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„The use of sesquitepene α-bisabolol in cosmetics products“

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To all the people who have been with me during my studies,

Thank you.

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LIST OF ABBREVIATIONS

AP-1: Activator Protein 1

cAMP: cyclic adenosine monophosphate

COX-2: Cyclooxygenase 2

CRE: cAMP response element

CREB: CRE binding protein

DMAPP: Dimethylallyl diphosphate

FDA: Food and Drug Administration

GC: Gas chromatography

GGPP: Geranylgeranyl diphosphate

GPP: Geranyl diphosphate

IFRA: International Fragrance Association

iNOS: Inducible nitric oxide synthase

IPP: Isopentenyl diphosphate

LB: Luria Bertani

MED: Minimum erythematous dose

MEP: 2-C-methyl-d-erythritol-4-phosphate pathway

MITF: Microphthalmia-associated transcription factor

MSH: Melanocyte-stimulating hormone

MVA: Mevalonate pathway

NCS: Natural Complex Substances

NESIL: No Expected Sensitization Induction Level

NK-B: Natural killer-B cells

NO: Nitric oxide

PGE2: Prostaglandin E_2

pTSN-MrBBS: Plasmid pTrc99A containing MrBBS (synthase gene) of *Matricaria recutita*

RIFM: The Research Institute for Fragrances

RP-HPLC: Reversed-phase high performance liquid chromatography

SCORAD: Scoring Atopic Dermatitis

SPF: Sun protection factor

SQL: Sesquieterpene lactone

TPS: Terpene synthase

UV: Ultraviolet

UVA: Ultraviolet A

UVB: Ultraviolet B

VAS: Visual analog scale

1 ABSTRACT

This thesis focuses on many pharmacological-toxicological properties of the sesquiterpene alcohol bisabolol, which then justify its wide use in many different cosmetic products. Several ways of synthesis, chromatographic identification and occurrence in plants are described. Many studies on the numerous effects and mechanisms of action, as well as toxicological evaluation of bisabolol confirm the safety and a wide range of application of this substance. This overview allows better understanding of the importance of bisabolol not only in cosmetics, but also in pharmacy in general, which has grown significantly in the last 25 years. From baby products and wound-healing ointments to perfumes and make-up products, bisabolol is shown to be a broad-acting ingredient that plays a significant role in cosmetic preparations. All information needed for this article was collected through PubMed, SciFinder, and Google Scholar.

2 ZUSAMMENFASSUNG

In dieser Arbeit werden zahlreiche pharmakologisch-toxikologischen Eigenschaften des Sesquiterpen-Alkohols Bisabolol untersucht, die seine breite Verwendung in vielen verschiedenen kosmetischen Produkten erklären. Es werden verschiedene Wege der Synthese, der chromatographischen Identifizierung und des Vorkommens in Pflanzen beschrieben. Zahlreiche Studien zu den zahlreichen Wirkungen und Wirkungsmechanismen sowie die toxikologische Bewertung von Bisabolol bestätigen die Unbedenklichkeit und ein breites Anwendungsspektrum dieser Substanz. Dieser Überblick ermöglicht ein besseres Verständnis für die Bedeutung von Bisabolol nicht nur in der Kosmetik, sondern auch in der Pharmazie, die in den letzten 25 Jahren stark zugenommen hat. Von Babyprodukten und Wundheilungssalben bis hin zu Parfüms und Make-up-Produkten erweist sich Bisabolol als ein breit wirkender Inhaltsstoff, der in kosmetischen Zubereitungen eine wichtige Rolle spielt. Alle für diesen Artikel notwendigen Informationen wurden über PubMed, SciFinder und Google Scholar gesammelt.

3 INTRODUCTION

In the European Union, the manufacture, labeling and dispensing of cosmetics is controlled by European Commission Regulation No. 1223/2009. This regulation defines cosmetic products as:

"any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours." [1]

But if you want to define the wide use of cosmetic products in more detail, you will have to go back a few years, namely 10000 years into the past. To cleanse and nourish their skin, as well as to protect it from the sun and wind, to make the skin smell pleasant, the ancient Egyptians used ointments and oils. The ancient use of cosmetic products also underlines the current subdivision into seven categories: body care, decorative cosmetics, hair care, oral care, perfume, skin care and sun care. A precise overview of the use of cosmetic products is shown in the figure 1. [2]

Quantified data indicate that Europeans see cosmetic products as an essential part of their everyday lifestyle. They use them primarily to enhance their well-being, protect their health, and improve their self-esteem. Depending on age and gender, a wide variety of cosmetic products are used with varying intensity. Some examples are presented in the figure 2. [2]

Figure 1. Overview of cosmetic categories. [2]

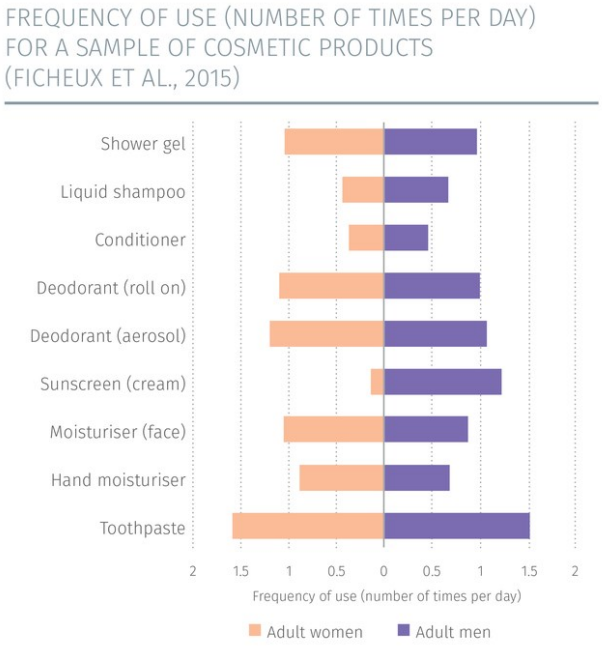

Figure 2. Frequency of use for a sample of cosmetic products. [2]

The interest in new skin care products, particularly those based on natural sources, has increased significantly in recent decades. The plant world provides a high-quality source of natural products, which in turn are used to manufacture various products for most human needs: from food to medicines and even for beauty purposes. Plant extracts provide a raw material with a complex composition of several active molecules, which explains the use of plants and their active ingredients for various skin conditions. [3][4][5]

One of the world's most popular medicinal plants is *Matricaria chamomilla* (synonym: *Matricaria recutita*, family *Asteraceae*), commonly known as German chamomile (figure 3). Due to the composition of its essential oil, chamomile is used in aromatherapy, perfumery, as well as in the food industry. The oil as such has anti-inflammatory, antiseptic, antispasmodic, antimicrobial, soothing, and wound healing properties, which are of great importance in the pharmaceutical industry and cosmetics. According to the European Pharmacopoeia, the most commonly used method for obtaining the essential oil from the chamomile flower heads in their almost fully bloomed stage is steam distillation. One of the main active ingredients in this oil is (α)-bisabolol, also recognized as levomenol. [6][7][8][9]

