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NUTRACEUTICALS AND BLOOD PRESSURE (BP)

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BACKGROUND

The importance of risk factors control is well established in high-risk patients with and without cardiovascular disease. The preventive effect can be also demonstrated in the early phase of the atherosclerotic disease or in patients with mild elevation of blood pressure (BP) and/or serum lipids and glucose levels. These conditions are largely represented in the population and contribute to the overall burden of cardiovascular (CV) disease [1]. According the European guidelines [1] these patients should be initially treated with a non-pharmacological approach including lifestyle changes and the use of healthy foods or nutraceutical products. Actually, the size of BP decrease with this approach is smaller than that of drug treatment, but it can contribute to CV risk control in combination with recommended medications or in subjects with high-normal BP. Several compounds of natural origin have been shown to improve BP control by interacting with the pathophysiological mechanisms involved in hypertension and metabolic disorders [2].

NUTRACEUTICALS: DEFINITION AND MECHANISM OF ACTION

The term "nutraceutical" is a portmanteau of the words "nutrition" (indicating a nourishing food or food component) and "pharmaceutical" (with reference to a drug) [3]. Originally, it identified a food or part of a food (vegetal or animal origin) with a potential health-promoting activity in humans, related to a demonstrated pharmacological activity. The term includes nutrients (vitamins, minerals, fatty acids, aminoacids, peptides, polyphenols) and non-nutrients (e.g., botanicals and specific molecules such as melatonin, carnitines, alpha-lipoic acid, coenzyme Q10). In Europe, the stringent regulation of allowed health claims set out by the European Union [4] has led to a rigorous (even if not strictly clinical) regulatory assessment by the EFSA (European Food Safety Authority) of the documentation submitted by the Marketing Authorisation Applicants for the approval of health claims.

Most of BP lowering compounds promote antioxidant activity, by modulating the nitric oxide metabolism (as for instance beetroot juice) or inhibiting the renin-angiotensin system (as for instance vitamin D). Other nutraceuticals, as cocoa flavonoids, have multiple mechanisms of action, that also include improvement in insulin-sensitivity, beyond their antioxidant and angiotensin II inhibition activities [4].

"ANTIHYPERTENSIVE" FOODS, NUTRIENTS AND NUTRACEUTICALS: THE CLINICAL EVIDENCE

The European Society of Hypertension (ESH) expert panel has recently published a position paper on nutraceuticals and BP control [5] that classified the natural compounds with clinically measurable effect on BP in foods, nutrients and non-nutrient nutraceuticals.

"ANTIHYPERTENSIVE" FOODS

- *Non-roasted green coffee.* Coffee, and in particular green or lightly roasted coffee, is rich in phytochemicals with beneficial properties for CV health and BP control. The phenolic content of coffee might also explain why habitual consumption of at least 3 cups/day is associated with lower risk of hypertension than drinking only one cup/day [6]. A recent meta-analysis on 36 studies reported a lower risk of CV disease in subjects drinking a median of 1.5 to 3.5 cups/day with no increase in [7].
- *Green and Black Tea.* In a meta-analysis of 18 prospective studies, the risk ratio for the highest vs. lowest category of green and black tea consumption were 0,67 (95% confidence intervals – CI- 0,46 to 0,96) and 0,88 (95%CI 0,77 to 1,01), respectively [8]. Regular consumption of both green and black tea (2 to 6 cups per day) is associated to significant BP reduction. [9]. The reason of a higher effect of green tea on BP is probably the high content of phenols and catechins in its leaves, suppressing the NADPH oxidase activity and reducing the numbers of reactive oxygen species in the vascular system [10].
- *Beetroot juice.* Meta-analytic data of randomized clinical trials (RCTs) show that beetroot juice consumption is associated with dose-dependent changes in SBP [11] for his content of Nitrate (NO3–). After ingestion this compound is metabolized in vivo to bioactive nitrite (NO2–) that circulated in human blood flow leading to functional nitrogen oxides, including nitric oxide (NO) [12].
- *Pomegranate juice.* Punica granatum L. is rich in antioxidant polyphenols, e.g., ellagitannins, [13] and a recent systematic review from eight RCTs confirmed its antihypertensive effect in humans [14].

