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Bergamot Polyphenols: Promising Agents for Health and Wellness

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Summary:

Introduction and purpose: Citrus bergamia, commonly known as bergamot, is a unique plant native to the Calabria region in Italy, prized for its fragrant fruits and versatile applications. Historically utilized for extracting essential oil, bergamot has garnered attention for its therapeutic properties, particularly its Bergamot-derived Polyphenolic Fraction (BPF), which exhibits lipid-lowering, antioxidant, and anti-inflammatory effects. This paper aims to provide a comprehensive summary of existing research on the therapeutic potential of BPF in humans.

Brief description of the state of knowledge: BPF has shown promise in supporting wound healing, alleviating neuropathic pain, and exhibiting antimicrobial properties. Research highlights BPF's role in modulating lipid metabolism, particularly in reducing LDL cholesterol and triglycerides while increasing HDL cholesterol levels. Additionally, BPF demonstrates anti-inflammatory effects, accelerating the recovery process in conditions such as non-alcoholic steatohepatitis (NASH) and potentially influencing pathways involved in cancer cell proliferation and apoptosis. Further studies explore BPF's impact on bone metabolism, erectile dysfunction, and its potential in dermatological applications, particularly in counteracting photoaging.

Conclusions: While existing studies underscore the promising therapeutic effects of BPF in various medical domains, further research is warranted to establish its efficacy and safety for broader clinical use. Continued investigation on a larger scale holds the potential to develop BPF as a valuable physiotherapeutic strategy across diverse medical fields.

Key words: citrus bergamia; bergamot polyphenols; hypercholesterolemia; anti-inflammatory; antioxidant effect; glucose-lowering.

1. Introduction

Citrus bergamia Risso & Poiteau (bergamot) is an endemic plant cultivated along the southern coast of the Calabria region (Italy) [1]. Morphologically, the trees have green, elongated, egg-shaped leaves with serrated edges, similar to those of lemons. They bear star-shaped, small, sweet-smelling flowers, and yield yellow fruits measuring 6-8 cm in length. These fruits are characterized by smooth, yellowish-green peel and a fragrant, sour flesh with a bitter taste [2]. The herbal preparations obtained from C. bergamia are bergamot essential oil (BEO) and bergamot juice (BJ) [3]. Historically, bergamot has been utilized primarily for extracting its essential oil from the fruit peel, which finds extensive application in the perfumery, cosmetic, and pharmaceutical industries [4]. Extensive analysis has revealed the presence of various flavonoids in bergamot juice, including neoeriocitrin, naringin, and neohesperidin, as well as C-glucosides, flavone O-glycosides, and flavanone O-glycosides [3]. Moreover, the oil extracted from bergamot is rich in bergapten, a compound utilized in suntan preparations due to its active melanogenic effect [5]. Beyond its applications in industries, bergamot essential oil (BEO) has been recognized for its therapeutic properties. It is known to support the wound-healing process [6] and alleviate neuropathic pain [7]. Additionally, BEO exhibits antimicrobial properties, inhibiting the growth of various microorganisms through the increased production of reactive oxygen species (ROS), including bacteria, fungi, and dermatophytes [8][9][910][11]. Furthermore, research has highlighted the therapeutic potential of Bergamot-derived Polyphenolic Fraction (BPF). This fraction, due to its lipid-lowering, antioxidant, and anti-inflammatory effects, demonstrates protective properties against cardiotoxicity, metabolic disorders, and atherosclerosis [12]. BPF acts on the regulation of fatty tissue feedback, significantly stimulating weight loss by enhancing the levels of cardioprotective adiponectin, improving leptin and ghrelin levels, insulin sensitivity, and reducing circulating insulin levels. Considering the well-established correlation between dyslipidemia and cardiovascular risk, bergamot exhibits a dose-dependent, homeostatic effect and may synergistically interact with statin administration to modulate the human lipid profile [13]. Dietary supplements containing BPF have been shown to influence adipose tissue, promoting weight loss by enhancing insulin sensitivity and regulating adiponectin, ghrelin, and leptin levels, thus aligning with the lipostatic theory. Furthermore, the concurrent administration of BPF and statins may produce a synergistic effect on lipid metabolism, potentially improving overall cardiovascular health [13].

