



## Anti-Inflammatory Effects of Bergamot on the Elderly: A Literature Review

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### Abstract

**Background:** Bergamot (*Citrus bergamia*) is a plant belonging to the Rutaceae family, genus "Citrus". The cultivation of this plant is concentrated almost exclusively in a narrow geographical area of Calabria (Italy), in particular, in the Reggio Calabria area. Bergamot has been heavily used in the cosmetic industry but, in recent years, it is also embracing the medical branch due to its properties and effects, not only cholesterol-lowering but also anti-inflammatory and antioxidant. Like most citrus fruits, Bergamot is also rich in flavonoids (phenolic derivatives with antioxidant capacity) present in the form of more polar glycosidic derivatives, such as neoeriocitrin, naringin and neoesperidin. It is now known how, bergamot extracts could represent the scientific basis for the development of new and alternative strategies, in order to improve the state of health and mitigate inflammatory conditions.

**Objectives:** The goal of our study was to analyze, through the scientific literature, the effects and anti-inflammatory and / or antioxidant properties of Bergamot on humans, particularly in the elderly.

**Methods:** We have drawn up a flow chart and compared the studies in the literature through the use of Pubmed, on the anti-inflammatory effects of Bergamot on humans. In the present study, only 2 scientific studies partially met our objectives.

**Results:** Despite the many scientific articles on Bergamot, to date there are still few those relating to the anti-inflammatory and/or antioxidant effects of Bergamot on humans. We excluded studies performed on mouse models, or in vitro, while others were excluded as they were not full-text.

**Conclusions:** An adequate and balanced diet, especially in the elderly, is an important factor of longevity and health. Inflammatory diseases represent an important risk factor for various chronic diseases, including those typical of old age. Often in the geriatric age there are greater comorbidities that are associated with a progressive loss of lean mass and an increase in fat mass, due to the presence of an inflammatory state. Furthermore, aging could also cause a dysregulation of the immune system and an increase in the production of reactive oxygen species (ROS). All this translates into greater susceptibility to disease and reduced healing capacity in the elderly, in fact, we are talking about the frailty of the elderly. Several classes of drugs, including corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and biologics are used to treat inflammatory disorders. However, they have several side effects, and biological ones are often expensive. To limit the side effects of these, in recent years, attention has shifted to the use of nutraceuticals in the treatment of inflammation. Of the many nutraceuticals we have focused our attention on Bergamot, as the polyphenols contained exert an anti-inflammatory activity both through antioxidant effects and by modulating the fundamental pro-inflammatory genes.

**Keywords:** Bergamot; Bergamot and Inflammation; Inflammation in Older Adults; Anti-Inflammatory Activity of Bergamot

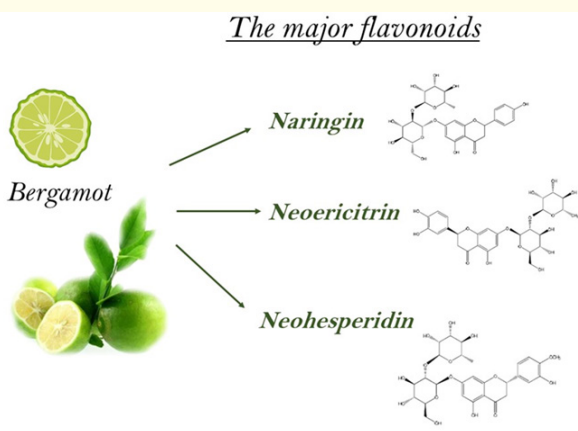
**Introduction**

Bergamot, scientific name *Citrus bergamia*, is a citrus fruit with many properties not only in the nutritional field but also in the field of herbal medicine, aromatherapy and cosmetics. The tree from which this citrus grows is part of the Rutaceae family and of the *Citrus* genus. This plant can grow and bear fruit only in the presence of a specific climate and ideal soil conditions. The area par excellence of its cultivation is an Italian region, in particular, the region of Calabria, where it is called “green gold”, so much so that in 20021 with a European Union decree, it became a D.O.P. (Protected Designation of Origin). Until recently it was a little known citrus fruit, today Calabria has the primacy for the cultivation of bergamot (Figure 1). This citrus fruit resembles orange in size and appearance and is different from the latter due to the smoother skin and light yellow color [1,2].



