



Review

Antihypertensive effects of the flavonoid quercetin

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Abstract:

The blood pressure lowering effect of a fruit and vegetable-rich diet is a necessary dietary lifestyle measure now included the guidelines for the management of arterial hypertension. Furthermore, flavonoids represent a major class of plant polyphenolics. The present review addresses the antihypertensive effect of quercetin, one of the most abundant flavonoids present in fruits and vegetables, and probably the best studied flavonoid because of its high biological activity. Quercetin has been shown to induce a progressive, dose-dependent and sustained reduction in blood pressure when given chronically in several rat models of hypertension, including spontaneously hypertensive rats, L-NAME-treated rats, DOCA-salt hypertensive rats, two-kidney one-clip Goldblatt rats, rats with aortic constriction and Dahl salt-sensitive hypertensive rats. Quercetin was also effective in reducing blood pressure in rat models of metabolic syndrome, including the obese Zucker rats as well as rats treated with a high-sucrose, high-fat diet. Quercetin also prevented morphological and functional changes in the heart, vessels and kidney, while increasing production of reactive oxygen species associated with hypertension. A high dose of quercetin also reduced blood pressure in stage 1 hypertensive patients in a randomized, double-blind, placebo-controlled, crossover study. Since raised blood pressure is the major cause of stroke as well as an important risk factor for ischemic heart disease, we propose that the blood pressure-lowering effect of quercetin could be an important mechanism contributing to the reduced risk of myocardial infarction and stroke observed with fruit and vegetables-rich diets, and possibly with flavonoid-rich diets.

Key words: quercetin, hypertension, flavonoids, nitric oxide, oxidative stress

Introduction

High blood pressure is one of the major risk factors for developing cardiovascular diseases, including coronary disease, stroke, peripheral artery disease, renal disease and heart failure [8, 25]. Efforts to reduce the prevalence of hypertension have focused on non-pharmacologic approaches that lower blood pressure.

Lifestyle measures are recommended for all patients, including those with high-normal blood pressure and those who have a higher risk and require drug treatment. The lifestyle measures that are widely agreed to lower blood pressure or cardiovascular risk associated with hypertension, include smoking cessation, weight reduction, physical exercise, reduction of excessive alcohol intake (particularly for binge drinking), and

dietary measures such as a reduction in sodium, an increase in potassium and a decrease in saturated and total fat intake [33]. An increase in fruit and vegetable intake has also been included in the guidelines for the management of arterial hypertension in recent years [33].

Earlier epidemiological studies suggested that vegetarians tend to have lower blood pressures than non-vegetarians. The blood pressure lowering effects of vegetables and a fruit-rich diet were later confirmed in randomized intervention studies [3, 34]. The reduction in blood pressure begins within two weeks, is maintained during the following weeks and is reversible [3, 34]. Interestingly, subjects with hypertension had greater reductions in blood pressure than normotensive subjects [34]. Because high blood pressure is the major cause of stroke, the blood pressure-lowering effect could be one of the major mechanisms contributing to a reduced risk of stroke with increased fruit and vegetable intake [20].

The specific components present in fruits and vegetables that reduce blood pressure are not fully characterized. It was originally suggested that an increase in the ratio of polyunsaturated to saturated fats, fibre, calcium and magnesium intake, and a decrease in the intake of protein and vitamin B12 might be responsible. However, the reduction in blood pressure produced by these substances in trials of dietary supplements has typically been small and inconsistent. The presence of multiple antioxidants in these foodstuffs has also been suggested to be involved [3, 38]. Among these plant antioxidants, polyphenolics have received considerable attention in recent years as compounds with potential beneficial effects for cardiovascular health.

Flavonoids represent the major class of polyphenolics, which, in addition to their antioxidant effects, show a wide range of pharmacological activities [32, 35]. These compounds have attracted both nutritionists and pharmacologists for a number of reasons: 1) based on their abundance in fruits and vegetables, flavonoids may account for some of the health-promoting effects of these foodstuffs, 2) some foods are particularly rich in flavonoids, such as tea, wine, onions, apples or dark chocolate, whose beneficial cardiovascular effects are well known, 3) some products derived from these flavonoid-rich foods, e.g. red wine polyphenolic extracts, have been commercialized as dietary supplements, 4) medicinal plants rich in flavonoids or their extracts (e.g. the standardized extract of *Ginkgo biloba* leaves) are used within alternative as well as academic medicine, and 5) specific fla-

vonoids (e.g. quercetin) are also available in certain countries as nutraceuticals. The present review addresses the antihypertensive effect of quercetin, one of the most abundant flavonoids in food and probably the best studied because of its high biological activity.

