RESEARCH ARTICLE

Mitophagy and Ayurvedic Rejuvenation: Exploring a Potential Molecular Basis of Rasayana Pharmacology

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Abstract

Rasayana is a distinctive therapeutic concept of *Ayurveda* traditionally associated with preservation of health, promotion of longevity, maintenance of strength, enhancement of cognition, resistance to disease and preservation of youthful physiological function. Classical descriptions of *Rasayana* encompass concepts such as Ojas, Bala, *Vayasthapana* and Medhya *Rasayana*, which collectively describe preservation of systemic resilience, tissue quality, vitality and cognitive function. Modern geroscience increasingly recognizes mitochondrial dysfunction, defective autophagy and impaired mitophagy as important determinants of cellular aging and age-associated disease. Mitophagy, the selective autophagic elimination of damaged mitochondria, maintains mitochondrial quality by removing dysfunctional organelles and supporting metabolic homeostasis.

Keywords: Ayurveda; *Rasayana*; rejuvenation; mitophagy; mitochondria; PINK1; Parkin; AMPK; mTOR; SIRT1; FOXO3; Ojas; *Vayasthapana*; Medhya *Rasayana*; healthy aging.

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1. Introduction

Aging is increasingly understood not as the consequence of a single molecular defect but as a multidimensional biological process involving interconnected alterations in genomic stability, nutrient sensing, proteostasis, cellular senescence, mitochondrial function, autophagy, inflammation and intercellular communication. The contemporary framework of the hallmarks of aging places mitochondrial dysfunction and defective cellular quality-control mechanisms among the major biological determinants of age-related decline [1,2].

Mitochondria occupy a central position in this process because they regulate ATP generation, redox signaling, calcium homeostasis, apoptosis and metabolic adaptation [3,4]. With increasing cellular stress and age, damaged mitochondria may accumulate, resulting in altered oxidative phosphorylation, excessive ROS generation, impaired bioenergetics and inflammatory signaling[3,5]. Mitophagy provides a critical quality-control mechanism by selectively eliminating dysfunctional mitochondria and thereby maintaining a functional mitochondrial population [6-9].

The discovery of the PINK1/Parkin pathway substantially expanded understanding of mitochondrial quality control. Loss of mitochondrial membrane potential stabilizes PINK1 on the outer mitochondrial membrane, promoting Parkin activation and ubiquitination of mitochondrial proteins, which subsequently facilitates autophagic recognition and lysosomal degradation of damaged mitochondria [7-10].

Importantly, PINK1/Parkin is not the only mitophagy mechanism. BNIP3, NIX, FUNDC1, BCL2L13, FKBP8 and other receptors can recruit autophagic machinery independently of Parkin [11-17]. Therefore, mitophagy should be viewed as a network of mitochondrial quality-control pathways rather than a single linear mechanism.

Ayurveda provides a fundamentally different conceptual vocabulary for maintaining biological resilience. Rasayana is traditionally described as a rejuvenative approach associated with longevity, strength, cognition, disease resistance and preservation of youthful characteristics. Contemporary reviews have identified antioxidant, anti-inflammatory, immunomodulatory, adaptogenic and cytoprotective activities among several Rasayana interventions.

This raises an important translational question: Could mitochondrial quality control—particularly mitophagy—represent one of the molecular processes underlying some biological effects traditionally described under Rasayana pharmacology?

This question has not been adequately investigated as a unified research theme.

2. Rasayana as a Biological Concept of Rejuvenation.

The Ayurvedic concept of Rasayana extends beyond treatment of an established disease. It encompasses measures intended to preserve physiological integrity, promote longevity, improve strength and support resistance against disease.

Classically, Rasayana is associated with preservation of Dhatus, promotion of Ojas, enhancement of Bala, maintenance of cognition and delayed functional deterioration.

From a modern biological perspective, these descriptions should not be directly equated with specific molecular pathways. Rather, they provide a conceptual framework from which testable biological hypotheses can be generated.

A contemporary interpretation can therefore be proposed:

Ayurvedic concept	**Potential modern biological domain**	**Proposed relationship**
Rasayana	Healthy aging / resilience	Systems-level phenotype
Ojas	Physiological resilience/homeostasis	Hypothesis-generating concept
Bala	Functional capacity/metabolic resilience	Muscle, immune and mitochondrial function
Vayasthapana	Healthy aging	Preservation of cellular function
Medhya Rasayana	Brain resilience/cognition	Neuronal mitochondrial and proteostatic homeostasis
Dhatu preservation	Tissue homeostasis	Cellular repair and turnover
Rasayana pharmacology	Multitarget pharmacology	Network modulation

This framework avoids the scientifically problematic practice of claiming that *Ojas* = mitochondria or *Rasayana* = mitophagy. Instead, it proposes functional correspondence requiring experimental validation.