**Figure 1:** Origin of *Citrus bergamia*: cultivation and fruit.

In the juice of citrus fruits, including bergamot, we find a series of aglycones that give the citrus the typical bitter taste and among these we find the flavanones neohesperidin, naringin, neoerictitrin and smaller amounts of flavones and furanocoumarins (Figure 2). These flavanones, which belong to the class of flavonoids, are compounds present in various citrus fruits, the consumption of which favors beneficial effects on the body’s homeostats [3,4]. It is an edible fruit but due to its bitter taste it is not consumed as a fruit and we find it in the form of juice, drink and essential oil.



**Figure 2:** The major flavonoids in *Citrus bergamia*. Adapted from *Molecules*. 2016 Oct; 21(10): 1273.

From a nutritional point of view, it is a healthy food due to its high content of antioxidants, able to slow down aging and fight free radicals [5,6]. Its cholesterol-lowering properties are able to lower blood cholesterol levels, while the presence of aglycones, such as hesperetin and naringenin, are able to block the enzyme responsible for the endogenous synthesis of cholesterol. In fact, thanks to the presence of these substances, similar to statins, the use of bergamot is also gaining ground in the treatment of hypercholesterolemia in those patients who cannot tolerate statins [7-13]. As the European Atherosclerosis Society (EAS) suggests, patients who have muscle symptoms associated with statins (SAMS) are patients who experience adverse muscle effects due to the use of statins [14,15]. Therefore, there are also cases in which one is intolerant to statins, for which the bergamot juice rich in natural statins, is a valid alternative. Hence the importance of nutraceuticals, a term that indicates the synthesis between nutrition and pharmaceuticals, or substances designed to prevent chronic diseases and which can also be produced synthetically. These nutraceuticals can be taken with foods that are naturally rich in it (eg., fish, rich in omega-3s) or with functional foods (eg., milk enriched with calcium). Today, more and more, there is a greater need for the intake of these functional foods and nutraceuticals because where the effect of the drug creates adverse reactions or is not very effective, it may be useful to recommend the intake of a nutraceutical [16-18].

Bergamot is an important nutraceutical, especially for its cholesterol-lowering power, as it is prescribed for the treatment of hypercholesterolemia [19]. Furthermore, still few studies have highlighted its anticancer, antibacterial and antiviral properties [20,21]. It should be remembered that in addition to the effects mentioned above, Bergamot is also used in aromatherapy to counteract and reduce mood disorders and depression, which often affect the quality of life of the elderly [22]. In this study [23] Xiong M. and colleagues wanted to analyze the effect of inhalation and aromatherapy massage based on bergamot, on the depressive states of elderly subjects, over 60 years of age. The results of the study suggest that aromatherapy inhalation and massage contributed significantly to the depression of the elderly. From a nutritional point of view, bergamot is composed of about 82% water, citric acid, vitamin C, vitamin A and minerals such as: sodium, potassium, magnesium and calcium. It provides about 42 kcal per 100g, 10.7g of carbohydrates (of which 1.4g of fiber), 0.25g of fat (of which 0.031g saturated). Bergamot juice can be taken by both children and the elderly. But despite its important properties there are some contraindications, as increased intake of bergamot juice could alter the gastric mucosa, due to the citric acid content of the citrus fruit. For this reason, it is advisable to avoid consumption if you are suffering from disorders or inflammation of the gastric mucosa. Also due to its effects on blood pressure, increased use is not recommended in people with glaucoma, asthma and bradycardia. Another contraindication concerns the possible interaction with some drugs that would increase skin photosensitivity [24-27]. To date, there are few studies in the literature on the effects, especially the anti-inflammatory ones, of bergamot on humans. More and

