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REVIEW ARTICLE

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# Highlight the major clinical outcomes of vitamins and minerals in healthy aging: a systematic review

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## Abstract

**Introduction:** In the context of healthy longevity, aging is a natural phenomenon that promotes a senescent phenotype, with the shortening of telomeres. The main ways to increase a healthy life expectancy include lifestyle modifications and pharmacological manipulations. Vitamins, minerals (as micronutrients), essential amino acids, polyunsaturated fatty acids (PUFA), probiotics, and plant metabolites such as polyphenols and terpenoids are widely recognized for preventing aging. **Objective:** It was to carry out a systematic review to highlight the main clinical outcomes of vitamins and minerals in healthy aging. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from August to September 2023 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 122 articles were found, and 40 articles were evaluated in full and 38 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 25 studies with a high risk of bias and 21 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with $X^2$=72.4%>50%. Zinc and copper govern many functions that characterize the so-called "oxy-aging". Selenium (Se) is a fundamental cofactor in many redox functions, vitamin C's role in aging has been investigated particularly for skin health and immunity, particularly in inflammatory and degenerative diseases. Retinoids, which represent a synthetic form of vitamin A, appear effective in preventing skin degeneration due to aging. The role of vitamin E in preventing and reducing ROS-induced injuries has been well described. Supplementation with selenium and coenzyme Q10 influenced the biomarkers analyzed to indicate an anti-aging effect. It was concluded that micronutrients such as vitamins and minerals have anti-oxidant, protective, and regenerative properties to promote healthy aging.

**Keywords:** Cellular senescence. Healthy longevity. Healthy aging. Anti-aging. Micronutrients.

## Introduction

In the context of healthy longevity, aging is a natural phenomenon that promotes a senescent phenotype with tissue degeneration, telomere shortening, dementia, cognitive deficits, functional impairments, and chronic pathologies **[1-3]**. There is a theory about genetically programmed longevity, showing that aging is the consequence of the initiation or interruption of certain genes and the shortening of telomeres **[1]**. Furthermore, there is an endocrine theory that aging is governed by a biological clock whose function is regulated by endocrine mechanisms, among which the insulin-like growth hormone IGF-1 plays an important role. And there is a theory about immunity, stating that the immune system is programmed to reduce its functionality (immunosenescence), increasing susceptibility to infectious diseases and inflammatory pathologies **[4]**.

In this scenario, reactive oxygen species (ROS) are probably the most important free radicals, with major

implications for the destruction and aging of cells and the body. It has been shown that mitochondria are the main site of chemical reactions that generate free radicals. Considering aging as a gradual decrease in the functional regulation of complex multifactorial biological processes, the individual's genotype certainly impacts the rate of aging **[4]**.

Given this, the main ways to increase a healthy life expectancy include lifestyle modifications and pharmacological (or genetic) manipulations **[1,2]**. Proper diet and calorie restriction are crucial for healthy aging **[5]**. One of the main goals of anti-aging medicine, however, is not only to extend life expectancy but, in particular, to sustain a healthy life for longer. Rattan proposed changing the approach in this field from "anti-aging" to "healthy aging", thus strengthening health-oriented research **[6]**.

Accordingly, essential nutrients such as defined vitamins, minerals (as micronutrients), essential and branched amino acids, polyunsaturated fatty acids (PUFA), probiotics, and plant metabolites such as polyphenols and terpenoids are widely recognized to prevent aging and promote healthy aging. Its role is mainly to neutralize oxidative stress in the body, according to the free radical theory of aging **[7-10]**. Older adults have an increased risk of atherosclerosis caused by chronic inflammation **[11]**. Natural compounds can increase life expectancy and improve health and quality of life, decreasing the development of some age-related chronic diseases, such as diabetes, cancer, neurodegeneration, and cardiovascular diseases **[12]**.

Furthermore, the mechanisms by which oxidative stress causes degenerative phenomena related to aging must be separated from the fundamental role played by ROS as signaling molecules, because they modulate and regulate important healthy and survival systems, maintained by mitochondria and membranes associated with mitochondria that ensure the viability and healthy state of cells and tissues **[13-15]**. Antioxidants are involved in the prevention of age-related diseases such as atherosclerosis, neurodegenerative processes, cancer, diabetes, and skin wrinkles at the molecular level, having a beneficial effect on digestion and the immune system, reducing the level of inflammatory and degenerative processes in the body **[14,15]**.