Figure 3. Different plant parts and habit of German chamomile: flowering plant (**a**); flower head (**b**); ray floret (**c**); disk floret (**d**); capitulum l (**e**); teeth/petals of disc floret (**f**); anthers (**g**); stigma (**h**); seed. (**i**); fresh flower harvest (**j**). [7]

4 BISABOLOL

4.1 CHEMICAL ASPECT, NATURAL SOURCES AND IDENTIFICATION

Bisabolol (α-4-dimethyl-α-(4-methyl-3-pentenyl)-3-cyclohexene-1-methanol) is a bioactive, liquid, unsaturated, monocyclic sesquiterpene alcohol, which is a major constituent in the essential oil of chamomile and other plants. It is used in many health products, as well as in medical and skin care cosmetics. In general, when one refers to bisabolol, (-)-α-bisabolol is implied. The colour of bisabolol, also known es levomenol, varies from colorless to pale yellow. It is a slightly viscous liquid with the chemical formula $C_{15}H_{26}O$ that has a weak sweet floral scent. It has the molecular weight of 222.37 Dalton, a boiling point at 299.83 ºC and a melting point of 55.96 ºC. Bisabolol is a very lipophilic substance, almost insoluble in water, that can be mixed with alcohols, oils and lipophilic substances. [8][10][11][12][13][14]

Bisabolol was first isolated from the blossoms of chamomile by Isaac and his associates in 1951. In the meantime, other sources of isolation are also known. These include aromatic plants such as *Eremanthus erythropappus*, *Smyrniopsis aucheri*, *Myoporum grassifolium* and *Vanillosmopsis species*. bisabolol has also recently been identified as the main ingredient of the essential oil of a plant native to South Africa, *Salvia runcinata*. [14][15] The list of plants cointaining bisabolol, composed by The International Fragrance Association is given in table 1.

Table 1. Natural Complex Substances (NCS) containing bisabolol. [16]

CONCENTRATION IN NCS (%)	NAME OF NCS	BOTANICAL NAME	CONCENTRATION IN NCS (%)	NAME OF NCS	BOTANICAL NAME
0.2	Angelica seed oil	Angelica archangelica L.	0.2	Lavandin concrete	Lavandula officinalis x Lavandula latifolia
0.15	Arnica absolute	Arnica montana L.	0.35	Lavandin grosso oil	Lavandula officinalis x Lavandula latifolia
0.6	Arnica oils, montana	Arnica montana L.	0.03	Lavandin oil	Lavandula officinalis x Lavandula latifolia
1.4	Baccharis dracunculifolia oil	Baccharis dracunculifolia	0.3	Lavandin super oil	Lavendula super
0.2	Basil oil chemotype linalool	Ocimum basilicum L.	0.5	Lemon oil folded (10x)	Citrus limon (L.) Burm. F.
2	Cabreuva oil	Myrocarpus frondosus Fr. Allem	0.3	Lime oil folded	Citrus aurantfolia (Christman) Swingle
0.3	Carrot seed oil	Daucus carota	0.08	Mastic oil	Pistacia lentiscus
0.6	Cedarwood oil, Chinese	Cupressus funebris Endl.	0.2	Populus nigra absolute	Populus nigra L.
0.5	Cedarwood oil,terpeneless	Juniperus Mexicana Schiede	0.5	Sandalwood oil	Santalum album L.
0.15	Cedarwood oil, Texas	Juniperus Mexicana Schiede	0.6	Sandalwood oil, New Caledonian	Santalum austrocaledonicum Vieill
0.6	Cedarwood oil, Virginian	Juniperus virginiana L.	0.3	Schinus terebenthifolius CO2 extract	Schinus terebenthifolius Raddi
4	Chamomile flower oil, blue	Matricaria chamomilla L.	0.1	Turmeric oil	Curcuma longa L
0.2	Fir needle oil, Siberian	Abies siberica Ledeb	0.3	Yarrow oil	Achillea millefolium L.
0.3	Lavandin absolute	Lavandula officinalis x Lavandula latifolia	2	Zdravetz oil	Geranium macrorrhizzum L.

Bisabolol can be identified by gas chromatography (GC) as well as by reversed-phase high performance liquid chromatography (RP-HPLC). The aim of the RP-HPLC method was to identify bisabolol in appropriate purity. A mixture of acetonitrile, water, and phosphoric acid in a ratio of 19:80:1 and acetonitrile were used as the mobile phase in a linear gradient elution program with a flow rate of 0.8 mL/min from 50:50 to 0:100 in 25 min, and back to 50:50 in 5 min. The injection volume was 20 µl. Bisabolol was detected at 200 nm. [12][17] (figure 4)

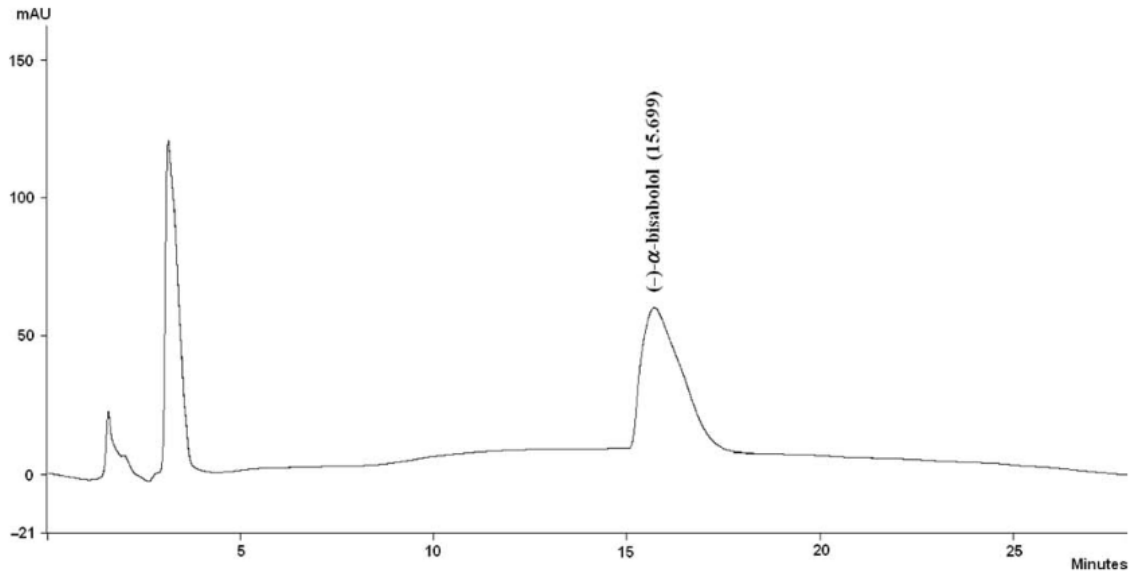

Figure 4. Representative chromatogram of bisabolol detection.[17]

There are several studies that indicate new sources of bisabolol, such as the one from 2009, which examined and confirmed that the essential oil from leaves of *Plinia cerrocampanensis (Myrtaceae)* contained bisabolol as its main ingredient, at a concentration of 42.8%. This plant is native to Panama and represents an outstanding new natural source of bisabolol. [18]

