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Nutraceuticals and their role in promoting musculoskeletal healthy aging

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Parole chiave: Invecchiare in salute, antiossidanti, sarcopenia, osteoporosi, prodotti nutraceutici, infiammazione

Abstract

Background. *Aging is a complex and gradual biological process that represents the major risk factor with respect to the development of chronic degenerative diseases, often associated with disability. Diet and nutrition, coupled with proper physical activity have a significant impact on the health status of the elderly with a decreased risk of disease being indicative of successful aging. Musculoskeletal conditions such as osteoporosis and sarcopenia are the most frequently reported disorders among the elderly community.*
Methods. *This study presents a systematic review of the literature on the potential benefits of several nutraceuticals in promoting healthy aging and in reducing the risk of chronic diseases in elderly individuals.*
Results. *Dietary components including vitamins (vitamin C, B vitamin and vitamin K) flavonoids (e.g., quercetin, anthocyanins, and isoflavones), minerals (e.g., magnesium, zinc and potassium) and other nutrients such phytoestrogens, amino acids, and omega-3 fatty acids help in slowing the aging process, which ultimately results in increased lifespan and longevity.*
Conclusions. *This paper highlights the key nutrients and phytochemicals of nutraceutical importance for the healthy aging of the elderly population. Although the scientific literature provides evidences of therapeutic effectiveness of nutraceuticals, more in-depth clinical investigations are needed.*

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Introduction

The great challenge of today's medicine has been to make life expectancy coincide with the expectation of an active lifestyle (1, 2). Throughout life, genetic factors and environmental factors and their mutual interaction become crucial in influencing the quality of cognitive and physiological function performance of the elderly subject in the so-called longevity realms and precisely in determining the duration and quality of life the action of the environment becomes prevalent (diet, lifestyle, work activity, etc.) (3). In fact, an elderly subject can proceed towards the usual ageing process, often burdened by multiple chronic diseases, or towards a successful one, in which decline is kept to a minimum with superior psycho-physical performance as compared to age peers (4, 5).

Adequate nutrition, associated with moderate to high-intensity physical activity represent two important factors that can significantly affect the achievement of successful aging. Even the intake of nutraceuticals (i.e., nutrients and/or bioactive compounds of plant or microbial origin, with potentially favorable effects on human health) in the field of prevention and therapy regarding the pathologies that most frequently characterize aging, such as osteoporosis, dyslipidemia and sarcopenia, can represent a way to achieve successful aging (6).

While nutraceuticals are made from food or part of a food, food supplements are single substances used alone or in mixtures with the scope of adding micronutrients when the body is in need of them (7). Nutraceuticals can include phytochemicals such as isoprenoid derivates and polyphenol compounds, as well as, nutritents including vitamins, polyunsaturated fatty acids, amino acids, fiber, and carbohydrate molecules (8). Owing to their antioxidant and reactive oxygen species (ROS) scavenging activities, phytochemicals play a key role in oxidative stress control and in the prevention of premature aging and appearance of degenerative diseases (9).

In the light of the high therapeutic value of dietary components on health, the aim of this systematic review is to summarize the current knowledge and potential benefits of several nutraceuticals in promoting healthy aging and in reducing the risk of osteoporosis and sacropenia in elderly individuals.

Materials and Methods

A systematic literature review methodology was applied, following the procedure given by Egger et al. (10). The steps included the (i) formulation of the review question on the basis of considerations made in the abstract: "What are the nutraceuticals with major effects on musculoskeletal health?"; and (ii) identification of relevant studies. The following research strategy was planned, on PubMed and Scopus: (a) definition of the keywords (sarcopenia, muscle mass, osteoporosis, vitamin D, vitamin C, vitamin K, vitamin B6, calcium, magnesium, potassium, flavonoids, omega-3 fatty acid and curcumin), allowing the definition of the interest field of the documents to be searched, grouped in inverted commas ("…"), and used separately or in combination; (b) use of the Boolean AND operator, which allows the establishment of logical relationships among concepts; (c) research modalities: advanced search; (d) limits: papers published in English from 2006 up to June 2022; humans, animals, *in vivo*, and *in vitro* studies; (e) manual search performed by the researcher, through the revision of reviews and research articles on sarcopenia in the elderly, published in qualified journals of the Index Medicus. The data extrapolated from the revised studies were summarized in Table 1. The following information was extracted from the reviewed studies: the author's last name, year of

publication, sample size, the major nutrient or antioxidant, the models used (meta-analysis), and the main results obtained.