In addition, several substances with geroprotective properties have been described. Among them, it is worth mentioning Gerovital – a geroprotective product based on the anesthetics procaine, resveratrol and other vegetable polyphenols, rapamycin, antioxidants, vitamins A, C and E, carotenoids, lipoic acid, coenzyme Q, selenium, etc., hormones (GH, hormones thyroid, adrenaline and sex hormones, melatonin), bioregulatory peptides (thymalin, epithalmin), biguanide (metformin, phenformin), adaptogen (ginseng). Geroprotective/anti-aging compounds (antioxidants) studied worldwide, such as resveratrol, rapamycin or procaine, α-tocopherol, ascorbic acid, retinol, ubiquinone, selenium, etc. oxidative balance **[4]**. Natural anti-aging compounds such as vitamins, polyphenols, hydroxy acids, polysaccharides, and many others play a crucial role in skin care **[16]**.

Inflammation is also one of the most important aspects of the aging process, which indicates the intimate relationship between aging and inflammation. In a review, Zhu et al. characterized aging as follows: "Dysregulated inflammation, alteration of epigenetic modifications, and metabolic imbalance converge to cellular senescence and aging" **[12]**.

In this aspect, the main biomarker is ICAM-1, which is a cell surface glycoprotein, which also exists as a soluble molecule. Some of the important functions of ICAM-1 are to recruit leukocytes from the circulation and act as a regulator of the immune response, also in the vasculature **[12,14]**. Adiponectin is referred to as an adipocytokine with anti-inflammatory properties. Adiponectin is secreted by adipocytes and myocytes and increases in situations of negative energy balance. Leptin is a pro-inflammatory cytokine expressed mainly in adipose tissue. It has a multitude of functions, including regulation of inflammation, energy metabolism, insulin secretion, and endothelial function **[12]**. An increased concentration of leptin has been associated with chronic diseases related to inflammation. Serum Stem Cell Factor (SCF) is a cytokine that exists both as a transmembrane protein and as a soluble protein. Among multiple functions, SCF increases the proliferation of lymphoid and myeloid cells **[1]**.

Moreover, osteoprotegerin (OPG) is an extracellular matrix-associated protein and a member of the TNF family. It is an activator of the nuclear factor kappa-B (NF-KB) ligand (RANKL) and is therefore involved in inflammation **[12]**. One of the main functions of OPG is the regulation of bone remodeling. There is also an association between OPG and endothelial function, being an independent prognostic indicator for metabolic syndrome. Elevated OPG levels have been associated with coronary artery disease and cardiovascular mortality **[1,13]**.

Regarding supplemented micronutrients, selenium is one of the trace elements necessary for the normal functioning of many essential cellular processes, such as red/ox regulation and protection against oxidative stress **[14]**. Coenzyme Q10, which is also essential for normal cellular functioning, is one of the most important

lipophilic antioxidants in the body and is of particular importance in the ATP generation steps in the mitochondrial chain. As endogenous production of coenzyme Q10 decreases with age **[15]**, supplementation may be beneficial. Selenoprotein thioredoxin reductase 1 (TXNDR1) is the main reducing enzyme in the activation of ubiquinone to ubiquinol (the active form of coenzyme Q10), and the synthesis of coenzyme Q10 and selenoproteins depends on a functional mevalonate pathway. Supplementation with selenium and coenzyme Q10 combined in the elderly reduces the level of inflammation and oxidative stress **[16]**.

Therefore, the present study aimed to carry out a systematic review to highlight the main clinical outcomes of vitamins and minerals in healthy aging.

## Methods

### Study Design

The present study followed the international systematic review model, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis). Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 09/11/2023. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 09/11/2023.

### Data Sources and Research Strategy

The literary search process was carried out from August to September 2023 and was developed based on Web of Science, Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various eras to the present. The descriptors (MeSH Terms) were used: *"Cellular senescence. Healthy longevity. Healthy aging. Anti-aging. Micronutrients"*, and using the Boolean "and" between the MeSH terms and "or" between historical discoveries.