4.2 SYNTHESIS OF BISABOLOL

The natural synthesis of monoterpenes, sesquiterpenes and diterpenes involves the enzyme terpene synthase (TPS), as well as building blocks isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP). There are two possible ways to obtain IPP and DMAPP: The mevalonate pathway (MVA) and the 2-C-methyl-d-erythritol-4-phosphate pathway (MEP). It can be noted that Gram-negative bacteria such as *Escherichia coli* use the MEP pathway, while eukaryotes, archaea, Gram-positive *cocci* and humans claim the MVA pathway. The enzyme prenyltransferase combines the IPP and DMAPP units to create the prenyl diphosphates. Prenyl diphosphates represent the terpenoid precursors and include geranyl diphosphate (GPP), farnesyl diphosphate (FPP), and geranylgeranyl diphosphate (GGPP). Subsequently, these prenyl diphosphate molecules are converted by plant into terpenoids via TPS.[19] (figure 5)

According to the current developments, it can be stated that a bisabolol synthase has been identified in German chamomile. This enzyme allows enantioselective synthesis of the single terpenoid product. Also, it should be noted that *Sacharomyces cerevisiae* expresses the bisabolol synthase enzyme as a natural source. Here, the yield of bisabolol after four days of cultivation corresponds to a concentration of 8 mg/L. The studies signify that a combination of the mevalonate pathway and farnesyl diphosphate synthase enables a serious increase in (-)-α-bisabolol production. This assumes genetically modified *E. coli*. The amount of bisabolol obtained from it corresponds to a concentration of 9.1 g/L. This way of obtaining bisabolol is considered promising and, after appropriate optimization of the process, may lead to lowering the cost of industrial production. [19]

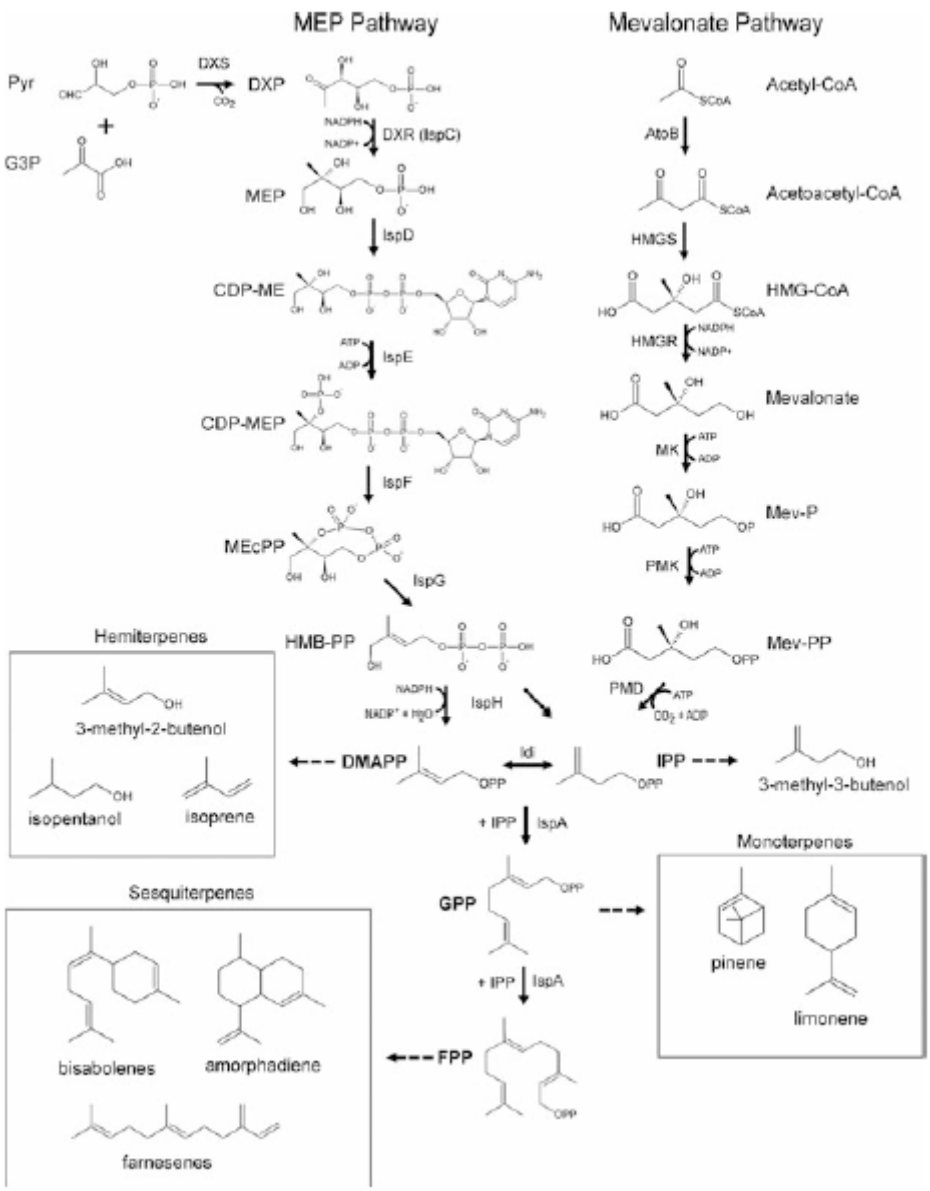

Figure 5. Isoprenoid biosynthetic pathways. The MEP pathway and mevalonate pathway.[20]

Bisabolol is obtained by distillation or by chemical synthesis. As active ingredient it can mainly be found in Brazilian candeia tree (*Eremanthus erythropappus*). However, the distillation method using this plant source has not proved successful. The synthesis product often suffers from impurities, which can be explained by undesirable isomers of α-bisabolol. As mentioned above, (-)-α-bisabolol can be chemically synthesized. The synthetic obtained (-)-α-bisabolol contains other diastereomers [(+)-α-bisabolol, (+/-)-*epi*-α-bisabolol] and other undesirable side products. (figure 6 - figure 9) It can be deduced that the synthetic production of bisabolol would require an economically unfavorable purification process to achieve

high optical purity. However, the synthetic provision of bisabolol and its stereoisomers has recently replaced the natural bisabolol production from the Brazilian Candeia Tree. [19][21]

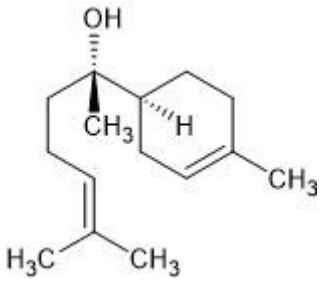

Figure 6. Structure of (-)-α-bisabolol

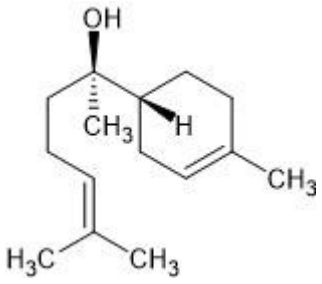

Figure 7. Structure of (+)-α-bisabolol

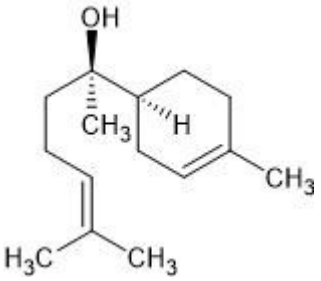

Figure 8. Structure of (-)-*epi*-α-bisabolol

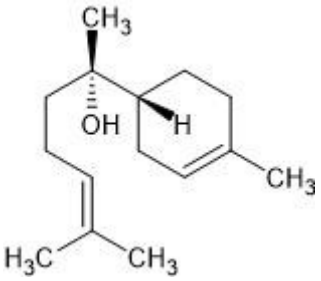

Figure 9. Structure of (+)-*epi*-α-bisabolol

A concrete example of the quantitatively high production of bisabolol is defined more precisely according to Fu and coworkers as follows [19]:

From an economic point of view, extraction with n-dodecane and vegetable oils is also a convenient method of production. For this purpose, an *E. coli* strain was generated, which contains highly concentrated bisabolol. Extraction was performed according to an *in-situ* extraction procedure using natural plant oils. The experiment was carried out using the combination of the mevalonate pathway and farnesyldiphosphate synthase, and it was this combinatorial expression that enabled a dramatic increase in bisabolol production. The bisabolol synthase required for the mevalonate pathway was isolated from German chamomile. After optimization of the culture conditions, a fed-batch fermentation was performed. This

resulted in efficient bisabolol production, with a titer of 9.1 g/L. Furthermore, an extraction procedure using vegetable oils was developed for *in-situ* extraction and showed a very high yield (> 98%). [19] Mass spectrometer of the standard is shown in figure 10, as well as the mass spectrometer of bisabolol produced in *E. coli* in figure 11.

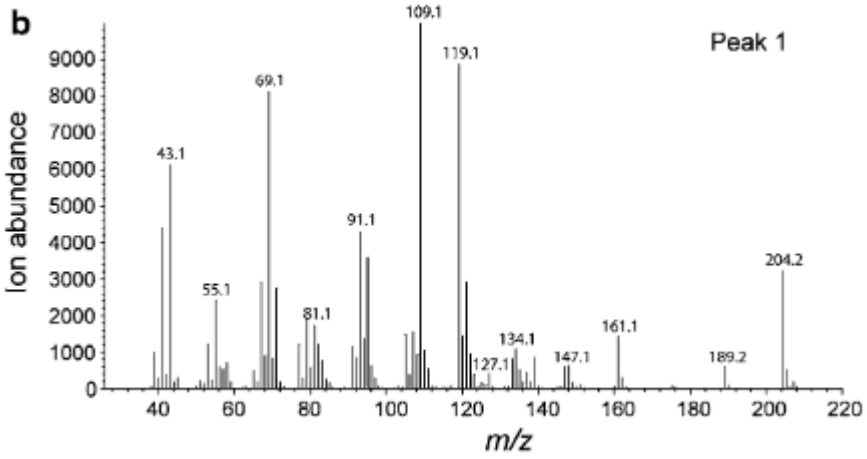

Figure 10. Mass spectra of bisabolol standard. [19]

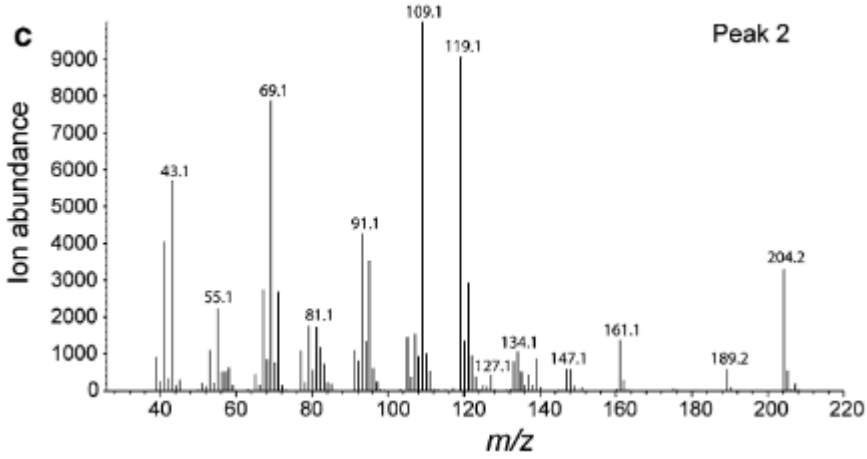

Figure 11. Mass spectra of bisabolol produced in *E. coli* cells harboring the plasmid pTSN-MrBBS. Each cell was cultivated in LB medium overlaid with 20% (v/v) n-dodecane at 30 °C for 48 h. [19]

4.3 MAIN EFFECTS

The plant ingredient bisabolol can be attributed a broad spectrum of effects, for external as well as for internal use. One of the proven effects of bisabolol is spasmolytic. Therefore, chamomile extracts in various dosage forms are recommended for spasmodic complaints. [22]

The spasmolytic effect is attributable to the hydrophilic groups at the structural level. In order to obtain a concrete comparison of the effects, the spasmolytic activity of chamomile preparations was evaluated in a study. The activity of the lipophilic, as well as hydrophilic compounds has been investigated on the isolated guinea pig ileum. The tests have shown that the ingredients of chamomile in the product KAMILLOSAN® exhibited dose-dependent effects on the smooth muscles of the intestine. Bisabolol oxides A and B, as well as chamomile oil itself have been shown to have a papaverine-like effect in experiments. These include spasmolytic and musculotropic effects. In comparison, the essential oil has shown the lowest effect. The effect of bisabolol was twice as strong as that of both bisabolol oxides A and B. It can be concluded that bisabolol has an equally strong effect as the comparative substance papaverine. The authors concluded from the experiment that the relative effects of bisabolol and papaverine were practically indistinguishable. [22]

The very important effect of bisabolol, which has been proven in numerous studies, is the anti-inflammatory activity. A comparative study was also conducted in this regard, with the following being provided as test substances: (-)-bisabolol, (+)-bisabolol, bisabolol oxide A and B, olive oil and DRAGOSTANOL®. The study was conducted in the context of an animal challenge. After peroral ingestion of various concentrations of the test substances, a 1% suspension of carageenin was injected into the rats, namely into the hind paw. The second hind paw was used to determine the edema mass. A linear relationship was observed when a dose-response curve was analyzed. With reference to bisabolol, it can be confirmed that DRAGOSTANOL® can be attributed 1/4 of the bisabolol effect, both oxides A and B each 1/3 of the effect of bisabolol and other test substances about half of the effect. [23]

In another experiment, the effect of α-bisabolol on ultraviolet (UV) erythema was investigated using depilated guinea pigs. The test substance was applied both orally and percutaneously. Salicylamide was defined as the standard. Subsequently, the animals were irradiated. In order to better localize the erythema, a plastic foil with holes was applied to the animals' backs. The analysis was performed two hours after irradiation. Compared to salicylamide, bisabolol showed 1/3 of the anti-inflammatory effect. Inhibition of erythema formation is also dose-dependent in this case. [23]

Furthermore, arthritis was induced in rats. Comparative experiments were then performed with prednisolone and bisabolol. It was possible to determine an effective dose that resulted in inhibition of inflammation, and this was 250 mg/kg bisabolol. The anti-inflammatory effect was shown in particular by regression of swelling. This means that a dose of 500 mg/kg bisabolol corresponded approximately to the effect of 1.5 mg/kg of the known anti-inflammatory agent from the group of glucocorticoids prednisolone. [23]

