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Bergamot Polyphenols: Pleiotropic Players in the Treatment of Metabolic Syndrome

Micaela Gliozzi, Ross Walker and Vincenzo Mollace*

Institute of Research for Food Safety & Health (IRC-FSH), University of Catanzaro "Magna Graecia", Catanzaro, Italy

***Corresponding author:** Vincenzo Mollace, Campus Universitario di Germaneto, Viale Europa, 88100 Catanzaro, Italy, Tel: 00393274758007; E-mail: mollace@libero.it

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Abstract

Metabolic syndrome (MS) represents a clustering of risk factors related to an elevated incidence of cardiovascular disease (CVD) and type 2 diabetes. Despite the possibility of multiple pharmacological interventions to treat metabolic changes related to MS, these therapeutic strategies often exhibit several side effects and inadequately prevents CVD. Among nutraceutical compounds presenting potential efficacy in this regard, bergamot polyphenols, via their multi-action properties, have been shown to positively modulate several mechanisms involved in MS suggesting their benefits as therapy. The purpose of this review is to discuss the beneficial effects of bergamot polyphenols providing a new therapeutic approach in the treatment of MS.

Keywords: Metabolic syndrome; Bergamot polyphenols; Hyperlipidemia; Cardiovascular disease

Introduction

Metabolic syndrome (MS) is a clustering of numerous age-related metabolic abnormalities that together increase the risk for cardiovascular disease (CVD) and type 2 diabetes. They include obesity which is thought to be a cause rather than a consequence of metabolic disturbance, high blood pressure, high blood glucose and dyslipidaemia [1]. In particular, increased concentrations of low-density lipoprotein cholesterol (LDL-C), total blood cholesterol (TC) and triglycerides (TG) comprise the main pathogenic risk profile. Moreover, conditions of insulin resistance such as impaired glucose tolerance or "prediabetes" are often accompanied by low levels of high-density lipoprotein cholesterol (HDL-C) which amplify the risk of CVD [2].

Recent studies highlight a relationship between dietary factors and MS, but the characteristics of an optimal diet to prevent or treat MS have yet to be better clarified [3]. Increasing experimental and epidemiological evidence suggests that dietary polyphenols, in particular flavonoids, may play an important role in ameliorating prediabetes due to their multi-action properties in counteracting pathophysiological mechanisms leading to the development of MS [4].

The health benefits of polyphenols are generally attributed to both non-specific mechanisms, dependent upon a broad anti-oxidant activity, and more specific mechanisms [5]. Indeed, the in vitro activity of polyphenols strongly suggests that their role extends much beyond their ability to limit oxidative processes as they have been also shown to modulate metabolic enzymes, nuclear receptors, gene expression and multiple signaling pathways [6].

Bergamot (Citrus bergamia) is an endemic plant of the Calabrian region in Southern Italy with a unique profile of flavonoid and flavonoid glycosides present in its juice and albedo, such as neoeriocitrin, neohesperidin, naringin, rutin, neodesmin, rhoifolin and poncirin. Bergamot differs from other Citrus fruits not only because of the composition of its flavonoids, but also because of their particularly high content [7,8]. Among them naringin, present also in grapefruit, has already been reported to be active in animal models of atherosclerosis [9], while neoeriocitrin and rutin have been shown to inhibit LDL oxidation [10]. Importantly, bergamot juice is rich in neohesperidosides of hesperetin and naringenin, such as melitidine and brutieridine. These flavonoids possess a 3-hydroxy-3-methylglutaryl moiety with a structural similarity to the natural substrate of HMG-CoA reductase and exhibit statin-like proprieties [11].

Recently, the therapeutic potential of bergamot derivatives has also been investigated in human studies [12-14]. Here, we provide a brief overview of these findings underlying the mechanism of action hypothesised for bergamot-derived polyphenols which suggests new and important insights in MS therapy.