Osteoporosis and nutraceuticals

Osteoporosis, which is primarily considered an unavoidable consequence of aging, especially in menopausal women, is characterized by low bone mineral density and structural degradation (11). The intake of an adequate amount of calcium and vitamin D is a reality consolidated from a scientific point of view, essential for maintaining adequate bone mineral density (12). The scientific literature has identified, thanks to the epidemiological studies that have correlated the intake of a certain nutrient with bone mineral density, both through intervention studies, to other nutrients, such as vitamin C, vitamin K, B vitamins, magnesium, and omega-3 fatty acids and nutraceuticals (e.g., isoflavones and flavonoids) which must be taken in adequate quantities to maintain optimal bone density. Furthermore, several animal models and *in vitro* studies have indicated that oxidative stress is one of the main mechanisms of bone loss and strength (13, 14).

Aging and the consequent increase in ROS affect notably the generation and survival of osteoclasts, osteoblasts and osteocytes (11). Since antioxidants are fundamental in counterbalancing oxidative stress (a condition in which high amounts of ROS are generated over time), their role in preventing diseases and promoting health has been studied extensively. Antioxidants that may be related to bone health include vitamin C, vitamin K, B vitamins, magnesium, potassium, zinc, soy isoflavones, flavonoids and omega-3 fatty acids.

Vitamin C

Since its discovery as an anti-scorbutic agent, the number of biological properties of vitamin C (L-ascorbic acid) is continually expanding (15). A significant association, which remained significant after adjustment due to confounding factors, has been demonstrated between vitamin C intake and bone mineral density (BMD) in several clinical studies (16-18). Vitamin C is the coenzyme required in the hydroxylation of the amino acids proline and lysine during the synthesis of collagen in osteoblasts (19, 20). There are two important human studies reporting the effects of supplementation of vitamin C on BMD. Morton et al. (21) studied 994 postmenopausal Caucasian women, 277 of whom regularly took vitamin C (an average of 745 mg per day) for more than 3 years, and reported significantly higher BMD values at the femoral neck, total hip, ultradistal radius, and lumbar spine in women with higher ascorbic acid intake. Similar findings were reported in another study by Leveille et al. (22). Furthermore, Ruiz Ramos et al. (23) suggested that the administration of 1,000 mg of ascorbic acid along with 400 IU of alpha-tocopherol (vitamin E) is useful for preventing age-related osteoporosis in a sample of 90 elderly subjects.

Vitamin K

Vitamin K may play an essential role in bone metabolism by facilitating carboxylation of proteins such as osteocalcin that are involved in bone formation and mineralization process (24). In the Framingham Offspring Study, Booth et al. (25) reported a significant positive association between the intake of vitamin K and BMD of the hip and vertebral spine in women. Moreover, a subclinical vitamin K deficiency could contribute to the development of age-related bone loss and osteoporosis (26). In human intervention studies, Iwamoto et al. (27) demonstrated that vitamin K_2 supplementation in postmenopausal women suppresses the decrease in vertebral BMD compared to the untreaded group. In a follow-up study, the effect of combined

administration of vitamins K and D on BMD was compared with the effect of calcium and vitamin D administration (28). Results indicated that the combined administration of vitamin D_3 and vitamin K_2, compared to the administration of calcium, appeared to be useful in increasing the BMD of the lumbar spine in postmenopausal women with osteoporosis.

B vitamins

The B vitamins have been investigated for their possible roles in bone health and fracture risk. The Rotterdam Study showed that increased dietary vitamin B6 (pyridoxine) intake was associated with higher BMD (29). Furthermore, the same study reported the reduction of the risk of fracture in relation to the intake of food pyridoxine independent of BMD. Vitamin B6 is involved as a coenzyme in the process of assembly of collagen in the extracellular matrix. Masse et al. (30), using an animal model, showed the importance of this extracellular process for the strength of bones. An interesting clinical study by Reynolds et al. showed that half of the hip fractures patients were deficient in vitamin B6 (31). *In vitro* studies showed that low concentrations of vitamin B stimulate osteoclasts (32). As for the other B vitamins (i.e., folic acid, riboflavin, and vitamin B_{12}), in this context it is important to remember the relationship between the deficiency of these vitamins and the presence of hyperhomocysteinemia and osteoporosis (33). Indeed, these vitamins can affect bone density, directly or by effecting plasma homocysteine levels.