Finally, the antipyretic effect of bisabolol was proved on female rats. A physiological saline solution, that contained 15% yeast and 15% traganth, was injected intramuscularly (1 ml/100 g body weight.) The purpose of the application of this solution was to produce a yeast fever. The test substances were applied perorally 16 hours later. An analgesic phenacetin served as a reference substance. To eliminate as much as possible the influence of room temperature on the test results, two control groups were also examined: a normal control group, which was untreated, and the fever control group, which received only yeast injection. The data showed that bisabolol at a dose of 2000 mg/kg reduced fever by 1.5 ºC for up to two hours. Compared to phenacetin, the onset of action is relatively late. [23]

Bisabolol also has a dose-dependent antipeptic, as well as gastroprotective effect. In particular, it reduces the proteolytic activity of pepsin by 50%. The effect of bisabolol on ulceracions caused by acetylsalicylic acid was investigated in rats. When bisabolol (0.8-80 mg/kg) was applied orally together with acetylsalicylic acid (200 mg/kg), significant protective properties of bisabolol were demonstrated. Another study in rats showed that bisabolol reduced the gastric damage caused by alcohol consumption. [24][25][26]

The antimicrobial effect of chamomile oil and bisabolol has also been confirmed. Due to its antifungal and bactericidal effects, bisabolol is nowadays widely used in cosmetic preparations, as well as in dental care products. [27][28][29]

There are studies that confirm that bisabolol exhibited leishimanicidal, and antitumor activity, as well as that it reduces visceral nociceptive pain. [30][31][32]

Due to its many beneficial effects, bisabolol is not only found in pharmaceutical products but also in over 1000 cosmetic products such as moisturizers, eye creams and cleansers. It is also a component in make-up industry, as well as in antiperspirants and sunscreens. [8]

4.4 SAFETY AND TOXICITY

With the exposure of cells to various mutagenic substances, cancer can occur. Therefore, it is mandatory to identify the certainty of non-mutagenic properties of substances used in therapy. So before specifying the uses of bisabolol in cosmetic industry, it is important to discuss the safety and toxicity aspects of this ingredient.[14]

Although considered and used in many formulations as a non-toxic ingredient, the full toxicological data on bisabolol were insufficient until recently. The mutagenicity of bisabolol was evaluated for the first time with TA100, TA98, TA97a and TA1535 *Salmonella typhi murium* with or without the addition of a metabolic activation system. Bisabolol doses were up to 100 g bisabolol (in ethanol) per plate. The increase in the number of revertants served as proof of positive mutagenicity. Since bisabolol did not increase revertant colonies in the tester strains, mutagenic activity of this substance in the Salmonella/microsome assay was excluded. In this assay, antimutagenicity was defined as a reduction in the mutagen-induced increase of the number of revertant colonies. The non-toxicity of the previously described non-toxic doses of bisabolol was tested, and since there was no reduction in the number of revertants and no change in background growth, the non-toxicity of the bisabolol doses was confirmed. To confirm the overall antimutagenic effect of bisabolol, the effect of this substance on direct-acting and indirect-acting mutagens was examined. Bisabolol inhibited the effect of multiple mutagens as for example

aflatoxin B1. It also showed a dose-dependent decrease in some indirect-acting mutagenic substances. This mechanism functions by inhibiting the activity of the hepatic monooxygenases CYP2B1/2 and CYP1A1. These enzymes are involved in the converting of promutagens into their active metabolites. [33][34]

Another study on rat liver microsomes showed that bisabolol inhibited pentoxyresorufin-o-deethylase and ethoxyresorufin-o-deethylase which are markers for cytochrome P450 isoforms, specifically the CYP2B and CYP1A subfamilies. CYP2B is responsible for the transformation of aflatoxin B1 into mutagenic metabolite, while CYPA1 isoform is involved in activation of promutagenic factors. Inhibition of these two enzymes could be taken as the mechanism of the antimutagenic effect of bisabolol. The interaction of bisabolol with cytochrome P450 enzymes, may indicate that this molecule is possibly metabolized by these enzymes. [35] In the chromosome aberration assay on V79-cells of Chinese hamster, where the genotoxicity of bisabolol was tested, bisabolol showed no relevant genotoxic effects. [33]

Bisabolol was also exanimated for photosensitization. 3% and 15% (v/v) alcohol solutions of bisabolol were applied to the shaved neck skin of male white Pirbright guinea pigs. Then the guinea pigs were irradiated with 7.9 kilolumen light with wavelength of 240-540 nm for 15 minutes. The protocol of dermal application followed by irradiation was carried out for five days. A group treated with 15% v/v bisabolol, but without irradiation was maintained to observe the high dose effect. The negative control was treated with alcohol and subsequently irradiated, the positive control with tetrachlorosalicylanilide and then radiation. After a nine-day nontreatment period, the protocol was repeated for two consecutive days. In this phase, bisabolol was dissolved in olive oil. Accordingly, negative control was also modified. After 12 days of no treatment, a soap solution was applied to the right shaved hind leg. On the left leg, the soap solution was applied, in which 3% and 15% bisabolol was dissolved. Positive control group was given tetrachlorosalicylanilide soap solution. Then followed irradiation and a three-day follow-up period. No photosensitivity was demonstrated in these animals. [36]

4.5 ALLERGENIC POTENTIAL

There are several cases indicating an allergenic potential of bisabolol. The first case dates to 1995, when a patient was tested with 1% bisabolol solution in petrolatum, which was followed by periorbital swelling. [37] In 2008, a second case of contact cheilitis was described, which was caused by lipstick containing bisabolol (Bisabolol 5% in petrolatum). [38]

In 2010, three cases of recurrent atopic dermatitis in children were reported that worsened with bisabolol-containing ointment treatment (Aquaphor®, Beiersdorf Inc, Hamburg, Germany). Since patch tests with lanolin and Amerchol L-101 gave negative results (also contained in the ointment) it appeared that bisabolol might have been the allergen. [39] Based on these three children, a further evaluation was performed on seven pediatric patients who showed intolerance to the same bisabolol-containing healing ointment. Four out of these seven patients who were tested with the manufacturer-provided ingredient had positive response to their own moisturizer in addition to bisabolol and to sesquiterpene lactone or Compositae or both. Improvement of allergy in these patients has occurred by avoidance of ointment. [40]

Another case report described a 14-year-old girl who suffered from acute cheilitis for more than two months. Patch tests, that were performed on this patient using the European baseline series and the patient's own cosmetics, showed positive reaction to the girl's lipstick. Ten ingredients of the lipstick were tested, and the results showed two positive reactions. Namely Bisabolol 5% pet. and Parsol® SL reacted positively to patch. [41]

In 2020, the Research Institute for Fragrances (RIFM) has evaluated bisabolol as a safe ingredient. The following criteria were tested: genotoxicity, repeated-dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety.
According to this evaluation, based on the RIFM criteria document, bisabolol was determined to be a non-genotoxic material with an exposure range appropriate for the repeated-dose toxicity endpoint. Bisabolol was labeled as a weak skin sensitizer with a defined NESIL (No Expected Sensitization Induction Level) value of 5500

μg/cm^2, showing no concern for phototoxicity or photoallergenicity and no risk to the aquatic compartment. This assessment also summarized the maximum acceptable concentrations for 12 different product categories of bisabolol, which can be seen in table 2. [42]

Table 2. The maximum acceptable concentrations in finished products for bisabolol. [42]

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.42
2	Products applied to the axillae	0.13
3	Products applied to the face/body using fingertips	2.5
4	Products related to fine fragrances	2.4
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.60
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.60
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.60
5D	Baby cream, oil, talc	0.20
6	Products with oral and lip exposure	1.4
7	Products applied to the hair with some hand contact	3.0
8	Products with significant ano-genital exposure (tampon)	0.20
9	Products with body and hand exposure, primarily rinse-off (bar soap)	4.6
10A	Household care products with mostly hand contact (hand dishwashing detergent)	4.6
10B	Aerosol air freshener	17
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.20
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No restriction

[a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity,skin sensitization, or any other endpoint evaluated in this safety assessment). For bisabolol, the basis was the reference dose of 2.0 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 5500 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet.

