https://doi.org/10.47552/ijam.v16iS2.6198 ISSN No: 0976-5921

Int J. of Ayurvedic Med, "Natural to Synthetic: The Convergence of Traditional Medicine to Modern Medicine" Supplement 2025

Bergamot unleashed: Exploring the multifaceted traits and healing powers of *Citrus bergamia*

Review Article

Gaurav Mude[1]*, Shantilal Singune[1], Raghvendra Dubey[1]

1. Institute of Pharmaceutical Sciences, SAGE University, Indore (MP), India.

Abstract

In this comprehensive review article, the focus is on Bergamot plant, elaborating on its various properties and applications. This article provides a detailed examination of the botanical aspects, significance, and characteristics of Bergamot plant, including its anatomy and chemistry. Additionally, it delves into the pharmacological activity exhibited by Bergamot plant, highlighting its diverse range of effects such as anti-anxiety, wound healing, neuroprotection, anti-depressant, antiproliferative, antibacterial, anticancer, antioxidant, anti-inflammatory, antinociceptive, anti-mycoplasmal, anti-fungal, and antiallodynic properties. The scientific designation of Bergamot, *Citrus bergamia* Risso, indicates its botanical lineage as a hybrid of Citrus limon L and Citrus aurantium, categorising it under the Rutaceae family and Citrus genus. This plant, is known for its unique combination of volatile and non-volatile fractions, each contributing to its therapeutic potential and aromatic profile. Through an exploration of its pharmacological activity and chemical composition, this article offers a comprehensive overview of the multifaceted nature of Bergamot plant, shedding light on its rich botanical heritage and promising therapeutic applications.

Keywords: Botanical aspects, Volatile, Neuroprotection, Pharmacological Activity, *Citrus bergamia Risso*.

Introduction

Citrus bergamia Risso, an intriguing hybrid of *Citrus limon L.* and *Citrus aurantium*, is technically identified as the bergamot citrus fruit. This unique citrus species is classified under the *Rutaceae* family and the Citrus genus. Easily distinguished by its vibrant greenish-yellow peel, bergamot boasts a notable acidity and emits a subtle yet delightful aroma. The principal derivative of this fruit is the esteemed bergamot chemical compounds, obtained by careful cold pressing or exact steam distillation of the peel area inside the fresh fruit's mesocarp. Due to its versatile nature, the bergamot chemical components, commonly referred to as BEO, plays a pivotal role in the global fragrance industry, particularly in solidifying the aromatic compositions of various perfumes. Beyond its fragrance applications, BEO finds extensive use in the culinary realm, where it imparts its distinct flavor profile to an array of treats, ranging from confectionery to teas and carbonated beverages. Notably, the refreshing and flavorful essence of BEO, along with its concentrated extracts, is often blended into the classic earl grey tea (EGT), enriching this beloved beverage with its invigorating citrus notes (1, 2).

*** Corresponding Author:**

Gaurav Mude

Research Scholar, Institute of Pharmaceutical Science, SAGE University, Indore (MP), India.

Email Id: gaurav21pharmamude@gmail.com

Fig. 1: Bergamot plant with its fruits

The flavor and quality of EGT are influenced by the tea blend used and the caliber and quantity of bergamot chemical components incorporated. Bergamot chemical components are used in aromatherapy to help with stress-related symptoms, as well as in dermatology, gynaecology, dentistry, and ophthalmology.

Italy is renowned in the global trade community for its high-quality bergamot chemical components, with the harvest season playing a significant role in determining its chemical composition. The volatile and nonvolatile fractions of bergamot chemical components contain compounds such as psoralens, coumarins, and bergamottin, contributing to its unique characteristics. Bergamot, a name that encompasses both the fragrant herbs belonging to the genus Monarda in the Lamiaceae family and the luscious fruit harvested from the bergamot orange tree, Citrus × aurantium. These distinct variations of bergamot, whether derived from plant or borne from citrus, boast a shared characteristic in their enchanting floral aroma. Revered for centuries, bergamot's captivating scent has found its way into the

realms of perfumery and culinary arts alike. The aromatic allure of bergamot infuses fragrances with a bright, uplifting note, adding depth and complexity to a myriad of scents. In the culinary world, the zest of bergamot imparts a refreshing citrusy touch, elevating dishes with its unique flavor profile. Among its varied applications, bergamot stands as a versatile ingredient that inspires creativity and sensory delight. From classic perfumes to delectable dishes, bergamot's essence weaves a thread of sophistication and allure through each creation it touches. Whether in the subtle hint of a perfume or the bold tang of a dish, bergamot's floral notes and citrus undertones beckon the senses, inviting exploration and appreciation of its multifaceted charm. Through its enduring presence in diverse fields, bergamot continues to captivate hearts and tantalize taste buds, a true testament to its timeless appeal and allure (3, 4).

Bergamot herbs, including perennial species indigenous to North America, are aesthetically pleasing as ornamentals and are vital for attracting significant pollinators such as bees, butterflies, and hummingbirds. The leaves of bee balm are flexible and are used to enhance the flavours of numerous beverages, including punches, lemonades, and other pleasant cold drinks. Moreover, lemon bergamot, also known as lemon bee balm (M. citriodora), and wild bergamot (M. fistulosa) provide further possibilities for enhancing beverages and infusing teas with their unique fragrant characteristics.

Shifting the focus to another type of bergamot, the bergamot orange stands out as a prized citrus fruit mainly cultivated in Italy. This fruit is particularly renowned for its association with Earl Grey tea, where the essence of the bergamot orange infuses a unique and captivating flavor into the tea blend. The tree producing this citrus fruit has unique yellow-green, pear-shaped fruits sought after by the flavouring and perfume industries for the valuable essential oil derived from the peel. The essential oil derived from bergamot orange peel enhances culinary dishes and plays a vital role in the fragrance industry, making it a highly desired component in both culinary and perfumery applications.