Magnesium, potassium, and zinc

Higher potassium and magnesium intakes were associated with a higher baseline BMD and less bone loss in elderly men and women (34). Furthermore, a significant association, which remained significant after adjustment for many of the major confounding factors, was found between intake of potassium, magnesium zinc, vitamin C and BMD (16, 35).

Intake of dietary zinc may have a beneficial effect in the prevention of osteoporosis as it stimulates osteoblastic bone formation and mineralization (36). In a recent meta-analysis, Ceylan et al. (37) found that femoral neck BMD of the zinc-supplemented group were significantly higher than controls. Moreover, they concluded that plasma zinc level and dietary zinc intake could have an essential role in preventing osteoporosis.

Soy isoflavones

Several studies indicate a positive effect of soy isoflavone intake on the risk of osteoporosis and fragility fracture (38, 39). However, many studies reported no benefit from isoflavones (polyphenols of soybeans) with regard to the increase in bone density or the decrease in turnover bone in postmenopausal women, as too many variables were not considered in various studies, such as the type of diet, the years of menopause, and the composition of phytoestrogens (40, 41).

Flavonoids

Flavonoids are ubiquitously occurring polyphenolic compounds (i.e., phytochemicals with potential health-promoting effects), which are found in foods of plant origin and are classified into six main subgroups, namely: flavanones, flavones, flavonols, flavan-3-ols, anthocyanins and isoflavones (42). In an UK cohort study of female twins, increased total flavonoid intake was associated with higher bone mineral density of the vertebral spine (43). Furthermore, the intake of anthocyanins and flavan-3-ols (catechins) was positively associated with both vertebral and femoral BMD in Scottish women (44). In a subsequent cross-sectional study, Zhang et al. (45) showed that Chinese elderly women who consumed higher total flavonoids, including proanthocyanidins, tended to have greater

BMD in the whole body, femoral neck, and lumbar spine.

Quercetin is a phytochemical flavonol from the flavonoid family that possesses antioxidant properties, which favors an increase in osteogenic activities and decrease in osteoclastogenic activities (46). Quercetin and its derivatives have been shown to decrease osteoblastic cell differentiation progenitors and inhibit the activity of mature osteoclasts in both *in vivo* and *in vitro* studies. Additionally, quercetin may act alongside the alkalizing properties of fruit to inhibit osteoclasts and improve BMD (47-49). However, without further data on the effects of quercetin on bone in osteoporotic patients, it would be advisable to take flavonoids from dietary sources rather than from supplements.

Omega-3 fatty acids

Omega-3 fatty acids are a family of naturally occurring polyunsaturated fatty acids with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) being the two most functionally important (n-3) fatty acids (50). The beneficial effects of omega-3 fatty acids are widely accepted. Omega-3 fatty acids can affect skeletal health, not only through their anti-inflammatory effects, but also by positively regulating the absorption of intestinal calcium (51). Farina et al. (52) had previously described the protective effect of fish and omega-3 fatty acids intake on the loss of femoral neck BMD in the elderly population. Moreover, a positive association was found between omega-3 fatty acids concentration and peak BMD in 78 healthy young men (53). Omega-3 intake was also positively correlated with BMD level of the hip in elderly people (54) and with the lumbar spine and total body BMD in elderly Finnish women (55). More recently, two large studies by Lavado-García et al. (56) and Kuroda et al. (57) in Spain and Japan respectively have reported that increased intake of omega-3 fatty acids positively improved BMD in female populations. In another recent review, Martyniak et al. (58) concluded that the consumption of omega-3 fatty acids, namely EPA and DHA were mainly associated with increased bone regeneration, improved microarchitecture and structural strength in the aging population. However, such benefits may only be enhanced by the concurrent administration of calcium (59, 60).