5 BISABOLOL IN COSMETIC PRODUCTS

The declaration of bisabolol as safe by Food and Drug Administration (FDA) and RIFM has encouraged its use as an active component in multiple commercial products. Due to its lower toxicity, bisabolol is nowadays used in decorative cosmetics, shampoos, baby products, fine fragrances, toiletries, but also in non-cosmetic products such as household cleaners and detergents. A detailed list of bisabolol-containing products from 1997 is shown in table 3. [36][42][43][44][45]

Table 3. Product formulation data for bisabolol. [36]

Product category	Number of formulations in category[1]	Number containing Bisabolol[1]	Concentration of use[2]
Baby lotions, oils, powders, creams	51	3	
Other bath preparations	141	1	0.25%
Eye lotion	18	2	
Eye makeup remover	80	3	
Mascara	158	2	
Other eye makeup preparations	116	4	<0.1%
Other fragrance preparations	137	3	0.01%
Hair conditioners	596	1	
Hair bleaches	104	1	
Foundations	283	3	
Lipstick	758	2	0.001% (lip balm 0.2%)
Makeup bases	125	2	
Cuticle softeners	19	1	0.05%
Other manicuring preparations	59	1	
Bath soaps and detergents	341	2	up to 0.02% (shower gel)
Deodorants (underarm)	241	4	1%
Other personal cleanliness	262	3	
Aftershave lotions	212	20	0.01%
Preshave lotions	14	1	
Shaving cream	138	2	0.01%
Other shaving preparation products	60	1	
Cleansing	630	14	0.01%
Depilatories	27	1	
Face and neck skin care	251	14	0.05%
Body and hand skin care	776	18	0.01%
Foot powders and sprays	32	1	
Moisturizing	743	21	0.01%
Night	185	6	0.02%
Paste masks (mud packs)	247	12	
Skin fresheners	181	4	
Other skin care preparations (creams/lotions/powders/sprays)	683	25	0.1–1%
Suntan gels, creams, and liquids	134	3	
Indoor tanning preparations	50	2	
Other suntan preparations	43	1	
1997 totals		**184**	

[1]FDA 1997.
[2]CTFA 1995.

The data submitted by the FDA in 1997 showed a total of 184 uses, while in 2015 999 uses were already reported, (table 4) indicating an increase in the frequency of use of bisabolol in cosmetics, but bisabolol concentration in these products has not changed. [36][46]

Table 4. Current and historical frequency of use of bisabolol according to exposure. [46]

	NUMBER OF USES	
	2015	**1997**
TOTALS[a]	999	184
Exposure type		
Eye-area	90	11
Incidental ingestion	31	2
Incidental inhalation spray	Spray: 10 Possible: 209[b]; 185[c]	Spray: 3 Possible: 37[b]; 33[c]
Incidental inhalation powder	Powder: 9 Possible: 185[c]; 5[d]	Possible: 33[c]; 3[d]
Dermal contact	912	176
Deodorant	34	4
Hair – non-coloring	35	1
Hair - coloring	5	1
Nail	3	2
Mucous membrane	86	6
Baby products	9	3

[a]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

[b]Includes products that can be sprayed, but it is not known whether the reported uses are sprays.

[c]Not specified whether this product is a spray or a powder or neither, but it is possible it may be a spray or a powder, so this information is captured for both
categories of incidental inhalation.

[d]Includes products that can be powders, but it is not known whether the reported uses are powders.

Bisabolol concentrations of up to 1.0% in leave-on products are considered as safe for use in cosmetics. In a study on rats, bisabolol was tested under semi-occlusive dressings in concentrations of 1%, 4% and 20%. Treatment lasted 28 days, and bisabolol was kept on the skin for six hours each day. At a concentration of 20%, moderate erythema could be observed. At concentrations of 1% and 4% no adverse effects were observed. Bisabolol could also be used in concentration of 4.0%, but since it is used in cosmetics only in concentrations up to 1.0%, the maximum concentration was limited to 1.0%. [36][46]

5.1 DERMAL ABSORPTION

This sesquiterpene alcohol has remarkable not only skin healing but also anti-inflammatory properties, which allows it a rich spectrum of use in cosmetics. It is used in many skin formulations such as face cream, lotion, wound healing ointment, baby care products, makeup products and many others. It was assumed that bisabolol is sufficiently well absorbed into the skin. This was verified by the biochemical incorporation of radioactive ^{14}C-acetate into the molecule. Radio-labeled bisabolol was then applied topically onto nude mice. After five hours the radioactivity was measured and already half of it was found in the skin. In order to demonstrate the distribution of this substance in the skin, part of the tissue was dissected into horizontal sections by a cryotome and autoradiograms were then obtained from these sections. Densitometry showed that bisabolol was rapidly absorbed into the skin. Already within the five hours, it was shifted from the outermost to the innermost areas. From this, not only rapid cutaneous absorption can be expected, but also long antiphlogistic and spasmolytic effect in the skin. [36][47]

5.2 WOUND HEALING

Since impaired wound healing is often a significant source of morbidities, and since it can lead to severe health complications related to diabetes, immune suppression, and malnutrition, it should not be underestimated. One of the many pharmacologically beneficial properties of bisabolol is its ability to heal wounds and

shorten the healing process. (+)-*epi*-α-bisabolol is a diastereomer of bisabolol contained in the ethanol extract of *Peperomia galioides*, that is responsible for the *in vivo* cicatrizing effect. All parts of the plant except the roots were crushed and extracts were prepared from them by maceration. These were applied to cuts and wounds. This confirmed acceleration of wound healing, concluding that (+)-*epi*-α-bisabolol has important structural features such as a 1-methylcyclohexene unit and the tertiary hydroxyl group on C-1´ in the side chain (figure 12), which are believed to be responsible for improving wound healing. [48][49]

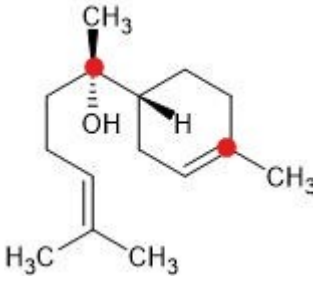

Figure 12. The structure of (+)-epi-α-bisabolol. The important structural parts responsible for wound healing are marked in red. [48]

