# A Review of the Application and Pharmacological Properties of α-Bisabolol and α-Bisabolol-Rich Oils

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REVIEW

# A Review of the Application and Pharmacological Properties of α-Bisabolol and α-Bisabolol-Rich Oils

**Guy P. P. Kamatou · Alvaro M. Viljoen**

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**Abstract** α-Bisabolol is a naturally occurring sesquiterpene alcohol which was first isolated from *Matricaria chamomilla* (Asteraceae) in the twentieth century and has since been identified in other aromatic plants such as *Eremanthus erythropappus*, *Smyrniopsis aucheri* and *Vanillosmopsis* species. Recently, α-bisabolol was identified as a major constituent of *Salvia runcinata* essential oil, a plant indigenous to South Africa. The use of α-bisabolol or bisabolol-rich oil as an anti-inflammatory agent is ubiquitous. This compound also exhibits several other pharmacological properties such as analgesic, antibiotic and anticancer activities. Mutagenicity and genotoxicity of bisabolol have also been investigated. Due to the low toxicity associated with bisabolol the Food and Drug Administration (FDA) has granted this constituent with Generally Regarded as Safe (GRAS) status which has promoted its use as an active ingredient in several commercial products. This review aims to summarise the role of α-bisabolol in pharmacological and/or physiological processes and to discuss some of the possible mechanisms of action of this commercially important molecule.

**Keywords** α-Bisabolol · Biological properties · *Matricaria chamomilla* · Toxicity

## Introduction

Terpenoids constitute a class of lipophilic secondary metabolites derived from mevalonate and isopentenyl pyrophosphate which occur widely in nature [1, 2]. These phytochemicals are diverse in structure and collectively, they comprise a major component of the volatile fraction of various aromatic plants. Monoterpenes and sesquiterpenes are compounds generally found in the essential oils of several aromatic plants. Sesquiterpenes ($C_{15}$), are formed biosynthetically from three five-carbon isoprene units or are synthesised industrially from monoterpenoid feedstocks [3]. Sesquiterpenes have been identified as the active constituents present in several medicinal plants used in traditional medicine, with a wide range of biological properties including anti-infective, anti-oxidant, anti-inflammatory, anticancer and anticholinesterase activities. Furthermore, sesquiterpenes are also associated with important biological and physiological functions such as pheromone interactions, antifeedants, phyto-alexins, etc. [4].

α-(−)-Bisabolol, is a monocyclic sesquiterpene alcohol which was first isolated in 1951 by Isaac and collaborators from the blossoms of chamomile (*Matricaria chamomilla*; Asteraceae) and it has since been established that α-(−)-bisabolol may exist in four possible stereoisomers (Fig. 1) [5].

α-(−)-Bisabolol has been widely used as an ingredient in dermatological and cosmetic formulations such as after-shave creams, hand- and body-lotions, deodorants, lipsticks, sun-care and after-sun products, baby care products and sport creams [6]. It is a preferred active ingredient for protection against the recurring stresses of the environment on the skin. The most important biological activities of bisabolol are the anti-inflammatory, anti-irritant, antibacterial and non-allergenic properties.

## Natural Origin of Bisabolol

Generally, when referring to bisabolol, α-(−)-bisabolol is implied. α-(−)-Bisabolol (also known as levomenol) is

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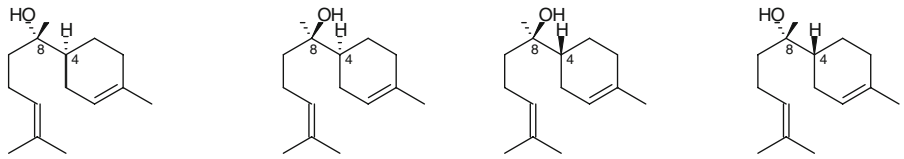


(–)-α-Bisabolol (–)-epi-α-Bisabolol (+)-α-Bisabolol (+)-epi-α-Bisabolol

**Fig. 1** Stereoisomers of α-(−)-bisabolol

present in various plants and can be obtained by hydrodistillation of German chamomile (*Matricaria chamomilla*), sage (*Salvia runcinata* and certain chemotypes of the closely related *S. stenophylla*), *Vanillosmopsis* sp. (e.g. *V. pohlii, V. arborea*) and *Myoporum grassifolium. Matricaria chamomilla* and *S. runcinata* contain up to 50 and 90% α-(−)-bisabolol, respectively [7, 8]. Another less explored source of α-bisabolol is the wood of Candeia (*Eremanthus erythropappus*) which may contain up to 85% of α-bisabolol [9].

