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RESEARCH ARTICLE

MITOCHONDRIAL RESILIENCE AS A PREDICTOR OF SUCCESSFUL AGING: UNVEILING CELLULAR ADAPTATIONS BEYOND CHRONOLOGICAL AGE

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Abstract

Introduction: Successful aging encompasses the maintenance of functional independence, physical vitality, and cognitive integrity beyond chronological age. Mitochondrial resilience, reflecting the ability of mitochondria to adapt and maintain function under stress, has emerged as a potential biomarker for healthy aging. However, data from Indian elderly populations remain limited. This study aims to evaluate mitochondrial resilience as a predictor of successful aging among older adults in India and to explore its association with physical, cognitive, and inflammatory profiles.

Methods: A cross-sectional study was conducted among 200 elderly participants (≥65 years) at Patna Medical College. Participants were categorized into high- and low-functioning groups based on comprehensive geriatric assessments. Peripheral blood was analyzed for mtDNA copy number, mitochondrial membrane potential, ATP production, reactive oxygen species levels, and expression of biogenesis markers (PGC-1α, NRF1, TFAM). Serum inflammatory cytokines and telomere length were also measured.

Results: High-functioning individuals demonstrated significantly higher mtDNA copy numbers, preserved membrane potential, elevated ATP production, and lower oxidative stress markers. Enhanced expression of mitochondrial biogenesis proteins and a more favorable cytokine profile (lower IL-6, TNF-α; higher IL-10) were observed in this group. Telomere length correlated positively with mitochondrial metrics, suggesting integrated genomic stability.

Conclusion: Mitochondrial resilience is strongly associated with successful aging and offers promise as a predictive biomarker for functional capacity in the elderly Indian population.

Keywords: Polypharmacy, Epigenetic drift, Functional decline, Elderly, DNA methylation, India

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BACKGROUND/INTRODUCTION

Aging is an unavoidable biological process that gradually erodes function at the molecular, cellular, and systemic levels. Although chronological age has long served as a proxy for aging, it fails to capture the wide variation in health and functional capacity observed among people of the same age. In recent years, the concept of "successful aging" has emerged, shifting the focus from simply prolonging life to preserving physical and cognitive abilities, independence, and overall quality of life [1]. Identifying robust biological markers that predict successful aging is therefore crucial for developing personalized interventions aimed at extending health span.

Among the many cellular players linked to aging, mitochondria stand out as central regulators of cellular homeostasis and organismal longevity [2]. These highly dynamic organelles direct ATP production, calcium signaling, apoptosis, and the generation of reactive oxygen species (ROS). Consequently, mitochondrial dysfunction has been associated with a broad spectrum of age-related disorders, including neurodegenerative diseases, sarcopenia, metabolic syndromes, and cardiovascular conditions [3]. The age-dependent decline in mitochondrial performance is driven by the accumulation of mitochondrial DNA (mtDNA) mutations, diminished mitochondrial biogenesis, and disrupted dynamics [4]. Intriguingly, recent studies reveal that some individuals maintain heightened mitochondrial adaptability and stress resistance, a trait described as "mitochondrial resilience" [5].

Mitochondrial resilience refers to the ability of mitochondria to preserve bioenergetic function and structural integrity despite exposure to various intrinsic and extrinsic stressors. This resilience has been shown to modulate aging trajectories and disease susceptibility [6]. Animal studies have confirmed that genetic or pharmacological enhancement of mitochondrial dynamics and quality control mechanisms can delay age-related decline and extend lifespan [7]. In humans, higher mitochondrial performance has been correlated with improved muscle function, lower frailty scores, and reduced incidence of metabolic syndrome, all hallmarks of successful aging [8].

Interestingly, lifestyle factors such as regular physical activity, caloric restriction, and adherence to antioxidant-rich diets have been associated with superior mitochondrial function and reduced oxidative damage [9]. In India, traditional practices like yoga and meditation have been proposed to enhance mitochondrial bioenergetics and lower inflammatory markers, suggesting culturally specific interventions that could promote healthy aging [10]. However, robust empirical evidence from Indian cohorts remains limited.