The term flavonoid describes several thousand plant-derived compounds sharing a common skeleton of phenylchromane [35]. This basic structure allows a multitude of substitution patterns leading to several flavonoid subclasses such as flavonols, flavones, flavanones, catechins, anthocyanidins, isoflavones, dihydroflavonols and chalcones. These compounds are widely distributed in the plant kingdom, and are present in variable amounts in dietary fruits, vegetables, nuts, seeds, herbs, spices, tea and red wine [46]. The daily human intake of flavonoids was initially estimated to be around one gram [27], which led to the commercialization of the flavonoid quercetin as a dietary supplement in the US in doses of one gram per day. Yet, more recent estimates are well below this amount. The average daily intake of the most abundant flavonoids, catechins, has been estimated to be below 100 mg, while flavonols plus flavones are around 20–25 mg [21]. However, there are large variations within countries depending on their nutritional habits, with flavonols plus flavones ranging from 6 to 94 mg [22]. Quercetin, present in foods as quercetin glycosides, represents 60–75% of the total dietary flavonols plus flavones intake.

The interest in dietary flavonoids has grown in the last 15 years after the publication of several epidemiological studies showing an inverse correlation between dietary consumption of flavonols and flavones and reduced incidence and mortality from cardiovascular disease and cancer [21]. For instance, the meta-analysis of seven prospective cohort studies concluded that the individuals in the top third of dietary flavonol intake are associated with a reduced risk of mortality from coronary heart disease as compared with those in the bottom third, after adjustment for known risk factors and other dietary components [23].

Antihypertensive effect of quercetin in animal models

The first report on the antihypertensive effects of quercetin was from a study carried out in spontane-

ously hypertensive rats (SHR) [11]. SHR is a genetic model of multifactorial hypertension, which is considered to resemble human essential hypertension. Quercetin at a single oral daily dose of 10 mg/kg for five weeks given to 14 week-old SHR (i.e. with established hypertension) induced a significant reduction in systolic (−18%), diastolic (−23%) and mean (−21%) arterial blood pressure and heart rate (−12%) in SHRs, but had no effect in normotensive Wistar Kyoto rats (WKY). A similar antihypertensive effect was later reported in SHRs treated with 10 mg/kg starting at a pre-hypertensive stage (6–7-week old) [30]. The antihypertensive effect of quercetin lasts for at least 13 weeks. In all of these studies, quercetin was dissolved in methylcellulose administered orally *via* gavage. In a more recent and puzzling report [6], 5 week-old SHRs were given a quercetin-supplemented diet (1.5 g quercetin/kg diet, approx. 130 mg/kg) for 5 or 11 weeks. Despite the fact that plasma quercetin levels were elevated, arterial blood pressure was similar in quercetin-treated SHRs compared to the untreated animals, while quercetin given by gastric gavage was effective. However, in a previous report by this group [24], the same quercetin-supplemented diet was reported to be effective in lowering blood pressure in rats with aortic constriction, questioning their conclusion that the mode of delivery is a critical determinant of the efficacy of quercetin. An enzymatically modified isoquercitrin (EMIQ), i.e. a water-soluble glycoside of quercetin produced from rutin by enzymatic treatment, at a dose of 3 and 26 mg/kg/day, has also been shown to exert antihypertensive effects in SHR. This compound was more effective than quercetin itself, possibly due to a higher bioavailability [14].

The effects of quercetin were also analyzed in a rat model of hypertension induced by inhibition of NO synthase with N-nitro-L-arginine methyl ester (L-NAME). L-NAME is a non-selective inhibitor of NO synthase, i.e. it inhibits the endothelial, the inducible and the neuronal NO synthase isoforms (eNOS or NOS-3, iNOS or NOS-2 and nNOS or NOS-1) and induces a progressive increase in arterial blood pressure. The L-NAME-induced hypertension was prevented by a single oral daily administration of quercetin [10]. When given simultaneously with L-NAME, 10 mg/kg quercetin fully prevented an increase in blood pressure. At 5 mg/kg, it was also highly effective, though the effect developed more slowly and was only significant after four weeks of treatment. Once hypertension was established (i.e. after 6 weeks of treatment),

quercetin was also able to reduce blood pressure (Duar-te, unpublished observations).

In deoxycorticosterone acetate (DOCA)-salt hypertensive rats, the effects of quercetin were compared to those of the Ca²⁺ channel blocker verapamil [17, 18]. The DOCA-salt is a model of volume-dependent hypertension, which is triggered by administration of NaCl and characterized by a suppressed plasma renin level due to sodium retention. In this animal model, some classes of antihypertensive drugs such as angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor antagonists show low efficacy. However, quercetin (10 mg/kg) inhibited the development of DOCA-salt-induced hypertension and this effect was similar to that of verapamil (20 mg/kg). The Dahl salt-sensitive rat is another salt-dependent model of hypertension. In this case, Dahl rats are genetically predisposed to develop hypertension when they receive NaCl. Two studies have reported that quercetin diminishes elevated systolic blood pressure in these rats [2, 31].