The subsequent sections of this research paper aim to provide a comprehensive summary of existing studies on the utilization of Bergamot-derived Polyphenolic Fraction for various therapeutic purposes in humans.

2. Methods

This bibliographic study was based on analyzing the published scientific literature since 2014 via search tools for scientific purposes: PubMed and Google Scholar and selecting relevant articles. The following keywords were used: citrus bergamia, bergamot, bergamot polyphenols, bergamot polyphenolic fraction in combination with hypercholesterolemia, anti-inflammatory, physicochemical properties, lowering of lipids, antioxidant effect, and glucose-lowering.

3. Bergamot – derived Polyphenolic Fraction

Bergamot juice is particularly rich in flavanones and flavones belonging to the flavonoids group and is characterized by a unique profile of flavonoids [14]. In this [15] case of study, each flavonoid has been characterized for accuracy on full scan HRMS experimental value but also related to the HRMS/MS (ddMS) fragmentation recognition. This procedure permits to identification of various isobaric flavonoids which would be indistinguishable only with full scan experiments. The classes of flavonoids present naturally in Citrus Bergamia, belong to the flavone and flavanone families[15].

Flavanoids present naturally on Citrus Bergamia

- ✓ Apigenin-6-8-di-C-glucoside
- ✓ Diosmetin-6-8-di-C-glucside
- ✓ Neoeriocitrin
- ✓ Diosmetin-8-C-glucoside
- ✓ Luteolin-7-O-neohesperidoside
- ✓ 4H-1-Benzopyran-4-one
- ✓ 7-dihydroxy-2-(4-hydroxy-3- methoxyphenyl)
- ✓ Naringin
- ✓ EsperetiN-7-O-glucoside
- ✓ Neoesperidin
- ✓ Rhoifolin
- ✓ Diosmin
- ✓ Neodiosmin
- ✓ Eriodictyol-7-O-neohesperidoside-600-O-HMG
- ✓ Diosmetin-7-O-glucoside
- ✓ Melitidin
- ✓ Bruteridin
- ✓ Naringenin-7-O-glucoside-600-O-HMG
- ✓ HEsperetin-7-O-glucoside-600-O-HMG
- ✓ Diosmetin-7-O-neohesperidoside-600-O-HMG
- ✓ Apigenin-7-O-neohesperidioside-600-O-HMG [15]

Flavonoids are soaked up in the small intestine, but a significant part passes into the large intestine, interacting with the intestinal microbiota. The microbiota supports the absorption and bioavailability of flavonoids through hydrolysis and fermentation processes. In the gastrointestinal tract, the resulting metabolites are transported to the liver. The next metabolic steps take place in this organ. Glucuronides are formed in the liver. Due to their properties, these already polarised molecules can be excreted in the bile, in the urine, or directly transported again into the intestinal lumen [12]. Further studies are required to gain a deeper understanding of the pharmacokinetics and bioavailability of Bergamot-derived Polyphenolic Fraction [15].

