The mediterranean way. Should elderly people eat leafy vegetables and beetroot to lower high blood pressure?

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Introduction

As the world's population ages, the number of people over 60 years is expected to increase from 901 million to 1.4 billion by 2030 [1]. The global burden of disease increases significantly with aging, and it is well established that high blood pressure is one of its leading risk factors. [2–5].

As of yet there is a relative paucity of broadly accepted effective primary prevention strategies for disability, cardiovascular disease and global disease burden [6, 7]. This is why identifying strategies that can impact their most relevant modifiable risk factors would contribute to the effort to avoid pharmacotherapeutics, an approach that has led to an increased interest in the use of food-based supplements and bioactive compounds to improve or maintain healthy body functions [8].

The Mediterranean diet (MeD), which is essentially a vegetarian regime, is generally regarded as one of the healthiest dietary patterns. It has been associated with a low incidence of cardiovascular disease, including stroke [9–13]. Indeed, vegetarian diets in general are associated with lower blood pressure [14–17] and, in this context, green leafy vegetables have been associated with a reduced incidence of nonfatal myocardial infarction, fatal coronary heart disease and stroke [18, 19].

The results of numerous studies suggest that the protective effects of the MeD and vegetarian diets are in general due to the impact of both their single components and the converging synergistic action of several components, namely

of antioxidants, glucosinolates, vitamins, nitrate, and fibers. The effect of these components has been shown to reduce the traditional risk factors of atherosclerosis [20–22] as well as of oxidative stress, inflammation, and endothelial dysfunction [20, 22–25].

Nitrate-rich vegetables (leafy vegetables, cruciferae such as kale, cabbage, turnips, and beetroot), which are important components of the MeD, have been shown to improve several artery wall-related functions, in particular blood pressure, as well as clotting activity, and endothelial functions [20–25]. The data available on nitrate have prompted many investigators to examine the role of nitrate-rich vegetables in lowering high blood pressure. These trials, however, have frequently produced conflicting results. While acute studies have consistently shown a significant blood pressure-lowering effect, long-term trials have frequently failed to demonstrate any effect of nitrate-rich vegetables on blood pressure. Although these conflicting results have not yet clarified the role of nitrate-rich vegetables on blood pressure, observational and prospective studies on the MeD, a diet noteworthy rich in vegetables as well as in olive oil and other active components, have consistently shown that people with high adherence to this diet for a sufficiently long period of time, i.e., 1–4 years, have significantly lower blood pressure values with respect to people with a low adherence, an effect that has been largely attributed to the diet's high content of vegetables [22, 23]. The DASH (Dietary Approaches to Stop Hypertension) diet, another vegetable-rich diet, has likewise been shown to keep blood pressure values lower in those who consistently adhere to it with respect to their low adherence counterparts [14, 17].

In the light of these results, it is unclear whether elderly people should consume nitrate-rich vegetables to keep their blood pressure lower. Below, some positive and negative results produced by studies investigating nitrate-rich vegetables are outlined.

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Studies showing positive results on blood pressure

An experimental study on hypertensive rats fed collard greens or other vegetables found that they had a significant reduction in blood pressure with respect to their counterparts [26].

In an open-label, cross-over study on 14 healthy subjects 18–45 years, Webb et al. [27] showed that the acute intake of a single dose of 500 mL of beetroot juice (containing 22.5 mmol, 1.40 g/L, of nitrate) reduced systolic and diastolic blood pressure by respectively 10.4 mmHg 2.5 h and 8.1 mmHg 3 h after ingestion. The blood pressure reduction coincided with the peak increase in plasma nitrite concentrations.

Kapil et al. [28] reported on the results of a prospective single-centre, double-blind, randomized, placebo-controlled trial investigating 34 drug-naïve and 34 treated patients between 18–85 years with hypertension. The patients were randomized to receive either 4-week daily supplementation of dietary nitrate (250 mL beetroot juice) or placebo (250 mL of nitrate-depleted beetroot juice). The study found that the ingestion of 250 mL of beetroot juice (6.4 mmol/L nitrate) once a day for 4 weeks reduced the patients' systolic blood pressure by 5.4 mmHg.

