REVIEW ARTICLE

A Review of Botanical Aspects and Various Pharmacological Actions of Bergamot (*Citrus bergamia*) Essential Oil

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ABSTRACT

In this review article, there is a brief about Bergamot essential oil, this article tells about the descriptive information about botanical aspects, significance and characteristics, anatomy, chemistry, its pharmacological activity, and toxicology of Bergamot essential oil. *Citrus bergamia Risso,* a *combination of Citrus limon L* and *Citrus aurantium* is the scientific name for the citrus fruit known as bergamot. It belongs to the family Rutaceae and the genus *Citrus*. BEO shows different type of pharmacological activity like anti-anxiety, wound healing, neuroprotective, anti-depressant, antiproliferative, antibacterial, anticancer, antioxidant, anti-inflammatory and antinociceptive, anti-mycoplasmal, anti-fungal andAntiallodynic. BEO contains various volatile and non-volatile fractions.

Keywords: *Citrus bergamia*, Antidepressant activity, Antinociception, Wound healing, Anxiolytic, Antiproliferative, Antibacterial, Antifungal, limonene.

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INTRODUCTION

Citrus *bergamia* Risso, a combination of *Citrus limon* L and *Citrus aurantium* is the scientific name for the citrus fruit known as bergamot. It belongs to the family Rutaceae and the genus *Citrus*.[1] The citrus fruit bergamot has a greenish-yellow peel, is acidic, and has a delicate aroma. Essential bergamot oil is its principal product, produced by cold processing or steam distillation of the pericarp region of the fresh fruit's mesocarp.[2] Since it may be combined with other essences, BEO is primarily utilized in the global fragrance business to fix aromatic bouquets of perfumes. BEO is employed in the culinary industry to flavor a variety of goods including candy, teas, and soft drinks. The flavorful invigorating aroma of BEO and its extracts is added to earl grey tea (EGT) blends.[3,4]

The blend of teas used in EGT and the caliber and quantity of bergamot essential oil used all affect its flavor and quality. Among the cosmetic and therapeutic uses cited are dermatology, gynecology, dentistry, and ophthalmology. In aromatherapy, BEO is also used to reduce stress-related symptoms. Italy's bergamot essential oil has a stellar reputation in the global trade community. Harvest season has a big impact on the chemical composition. Psoralens, coumarins and bergamottin are found in volatile (93–96%) and nonvolatile (4–7%) fractions of bergamot essential oil.Linalool (8.8%), linalyl acetate (30.1%), terpinene (6.8%), limonene (37.2%), and pinene (6.2%), among others. (Z) Geraniol, decanal, linalyl acetate, and limonene oxide are aroma chemicals that mimic bergamot. In contrast to other citrus oils, bergamot essential oil contains very little limonene and a lot more linalyl acetate and linalool.[5,6] Among the characteristics of BEO to look for is the proportion of linalyl acetate to linalool, often known as "essence degree" because it affects the aroma. Melanogenic, antinociceptive, antiproliferative, anxiolytic, neuroprotective, antioxidant, and antibacterial are just a few of the pharmacological effects it has. cytotoxic, anti-allergic, and wound-healing sedative, calming, and soothing, anti-tumor mood booster, anti-dermatophyte, anti-fungal, anti-bacterial, and anti-mycoplasmal.[7]

Botanical Aspects

The name bergamot (*C. bergamia* Risso and Poiteau) was initially presented in 1818 by Joseph Antoine Risso and Pierre Antoine Poiteau. Two subspecies of *Citrus aurantium* L. are recognized by *C. aurantium* ssp. *aurantium* L., sometimes known as sour orange and *C. aurantium* ssp. *bergamia* is