Key components like linalool, linalyl acetate, terpinene, limonene, and pinene are present in bergamot chemical components, along with aroma chemicals like geraniol, decanal, and limonene oxide that mimic its fragrance. Bergamot's chemical composition is distinguished from other citrus oils by a higher concentration of linalyl acetate and linalool relative to limonene. The ratio of linalyl acetate to linalool, referred to as the "essence degree," profoundly influences the aromatic character of bergamot's chemical constituents. Beyond its aromatic properties, bergamot chemical components exhibit a range of pharmacological effects, including melanogenic, antinociceptive, antioxidant, and antibacterial properties, as well as cytotoxic, wound-healing, anxiolytic, and anti-tumor effects. Additionally, it possesses sedative, calming, and soothing qualities, making it a versatile natural remedy for various conditions such as allergies, fungal infections, and bacterial issues (5, 6).

Pharmacognostical features of bergamot

Bergamot, a citrus fruit, was first introduced in 1818 by Joseph Antoine Risso and Pierre Antoine Poiteau. It is said to be a hybrid of sour orange and lemon. Bergamot trees may reach a height of 12 meters, with an erect, dark grayish-brown trunk and slender, irregular roots. They are known for their resilient, enduring trees that withstand inclement weather. The fruit, classified as a hesperidium or subglobose to pyriform berry, with many glands and a peel that is 3 to 6 mm thick, containing chemical component cavities. The degradation of chlorophyll and an elevation in carotenoid levels result in alterations in rind colouration. The fruit's fragrance originates from aromatic compounds. The word "bergamot" may have derived from the Turkish phrase "beg-a-mudi," which translates to "pears of the prince," due to the resemblance of the pears to that expression (7, 8, 9).

Table 1: Biological classification of bergamot

Sr. no.	Type of classification	Classification
1	Kingdom	Plantae
2	Clade	Tracheophytes
3	Clade	Angiosperms
4	Clade	Eudicots
5	Clade	Asterids
6	Order	Lamiales
7	Family	Lamiaceae
8	Genus	Monarda
9	Species	M. didyma

Chemical constituents and important features

The ISO characterises a chemical component as a product derived from naturally existing raw materials sourced from plants, using techniques such as dry distillation, steam distillation, or mechanical extraction from the epicarp of many plants and fruits. These processes aim to separate any aqueous phases and yield chemical components distinct in their chemical composition and manufacturing techniques. Specifically, Citrus components stand out due to a production method exclusive to them among the three processes employed. This exclusivity facilitates easy differentiation of Citrus components from other chemical components. Furthermore, a notable disparity lies in the compositions of distilled chemical components and pressed cold chemical components. Distilled chemical components predominantly comprise unstable compounds, whereas pressed cold chemical components contain larger chemical compounds and molecules absent in their distilled counterparts (10).

Citrus fruits are multifunctional, containing chemical components, by-products, and fruit juice. Popular varieties include mandarins, lemons, sweet oranges, and grapefruits. Bergamots and bitter oranges, though not widely produced, have higher costs due to their limited production. This economic aspect sheds

https://doi.org/10.47552/ijam.v16iS2.6198 ISSN No: 0976-5921

Int J. of Ayurvedic Med, "Natural to Synthetic: The Convergence of Traditional Medicine to Modern Medicine" Supplement 2025

light on the pricing disparity between citrus chemical components derived from different fruit types (11).

Anatomy of citrus fruits

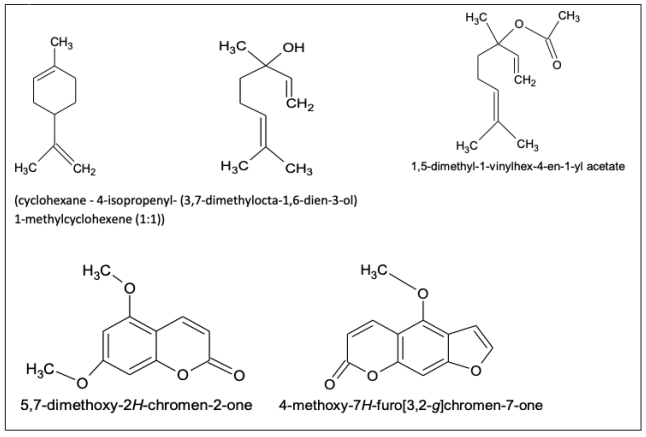
The hesperidium, a citrus berry characterised by a robust outer rind, albedo mesocarp, and flavedo exocarp, is spherical in shape, including lacunae, essential oil-filled cavities, and dense cellular structures. Their sizes range from 0.4 to 0.6 mm and are often categorised into primary, secondary, and tertiary cavities. The optimal technique for extracting citrus chemical constituents is attributed to the surface dispersion of oil glands, cold pressing, or mechanical processing (12).

Chemical constituents of bergamot

Bergamot Chemical components is a unique citrus chemical component with higher levels of oxygenated terpenes like linalyl acetate and linalool, contrasting with the high limonene content found in other oils (13, 14).

Bergamot Chemical components, classified as volatile or non-volatile, are susceptible to fraudulent activities due to their high market value and complexity, making detection challenging. Compared to other citrus chemical constituents, the primary components of Bergamot—limonene, linalool, pinene, linalyl acetate, and terpinene—constitute less than 90% of the total composition, underscoring the complex and varied nature of these valued chemical constituents (15, 16, 17). The chemical components of bergamot shown in Fig. 2 are as follows: 3,5-dimethyl-1-vinylhex-4-en-1-yl acetate, 3,7-dimethoxy-2H-chromen-2-one, 4-methoxy-7H-furo[3,2-g]chromen-7-one, and 3,7-dimethoxy-2H-chromen-2-one.