### Study Quality and Risk of Bias

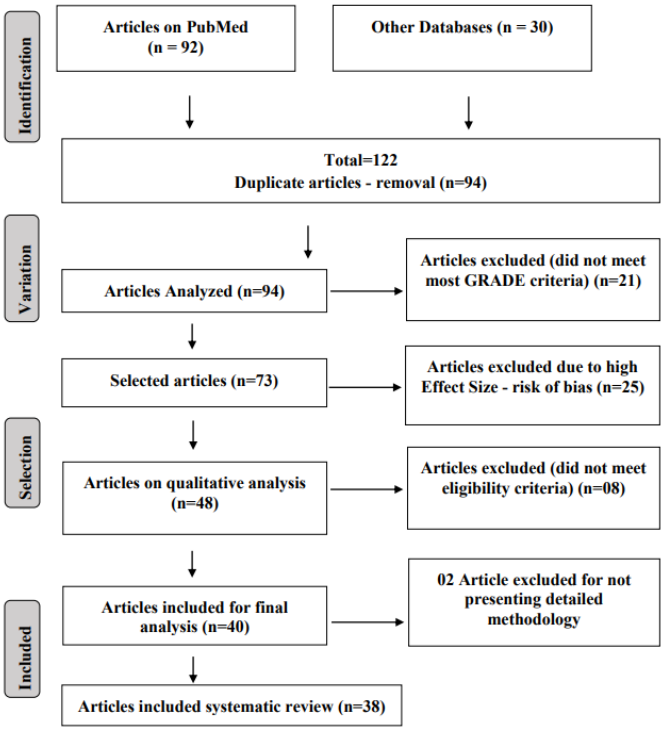
Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using the Cohen test (d).

## Results and Discussion

### Summary of Findings

A total of 122 articles were found that were subjected to eligibility analysis, with 38 final studies being selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with $X^2$=72.4%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 25 studies with a high risk of bias and 21 studies that did not meet GRADE and AMSTAR-2.

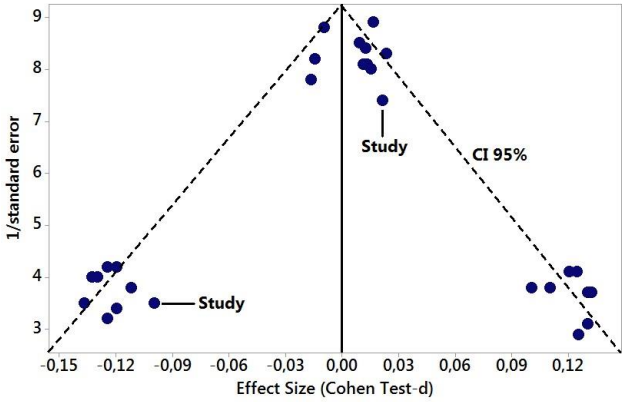
Figure 1. Flowchart showing the article selection process.




Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the bottom of the graph and in studies with a large sample size that are presented at the top.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (n=38 studies).




Source: Own authorship.

## Main Outcomes- Healthy Aging

Based on the results found, it was evident that the role of zinc (Zn) in aging and immunosenescence has been reviewed and the elderly are deficient. Zn governs many functions that characterize the so-called "oxy-aging", at least due to the functions mentioned above at a biochemical level **[17,18]**. An adequate plasma level of trace elements, such as Zn or copper (Cu), promotes optimal immune response function. High levels of copper, for example, have been linked to cognitive impairment **[19]**.

Furthermore, selenium (Se) is a fundamental cofactor in many redox functions, which reduces ROS-induced degeneration in the senescent phenotype. Cofactors of the main enzymes involved in the elimination of oxidative stressors are certainly beneficial in preventing aging-related damage **[20,21]**. In the case of Zn, its role in the optimal functioning of immune responses seems particularly crucial, as elderly people with reduced zinc levels reported an increased profile of pro-inflammatory cytokines such as MCP1 and IL6 in serum, they also showed increased Th1 /Th17/ inflammatory cytokines (IFNγ, IL17, TNFα, respectively) and decreased naïve CD4 T cells in mesenteric lymph nodes (MLN) **[21-28]**.

Vitamin C (L-ascorbic acid) is a very important water-soluble antioxidant and probably the most common water-soluble vitamin known to date. This vitamin is recommended for dietary intake and topical applications to the skin, as it stimulates collagen synthesis in the dermal layer and contributes to protection against UV-induced damage **[29]**. According to national recommended energy and nutrient intake levels, optimal daily intake of L-ascorbic acid ranges from 35 mg/d (6 months to 3 years of age) to 105 mg/d (men) or 85 mg/d (women), except during lactation (130 mg/d). Furthermore, the role of vitamin C in aging has been investigated particularly for skin health and immunity, particularly in inflammatory and degenerative diseases **[29-33]**.

Added to this, vitamin A can be found in nature as vitamin A (retinol) and provitamin A (carotene) which is found in animal and vegetable products. Retinol is a highly effective antioxidant. Retinoids, natural or synthetic, such as tretinoin and tarazotene. Retinoids, which represent a synthetic form of vitamin A, appear effective in preventing skin degeneration due to aging **[34]**.