## Uses

α-(−)-Bisabolol is used in decorative cosmetics, fine fragrances, shampoos and other toiletries as well as in non-cosmetic products such as household cleaners and detergents and also in pharmaceutical formulations [10, 11]. The main application of α-bisabolol in the pharmaceutical sector is related to its anti-inflammatory, antispasmodic, anti-allergic, drug permeation and vermifuge properties [9, 12].

## Chemical and Physical Properties

Bisabolol, also known as alpha,4-dimethyl-alpha-(4-methyl-3-pentenyl)-3-cyclohexene-1-methanol, is a sesquiterpene alcohol with the chemical formula $C_{15}H_{26}O$. Bisabolol has a weak sweet flora aroma. It is a colourless liquid with a relatively low density (0.93) and a boiling point of 153 °C at 12 Torr [13]. Bisabolol is a very lipophilic substance, with a propensity to oxidise. It is almost insoluble in water, nevertheless, soluble in ethanol. The oxidation products are mainly bisabolol-oxide A and B [14]. The enantiomer α-(+)-bisabolol is rare in nature and the synthetic equivalent is generally a mixture of α-(±)-bisabolol.

## Biological Properties of Bisabolol and Bisabolol-rich Oil

In many parts of the world, German chamomile (confusingly referred to as "European ginseng") is considered to have panacea-like properties (universal drug) and it used to treat a diversity of conditions [15]. The high level of α-bisabolol present in chamomile oil is credited for providing the several biological properties ranging from anti-infective activity to anticancer, anti-inflammatory, anticholinesterase properties, and also for its ability to enhance transdermal drug permeation [16–20].

### Anti-infective Properties of Bisabolol

Several aromatic plants (chamomile and sage) are used as traditional remedies to treat various ailments. Many studies have described the composition of essential oils and reported the biological activity of the major constituents [21]. Although the antimicrobial activity of certain compounds such as carvacrol, 1,8-cineole and camphor is well established [22, 23], the antimicrobial activity of many sesquiterpenes such as bisabolol has only been reported for a limited number of pathogens. For instance, α-bisabolol tested active against Gram-positive bacteria, fungi and *Candida albicans* [24]. The antimicrobial activity of 20 essential oil constituents including α-bisabolol was investigated using the microdilution method. Although, α-bisabolol exhibited poor activity against *Staphylococcus aureus*, *Bacillus cereus* and *Escherichia coli*, the activity against *C. albicans* was promising and comparable to linalool (MIC values: 36 and 39 mM, respectively) [18].

The antifungal activity of sesquiterpenes including bisabolol against *Botrytis cinerea* was examined using the fungal growth inhibition assay. Bisabolol showed mycelial growth inhibition from 50 ppm, retaining an inhibition percentage of 49 and 64% at 100 and 200 ppm, respectively, after 6 days [25]. *Salvia runcinata* (≈60% bisabolol) also exhibited in vitro antibacterial activity against *S. aureus*, *S. epidermidis*, *B. cereus* and *B. subtilis* with the MIC values ranging from 1.6 to 3.1 mg/ml [26].

The antimicrobial activity of chamomile oil varies in the literature according to the method used and the test organism implicated. While promising antimicrobial activity of the oil was recorded against *Aspergillus ochraceus* and *S. aureus* [27], in other studies, chamomile oil showed no zone of inhibition against *Corynebacterium amycolatum*, *S. aureus*, *E. coli*, *C. amycolatum* and *C. albicans* [28].