more people prefer to treat themselves and/or prevent diseases by using nutraceuticals, food supplements and functional foods, therefore, we strongly believe that in the coming years there will be a greater demand for the latter. The management of the complex patient with multipathology represents one of the greatest healthcare challenges of the future. It should not be forgotten that, especially among elderly people, due to the various comorbidities, there is the need to take more drugs, we are talking about polytherapy, and this often leads to a lack of adherence to drug therapy. A single patient can have numerous risk factors and this requires the daily intake of many drugs. This often results in reduced adherence to therapy and/or medication errors. Generally, the elderly person has a loss of appetite, is malnourished due to improper nutrition, may have a low income that cannot afford dental prostheses or the purchase of all prescribed drugs. Furthermore, in the geriatric age there is a progressive loss of lean mass and an increase in fat mass, especially the abdominal one. On the other hand, we have a part of the elderly population that is better fed than it was in the past, so today there are also obese elderly people. So, if on the one hand we have elderly subjects with sarcopenia (loss of muscle mass and strength), on the other we have obese elderly subjects. All these problems often lead the elderly person to not follow the prescribed therapy and a balanced diet adequately [28]. Hence the need, on the part of the Dietitian, to meet the needs of the elderly, deeming the supplementation of some nutraceuticals with scientifically proven efficacy useful. The purpose of our study is to analyze the anti-inflammatory and antioxidant effects of Bergamot on humans, in particular in the elderly, by evaluating and comparing the studies in the literature, in order to trace useful information for a targeted therapy, not only pharmacological. but also nutritional.

## Materials and Methods

Since polyphenols have numerous beneficial properties, including anti-inflammatory and antioxidant and cholesterol-lowering properties, this review collects what is known about the beneficial effects of bergamot fruit on adult people. The following systemic review was performed through a careful bibliographic search (from 2007 to 2022) in the main scientific databases (PubMed, Scopus, Google Scholar). We used as keywords or combination of words: bergamot, citrus bergamot, citrus bergamia, bergamot and inflammatory, effect anti-inflammatory of bergamot, effect of bergamot, bergamot and older adults. Systematic selection and review of clinical studies written in English and regarding the anti-inflammatory and antioxidant effect of *C. bergamia*, they were performed in accordance with Preferred Reporting Articles for systematic reviews and meta-analyses (PRISMA) [29]. The purpose of the study was to evaluate the properties and the anti-inflammatory and antioxidant effect of bergamot, and its derivatives, on humans and in particular on elderly subjects. Therefore, all studies evaluating the anti-inflammatory and antioxidant effects on humans and not on animal models or cell lines or *in vitro* were included. The articles excluded, because they did not meet the inclusion criteria, were divided into 3 groups: excluded because they were not full-text [30-35], ex-

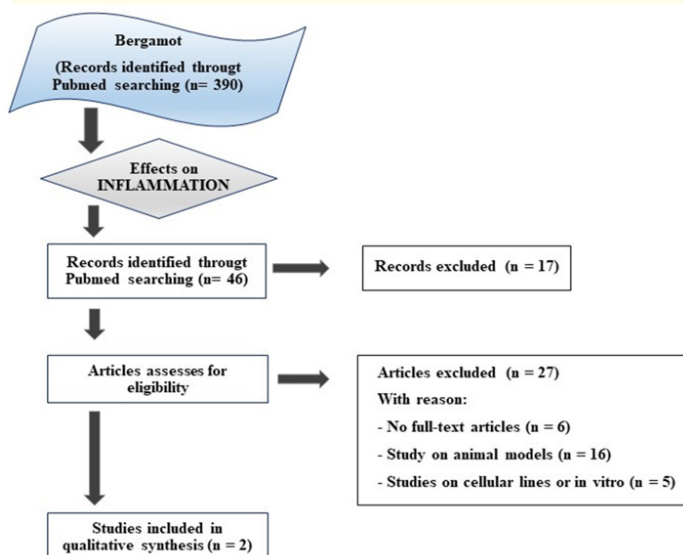
cluded because they were performed on animal models [36-51], excluded because they were performed on cellular lines or *in vitro* [52-56]. In more detail, in their study, Giovanni Enrico Lombardo and colleagues analyzed the anti-inflammatory and antinociceptive activity of bergamot oil. Studying on animal models (rats) they induced the edema of the paw of rats with carrageenan and it was seen that the administration of the fraction BEO deprived of these compounds, induced an inhibition of the edema of the rat paw and also the levels of some inflammatory interleukins (IL-1, IL-6 and TNF- $\alpha$ ). But this study was excluded because it was carried out on rats, while our goal is to search for studies that demonstrate the anti-inflammatory efficacy of bergamots on humans. Furthermore, in the study by Marina Russo and colleagues, the authors isolated flavonoids from bergamot juice by mass spectrometry (MS). The anti-inflammatory effect of these isolated compounds in inhibiting the release of nitric oxide (NO) was studied on mouse J774A.1 macrophages. In this study, the authors used LPS to induce J774A.1 murine macrophages to release NO, thus triggering an immune response. Bergamot juice contains a variety of flavonoids, such as Naringin and Neohesperidin. In particular, the authors found that Naringin inhibited NO release from these LPS-stimulated macrophages, while neohesperidin significantly inhibited NO release.