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included in the Integrated Taxonomic Information System (Risso and Poiteau) Engler, Wight & Arn. Ex, commonly referred to as orange bergamot. It is believed that bergamot is either a mutation of the lemon or a mix of sour orange and lemon. Bergamot tree is an evergreen little tree that can reach a height of 12 meters. It has an upright, dark grayish-brown cylindrical trunk and very thin, erratic roots that may or may not have spines. It spreads through grafting, bitter orange produces the finest outcomes since it produces robust, trees with lengthy lives that are especially unresponsive to adverse weather. Fruits of the plant of bergamot ripen between November and March, and the plant blooms in April and May. The fruit, known as a hesperidium or subglobose to pyriform berry with a little flattening, has several glands plus a peel that's 3 to 6 mm thick; the tissue that contains the essential oil cavities is this peel. Chlorophyll breakdown and an increase in carotenoids are the main causes of changes in rind color. The main pigments are xanthophylls and carotenoids. Contribute to the prevailing yellow concentration of flavonoids. Aromatic substances offer the pulp and juice their strongest scent. It seems that bergamot appeared later in the *Citrus* phylogeny group and was not recognized by the ancient writers.[8] Some others assert that the hybrid originated outside of Italy, either in the Canary Islands, Greece, or the Antilles, and that Calabria was only later introduced to it. One legend claims that Columbus brought the hybrid to Italy by way of the Spanish city of Berga, which gave rise to the name "bergamot" for fruit. A more convincing explanation for the name's derivation is that the Turkish term "beg-a-mudi," which translates to "pears of the Prince," is where the name "bergamot" originates, considering how similar the pears are to that phrase.[9]

Significance and Characteristics of *Citrus* Eos

"Product made from a naturally occurring raw material derived from plants, either through dry distillation, steam distillation, or mechanical extraction from the epicarp of the citrus fruit following physical methods to separate any aqueous phase." is how the ISO defines an EO (ISO 2020 document ISO 9235: 2013-2.11). Three production processes are used, one of which is reserved only for *Citrus* EOs. As a result, *Citrus* EOs may be easily identified from other EOs based on their chemical composition and method of manufacturing. Distilled essential oils only contain unstable compounds; pressed cold essential oils constitute larger chemical compounds and molecules not present in distilled essential oils. The citrus fruit's second characteristic essential oil is that the fruit itself can be used to make other products such as candy peels, "cells," albedo, etc., and the essential oil is often a supplementary item, with fruit juice serving as the main offering from an economic standpoint. Mandarins, lemons, sweet oranges, and grapefruits are all covered by this; however, bergamots and bitter oranges are not, as their fruit juice is usually produced in trace amounts, if at all. This helps to explain why both EOs are more expensive.[10]

Citrus Fruits Anatomy

The modified berry known as "hesperidium," which is produced by citrus species, is nearly spherical in shape and has a peel or thick and tough outer rind that shields the juicy segments of the fruit, or endocarp which are composed of fluid-filled trichomes. The rind is composed of a thicker, Albedo is the name of the deeper, spongy mesocarp (from Latin albedo, a derivation of albus) and a colored, thin, and superficial exocarp known as flavedo (from the classical Latin *flavus*). The flavedo has numerous EO-containing spaces known as lacuna and is composed of tiny, dense collenchyma cells with chromoplasts. It is comprised of many EO-bearing cavities known as lacuna or lumina and is made up of tiny, dense chromoplast-containing collenchyma cells. Within the epidermis' outermost layer, it has distinct stomata and is covered by a waterproof cuticle. The bergamot fruit's roughly spherical center cavities are encircled by four to six secretory cell layers, which are produced in a schizolysigenous way. Parenchymal cells first split apart (schizogenesis of the intercellular gap), and then in later stages of cavity growth, more cell disintegration occurs (lysogeny). These EO-filled lacunae have no walls, are scattered at varying depths, and fill with ripening fruit. Their diameters vary from 0.4 to 0.6 mm, and are commonly divided into three categories: primary, secondary, and tertiary cavities. The preferred method for obtaining citrus essential oils is now because of the oil holes' surface dispersion, cold pressing or mechanical treatment[11].

Chemistry of BEO

BEO stands out in the domain of citrus essential oils. Although limonene, which can make up 80 to 95% of the total composition, is the most prevalent monoterpene hydrocarbon, BEO contains a greater quantity of oxygenated terpenes like linalyl acetate, linalool and a lower concentration of limonene and related monoterpenes. All c.p. EOs fall into one of two categories: volatile or non-volatile. Numerous factors, including phenology, geographic provenance, pedoclimatic traits of the producing region, and genetics (cultivars), modifications to agronomical practices, long-term climate changes, and evolving technologies for the expression of apparel, influence the volatile fraction's composition, which is highly variable. Adulteration detection is important but difficult with BEO due to its high market value and complex of influencing factors, which makes it a popular target for fraudulent manipulations. This is especially true in contrast to other citrus essential oils. Despite this variety, the essential oil (EO)'s main components–limonene, linalool, pinene, linalyl acetate, and terpinene–makeup < 90% of the mixture[12].

