Managing Hypertension by Polyphenols

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Abstract

Some polyphenols, obtained from plants of broad use, induce a favorable endothelial response in hypertension and beneficial effects in the management of other metabolic cardiovascular risks. Previous studies in our laboratories using the calyces of *Hibiscus sabdariffa* as a source of polyphenols show that significant effects on hypertension are noticeable in humans only when provided in high amounts. Available data are suggestive in animal models and *ex vivo* experiments, but data in humans are difficult to acquire. Additionally, and despite the low bioavailability of polyphenols, intervention studies provide evidence for the protective effects of secondary plant metabolites. Assumptions on public health benefits are limited by the lack of scientific knowledge, robust data derived from large randomized clinical trials, and an accurate assessment of the bioactive components provided by common foodstuff. Because it is likely that clinical effects are the result of multiple interactions among different polyphenols rather than the isolated action of unique compounds, to provide polyphenol-rich botanical extracts as dietary supplements is a suggestive option. Unfortunately, the lack of patent perspectives for the pharmaceutical industries and the high cost of production and release for alimentary industries will hamper the performance of the necessary clinical trials. Here we briefly discuss whether and how such limitations may complicate the extensive use of plant-derived products in the management of hypertension and which steps are the necessary to deal with the predictable complexity in a possible clinical practice.

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Hypertension: Multiple Guidelines Reflecting an Unsolved Issue

Hypertension is the most important risk factor in the development of cardiovascular diseases (CV) but its pathophysiology remains incompletely understood. Hypertension is clinically defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg. Taking an antihypertensive medication is also used as an alternative description. The publication of multiple hypertension guidelines reflects a continuous debate and an unsolved issue. The upper levels of normal ranges of blood pressure (BP) are based on, firstly, epidemiological findings relating BP levels to risks for adverse outcomes and, secondly, clinical trials demonstrating a reduced risk of adverse outcomes with antihypertensive therapies. Recently, members appointed to the Eighth Joint National Committee, independent of any sponsoring agency, have updated the management of high BP [1]. The recommendation to change the treatment goal for individuals aged 60 years or older with hypertension has raised some concerns in scientific associations with an interest in hypertension. The new guideline sets goals for SBP and diastolic DBP at less than 150/90 mmHg (previously 140/90 mmHg) in these patients. The diastolic goal of less than 90 mmHg is also recommended for hypertensive persons 30 through 59 years of age. They did not find evidence in hypertensive persons younger than 60 years for a systolic goal, or in those younger than 30 years for a diastolic goal, and recommend a BP of less than 140/90 mmHg for those groups. It is generally accepted that among patients with hypertension, those with an elevated SBP carry the highest risk for cardiovascular events but once the SBP is below 140 mmHg, the risk of incident CV does not change [2]. Relevant to our discussion, the diag-

nosis of prehypertension in a child or adolescent represents an increased risk for early-onset CV disease, and it is apparently related to being overweight, insulin resistance, and metabolic syndrome [3]. Also, the prevalence of resistant hypertension, high BP that remains above the accepted goals despite concomitant use of three or more antihypertensive agents, is increasing and apparently related to older age and metabolic disturbances [4].

Underdiagnosis of hypertension is apparently high. There are no reliable data, but substantial reductions in the number of unaware and/or untreated hypertensive patients should be a major clinical goal. Despite an increase in the number and tolerability of antihypertensive medications, undertreatment is extraordinarily high, a situation that is also observed with respect to other cardiovascular risk factors. In clinical trials, the control rates in hypertensive patients is 60–70% [5], but in the "real world" it appears to be < 30% [6]. Multiple factors have been cited for the low BP control (e.g., low compliance or limited access to medication), but the impact of therapeutic inertia seems to be high and an impediment to achieve satisfactory control rates [7]. Therapeutic inertia is defined as the failure to increase therapy when treatment goals are unmet, and in a context of multiple guidelines, it is likely to increase. We propose a pragmatic alternative or complementary approach based on the increase of the daily intake of polyphenols to decrease the failure to control ≥ 70% of treated patients.