The effect of three oils (anise oil, dwarf-pine oil and chamomile oil) was investigated in vitro against acyclovir-sensitive and acyclovir-resistant herpes simplex virus type 1 (HSV-1) using a plaque reduction assay. All three oils exhibited antiviral activity against the acyclovir-sensitive

HSV strain KOS and acyclovir-resistant clinical HSV isolates as well as acyclovir-resistant Angelotti with chamomile oil exhibiting the highest activity against the clinical acyclovir-resistant HSV-1 strains [29]. Plaque formation was reduced by 97–99.9% when the viruses were pre-incubated with acyclovir before attachment to the host cell [29]. The essential oil of chamomile also demonstrated dose-dependent virucidal activity against the HSV-2 with an $IC_{50}$ value of 0.003%. The possible mechanism of action was further investigated and the results showed that the essential oils affected the virus by interrupting adsorption of herpes viruses in a different manner compared to the acyclovir which is effective after attachment inside the infected cells [29, 30].

Four sesquiterpenes; nerolidol, farnesol, bisabolol and apritone were investigated for their ability to increase the susceptibility of *S. aureus* to some conventional antibiotics (ciprofloxacin, clindamycin, erythromycin, gentamicin, tetracycline and vancomycin). The results showed that low concentrations (0.5–2 mM) of nerolidol, bisabolol or apritone enhanced the susceptibility of *S. aureus* to the antibiotic tested [31]. Furthermore, it was suggested that the sesquiterpenoid compounds may act by disrupting the normal barrier function of the bacterial cell membrane, allowing the permeation into the cell of exogenous solutes such as antibiotics. This effect was found to be more pronounced for Gram-positive bacteria, probably due to the lack of additional permeability barriers, particularly the outer membrane of Gram-negative bacteria. A possible structural resemblance of sesquiterpenes to membrane lipids (e.g., linear molecules with internal lipophilic character and a more polar terminus) may also account for the effectiveness of sesquiterpenes as enhancers of membrane permeability. For instance, nerolidol and farnesol (with longer hydrocarbon tails) were found to be more effective as skin penetration enhancers than bisabolol [32].

## Antiplasmodial Activity

German chamomile oil (with bisabolol as the major compound) is used to treat conditions such as dizziness, neuralgia, muscle cramping, headache, malaria and fever. Various essential oils containing bisabolol have shown antiplasmodial activity. For instance, the antiplasmodial activity of *S. runcinata* ($\approx$60% of α-bisabolol) tested against the chloroquine-resistant strain FCR-3 using the $^{3}$H-hypoxanthine assay exhibited good activity ($IC_{50}$ value: 1.2 μg/mL) [26]. However, when α-bisabolol was evaluated as a single component, poor activity was recorded in comparison to the positive control quinine ($IC_{50}$ value: 307 and 0.29 μM, respectively). This result implies other compounds (either minor or major) are important in the biological activity of the oil and suggest that the activity of the crude oil is not always derived from its major constituent as generally speculated.

## Anti-oxidant, Anti-inflammatory Activity and the Effect of Bisabolol on the Skin

### *Anti-oxidant and Anti-inflammatory Activity*

Increasing evidence has suggested that many degenerative diseases such as brain dysfunction, cancer, heart disease and immune system decline could be the result of cellular damage caused by free radicals and that anti-oxidants may play an important role in disease prevention [33]. The commonly used anti-oxidants, butylated hydroxyanisol and butylated hydroxytoluene are synthetic chemicals and the possible toxicity of these anti-oxidants has resulted in their reduced use [34]. In recent years, several natural anti-oxidants have appeared on the market and are generally regarded as safe [35]. The anti-oxidant activity has been determined by investigating the effects of α-bisabolol to interfere with reactive oxygen species (ROS) on chemiluminescence of human neutrophil bursts (*C. albicans* and *N*-formyl-methionyl-leucyl-phenylalanine) and cell-free systems (SIN-1 and $H_2O_2$/$HOCl^-$). The results indicated that α-bisabolol significantly inhibits the luminol-amplified chemiluminescence at concentrations ranging from 7.7 to 31 μg/mL for *C. albicans* and *N*-formyl-methionyl-leucyl-phenylalanine, respectively. A similar effect was observed in the SIN-1 and $H_2O_2$/$HOCl^-$ systems suggesting bisabolol as a means of improving the antioxidant capacity [36]. Although bisabolol has been claimed to exhibit anti-oxidant activity on chemical and/or biological tests, an in vitro study showed that α-bisabolol exhibited poor antioxidant activity against the DPPH radical ($IC_{50}$ value $>$ 450 μg/mL) [18].