Volatile Fraction

In 93–96% of BEO's total content is made up of the volatile component. Linalool, linalyl acetate, and limonene make up the majority of this fraction. However, In the scientific literature, more than 100 chemicals have been identified and described. While BEO has a much lower hydrocarbon content than other citrus essential oils, monoterpene hydrocarbons–α-pinene (4–11%), limonene (25–55%) and γ-terpinene (5–11%)–dominate the volatile fraction. Sesquiterpene hydrocarbons like -bisabolene,caryophyllene, (E)-bergamotene, are also present in volatile fraction. When compared to other citrus essential

oils, mono and sesquiterpene hydrocarbons' oxygenated derivatives can make up over half of the volatile component and are found in much higher concentrations; in extra citrus EOs, their percentage ranges from 1 to 6%. Terpenic alcohols and ester (to a lesser extent, aldehydes and oxides) are notably prevalent. The most significant monoterpene alcohol is linalool, which is contemporary in extremely more concentrations (2–20%), although bisabolol, a sesquiterpene alcohol that is rare but seems exclusive to Bergamot, is present in very small amounts.[12]

Non-volatile Fraction

Apart from inert chemicals like pigments and waxes, this fraction accounts for 4–7% of the overall content of the EO and is primarily composed of oxygen-containing heterocyclic compounds, primarily coumarins and psoralens, with modest quantities of polymethoxyflavones (tetra-O-methyl scutellarin, sinensetin). This fraction is primarily composed of four compounds: bergapten and bergamottin are two psoralens, and 2 coumarins, geranyloxy-7-methoxycoumarin (0.08–0.22%) and citropten are characteristic but not unique to Candida *bergamia*. Psoralens found in genuine EOs include by akangelicin, bergaptol, epoxybergamottin, isoimperatorin, biakangelicol, oxypeucedanin, and oxypeucedanin hydrate.[13]

Organoleptic Characteristics

- Color: The color range is green to yellow-brown to greenish-yellow. The color diminishes with age, specifically if the EO is left in direct sunlight.
- Odor: Rich, crisp, lemony, and sweet lavender-like and tea-like is the top note. The dry-down is balsamic, greasy-herbaceous, and lemony-citrus.
- The distilled FCF EO smells lighter, with notes of p-cymene and linalyl acetate coming through. It also has a very clean and fresh, zesty, and pithy lemony dry-down.
- The terpene-less EO is far less fresh and just somewhat stronger than the c.p. one.[14]