Figure 2: Major chemical composition of bergamot plant



Fraction of volatility

93–96% of BEO's total content consists of volatile components, mostly including linalool, linalyl acetate, and limonene. Despite these prevalent compounds, the scientific literature reveals a comprehensive array of over 100 substances that have been thoroughly discovered and recorded. BEO has a much-reduced hydrocarbon concentration relative to its citrus equivalents, however prominent monoterpene hydrocarbons such as α-pinene (4–11%), limonene (25–55%), and γ-terpinene (5–11%) dominate its volatile composition. Furthermore, the presence of sesquiterpene hydrocarbons such as -bisabolene and caryophyllene, along with notable elements like (E)-bergamotene, adds depth to the aromatic bouquet of BEO (18). Noteworthy distinctions from other citrus chemical components emerge when considering the oxygenated derivatives of mono and sesquiterpene hydrocarbons, which can account for over Half of the volatile compound, far surpassing the levels found in most extra citrus EOs which tend to average between 1 to 6%. Among the array of compounds, terpenic alcohols and esters emerge as prominent players, with linalool standing as the most significant monoterpene alcohol due to its prevalent presence ranging from 2–20%. Additionally, the rare sesquiterpene alcohol, bisabolol, known to be exclusive to Bergamot, can be detected in minute quantities, adding a unique flair to the overall composition (19, 20, 21).

Fraction of non-volatile content

In addition to inert substances like as pigments and waxes, which constitute 4–7% of the overall essential oil content, this particular fraction mostly comprises oxygen-containing heterocyclic compounds. The main components within this fraction are coumarins, psoralens, and polymethoxyflavones such as tetra-O-methyl scutellarin and sinensetin. Specifically, it is dominated by four key compounds: the psoralens bergapten and bergamottin, along with the coumarins geranyloxy-7-methoxycoumarin and citropten, which are commonly associated with Candida bergamia (22, 23, 24). Genuine essential oils include many psoralens, including akangelicin, bergaptol, epoxybergamottin, isoimperatorin, biakangelicol, oxypeucedanin, and oxypeucedanin hydrate. This particular fraction showcases a diverse array of compounds that collectively contribute to the characteristic composition of chemical components (25, 26, 27, 28).

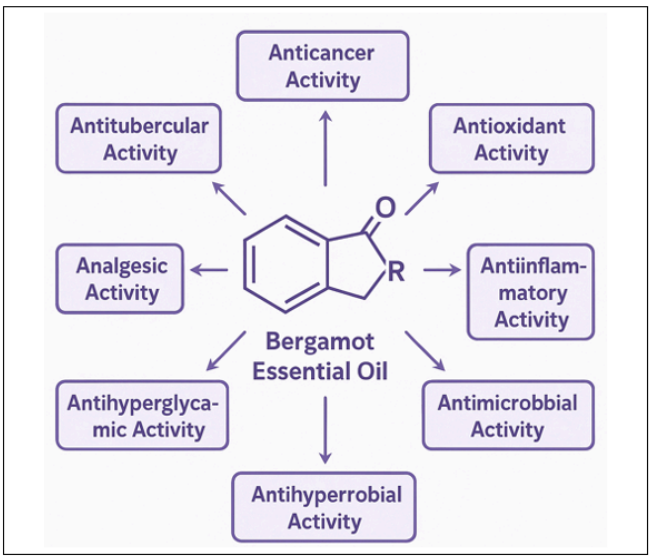
Pharmacological activities

The chemical components of bergamot are extensively used in the pharmacological, culinary, and cosmetics sectors because to their melanogenic qualities. It is used in suntan products and supplementary medicine to alleviate neuropathic and nociceptive pain. BEO has shown cytotoxicity against human neuroblastoma cells, inhibiting their proliferation by more than 70%. The bioactive chemicals 5-geranyloxy-7-methoxycoumarin and bergamottin are accountable for these actions. BEO and d-limonene have shown the ability to alter autophagic pathways in SH-SY5Y cells, with lipidomal BEO exhibiting enhanced anticancer activity against these cells (29, 30, 31).

The agreeable scent of bergamot has shown efficacy in reducing behavioural sadness and stress-induced anxiety in rats subjected to prolonged stress. It also exhibits broad antifungal activity against various bacteria and fungi, including Fusarium solani, Penicillium italicum, and Trichophyton, Microsporum, and Epidermophyton dermatophytes. The antibacterial

and antifungal properties are believed to be facilitated by enhanced generation of reactive oxygen species (ROS) in human polymorphonuclear leukocytes. The powerful anti-mycoplasmal actions of bergamot chemical components have been identified against Mycoplasma fermentans, Mycoplasma hominis, and Mycoplasma pneumoniae. Overall, BEO's potential benefits in various industries make it a valuable addition to the natural remedies and treatments for various health conditions (32, 33, 34). Fig. 3. Biological activities of primary chemical components of bergamot, emphasizing their contributions to antioxidant, anti-inflammatory, antibacterial, cardiovascular, and neuroprotective properties.

Figure 3: Biological activities of chemical components present in bergamot



Neuroprotective activity

In developed countries, it is common to utilize a botanical extract known as BEO to address various mood-related issues and alleviate mild symptoms of stress-related conditions such as depression, anxiety, behavioral abnormalities linked to dementia, and chronic pain. This natural remedy is frequently employed due to its potential therapeutic benefits. BEO comprises multiple constituents, each of which plays a crucial role in its efficacy. Upon delivery via many routes, the constituents of BEO may traverse the blood-brain barrier, therefore accessing the central nervous system. This unique characteristic of BEO enhances its effectiveness in targeting the underlying causes of these conditions and providing relief to individuals suffering from these health concerns. The process through which the constituents of BEO cross the blood-brain barrier underscores the intricate mechanisms by which this botanical extract exerts its positive effects on mental health and overall well-being, making it a valuable option in the treatment and management of a diverse range of psychological and physiological symptoms (35, 36, 37).