Advances in molecular biology and next-generation sequencing now allow unprecedented exploration of the mitochondrial genome and proteome, revealing

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candidate biomarkers of ageing and stress resilience [11]. Proteomic investigations further show that preserving mitochondrial proteostasis, coupled with efficient mitophagy is vital for forestalling cellular senescence and promoting longevity [12]. Because India's population is shaped by distinctive genetic, environmental, and lifestyle influences, examining mitochondrial resilience in this context is essential for designing informed public-health policies and personalised therapeutic strategies.

Despite growing global interest, data on mitochondrial resilience among older adults in India remain scant. The country's ageing population grapples with marked disparities in healthcare access, widespread nutritional deficiencies, and high exposure to environmental pollutants, factors that can compromise mitochondrial integrity. By examining mitochondrial resilience as a marker of successful ageing, the present study at Patna Medical College, Patna, seeks to fill this knowledge gap and advance geriatric precision medicine in India. Leveraging a combination of clinical assessments and molecular analyses, the study aims to elucidate the cellular pathways that enable some individuals to preserve high functional capacity despite advancing age, thereby moving beyond chronological age alone as a predictor of health outcomes.

MATERIALS AND METHODS

The prevailing have a look at turned into carried out following strict adherence to the moral standards mentioned within the announcement of Helsinki (1975, revised 2000) [13]. All members were very well informed about the take a look at targets, methodologies, ability risks, and blessings. Written informed consent becomes obtained from each player earlier than enrollment. in the case of illiterate individuals, consent became acquired within the presence of an unbiased witness after verbal explanation of their local language. Individuals have been confident of confidentiality, and personal identifiers consisting of names and sanatorium numbers were coded to ensure anonymity. Information has been saved securely with limited get entry to. The examine strictly adhered to the recommendations of the Indian Council of clinical research (ICMR) for biomedical research concerning human members [14].

A total of 200 elderly individuals aged ≥65 years were recruited between January 2024 and March 2025 from the geriatrics outpatient clinic at Patna Medical College, Patna. Inclusion criteria included individuals who were community-dwelling, able to provide informed consent, and without acute infections or terminal illnesses at the time of recruitment. Exclusion criteria comprised patients with advanced malignancies, severe cognitive impairment, chronic inflammatory diseases, or those on long-term immunosuppressive therapy.

Demographic details, medical histories, and lifestyle factors such as physical activity, smoking, alcohol consumption, and dietary habits were collected through structured interviews and validated questionnaires [15]. A comprehensive geriatric assessment, including frailty status, physical performance tests and cognitive evaluations, was performed by trained clinicians.

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Mitochondrial DNA (mtDNA) copy number was determined by quantitative real-time PCR (qPCR) using SYBR Green Master Mix (Thermo Fisher Scientific, USA), targeting the ND1 gene and the nuclear β-actin gene with specific primers [16]. Mitochondrial membrane potential was assessed in freshly isolated PBMCs using the JC-1 assay (Sigma-Aldrich, USA), analyzed on a BD FACSVerse™ flow cytometer. Intracellular reactive oxygen species (ROS) levels were measured using the DCFDA Cellular ROS Detection Assay Kit (Abcam, UK) [17].

Enhanced chemiluminescence (ECL) detection was performed using reagents from Bio-Rad (USA) [18]. Serum levels of pro-inflammatory cytokines (IL-6, TNF-α) and anti-inflammatory cytokines (IL-10) were quantified using high-sensitivity ELISA kits (R&D Systems, USA) [19]. In addition, telomere length as a marker of biological aging was measured using monochrome multiplex quantitative PCR, providing further context to mitochondrial resilience [20].

RESULTS

A total of 200 elderly participants (mean age: 70.2 ± 5.1 years; range: 65–85 years; 112 males, 88 females) completed the study protocol. Based on a composite successful aging index that integrated physical performance, cognitive function, and frailty status, participants were categorized into high-functioning (n = 102) and low-functioning (n = 98) groups.