Pharmacological Activities

The pharmaceutical, culinary, and cosmetics industries all commonly use BEO**.** It is used in suntan preparations because it contains bergapten, the active melanogenic ingredient. By altering sensitive pain perception, bergamot essential oil is applied in complementary medicine to lessen neuropathic and nociceptive pain.[15,16] Intraplantar injections of linalool, linalyl acetate, and bergamot essential oil demonstrated a peripheral opioid pathway-produced response in the capsaicin test.[17] Mice were shown to exhibit antiallodynic effects.[18] Wounds can heal more quickly when the oil is used.[19] It was discovered that bergamot essential oil was cytotoxic to Human neuroblastoma cells SH-SY5Y, reducing the speed of their expansion via a process that involved both necrotic and apoptotic cell death.[20,21] The bioactive compounds 5-geranyloxy-7-methoxycoumarin and bergamottin were found to be in charge of the cytotoxic effects of BEO. *In-vitro*, bergamot essential oil (EO) reduced the growth of NDMA-induced tumors by over 70%. BEO and d-Limonene have been demonstrated to modify autophagic pathways in cells from SH-SY5Y. Liposomal BEO exhibits superior anticancer efficaciousness against SH-SY5Y cells due to its enhanced bioavailability and stability.[22] Additionally, it has been discovered to lessen injury-induced decreases in phosphorylated glycogen synthase kinase 3 (phospho-GSK-3), phosphorylated protein kinase B (phospho-Akt), which lessen neuronal damage produced by excitotoxic stimuli *in-vitro*.[23] The nervous system is calmed and soothed by the mild sedative properties of bergamot essential oil. Bergamot's pleasant, revitalizing aroma has been shown to alleviate behavioral depression and stress anxiety in rats exposed to chronic stress.[24-26] In a β-carotene bleaching test, bergamot EO demonstrated good radical scavenging activity (IC_{50} = 42.6 g/mL) because of its high d-limonene content[27-29]. Bergamot essential oil (EO) inhibits growth of *S. typhimurium, Salmonella enterica, Arcobacter butzleri, Pseudomonas putida, E. faecalis,* and *Listeria monocytogenes*[30,31]. According to several studies, bergamot essential oil (EO) exhibits broad antifungal activity against *Fusarium solani, Penicillium italicum, F. sporotrichioides, Debaryomyces hansenii, F. oxysporum, Aspergillus niger ,Rhodotorula rubra, Candida albicans, A. flavus, Penicillium italicum*[32]. Antifungal properties against *Trichophyton, Microsporum*, and *Epidermophyton dermatophytes* were also discovered.[33] It might be applied in the treatment of animal dermatophytosis. Its antibacterial and antifungal effects are thought to be mediated through increased production of ROS, which is crucial to its accomplishment in human polymorphonuclear leukocytes. Potent antimycoplasmal effects of bergamot essential oil were also discovered against *Mycoplasma fermentans, Mycoplasma hominis,* and *Mycoplasma pneumoniae*[34] (Figure 1).

CNS Pharmacology of BEO

Neuropharmacology

Aromatherapy, a complementary medicine that is most utilized in developed countries to treat mood and moderate signs of stress-related diseases like depression, anxiety, behavioral abnormalities associated with dementia, and chronic pain, frequently uses BEO. The each constituent of BEO enters the CNS through Blood brain barrier after administration by different routes.

Effects on behavior, on EEG spectrum power

BEO acts in a recognizable and recurring manner on the rat CNS. When administered systemically at increasing dosages. It produces sedative and stimulant effects on EEG spectra. Increased movement and behavior have been observed after receiving higher dosages of BEO; this is consistent with a predominant greater in the fast frequency bands documented from the cortex and hippocampus. After receiving 250 l/kg of the Plant complex, rats exhibited behavioral arousal, which was defined by stereotyped movements and an increase in energy power in relation to theta (4.25–8 Hz) and α frequency bands in the cortex, as well as beta (13.25–21 Hz) and alpha (8.25–13 Hz) rhythms in the hippocampus. The large dose

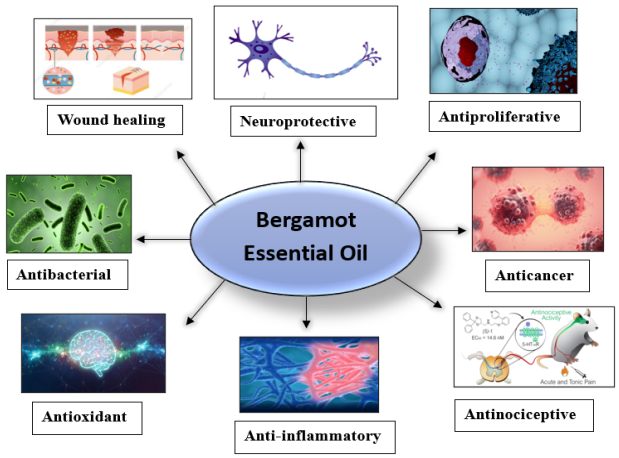

Figure 1: Reported biological activities of BEO

of BEO induced behavioral excitation and EEG loss of synchronization along with a noteworthy rise in the cortical theta band strengths and hippocampal beta band strength. Furthermore, recent studies conducted Research conducted in vivo and *in-vitro* has shown that BEO specifically affects fundamental synaptic neurotransmission pathways including synaptic release mediated by exocytosis and carriers.

Impact on normal transmission in synaps

According to Microdialysis Research, BEO increases extracellular amino acids like glycine, taurine and aspartate in the hippocampal region of rats that are free to move around. However, the latter effect is inhibited in experiments where there is no Ca^{2+} in the cerebrospinal fluid.