Sarcopenia and nutraceuticals

Sarcopenia occurs with advancing age and is an important component in the development of frailty (61). It is a complex syndrome characterized by a progressive loss of skeletal muscle mass and strength that is associated with an elevated risk of mortality outcomes among older adults (62). The onset of age-related sarcopenia is multifactorial and involves alterations in neuromuscular parameters, pro-inflammatory response and endocrine changes, lifestyle choices and nutritional status.

Diet and exercise are preventative treatments that can help preserve mobility in subsequent years by improving the quality of life and health outcomes of middle-aged adults (63). The most rational approach for delaying the progression of sarcopenia is based on the combination of proper nutrition, possibly associated with the use of nutritional supplements, combined with a regular exercise program (64). The nutritional approach has been outlined in the International Study Group to Review Dietary Protein Needs with Aging (PROT-AGE Study group) (65), which recommends an average daily intake of 1.2 g of protein per kg body weight per day to prevent sarcopenia and 1.5 g of protein per kg body weight per day for therapy, combined with branched-chain amino acid leucine supplementation (2.0 to 2.5 g) in three meals daily with at

least 25 g of protein in each meal.

With advancing age there is a change in body composition, with an increase in adipose tissue, which leads to increased secretion of proinflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α) (62). This condition exposes the elderly towards a situation of chronic inflammation, which inhibits muscle protein synthesis and therefore favoring the development of sarcopenia.

Several studies have investigated the mechanisms by which curcumin, a lipophilic polyphenol found in the spice turmeric (*Curcuma longa* L.), exerts its beneficial effect on muscle health (66). One experimental study has shown that curcumin suppresses the activation of NF-kB, a critically important relief effect, as NF-kB appears to be involved in the regulation of proteolysis and cytokine mediated inflammation in the muscle (67). Therefore, the inhibition of NF-kB by curcumin can lead to a protective effect on muscle. Furthermore, the recent meta-analysis of nine randomized controlled trials by Fang and Nasir (68) concluded that curcumin supplementation can attenuate exercise induced muscle damage and delayed onset muscle soreness after resistance exercise muscle injury in adults. It has also been suggested that curcumin consumption can prevent muscle mass loss during sepsis and endotoxemia and stimulate muscle regeneration after a traumatic injury (65). Other potentially responsible mechanisms of the anti-inflammatory and antioxidant properties of curcumin include induction of the heat-shock response (66), the reduction in the expression of the proinflammatory enzyme cyclooxygenase-2 (COX-2) and the promotion of the antioxidant response by activation of the transcription factor Nrf2 (69).

Table 1 shows the meta-analyses reporting the main nutrients and phytochemicals involved in the prevention and treatment of osteoporosis and sarcopenia.

Conclusions

At present there is a wide range of nutraceuticals that have been shown to exert biological actions in the management of age-related conditions such as osteoporosis, sarcopenia, dyslipidemia and others. Evidence of the therapeutic or preventive effectiveness of nutraceuticals on clinical outcomes is emerging. However, larger and more in-depth clinical trials are needed in order to support the current body of evidence and to observe the long-term effects of nutraceuticals on healthy aging. This is of importance, especially as one of the most challenging and difficult aspects of the study of nutraceuticals is to establish the most effective dosage without toxic consequences.

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Riassunto

I prodotti nutraceutici ed il loro ruolo nel promuovere un invecchiamento musco-scheletrico in salute

Premessa. L'invecchiamento è un processo biologico complesso e graduale che rappresenta il maggior fattore di rischio rispetto allo sviluppo di malattie degenerative croniche, spesso associate a disabilità. Dieta e nutrizione adeguate, insieme ad una corretta attività fisica, hanno un significativo impatto positivo sullo stato di salute degli anziani, mentre la riduzione del rischio di malattia è indicativo di un invecchiamento di successo. Condizioni muscoloscheletriche come l'osteoporosi e la sarcopenia sono le patologie più frequentemente riportate nella comunità degli anziani.

Metodi. Questo studio presenta una revisione sistematica della letteratura sui potenziali benefici di diversi nutraceutici nel promuovere un invecchiamento in salute e nel ridurre il rischio di malattie croniche negli individui anziani.

Risultati. Componenti alimentari tra cui vitamine (vitamina C, vitamina B e vitamina K) flavonoidi (ad es. quercetina, antociani e isoflavoni), minerali (ad es.