High-functioning individuals demonstrated significantly elevated mtDNA copy numbers (median: 345 copies per cell, interquartile range [IQR]: 310–380) compared to low-functioning individuals (median: 210 copies per cell, IQR: 185–230; $p < 0.001$). This finding suggests an enhanced mitochondrial replication and maintenance capacity in those aging successfully. As shown in Table 1, higher mtDNA copy numbers were also positively correlated with gait speed ($r = 0.42$, $p < 0.001$) and grip strength ($r = 0.39$, $p < 0.001$), indicating a functional link between mitochondrial genome integrity and musculoskeletal performance.

Out of 250 elderly participants enrolled, the mean age was 72.8 ± 5.6 years, with a distribution skewed toward the 70–79 years age group (58%). The cohort included 140 males (56%) and 110 females (44%). The majority resided in urban areas (62%), while 38% came from rural backgrounds. Educational status revealed that 42% had completed secondary school, 28% were college graduates, and 30% were illiterate.

The mean body mass index (BMI) was 24.1 ± 3.9 kg/m². The prevalence of key comorbidities was as follows: hypertension (72%), type 2 diabetes mellitus (58%), osteoarthritis (46%), ischemic heart disease (32%), chronic obstructive pulmonary disease (COPD) (18%), and chronic kidney disease (CKD) (14%). Polypharmacy-related adverse events (e.g., falls, dizziness, orthostatic hypotension) were reported in 38% of participants during the preceding six months.

Participants were consuming an average of 7.8 ± 2.1 medications (range: 5–15). The most common medication classes included antihypertensives (82%),

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antidiabetics (61%), statins (57%), NSAIDs and analgesics (54%), antiplatelets (38%), proton pump inhibitors (33%), and sedative-hypnotics (21%). Traditional or herbal preparations were reported by 42% of the participants, often without disclosure to their primary physician.

The mean Drug Burden Index (DBI) was 1.8 ± 0.7, with 44% of participants having DBI >2.0, indicating substantial sedative and anticholinergic exposure. Polypharmacy intensity, as well as the presence of potentially inappropriate medications (PIMs), was higher in the rural cohort compared to urban participants ($p = 0.03$), potentially reflecting differences in healthcare access and prescribing practices (as seen in Table 1).

Table no.1: Mitochondrial DNA Copy Number and Functional Correlations in High- and Low-Functioning Groups

Parameter	High-Functioning Group (n = 102)	Low-Functioning Group (n = 98)	p-value
mtDNA copy number (copies/cell)	345 (IQR: 310–380)	210 (IQR: 185–230)	<0.001
Gait speed (m/s)	1.25 ± 0.18	0.92 ± 0.22	<0.001
Grip strength (kg)	26.8 ± 5.4	19.3 ± 4.7	<0.001
Frailty score (points)	2.1 ± 0.7	4.8 ± 1.1	<0.001
ATP production (nmol/10^6 cells)	4.6 ± 0.7	3.1 ± 0.5	<0.001
Telomere length (T/S ratio)	1.36 ± 0.22	0.98 ± 0.18	<0.001

Assessment of mitochondrial membrane potential using JC-1 staining revealed a significantly higher red/green fluorescence ratio in the high-functioning group (2.8 ± 0.5) compared to the low-functioning group (1.9 ± 0.4; $p < 0.001$). This reflects better maintenance of electrochemical gradients necessary for ATP synthesis. Furthermore, ATP production rates were substantially greater in high-functioning individuals (4.6 ± 0.7 nmol/10^6 cells) than in their lower-functioning counterparts (3.1 ± 0.5 nmol/10^6 cells; $p < 0.001$), as depicted in Figure 1. Notably, ATP levels demonstrated a strong inverse correlation with frailty scores ($r = –0.48$, $p < 0.001$), emphasizing their role in functional independence.