The effects of quercetin were also analyzed in two-kidney, one-clip (2K1C) Goldblatt hypertensive rats [19], which is a model of renovascular hypertension with reduced blood flow to one kidney. The ischemic kidney secretes renin, which leads to increased angiotensin II formation and hence elevation of blood pressure. Sodium excretion by the intact contralateral kidney increases (pressure natriuresis); therefore, there is no sodium retention. Oral quercetin treatment (10 mg/kg) also reduced systolic blood pressure in this animal model. The clipping of the aorta at the suprarenal level is a common procedure used as a model of cardiac hypertrophy induced by pressure overload. In these animals, the elevated carotid arterial blood pressure was reduced by chronic treatment with 1.5 g quercetin/kg diet [24].

The effects of quercetin were also studied on the elevated blood pressure observed in metabolic syndrome, i.e. a common clinical condition associated with obesity and type 2 diabetes in which patients exhibit abdominal obesity, insulin resistance, dyslipidemia and hypertension. Obese Zucker rats are a genetic model of metabolic syndrome, demonstrating obesity, hypertriglyceridemia, hypercholesterolemia, hyperglycemia and elevated blood pressure. In this model, a daily dose of quercetin (2 or 10 mg/kg) for 10 weeks induced a progressive reduction in blood pressure without an effect on the control lean Zucker rats [42]. Another model of metabolic syndrome can be gener-

ated by administration of a high-fat and high-sucrose diet. The elevation in blood pressure induced by this diet was reduced in a dose-dependent manner by including 0.02–0.5% of quercetin (approx. 5–300 mg/kg/day) in the diet [47].

To summarize, quercetin has demonstrated antihypertensive effects when given chronically in the most common rodent models of hypertension. The dose most frequently used is 10 mg/kg per day, as used in the seminal report [11], but the effective doses used range from 2 to 300 mg/kg per day. When different doses were analyzed, the antihypertensive effect was dose-dependent [11, 42, 47]. Except in one report [6], the effect was independent of the mode of administration, i.e. given as a single daily oral administration by gavage or by including it in the diet. The time course of the antihypertensive effect has been followed by measuring systolic blood pressure by tail-cuff plethysmography. This effect does not appear immediately, usually starting during the second week of treatment, though it is sustained during the treatment period. Blood pressure was measured directly *via* arterial canulation at the end of the treatment period in most studies and quercetin reduced the systolic, the diastolic and the mean blood pressure. Interestingly, the reduction in blood pressure is long lasting, remaining after 48 h of discontinuation of treatment. To our knowledge, the reversibility of the antihypertensive effect of quercetin upon longer treatment discontinuation has not been analyzed. A modest reduction in heart rate was also observed in some studies. Remarkably, quercetin was effective in all models of hypertension analyzed, independently of the origin of the hypertension, the status of renin-angiotensin system, oxidative stress, nitric oxide, and other factors. However, it is also clear that quercetin does not exert hypotensive effects, because it did not modify blood pressure in control normotensive animals in any of the published studies.

End-organ damage associated with hypertension

Sustained high blood pressure is one of the most powerful determinants of the development of cardiac, vascular and renal diseases [8, 16, 25]. Current therapeutic options for hypertensive patients must consider not

only the reduction of blood pressure, but also its long term effects, i.e. the preventive effects on end-organ damage. It should also be noted that most of the benefits of antihypertensive treatment are a result of lowered blood pressure *per se* and is largely independent of the drugs or class of drugs employed [33].

Left ventricular hypertrophy

Left ventricular hypertrophy is found in most animal models of hypertension. In SHR, the left ventricular weight relative to body weight is significantly greater than in control WKY and this parameter was significantly reduced in quercetin-treated SHR in parallel with the reduction in systolic blood pressure [11]. A modest left ventricular hypertrophy can also be found in the L-NAME model of hypertension, which was significantly attenuated by quercetin [10]. Similarly, quercetin reduced cardiac hypertrophy in the 2K1C Goldblatt rats [19] and in the DOCA-salt model [17]. The effects of quercetin on cardiac hypertrophy were specifically assessed in rats with aortic constriction, a widely used model of cardiac hypertrophy [6]. In this paper, cardiac hypertrophy was attenuated by quercetin and this was accompanied by changes in the expression and localization of several proteins in the heart. Thus, the cardiac protein kinase C betaII translocation and the expression of cardiac beta-myosin heavy-chain mRNA were strongly reduced by quercetin. The antihypertrophic effect of quercetin may be at least partly due to a reduction in systolic load, which is a very potent stimulus for cardiac growth. However, because quercetin can interfere with many signaling pathways involved in cell growth and apoptosis, it cannot be ruled out that quercetin might limit hypertensive cardiac hypertrophy *via* other mechanisms. In fact, quercetin inhibited angiotensin 2-induced hypertrophy *in vitro* in cultured neonatal rat cardiomyocytes [40].

