mitogen-activated protein kinase (MAPK), is then evaluated, together with upstream regulators such as interleukin-1 receptor-associated kinase 1 (IRAK1) and transforming growth factor-beta-activated kinase 1 (TAK1), as well as NLR family pyrin domain containing 3 (NLRP3) inflammasome activation (Guo *et al.*, 2015; Cho *et al.*, 2020; He *et al.*, 2024). Specifically, asiatic acid reduces the production of inflammatory mediators, including nitric oxide (NO), prostaglandin E2 (PGE2), and pro-inflammatory cytokines such as TNF-α and IL-6 in LPS-stimulated BV2 microglial cells via modulation of SIRT1 and Notch signaling pathways (Qian *et al.*, 2018; Cho *et al.*, 2020; Md Pisar *et al.*, 2023). Additionally, in disease-related models such as osteoarthritis and psoriasis, treatment with madecassoside or madecassic acid is followed by evaluation of Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) and extracellular signal-regulated kinase (ERK)/p38 signaling pathways, along with corresponding changes in inflammatory markers. (Tan *et al.*, 2021; Fu *et al.*, 2022; Lin *et al.*, 2023).

Beyond natural aging models, *C. asiatica* has shown protective effects in models of chronic stress, which is often utilized to simulate accelerated brain aging. In rats subjected to chronic unpredictable stress, *C. asiatica* extract prevented the surge of the pro-inflammatory cytokine TNF-α in the hippocampus. Notably, this anti-inflammatory action occurred independently of BDNF levels, suggesting that the extract targets the 'inflammaging' component of cognitive decline through pathways distinct from neurotrophic support (Ar Rochmah et al., 2019).

These molecular mechanisms provide multi-systemic therapeutic benefits in *in vivo* models. The administration of *C. asiatica* extracts attenuates experimental colitis and dental pulp inflammation by suppressing mitochondrial-mediated inflammatory pathways (Nurhapsari et al., 2023; Shin et al., 2026). In respiratory and renal models, asiaticoside and asiatic acid alleviate acute lung injury and acute kidney injury by reducing inflammatory cell infiltration and stabilizing vascular barrier integrity (Qiu et al., 2015; Sari et al., 2021; Sung et al., 2025; Yang et al., 2018). Furthermore, specialized formulations (Centevita™) also demonstrate significant "anti-inflammaging" and photoprotective effects in murine by activating HO-1 and reducing the accumulation of advanced glycation endproducts (AGEs) (Huang et al., 2011; Lee et al., 2020; Maramaldi et al., 2013; Wan et al., 2013).

Altogether, *C. asiatica* functions as a comprehensive antagonist to inflammaging by targeting the core molecular drivers of systemic inflammation (Figure 1, Table 1). By suppressing the NLRP3 inflammasome and NF-κB signaling while simultaneously activating protective pathways like HO-1 and SIRT1, it effectively lowers the inflammatory levels of the organism. These findings highlight its therapeutic potential not only in treating acute inflammatory injuries but also in mitigating the chronic, low-grade inflammation that accelerates age-related decline in the brain, skin, and metabolic organs.

3.5. Intercellular communication

Maintaining homeostasis requires the precise coordination of neural, endocrine, and immune signals, a complex regulatory network that inevitably degrades with age. This breakdown is driven by the systemic accumulation of aging factors in the bloodstream, such as CCL11, β2-microglobulin, IL-6, alongside the chronic secretion of the pro-inflammatory SASP by senescent cells (Smith et al., 2015; Valletta et al., 2020; Villeda et al., 2011). Contemporary strategies to restore this vital communication focus on both neutralizing these harmful circulating elements and harnessing "young" blood factors, such as GDF11, TIMP2, and VEGF. Furthermore, interventions aimed at improving the elasticity of the extracellular matrix, modulating the neuro-endocrine signaling axis, and restoring gut microbiota balance have shown great promise in rejuvenating immune function. By targeting the systemic environment, these strategies not only preserve the integrity of the cellular communication system but also offer a path toward slowing the aging process and preventing the onset of related multi-systemic diseases.