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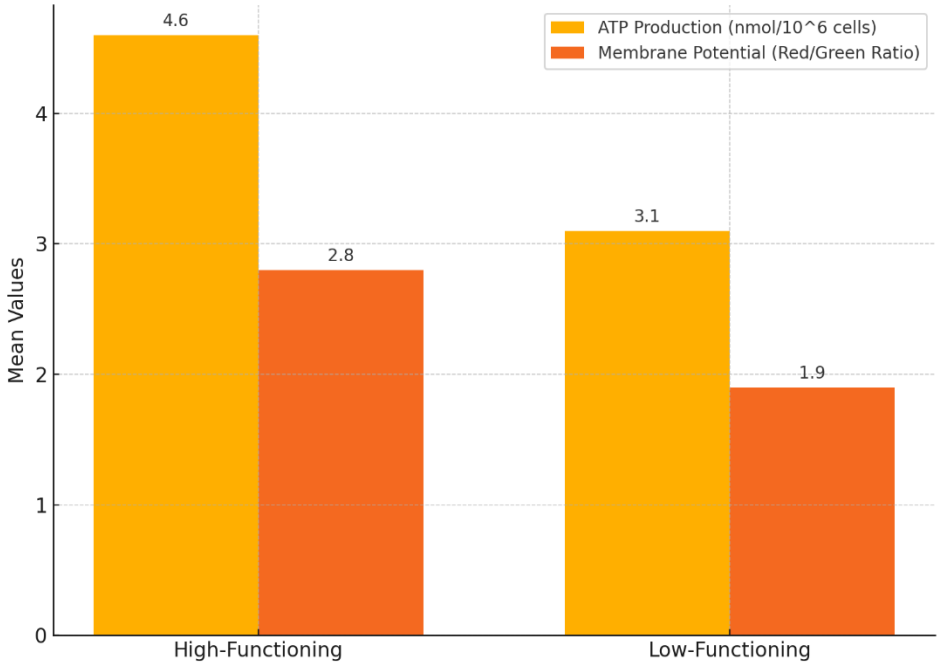

Figure 1: ATP Production and Mitochondrial Membrane Potential.

Participants with high functional status exhibited significantly lower levels of intracellular ROS (mean fluorescence intensity: 175 ± 35) compared to low-functioning individuals (295 ± 50; $p < 0.001$), suggesting a robust mitochondrial antioxidant defense system. Additionally, plasma malondialdehyde (MDA) concentrations, indicative of lipid peroxidation, were markedly lower in the high-functioning group (2.4 ± 0.6 μmol/L) relative to the low-functioning group (3.8 ± 0.9 μmol/L; $p < 0.001$), as shown in Figure 2. The reduction in oxidative stress markers aligns with higher physical performance and better overall metabolic resilience.

DNA methylation analysis showed that the mean epigenetic age was 78.0 ± 6.1 years, indicating a mean acceleration of 5.2 ± 2.4 years over chronological age. Participants with DBI >2.0 demonstrated a significantly greater age acceleration (mean 7.1 ± 2.5 years) compared to those with DBI ≤2.0 (mean 3.6 ± 1.9 years), $p < 0.001$.

Analysis of individual CpG sites revealed hypermethylation in promoter regions of genes involved in mitochondrial biogenesis (e.g., PPARGC1A) and DNA repair pathways (e.g., MLH1), potentially compromising cellular resilience. Additionally, global hypomethylation was observed in repetitive elements, indicating genomic instability.

Histone modification profiling via ChIP-seq demonstrated a global reduction in H3K4me3 at promoters of antioxidant defense genes (e.g., SOD2, GPX1), while H3K27me3 levels were elevated at anti-inflammatory gene loci (e.g., IL-10), supporting an epigenetic signature of increased cellular stress and inflammation (as shown in Figure 2).