Neuroprotection against excitotoxicity

The excitatory amino acid leakage from nerve terminals and the absence of the motivating factor necessary for transporters of membranes to operate in ischemia conditions are both results of anoxic depolarization. Additionally, the concurrent generation of reactive oxygen species (ROS) induce the inverted mode of action of glutamate transporters, which results in abnormally high levels of excitatory amino acids at synapses. This ultimately leads to damage of neurons caused by ischemia insult.[35] Particularly, BEO administered intraperitoneally to rats lessens the brain damage brought on by localized cerebral ischemia in a dose-dependent way. Microdialysis experiments reveal, surprisingly, that BEO significantly lowers excitatory amino acid efflux, which is normally increased in the brain region shortly afterward occlusion of the middle cerebral artery (MCA)

Anxiolytic effect

The anxiolytic/sedative-like effects of BEO were investigated in rats. The results show that in animal behavioral tasks that cannot be superimposed on the DZP, BEO has anxiolytic/relaxant effects. The rats were administered BEO i.p. half an hour before each test. The results of this investigation indicate that when it comes to the calming and anxiolytic effects, BEO behaves differently from DZP.[36]

Antidepressant activity

The investigation of antidepressant effects resulting from olfactory stimulation with various odorants was conducted using the forced swimming test, a validated technique for evaluating antidepressant effects. In the experiment, the smell of lemons reduced overall immobility time and enhanced reduction in total motionlessness time caused by imipramine. It cannot be assumed that the synergistic effect of imipramine and lemon scent resulted from lemon scent blocking imipramine metabolism. Lemon scent reduced locomotor activity in open space, suggesting that its effects are more akin to those of antidepressants than psychostimulants. Citral, one of the principal components in lemon odor, has properties similar to those of lemon odor.

Antinociception

The study show the impact of BEO, which contains linalyl acetate and linalool as its primary unstable components, on the capsaicin test. After an intraplantar injection of 1.6 g of capsaicin, the injected paw experienced a brief reflexive licking and biting response. A dose-dependent reduction in the nociceptive behavioral response induced by capsaicin was observed upon intraplantar injection of BEO. Male ddY (SD) mice, weighing between 22 and 26 g utilized. (Shizuoka Laboratory Centre, Japan). The effects of artificial or saline CSF on pain induced by capsaicin were not statistically significant when administered intraplantarly as BEO (5 g) and linalool (1.25 g). When morphine, benzophenone, and linalool were injected together, the nociceptive response elicited by capsaicin was more strongly affected.[37]

Wound healing

Traditional medicine uses BEO (subsp. *bergamia C. aurantium* L) as an anthelminthic and antibacterial agent, as well as to promote wound healing. Though research on BEO's impact on immunity is lacking, it seems to have strong antibacterial activity. They examined how BEO impacted human polymorphonuclear leukocytes (PMN) production of ROS and how Ca^{2+} contributed to the functional reactions that BEO induced in these cells. The findings imply that BEO enhanced the production of intracellular ROS in human PMN, with extracellular (and, to a lesser degree, intracellular) Ca^{2+} having a part. Ultimately, this study is the first to show that BEO can increase the production of ROS in human PMN. This effect may support BEO's natural proinflammatory potential and aid in its ability to fight infections and heal tissue. It is important to carefully consider how these discoveries may affect BEO needs therapeutic applications.

Antiproliferative effect

The human neuroblastoma cell line SH-SY5Y was employed in the studies. The omission of the trypan blue dye experiment was the initial test in which the cytotoxic effects of BEOs were evaluated. When colored BEOs (0.01–0.03%) were added to

SH-SY5Y cells for a full day, the percentage of cells that died increased significantly, beginning at 0.02%. The cell count assay and the MTT test were used to gauge the rate of cell proliferation. A potential role for BEO in cancer prevention is suggested by its pharmaco-toxicological profile, which for the first time suggests that 5-geranyloxy-7-methoxycoumarin and bergamottin may have a significant role in the antiproliferative impact of BEO.