At the cellular level, *C. asiatica* extracts and their constituents actively orchestrate cellular differentiation and tissue repair. Human mesenchymal stem cells (hMSCs) and neuro-differentiated mesenchymal stem cells (ndMSCs) conditioned with these extracts undergo accelerated neural differentiation, characterized by enhanced axonal regeneration, increased myelin thickness, and optimized synaptic connectivity (Hussin et al., 2020; Omar et al., 2019). Within the intricate framework of the central nervous system, water extracts and their caffeoylquinic acid constituents stimulate mouse primary hippocampal neurons to expand their dendritic arborization and synaptic complexity (Rowe et al., 2024). Furthermore, asiatic acid derivatives and araliadiol modulate the extracellular matrix by upregulating osteogenic proteins (BMP2, WNT3A, ALP) via ERK signaling and promoting hair growth through the p38/PPAR-γ axis (Park et al., 2024; Thamnium et al., 2023).

Translating these cellular findings into a systemic context, *in vivo* research demonstrates significant functional recovery. The administration of water extracts effectively mitigates age-related locomotion deficits in models such as *Drosophila*by preserving neuronal arborization (Rowe et al., 2024). Moreover, the transplantation of ndMSCs pre-treated with *C. asiatica* significantly accelerates the physical repair of peripheral nerves, restoring both structural integrity and nerve conduction velocity in injury models (Hussin et al., 2020). These results suggest that the botanical not only provides the raw signaling cues for repair but also enhances the functional capacity of transplanted cells to integrate into damaged tissues.

In conclusion, *C. asiatica* supports intercellular communication during aging by enhancing synaptic connectivity and regulating ECM signaling pathways (Figure 1, Table 1). By fostering a microenvironment conducive to stem cell differentiation and axonal growth, it addresses the age-related decline in tissue regenerative capacity. This ability to modulate the structural and chemical dialogue between cells, whether through the upregulation of osteogenic proteins or the preservation of neuronal architecture, positions *C. asiatica* as a vital agent for maintaining systemic coordination and functional integrity throughout the aging process.

3.6. Antioxidant mechanisms

Under physiological conditions, ROS act as critical signaling molecules. However, during aging, the progressive decline in mitochondrial efficiency driven by mtDNA mutations and proteostatic imbalance leads to a pathological surge in ROS production (Amorim et al., 2022; López-Otín & Kroemer, 2021). When the leakage of ROS or mtDNA into the cytoplasm exceeds the cell's neutralizing capacity, it triggers a cascade of genetic damage, lipid peroxidation, and accelerated telomere shortening (Amorim et al., 2022; López-Otín & Kroemer, 2021). To mitigate this progression, antioxidants play a central role in preserving genomic integrity, stabilizing cellular membranes, and maintaining mitochondrial function while suppressing the chronic inflammatory responses associated with the aging process.

A primary mechanism for counteracting this cellular toxicity is the direct scavenging of ROS, which prevents their deleterious interaction with macromolecules like DNA. Non-enzymatic antioxidants, such as vitamin C, vitamin E, glutathione, and natural polyphenols, neutralize ROS by donating electrons or hydrogen atoms, converting them into stable, non-oxidizing molecules. Complementing this direct action, the body's enzymatic antioxidant system comprising SOD, catalase (CAT), and GPx actively metabolizes and eliminates free radicals (Hossain et al., 2022; Petr et al., 2020). Together, these systems preserve the structural and functional integrity of the cell against the oxidative pressures that define biological aging.

Beyond direct scavenging by vitamins and polyphenols, *C. asiatica* provides advanced cellular defense by activating of the Nrf2/antioxidant response element (ARE) pathway (Kim & Jeon, 2022). In *in vitro* settings, its constituents promote the dissociation of Nrf2 from its negative regulator, Kelch-like ECH-associated protein 1 (Keap1), thereby inducing the expression of cytoprotective enzymes. These include heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1), glutamate-cysteine ligase catalytic subunit (GCLC), SOD, CAT, and GPx (Papaiahgari et al., 2006; Qi et al., 2017). Specifically, asiatic acid activates Nrf2 via protein kinase B (AKT) and ERK signaling to bolster cellular resilience (Qi et al., 2017). Interestingly, while ethanolic extracts provide broad cytoprotection, specific fractions can modulate differentially in contexts. Madecassoside preserves mitochondrial membrane potential (ΔΨm) and stimulates autophagy to clear damaged organelles in human umbilical vein endothelial cells (HUVECs) and melanocytes, protecting them against oxidative stress-induced injury (Bian et al., 2012; Ling et al., 2017).

Translating to *in vivo* models, these mechanisms provide robust protection across multiple systems. In skin aging and photoaging, *C. asiatica* and its extracellular vesicles (EVs) attenuate hydrogen peroxide-induced damage, inhibit collagenase and elastase, and restore cutaneous density and hydration (Firdaus et al., 2024; Haftek et al., 2008; Kim et al., 2023; Zofia et al., 2020). These findings are supported by clinical evaluations of topical formulations, such as water-in-oil creams containing *C. asiatica* and ferulic acid, which demonstrate significant increases in cutaneous density, hydration, and overall antioxidant activity (Moldovan et al., 2017; Ramesh et al., 2014).