Using a balanced, randomized crossover study design, Vanhatalo et al. [29] studied the effects of drinking 500 ml of beetroot juice containing ~5.2 mmol of nitrate or placebo for 15 days on eight healthy volunteers whose mean age was 29 ± 6 yrs. All eight subjects underwent both beetroot juice or placebo supplementations with 15-day supplementation periods followed by a 10-day wash-out period. The systolic and diastolic blood pressures (baseline: 127 ± 6 and 72 ± 5 mmHg, respectively) were reduced by ~4% (the systolic blood pressure was reduced by 7 mmHg and the diastolic one by 5 mmHg), 2 h after ingestion and throughout the period they were taking beetroot. The Authors concluded that dietary NO_3^- supplementation acutely reduces BP and the O_2 cost of submaximal exercise and that these effects are maintained for at least 15 days if supplementation is continued.

Bondonno et al. [30] designed a randomized, controlled, crossover trial involving 30 healthy men and women to investigate the independent and additive effects of flavonoid-rich apples and nitrate-rich spinach on nitric oxide status, endothelial function, and blood pressure. Compared to the controls, all the treatments resulted in higher plasma nitric oxide (NO) levels and higher low-mediated dilatation of the brachial artery. As far as blood pressure was concerned, a reduction in systolic blood pressure of 2.7 mmHg was observed in the participants after they ate 200 g of spinach (3 mmol nitrate, ~180 mg). Similar

results were observed in the group treated with flavonoid-rich apples, but the apple and spinach combination did not result in additive effects on NO, endothelial function or blood pressure. The investigators concluded that flavonoid-rich apples and nitrate-rich spinach can independently augment nitric oxide status, enhance endothelial function, and lower blood pressure acutely, all outcomes that may benefit cardiovascular health.

Hobbs et al. [31] designed a study in which two separate randomized, controlled single-blind, cross-over, test-meal studies were carried out to investigate the effects of increasing doses of beetroot juice (0, 100, 250, 500 ml) in 18 normotensive males mean age 31.4 years, or enriched bread (200 g bread enriched with 100 g of red or white beetroot) in 14 healthy men mean age 25.1 years. Beetroot juice ingestion significantly and in an almost dose-dependent manner was found to lower systolic and diastolic blood pressures over a 24-h period with respect to the values of the control volunteers who drank water (0 g beetroot juice). The consumption of 200 g of bread enriched with 100 g of red or white beetroot, respectively, reduced the systolic and diastolic blood pressures by 19.3 and 23.6 mmHg and 16.5 and 23.2 mmHg with respect to a control group eating a control bread (0 beetroot).

A 6-week randomized, double-blind, placebo-controlled parallel study was carried out to investigate the effect of 250 ml of naturally nitrate-rich beetroot juice containing 6 mmol nitrate taken once a day for 6 weeks on 67 hypercholesterolemic subjects (serum cholesterol > 6 mmol/L) whose mean age was 53 ± 10 years. Primary end point was the change in in vascular function evaluated with the use of ultrasound low-mediated dilatation. The effect of the beetroot juice intake was compared with that of the same amount of a nitrate-depleted beetroot juice. The subjects receiving the active agent showed a significant improvement in flow-mediated dilatation (~24%) and arterial stiffness with respect to counterparts receiving the placebo, and a significant reduction in systolic blood pressures (~7.2 mmHg active treatment vs ~3.1 mmHg placebo) [8].

Studies showing null results

A randomized, placebo-controlled, double-blind crossover trial investigated the effect of a week's intake of nitrate-rich beetroot juice (70 mL with breakfast and 70 mL with dinner for a total mean of 434 mg/day nitrate) on the blood pressure of 27 hypertensive volunteers (with ages between 57 and 70), which was compared with the effect of a week's intake of nitrate-depleted beetroot juice (placebo). No differences in blood pressure were observed in the two groups at the end of the 1-week trial [32].