Hibiscus sabdariffa and Hypertension: The Importance of the Preparation and the Assessment of Phytochemical Composition

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"I've heard the hibiscus tea is helpful for high blood pressure. Is that true?" [8]. Despite a possible disagreement, our data suggest a negative answer [9]. Simply, the amount of ingested bioactive compounds is too low in current herbal teas. Frequently, herbal tea manufacturers do not provide information on the source and origin of *Hibiscus sabdariffa* L. (HS), the mode of preparation, phytochemical composition of the plant used in their products, and the resulting dose in the hibiscus beverage. Of note, data on the amount of imported plants are unreliable but apparently England, Germany, and the USA are the most prominent markets in Western societies. In these countries, HS is combined with many other ingredients used for the manufacturing of herbal teas including other natural products (i.e., mainly by-products of lemon, apple, or orange) and commercialized as "red or sour teas".

Our findings in humans, animal models, and *in vitro* experiments strongly suggest that polyphenols have a beneficial role in the prevention and therapy of hypertension, but the phytochemical composition of the HS extract is important information needed to provide the required amount (our data indicate that this should be approximately 70 mg/kg, p.o.) [9]. The description of the raw material, harvested in Senegal, and the extracts we used in our experiments may be found as Supporting Information. The genus *Hibiscus* (Malvaceae) includes more than 300 species of annual or perennial herbs, shrubs, or trees. There are two main varieties of HS, *altissima* and *sabdariffa*, with different races, *bhagalpuriensi, intermedius, albus*, and *ruber*. The information provided in this report to highlight the beneficial effect of HS in hypertension has been obtained with the calyces of HS race *ruber*, which is an annual, erect, bushy, herbaceous subshrub. The calyx is red, consisting of five large sepals and bracteoles around the base that enclose a velvety capsule, which turns brown and splits open when mature and dry [10]. The calyx aqueous extract is acid, resembles the cranberry in flavor, and has a potent *in vitro* antioxidant effect. Of note, in the quest for pharmacological actions, it is important to recognize that the polyphenol content of the extract is likely responsible for the effect, but also that this is a poorly defined term, which may include other possible bioactive compounds. There are significant amounts of saccharides in HS extracts (approximately 15%) including arabinose, galactose, and glucose. The mucilage content is approximately 20% and predominantly composed by anhydrouronic acid. This "complete" aqueous extract is apparently safe, and in mice the LD_{50} is consistently > 2500 mg/kg body weight (unpublished data). It is relatively easy but substantially more expensive to prepare pure polyphenolic extracts (see Supporting Information), but the toxicity has not been tested. Additionally, no therapeutically relevant interaction potential has been reported, and we did not find significant effects on CYP450 activity in mice cotreated with acetaminophen (unpublished data). The mode of harvesting, conservation, and preparation necessarily alters this information and requires standardization in the preparation of each batch [11]. This is a considerable obstacle for the correct assessment of clinical effects. Further, the "quality" of HS (measured as the amount of polyphenols per gram of dried calyces) strongly depends on local agricultural methods and the geographic origin. To our knowledge, different preparations of HS are available, at least, from China, Thailand, Sudan, Mexico, Egypt, Senegal, Tanzania, Mali, and Jamaica, countries in which HS has been traditionally used for food and medicine.

Polyphenols and Hypertension: Anecdotes Coalesce into Data and Probably Useful Knowledge

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In clinical trials and preclinical experiments, it is common to find disparate results regarding the size of the effect on BP attributed to polyphenols, but results seem to indicate the concurrence of multiple mechanisms. In animals, most data suggest a diuretic effect, but HS extracts may also improve metabolism, and the anti-inflammatory and antioxidant activities are prominent [9–16]. Moreover, HS extracts significantly reduced BP in spontaneously hypertensive rats (125 or 60 mg/kg in a single dose or daily for one week) [9]. In humans with metabolic syndrome, the effects are similar. In patients with mild to moderate hypertension, a diuretic effect was observed during treatment with an HS extract characterized as containing 9.6 mg of anthocyanins [17]. However, using different compositions, clinical studies performed in Thailand failed in finding a diuretic effect [18,19]. Because composition and the amount of polyphenols provided differ in all published studies, or the data are not well characterized, the effectiveness of HS for the treatment of hypertension and its putative diuretic effect are apparently inconclusive when the criteria to establish the quality of randomized clinical trials (RCTs) are exclusively based on randomization and blinding [20,21]. However, clinical observations in patients with concomitant metabolic disturbances indicate uniform and constant beneficial effects of polyphenols in their BP. The fact that a placebo effect is apparently negligible using 24 h ambulatory blood pressure oscillometric monitoring is also clinically important [22]. Additionally, adherence seems to be higher than that obtained with marketed drugs, and this effect may be important to reduce the factors affecting the low control rates in hypertensive patients. It has also been