Behavioral activity

BEO, has shown a consistent impact on the rat central nervous system when supplied at escalating doses. It induces both hypnotic and stimulating effects on EEG spectra, resulting in enhanced movement and behaviour.

Following the administration of 250 l/kg of the Plant complex, rats demonstrated behavioural arousal, marked by stereotypical movements and heightened energy levels in the theta and alpha frequency bands in the cortex, as well as beta and alpha rhythms in the hippocampus. The substantial dosage of BEO elicited behavioural excitement and EEG desynchronisation, accompanied by a significant increase in cortical theta band amplitudes and hippocampus beta band strength. Recent findings indicate that BEO selectively influences essential synaptic neurotransmission pathways (38, 39, 40, 41).

Effect on synapses' regular transmission

Research using Microdialysis indicates that in freely moving rats, BEO enhances the levels of extracellular amino acids, including glycine, taurine, and aspartate, especially within the hippocampus area. Interestingly, this effect seems to be modulated by the absence of Ca2+ in the cerebrospinal fluid as studies have shown that in experiments where calcium ions are lacking, the ability of BEO to increase these particular amino acids is hindered. This highlights the intricate interplay between BEO and the presence of calcium ions in influencing amino acid levels in the hippocampus of rats (42, 43).

Neuroprotection from excitotoxicity

Under ischaemic circumstances, anoxic depolarisation causes the loss of excitatory amino acids from nerve terminals, impairing the essential driving force for the proper operation of membrane transporters. This disturbance induces the production of reactive oxygen species (ROS), leading to the aberrant functioning of glutamate transporters and elevated levels of excitatory amino acids at synapses. As a result, neurones sustain damage from the ischaemic insult. Intraperitoneal administration of BEO in rats has shown encouraging outcomes in mitigating brain damage resulting from localised cerebral ischaemia in a dose-dependent fashion. Microdialysis tests have shown that BEO significantly reduces excitatory amino acid outflow, opposing the usual rise in efflux seen in the brain area quickly after middle cerebral artery closure (44).

Anxiolytic activity

This research examined the anxiolytic and sedative-like effects of BEO in rats. The results unequivocally indicated that in animal behavioural evaluations when DZP could not be directly contrasted, BEO had anxiolytic and sedative effects. The rats were intraperitoneally injected with BEO thirty minutes prior to each behavioral test, highlighting the timing of administration. Overall, the results of this particular research point towards a distinction in how BEO interacts in terms of its calming and anxiolytic properties when compared to DZP, shedding light on potential differences in their pharmacological effects (45).

Antidepressant activity

The inquiry into the antidepressant effects of olfactory stimulation using diverse odorants was rigorously executed using the validated forced swimming test, a recognised method for evaluating antidepressant qualities. In the experiment, the addition of a lemon aroma significantly reduced the overall length of immobility while concurrently amplifying the decrease in total motionlessness caused by imipramine treatment. The observed synergistic impact of imipramine and lemon fragrance should not be prematurely ascribed to the potential interference of lemon scent with the metabolism of imipramine. The lemon smell was seen to reduce locomotor activity in open space, suggesting that its mechanisms of action resemble those of conventional antidepressants rather than psychostimulants. Significantly, the primary component of lemon scent, citral, demonstrates characteristics that closely mirror those inherent in lemon odour itself (45, 46).

Anti-nociceptive activity

The research examined the effects of BEO, a chemical abundant in linalyl acetate and linalool, its principal volatile constituents, on the capsaicin test. In the capsaicin test, after an intraplantar injection of 1.6 g of capsaicin, the paw that received the injection had a transient reflexive reaction characterised by licking and biting. A significant finding was observed: a dose-dependent reduction in nociceptive behavioural response induced by capsaicin occurred after the intraplantar administration of BEO. The research only included male ddY (SD) mice weighing between 22 and 26 g, obtained from the Shizuoka Laboratory Centre in Japan. The administration of artificial or saline cerebrospinal fluid (CSF) did not provide statistically significant effects on capsaicin-induced pain when administered intraplantarly at dosages similar to those of BEO (5 g) and linalool (1.25 g). Notably, the concurrent administration of morphine, benzophenone, and linalool resulted in a significantly enhanced effect on the nociceptive response elicited by capsaicin (46).

Wound healing activity

Traditional medicine use BEO (subsp. bergamia C. aurantium L) as an anthelmintic and antibacterial agent, as well as to facilitate wound healing. Research on BEO's influence on immunity is few; nonetheless, it seems to have significant antibacterial properties. Research investigated the effect of BEO on the formation of reactive oxygen species (ROS) by human polymorphonuclear leukocytes (PMN) and the role of Ca2+ in functional responses. The results indicate that BEO may enhance intracellular ROS generation in human PMN, corroborating its inherent proinflammatory capacity and facilitating infection combat and tissue repair (47).

Antiproliferative activity

The research used the human neuroblastoma cell line SH-SY5Y to assess the cytotoxic effects of blue-eyed octahedral structures (BEOs). The preliminary test indicated that the introduction of coloured BEOs to SH-SY5Y cells considerably increased the proportion of cell mortality. The cell count assay and MTT assay were used to quantify cell proliferation. The pharmacotoxicological profile indicates that 5-geranyloxy-7-methoxycoumarin and bergamottin may significantly contribute to the antiproliferative effects of BEO (47).