In neurodegenerative models, including Parkinson's disease (PD) and Alzheimer's disease (AD), asiatic acid acts as a mitochondrial complex-I protector, preserving ΔΨm and reducing amyloid-*β*-induced oxidative damage (Gray et al., 2017; Nataraj et al., 2017; Rather et al., 2018). These effects are further supported by the restoration of cholinergic function and enhancement of electron transport chain activity, effectively mitigating cognitive impairment and age-related neurological decline (Chiroma et al., 2019; Kumar et al., 2011; Mansor et al., 2023; Subathra et al., 2005; Zhong et al., 2025). Additionally, these antioxidant benefits extend to reproductive health, where asiatic acid improves reproductive competence by enhancing ATP production and blastocyst development under oxidative stress (Qi et al., 2021).

In conclusion, Centella asiatica provides a sophisticated, multi-level antioxidant defense that transcends simple free-radical scavenging (Figure 1, Table 1). By orchestrating the genetic response and safeguarding mitochondrial complex activity, it reinforces the cell's internal machinery against the primary drivers of aging. Whether through protecting the structural integrity of the skin, preserving cognitive function in the brain, or stabilizing systemic metabolic health, *C. asiatica* demonstrates a unique ability to mitigate aging-related damage across diverse tissues, making it a powerful candidate for geroscience-based interventions.

3.7 Beyond the core hallmarks

In addition to addressing the core molecular hallmarks of aging, *C. asiatica* modulates systemic physiology and complex behaviors, offering a holistic impact on the aging organism (Figure 2).

High-dose water extracts of *C. asiatica* (1000 mg/kg/day) have been reported to improve REM sleep, enhance cognitive performance, and reduce anxiety-like behaviors in aging and Alzheimer's animal models (Gray et al., 2024; Kitzes et al., 1985; Ridker et al., 2017; Speers et al., 2024). A notable neuroprotective mechanism was recently identified in the standardized extract ECa 233, which demonstrated a significant reduction in brain iron accumulation (Yatmark et al., 2025).

In the clinical sphere, *C. asiatica* has established a strong presence in cosmeceutical applications. Topical formulations have been shown to reduce wrinkle depth and improve skin hydration, two primary markers of dermatological aging commonly observed in the elderly (Kongkaew et al., 2020). Advanced formulations, such as those combining the plant with mandelic acid, further enhance skin thickness and collagen synthesis while reinforcing barrier integrity to promote tissue repair (Widgerow et al., 2025). Although many of these clinical trials are relatively small, they provide moderate, evidence-based support for its efficacy in dermatological anti-aging.

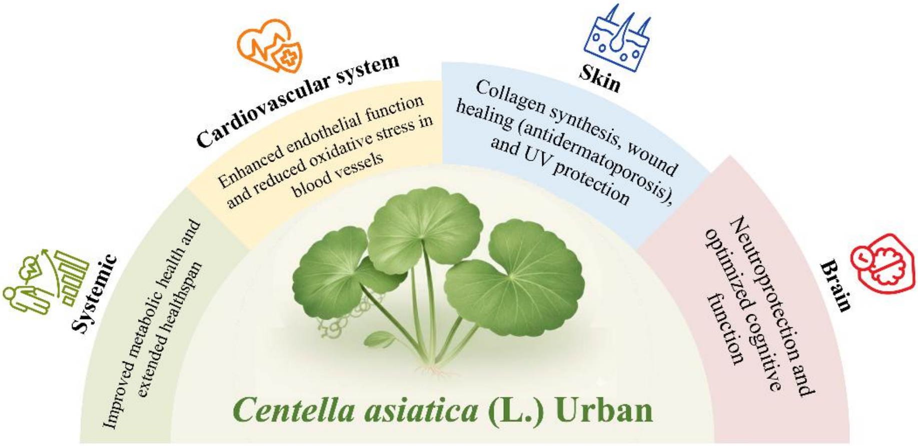

Figure 2. Multi-system protective effects and biological activities of *Centella asiatica*. The radius of each pie chart segment corresponds to the strength of evidence from direct research. *C. asiatica* demonstrates robust neuroprotective and cognitive benefits, followed by significant effects on skin repair, collagen synthesis, and protection against UV-induced damage. Additionally, it supports cardiovascular function and overall systemic health. Created in Adobe Illustrator.