A four arm randomized crossover study investigating the effect of a 3-day control diet (0.7 mmol, 43 mg nitrate) vs. a high nitrate diet (2.5 mmol, 155 mg nitrate) with or without nitrate supplement (beetroot juice, 8.5 mmol, 527 mg nitrate) on the plasma nitrate and blood pressure of eight normotensive volunteers (mean age 72 years) was carried out. No significant differences in blood pressure values were observed between the control and treatment populations [33].

In a double-blind, randomized, placebo-controlled crossover trial, 27 diabetics (T2DM) with a mean age of 67 yrs were given 250 ml of beetroot juice daily (active) or 250 ml nitrate-depleted beetroot juice (placebo). The subjects' mean ambulatory systolic blood pressure was unchanged after 2 weeks of taking beetroot juice (7.5 mmol/die nitrate): the mean values of the placebo vs treated subjects were 134.6 ± 8.4 mm Hg versus 135.1 ± 7.8 mmHg; there was a mean difference of -0.5 mm Hg (placebo-active), ($p=0.737$). Moreover, no changes in endothelial function or insulin sensitivity were found. In short, the nitrate supplementation did cause an increase in plasma nitrite and nitrate concentration, but it did not lower the blood pressure, nor did it improve endothelial function or insulin sensitivity in the diabetic population [34].

In another randomized study, 30 middle-aged and older adults (62 ± 5 years) were given 140 ml of concentrated beetroot juice or a placebo for 7 days to evaluate the impact of nitrate on handgrip, blood pressure and arterial volume distensibility. No effects on systolic/diastolic blood pressure, handgrip or arterial volume distensibility were found at the end of the 7-day treatment with beetroot juice [35].

The authors of the previous paper also published a meta-analysis examining four independent randomized clinical trials investigating the effect of dietary nitrate on circadian oscillations and nocturnal blood pressure dipping patterns [36]. Two of the trials had an open-label parallel design and 2 had a cross-over, double blind one; a total of 85 participants with ages ranging between 55–76 years were studied. It was found that beetroot juice determined a significant decrease in nocturnal systolic blood pressure in the subjects younger than 65 years (2.8 mmHg, $-4.5 - 1.0$, $p=0.002$) with respect to the older ones (≥ 65 years; 1.0 mmHg, $-2.2 - 4.2$, $p=0.54$). A greater change in NO_2^- concentrations after beetroot supplementation was associated with significant differences in the nocturnal mean (-3.4 mmHg, $-0.6 - 2.4$, $p=0.02$) and variability (-0.8 mmHg, $-1.5 - 0.06$, $p=0.03$) of the systolic blood pressure. Based on the results of these four trials, the authors concluded that the vascular responsiveness to inorganic nitrate may be modified by mechanisms linked to vascular ageing influencing the reduced capacity to convert inorganic nitrate into nitrite and tissue-specific responses to dietary nitrate supplementation [36].

In a randomized controlled crossover trial with 3 4-week treatment periods, 30 hypertensive participants were randomly assigned to one of 6 sequence orders for 3 treatments consisting of: (1) increased intake of nitrate-rich vegetables (~ 200 g/day; ~ 149 mg/dL nitrate plus nitrite); (2) increased intake of nitrate-poor vegetables (~ 200 g/day; ~ 21.5 mg/dL nitrate plus nitrite); and (3) no increase in vegetables (control diet). With respect to the low-nitrate diet and placebo, the high-nitrate diet did not reduce blood pressure. Nor were there any significant differences in arterial stiffness linked to the high- and low-nitrate diets [37].

In a 5-week randomized, placebo controlled, single blinded study, 243 subjects, between 50 and 70 with a systolic blood pressure of 130–159 mmHg were randomly assigned to receive daily one of the 3 interventions: (1) low nitrate vegetables + placebo pills, (2) low-nitrate vegetables + nitrate pills (300 mg nitrate), or (3) leafy green vegetables containing 300 mg nitrate + placebo pills. No significant differences in blood pressure values were observed in the 3 study groups, in the 231 subjects who completed the study [38].