Chamomile essential oil is well known and has been used for centuries as an anti-inflammatory agent and for alleviating the symptoms associated with eczema, dermatitis and other pronounced irritation. Volatile constituents of the essential oil of chamomile, notably chamazulene and α-bisabolol, exert anti-inflammatory activity partly due to the inhibition of leukotriene synthesis [15, 37]. The sesquiterpenes such as α-bisabolol appear to be good 5-lipoxygenase (5-LOX) inhibitors and have been widely reported to have a skin soothing action which strongly inhibits 5-LOX in vitro. The $IC_{50}$ value of this compound on 5-LOX ranged between 10 and 30 μg/mL [17]. As α-bisabolol exhibited activity against the 5-LOX assay, the essential oils containing higher levels of this sesquiterpene alcohol are thus expected to inhibit the enzyme. Studies have demonstrated that *S. runcinata* oil is good 5-LOX inhibitor with the $IC_{50}$ value of 22.5 μg/mL. However, the activity of the oil against the COX-2 enzyme was poor [26].

*Effect of Bisabolol on the Skin*

Hyperpigmentation is the darkening of an area of skin generally due to the increase of melanin. Several factors such as inflammatory skin disorders, allergic contact and irritant contact dermatitis are the main cause of hyperpigmentation. The increase of melanogenic enzyme activity or number of melanocytes may be associated with epidermal and dermal hyperpigmentation [38]. It is known that the cAMP response element (CRE) is involved in the α-melanocyte-stimulating hormone (α-MSH) production. A study was conducted in order to determine the depigmentation effect of α-bisabolol using two different assays: a cAMP response element luciferase reporter assay and melanin assay. The results indicated that α-bisabolol inhibited the CRE activation induced by α-MSH. Similarly, the compound reduced the melanin content induced by α-MSH.

Tyrosinase is an enzyme that catalyses the production of melanin. Studies have demonstrated that α-MSH induces tyrosinase gene expression via the activation of MITF (Microphthalmia-associated transcription factor) gene expression. An investigation was conducted to determine the effect of α-bisabolol on the α-MSH-induced expression of MITF and tyrosinase genes and results indicated that α-bisabolol inhibited the gene expression of MITF and tyrosinase implying that α-bisabolol inhibits melanogenesis by lowering intra cellular cAMP levels [38].

## Bisabolol as Permeation Enhancers

The percutaneous route of drug delivery is advantageous over intravenous and oral administration. Nevertheless, the architecture of the stratum corneum makes it a formidable barrier to the topical and transdermal administration of therapeutic agents [39, 40]. The most common approach to alleviate stratum corneum permeability is the concomitant use of penetration enhancers [41]. There are several classes of penetration enhancers and terpenes obtained by distillation from aromatic plants are very efficient for several reasons. They are natural substances, non toxic, extensively used in transdermal delivery as permeation enhancers and Generally Regarded as Safe (GRAS) [42].

Dapiprazole, a known α-blocking drug, is used in topical eye therapy for the treatment of chronic simple glaucoma, for induction of pre-operative miosis and for reversion of pharmacologically induced mydriasis. Many scientists have suggested that transdermal administration might present some advantages over the oral route in subjects suffering from the conditions described above by lower doses, provide sustained and constant plasma levels, and improve the patients' compliance [43]. The in vitro permeation rate of dapiprazole base through hairless mouse skin was investigated in a series of liquid and semisolid vehicles, both in the absence and in the presence of different penetration enhancers. It was found that the permeability coefficient of dapiprazole was significantly promoted (up to 73 times) by some terpenes such as *l*-limonene, α-bisabolol and terpinolene [43]. Furthermore, the natural occurring (−)-α-bisabolol was twice as active as enhancer for dapiprazole penetration than racemic (±)-α-bisabolol [43]. The variation in the activity of bisabolol demonstrated the role of functional groups in the pharmacological properties of certain compounds.