Bergamot polyphenolic fraction (BPF) and MS

The National Cholesterol Education Program Adult Treatment Panel III (NCEPATP III) clinical definition of MS requires the presence of at least three out of five risk factors which include abdominal obesity, high plasma triglycerides, low plasma HDL, high blood pressure and high fasting plasma glucose [15].

Experimental and epidemiological studies have demonstrated that bergamot polyphenolic fraction (BPF) ameliorates serum lipemic profile and normalizes blood pressure in patients suffering from MS. Previous scientific evidence obtained with Citrus flavonoids and other non-nutritive constituents of Citrus fruits, explain their beneficial effects and to further clarify some mechanisms involved in MS [12,13,16].

Indeed, it has been demonstrated that Citrus peel extracts, rich in pectins and flavonoids, cause lowering of cholesterol levels by modulating hepatic HMG-CoA levels [9,17,18] and bergamot juice has been shown to enhance the excretion of fecal sterols in rats [19] thereby contributing to its hypolipemic and hypoglycemic effect subsequently found in patients on BPF treatment.

A special contribution to the hypolipemic response of BPF seems to be related to the modulatory properties of naringin and neohesperidin. Indeed, evidence exists that dietary hesperetin reduces hepatic TG accumulation and this is associated with the reduced activity of TG synthetic enzymes, such as phosphatidate phosphohydrolase [20]. In addition, in vitro studies suggest that naringenin and hesperein decrease the availability of lipids for assembly of apoB-containing lipoproteins, an effect mediated by reduced activities of acyl CoA: cholesterol acyltransferases (ACAT) [21].

Importantly, BPF is rich in brutieridine and melitidine, which are 3-hydroxy-3-methylglutaryl derivatives of hesperetin and naringenin, respectively. In addition, the classical glycoside derivative of naringenin, which is naringin, has been shown to inhibit hepatic HMG-CoA reductase [22]. Therefore it is likely that melitidine and brutieridine in concert with naringin and other flavonone glycosides might be responsible for the striking potency of BPF in reducing cholesterol levels.

The recent finding that eNOS knockout mice present a cluster of cardiovascular risk factors comparable to those of MS suggests that defects in eNOS function may cause human MS and that its dysfunction induces an impaired vasodilation mediated by reduction of NO levels [15,23,24].

The unifying hypothesis of eNOS-reduced activity and subsequent endothelial dysfunction caused by oxidative stress and inflammatory processes observed in MS might justify the reduced NO-dependent vasodilation.

Well documented antioxidant and anti-inflammatory mechanisms regulated by Citrus flavonoids, such as increasing superoxide dismutase and catalase activities and protection of plasma vitamin E [25], may attenuate overproduction of oxygen reactive species in the vascular wall thereby restoring the imbalanced endothelial function, as also observed in patients under BPF treatment (Figure 1).

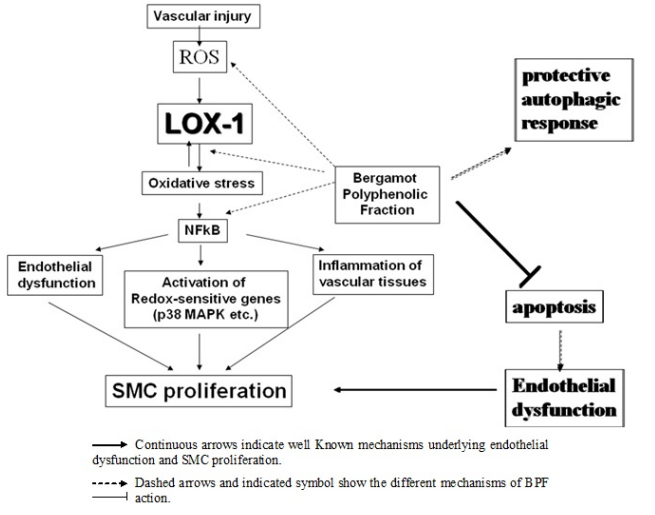

Figure 1: Proposed mechanism of BPF-induced pleiotropic vasoprotective effect

Another potential benefit of BPF is related to its hypoglycemic activity. Among the few mechanistic studies on the hypoglycemic effects of flavonoids, it has been shown that naringenin, similarly to other polyphenols, significantly increased AMP kinase (AMPK) activity and glucose uptake in muscle cells and liver [26,27]. The hypoglycaemic activity of insulin sensitivity and glucose tolerance has been shown in animal models of MS [28].

