Natural Killer cells Plasticity and Aging. The Role of (Poly)phenols on Modulating Immunoaging.

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Abstract

Background and Objectives
Aging is intricately linked to immunosenescence, a process marked by the deterioration of adaptive and innate immunity, chronic low-grade inflammation, and heightened vulnerability to infections, malignancies, and age-related pathologies. Natural Killer (NK) cells, critical mediators of antiviral and antitumor responses, undergo functional decline with age, including reduced cytotoxicity, impaired cytokine production, and diminished numbers, exacerbating immune dysfunction. While immunosenescence mechanisms are well-documented, interventions to restore NK cell efficacy remain limited. Recent evidence suggests dietary polyphenols—bioactive compounds with antioxidative and anti-inflammatory properties—may counteract age-related immune decline. This review synthesizes current findings on polyphenols' capacity to rejuvenate NK cell function, offering insights into their potential as therapeutic agents for healthy aging.

Methods
A systematic analysis of preclinical studies and experimental models was conducted, focusing on polyphenols' effects on NK cells in aging contexts. In vivo studies utilized aged murine models, while in vitro assays evaluated molecular mechanisms. Key outcomes included NK cytotoxicity, cytokine secretion, population dynamics, and biomarkers such as NKG2D, perforin, and sirtuins.
Polyphenols examined included resveratrol, epigallocatechin gallate (EGCG), verbenalin, quercetin, curcumin, apigenin, and pterostilbene.

Results
Resveratrol enhanced NK cytotoxicity in aged rats by upregulating NKG2D receptors and perforin expression, coupled with sirtuin activation—a pathway implicated in longevity. EGCG restored NK cell populations in aged mice, reversing age-associated lymphopenia. Verbenalin accelerated NK cell-target cell interactions, improving viral clearance. Quercetin reduced senescence markers (e.g., p16) while boosting NK activity, whereas curcumin attenuated inflammation via NF-κB inhibition, indirectly supporting NK function. Apigenin enhanced cytotoxicity and mitigated autoimmune responses, and pterostilbene improved mitochondrial efficiency, critical for sustained NK activity.

Discussion
Polyphenols exhibit multifaceted immunomodulatory effects, targeting oxidative stress, inflammation, and cellular senescence to rejuvenate NK cell function. Their synergistic mechanisms—ranging from receptor upregulation to epigenetic modulation—position them as promising candidates for combating immunosenescence. While animal studies are compelling, clinical trials are essential to validate efficacy in humans. Future research should explore combinatorial polyphenol interventions and their integration into dietary strategies for aging populations. Harnessing these bioactive compounds could transform immune resilience in the elderly, reducing disease burden and enhancing quality of life.

Keywords: immune system; polyphenols; aging; bioactive; NK cells; immunosenescence