Neuroprotection against ischemic conditions

This research systematically evaluated the influence of BEO on the brains of rats experiencing chronic localised cerebral ischaemia. After a 24-hour middle cerebral artery occlusion (MCAo) period, various doses of BEO (from 0.1 to 0.5 mL/kg, except 1 mL/kg) were delivered intraperitoneally, indicating a potential decrease in infarct size. The therapeutic dosage of 0.5 mL/kg demonstrated considerable efficiency in reducing cell death throughout the brain, particularly in the striatum and motor cortex, as seen by tissue slice staining with TTC. Results from Little Dialysis experiments also indicated that BEO at 0.5 mL/kg significantly reduced the efflux of excitatory amino acids, including glutamate, in the frontal parietal cortex, while without altering baseline amino acid concentrations. Furthermore, during 24 hours of continuous MCAo, there was a significant elevation in the phosphorylation and activation of Akt, a pro-survival kinase, as shown by Western blotting experiments. BEO demonstrated an elevated degree of GSK-3 phosphorylation, a significant kinase whose activity is inhibited by Akt phosphorylation (48, 49).

Anti-inflammatory and antioxidant activity

The research examined the anti-inflammatory effects of D-limonene in a rat model of ulcerative colitis (UC). The rats received several treatments, with D-limonene markedly decreasing disease activity and intestinal mucosal injury. The therapy elevated antioxidant protein levels in UC rats and regulated the expression of MMP2 and MMP9 mRNA in the UC rat model, suggesting possible antioxidant and anti-inflammatory capabilities (49).

Antibacterial and antifungal activity

The research revealed that bergamot oil had significant efficacy, with linalool identified as the most efficient antibacterial agent. The in vitro trials demonstrated increased susceptibility of both gram-positive and gram-negative bacteria to these compounds. The vapour of linalool and bergamot oils significantly inhibited E. coli O157 and Campylobacter jejuni. This study highlighted the significant effectiveness of Bergamot Chemical components (BEO) against several clinical isolates from diverse pathogenic dermatophytes. The research included ninety-two isolates from seven unique types of dermatophytes. Twelve isolates were obtained from the clinical isolate collection at the Mycology Section of the Catholic University Medical Centre. This collection included specimens of Epidermophyton floccosum, Trichophyton rubrum, Trichophyton interdigitale, Trichophyton

tonsurans, Microsporum canis, and Microsporum gypseum (50, 51).

Major components of bergamot

Limonene, a monoterpene hydrocarbon, has anxiolytic properties in male Swiss albino mice. The EPM test revealed substantial alterations in parameters after the inhalation of 0.5% and 1.0% (+)-limonene. Mice treated with limonene exhibited mechanical hyperalgesia resulting from spared nerve injury (SNI), which may be alleviated by limonene. Intraperitoneal injection of limonene enhanced the survival rate of mice experiencing provoked seizures and postponed convulsions. It also inhibited ischemia-related cerebral damage in stroke-prone animals (51).

Linalool, a monoterpene alcohol, has anticonvulsant effects due to NMDA receptor antagonistic activity and decreased potassium-stimulated glutate release in cortical synaptosomes. It exhibits proliferative and anti-inflammatory properties. The antinociceptive properties of linalyl acetate and linalool are dependent on the quantity of linalool it contains. Behavioral testing showed that a local linalool intraplantar injection decreased pain perception in mice with hypersensitive neuropathy caused by partial sciatic nerve ligation (51).

Linalool may assist in alleviating sadness and anxiety. Additional study is required to establish techniques for antiepileptic pharmacotherapy (51).

Toxicity assessment of bergamot oil

The European Medicines Agency indicates that significant concerns about BEO toxicity pertain to its melanogenic and photosensitive constituents. These traits are historically linked to the presence of furocoumarins, particularly psoralens like bergapten, in BEO. Notably, personal characteristics such as age, gender, and UV sensitivity seem to have little influence on skin response to BEO. The emphasis transitions to certain components such as the ethanol and psoralens concentration in the formulation, the degree of skin moisture, and the individual's inherent skin pigmentation. This pattern may indicate a probable decrease in reported instances for several causes. Alternatively, it may also indicate that the market is progressively providing safer options via psoralen-free bergamot derivatives. This transition to safer alternatives indicates a continuous endeavour to reduce possible hazards linked to the conventional usage of BEO, signifying a constructive progression in product safety within the industry (51, 52, 53).

The International Fragrance Association (IFRA) recommends capping the BEO concentration in skincare products at 0.4%, in addition to restricting psoralen levels. Light-induced dermal responses may manifest 2 to 72 hours post-BEO treatment, mimicking bullous dermatitis. The predominant minor chemicals and principal components are safe for systemic use. BEO should be contraindicated in breastfeeding or pregnant individuals, those with allergy diathesis, youngsters, and the elderly owing to insufficient safety evidence. Prolonged and excessive use of BEO may induce neurological symptoms and photosensitivity of the skin. The safety profile of BEO is under evaluation; nevertheless, using formulations devoid of psoralen and limiting intake to brief durations may alleviate significant adverse effects (54).

Table 2. Citrus bergamia (bergamot) safety guidelines, revised in light of suggestions from the IFRA and the EMA, including a review of toxicity data, an explanation of contraindications, and suggested dosage limits for both topical and oral use. In especially for those who are photosensitive or otherwise susceptible, these recommendations stress the need of managing the risk of phototoxicity, establishing safe dose levels, and identifying and avoiding contraindications.