How nitrate-rich vegetables work. The nitrate-nitrite-NO pathway

Although the clinical studies carried out until now have produced ambiguous results, quite a bit is known about the biochemical pathway of nitrate. Below, is a synopsis of the underlying mechanism of dietary sources of nitrate.

Endogenous nitrate and nitrite originate predominantly from the oxidation of endogenously produced nitric oxide (NO) in biological fluids. A significant percentage of body nitrates has however been shown to originate from the diet. Dietary nitrate (the inorganic nitrate anion, NO_3^-) derives in part from cured meats, to which it is added to inhibit the formation of botulinum toxin, and from drinking water, but the source of 85% of exogenous nitrate is from vegetables, in particular leafy ones (Table 1).

The discovery that dietary (inorganic) nitrate has important vascular effects, particularly hypertension, is linked to the relatively recently identified “nitrate-nitrite-nitric oxide pathway”.

Until recently, dietary nitrate (NO_3^-) and nitrite (NO_2^-) were considered inert end products of NO metabolism lacking any relevant physiological activity in the circulation, despite the fact that these inorganic anions are derived from NO, a reactive free radical and potent vasodilator produced endogenously by the action of the nitric oxide synthase (NOS) on the substrate amino acid, L-arginine [40–42]. Recent studies, however, have shown that nitrate and nitrite are physiologically recycled in the blood and tissue to form NO and other bioactive nitrogen oxides. The nitrate-nitrite

Table 1 Classification of vegetables according to their nitrate content [39]

Nitrate content (mg/100 g)	Vegetables varieties fresh weigh
Very high, > 250	Celery, cress, chervil, lettuce, reed beetroot, spinach, rocket
High, 100 to < 250	Chinese cabbage, endive, escarola, fennel, leaf cicory, leek, parsley
Middle, 50 to < 100	Cabbage, dill, turnips, savoy cabbage, cime di rapa (turnip greens), radicchio
Low, 20 to < 50	Broccoli, carrots, cauliflower, cucumber, pumpkin, "puntarelle" (a type of Italian chicory)
Very low, < 20	Artichokes, asparagus, broad beans, eggplant, garlic, onion, green beans, ushrooms, peas, pepper, potatoes, summersquash, sweet potatoes, tomatoes, watermelon

pool, therefore, appears to be implemented by exogenous, dietary nitrate which has a non-secondary role in the nitrate-nitrite-NO pathway. The nitrate pool could be viewed as a storage reserve for NO-like bioactivity, thereby complementing the NO synthase-dependent pathway (Fig. 1).

Ingested nitrate is destined to be reduced to NO. The dietary nitrate reduction to NO in the body involves an initial reduction to nitrite and then to NO. Nitrate reduction to nitrite in humans takes place almost exclusively on the surface of the posterior third of the tongue. After it has been swallowed and absorbed through the stomach wall, 20–28% of ingested nitrate (NO_3^-) enters the entero-salivary circulation, concentrated tenfold in the salivary glands, then secreted in the saliva and reduced to nitrite (NO_2^-) by bacterial nitrate reductase contained in commensal Gram-negative bacteria, predominantly *Veillonella* species, as well as *Actinomyces*, *Rithia* and *Staphylococcus epidermidis*, residing

on the dorsal surface of the tongue [43, 44]. The bacteria uses nitrate as an alternative electron acceptor to produce energy, thereby effectively reducing it to nitrite. The use of an antibacterial mouth wash after dietary nitrate load has been reported to attenuate the rise in systemic nitrite levels [45]. Allopurinol-sensitive tissue nitrate reductase enzymes, which reduce nitrate to nitrite, also seem to contribute to nitrate reduction to nitrite in the body, but the impact of this pathway is unclear [46]. Once the swallowed nitrite enters the stomach, it is partly converted to NO by local acidic conditions. Nitrite and NO then diffuse into portal circulation and NO is oxidized to nitrite, which in turn is transported via arterial circulation to resistance vessels where it lowers O_2 tension and favours the reduction of nitrite to NO which causes vasodilation and thus lowers blood pressure.