proposed that criteria for RCTs could be expanded in the assessment of evidences related to the medicinal use of botanicals [23, 24]. Consequently, when RCTs are reviewed in the context of the phytochemical, ethnomedical, pharmacological, and toxicological information, the conclusion is that extracts of HS are "promising" as a treatment for hypertension [25]. The establishment of the actual relevance for public health benefits requires high-quality human studies, and recent reports include a substantial number of the CONSORT items relevant to all RCTs. Robust conclusions face a number of limitations derived from the diverse clinical population (i.e., included healthy participants as well as those with metabolic syndrome, hyperlipidemia, hypertension, or type 2 diabetes mellitus), different doses of HS, as well as differing preparation of the extracts and frequency of administration. Other limitations that should be carefully assessed relate to the information on phytochemical composition and the duration of treatment; most lasted from 15 days to 2 months [9, 17, 26–31]. Hence, comparisons are difficult to sustain.

We therefore believe that the beneficial effects of HS on hypertension are not a folkloric claim but will remain anecdotic until further investments in financial and research effort clarify these important questions. This may be apparently profitable because, when taking into account the available data, it seems to coalesce into a considerable body of reliable knowledge. Importantly, plant-derived compounds may also increase the compliance in the treatment of hypertension. This is an important issue because it is a common observation that physicians do not correctly prescribe first-line drugs for their patients with high BP and when prescribed, these are not taken by the patients [32]. As mentioned above, the consequence is that hypertension is generally undertreated [33–35]. Dietary supplements may provide an additional tool to be successful in the effort to reverse this situation. In addition to evidences provided by HS, this may also be applied to the extract of leaves from *Camellia sinensis* or "green tea", which is one of the most commonly consumed beverages worldwide and contains different phytochemicals including phenols and catechins [36]. In this case, probably due to evident economic profits, the manufacturers of green tea have financed a substantial number of RCTs to prove effects on hypertension. High doses have not been tested. Value for evidence-based medicine should not be granted, but it should be remembered that methodological flaws are common in published medical research (> 20%) and that RCTs have as many limitations as non-RCTs [37]. Case-control studies and epidemiological studies strongly suggest that green tea intake is cardioprotective, but meta-analyses are not conclusive. One study [38] indicated that green tea had no beneficial effect on BP, but another one [39] reported beneficial effects from green tea on "blood-vessel vasodilation". Recently, a systematic review using blinded-only clinical trials to assess the evidence for the efficacy of the green tea extracts on BP concluded that these may cause significant reductions in SBP and recommend long-term independent clinical trials [40].

It should be mentioned that sometimes the cross-cultural approach is successful to discover the potentially useful effects of plants in the management of hypertension. For example, the effects of cocoa (a complex mixture of polyphenols) were detected observing a different prevalence of hypertension after drastic dietary changes. Some Kuna Indians living on San Blas Island (Panama), who consistent had a healthy low blood pressure unaffected by age, migrated to the mainland and consumed up to 10 times less cocoa. In this subpopulation, the prevalence of hypertension increased, and the age-dependent rise of blood pressure appeared in a short period of time [41]. Cocoa, a product derived from the beans of the *Theobroma cacao* tree, is a potential source of bioactive compounds, but the commercial products may add undesirable calories, sugars, and fats to the diet. However, the European Food Safety Authority recently issued a positive scientific statement on cocoa flavanols, indicating a possible role in the maintenance of "normal endothelium-dependent vasodilation" [42]. We have recently characterized the composition in polyphenols of a novel *T. cacao* extract, and we found a high antioxidant activity of flavonoids and their metabolites *in vitro,* which depends on the arrangement of functional groups around the nuclear structure and the substitution pattern of the hydroxyl groups [43]. The use of extracts avoids the ingestion of non-desired nutrients, but has not been proved clinically. Cocoa, however, has been associated with a modest but statistically significant effect on lowering SBP and DBP (of 2.8–3.7 mmHg and 2.2–2.7 mmHg, respectively). None of the studies measured health outcomes [44, 45].