3. Mitochondria and Cellular Aging

Mitochondria are dynamic organelles undergoing continuous fission, fusion, biogenesis and degradation. Their functional integrity depends upon coordinated mitochondrial quality-control systems.

Damaged mitochondria may exhibit:

- reduced membrane potential;
- impaired electron transport;
- increased ROS;
- altered ATP production;
- calcium dysregulation;
- abnormal mitochondrial morphology;
- release of mitochondrial danger-associated molecular patterns;
- activation of inflammatory pathways.

If damaged mitochondria are not adequately removed, mitochondrial dysfunction can become self-reinforcing.

Mitophagy counteracts this process by selectively directing dysfunctional mitochondria toward autophagic degradation. Contemporary evidence supports an important relationship between impaired mitophagy, aging and age-associated disease.

4. PINK1/Parkin-Mediated Mitophagy

The PINK1/Parkin system represents one of the best-characterized mitophagy pathways.

Under normal mitochondrial membrane potential, PINK1 is continuously imported and degraded. Following mitochondrial depolarization, PINK1 accumulates on the outer mitochondrial membrane.

PINK1 then phosphorylates ubiquitin and Parkin, activating Parkin's E3 ubiquitin-ligase activity. Parkin ubiquitinates multiple outer mitochondrial membrane proteins. These ubiquitin signals recruit autophagic adaptor proteins, including p62/SQSTM1, OPTN and NDP52, facilitating LC3-dependent autophagosome formation around damaged mitochondria.

This can be simplified as Mitochondrial damage → ΔΨm loss → PINK1 stabilization → Parkin activation → ubiquitination → autophagy adaptor recruitment → LC3 engagement → autophagosome → lysosomal degradation

The relevance to Rasayana research is significant because several phytochemicals traditionally encountered in Ayurvedic medicine have demonstrated mitochondrial protective or autophagy-modulating activities. However, mitochondrial protection alone does not prove mitophagy activation.

This distinction is critical for a high-quality review.

5. PINK1/Parkin-Independent Mitophagy

A modern review of Rasayana pharmacology should not restrict the discussion to PINK1/Parkin.

Mitophagy can also occur through mitochondrial receptors including:

- BNIP3
- NIX/BNIP3L
- FUNDC1
- BCL2L13
- FKBP8
- PHB2
- AMBRA1

These receptors interact directly or indirectly with LC3/GABARAP proteins and facilitate mitochondrial sequestration by autophagic membranes.

BNIP3 and NIX are particularly relevant to metabolic stress, hypoxia and mitochondrial remodeling.

Therefore, future studies evaluating Ayurvedic interventions should measure both:

PINK1/Parkin-dependent mitophagy and

PINK1/Parkin-independent receptor-mediated mitophagy.

6. AMPK–mTOR Axis: The Energy-Sensing Gateway

AMPK is an intracellular energy sensor activated during conditions associated with increased AMP/ATP or ADP/ATP ratios.

Activation of AMPK can promote autophagy through phosphorylation of ULK1 and inhibition of mTORC1. mTORC1 generally acts as a nutrient-sensitive inhibitor of autophagy, whereas AMPK can favor catabolic and cellular maintenance pathways.

The simplified pathway is:

Energy stress → AMPK ↑ → mTORC1 ↓ → ULK1 activation → autophagy ↑

Because mitophagy is a specialized form of autophagy, AMPK–mTOR signaling provides an important mechanistic connection between cellular energy sensing and mitochondrial quality control [20-24].

Recent experimental work has further strengthened this conceptual connection. For example, urolithin A has been shown to induce mitophagy through an AMPK-related mechanism, illustrating how natural-product-derived molecules can influence mitochondrial quality-control networks.

7. SIRT1: A Metabolic and Longevity-Associated Regulator

SIRT1 is an NAD+-dependent deacetylase that participates in metabolic adaptation, stress responses, mitochondrial biology and autophagy.

SIRT1 can regulate autophagy-related proteins and transcription factors through deacetylation. Its interaction with FOXO proteins is particularly relevant to oxidative stress resistance and cellular adaptation.

The SIRT1–autophagy relationship provides another potential mechanistic entry point for investigating Rasayana interventions.

Of particular interest, recent experimental evidence indicates that Withania somnifera can regulate mitochondrial biogenesis and energetic pathways involving SIRT1 in neuronal models [30-33].

