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# The NAD$^+$-mitophagy axis in healthy longevity and in artificial intelligence-based clinical applications

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ABSTRACT

Nicotinamide adenine dinucleotide (NAD$^+$) is an important natural molecule involved in fundamental biological processes, including the TCA cycle, OXPHOS, β-oxidation, and is a co-factor for proteins promoting healthy longevity. NAD$^+$ depletion is associated with the hallmarks of ageing and may contribute to a wide range of age-related diseases including metabolic disorders, cancer, and neurodegenerative diseases. One of the central pathways by which NAD$^+$ promotes healthy ageing is through regulation of mitochondrial homeostasis via mitochondrial biogenesis and the clearance of damaged mitochondria via mitophagy. Here, we highlight the contribution of the NAD$^+$-mitophagy axis to ageing and age-related diseases, and evaluate how boosting NAD$^+$ levels may emerge as a promising therapeutic strategy to counter ageing as well as neurodegenerative diseases including Alzheimer's disease. The potential use of artificial intelligence to understand the roles and molecular mechanisms of the NAD$^+$-mitophagy axis in ageing is discussed, including possible applications in drug target identification and validation, compound screening and lead compound discovery, biomarker development, as well as efficacy and safety assessment. Advances in our understanding of the molecular and cellular roles of NAD$^+$ in mitophagy will lead to novel approaches for facilitating healthy mitochondrial homoeostasis that may serve as a promising therapeutic strategy to counter ageing-associated pathologies and/or accelerated ageing.

## 1. Introduction

Ageing is an inevitable biological process but over the years there has been a dramatic increase in human life expectancy. A recent United Nations report estimated that over 700 million people (representing 9% of the world population) were over 65 years old in 2019, a figure that is expected to double by 2050 (United Nations, 2019). A rise in human longevity has led to an increased global burden of age-related diseases, such as cardiovascular diseases, cancer, and neurodegenerative diseases (especially Alzheimer's disease/AD) (Fang et al., 2015; Partridge et al., 2018). These age-related conditions not only result in reduced quality of life of the elderly population, but also present as a formidable healthcare and socio-economic challenge. Interestingly, there is a sub-population of elderly individuals that experience little ill-health. One aim of molecular gerontology is to define the features of such super-aged individuals in order to be extended to the general population. In

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