The wound-healing and anti-inflammatory efficacy of bisabolol in the topical treatment of chronic venous leg ulcers was tested together with ozonated oil in a spray formulation. A standard epithelializing cream served as a comparison. Twenty-nine patients participated in this controlled randomized divided randomly into two groups. One group was treated with standard wound care and bisabolol-containing spray, with a protective gauze placed over the wound. In the control group, patients were given standard wound care and an epithelializing cream containing vitamin A, vitamin E, talc, and zinc oxide, covered also with a protective gauze. Both treatments were performed for 30 days. Patients were examined at four different dates, days 0, 7, 14, and 30. At each date, the wound surface and mechanical debridement of the lesions were measured. The results of this study show that the percentage of patients with complete healing of the ulcer was higher after treatment with ozonated oil and bisabolol (25% versus 0%). Furthermore, a significant and progressive reduction in wound surface area of 34%, 59%, and 73% was observed after seven, 14, and 30 days of treatment. [50]

Topical preparations for the treatment of eczema should provide an anti-inflammatory effect and be well tolerated for long-term use. Bisabolol is therefore a common ingredient of skin care products in topical preparations for the treatment of allergic skin diseases such as atopic dermatitis. Bisabolol has been shown to significantly reduce not only production of nitric oxide (NO) and prostaglandin E_2 (PGE_2) in a dose-dependent manner, but also the expression of proinflammatory mediators: inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2). It down-regulates Activator Protein 1 (AP-1) and Natural Killer-B cells (NK-B) so that the production of cytokines is reduced, causing an improvement in skin inflammation. [51][52][53]

A controlled double-blind trial, which included 278 participants with atopic dermatitis, confirmed that bisabolol in combination with heparin had an anti-allergic, anti-inflammatory, and curative healing effect. All patients were randomized into four groups: 79 of them were treated with a topical combination of bisabolol and heparin (A), 80 patients were treated with bisabolol alone (B), 78 patients with heparin alone (C), and 41 patients with the cream base without active ingredients (D). The patients applied medication twice daily for eight weeks. The criteria by which the efficacy was evaluated were the intensity of pruritus (visual analog scale Scale, VAS) and the SCORing Atopic Dermatitis (SCORAD) Index, as well as an overall evaluation of efficacy and tolerability by the physician and patient. The results showed an improvement in itching and SCORAD scores in group A, which was significantly higher than in groups B-D, suggesting not only a cumulative effect of the two single agents, but also a very good local tolerability. All these studies pointed to the evidence-based use of this sesquiterpene alcohol in numerous wound-healing and skin-soothing ointments and creams, intimate lotions, baby products, lip products and shampoos. Some of the product examples are listed below: [53][54]

- Avene® Cold cream Nourishing Lip Balm
- DM Babylove® Ultra Senditive Cream
- Dermalogica® Ultracalming Barrier Repair
- Kamill® Sensitive Skin Cream

- Layctacyd® Intimate Wash Sensitive
- Nivea® Sensitive Cooling Post Shave Balm
- Neutrogena® Intense Repair Lip Balm
- Vichy® Dercos Anti-Dandruff Shampoo for Sensitive Scalp

5.3 WHITENING EFFECT

Hyperpigmentation is a problem caused by many different inflammatory disorders of the skin including eczema, allergic as well as irritant contact dermatitis. A cream containing bisabolol was tested on the pigmented skin of a group of 28 female subjects, whose pigmentation was induced from a solar simulator by ultraviolet A (UVA) and UVB. The cream was applied to the back once a day for eight weeks. They also used a control cream on the pigmented skin. After treatment time, the majority of the subjects showed a significant lightening of the pigmented skin. It has been confirmed that the depigmenting effect of bisabolol was based on the inhibition of melanogenesis through its significant effect on lowering the intracellular cAMP (cyclic adenosine monophosphate) level. By Western blot analysis, it was confirmed that bisabolol reduced CREB (CRE binding protein.) phosphorylation, resulting in inhibition of activation of the CRE (cAMP response element) luciferase reporter induced by MSH and further leading to a decrease in melanin content. The effect of bisabolol on a-MSH-induced expression of MITF (microphthalmia-associated transcription factor) and tyrosinase genes was also evaluated. Bisabolol inhibited the production of both MITF protein and tyrosinase, which led to a conclusion that bisabolol also inhibited the production of TRP-1. In summary, the data collected in these studies indicated that bisabolol lightened the skin *in vivo* and that the use of the depigmenting and whitening effect of bisabolol could be beneficial for the treatment of hyperpigmentation disorders. This is considered to be a basis for the use of bisabolol in skin care products as a strong lightening agent, with the aim of targeting pigmentation, age spots, uneven skin tone and acne scars. Some bisabolol-containing products used for those skin disorders are given below: [54][55][56]

- Caudalie® Vinoperfect Anti Dark Spot Serum
- Paula's Choice® Clear Extra Strength Daily Skin Clearing Treatment With 5% Benzoyl Peroxide
- Sebamed® Anti-Pimple Gel

5.4 PERMEATION ENHANCER

The complexity of the skin structure makes it very difficult for topically and transdermally administered active ingredients to penetrate. The outermost layer of the skin, the *Stratum corneum* represents a formidable barrier, so that it is often necessary to add penetration enhancers. Several classes are known, but one of the most important is represented by terpenes and other natural non-toxic substances, which are widely used as permeation enhancers in transdermal administration. [57]

Dapiprazole is an α-blocker used topically in ophthalmic therapy not only to treat chronic simple glaucoma, but also to reverse pharmacologically induced mydriasis and induce preoperative miosis. Transdermal administration of dapiprazole should have some advantages over oral administration. These include better patient compliance, use of lower doses, and sustained and consistent plasma levels. The permeation rate of dapiprazole was studied *in vitro* on hairless mouse skin. Many different liquid and semisolid vehicles were investigated, some containing penetration enhancers and some not. The results showed up to a 73-fold increase in the permeability coefficient of dapiprazol when co-administered with racemic bisabolol as a penetration enhancer. What else can be concluded from this study was that naturally occurring (-)-α-bisabolol was twice as active as a penetration enhancer for dapiprazole than bisabolol racemate. Since bisabolol is used in baby lotions, it has been pointed out the possibility of increased absorption of other ingredients that are also found in the formulation, specifically if their safety is based on the lack of absorption through the skin. [14][36][57][58][59][60]

5.5 SUNSCREENS AND FRANGRANCES

Sunscreens are classified as cosmetic products, not medical products, intended to reduce the risk of premature aging and skin cancer by protecting the skin from UV rays. In the European Union, all sun protection factors are divided into four categories [61]:

a) low (SPF 6 and 10).

b) medium (SPF 15,20 and 25)

c) high (SPF 30 and 50)

d) very high (SPF 50+)

The quantification of sun protection factors (SPF) is done with a standardized test method, using already just-perceptible redness as biological end point, and measuring the minimum erythematous dose (MED) on unprotected and sun-protected skin.