This finding does not establish that Ashwagandha induces mitophagy, but it provides a biologically relevant rationale for investigating the broader SIRT1–mitochondrial quality-control network.

8. FOXO3 and Cellular Stress Resistance

FOXO3 belongs to the forkhead box O family of transcription factors and plays an important role in cellular responses to oxidative and metabolic stress.

FOXO signaling has been associated with:

- antioxidant defense;
- autophagy;
- DNA repair;
- stress resistance;
- metabolic adaptation;
- mitochondrial homeostasis.

FOXO3 therefore occupies a strategic position between oxidative stress, autophagy and longevity biology.

A potential Rasayana-related pathway can consequently be conceptualized as:

Rasayana bioactive compounds → AMPK/SIRT1 modulation → FOXO3 activation → antioxidant/autophagy programs → mitochondrial quality maintenance

This remains a hypothesis requiring direct experimental testing.

9. Mitochondrial ROS: From Damage Marker to Signaling Molecule

ROS should not be regarded exclusively as harmful molecules.

Low or transient ROS levels can act as signaling molecules, whereas sustained excessive mitochondrial ROS can contribute to oxidative damage, mitochondrial dysfunction, inflammation and cellular senescence.

This distinction is particularly important for Ayurvedic pharmacology because many Rasayana plants have been investigated primarily through antioxidant assays.

An antioxidant assay demonstrating increased SOD, catalase or reduced lipid peroxidation is not equivalent to evidence of mitophagy.

Future investigations should therefore combine:

ROS measurements + mitochondrial membrane potential + mitophagic flux + PINK1/Parkin + LC3/p62 + mitochondrial mass

rather than relying on one antioxidant endpoint.

10. Autophagy as the Final Cellular Disposal System

Autophagy is an intracellular degradation system that removes damaged proteins, organelles and cytoplasmic material.

Mitophagy represents its mitochondria-selective component.

The classical sequence is:

Initiation → phagophore formation → mitochondrial recognition → autophagosome formation → autophagosome–lysosome fusion → lysosomal degradation

An important methodological issue is that increased LC3-II alone cannot establish increased autophagic flux.

Similarly:

PINK1 ↑ ≠ mitophagy proven

Parkin ↑ ≠ mitophagy proven

LC3-II ↑ ≠ autophagic flux proven

A rigorous future Ayurvedic study should demonstrate mitophagic flux, ideally using complementary approaches such as mt-Keima or mito-QC reporters, mitochondrial–lysosomal colocalization, LC3 turnover and pharmacological/genetic pathway inhibition.

This methodological point can become one of the strongest aspects of the proposed review.

11. Ayurvedic Rasayana and the Mitophagy Hypothesis

Several Ayurvedic medicinal plants have already demonstrated effects relevant to mitochondrial homeostasis, oxidative stress, autophagy or neuroprotection [38-43].

However, the evidence is heterogeneous.

11.1 Withania somnifera

Withania somnifera is traditionally used as a Rasayana and adaptogenic medicine.

Experimental studies have reported protection against oxidative stress and mitochondrial dysfunction. In an experimental stroke model, W. somnifera supplementation improved mitochondrial respiratory-chain abnormalities, membrane potential, oxidative stress and apoptotic changes.

More recently, experimental work reported regulation of mitochondrial biogenesis and energetics involving BDNF and SIRT1 in rat cortical neurons.

These findings make W. somnifera a particularly attractive candidate for investigation of:

SIRT1 → mitochondrial biogenesis → mitochondrial quality control → mitophagy

However, direct demonstration of mitophagic flux remains necessary.

11.2 Tinospora cordifolia

Tinospora cordifolia is included among classical Medhya Rasayana-associated plants and has been extensively investigated for antioxidant, immunomodulatory and cytoprotective properties.

A contemporary review has described its potential against oxidative-stress-associated diseases and summarized multiple antioxidant and protective mechanisms.

The important research gap is whether these effects involve:

AMPK → autophagy → mitophagy

or instead arise primarily from direct antioxidant, anti-inflammatory or other mechanisms.

11.3 Bacopa monnieri

Bacopa monnieri is traditionally associated with Medhya Rasayana activity.

Experimental evidence demonstrates that B. monnieri can induce protective autophagy under chemically induced cellular stress.

This makes Bacopa especially interesting for investigating the relationship between:

Medhya Rasayana → autophagy → mitochondrial quality control → neuronal resilience.

Nevertheless, autophagy induction should not automatically be interpreted as mitophagy.

11.4 Phyllanthus emblica

Amla is a prominent Rasayana-associated plant and contains polyphenolic and antioxidant constituents.