Nitrite appears to mediate a large part of its effects through bioactivation to NO. This occurs mainly via nitrite

Fig. 1 Nitric oxide (NO) predominantly originates by L-arginine metabolic pathway, but also by exogenous dietary nitrate

reductases, which have selective activity under oxygen/hypoxic/ischaemic conditions; these reductases include xanthine oxidoreductase and the deoxygenated globins, i.e., haemoglobin, myoglobin, cytoglobin and neuroglobin [47]. It is noteworthy that the conversion of nitrite to NO requires a reaction with deoxygenated globins, particularly haemoglobin, suggesting a novel function of haemoglobin as a deoxygenation-dependent nitrite reductase [47]. It is important to underline moreover that unlike NO production from the endothelial NOS (eNOS) whose activity is oxygen-dependent, NO production from the nitrate-nitrite-NO pathway increases with diminished oxygen [47]. That is why the generation of NO from several pathways is greatly enhanced during hypoxia and acidosis, ensuring NO production in situations in which oxygen-dependent NO-synthase enzyme activities are compromised. Nitrite reduction to NO during physiological hypoxia appears therefore to contribute to physiological hypoxic signalling by vasodilation as well as by the modulation of cellular respiration and cellular response to ischaemic stress.

NO influences vascular homeostasis in several ways [48–51]: it enters vascular smooth muscle cells where it increases cyclic guanosine 3',5'-monophosphate (cGMP) production leading to smooth muscle relaxation (vasodilation). In addition, NO inhibits platelet aggregation and platelet adhesion to the endothelium. Moreover, NO suppresses vascular smooth muscle cell proliferation, the adhesion and migration of leukocytes/monocytes into the arterial wall, the activity of inflammatory factors, and the expression of certain adhesion molecules. Increased levels of superoxide anions have been implicated in the reduction of NO bioavailability in the vasculature [52–54].

Considerations on the conflicting results

Notwithstanding our knowledge of the nitrate-nitrite-NO pathway, the conflicting results that have been reported by these and other papers remain a conundrum. There are some variables, however, that should be considered and that could at least in part explain the conflicting results of nitrate intake on blood pressure. These variables include:

Differences in the duration of the trials, with some lasting a few days and others continuing for several weeks.

Differences in the nitrate dosages used by the studies (doses ranged from 149 to 527 mg). An analysis of the DASH dietary pattern [33, 55], characterized by high nitrate-containing vegetables, showed that the dietary nitrate levels ran as high or even higher than 16 mmol (1000 mg; 12 mg/kg body weight) as compared to other studies in which only 2.5 mmol of nitrate was used [33].

Differences in the participants' demographics and health conditions and, in particular, their ages. It has been

observed, for example, that the vascular responsiveness to inorganic nitrate may be modified by mechanisms of vascular ageing reducing the capacity to convert inorganic nitrate into nitrite and the tissue-specific responses to dietary nitrate supplementation [36].

Differences in the dosage and the frequency of the dietary nitrate supplements, i.e., a single acute dose or several smaller doses during the day. It should be remembered that the first clinical studies on dietary nitrate were conducted primarily to investigate the effect on blood pressure of a single acute dose of supplementation or of long-term exposure. It should be considered in any case that in some studies with null results the amount of nitrate was spread over several meals and snacks throughout the day, and may not have provided a large enough bolus dose of nitrate at any meal or snack to raise the nitrate or nitrite plasma levels.

Individual differences in the production of saliva or other conditions that could alter the conversion of nitrate to nitrite and the swallowing. The nitrate/nitrite/NO cycle is known to be affected by a number of variables that may be altered in older adults, including achlorhydria, medications that can modify gastric pH, dry mouth, oral bacteria, and intestinal health. In a study on the effect of a high nitrate diet on blood pressure [33], the plasma level of nitrite showed a secondary rise following the evening meal beginning at the 7.5 h time point. It is plausible that the effect was due to an increase in saliva production linked to the evening meal with a subsequent to conversion of nitrate to nitrite and swallowing saliva while eating.