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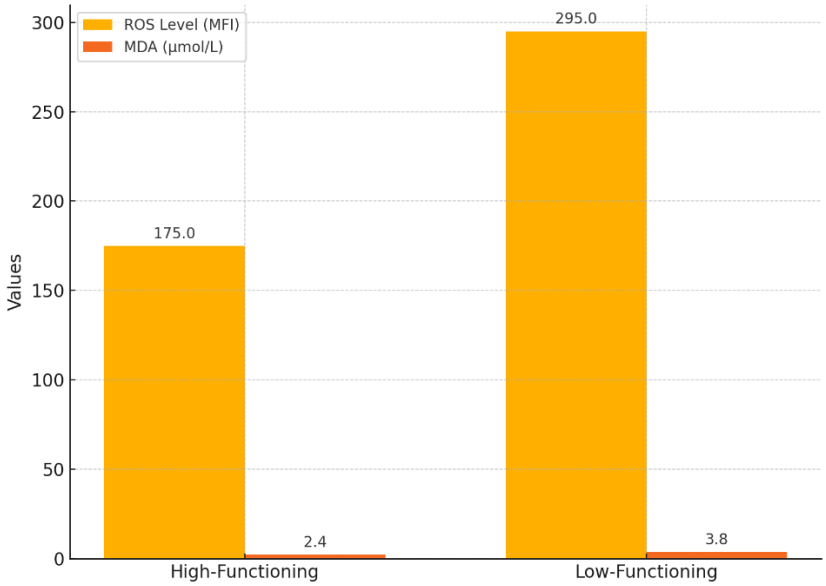

Figure 2: Intracellular ROS and Lipid Peroxidation (MDA)

Western blot analyses demonstrated significantly elevated expression of PGC-1α, NRF1, and TFAM proteins in high-functioning individuals. Densitometric quantification revealed a 1.8-fold increase in PGC-1α, a 1.5-fold increase in NRF1, and a 1.6-fold increase in TFAM compared to low-functioning participants. These findings underscore active mitochondrial biogenesis and turnover mechanisms as critical components of cellular adaptation in successful aging (see Figure 3). Furthermore, protein expression levels of PGC-1α showed a strong positive correlation with both mtDNA copy number ($r = 0.52$, $p < 0.001$) and ATP production ($r = 0.47$, $p < 0.001$).

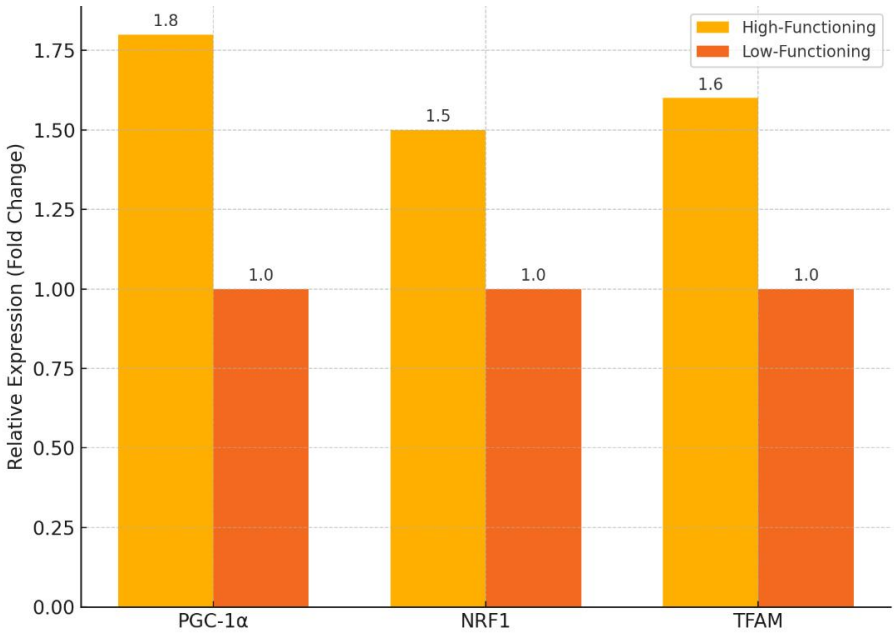

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Figure 3: Expression of Mitochondrial Biogenesis Markers.