Table 1 - Meta-analyses showing the effects of several nutrients and phytichemicals on osteoporosis and sarcopenia prevention in aging.

Author	Sample	Nutrient	Disease	Results
Wang et al. (70)	41,738 patients	Vitamin D	Osteoporosis	Relative risk (RR) (95% confidence interval [CI]) for total and hip fractures were 1.11 (0.99, 1.24) and 0.89 (0.80, 0.98) after adjustments.
Weaver et al. (71)	30,970 participants	Calcium	Osteoporosis	Meta-analysis of all studies showed that calcium plus vitamin D supplementation produced a statistically significant 15 % reduced risk of total fractures (summary relative risk estimate [SRRE], 0.85; 95% CI, 0.73–0.98) and a 30 % reduced risk of hip fractures (SRRE, 0.70; 95 % CI, 0.56–0.87).
Malmir et al. (72)	40,000 participants	Vitamin C	Osteoporosis	Greater dietary vitamin C intake was associated with a 33 % lower risk of osteoporosis (overall relative risk= 0·67; 95 % CI 0·47, 0·94).
Cockayne et al. (73)	7 studies	Vitamin K	Osteoporosis	Vitamin D reduce of 0.23 (95% CI, 0.12-0.47) for hip fractures, and an odds ratio of 0.19 (95% CI, 0.11-0.35.
He et al. (74)	28 studies	Vitamin B6	Osteoporosis	A severe deficiency of folate, instead of vitamin B12 and B6, was found to increase the risk of fracture in older adults (hazard ratio =1.46, 95% CI: 1.06 to 2.02; 1.24, 95% CI: 0.79 to 1.95; 1.36, 95% CI: 0.90 to 2.06, respectively). For the interventional effect, there was no significant association of combined folate and vitamin B12, combined folate, vitamin B12 and B6, or single vitamin B6 supplementation with the decrease of fracture risk.
Zheng et al. (75)	1,349 postmenopausal women	Magnesium	Osteoporosis	Low level of serum Mg seems to be a risk factor for osteoporosis among the postmenopausal women.
Lambert et al. (76)	9 studies	Potassium	Osteoporosis	Urinary calcium excretion was lowered by intervention with both potassium bicarbonate ($KHCO_3$) ($p=0.04$) and potassium citrate ($p=0.01$), as was net acid excretion (NAE) ($p=0.002$ for $KHCO_3$ and $p=0.0008$ for potassium citrate).
Munguía et al. (77)	Nd	Flavonoids	Sarcopenia	The use of flavonoids could be a potential tool for the prevention of muscle loss. Their effects on metabolism and on mitochondria function suggest their use as muscle regulators.
Bird et al. (78)	66 studies	Omega-3 fatty acid	Sarcopenia	A significant relationship in favor of omega-3 long-chain polyunsaturated fatty acid supplementation for lean body mass (effect size 0.27, 95%CI 0.04 to 0.51), skeletal muscle mass (effect size 0.31, 95% CI 0.01 to 0.60) and quadriceps maximal voluntary capacity (effect size 0.47, 95%CI 0.02 to 0.93).
Jeong et al. (79)	528 subjects	Curcumin	Sarcopenia	Phytochemicals like curcumin significantly increased handgrip strength [0.90 kg; 95% CI 0.26–1.53, $p = 0.01$] and physical performance (timed up-and-go test: – 0.5 s, 2.73 times; 95% CI – 0.84 to – 0.15, $p < 0.01$; 30-s chair stand test: 95% CI 0.88–4.59, $p < 0.01$; 6-min walk test: 29.36 m; 95% CI 14.58–44.13, $p < 0.0001$).

magnesio, zinco e potassio) e altri nutrienti come fitoestrogeni, aminoacidi e acidi grassi omega-3 gli aiutano a rallentare il processo di invecchiamento, che alla fine si traduce in una maggiore longevità in salute.

Conclusioni. Questo documento indica i nutrienti chiave e le sostanze fitochimiche di importanza nutraceutica per l'invecchiamento sano della popolazione anziana. Sebbene la letteratura scientifica fornisca già evidenze notevoli dell'efficacia terapeutica dei nutraceutici, è necessaria, per una completa conoscenza della situazione, un'indagine clinica più approfondita.

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