Table 2: Updated Safety Guidelines for Citrus bergamia (Bergamot) Based on IFRA and EMA Recommendations

Parameter	Details	Source/Guideline
Phototoxicity	Bergamot essential oil contains bergapten (5-MOP), a furanocoumarin known to cause phototoxic reactions upon UV exposure.	IFRA, EMA
Recommended Usage Limit (Leave-on Products)	≤ 0.4% (maximum concentration in finished leave-on cosmetic products to avoid phototoxicity)	IFRA Amendment 49 (2020)
Recommended Usage Limit (Rinse-off Products)	≤ 2.0% (lower risk due to reduced skin contact time)	IFRA Amendment 49 (2020)
Toxicological Concerns	High doses linked to photosensitivity, neurotoxicity (in rare cases of excessive intake), and hepatotoxicity (with prolonged or excessive use of unmodified oil)	EMA, EFSA
Contraindications	- Avoid during pregnancy and lactation (due to lack of safety data) - Not recommended for individuals with known photosensitivity disorders - Avoid concurrent use with other photosensitizing agents (e.g., tetracyclines)	EMA monograph on herbal medicinal products
Systemic Exposure Limit (SEL)	15 mg/kg/day (based on bergapten content)	IFRA Safety Assessment Reports
Sensitization Potential	Low to moderate; patch testing advised for sensitive individuals	IFRA, European SCCS

Drug Interactions	Potential inhibition of CYP450 enzymes (particularly CYP3A4), which may alter metabolism of medications like statins, benzodiazepines, and calcium channel blockers	EMA, PubChem Toxicology Data
Recommended Daily Oral Dose (Standardized Extract)	≤ 1000 mg/day of flavonoid-rich extract (under medical supervision)	EMA Assessment Reports, Clinical Guidelines
Children and Infants	Use not recommended due to insufficient safety data	EMA, IFRA

Conclusion

The distinctiveness of Bergamot Chemical components (BEO) is in its composition among citrus chemical constituents. A notable characteristic of BEO is its potential to contain elevated concentrations of limonene, ranging from 80% to 95%. Limonene, representing around 4% to 7% of the entire chemical composition, is a significant percentage mostly consisting of oxygen-rich heterocyclic molecules. The chemicals include coumarins, psoralens, and minimal quantities of polymethoxy flavones, in addition to inert materials such as pigments and waxes. BEO demonstrates varied biological actions that significantly impact many body systems, particularly the central neurological and cardiovascular systems. Research has validated its antibacterial, anti-inflammatory, antiproliferative, and analgesic characteristics. Although clinical investigations have mostly examined the benefits of aromatherapy using BEO, these results indicate possible future therapeutic uses of this chemical component. These investigations have specifically aimed at modulating stress responses and enhancing anxiolytic effects with aromatherapy treatments utilising BEO. The findings suggest that aromatherapy therapies using BEO may relieve symptoms of stress and anxiety, indicating a therapeutic route worthy of future exploration.

References

1. Fisher K, Rowe C, Phillips CA. The survival of three strains of Arcobacter butzleri in the presence of lemon, orange and bergamot chemical components and their components in vitro and on food. Letters in Applied Microbiology. 2007 May 1;44(5):495-9.
2. Verzera A, Trozzi A, Gazea F, Cicciarello G, Cotroneo A. Effects of rootstock on the composition of bergamot (Citrus bergamia Risso et Poiteau) chemical components. Journal of agricultural and food chemistry. 2003 Jan 1;51(1):206-10.
3. Avila-Sosa R, Navarro-Cruz AR, Sosa-Morales ME, López-Malo A, Palou E. Bergamot (Citrus bergamia) oils. In Chemical components in Food Preservation, Flavor and Safety 2016 Jan 1 (pp. 247-252). Academic Press.
4. Bagetta G, Morrone LA, Rombolà L, Amantea D, Russo R, Berliocchi L, Sakurada S, Sakurada T, Rotiroti D, Corasaniti MT. Neuropharmacology of the chemical components of bergamot. Fitoterapia. 2010 Sep 1;81(6):453-61.
5. Finsterer J. Earl Grey tea intoxication. The Lancet. 2002 Apr 27;359(9316):1484.
6. Dosoky NS, Setzer WN. Biological activities and safety of Citrus spp. chemical components. International journal of molecular sciences. 2018 Jul 5;19(7):1966.
7. Beal MF. Bioenergetic approaches for neuroprotection in Parkinson's disease. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 2003;53(S3): S39-48.
8. Valussi M, Donelli D, Firenzuoli F, Antonelli M. Bergamot oil: Botany, production, pharmacology. Encyclopedia. 2021 Feb 3;1(1):152-76.
9. Verzera A, Lamonica G, Mondello L, Trozzi A, Dugo G. The composition of bergamot oil. Perfumer and Flavorist. 1996; 21:19-42.
10. Navarra M, Mannucci C, Delbò M, Calapai G. Citrus bergamia chemical components: from basic research to clinical application. Frontiers in pharmacology. 2015 Mar 2; 6:36.
11. González-Mas MC, Rambla JL, López-Gresa MP, Blázquez MA, Granell A. Volatile compounds in citrus chemical components: A comprehensive review. Frontiers in plant science. 2019 Feb 5; 10:12.
12. Sawamura M, Onishi Y, Ikemoto J, Tu NT, Phi NT. Characteristic odour components of bergamot (Citrus bergamia Risso) chemical components. Flavour and fragrance journal. 2006 Jul;21(4):609-15.
13. Adorisio S, Muscari I, Fierabracci A, Thi Thuy T, Marchetti MC, Ayroldi E, Delfino DV. Biological effects of bergamot and its potential therapeutic use as an anti-inflammatory, antioxidant, and anticancer agent. Pharmaceutical Biology. 2023 Dec 31;61(1):639-46.
14. Wong ST, Kamari A, Abdullah NN, Yusof N, Sutapa IW. Preparation and Characterization of Bergamot Chemical components Nanoemulsion. In IOP Conference Series: Earth and Environmental Science 2024 Dec 1 (Vol. 1425, No. 1, p. 012031). IOP Publishing.
15. Russo R, Cassiano MG, Ciociaro A, Adornetto A, Varano GP, Chiappini C, Berliocchi L, Tassorelli C, Bagetta G, Corasaniti MT. Role of D-Limonene in autophagy induced by bergamot chemical componentsin SH-SY5Y neuroblastoma cells. PloS one. 2014 Nov 24;9(11): e113682.
16. Kuwahata H, Komatsu T, Katsuyama S, Corasaniti MT, Bagetta G, Sakurada S, Sakurada T, Takahama K. Peripherally injected linalool and bergamot chemical components attenuate mechanical allodynia via inhibiting spinal ERK phosphorylation. Pharmacology Biochemistry and Behavior. 2013 Feb 1;103(4):735-41.
17. Lauro F, Ilari S, Giancotti LA, Morabito C, Malafoglia V, Gliozzi M, Palma E, Salvemini D, Muscoli C. The protective role of bergamot

polyphenolic fraction on several animal models of pain. PharmaNutrition. 2016 Oct 1;4: S35-40.