## Results

This review included a total of 46 scientific studies. We considered all human studies and excluded those on rats or other animal models and *in vitro* studies. Figure 3 represents the flow chart of the study selection process.

### Anti-inflammatory and antioxidant effects of bergamot on humans

It is now known the effect of taking nutraceuticals based on bergamot on the reduction of blood levels of total cholesterol, LDL cholesterol and triglycerides both in patients with metabolic syndrome and with hypercholesterolemia [57-60]. According to the study by Mollace and colleagues [61], bergamot is effective and safe in patients with dyslipidemia. In this study, subjects were divided into 4 groups, including, subjects with hypercholesterolemia treated with bergamot, subjects with hyperlipidaemia treated with bergamot, subjects with metabolic syndrome treated with placebo and subjects with hyperlipidaemia treated with statins. The study results state that subjects treated with bergamot experienced dose-dependent reductions in cholesterol, while subjects with placebo showed no major reductions in cholesterol, and subjects treated with statins showed reductions in LDL cholesterol and triglyceride levels with no effect. adverse to statins. The aim of our study was not to describe the now known cholesterol-lowering effects of bergamot. Despite studies relating to the presence of specific substances present in bergamot that promote the reduction of blood and endogenous cholesterol levels, there are still few studies that demonstrate the mechanisms of action and anti-inflammatory mechanisms of the polyphenols and flavanones contained in bergamot. Of the articles examined, only 2 scientific articles satisfied our



**Figure 3:** PRISMA flow chart showing the process of literature search and studies selection.

research. Table 1 shows the anti-inflammatory effects of bergamot on humans.

In this study, Maria Chiara Cristiano and colleagues wanted to demonstrate the effect of 2 naturally derived compounds, Bergamot essential oil (BEO) and Ammonium glycyrrhizinate (AG). These have been encapsulated in nanosystems for dermal and/or intradermal application in order to demonstrate the anti-inflammatory efficacy of these 2 compounds in the topical treatment of skin disorders. Bergamot essential oil (BEO) would seem to guide the release of Ammonium glycyrrhizinate (AG) for up to 7 days and this demonstrates how this formulation has its effectiveness against inflammatory conditions of the skin, despite a gradual reduction in therapeutic application [62]. In this study [63] Valentina Spigoni and colleagues wanted to study the effect of bergamot on endothelial repair. When a pathogen intervenes or if there are damaged tissues or toxic events, the body initiates a response, namely inflammation. In the case of endothelial damage, mediators are in-

Article	Compound	Main effects	Sample	Posology	Main results
Maria Chiara Cristiano, <i>et al.</i>	Bergamot essential oil (BEO) and Ammonium glycyrrhizinate (AG)	BEO heavily affected the release profile kinetic of AG, thus providing a more controlled and sustained release up to 7 days, suggesting a reduction in application frequency	Man	3.2 ± 0.064 mg mL <sup>-1</sup> and 2.6±0.034 mg mL <sup>-1</sup> of AG and BEO, respectively	treatment of skin disorders
Valentina Spigoni, <i>et al.</i>	Bergamot juice	naringenin-4'-O-glucuronide and hesperetin-7-O-glucuronide were able to modulate inflammation	Three healthy adults	400 ml di BJ (Bergasterol®)	Derived from the metabolism of BJ phenolics in humans, ameliorated SA-induced inflammation in MACs