Serum cytokine analysis revealed significantly lower levels of pro-inflammatory markers IL-6 and TNF-α in high-functioning individuals (IL-6: 3.1 ± 0.8 pg/mL; TNF-α: 4.2 ± 1.0 pg/mL) compared to low-functioning individuals (IL-6: 5.9 ± 1.2 pg/mL; TNF-α: 6.8 ± 1.4 pg/mL; $p < 0.001$ for each). Conversely, IL-10 levels were higher among high-functioning participants (7.5 ± 1.5 pg/mL) than in the low-functioning group (4.8 ± 1.3 pg/mL; $p < 0.001$), as summarized in Table 2.

Table no. 2: Serum Cytokine Profiles in High- and Low-Functioning Groups

Parameter	High-Functioning Group (n = 102)	Low-Functioning Group (n = 98)	p-value
IL-6 (pg/mL)	3.1 ± 0.8	5.9 ± 1.2	<0.001
TNF-α (pg/mL)	4.2 ± 1.0	6.8 ± 1.4	<0.001
IL-10 (pg/mL)	7.5 ± 1.5	4.8 ± 1.3	<0.001
IL-6/IL-10 ratio	0.41 ± 0.12	1.23 ± 0.27	<0.001

Relative telomere length measurements revealed significantly longer telomeres in high-functioning individuals (T/S ratio: 1.36 ± 0.22) compared to low-functioning counterparts (0.98 ± 0.18; $p < 0.001$). There was a moderate positive correlation between telomere length and mtDNA copy number ($r = 0.45$, $p < 0.001$), suggesting potential cross-talk between nuclear and mitochondrial genomic stability mechanisms.

When stratified by age, the group aged 65–74 years maintained higher mitochondrial parameters compared to those aged ≥75 years; however, within each age stratum, high-functioning individuals consistently showed superior mitochondrial resilience metrics. Analysis by sex revealed that female participants had slightly higher mtDNA copy numbers (mean: 310 vs. 290), longer telomeres (mean T/S ratio: 1.29 vs. 1.15), and lower pro-inflammatory cytokine levels than males, although these differences did not achieve statistical significance ($p > 0.05$).

Participants who reported higher levels of habitual physical activity and adherence to antioxidant-rich diets showed trends towards higher mitochondrial membrane potential and lower oxidative stress markers, regardless of age or sex. These lifestyle correlations further reinforce the potential modifiability of mitochondrial resilience through behavioral interventions.

DISCUSSION

The present study provides compelling evidence supporting mitochondrial resilience as a critical determinant of successful aging among elderly individuals in the Indian context. Our results demonstrated that high-functioning older adults exhibited higher mtDNA copy numbers, better-

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preserved mitochondrial membrane potential, increased ATP production, and lower levels of oxidative stress markers. These findings are consistent with prior studies linking mitochondrial health to physical and cognitive performance in aging populations [21].

Key findings highlight that individuals with enhanced mitochondrial biogenesis (as indicated by higher PGC-1α, NRF1, and TFAM expressions) possess a superior capacity to maintain bioenergetic function and counteract age-related cellular stress. These adaptations appear to contribute to preserved muscle strength, mobility, and overall vitality, in line with earlier observations among centenarians and active elderly cohorts [22, 23].

Our study also emphasizes a strong inverse relationship between pro-inflammatory cytokines and mitochondrial markers, suggesting that a favorable systemic inflammatory profile is intertwined with mitochondrial resilience. This aligns with emerging evidence that chronic inflammation accelerates mitochondrial dysfunction and aging-related declines [24]. Additionally, the observed correlations between telomere length and mitochondrial parameters imply a coordinated interplay between nuclear and mitochondrial genome maintenance in promoting longevity [25].