18. Cosentino M, Luini A, Bombelli R, Corasaniti MT, Bagetta G, Marino F. The chemical componentsof bergamot stimulates reactive oxygen species production in human polymorphonuclear leukocytes. Phytotherapy Research. 2014 Aug;28(8):1232-9.
19. Navarra M, Ferlazzo N, Cirmi S, Trapasso E, Bramanti P, Lombardo GE, Minciullo PL, Calapai G, Gangemi S. Effects of bergamot chemical components and its extractive fractions on SH-SY5Y human neuroblastoma cell growth. Journal of Pharmacy and Pharmacology. 2015 Aug;67(8):1042-53.
20. Berliocchi L, Ciociaro A, Russo R, Cassiano MG, Blandini F, Rotiroti D, Morrone LA, Corasaniti MT. Toxic profile of bergamot chemical components on survival and proliferation of SH-SY5Y neuroblastoma cells. Food and chemical toxicology. 2011 Nov 1;49(11):2780-92.
21. Malviya V, Arya A, Burange P, Gajbhiye K, Rathod G, Tawar M. To evaluate the cardioprotective effect of hydroalcoholic extract of Matricaria chamomilla linn in isoproterenol induced myocardial infarction in wistar rats. Research Journal of Pharmacy and Technology. 2022;15(9):3887-92.
22. Sakurada T, Mizoguchi H, Kuwahata H, Katsuyama S, Komatsu T, Morrone LA, Corasaniti MT, Bagetta G, Sakurada S. Intraplantar injection of bergamot chemical componentsinduces peripheral antinociception mediated by opioid mechanism. Pharmacology Biochemistry and Behavior. 2011 Jan 1;97(3):436-43.
23. Amantea D, Fratto V, Maida S, Rotiroti D, Ragusa S, Nappi G, Bagetta G, Corasaniti MT. Prevention of glutamate accumulation and upregulation of phospho-akt may account for neuroprotection afforded by bergamot chemical components against brain injury induced by focal cerebral ischemia in rat. International Review of Neurobiology. 2009 Jan 1; 85:389-405.
24. Celia C, Trapasso E, Locatelli M, Navarra M, Ventura CA, Wolfram J, Carafa M, Morittu VM, Britti D, Di Marzio L, Paolino D. Anticancer activity of liposomal bergamot chemical components (BEO) on human neuroblastoma cells. Colloids and Surfaces B: Biointerfaces. 2013 Dec 1; 112:548-53.
25. Gioffrè G, Ursino D, Labate ML, Giuffrè AM. The peel chemical components composition of bergamot fruit (Citrus bergamia, Risso) of Reggio Calabria (Italy): A review. Emirates Journal of Food and Agriculture. 2020 Nov 1;32(11):835-45.
26. Navarra M, Mannucci C, Delbò M, Calapai G. Citrus bergamia chemical components: from basic research to clinical application. Frontiers in pharmacology. 2015 Mar 2; 6:36.
27. Amantea D, Fratto V, Maida S, Rotiroti D, Ragusa S, Nappi G, Bagetta G, Corasaniti MT. Prevention of glutamate accumulation and upregulation of phospho-akt may account for neuroprotection afforded by bergamot chemical components against brain injury induced by focal cerebral ischemia in rat. International Review of Neurobiology. 2009 Jan 1; 85:389-405.
28. Morrone LA, Rombolà L, Pelle C, Corasaniti MT, Zappettini S, Paudice P, Bonanno G, Bagetta G. The chemical components of bergamot enhance the levels of amino acid neurotransmitters in the hippocampus of rat: Implication of monoterpene hydrocarbons. Pharmacological research. 2007 Apr 1;55(4):255-62.
29. Valussi M, Donelli D, Firenzuoli F, Antonelli M. Bergamot oil: Botany, production, pharmacology. Encyclopedia. 2021 Feb 3;1(1):152-76.
30. Yu L, Yan J, Sun Z. D-limonene exhibits anti-inflammatory and antioxidant properties in an ulcerative colitis rat model via regulation of iNOS, COX-2, PGE2 and ERK signaling pathways. Molecular medicine reports. 2017 Apr 1;15(4):2339-46.
31. Roberto D, Micucci P, Sebastian T, Graciela F, Anesini C. Antioxidant activity of limonene on normal murine lymphocytes: relation to H2O2 modulation and cell proliferation. Basic & clinical pharmacology & toxicology. 2010 Jan;106(1):38-44.
32. Tundis R, Loizzo MR, Bonesi M, Menichini F, Mastellone V, Colica C, Menichini F. Comparative study on the antioxidant capacity and cholinesterase inhibitory activity of Citrus aurantifolia Swingle, C. aurantium L., and C. bergamia Risso and Poit. peel chemical components. Journal of food science. 2012 Jan;77(1):H40-6.
33. Fisher K, Phillips CA. The effect of lemon, orange and bergamot chemical components and their components on the survival of Campylobacter jejuni, Escherichia coli O157, Listeria monocytogenes, Bacillus cereus and Staphylococcus aureus in vitro and in food systems. Journal of applied microbiology. 2006 Dec 1;101(6):1232-40.
34. Kirbaşlar FG, Tavman A, Dülger B, Türker G. Antimicrobial activity of Turkish citrus peel oils. Pakistan Journal of Botany. 2009;41(6):3207-12.
35. Rossi DJ, Oshima T, Attwell D. Glutamate release in severe brain ischaemia is mainly by reversed uptake. Nature. 2000 Jan 20;403(6767):316-21.
36. Stević T, Berić T, Šavikin K, Soković M, Gođevac D, Dimkić I, Stanković S. Antifungal activity of selected chemical components against fungi isolated from medicinal plant. Industrial Crops and Products. 2014 Apr 1; 55:116-22.
37. Rombolà L, Tridico L, Scuteri D, Sakurada T, Sakurada S, Mizoguchi H, Avato P, Corasaniti MT, Bagetta G, Morrone LA. Bergamot chemical components attenuate anxiety-like behaviour in rats. Molecules. 2017 Apr 11;22(4):614.
38. Sakurada T, Kuwahata H, Katsuyama S, Komatsu T, Morrone LA, Corasaniti MT, Bagetta G, Sakurada S. Intraplantar injection of bergamot chemical components into the mouse hindpaw: Effects on capsaicin-induced nociceptive behaviors.