**Table 1:** Anti-inflammatory effects of bergamot on humans.

involved in trying to renew the endothelial layer, defined as myeloid angiogenic cells (MAC) and their role can be counteracted by the toxic effects of some molecules, such as stearic acid in the case of the study. Since toxic damage agents can negatively affect endothelial repair, the authors analyzed that there are substances that can intervene to repair endothelial damage. On healthy subjects, who had offered themselves as volunteers, bergamot juice was administered, after which the circulating metabolites of the flavanones of the juice were evaluated, both on plasma and urine, after its consumption. Therefore, the authors also evaluated the metabolites on the gene expression of inflammatory markers and on the apoptosis of MACs exposed to stearic acid. It is now known that flavonoids help prevent damage to the body and also have anti-inflammatory and antioxidant effects. By analyzing cell cultures, they saw that a metabolite identified in the study, naringenin-4'-O-glucuronide (H7G), inhibited the gene expression of some inflammatory cytokines such as IL-1β and TNF-α. Furthermore, the authors found that none of the metabolites tested had toxic effects on MACs. To date, few studies have analyzed the anti-inflammatory effect of bergamot but these results help us understand that there are some metabolites of flavanone, derived from bergamot juice, which can reduce

the inflammation induced by stearate acid in MACs. As reported in the study by Nadia Ferlazzo and colleagues [64], the antioxidant activity of bergamot derivatives allows to reduce the production of ROS and lipid peroxidation of the cell membrane, avoiding oxidative damage to DNA. Therefore, the flavonoids present in bergamot would behave by scavenging free radicals, contributing to a greater antioxidant defense. While the anti-inflammatory effect concerned the reduction of inflammatory mediators (TNF-α and IL-1) in animal models. There are still very few studies that demonstrate in detail the effectiveness of using bergamot, or its derivatives, as an alternative therapy against inflammatory states, which unfortunately increasingly affect the elderly population.

**Anti-inflammatory and antioxidant effects of polyphenols**

Given the few studies on the anti-inflammatory and antioxidant effects of Bergamot on humans, in this study we wanted to describe, based on the current literature, in addition to the anti-inflammatory and antioxidant effects of Bergamot, also those of polyphenols. It should be remembered that cellular damage occurs when the cells are no longer able to respond to a stimulus of a different nature, therefore, a response will be activated that will

depend on the nature, duration and severity of that stimulus. If the cell is able to respond to the stimulus it is possible to return to a state of normality. On the contrary, irreversible damage can occur. Cell damage has different mechanisms that act on several essential cellular components [65-67]. As a result of the harmful insults, an increased production or reduced detoxification is observed which will result in an accumulation of Reactive Oxygen Species or ROS (elements of high reactivity that attack or modify fundamental adjacent molecules within the cell) which will lead to oxidative stress. Therefore oxidative stress is due to the excess of ROS in the cell. This situation can lead to the initiation and increase of a state of cell damage or it can contribute to pathological conditions such as cancer, aging and degenerative diseases. ROS, in the case of pathological conditions of noxious stress that activate their production, not only represent a response that is dangerous for the cell itself but also represent important products in the reaction that cells and tissues have towards an invasion of microorganisms during the inflammation [68,69]. Inflammation is a protective response that the body puts in place when some pathogen intervenes, or if there are damaged tissues inside some organ. Thus, oxidative stress and inflammation are closely related physiological events that lead to the onset of a number of chronic diseases, including cardiovascular disease, neurodegenerative disease, alcoholic liver disease, chronic kidney disease, diabetes, cancer and aging [70]. Inflammation begins when the presence of pathogens or damaged cells are recognized by some damage receptors or sensors. The first inflammatory response to intervene is acute inflammation, known as innate or non-specific immunity, because regardless of the cause it will always manifest itself in the same way. While, chronic inflammation guarantees a response against a specific organism and not against another. The inflammatory response begins with the coordinated activation of some signaling pathways that regulate the expression of pro and anti-inflammatory molecules at the damage site, followed by a series of cellular events (margination, rolling, adhesion to the endothelium, transmigration/diapedesis, chemotaxis) up to phagocytosis, or the elimination of the substances that caused the damage. From a clinical point of view, various drugs (NSAIDs, corticosteroids) are used to resolve the inflammation, which can have some side effects. In order to limit these effects, in recent years, attention has shifted towards something alternative and more natural and not strictly pharmacological, something that could be more accepted by the patient than the classic anti-inflammatory drug, namely nutraceuticals. Nutraceuticals are a synthesis between nutrition and pharmaceuticals and have medicinal properties present in various foods from which they can be isolated and purified, and can also be synthetically produced. Nutraceuticals are recommended for the prevention of chronic diseases and are taken with foods that are naturally rich in them and with functional foods enriched with nutraceuticals, for preventive, health and therapeutic purposes [71,72]. Nutraceuticals is the field in which polyphenols are most used, secondary metabolites produced by different parts of plants, rich in anti-inflammatory and antioxidant properties. The antioxidant properties of polyphenyls determine the elimination of ROS and increase the expression of antioxidant genes; while the