4. Effects on lipid metabolism

Referring to this scientific work [16] Nauman et al. (2019) collated research papers that tested the correlation between bergamot and lipid metabolism. The paper collected studies [17] [18][19][20][21] whose results claimed, to a greater or lesser extent, that polyphenols were able to raise HDL-C levels and lower triglycerides. It should be noted that the results of the studies are not consistent across the board. It is suspected that the reason for these differences in results is related to the different methodologies of using bergamot in the studies. It should be added that, depending on the studies and the duration of BPF use between 30 days to 6 months, polyphenols were well tolerated. Three of the researchers included in their results an increase in HDL levels up to 4 mg/dl. Various potential mechanisms responsible for these properties of BPF have been considered. One of these is the inhibition of Pancreatic cholesterol ester hydrolase (pCEH). pCEH is an enzyme involved in the hydrolysis of sterol esters to fatty acids and sterols. Another mechanism under consideration concerns the activation of AMPK (adenosine monophosphate-activated protein kinase). It has been noted that narginine, one of the polyphenols in the liver promotes phosphorylation of AMPK in rat studies. Another point of reference in the study is that naringin and neohesperidin, have structural similarities to statins. Statins are substances with proven positive effects on the body's lipid metabolism. They lower bad cholesterol levels. So far, not enough research has been done to confirm the validity of the potential mechanisms listed above. [16].

Research by Mirarchi et al. (2022) has investigated the effect of Bergamot-derived Polyphenolic Fraction on intracellular lipids of liver cells. The results showed that incubation with BPF extract causes a decrease in intracellular lipid content in human hepatocytes, which could potentially be due to an increase in beta-oxidation. It should be added that this study has some limitations because of the instability of BPF at neutral pH values and the fact that about 50% of the BPF extract did not consist of polyphenols. The effects of the study may come from other substances contained in the extract [22]. Another clinical study on bergamot-derived Polyphenol Fraction shows that in a dose-dependent manner (largely variable depending on the purification of the extract) are able to fasting plasma insulin, leptin, leptin/adiponectin ratio, hs-CRP and tumour necrosis factor alpha (TNF-α) [23].

A double-blind placebo-controlled trial lasting 12 weeks was performed by Rondanelli et al. (2021). The scientists investigated whether bergamot phytosome could be used for metabolic management in overweight and obese class I subjects with newly diagnosed mild hypercholesterolemia. 64 Participants were randomized and divided into two groups: those using BPF and a second group with a placebo. Selected subjects had to meet inclusion and exclusion criteria. The exclusion criteria were: diet without supplements affecting lipid metabolism and appetite and subjects who smoked or drank more than two standard alcoholic beverages per day. The inclusion criteria: age, adequate cholesterol level, BMI, not taking medications that may affect lipid metabolism, no history of chronic venous disease, exclusion of liver, thyroid, or renal disease groups, and a non-sedentary lifestyle. After analyzing the data collected at the end of the study, conclusions were drawn that there is strong evidence that BPF provides beneficial effects such as a decrease of visceral adipose tissue and modulation of metabolic alterations [24].

This study performed by Mallace et al. (2019) investigated the effect of Bergamot-derived Polyphenolic Fraction in patients with hyperlipemia and type 2 diabetes mellitus

(2 DM). A randomized, double-blind, placebo-controlled study was carried out in 60 patients. Subjects were divided into three groups receiving: standard BPF or BPF Phyto or placebo. The results of the study are that both groups receiving supplements containing Bergamot-derived Polyphenolic Fraction indicated a significant reduction of triglycerides, LDL cholesterol, and fasting plasma glucose. Also, an effect on the increase of HDL cholesterol was observed. Furthermore, it was additionally demonstrated a significant reduction of small dense atherogenic LDL particles [25]. Bergamot-derived Polyphenolic Fraction has impact on homeostasis including cholesterol, carbohydrate, and fat metabolism regulation. The pharmacological effects of natural preparations based on bergamot flavonoids may affect organisms in a similar way as biguanide derivatives and statins. Bergamot polyphenols can create positive results by AMPK or QR2 activation – signaling/metabolic regulatory proteins, also HMG-Co reductase, and PDE inhibition. Further scientific research into the molecular mechanism of bergamot polyphenols is needed to understand and bring it into general use [26].