Renal injury

Several of the studies with quercetin in animal models of hypertension have also analyzed its effect on the kidney. In the study carried out in the L-NAME model, an in depth analysis of the histological changes induced by quercetin was performed [10]. Chronic inhibition of NO synthesis is consistently associated with renal injury presenting with an elevated kidney weight index, glomerulosclerosis with a prominent in-

crease in mesangial matrix in scattered glomeruli, many hyaline casts, tubular necrosis, and mild and scattered tubular atrophy [48]. The main and most intense vascular lesion found in L-NAME rats is hyaline arteriopathy and thickening of the vascular wall (proliferative arteriopathy) with a moderate decrease in the lumen, which was almost always observed in medium-sized vessels. These histological findings were associated with proteinuria, indicating functional impairment of the glomerular wall barrier. Quercetin prevented renal hypertrophy and reduced the renal parenchyma and vascular lesions and proteinuria, indicating that quercetin protects, at least partially, from L-NAME-induced renal injury. In the 2K1C Goldblatt model, quercetin treatment also reduced proteinuria [19] and prevented renal hypertrophy in the DOCA-salt model [17]. In contrast, in the SHR model, a weak increase in kidney weight index was not significantly modified by quercetin [11]. In the Dahl model, quercetin also downregulated the expression of the epithelial Na⁺ channel (ENaC) in the kidney [2].

Vascular structure and function

Resistance vessels from hypertensive patients and animals show structural changes mostly characterized by an inward eutrophic remodelling, i.e. increased media-to-lumen ratio with little or no change in the amount of material [36]. In SHRs, quercetin also tended to reduce remodelling following the trend of blood pressure reduction, but this effect was not statistically significant. Endothelial dysfunction, characterized by an altered balance between vasodilators and vasoconstrictors and an inflammatory and prothrombotic state, is consistently found in animal models of hypertension and in essential hypertensives, as well as people suffering from other cardiovascular diseases [4, 15]. We have recently reviewed the effects of quercetin on endothelial function [38]. Briefly, the chronic administration of quercetin restored the impaired endothelial vasodilator function as measured by the relaxant response to acetylcholine in SHR, in DOCA-salt and in 2K1C Goldblatt rats [11, 17, 19]. The improved endothelial function is attributed to a reduction in oxidative stress and particularly to diminished superoxide-driven NO inactivation. Moreover, in SHRs, quercetin has been shown to downregulate aortic p47^{phox}, a regulatory subunit of NADPH oxidase, which is the main source of vascular superoxide

[44]. Enhanced eNOS activity may also play a role in the improvement of endothelial function and the anti-hypertensive effects of chronic quercetin [44]. Additionally, chronic quercetin markedly inhibited endothelium-dependent vasoconstriction in the L-NAME and Goldblatt models [10, 19]. Furthermore, restoration of endothelial dysfunction by quercetin has also been observed in diabetic rats [29].

Reactive oxygen species

Excessive production of reactive oxygen species is a hallmark of cardiovascular diseases, including hypertension. In fact, it has been suggested that oxidative stress (an increase in the production of reactive oxygen species) is a pathogenetic factor in the development of essential hypertension [26]. Therefore, the studies carried out with quercetin in animal models of hypertension have analyzed multiple markers of oxidative stress in vascular tissues, liver, plasma or urine. For instance, the 24 h urinary isoprostane F_{2α} excretion and the plasma malonyldialdehyde (MDA) levels in SHRs were increased compared to the levels in WKY rats. However, in quercetin-treated SHRs, both parameters were similar to those in vehicle-treated WKY [11]. In the livers from SHRs, decreased glutathione peroxidase activity, increased total glutathione levels and increased MDA concentrations were observed compared to those in WKY rats [9]. Treatment with quercetin increased glutathione peroxidase activity and reduced malondialdehyde levels. As mentioned above, in SHRs, quercetin reduced the vascular production of superoxide radicals, an effect associated with the downregulation of NADPH oxidase subunits [44]. However, none of these effects were observed in Wistar Kyoto rats. The L-NAME model of hypertension has also been associated with increased oxidative stress. As found above for SHRs, hepatic glutathione peroxidase activity was decreased, while the plasma and liver contents of MDA were increased in L-NAME-treated animals [10]. Quercetin increased glutathione peroxidase activity in livers from L-NAME-treated animals. However, this is not a direct effect of quercetin, as quercetin had no effect on hepatic glutathione peroxidase activity *in vitro*. In addition, quercetin restored the plasma and hepatic content of MDA as enhanced by L-NAME. Increased plasma and heart thiobarbituric acid reactive substances (TBARS) and total glutathione levels in the liver and heart, decreased liver glutathione peroxidase and liver and kid-