"ANTIHYPERTENSIVE" NUTRIENTS

- *Omega-3 Polyunsaturated fatty acids (PUFAs).* Epidemiological and clinical studies suggest that consumption of ω-3 PUFAs contributes to CV health through different mechanisms including BP control [60]. Several evidence suggest that an adequate ω-3 PUFAs dietary intake or supplementation (generally 2-4 g/day) can lead to a slight BP reduction in individuals with untreated hypertension [15,16].
- *Proteins, peptides and amino-acids.* According to a meta-analysis of 40 RCTs, dietary protein intake, in comparison with carbohydrate intake, resulted in a small but significant decrease of SBP and DBP [17]. ACE inhibition may be obtained with milk tripeptides Val-Pro-Pro and Ile-Pro-Pro, particularly in Asian populations [18]. As far as specific amino acids are concerned, a detectable effect on BP was found with the use of L-arginine, a semi-essential amino acid, administered at doses ranging from 4 to 24 gr/die [19] leading to the release of NO.
- *Calcium.* Evidence exists of a reduction of the risk of preeclampsia

and of offspring's BP level later in life with maternal calcium supplementation during pregnancy. While high dietary calcium intake coming was associated in the long term with a decreased risk of incident atherosclerosis, calcium supplements were associated with an increased risk of myocardial infarction and coronary artery calcification and should be prescribed with caution [20].

- *Magnesium (Mg).* Preclinical studies suggest that Mg affects BP regulation by directly stimulating prostacyclin and NO formation, [21] by modulating endothelium-dependent and endothelium-independent vasodilation, by reducing vascular tone and reactivity, [22] and by preventing vascular injury through antioxidant and anti-inflammatory effects. [23] A meta-analysis of RCTs investigating the effects on BP of Mg supplementation at a median dose of 368 mg/d reported a significant decrease in SBP and DBP [24].
- *Potassium.* Data from meta-analyses and cohort studies support the link of low dietary intake of potassium with the rise of BP and CV risk while a potassium supplementation exerts favourable cardiovascular effects particularly in hypertension. Potassium supplementation of 90- 120 mEq/day may lower elevated BP by up to 7/4 mm Hg particularly in hypertensive patients with a greater effect and was associated with a 21% lower risk of stroke [25].
- *Vitamins C and D.* Vitamin C or plasma ascorbate concentration in humans is inversely correlated to BP [26]. Numerous mechanisms have been supposed to be the cause of Vitamin C induced BP reduction: NO and PGI2 release, diuresis and natriuresis, decrease of adrenal steroid production, improvement in sympatho-vagal balance, cyclic GMP increase, potassium channels activation, and cytosolic calcium reduction. Vitamin C seems to reduce the affinity of angiotensin II for the angiotensin type 1 (ATR1) receptor by disrupting the ATR1 disulfide bridges [27]. In a meta-analysis of RCTs with a median vitamin C dose of 500 mg
- *Slow-release melatonin.* Melatonin is a hormone normally secreted from the pineal gland that works as the signal of darkness in the organism playing a pivotal role in the physiological regulation of circadian rhythms. Melatonin seems to improve BP control both by central and peripheral mechanisms, by protecting vessels from oxidation, improving NO metabolism and consequently improving endothelial function [28]. A recent meta-analysis of RCTs showed that controlled-release melatonin (2-5 mg/day) significantly decrease night SBP and DBP [29].

ESH POSITION AND SUGGESTIONS IN CLINICAL PRACTICE

The ESH position paper is focused only on those nutraceuticals whose BP lowering efficacy has been tested through reliable RCTs with the exclusion of observational, uncontrolled and anecdotic results. According to this approach, the ESH panel thus resumed their recommendation as reported in table 1.

Table 1: Foods, nutrients and nutraceuticals with the most convincing evidence of antihypertensive effect.

Foods	Nutrients	Non nutrient-nutraceuticals
Beetroot	Magnesium	Soy isoflavones (perimenopausal women)
Catechin-rich beverages	Potassium (warning is needed in patients with advanced chronic kidney failure and those receiving potassium sparing diuretics/mineralo-corticoid receptor antagonists	Resveratrol (insulin-resistant patients)
Pomegranate juice, karkadè teas and sesame (effectiveness been demonstrated in Middle-East people, only)		Slow-release melatonin (subjects with night hypertension)

In any case, the nutraceutical approach has never to substitute the drug treatment, when needed.

The nutraceutical approach can be proposed as a dietary or "pharmacological" supplementation with an accurate choice of the possible solution based on simple criteria: mild BP elevation, lack of recommended antihypertensive treatment, and inclusion of the nutraceutical among the list of compounds with demonstrated efficacy.

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