On the basis of these findings, supplementing an ordinary diet with BPF represents a phytotherapeutic approach for the better management of prediabetic states in patients with MS by lowering plasma cholesterol and lipids, ameliorating NO-dependent vasoreactivity and by reducing blood glucose [12] (Figure 1).

Potential benefits of BPF in reducing statin dosage

A meta-analysis of placebo-controlled "standard dose" statin trials show a reduction in cardiovascular mortality averaging 20% and a decrease in major cardiovascular events by approximately 25% [13]. Treatment with high-dose statins was shown to reduce the morbidity by 36%, and a reduction of cardiovascular events up to 40% [13]. Despite the significant clinical benefits provided by statins, many patients, in particular those with diabetes or metabolic syndrome do not achieve their recommended LDL-C and HDL-C target goals with statins alone [13]. Moreover, statins have been reported to cause dose-related side effects, the more serious including liver disease or severe myopathy, in up to 22% of patients eligible for this therapeutic approach [13]. This limits the use of statins and suggests the need for alternative and/or supplementary therapeutic approaches.

The enriched composition of BPF in naringin, neoeriocitrin and neohesperidin produces antilipidemic effects in patients with pure or mixed hypercholesterolemia. This effect is a prominent reduction of both total cholesterol and LDL-C and a moderate increase of HDL-C, thus suggesting a potential benefit in reducing cardiometabolic risk. Given the structural similarity to HMG-CoA reductase substrate brutieridine and melitidine have been shown to possess statin-like properties, by selective inhibition of HMG-CoA reductase [29]. The direct action of BPF on HMG-CoA reductase activity has been confirmed by a significant reduction of the end product of HMG-CoA reductase activity, mevalonate (MVA), detected in the urine of patients under BPF treatment [12,13,16,30].

This effect of BPF suggests a potential benefit of attenuating statin-induced side effects through the co-administration of bergamot polyphenols and low dose of statins. Indeed, on the basis of this hypothesis, it has been demonstrated that BPF, given orally in patients with mixed hyperlipidemia, allows the reduction of daily dosage for rosuvastatin but maintain target lipid values of hypolipemic treatment. On the other hand, reduction of serum cholesterol in patients taking both BPF and rosuvastatin is accompanied by a significant reduction in triglyceride levels, an effect which has not been found with rosuvastatin alone, and by a further elevation of HDL-C thus suggesting a synergistic role of BPF in statin-induced hypolipidemic response.

The significant synergism of BPF with rosuvastatin is also demonstrated by the further reduction seen in urinary MVA in patients after treatment with both BPF and lower doses of rosuvastatin [13].

The hypolipidemic response found in patients undergoing BPF treatment seems to be related to the modulatory properties of naringin and neo-hesperidin. Indeed, dietary hesperetin not only reduces the hepatic TG accumulation but also reduces apoB levels [31] which together with an enhanced expression of the LDL receptor may

explain, at least in part, the hypocholesterolemic properties of BPF. Naringenin shows to act at multiple levels in regulating lipid metabolism in patients [32] probably increasing hepatic fatty acid oxidation through a peroxisome proliferator-activated receptor (PPAR) gamma coactivator alpha/PPARalpha-mediated transcription program, preventing sterol regulatory element-binding protein 1c-mediated lipogenesis in both liver and muscle by reducing fasting hyperinsulinemia and decreasing hepatic cholesterol and cholesterol ester synthesis. Moreover, naringin is able to reduce both VLDL-derived and endogenously synthesized fatty acids, preventing muscle triglyceride accumulation and, finally, improving overall insulin sensitivity and glucose tolerance [33].