Neuroprotection opposing brain injury induced by lschemic condition

The impact of BEO on the brain in rats suffering from chronic localized cerebral ischemia were investigated. After 24 hours of middle cerebral artery occlusion (MCAo), BEO (0.1–0.5 mL/kg, but not 1-mL/kg) was administered i.p. suggestively reduced size of the infarct. The most therapeutic dose (0.5 mL/kg) significantly reduced cell death in the overall brain, particularly in the striatum and motor cortex region, according to tissue slice staining with TTC. Little Dialysistests revealed that BEO (0.5 mL/kg) significantly decreased excitatory amino acid efflux, particularly glutamate and glutamate, in the frontal parietal cortex, but had no effect on basal amino acid levels. 24 hours following continuous MCAo, there was Akt, the prosurvival kinase, has been phosphorylated and activated significantly more. as demonstrated by Western blotting tests. Yes, BEO phosphorylated GSK-3 more highly. GSK-3 is a detrimental subsequent kinase whose activity is adversely controlled by the phosphorylation of Akt.

To treat mental health, improve positive feelings: pilot study

Treatments for mental illnesses are desperately needed globally because of the shortcomings high cost of the current medical care systems. EO aromatherapy is not a toxic, affordable treatment option for a range of mental health conditions. This pilot study examined how BEO inhalation affects mental health and well-being as determined by a mental health assessment's positive and negative affect scale treatment center in Utah, USA. The study involved fifty-seven women, ages 23 to 70, who were deemed suitable volunteers. Participants' happy moods were 17% higher after 15 minutes of exposure to bergamot essential oil than in the control group. This study suggests that BEO aromatherapy may be a helpful adjunct treatment to enhance people's mental health and well-being. It offers preliminary proof of the effectiveness and safety of inhaling BEOon mental health in a facility for mental health care.

anti-inflammatory and antioxidant due to D-limonene present in beo

This study used rat model of ulcerative colitis (UC) to examine the anti-inflammatory properties of D-limonene. Male SD rats in good health take randomly: control, UC (untreated), and UC (treatment with 50 or 100 mg/kg D limonene). In UC rats, D-limonene's anti-inflammatory qualities significantly decreased disease activity and colonic mucosal damage. Furthermore, UC rats produced higher levels of antioxidant proteins, COX-II, and inducible nitric oxide synthase (iNOS) rats by D-limonene therapy. By controlling the iNOS, COX2, PGE2, TGF, and ERK1/2 signaling pathways, D-limonene reduced the expression of MMP2 and 9 mRNA in a UC rat model, suggesting that it may have antioxidant and anti-inflammatory properties.

Antibacterial effect

The most potent oil was bergamot, and the most potent antibacterial ingredient was linalool. *In-vitro*, compared to gram-positive bacteria and negative bacteria, demonstrated more sensitivity; however, *E. coli* O157 and *Campylobacter jejuni* were inhibited by linalool vapor bergamot and linalool oils.

Antifungal activity

This study showed the substantial in vi-tro efficaciousness of BEO oppose to a broad spectrum of clinical isolates of different harmful dermatophytes. Tests were conducted on ninety-two isolates from seven distinct dermatophyte species. The isolates 12 isolates were obtained from culture collection of clinical isolates kept at the Catholic University Medical Center's Mycology Section. of *Epidermophyton floccosum*, 18 isolates of *Trichophyton rubrum*, 15 isolates of *Trichophyton interdigitale*, 2 isolates of *Trichophyton tonsurans,* 24 isolates of *Microsporum canis*, and 1 isolate of *Microsporum gypseum*.

Component Present in BEO

Limonene

Limonene is a monoterpene hydrocarbon. To evaluate anxiolytic activity, male Swiss albino mice were utilized. The EPM test revealed significant changes in all the parameters measured upon inhaling 0.5 and 1.0% (+)-limonene[38]**.** The anti-AChE and anti-BChE properties of limonene was shows in relation to Alzheimer's disease[39]. Limonene-prevented mice that received a glycoprotein intrathecal injection showed mechanical hyperalgesia brought on by spared nerve injury (SNI). The potential of limonene to lessen hyperalgesia and thus relieve migraine pain.[40] Intraperitoneal limonene administration improved the survival rate of animals with induced seizures and the delay of convulsions.[41] Tested on impulsively hypertensive rats, D-limonene's ability to prevent ischemia-associated brain damage was examined those who were prone to stroke. The ability of D-limonene to reduce the systolic BP in SHRsp rats following a stroke.[42] To ascertain The mechanism of action of limonene as an antidepressant impact affecting hormone levels of the HPA axis and neurotransmitters in the prefrontal cortex and hippocampal regions was investigated. When D-limonene was taken orally, the increase in immobility caused by SNI in the FST was reduced.[43]