5. Antioxidant and anti-inflammatory impact on humans

The definition of inflammation is a response to deviations from homeostasis that cannot be reversed by homeostatic mechanisms alone. Homeostasis and inflammation are described as opposing states of biological systems usually associated with health and disease [27]. Antioxidants are attractive because of their protective role in food and pharmaceutical products against oxidative degradation in the body and pathological processes associated with oxidative stress. The study of the antioxidant properties of plant-derived compounds involves methods that include the mechanism of antioxidant action and focus on the kinetics of antioxidant-mediated reactions [28].

Bergamot derivatives and byproducts have an impact on many chemokines, enzymes, and nuclear factors. The list below shows how many biochemical elements are affected by BPF [29].

CAT	ICAM-1	Il-37	MDA	p38
collagen I/II	IL-1α	IL-38	MIG	P-selectin
ERK	IL-1β	iNOS	miR-21/-146a	SOD
GPx	IL-4	IP-10	NF-κB	VCAM-1
GSH	Il-5	I-TAC	NQO1	
HMOX1	IL-6	JAK/STAT	TIMP-1/2	
hs-CRP	IL-13	MAPKs	TNF-α	
	IL-32	MCP-1	PAI-1	
			PGE2	[29]

The finding of Parafati et al. (2018) is that Bergamot-derived Polyphenolic Fraction shows a significant anti-inflammatory effect on NASH livers in rats, concerning 10-week normocaloric standard chow diet treatment. The authors suggest that BPF supplementation accelerates recovery during the intervention phase. The scientists observed moderately increased Il1b gene expression TNFα and increased levels of Il-6 mRNAs, which are the main pro-inflammatory cytokines typically elevated in NASH. The process is associated with

a moderate increase in anti-inflammatory Il10 mRNA. It was shown that BPF flavonoids induced suppression of pro-inflammatory Il6 and potently boosted the gene expression of anti-inflammatory Il10, which was moderately up-regulated. This suggests that, during diet-induced recovery from NASH, some inflammatory features persist, while BPF reduces inflammation by acting on Il6 and Il10. It was found, increased numbers of mainly Kupffer cells and some lymphocytes, which are immune effector cells. In conclusion, antioxidant and anti-inflammatory supplements such as BPF are strongly accelerated with the recovery process [30].

Several studies have found proof that Bergamot-derived substances can modify the activity of several biological pathways, leading to antiproliferative and proapoptotic effects on cancer cells [31]. For example, the investigation of Navarra et al. (2020) consisted of examining whether bergamot extract will have a protective effect on intestinal carcinogenesis in vivo. In the experiment, rats with the APC mutation were fed with bergamot extract at two different doses for 12 weeks. Results showed a significant dose-related reduction in the colon preneoplastic lesions mucin-depleted foci (MDF). In the experiment, markers of apoptosis and inflammation were determined to see what mechanisms were involved in the process. It was found that rats fed bergamot extract had a greater down-regulation of genes: Arginase1, COX-2, IL-1β, IL-6, IL-10, and iNOS, which are responsible for the regulation of inflammation, than control subjects. In addition, increased up-regulation of p53 and down-regulation of survivin and p21 genes was detected, suggesting increased apoptosis in colon tumours in subjects fed bergamot extract relative to control subjects [32].

Jiang et al. (2023) tested whether bergapten, a polyphenolic substance belonging to the composition of bergamot essential oil, could be a therapeutic agent for CARAS-combined allergic rhinitis and asthma syndrome. In a mice study, Bergapten was shown to attenuate nasal symptoms by reducing the inflammatory response. It has been established that it affects the reduction of the cytokines IL-1β, IL-6, and TNF-α. In addition, effects on: ovalbumin, IL-4, IL-5, IL-10, IL-12, IL-13, IL-17 interferon gamma, FOXP3, and RORγ have been demonstrated. Significant antioxidant and anti-inflammatory activity of Bergapten was confirmed in the study [33].