ney glutathione transferase activities were observed in DOCA-salt-treated rats compared to the control animals [18]. The antihypertensive effect of quercetin in this model was accompanied by normalization of plasma TBARS values, improvement of the antioxidant defence system in the heart and liver, restoring total glutathione levels in both organs, altered liver glutathione transferase and glutathione peroxidase activities, and improved kidney glutathione transferase activity [17, 18]. Increased TBARS and decreased liver total glutathione levels and glutathione peroxidase activity were also observed in 2K1C Goldblatt hypertensive rats compared to the control animals. Quercetin treatment normalized plasma TBARS concentrations and improved the antioxidant defence system in the liver [19]. Quercetin also reduced TBARS in the high-sucrose high-fat fed rats [47]. All of these results indicate that quercetin reduced oxidative stress in the hypertensive animals. Furthermore, it had no effect on the markers of oxidative stress in normotensive animals.

Mechanisms of antihypertensive action

Flavonoids, and especially quercetin, chemically interact with reactive oxygen species and exert inhibitory activity against a diverse variety of enzymes, ion channels and transcription factors [35] (Fig. 1). Therefore, quercetin interferes with many signal transduction pathways and produces multiple changes in gene expression and cell function. When any given cellular function is modified by quercetin, it is relatively easy to identify a potential mechanism implicated, but difficult to ascertain whether this proposed target is the true and only biochemical mechanism involved. It should also be emphasized that free plasma quercetin concentrations are low; most of it circulates as glucuronidated and sulfated metabolites. Thus, it has been suggested that the *in vivo* effects of quercetin are due to the activity of the conjugated metabolites. However, the information available on the biological properties of these metabolites is still limited. On the other hand, these metabolites can be at least partly de-glucuronidated in target tissues. In a recent report, a variable amount of deconjugated quercetin (in the range of 30–100% of total flavonols) was found in all tissues except in blood plasma [5]. Therefore, at pres-

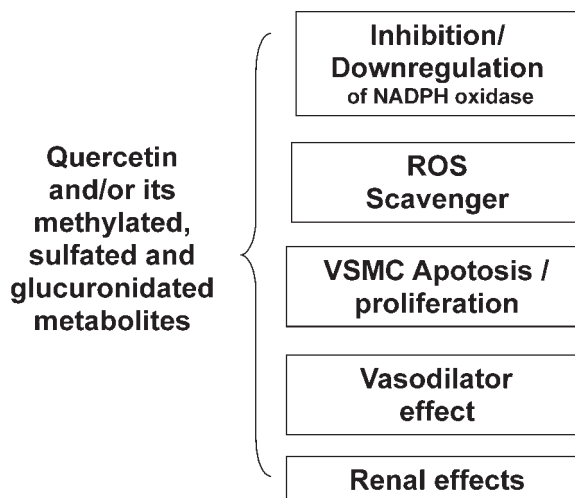


Fig. 1. Potential mechanisms underlying the antihypertensive effect of quercetin

ent, it is unclear whether the *in vivo* effects are attributable to quercetin itself, or to its metabolites.

Quercetin and its methylated metabolite isorhamnetin exhibit endothelium-independent vasodilator effects *in vitro* [12, 39]. Therefore, a potential mechanism that might contribute to the *in vivo* antihypertensive effects of quercetin observed in the present study is a direct vasodilator action. In contrast, the glucuronidated and sulfated metabolites have no direct vasodilator effect in the rat aorta [28]. In any case, quercetin had no effect on angiotensin converting enzyme (ACE) activity [1], ruling out this potential target in the antihypertensive effect.

According to the hypothesis that reactive oxygen species play a pathophysiological role in the development of essential hypertension, a reduction in the markers of oxidative stress induced by quercetin in animal models could be a mechanism involved in the antihypertensive effect. The most plausible explanation would be that *via* either a direct superoxide anion scavenger effect or by inhibition of superoxide generating enzymes quercetin might increase the bioavailability and the biological activity of nitric oxide [38]. The apparent lack of changes in oxidative markers in hypertensive patients treated with quercetin (see below) [13]) seems to argue against this possibility in humans. Direct renal effects might also play some role in the antihypertensive effect of quercetin [2, 31]. For instance, the downregulation of ENaC in the kidney may also contribute to the blood pressure lowering effect in Dahl salt-sensitive hypertension [2].

Concerning the mechanism by which quercetin prevented end-organ damage associated with hypertension, as occurs with current antihypertensive drugs, the reduction of blood pressure induced by quercetin is probably the main mechanism accounting for diminished cardiac hypertrophy, renal injury or vascular remodelling. However, quercetin can interfere with multiple signalling pathways, especially protein kinases, matrix metalloproteinases and other inflammatory molecules, which may interfere with cell growth and apoptosis, affecting end organ damage independently of the changes in blood pressure [35, 37, 40, 43].