Different mixtures of polyphenols provide beneficial effects in the management of hypertension. Whether mixing extracts from different plants may result in a safe and correct approach remains to be established. Data in the literature are difficult to compare but apparently confirm that the use of high doses of polyphenols is essential to obtain significant reductions in BP. We recognize that the differences in the phytochemical composition limit comparisons between extracts in assessing the effects on BP. For example, we obtain substantially higher effects with elevated doses of HS extract in patients with metabolic syndrome (a change in 24-h SBP of -11.0 ± 6.3 mmHg; $p < 0.001$ vs. baseline) and 24-h DBP (-4.2 ± 1.9 mmHg; $p < 0.001$ vs. baseline). Of note, reductions only occurred during the daytime, and the heart rate was significantly ($p = 0.012$) decreased after the intervention period (70.5 ± 11.5 beats/min) with respect to the baseline value (76.3 ± 11.8 beats/min) [9].

Polyphenols and Hypertension: Teas, Extracts, or Isolated Compounds?

Because dose is important for the size of the effect, herbal teas cannot provide the necessary amounts of polyphenols unless the consumption is continuous during the day. In contrast to HS extracts or related beverages, some herbal teas or other sources of polyphenols may depict side effects (i.e., excitatory effect, increase in caloric intake, etc.). Therefore, our recommendation of high doses, which requires preparation and the release of extracts, significantly increases the cost of fabrication, especially when polyphenols are further isolated to manufacture capsules (see Supporting Information) [46–52]. Additionally, polyphenols exist as complex mixtures of related compounds in foods. The amino acid phenylalanine, in which one or more hydroxyl groups are introduced into the phenyl ring, producing phenols, is the first building block to produce thousands of different structures by adding acetate and sugars. It remains unknown whether this complexity is relevant for our diet [47]; synergism among polyphenols cannot be discarded [48]. The phytochemical composition of foods reveals a high variety of polyphenols (> 500) in common plant foods (http://www.phenol-explorer.eu), and the possibility of finding structure-activity relations is unlikely. On the other hand, the study individual polyphenols is not frequent (e.g., resveratrol, quercetin, epigallocatechin-3-gallate, naringenin, curcumin), but substantial efforts have been made under

false assumptions implicating that complexity decreases when polyphenols are isolated. Besides, the likelihood of toxic effects is higher than the administration of equivalent amounts as natural mixtures. Indeed, most marketed drugs for single actions synchronously modulate dozens of proteins and receptors. We have already documented this phenomenon with simple drugs such as glitazones or fibrates using the combination of metabolomics and transcriptomics with a focus on obtaining changes in the metabolic status (i.e., the so-called modern Systems Biology) [53]. Moreover, the assessment of the predictive value of the effects of isolated compounds using common *in vitro* models should be cautious, and extrapolations to *in vivo* models are useless, especially when explorations are performed with non-metabolized polyphenols and nonphysiological, usually high, doses.

The theoretical basis to explain the effect of polyphenols remains unclear, but it appears now well established that polyphenols seem to have evolved to adapt to different metabolic structures, suggesting an inherent potential to exert multiple pharmacological effects [54]. Taken together, our results and those reviewed in the literature suggest that a multifaceted and likely synergistic mechanism accounts for the hypotensive action of polyphenol-rich HS, which acts through different molecular targets specifically directed to improve endothelium-dependent vasodilation. Inflammation, endothelial dysfunction, and oxidation are apparently interrelated mechanisms that play a substantial role in the pathogenesis of hypertension [55]. Effects on diuresis should be added to these mechanisms [56]. We have also found that the HS extract strongly inhibits xanthine oxidase, a superoxide-producing enzyme, and 15-lipoxygenase, which may control the formation of eicosanoids in inflammatory cells [9]. Polyphenols also decrease the circulating levels of inflammatory cytokines regulating the migration of immune cells to tissues, and it is likely that these actions could improve cardiovascular health [48,49]. The inflammation inhibition of polyphenols is mostly observed at the transcription level in *ex vivo* models with a reduced production (and likely activation and translocation) of NF-κB, a major transcription peptide involved in the expression of inflammatory mediators [9].