The effect of diet, and in particular of the dietary fatty acids that are normally ingested. The intake of dietary free fatty acids (FFA) may have an important impact on blood pressure and vascular reactivity. In a study on rats [55], the effects of saturated fatty acid (SFA) (palmitic acid), mono-unsaturated fatty acid (MUFA) (oleic acid) and polyunsaturated fatty acid (PUFA) (linoleic acid) on the contractility of isolated mesenteric and deep femoral arteries, the endothelium-dependent relaxation was evaluated by full relaxation to acetylcholine, in the presence of pre-constriction to α -adrenergic agonist (phenylephrine). The phenylephrine-induced contraction was enhanced in the presence of SFA, but the application of MUFA attenuated the phenylephrine-induced contraction in both types of arteries. These data concord with those of other studies [56–58] showing that in vitro exposure to palmitic acid in physiologic concentrations attenuates the response to endothelium-dependent relaxation, suggesting that SFA impairs the production of endothelium-derived NO. Another study [59] investigating the effect of dietary fatty acids on vascular endothelial cells showed that the application of oleic acid may prevent or improve vascular function by maintaining or increasing NO production by the endothelium. In a study in human, 57 normotensive volunteers aged 30–50 years who followed

a Mediterranean diet underwent a dietary intervention with a 70% increase in energy from SFA and a corresponding decrease in MUFA and carbohydrate. After 6 weeks, a significant increase in systolic and average blood pressure was observed. Blood pressure reverted to baseline values when participants returned to their usual diet [60].

These data show that dietary fatty acid intake may be crucial to vascular responses, and in particular to NO production, vascular relaxation and blood pressure regulation. The dietary style of a study's participants may have influenced their results because individuals consuming a western diet pattern with, for example, a breakfast based on eggs, bacon and other foods rich in SFA may have led to a different response with respect to people following more vegetarian diets like MeD or DASH in which the MUFA oleic acid is generally the predominant fat consumed and the SFA content is quite negligible.

The effect of drugs. Elderly people usually take numerous medications that can interfere with the action of nitrate. It has been shown, for example, that acid-suppressing drugs abolish the blood pressure-lowering effects of oral nitrite ingestion despite the increase in plasma nitrite concentrations [61]. It should be remembered that gastric pH differs from individual to individual, particularly in older people, and this could affect blood pressure levels after nitrate ingestion.

Can we reach a conclusion?

The data outlined above suggest that the effect of nitrate intake on blood pressure can be influenced by several factors. Based on the data available, it seems possible to draw some conclusions.

High dose nitrate supplementation demonstrates a dose–response reduction in blood pressure in the short term. A single high dose of nitrate, > 500 mg in the form of nitrate-rich vegetable extract (beetroot juice) has significantly reduced blood pressure within 3 h with acute effect lasting for several hours and a residual effect still present after 24 h [27]. An obvious question arises as to whether high dose of nitrate needed to achieve these blood pressure results is feasible from the vegetables common daily intake.

Clinical trials investigating nitrate intake lasting between 3 days and 5–6 weeks have not infrequently failed to reduce blood pressure [32–38]. The results of these negative trials, however, may have been influenced by some factors: a too-short duration of the study design; the possibility that the fractionation of the nitrate intake administered over a single day did not ensure a bolus effect; the differences in the total amount of nitrate ingested; the diets the participants were following, with a possible elevated intake of SFA and a low

intake of MUFA; and the medications the participants were taking, in particular acid-suppressing drugs.

On the other hand, a chronic exposure to dietary nitrate appears to produce consistent results in terms of blood pressure reduction. People with a chronic (meaning years) high adherence to essentially vegetarian diets, for example MeD or DASH, have significantly lower blood pressure levels with respect to people with a low adherence to these diets or who follow these diets for only short periods (weeks or months). It cannot be overlooked, however, that the two diets mentioned are also rich in other active compounds, as antioxidants and organosulfur compounds, which may independently contribute to lower blood pressure.