anti-inflammatory activity of polyphenols favors the suppression of some pro-inflammatory signaling pathways, such as NFκB. Polyphenols include different classes of heterogeneous compounds (flavonoids, phenolic acids), whose structural characteristics allow these compounds to play an active role against free radicals and pathogens. In particular, in fruit and beverages (such as green tea and red wine, citrus fruits) we find the main source of polyphenols. The flavonoids, water-soluble compounds, generally present in plants as glycosides and/or as aglycones, belong to the family of polyphenols. Several studies show how flavonoids have multiple beneficial effects on humans, for example, reduction of mortality from cardiovascular disease and reduction of platelet aggregation, permeability and capillary fragility [73,74]. Furthermore, some substances possess antiviral, antibacterial and anti-inflammatory activity. Of all the flavonoids present, our attention has focused on those belonging to Bergamot. By carefully analyzing the present literature, unfortunately we have not found enough scientific studies on the anti-inflammatory and antioxidant effects of Bergamot on the adult population, especially on the elderly.

## Conclusions

Understanding the relationship between inflammation and aging is important in achieving longevity. Aging is an age-related process and the presence of an inflammatory state can worsen the health of the subject, especially in the elderly. Today we find two types of elderly: those who have a state of malnutrition and those who have a high calorie intake. In the latter, the increase in adipose tissue with the increased caloric intake initiates inflammation processes and all this can lead to obesity and metabolic syndrome. Adipose tissue is able to secrete some inflammatory cytokines and hormones which, together with oxidative stress, lead to a low-grade inflammatory state up to premature aging. In addition, a sedentary lifestyle, incorrect nutrition, stress, alterations in the intestinal microbiota and physical inactivity, promote greater degeneration of tissues and organs in the elderly. So, how can we intervene from a food point of view, in order to delay aging as much as possible? The figure of the Dietitian could intervene through a balanced and personalized diet. In addition to the Mediterranean diet, important for its anti-inflammatory and antioxidant effects, the ketogenic diet is able to improve the inflammatory state through greater loss of body weight than the Mediterranean diet, but given the age of the elderly subject it is difficult to prescribe a ketogenic diet. In association with the diet, it is necessary to look for other therapeutic strategies to combat aging, for example through the use of nutraceuticals, in particular, polyphenols. Polyphenols are substances that help prevent various diseases, including those related to aging. They help modulate the immune system by reducing pro-inflammatory molecules and oxidative stress. In our scientific study we focused on a particular citrus fruit, namely Bergamot. The purpose of our study was to research in the scientific literature, studies on the anti-inflammatory and antioxidant effect of this citrus fruit, particularly in the elderly population. Unfortunately, there are very few studies in the literature that analyze these effects on humans, especially in the elderly. The studies analyzed, and object of our

study, show that the derivatives of bergamot (bergamot juice and oil) have important anti-inflammatory effects in skin disorders and cell repair. However, despite these 2 scientific studies, the image is still far from complete and requires confirmation from further studies to consider the hypothesis that bergamot and its derivatives can reduce inflammatory states and delay aging as much as possible in elderly subjects.

### Conflict of Interest

The authors declared no conflict of interest.

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