Chemically, all polyphenols are antioxidant (*in vitro*). According to the antioxidant hypothesis, the oxidant by-products of normal metabolism cause extensive damage to biomolecules, which is associated with diseases of aging, such as cardiovascular disease. Consequently, the antioxidant defenses are important against this damage, and it is plausible that a supplemental intake of antioxidants would protect against diseases [57–59]. In this scenario, polyphenols show a common and potent antioxidant activity *in vitro*, but the possible effect *in vivo* is debatable and does not necessarily represent a common biological action. The absence of significant changes in the antioxidant capacity of plasma after the ingestion of considerable amounts of polyphenols is unsatisfactory [59,60]. The detection of effects in the markers of lipid peroxidation and natural antioxidant enzymes are either low or negligible. Whether the effects of polyphenols are relevant in oxidative stress remains to be ascertained, but it is most unlikely as a result of their poor absorption and rapid metabolism and elimination. Additionally, polyphenols represent < 1–2% of the plasma antioxidants, which include proteins, ascorbate, tocopherol, carotenoids, bilirubin, uric acid, and several other compounds [60,61]. More importantly, the antioxidant activity is obviously welcome, but it is not necessary to explain the effects on BP. Effects on enzymes, cell-signaling pathways, and effects in gene expression may readily explain the beneficial effects on endothelial function, metabolic disturbances, and vascular inflammation [62–65]. Intriguingly, although less explored, it has been recently suggested that polyphenols may be important on mitochondrial processes relevant to hypertension, such as membrane potential maintenance and cell survival [66]. Finally, the HS extract decreases the activity of the renin-angiotensin system (RAS) in animal models and in patients with metabolic syndrome and hypertension [9,67]. This effect was further sustained by the finding of elevated serum concentrations of a vasodilator, des-Arg (9)-bradykinin, which strongly suggests the action of the HS extract as a potent inhibitor *in vivo* of the angiotensin converting enzyme (unpublished data). The interrelated effects resulting in a decrease of RAS activity may help to understand the beneficial actions of polyphenols and/or associated compounds. Hypertension, diabetes, obesity, and cortisol stimulate RAS activity, and an activated RAS is closely related to the metabolic syndrome [68]. Conversely, the inhibition of RAS activity improves the mentioned derangements [69].

Perspectives and Implications

Hypertension prevalence is on the rise. Despite advances in hypertension treatment, only about one-third of all patients with hypertension are controlled in Western societies. We present evidence that polyphenols (at least those from HS, green tea, and cocoa) could be important additions to improve the management of hypertension. Epidemiological data also suggest that a regular consumption of phytochemicals is associated with a reduced risk of developing cardiovascular diseases [70]. However, these findings are difficult to verify without further financial effort. Well-conducted, adequately powered clinical trials with a long duration of intervention and a standardized composition in polyphenols to evaluate their effects on BP and other metabolic derangements are warranted. This is expensive, and reluctance is a common feeling in industries dealing with hypertension.

We acknowledge that it is of great significance to elucidate the therapeutic mechanisms of polyphenols. This is a considerable challenge because polyphenols hit multiple targets with relatively weak affinity, and multiple polyphenols may represent an increase in the number of effects. To clarify these mechanisms, the metabolism of polyphenols should be incorporated into future approaches. Complexity is an inherent characteristic in the assessment of both pharmacological and dietary interventions, as the concentration of many metabolites may change in a scenario in which thousands of reactions continuously transform metabolites into each other. Ongoing studies will probably refine and confirm this approach as a promising tool for capturing metabolic complexity caused by plant-derived extracts. We expect that the interpretation of the induced metabolic changes using this technology and potent bioinformatics tools [71] will result in the knowledge of the effects on hypertension caused by specific polyphenol metabolites. Indeed, recent efforts reinforce this approach [72] recognizing the fact that we generally have incomplete knowledge of the molecular pathways by which drugs act [73]. The current relationship between polyphenols and hypertension is questionable and disappointing in some aspects. It is acknowledged that the undertreatment of hypertension is a serious medical problem and that plant-derived polyphenols, as a complementary approach, may be potentially helpful. Substantial knowledge to ascertain the benefit in the population has been

developed, and it is available, but existing efforts are troubled by financial or patent-related difficulty.

Supporting information

The methods used to obtain and characterize HS aqueous extracts and the corresponding purified extracts are available as Supporting Information.

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Conflict of Interest

All authors contributed to and have approved the final manuscript. We declare not to have any conflict of interest regarding the publication of this manuscript.

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