In addition to their lipid-lowering properties, BPF synergizes with statins to enhance antioxidant activity. In particular, it has been shown that statins display cholesterol-independent pleiotropic effects including antioxidative actions such as suppression of NADPH oxidase expression and activity [34,35], induction of antioxidant enzymes (SOD1, SOD3, and GPx) [36,37], prevention of eNOS uncoupling [34,35], and enhancement of eNOS expression and activity. All these beneficial properties are limited by well known side effects of statins; however, this restriction may be overcome by the use of a combination therapy with antioxidants [38]. Indeed, in patients with mixed hyperlipidemia, it has been observed that BPF administration enhances antioxidant properties of rosuvastatin inducing a significant reduction of oxidative stress in circulating polymorphonucleates (PMC). In particular, malonyldialdheyde (MDA) levels, a viable marker of lipid peroxidation, in PMC decreases when adding BPF to rosuvastatin [12,13].

Moreover, the measured oxidative stress in the PMC of patients with hyperlipidemia, treatment with rosuvastatin or BPF alone reduced the expression of LOX-1 and Phospho PKB and these effects were enhanced in patients taking both compounds [13].

Since both LOX-1 and phospho PKB expression are relevant biomarkers of vascular cell viability, it is likely that an additional vaso-protective effect when using both statins and BPF may be expected in patients with high or moderate cardiometabolic risk [13].

Effects of BPF on liver steatosis and LDL particles

The effect of BPF in lowering cholesterol, triglycerides and glucose in patients suffering from MS is accompanied by reduction of LDL-C and elevation of HDL-C as described above. This beneficial effect in the lipemic profile of patients suffering MS is also characterized by prominent re-arrangement of lipoprotein particle profile found following 120 day BPF treatment. Indeed, BPF reduced small size, atherogenic LDL particles. This effect, combined with reduction of inflammatory biomarkers, suggests that BPF leads to an attenuation of atherogenic risk in patients with MS [14].

The mechanism of such an effect in lipoprotein particle size is not clear to date. The combined effect of BPF in reducing both cholesterol and triglycerides may well explain lipoprotein re-arrangement due to prolonged BPF treatment. Indeed, an increased clearance of TG-rich lipoprotein particles makes these particles became better substrates for lipoprotein lipase. This would be expected to result in decreased levels of large and medium-sized VLDL and perhaps even intermediate density lipoprotein (IDL), which contains roughly equal amounts of TG and cholesterol [14].

The increased cascade of VLDL to IDL to LDL would result in increased numbers of large LDL particles and provide surface constituents for the formation of large HDL. The formation of small LDL is mainly due to cholesteryl ester transfer protein-mediated exchange of VLDL-TG for LDL cholesterol ester and the subsequent hydrolysis of LDL-TG. The decrease in large and medium VLDL diminishes the cholesteryl ester transfer protein-mediated exchange, decreasing the formation and number of small LDL particles. A similar mechanism may also explain the decrease in the number of medium-sized HDL particles.

Recently, it has been shown that MS is associated with non alcoholic fatty liver disease (NAFLD) [14].

The improvement of hepatocyte function found in patients with MS and associated NAFLD after taking BPF might also contribute in the amelioration in lipoprotein profile thereby attenuating cardiometabolic risk [14].

Some studies have demonstrated that insulin resistance almost universally induces NAFLD [39,40]. It is known that this condition may precede the development of cardiovascular disease [41,42]. To confirm the connection between NAFLD and atherosclerosis, carotid atherosclerosis has recently been detected in patients with NAFLD [43]. Pathogenetic mechanisms responsible for that include an increased lipolysis and increased delivery of free fatty acids to the liver [44]. The improvement of steato test and hepatorenal index in patients with MS and NAFLD following BPF treatment gives a quantitative estimation of steatosis and leads to the conclusion that BPF improves both liver function and signs of chronic liver inflammation, as confirmed by reduction of TNF-α and CRP [14].