Linalool is a monoterpene alcohol. Its anticonvulsant effects, which are attributed to NMDA receptor antagonistic activity and a decrease in potassium-stimulated (but not basal) glutamate release in cortical synaptosomes, call for more research as a potential strategy for antiepileptic medication development.[44] It exhibits proliferative and anti-inflammatory properties. linalyl acetate and Linalool are the main components of BEO, and the oil's antinociceptive properties

are dependent on the quantity of linalool it contains. Behavioral testing revealed that a local linalool intraplantar injection decreased pain perception in mice protocol of hypersensitive neuropathic caused by partial sciatic nerve ligation (PSNL). The anti-allodynic benefits may result from a decrease in spinal ERK activation, according to a more in-depth molecular analysis. In addition, it helps with depression and anxiety.[45]

Toxicity of bergamot essential oil

According to the European Medicines Agency majority of important issues regarding BEO toxicity include melanogenic and photosensitive components. characteristics, which have historically been linked due to the furocoumarins (psoralens) it contains, such as bergapten. When used as a pure material, BEO may even be photo-mutagenic.[46] Individual characteristics such as the patient's age, sex, and sun sensitivity appear to have no effect on skin reactivity, but a number of particular elements, like the amount of ethanol and psoralens in the car, the amount of skin hydration, and degree of natural pigmentation, can influence psoralen-induced photosensitivity.[47] The number of examples describing the negative effects of BEO has not significantly increased, despite the increased use of products derived from bergamot in recent years. This may be because fewer real cases are reported, but it may also be because safer psoralen-free bergamot derivatives are more widely available. The International Fragrance Association (IFRA) recommends keeping the BEO level of skin care products to no more than 0.4%, in addition to limiting the psoralen content. Initially 2 to 72 hours after BEO with psoralens application, a light-related skin reaction typically manifests as an appearance similar to bullous dermatitis[48]. According to Tisser and Young, the bulk of minor compounds in BEO, as well as all three of the major constituents–limonene, linalyl acetate, and linalool, are safe for systemic usage. The EO's acute toxicity in rats has only ever been documented at dosages greater than the 10 g/kg threshold. However, until further clinical data are obtained, BEO should be avoided in patients who are lactating or pregnant, as there is a lack of specific information regarding its safety profile in these populations. Furthermore, patients with allergic diathesis and other more susceptible populations, such as children and the elderly, should use caution due to a lack of safety data. Finally, prolonged and excessive use of because of the cytotoxic and antiproliferative effects of large dosages that have been shown *in-vitro*, BEO over time may produce issues even in healthy patients. Ingestion of large quantities of BEO orally, followed by artificial or natural sunbathing, has been reported to cause neurological symptoms (including muscle cramps, fasciculations, paraesthesias, and blurred vision) and skin photosensitivity.[49] Overall, the safety profile of BEO is still being determined; however, by utilizing formulations devoid of psoralen and restricting consumption to short intervals, severe adverse effects (such as photosensitivity and neurological symptoms) can be circumvented.

CONCLUSION

Regarding citrus essential oils, BEO is unique. However, 80–95% of the composition can consist of limonene. This fraction makes about 4–7% of the total content of the EO and is mostly made up of heterocyclic compounds that include oxygen, mainly coumarins and psoralens, with small amounts of polymethoxyflavones, aside from inert substances like pigments and waxes. Numerous biological activities of BEO, including impacts on the central nervous and cardiovascular systems, were demonstrated. These activities included antibacterial, anti-inflammatory, antiproliferative, and analgesic properties. Only clinical trials examining the effects of aromatherapy have been reported to date, despite the fact that these findings suggest possible clinical applications for BEO in the future. These studies were conducted mainly to look at the lowering of stress reactions and anxiolytic effects. According to their findings, aromatherapy treatments using BEO may help lessen the symptoms of stress and anxiety.

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