## In Vitro and in Vivo Toxicity of Bisabolol and Bisabolol-Rich Oil

Several studies have been conducted to determine the toxicity of α-bisabolol. Twenty essential oil constituents from various classes (ketones, aldehydes, alcohols, phenols and terpene hydrocarbons) were tested on human epithelial cells using the MTT assay. α-Bisabolol and nerolidol were the most toxic compounds ($IC_{50}$ value of 41.8 and 5.5 μM, respectively) [18]. *Salvia runcinata* (≈60% of the oil) was also found to be toxic on human epithelial cells ($IC_{50}$ value: 2.5 μg/ml). However, this toxicity was not correlated to the level of α-bisabolol since toxic compounds such as nerolidol and camphor were also identified in the oil [26]. The effect of α-bisabolol on the gastrotoxicity of acetylsalicylic acid was examined and it was found that when α-bisabolol is administered orally (dose 0.8–80 mg/kg) with acetylsalicylic acid (dose 200 mg/kg), a significant protective effect is observed ($P < 0.05$) [44]. It is important to mention that the results of any bioassay depend on the method and the organisms implicated in the experiment and extrapolating the results of an in vitro experiment to animal models is not always correct. Numerous studies have confirmed the safety of chamomile essential oil which contains a high level of bisabolol [42].

## Mutagenicity, Genotoxic Effects and Anticancer Activity of α-Bisabolol and Bisabolol-rich Oil and Possible Mechanism of Action

Cancer is a genetic disease and a possible solution to fight the disease is to reduce exposure to mutagens, chemicals capable of inducing genomic mutations and disrupting cellular functions potentially leading to cancer. The ability of α-bisabolol to induce or increase the frequency of mutation in TA100, TA98, TA97a and TA1535 *Salmonella typhimurium* strains, using the microsome assay with and without addition of S9 mixture was evaluated. No increase in the number of $his^+$ revertant colonies over the negative control values was observed with any of the four tested strains at concentrations ranging from 0 to 5000 μg/plate [6].

The capacity of α-bisabolol in chamomile essential oil to reduce the frequency of micronucleated polychromatic erythrocytes (MNPE) induced by daunorubicin in mice was studied by flow cytometry before the administration of the compounds and at interval periods of 24 h for 72-h post-administration. Results showed no capacity of α-bisabolol to significantly increase the rate of micronuclei. However, a significant dose-dependent inhibitory effect of the molecule was noted. After 48-h exposure, the percentage inhibition with 120 and 1200 mg/kg of α-bisabolol was 52 and 65%, respectively [45]. The study also suggested that α-bisabolol was the molecule responsible of the biological activities of the volatile fractions of the plant [45].

An experiment was conducted in order to investigate the effects of α-bisabolol on human and rat glioma cells. It was found that α-bisabolol has a strong time- and dose-dependent cytotoxic effect on highly malignant human and rat glioma cell lines ($EC_{50} = 2$ μM). At a lower concentrations (2.5–3.5 μM), the viability of these cells was reduced after 24 h by 50% with respect to untreated cells [46]. Glioma cells treated with a high concentration of α-bisabolol (10.0 μM) resulted in a 100% cell death. The study also revealed that the viability of normal rat glial cells (non-neuronial cells) was not affected by treatment with α-bisabolol at the same concentrations as above. Suggestions were made that α-bisabolol-induced cytotoxicity in glioma cells may result from the induction of apoptosis through the mitochondrial pathway [46]. Recent research has demonstrated that α-bisabolol exerts a rapid and efficient apoptosis-inducing action selectively towards human and murine malignant glioblastoma cell lines through mitochondrial damage. Studies have also established that α-bisabolol can initiate the apoptosis-inducing action towards highly malignant human pancreatic carcinoma cell lines without affecting human fibroblast viability [47].

## Effect of Bisabolol on Animal Reproduction and Development

The effects of α-bisabolol was investigated on pregnant rats dosed daily via gavage on days 6–15 of gestation, at concentrations ranging from 250 to 3000 mg/kg body weight. There was no toxic effect on pre-natal development at doses up to 1000 mg/kg body weight. However, at concentrations higher than 1000 mg/kg body weight, a significant reduction in fetal number and subsequent increase in resorption rate was observed. In addition, slight sedation, reduced feed intake and reduction of body weight gain were observed at high dose [48].