Mild to moderate elevations of serum aminotransferases (ALT and AST) found in BPF-treated patients subjects at baseline represents the most common abnormality found in patients with NAFLD. Their serum levels were significantly reduced after BPF, thereby confirming data obtained with steato test and hepatorenal index.

The mechanism of the hepato-protective effect of BPF still remains to be elucidated. However, evidence shows that BPF acts as a cytoprotective agent in liver of rats administered an high cholesterol diet [30,45]. The probable explanation is related to BPF BPF activities in oxidative inflammation and changes in hepatocyte membrane permeability probably via stabilization of the hepatocyte membrane structure, thereby preventing toxins from entering the cells. In addition, other indirect cytoprotective effect may be due to the modulation of hepatic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) levels, possibly by binding bile acids and increasing the turnover rate of blood and liver cholesterol [46-50], and to the enhancement in the excretion of fecal sterols. As mentioned above, the hypolipidemic response found in patients undergoing BPF treatment may be related to the modulatory properties of naringin and neo-hesperidin, via inhibition of hepatic TG accumulation. Thus, BPF polyphenolic components, through different mechanisms reduce liver accumulation of fat thereby producing an overall improvement of liver function.

Effects of BPF in a balloon injury model

It has been demonstrated that bergamot-derived polyphenols are able to antagonize smooth muscle cell (SMC) proliferation and neointima formation in rat carotid artery subsequent to balloon injury. This effect is clearly related to the antioxidant activity of polyphenols,

as shown by the significant reduction of nitrated tyrosine staining into injured blood vessels, an action due to the reduced generation of peroxynitrite, a powerful oxidant free radical. Moreover, BPF prevented balloon injury-related overexpression of LOX-1, the receptor for oxidized-LDL (oxyLDL), underling the imbalance of redox status of arterial blood vessels [51], thereby leading to SMC proliferation. Peroxynitrite generation is a crucial step in activating proliferation of subintimal SMCs which follows vascular injury; also, LOX-1 expression is involved in this process, which leads to the reactive neointima formation [51].

Oxidative stress and LOX-1 expression are early events in the biochemical changes that can be found in vascular tissue after induction of injury, and restoring antioxidant status by treating rats with BPF reduces restenosis of injured arterial vessels by counteracting free radical formation and LOX-1 expression [16].

In summary, our studies suggest that BPF, a natural antioxidant rich fraction of bergamot (citrus bergamia), inhibits oxidative stress which occurs in injured arteries and modulates both LOX-1 expression and neointima formation. This may be relevant as an alternative approach to conventional anti-atherogenic compounds in the treatment of vascular disorders in which proliferation of vascular SMCs and oxyLDL-related endothelial dysfunction occur [16].

Conclusion

The nutraceutical approach for the management of MS may represent a promising strategy in preventing cardiometabolic risk. In particular, polyphenols used in clinical practice have been shown to target the pathogenesis of diabetes mellitus, MS and their complications and to favourably modulate a number of biochemical and clinical endpoints [52].

Bergamot-deriving polyphenolic fraction has been shown to possess beneficial effects in patients suffering MS as demonstrated by a concomitant amelioration of lipemic and glycemic profile and by an improvement of the impaired endothelium-mediated vasodilation. In addition, in patients with MS and NAFLD, BPF substantially reduces liver steatosis.

All these effects are due to multi-action properties of bergamot derivatives which modulate key signalling proteins involved in the pathogenesis of MS and, on the other hand, directly counteract oxidative stress shedding new light on the potential use of BPF for reducing cardiometabolic risk in patients with MS.

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