Clinical trials

Several clinical trials have demonstrated a reduction in blood pressure and an improvement in endothelial function after the administration of flavonoid-containing foods, such as tea, cocoa or fruit juices, in mild to moderate hypertensive patients [41, 45].

A clinical trial analyzing the effects of pure quercetin on cardiovascular risk factors was carried out in healthy volunteers [7]. Quercetin intake (1 g/day) in this study was 10- to 50-fold greater than the dietary intake associated with lower coronary heart disease mortality on the basis of epidemiologic studies. Subjects consuming quercetin-containing capsules for 28 days had plasma quercetin concentrations approximately 23-fold higher than those of subjects consuming the control capsules. However, despite the marked increases in quercetin concentrations in plasma, no significant modifications of selected risk factors for heart disease were observed, including blood pressure, resting heart rate, plasma cholesterol or triglyceride levels, and thrombogenic risk factors like platelet aggregation and platelet thromboxane B₂ production [7]. Nonetheless, this lack of effect in healthy humans may not be surprising given the lack of effect of quercetin in healthy animals as described above.

To our knowledge, only one study has analyzed the effects of quercetin in human essential hypertensives. In this study [13], men and women with prehypertension and stage 1 hypertension were enrolled in a randomized, double-blind, placebo-controlled, crossover study to test the efficacy of 730 mg quercetin/day for 28 days vs. placebo. Blood pressure was not significantly altered in prehypertensive patients after quer-

etin supplementation. In contrast, reductions in systolic, diastolic and mean arterial pressures were observed in stage 1 hypertensive patients after quercetin treatment. In contrast with the animal studies discussed above, indices of oxidant stress measured in the plasma and urine were not affected by quercetin. It should be stressed that the amount of quercetin administered to the patients is far greater than the regular quercetin intake of a normal diet.

Conclusions and perspectives

Quercetin has been shown to induce a progressive, sustained and dose-dependent reduction in blood pressure when given chronically in the most common rodent models of hypertension, independently of the status of the renin-angiotensin system, oxidative stress or nitric oxide. However, it had no effect in control normotensive animals in any of the published studies. Quercetin also prevented morphological and functional changes in the heart, vessels and kidney, and the increased production of reactive oxygen species associated with hypertension in rat models. Reductions in systolic, diastolic and mean arterial pressures were observed in stage 1 hypertensive patients after a high dose quercetin treatment in a randomized, double-blind, placebo-controlled, crossover study.

Since elevated blood pressure is the major cause of stroke, and since it is also an important risk factor for ischemic heart disease, we propose that the blood pressure-lowering effect of quercetin could be an important factor contributing to the reduced risk of myocardial infarction and stroke observed with flavonoid-rich diets and possibly with fruit and vegetable-rich diets.

Acknowledgments:

This research is supported by a joint Grant from Comisión Interministerial de Ciencia y Tecnología (CICYT) AGL2007-66108. Financial support was also obtained by CICYT grants (SAF2005-03770 and SAF 2008-03948 to F.P.V.), from Junta de Andalucía, Proyecto de Excelencia (P06-CTS-01555) and by the Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III (Red HERACLES RD06/0009) to J.D., from Junta de Castilla y León (SA003A07) and through the Consortium FUN-C-FOOD (CSD2007-00063) funded by the Consolider-Ingenio 2010 Programme to C.S-B.

The authors declare no conflicts of interest.

References:

1. Actis-Goretta L, Ottaviani JI, Fraga CG: Inhibition of angiotensin converting enzyme activity by flavanol-rich foods. *J Agric Food Chem*, 2006, 54, 229–234.
2. Aoi W, Niisato N, Miyazaki H, Marunaka Y: Flavonoid-induced reduction of ENaC expression in the kidney of Dahl salt-sensitive hypertensive rat. *Biochem Biophys Res Commun*, 2004, 315, 892–896.
3. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA et al.: A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med*, 1997, 33, 1117–1124.
4. Bauersachs J, Widder JD: Endothelial dysfunction in heart failure. *Pharmacol Rep*, 2008, 60, 119–126.
5. Bieger J, Cermak R, Blank R, de Boer VC, Hollman PC, Kamphues J, Wolffram S: Tissue distribution of quercetin in pigs after long-term dietary supplementation. *J Nutr*, 2008, 138, 1417–1420.
6. Carlstrom J, Symons JD, Wu TC, Bruno RS, Litwin SE, Jalili T: A quercetin supplemented diet does not prevent cardiovascular complications in spontaneously hypertensive rats. *J Nutr*, 2007, 137, 628–633.
7. Conquer JA, Maiani G, Azzini E, Raguzzini A, Holub BJ: Supplementation with quercetin markedly increases plasma quercetin concentration without effect on selected risk factors for heart disease in healthy subjects. *J Nutr*, 1998, 128, 593–597.
8. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB: General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*, 2008, 117, 743–753.
9. Duarte J, Galisteo M, Ocete MA, Pérez-Vizcaino F, Zarzuelo A, Tamargo J: Effects of chronic quercetin treatment on hepatic oxidative status of spontaneously hypertensive rats. *Mol Cell Biochem*, 2001, 221, 155–160.
10. Duarte J, Jimenez R, O'Valle F, Galisteo M, Perez-Palencia R, Vargas F, Perez-Vizcaino F et al.: Protective effects of the flavonoid quercetin in chronic nitric oxide deficient rats. *J Hypertens*, 2002, 20, 1843–1854.
11. Duarte J, Pérez-Palencia R, Vargas F, Ocete MA, Pérez-Vizcaino F, Zarzuelo A, Tamargo J: Antihypertensive effects of the flavonoid quercetin in spontaneously hypertensive rats. *Br J Pharmacol*, 2001, 133, 117–124.
12. Duarte J, Perez-Vizcaino F, Zarzuelo A, Jimenez J, Tamargo J: Vasodilator effects of quercetin on isolated rat vascular smooth muscle. *Eur J Pharmacol*, 1993, 239, 1–7.
13. Edwards RL, Lyon T, Litwin SE, Rabovsky A, Symons JD, Jalili T: Quercetin reduces blood pressure in hypertensive subjects. *J Nutr*, 2007, 137, 2405–2411.
14. Emura K, Yokomizo A, Toyoshi T, Moriwaki M: Effect of enzymatically modified isoquercitrin in spontaneously hypertensive rats. *J Nutr Sci Vitaminol (Tokyo)*, 2007, 53, 68–74.
15. Endemann DH, Schiffrin EL: Endothelial dysfunction. *J Am Soc Nephrol*, 2004, 15, 1983–1992.
16. Frochlich E, Apstein C, Chobanian A, Devereux R, Dustan H, Dzau V, Fauad-Tarazi F et al.: The heart in hypertension. *N Engl J Med*, 1993, 327, 998–1008.
17. Galisteo M, García-Saura MF, Jiménez R, Villar IC, Wangenstein R, Zarzuelo A, Vargas F et al.: Effects of quercetin treatment on vascular function in deoxycorticosterone acetate-salt hypertensive rats. Comparative study with verapamil. *Planta Med*, 2004, 70, 334–341.
18. Galisteo M, García-Saura MF, Jiménez R, Villar IC, Zarzuelo A, Vargas F, Duarte J: Effects of chronic quercetin treatment on antioxidant defence system and oxidative status of deoxycorticosterone acetate-salt-hypertensive rats. *Mol Cell Biochem*, 2004, 259, 91–99.
19. García-Saura MF, Galisteo M, Villar IC, Bermejo A, Zarzuelo A, Vargas F, Duarte J: Effects of chronic quercetin treatment in experimental renovascular hypertension. *Mol Cell Biochem*, 2005, 270, 147–155.
20. He FJ, Nowson CA, MacGregor GA: Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. *Lancet*, 2006, 367, 320–326.
21. Hertog MG, Feskens EJ, Hollman PC, Katan MB, Kromhout D: Dietary antioxidant flavonoids and risk of coronary heart disease: The Zutphen elderly study. *Lancet*, 1993, 342, 1007–1011.
22. Hertog MG, Kromhout D, Aravanis C, Blackburn H, Buzina R, Fidanza F, Giampaoli S et al.: Flavonoid intake and long-term risk of coronary heart disease and cancer in the seven countries study. *Arch Intern Med*, 1995, 155, 381–386.
23. Huxley RR, Neil HA: The relation between dietary flavonol intake and coronary heart disease mortality: a meta-analysis of prospective cohort studies. *Eur J Clin Nutr*, 2003, 57, 904–908.
24. Jalili T, Carlstrom J, Kim S, Freeman D, Jin H, Wu TC, Litwin SE et al.: Quercetin-supplemented diets lower blood pressure and attenuate cardiac hypertrophy in rats with aortic constriction. *J Cardiovasc Pharmacol*, 2006, 47, 531–541.
25. Kannel WB: Risk stratification in hypertension: New insights from the Framingham Study. *Am J Hypertens*, 2000, 13, 3S–10S.
26. Kojda G, Harrison D: Interactions between NO and reactive oxygen species: pathophysiological importance in atherosclerosis, hypertension, diabetes and heart failure. *Cardiovasc Res*, 1999, 43, 562–571.
27. Kühnau J: The flavonoids. A class of semi-essential food components: their role in human nutrition. *World Rev Nutr Diet*, 1976, 24, 117–191.
28. Lodi F, Jimenez R, Moreno L, Kroon PA, Needs PW, Hughes DA, Santos-Buelga C et al.: Glucuronidated and sulfated metabolites of the flavonoid quercetin prevent endothelial dysfunction but lack direct vasorelaxant effects in rat aorta. *Atherosclerosis*, 2008, in press.
29. Machha A, Achike FI, Mustafa AM, Mustafa MR: Quercetin, a flavonoid antioxidant, modulates endothelium-derived nitric oxide bioavailability in diabetic rat aortas. *Nitric Oxide*, 2007, 16, 442–447.
30. Machha A, Mustafa MR: Chronic treatment with flavonoids prevents endothelial dysfunction in spontaneously hypertensive rat aorta. *J Cardiovasc Pharmacol*, 2005, 46, 36–40.