International review of neurobiology. 2009 Jan 1; 85:237-48.

39. Piccinelli AC, Santos JA, Konkiewitz EC, Oesterreich SA, Formagio AS, Croda J, Ziff EB, Kassuya CA. Antihyperalgesic and antidepressive actions of (R)- (+)-limonene, α-phellandrene, and chemical components from Schinus terebinthifolius fruits in a neuropathic pain model. Nutritional neuroscience. 2015 Jul 1;18(5):217-24.
40. Lima NG, De Sousa DP, Pimenta FC, Alves MF, De Souza FS, Macedo RO, Cardoso RB, De Morais LC, Margareth de Fátima F, De Almeida RN. Anxiolytic-like activity and GC–MS analysis of (R)-(+)-limonene fragrance, a natural compound found in foods and plants. Pharmacology Biochemistry and Behavior. 2013 Jan 1;103(3):450-4.
41. Piccinelli AC, Morato PN, dos Santos Barbosa M, Croda J, Sampson J, Kong X, Konkiewitz EC, Ziff EB, Amaya-Farfan J, Kassuya CA. Limonene reduces hyperalgesia induced by gp120 and cytokines by modulation of IL-1 β and protein expression in spinal cord of mice. Life sciences. 2017 Apr 1; 174:28-34.
42. Sanguinetti M, Posteraro B, Romano L, Battaglia F, Lopizzo T, De Carolis E, Fadda G. In vitro activity of Citrus bergamia (bergamot) oil against clinical isolates of dermatophytes. Journal of Antimicrobial Chemotherapy. 2007 Feb 1;59(2):305-8.
43. Furneri PM, Mondello L, Mandalari G, Paolino D, Dugo P, Garozzo A, Bisignano G. In vitro antimycoplasmal activity of Citrus bergamia chemical componentsand its major components. European Journal of Medicinal Chemistry. 2012 Jun 1; 52:66-9.
44. Wang X, Li G, Shen W. Protective effects of D-Limonene against transient cerebral ischemia in stroke-prone spontaneously hypertensive rats. Experimental and therapeutic medicine. 2018 Jan 1;15(1):699-706.
45. Ogunwande IA, Avoseh ON, Igile DO, Lawal OA, Ascrizzi R, Guido F. Chemical constituents, anti-nociceptive and anti-inflammatory activities of chemical components of Phyllanthus muellerianus. Natural Product Communications. 2019 May;14(5):1934578X19846356.
46. Lee YM, Son E, Kim SH, Kim DS. Anti-inflammatory and analgesic effects of Schisandra chinensis leaf extracts and monosodium iodoacetate-induced osteoarthritis in rats and acetic acid-induced writhing in mice. Nutrients. 2022 Mar 24;14(7):1356.
47. Eddin LB, Jha NK, Meeran MN, Kesari KK, Beiram R, Ojha S. Neuroprotective potential of limonene and limonene containing natural products. Molecules. 2021 Jul 27;26(15):4535.
48. Zaynoun ST, Johnson BE, Frain-Bell W. A study of oil of bergamot and its importance as a phototoxic agent: II. Factors which affect the phototoxic reaction induced by bergamot oil and psoralen derivatives. Contact Dermatitis. 1977 May;3(5):225-39.
49. Brun JP. The production of perfumes in antiquity: the cases of Delos and Paestum. American Journal of Archaeology. 2000 Apr 1;104(2):277-308.
50. Kaddu S, Kerl H, Wolf P. Accidental bullous phototoxic reactions to bergamot aromatherapy oil. Journal of the American Academy of Dermatology. 2001 Sep 1;45(3):458-61.
51. Russo C, Lombardo GE, Bruschetta G, Rapisarda A, Maugeri A, Navarra M. Bergamot Byproducts: A Sustainable Source to Counteract Inflammation. Nutrients. 2024 Jan;16(2):259.
52. Custureri IM, Giuffrè AM, Loizzo MR, Tundis R, Soria AC, Sicari V. Bergamot flavoured olive oil: Comparison between enrichment processes, evaluation of shelf-life and health properties. Applied Food Research. 2024 Jun 1;4(1):100400.
53. Osaili TM, Dhanasekaran DK, Zeb F, Faris ME, Naja F, Radwan H, Ismail LC, Hasan H, Hashim M, Obaid RS. A status review on health-promoting properties and global regulation of chemical components. Molecules. 2023 Feb 14;28(4):1809.
54. Corasaniti MT, Bagetta G, Morrone LA, Tonin P, Hamamura K, Hayashi T, Guida F, Maione S, Scuteri D. Efficacy of chemical components in relieving cancer pain: a systematic review and meta-analysis. International journal of molecular sciences. 2023 Apr 11;24(8):7085.

*****