6. Further beneficial impacts of the Bergamot-derived Polyphenolic Fraction

Bergamot derivatives are not only being investigated for lipid metabolism, antioxidant and anti-inflammatory properties. For example, research is being conducted into the use of BPFs in bone metabolism. WNTs are extracellular proteins that activate various receptors on the cell surface associated with WNT signaling pathways. Several studies have shown that WNT signaling is crucial for bone mass. Neutralization of the bone-specific WNT inhibitor is currently being evaluated as a promising anabolic therapy for patients with osteoporosis [34]. A study by Pujia et al (2018) examined the effects of bergamot polyphenols in bone cell models and showed that RUNX2, β-catenin, ERK 1/2, and intracellular COL1A proteins are up-regulated by exposure to increasing doses of BPF. In addition, the expression of RANKL, which is a known stimulus for increased osteoclast activity, is reduced in these cells, suggesting that BPF decreases RANKL and may play a potential role in bone resorption. The results of the study indicate a potential positive effect of the polyphenol fraction derived from bergamot on osteoblast differentiation and collagen production. BPF also reduces RANKL expression,

suggesting that it may inhibit osteoclastogenesis. Further studies are necessary to validate this study [35].

In another field of scientific research, the effects of Bergamot derivatives on erectile dysfunction (ED) were examined. Erectile dysfunction formerly termed impotence, is defined as the failure to achieve or maintain a rigid penile erection suitable for satisfactory sexual intercourse [36]. Mollace et al (2016) reported on some of the recent improvements in the treatment of erectile dysfunction in diabetic patients using the Bergamot-derived Polyphenolic Fraction. The researchers investigated the effects of BPF alone or in combination with other plant extracts (Epimedium, Tribulus Terrestris) on supporting endothelial function and reactive vasodilation. Conclusions began to be drawn after 120 days of treatment. The results indicated an effect in the treatment of erectile dysfunction by improving overall parameters. BPF counteracts erectile dysfunction in patients with cardiometabolic disorders due to its activity insupportingendothelialfunctionandmodulatingbloodflowinpenilearteriolesindependentlyorwith- other plant extracts with similar properties [37].

Another interesting aspect of the use of bergamot can be found in dermatology. The skin is a natural barrier against sunlight's ultraviolet (UV) radiation. Long-term repetitive exposure to sunlight and related UV radiation may change the skin structure, decreasing collagen production, and promoting photoaging [38]. Nisticò et al. (2016) investigated whether Bergamot-derived Polyphenolic Fraction counteracts photoaging in human keratinocytes [39]. Investigators describe that BPF can inhibit overexpression of inflammatory cytokine biomarker interleukin-1beta (IL-1b), telomere shortening, and decreases in telomerase activity. UVB irradiation causes loss of skin cell viability, whereas, BPF, by using, restores cell viability to control levels in a progressive dose-dependent manner with the least cytotoxicity. BPF also reduces peroxynitrite levels, which is associated with cytotoxic free radicals affecting oxidative stress [39]. These results show the interrelated mechanisms involved in photo-aging, in which BPFs are involved.

7. Conclusions

This comprehensive review underscores the considerable potential for leveraging Bergamot-derived Phenophenolic Fractions across various medical domains. Both animal and human studies collectively indicate the promising health benefits associated with bergamot derivatives. While existing research has elucidated their effects on lipid-lowering, antioxidant, anti-inflammatory, and anti-aging properties, among others, there remains a need for further investigation to firmly establish the utility of this natural supplement in achieving therapeutic objectives. It is hoped that future large-scale research endeavors will not only validate these findings but also pave the way for the development of innovative physiotherapeutic strategies that can positively impact diverse aspects of human health and well-being.

Author Contributions

Conceptualization, D.G; methodology, D.G.; validation, M.Z; investigation, M.W., D.G., and M.Z.; resources, P.Z and W.W. data curation, W.W, and P.Z.; writing-original draft preparation,

A.R, M.T and D.G.; writing-review and editing, M.W., M.Z, and A.R .; visualization, D.G and A.R.; supervision, P.Z.; funding acquisition, not applicable.

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