31. Mackraj I, Govender T, Ramesar S: The antihypertensive effects of quercetin in a salt-sensitive model of hypertension. *J Cardiovasc Pharmacol*, 2008, 51, 239–245.
32. Manach C, Scalbert A, Morand C, Remesy C, Jimenez L: Polyphenols: Food sources and bioavailability. *Am J Clin Nutr*, 2004, 79, 727–747.
33. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G et al.: ESH-ESC Task Force on the Management of Arterial Hypertension. 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. *J Hypertens*, 2007, 25, 1751–1762.
34. Margetts BM, Beilin LJ, Vandongen R, Armstrong BK: Vegetarian diet in mild hypertension: a randomised controlled trial. *BMJ*, 1986, 293, 1468–1471.
35. Middleton E Jr, Kandaswami C, Theoharides TC: The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. *Pharmacol Rev*, 2000, 52, 673–751.
36. Mulvany MJ, Baumbach GL, Aalkjaer C, Heagerty A, Orsgaard N, Schiffrin EL, Heistad DD: Vascular remodeling. *Hypertension*, 1996, 28, 505–506.
37. Perez-Vizcaino F, Bishop-Bailley D, Lodi F, Duarte J, Cogolludo A, Moreno L, Bosca L et al.: The flavonoid quercetin induces apoptosis and inhibits JNK activation in intimal vascular smooth muscle cells. *Biochem Biophys Res Commun*, 2006, 346, 919–925.
38. Perez-Vizcaino F, Duarte J, Andriantsitohaina R: Endothelial function and cardiovascular disease: effects of quercetin and wine polyphenols. *Free Radic Res*, 2006, 40, 1054–1065.
39. Perez-Vizcaino F, Ibarra M, Cogolludo AL, Duarte J, Zaragoza-Arnaez F, Moreno L, Lopez-Lopez JG, Tamargo J: Endothelium-independent vasodilator effects of the flavonoid quercetin and its methylated metabolites in rat conductance and resistance arteries. *J Pharmacol Exp Ther*, 2002, 302, 66–72.
40. Qin TC, Chen L, Yu LX, Gu ZL: Inhibitory effect of quercetin on cultured neonatal rat cardiomyocytes hypertrophy induced by angiotensin. *Acta Pharmacol Sin*, 2001, 22, 1103–1106.
41. Reshef N, Hayari Y, Goren C, Boaz M, Madar Z, Knobler H: Antihypertensive effect of sweetie fruit in patients with stage I hypertension. *Am J Hypertens*, 2005, 18, 1360–1363.
42. Rivera L, Morón R, Sánchez M, Zarzuelo A, Galisteo M: Quercetin ameliorates metabolic syndrome and improves the inflammatory status in obese Zucker rats. *Obesity (Silver Spring)*, 2008, 16, 2081–2087.
43. Saeed SA, Connor JD, Imran, Quadri J, Tasneem S, Ahmed S, Mesaik MA, Choudhary MI: Inhibitors of phosphatidylinositide 3-kinase: effects on reactive oxygen species and platelet aggregation. *Pharmacol Rep*, 2007, 59, 238–243.
44. Sanchez M, Galisteo M, Vera R, Villar IC, Zarzuelo A, Tamargo J, Perez-Vizcaino F, Duarte J: Quercetin down-regulates NADPH oxidase, increases eNOS activity and prevents endothelial dysfunction in spontaneously hypertensive rats. *J Hypertens*, 2006, 24, 75–84.
45. Taubert D, Roesen R, Lehmann C, Jung N, Schömig E: Effects of low habitual cocoa intake on blood pressure and bioactive nitric oxide: a randomized controlled trial. *JAMA*, 2007, 298, 49–60.
46. Williams RJ, Spencer JP, Rice-Evans C: Flavonoids: antioxidants or signalling molecules? *Free Radic Biol Med*, 2004, 36, 838–849.
47. Yamamoto Y, Oue E: Antihypertensive effect of quercetin in rats fed with a high-fat high-sucrose diet. *Biosci Biotechnol Biochem*, 2006, 70, 933–939.
48. Zatz R, Baylis C: Chronic nitric oxide inhibition model six years on. *Hypertension*, 1998, 32, 958–964.

Received:

October 16, 2008; in revised form: January 12, 2009.