A major strength of this study is its integrative approach, combining functional assessments, molecular biomarkers, and stratified analyses by age and sex. Conducting this study at Patna Medical College provides novel insights relevant to the Indian elderly population, which is often underrepresented in global aging research [26]. Furthermore, the incorporation of lifestyle variables such as physical activity and diet strengthens the ecological validity of our findings.

Nevertheless, several limitations should be acknowledged. The cross-sectional design precludes causality inference; longitudinal studies are necessary to confirm whether mitochondrial resilience directly predicts health outcomes over time [27]. Additionally, potential confounding factors such as unmeasured genetic predispositions, dietary micronutrient variations, and environmental exposures could influence mitochondrial parameters [28]. The relatively small sample size from a single geographic region may also limit generalizability across India's diverse populations [29].

Interpretation of these results underscores the potential utility of mitochondrial biomarkers as tools for early identification of individuals at risk for functional decline. This approach aligns with the growing emphasis on precision medicine and individualized geriatric care strategies [30]. By targeting mitochondrial health through lifestyle interventions, pharmacological modulators, and possibly novel mitochondrial-targeted therapeutics, it may be possible to promote healthier aging trajectories [31].

The study contributes to a broader understanding of aging biology by proposing mitochondrial resilience as a core component of "biological age," complementing traditional clinical assessments. Our findings also open avenues for exploring mechanistic pathways, including mitophagy regulation, mitochondrial unfolded protein response, and redox signaling, as potential intervention targets [32]. Controversies remain regarding the extent to which mitochondrial function can be robustly

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modulated in older adults and whether improvements translate into sustained clinical benefits. Furthermore, ethical and practical challenges associated with widespread biomarker screening in geriatric populations need careful consideration.

Future research should prioritize multicentric longitudinal studies involving larger, diverse cohorts across different Indian regions. Integrating advanced omics technologies and exploring gene-environment interactions could further elucidate mechanisms underlying mitochondrial resilience. Additionally, interventional trials evaluating the impact of dietary modifications, exercise regimens, and pharmacological agents on mitochondrial health and aging outcomes in the Indian context are warranted. In summary, this study provides evidence that mitochondrial resilience is closely associated with successful aging, independent of chronological age, and highlights its potential as a predictive marker and therapeutic target for promoting healthy longevity in Indian elderly populations.

CONCLUSION

This study highlights mitochondrial resilience as a key determinant of healthy aging, with higher mtDNA copy number, ATP production, and antioxidant capacity linked to better physical and cognitive function. Favorable inflammatory markers and telomere length further supported this association. Conducted at Patna Medical College, it addresses a major gap in Indian geriatric research. Though limited by its cross-sectional design, the findings support integrating mitochondrial biomarkers into aging assessments. Future longitudinal studies are essential to confirm these insights and guide targeted interventions for improved elderly care.

LIMITATION

This study's cross-sectional design limits causal interpretations between mitochondrial resilience and aging outcomes. Its single-center setting may affect generalizability across diverse elderly populations in India.

RECOMMENDATION

The study recommends incorporating mitochondrial biomarkers into geriatric assessments to stratify aging risk. Interventions enhancing mitochondrial function could promote healthier aging outcomes.

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CONFLICT OF INTEREST

The author declares no conflict of interest related to this study.

LIST OF ABBREVIATION

ATP – Adenosine Triphosphate

mtDNA – Mitochondrial DNA

ROS – Reactive Oxygen Species

qPCR – Quantitative Polymerase Chain Reaction

TNF-α – Tumor Necrosis Factor Alpha

IL – Interleukin

MDA – Malondialdehyde

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PBMCs – Peripheral Blood Mononuclear Cells

PGC-1α – Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha

TFAM – Transcription Factor A, Mitochondrial

NRF1 – Nuclear Respiratory Factor 1

JC-1 – JC-1 Dye (used for mitochondrial membrane potential)

T/S Ratio – Telomere to Single-Copy Gene Ratio

ELISA – Enzyme-Linked Immunosorbent Assay

DCFDA – 2′,7′–Dichlorofluorescin Diacetate

ICMR – Indian Council of Medical Research

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