A comprehensive pharmacological review has described its molecular activities across oxidative stress, inflammation, metabolic disorders and other biological systems.

Because oxidative stress and mitochondrial dysfunction are interconnected, P. emblica represents another candidate for direct mitophagy investigation.

11.5 Triphala

Triphala combines:

- Phyllanthus emblica
- Terminalia chebula
- Terminalia bellirica

A comprehensive review has summarized antioxidant, anti-inflammatory, immunomodulatory, metabolic and other pharmacological activities and highlighted its traditional rejuvenative positioning.

A major unanswered question is whether Triphala's multitarget activity includes modulation of mitochondrial turnover.

12. Medhya Rasayana and Brain Mitochondrial Homeostasis

The brain has exceptionally high energy requirements and is therefore highly dependent upon mitochondrial integrity.

Neuronal aging involves alterations in:

- mitochondrial respiration;
- ATP generation;
- oxidative stress;
- mitophagy;
- proteostasis;
- neuroinflammation.

Classical Medhya Rasayana plants have traditionally been associated with cognition and nervous-system health. Modern reviews have documented neuroprotective and nootropic activities of plants such as Bacopa monnieri, Centella asiatica, Tinospora cordifolia and Glycyrrhiza glabra.

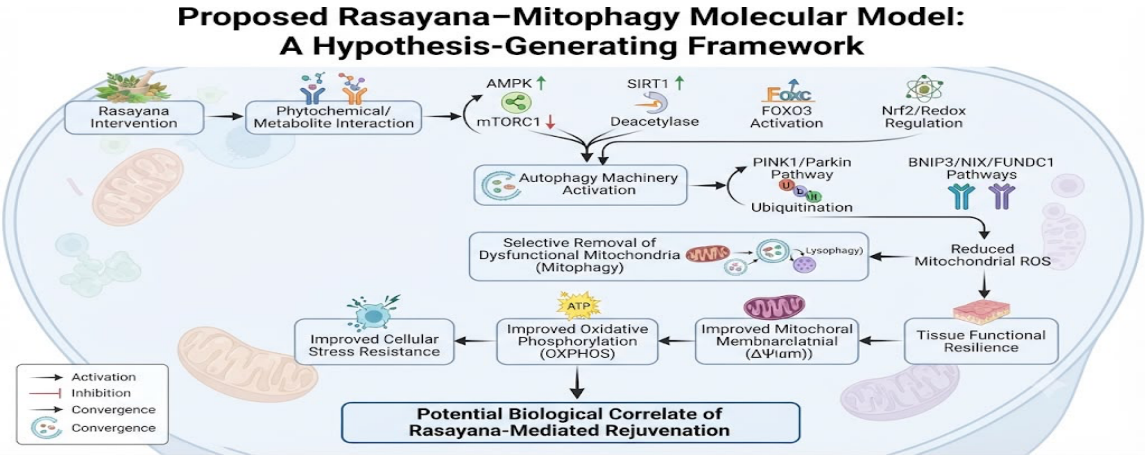
This creates a compelling research hypothesis:

Medhya Rasayana → mitochondrial quality control → neuronal bioenergetics → synaptic resilience → cognitive preservation

This is considerably more testable than simply describing Medhya Rasayana as "memory enhancing."

13. Proposed Rasayana–Mitophagy Molecular Model

Based on current evidence, the following conceptual model can be proposed:



This model should be explicitly presented as a hypothesis-generating framework, not as an established molecular explanation of Rasayana [44-49].

14. Evidence Hierarchy

One of the most important features of a Scopus-oriented review should be separating evidence according to strength.

Evidence level	Example	Interpretation
Level 1	Human clinical evidence of mitophagy modulation	Strong
Level 2	Animal evidence demonstrating mitophagic flux	Moderate–strong
Level 3	Cellular PINK1/Parkin/autophagy evidence	Mechanistic
Level 4	Mitochondrial function/ROS studies	Indirect
Level 5	Antioxidant assays	Preliminary
Level 6	Classical textual description	Traditional evidence, not molecular evidence

This distinction will prevent overstatement.

15. Major Research Gap

The literature currently contains three relatively well-developed areas:

1. Mitophagy and aging

2. Rasayana and healthy aging

3. Ayurvedic plants and antioxidant/cytoprotective activity

What is relatively underdeveloped is the intersection:

Rasayana × mitophagy × mitochondrial quality control

The novelty of the proposed review therefore lies not in claiming that Ayurveda has already been proven to regulate mitophagy, but in identifying mitophagy as a testable molecular hypothesis for Rasayana pharmacology.