Mechanistic insights have further highlighted the role of triterpenes and caffeoylquinic acids in regulating genes involved in extracellular matrix organization, metabolism, and immune signalling. Such molecular actions likely contribute to the improvements in cognitive and behavioural functions observed in animal models (Chamberlin et al., 2024; Hack et al., 2025; Tsoukalas et al., 2021). These findings emphasize that *C. asiatica* acts not only at the cellular and molecular levels but also influences systemic physiology and inter-organ interactions.

Taken together, *C. asiatica* presents a promising profile of neuroprotective, and cosmeceutical properties that extend its utility beyond basic antioxidant support. While clinical evidence is most robust in dermatological applications, its potential to stabilize sleep patterns, reduce and neurotoxic iron loading provides a compelling case for its role as a systemic anti-aging agent.

Discussion

Centella asiatica exhibits a diverse range of bioactivities that directly address the core drivers of aging, primarily through modulation of oxidative stress, mitochondrial function, and inflammation. Its major triterpenoids, including asiaticoside, madecassoside, asiatic acid, and madecassic acid, have demonstrated potent antioxidant and cytoprotective effects across multiple experimental systems. These compounds work by reducing intracellular ROS, preserving mitochondrial integrity, and regulating apoptosis-related signalling (Ling *et al.*, 2017). These molecular actions are further supported by *in vivo* studies highlighting neuroprotective and cardioprotective benefits (Nataraj *et al.*, 2017; Qiu et al., 2022). Importantly, the efficacy of C. asiatica lies in its ability to target interconnected biological processes central to the "Hallmarks of Aging" (López-Otín *et a*l., 2013), suggesting that its constituents act on integrated mechanistic nodes rather than isolated targets. This interconnectedness suggests that these pathways may represent key mechanistic nodes underlying the potential anti-aging effects of *C. asiatica*, rather than acting as isolated targets.

Despite this promising evidence, several factors limit the current literature. Most studies are confined to *in vitro* systems or animal models, which often fail to replicate the complexity of human physiology and systemic pharmacokinetic interactions (Gray *et al.*, 2017; Lu *et al.*, 2016). A critical challenge is the limited bioavailability of triterpenoid compounds. Due to poor absorption and rapid metabolism, oral administration often results in low systemic exposure (He *et al.*, 2023; Yuan *et al.*, 2015). Moreover, many *in vitro* studies utilize micromolar concentrations that exceed physiologically achievable levels *in vivo*, creating a significant gap in extrapolating experimental efficacy to clinical outcomes (Songvut *et al.*, 2021; Tan *et al.*, 2021). These discrepancies highlight a key limitation in extrapolating *in vitro* findings to *in vivo* contexts and may partially explain inconsistencies between experimental efficacy and clinical outcomes. In addition, variations in plant sources and extraction methods lead to phytochemical heterogeneity, complicating reproducibility (Idris and Mohd Nadzir, 2021). Furthermore, long-term safety data and potential herb-drug interactions remain under-researched (Hein *et al.*, 2025).

Future research should address these limitations through strategically designed studies aimed at enhancing translational applicability. Priority should be given to randomized, placebo-controlled clinical trials utilizing standardized extracts with well-characterized phytochemical profiles and endpoints related to aging hallmarks. Parallel investigations on pharmacokinetics and formulation development are essential to improve bioavailability and establish robust dose-response relationships. Long-term safety studies across diverse populations are also necessary to ensure generalizability and clinical relevance. Addressing these gaps will be crucial for bridging the current divide between preclinical findings and therapeutic implementation.

In conclusion, *C. asiatica* represents a promising multi-target botanical with significant anti-aging potential. While further clinical validation is required, current preclinical evidence highlights its potential to contribute to strategies aimed at delaying aging and improving healthspan.

Authors' contributions:

Research concept and design, Nguyen Ngoc NA, Pham Thi TT, Ngo Huynh BC, Do Thi AT, Ly Hong HH; Collection and assembly of data, data analysis and interpretation, and writing the article, Nguyen Ngoc NA, Pham Thi TT, Ngo Huynh BC, collection of data, Tran AV; Critical revision of the article, Do Thi AT, Ly Hong HH; and Final approval of the article, Ly Hong HH. Nguyen Ngoc NA, Pham Thi TT, and Ngo Huynh BC contributed equally to the study.

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Conflict of interests

The authors declare that they have no conflicts of interest that could have influenced the conduct, analysis or presentation of the research.

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