The chemoprotection of fertility by chamomile essential oil (rich in α-bisabolol) was investigated by administration of 500 mg/kg of essential oil and 5 mg/kg of daunorubicin (a free radical inductor) to mice and the sperm concentration, motility, viability and fertilisation capacity were examined. Sperm viability was over 90%, while no effect on motility and sperm concentration could be observed. The fertilisation capacity decreased considerably in the group of animals treated with daunorubicin, while the fertilisation capacity in the groups receiving chamomile essential oil was maintained [48] indicating that the essential oil exhibited a chemopreventive capacity.

## Insecticidal Activity and Insect Repellent Capacity of Bisabolol

Many studies have been undertaken to find new insecticidal compounds of plant origin. The insecticidal activity of the heartwood essential oil (*Vanillosmopsis pohlii*) (which contains α-bisabolol in high levels) and the pure sesquiterpene α-bisabolol have been investigated. The oil and α-bisabolol exhibited insecticidal activity against *Bemisia argentifolii*, the white fly fruit plague. In the search for alternative chemical control against *Aedes aegypti*, the larvicidal effect based on the percentage mortality after 24 h of ten essential oils was tested against the yellow fever mosquito *Aedes aegypti*. Among the oils tested, the essential oil of *Vanillosmopsis arborea* (rich in α-bisabolol) displayed the highest larvicidal activity, with $CL_{50}$ of 15.9 mg/mL and $CL_{90}$ of 28.5 mg/mL [49].

## Other Points Not Discussed

The oil obtained from *Matricaria chamomilla* was investigated for attention-deficit hyperactivity disorder (ADHD). The observational study was carried out on three (14–16 year old) male psychiatric out patients, diagnosed with ADHD. Using comparisons of Conners' parent ratings, an improvement in ADHD symptoms rated by a clinician, who did not have any information about the *Matricaria chamomilla* medication, was observed [50]. The bisabolol (applied at 50, 200 and 1000 mg/kg body weight/day) a NOAEL of 200 mg/kg body weight/day was found in a 28-day study on rats. At 1000 mg/kg body eight/day, body weight gain was slightly reduced.

Chamomile was found to exhibit antispasmodic activity with α-bisabolol and flavonoids identified as compounds responsible for the activity [24]. Furthermore, α-bisabolol exhibited capacity protection against gastric effects of aspirin ($PH_2$). The antipeptic action and proteolytic capacity of α-bisabolol was examined and results showed that bisabolol exhibited antipeptic action in a dose dependent manner. It was also found that the proteolytic activity of pepsin is reduced by 50% through addition of bisabolol

[51]. Essential oil obtained from chamomile is also known to display no irritant properties. Studies conducted on hen's eggs chorioallantoic membrane revealed no irritating effects of the oil [29]. In vitro studies found that α-bisabolol and α-terpineol exhibited wound-healing properties with $EC_{50}$ of 228 and 240 μg/g mouse, respectively [52].

## Concluding Comments

Bisabolol is a naturally occurring constituent accumulated in the essential oil of various species with a vast range of uses (cosmetics, fine fragrances, pharmaceutical). This compound although identified in various aromatic plants is present in substantial amounts in *Matricaria chamomilla*, *Salvia runcinata*, *Myoporum grassifolium* and *Eremanthus erythropappus* essential oils. The in vitro and in vivo investigation of bisabolol and bisabolol-rich oil has demonstrated several pharmacological properties ranging from anti-inflammatory to anticancer activities. Although the antimicrobial activity of bisabolol is known, it is imperative that this molecule be tested on a broader range of pathogens to establish the spectrum of antimicrobial activity. Bisabolol and bisabolol rich-oil have also demonstrated the capacity to enhance the percutaneous absorption of certain molecules and may prove to be an important ingredient in future cosmetic and skin care products. Taking into account the low toxicity of bisabolol, it is important to determine other pharmacological properties such as the potential use of this compound in alleviating conditions related to the central nervous system. The action of essential components in the cytoplasmic membrane and on membrane-bound phospholipids is not yet fully understood and this could prove to be a rewarding topic in future investigations. Elucidation of the various mechanisms of action ascribed to bisabolol may be useful to provide a firm scientific basis for the inclusion of this bioactive molecule in various consumer products.

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