Another antioxidant synthesized by plants is vitamin E, the main sources of which are nuts, grains extra virgin olive oils, corn, etc. Vitamin E (α-tocopherol) is an essential nutrient derived from a plant lipid antioxidant. The role of vitamin E in preventing and reducing ROS-induced injuries has been well described **[35]**. Tocopherol can prevent UV lipid peroxidation and has a very positive impact on dermal protection. The role of vitamin E in aging is wellknown, as it has been associated with the prevention of cognitive decline during senescence, particularly in Alzheimer's disease **[35]**.

Still in this context, vitamin E deficiency causes enzymatic changes, such as decreased activity of the cytochrome P450-dependent oxidase system of the microsomal fraction, increased cAMP-phosphodiesterase activity, decreased level of cellular respiration, preventing the conversion of cyanobenamine into its form active coenzymatic, etc. **[35]**.

In this scenario, aging is associated with cardiovascular diseases (CVD). As no biomarker reflects the complete aging process, a randomized clinical study carried out by authors Alehagen et al. (2023) **[36]** investigated five markers related to cardiovascular diseases and age and the effects of intervention with selenium and coenzyme Q10 to elucidate the mechanisms that may influence the course of aging. 441 individuals with low selenium were included (mean age 77 years, 49% women). The active treatment group (n = 220) received 200 µg/day of selenium and 200 mg/day of coenzyme Q10, combined. Blood samples were collected at inclusion and after 48 months for measurements of intercellular adhesion molecule (ICAM-1), adiponectin, leptin, stem cell factor (SCF), and osteoprotegerin (OPG). Correlation analyses of biomarker values at inclusion about age and relevant markers related to inflammation, endothelial dysfunction, and fibrosis demonstrated the association of biomarkers with these pathological processes;

however, only ICAM1 and adiponectin were directly correlated with age. SEM analyses showed, however, that the biomarkers ICAM-1, adiponectin, SCF, and OPG, but not leptin, had significant associations with age and formed two independent structural factors, both significantly related to age. Although no differences were observed at inclusion, biomarkers changed differently in the active treatment and placebo groups (decreasing and increasing levels, respectively) at 48 months ($p \leq 0.02$ in all, adjusted), and in the SEM model, they showed an anti-aging impact.

Scientific evidence has revealed that healthy diets, including good fats, vitamins, minerals, or polyphenolics, can have antioxidant and anti-inflammatory activities, with anti-aging effects. Recent studies have shown that vitamin K is a vital cofactor in the activation of several proteins, which act against age-related syndromes. Thus, vitamin K can carboxylate osteocalcin (a protein capable of transporting and fixing calcium in bones), activate matrix Gla protein (an inhibitor of vascular calcification and cardiovascular events), and carboxylate the Gas6 protein (involved in brain and cognitive decline and neurodegenerative diseases). By improving insulin sensitivity, vitamin K reduces the risk of diabetes. It also exerts antiproliferative, proapoptotic, and autophagic effects and has been associated with a reduced risk of cancer. Recent research shows that protein S, another vitamin K-dependent protein, can prevent the cytokine storm seen in COVID-19 cases. Reduced protein S activation due to pneumonia-induced vitamin K depletion has been correlated with increased thrombogenicity and possibly fatal outcomes in COVID-19 patients **[37]**.

Also, vitamin K is a multifunctional micronutrient implicated in age-related diseases such as cardiovascular disease, osteoarthritis, and osteoporosis. Although vitamin K-dependent proteins (VKDPs) have been reported to play a crucial role in the pathogenesis of these diseases, new roles have emerged for vitamin K, independent of its role in the carboxylation of VKDPs. Vitamin K has been shown to act as an anti-inflammatory, suppressing nuclear factor κB (NF-κB) signal transduction and exerting a protective effect against oxidative stress by blocking the generation of reactive oxygen species. Available clinical evidence indicates that a high level of vitamin K may play a protective role in the inflammatory and mineralization processes associated with the onset and progression of age-related diseases. Furthermore, the involvement of vitamin K as a protective super micronutrient in aging and "inflammation" is emerging, highlighting its future use in clinical practice **[38]**.

## Conclusion

It was concluded that micronutrients such as vitamins and minerals have anti-oxidant, protective, and regenerative properties to promote healthy aging.

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## Ethical Approval

Not applicable.

## Informed consent

Not applicable.

## Funding

Not applicable.

## Data sharing statement

No additional data are available.

## Conflict of interest

The authors declare no conflict of interest.

## Similarity check

It was applied by Ithenticate@.

## Peer review process

It was performed.



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