The antioxidants, in particular the polyphenols contained in vegetables and fresh fruit (flavonoids) and in virgin olive oil (secoiridoids), have been shown to lower blood pressure by increasing the synthesis and secretion of vascular NO, although it has been demonstrated that flavonoids and nitrate independently but not synergistically augment the nitric oxide status [30].

The organosulfur compounds, potent antioxidant abundantly found in cruciferous vegetables (broccoli sprouts for example), could also play a non-secondary role in reducing blood pressure by attenuating oxidative stress. Oxidative stress has been implicated as a causal factor in hypertension due to a decrease in NO bioavailability [62, 63]. It has been shown that an increased production, or decreased scavenging, of oxidants such as superoxide anion can lead to hypertension by superoxide interacting with nitric oxide, forming peroxynitrite [64–66], thereby decreasing nitric oxide availability for smooth muscle relaxation. In an animal study, sulforaphane, a potent organosulfur compound with a phase 2 protein inducer activity, has been shown to significantly reduce oxidative stress and promote improved endothelial-dependent relaxation of the aorta leading to a significant reduction in blood pressure (20 mmHg) [67].

These data point to the hypothesis that regardless of the age of the individual, diets that are predominantly vegetarian with low SFA and high MUFA content and containing other important components such as polyphenols and organosulfur compounds likely permit nitrate to act more efficiently on blood pressure provided that the diet has been followed for years.

Summarizing

Green, leafy vegetables are consistently reported as one of the healthiest varieties of plant foods, with regards to protection against numerous diseases. Concerning their effects on blood pressure, despite the inconsistencies and limitations of several trials showing null results, corroborated to some extent by the contrasting conclusions reached by systematic

reviews and meta-analyses of randomized controlled trials [68–70], it could be reasonable to suggest, based on other numerous convincing data of the literature, that older people strive to include generous portions of vegetables in their daily diets because they may reduce high blood pressure, likely under the conditions illustrated above. It hardly needs mentioning that in addition to the effects on blood pressure and to the benefits derived by the ingestion of soluble and insoluble fibers, a high daily intake of nitrate-rich vegetables could give numerous other health benefits, ranging from preventing endothelial dysfunction [71–73] to improving platelet function [27, 74], arterial stiffness [75, 76], cerebral blood flow [77], pulmonary circulation [78–80], and exercise performance [81–84]. Vegetables and dietary nitrate have also been linked to strategies to lower the risk of atherosclerosis [20–23] and to prevent cancer [85–88].

Further studies are nevertheless needed to further clarify the impact of dietary nitrate on blood pressure and particularly to bridge the gaps between current evidence and translation into dietary recommendations for blood pressure.

What about the carcinogenic effect of N-nitroso compounds?

This article cannot come to its conclusion without making mention to the supposed carcinogenic effects of N-nitroso compounds.

While N-nitroso compounds have repeatedly been shown to be carcinogenic in animal experiments [89, 90], reports such as that on the 2003 Joint FAO/WHO Expert Committee on Food Additives (JEFCA) meetings examining epidemiological and toxicological studies in humans failed to establish a definite link between nitrate intake and the risk of developing cancer [91–93]. Nor did the Second Report of the World Cancer Research Fund/American Institute of Cancer Research published in 2007 report on an increased risk of cancer development of, for example, stomach or ovarian tumors, linked to green leafy vegetables, and, instead, referred to findings demonstrating beneficial effects [94]. Indeed, the report's final recommendation was that of eating at least five portions/servings (400 g) of a variety of non-starchy vegetables and fruits every day, and it specifically made mention to green, leafy vegetables.

A review in the *American Journal of Clinical Nutrition* wrote that “If nitrite were, indeed, a carcinogen, we would be advised to avoid swallowing because saliva contains nitrite.”[95].

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Statement of human and animal rights This paper neither involves human participants nor animals.

Informed consent For this reason, neither ethical approval nor informed consent was requested.

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