16. Recommended Experimental Validation

Future studies should incorporate a multimodal mitochondrial-quality-control panel.

Primary mitophagy endpoints

- PINK1
- Parkin
- phospho-Parkin
- phospho-ubiquitin
- BNIP3
- NIX
- FUNDC1
- LC3-I/LC3-II
- p62/SQSTM1
- lysosomal markers

Functional mitochondrial endpoints

- mitochondrial membrane potential
- ATP
- oxygen consumption rate
- respiratory-chain complexes I–V
- mitochondrial mass
- mitochondrial morphology
- mitochondrial ROS

Signaling pathways

- p-AMPK/AMPK
- p-mTOR/mTOR
- ULK1
- SIRT1
- FOXO3
- Nrf2
- PGC-1α

Gold-standard approaches

Where feasible: mt-Keima or mito-QC should be incorporated to demonstrate actual mitophagic flux.

17. Translational Implications

The proposed framework may have relevance to several age-associated conditions:

- neurodegenerative disorders;
- sarcopenia;
- metabolic syndrome;
- cardiovascular aging;
- cognitive decline;
- chronic inflammatory disorders;
- age-related mitochondrial dysfunction.

However, the therapeutic implication should remain cautious.

It would be scientifically inappropriate to claim: “Rasayana cures aging by activating mitophagy.”

A more defensible statement is: “Mitophagy represents a plausible molecular pathway through which selected Rasayana interventions may influence mitochondrial quality control and cellular resilience.”

That wording is much more suitable for a high-quality review.

18. Limitations

Several limitations must be acknowledged.

First, direct molecular evidence connecting classical Rasayana formulations with mitophagic flux is currently limited.

Second, many Ayurvedic studies focus on antioxidant activity rather than mitochondrial turnover.

Third, studies frequently use different extracts, doses, extraction procedures and phytochemical profiles, making cross-study comparison difficult.

Fourth, mitophagy markers are sometimes interpreted without demonstrating autophagic flux.

Fifth, results obtained from isolated phytochemicals or animal models cannot automatically be extrapolated to classical Ayurvedic formulations or human clinical outcomes.

Finally, Ayurvedic constructs such as Ojas, Bala and Vayasthapana should not be reduced to single molecular entities. They may be more appropriately treated as multidimensional physiological concepts that can generate experimentally testable hypotheses.

19. Future Research Priorities

The following research agenda is proposed:

Priority 1 Standardize Rasayana extracts using chemical fingerprinting and validated biomarkers.

Priority 2 Determine whether Rasayana interventions alter mitochondrial membrane potential and mitochondrial ROS.

Priority 3 Demonstrate actual mitophagic flux using mt-Keima or mito-QC.

Priority 4 Investigate PINK1/Parkin-dependent mitophagy.

Priority 5 Investigate PINK1/Parkin-independent pathways including BNIP3/NIX and FUNDC1.

Priority 6 Evaluate AMPK–mTOR–ULK1 signaling.

Priority 7 Investigate SIRT1–FOXO3 and SIRT1–PGC-1α signaling.

Priority 8 Determine whether mitochondrial biogenesis and mitophagy are coordinately regulated.

Priority 9 Translate promising findings into aged-animal models.

Priority 10 Ultimately conduct biomarker-supported human studies [50-58].

20. Conclusion

Rasayana represents one of Ayurveda’s most sophisticated frameworks for maintaining health, vitality, strength, cognition and longevity. Contemporary mitochondrial biology provides a complementary molecular framework in which cellular resilience depends upon continuous maintenance of mitochondrial quality.

Mitophagy is emerging as a central component of this quality-control system. The PINK1/Parkin pathway, receptor-mediated mitophagy, AMPK–mTOR signaling, SIRT1, FOXO3, mitochondrial ROS and autophagy form an interconnected network capable of influencing mitochondrial turnover and cellular adaptation.

Several Ayurvedic Rasayana and Medhya Rasayana plants demonstrate antioxidant, mitochondrial, neuroprotective or autophagy-related activities. Evidence concerning Withania somnifera, Tinospora cordifolia, Bacopa monnieri and Triphala provides a rational starting point for mechanistic investigation.

Nevertheless, the present evidence does not justify concluding that Rasayana pharmacology has already been demonstrated to act through mitophagy. Instead, the Rasayana–mitophagy axis should be regarded as a novel, biologically plausible and experimentally testable hypothesis.

Future research combining classical Ayurvedic pharmacological concepts with quantitative mitochondrial biology could transform the study of Rasayana from predominantly phenomenological descriptions toward mechanism-based geroscience.

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