Nowadays, sunscreens have very often been formulated with anti-inflammatory ingredients such as bisabolol and panthenol. These are supposed to relieve pain, burning and redness. One study examined the influence of these two ingredients in sunscreens. According to results, it could be confirmed that no significant differences in erythematous response exist between the formulas with and without these two agents when measured *in vitro*. In conclusion, the ingredients panthenol and bisabolol did not affect the SPF value *in vivo*. This lead to the conclusion that it does not seem to be necessary to include anti-inflammatory agents in active sunscreens. They should be used in after-sun products to reduce inflammation. [61]

Some of the sunscreen products that contain bisabolol in their ingredients list are listed below. [54]

- Acure® Radically Rejuvenating Spf30 Day Cream
- Bijindo® Sunblock Cream Professional

- C'est Moi® Sunshine Mineral Sunscreen Face Stick Broad Spectrum SPF 50 Water Resistant (80 Minutes)
- Cheryl's cosmeceuticals Dermashade SPF 30 Spray
- Glytone® Age Defense UV Mineral Sunscreen Serum Broad Spectrum SPF 50+
- Pacifica® Beauty Sun + Skincare Mineral Body Butter Pineapple Flower Spf 50

Essential oils find their use in cosmetics, mostly because of their pleasant smell. Other ingredients needed for the production of cosmetic products, such as fatty oils, surfactants and fatty acids, often produce an unpleasant scent. In order to mask it, effective perfume mixtures are added. This is the reason why bisabolol, with its slight floral aroma, is commonly used as a perfume ingredient in many decorative cosmetics, soaps, fine fragrances, shampoos and other toiletries. The use of bisabolol-containing fragrances results in a maximum skin concentration of 0.08%, whereby the concentration of fragrance oil in the final product is up to 20%. [44][62]

6 CONCLUSION

In this work, various more or less known activities and properties of bisabolol were researched. [22] Since bisabolol is included in the list of ingredients of many cosmetic products, it was important to identify the chemical effects, mechanisms and underlying significance of this substance.

For a long time, it has been known that this sesquiterpene alcohol, which occurs naturally in chamomile oil and in oil of many other plants, exerts an anti-inflammatory effect. This justifies its use in many wound-healing ointments and creams.

The most recent studies related to bisabolol show a lightening effect, which gives it the possibility to be an important part in the therapy of hyperpigmentation, scars and acne.

Evidence-based bisabolol is well absorbed into the skin. This ability allows it to play an important role in permeation of other substances because it is applied in many formulations as a penetration enhancer. It is also added to many sunscreen preparations, although it has not been confirmed that it plays a role in sun protection. Obviously, its significance as a perfume ingredient is large, as it finds its use in many products as an odorant.

The basis for all these indications is the results of many studies that exclude phototoxicity, genotoxicity and reproductive toxicity. In particular, bisabolol has been declared as a safe ingredient, although there have been cases where an allergenic potential has been described. This leads to a conclusion that patch testing in cosmetics plays an important role, especially for ingredients that can be associated with Compositae.

7 TABLE OF TABLES

8 TABLE OF FIGURES

REFERENCES

[1] Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02009R1223-20190813 (accessed on 11 February 2022)

[2] Cosmetics Europe, https://cosmeticseurope.eu/cosmetic-products/ (accessed on 10 February 2022)

[3] Greta, F. (2020): Plant complexity and cosmetic innovation. iScience, 101358.

[4] Chiocchio, I., Lianza, M., Mandrone, M., Marincich, L., Poli, F., & Tomasi, P. (2020): Screening of ninety herbal products of commercial interest as potential ingredients for phytocosmetics. Journal of Enzyme Inhibition and Medicinal Chemistry, 35(1):1287-1291.

[5] Costa I. (2015): Phytocosetics – where nature meets well-being. International Journal of Phytocosmetics and Natural Ingredients. 2:1

[6] Bayliak, M., Dmytriv, T., Lushchak, V., Melnychuk,A., Strilets, N. & Storey, K. (2021): Chamomile as a potential remedy for obesity and metabolic syndrome. EXCLI Journal, 20:1261-1286.

[7] Chauhan, R., Kumar, A., Kumar, V., Kumar, R., Kumari, A., Rathore, S. & Singh, S. (2021); A comprehensive review on biology, genetic improvement, agro and process technology of German chamomile (Matricaria chamomilla L.). Plants, 11(1):29.

[8] Jacob, S. & Russell, K. (2010): Bisabolol. Dermatitis, 21(1):57-8.

[9] Ph. Eur. (Pharmakopeia Europaea), Europäisches Arzneibuch, 2020, 10th Edition, 2253.

[10] Kim S-U., Kwon M., Ro D-K. & Son Y-J. (2014): Enantioselective microbial synthesis of the indigenous natural product (-)-α-bisabolol by a sesquiterpene synthase from chamomile (*Matricaria recutita*). Biochem J., 463(2):239-48.

[11] Caldini, R., Chevanne, M., Magnelli, L., Schiavone, N. & Suzuki, H. (2010): Differentiating and apoptotic dose-dependent effects in (−)-α-bisabolol-treated human endothelial cells. Journal of Natural Products, 73(4):523-6.

[12] Andre, D., Duclos, R., Failly, F., Orecchioni, A. M. & Verite, P. (1991): Determination of a-bisabolol and D-panthenol in cosmetic products by gas chromatography. International Journal of Cosmetic Science, 13(3):137-42.

[13] Api, A. M., Belsito, D., Biserta, S., Botelho, D., Bruze, M., Burton, G. A., Buschmann, J., Cancellieri, M. A., Dagli, M.L., Date, M., Dekant, W., Deodhat, C., Fryer, A. D., Gadhia, S., Jones, L., Joshi, K., Laczynski, A., Lavelle, M., Liebler, D. C., Na, M., O'Brien, D., Patel, A., Penning, T.M., Ritacco, G., Rodriguez-Ropero. F., Romine, J., Sadekar, N., Salvito, D., Schultz, T. W., Siddiqi, F., Sipes, I. G., Sullivan, G., Thakkar, Y., Tokura, Y., Tsang, S. (2020): RIFM fragrance ingredient safety assessment, α-bisabolol, CAS registry number 515-69-5. Food and Chemical Toxicology, 111238.

[14] Kamatou, G. P. P., & Viljoen, A. M. (2009). A review of the application and pharmacological properties of α-bisabolol and α-bisabolol-rich oils. Journal of the American Oil Chemists' Society, 87(1):1-7.

[15] Commission Decision (EU) 2019/701 of 5 April 2019 establishing a glossary of common ingredient names for use in the labelling of cosmetic products, https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX:32019D0701 (accessed on February 11, 2022)

[16] IFRA Standard, Amendment 49, α-bisabolol, https://ifrafragrance.org/pdf/web/viewer.html?file=/standards/IFRA_STD_192.pdf (accessed on February 11, 2022)

[17] Cabral-Albuquerque, E., Detoni, C., Ferreira, D., Pedro, A. S. & Sarmento, B. (2009): Validation of a high-performance liquid chromatography method for the determination of (−)-α-bisabolol from particulate systems. Biomedical Chromatography, 23(9):966-72.

[18] Cañigueral, S., Castelli, M. V., Gupta, M. P., Mendonca, S., Pérez-Rosés, R., Santana, A. I., Valderrama, A., Vila, R. & Zacchino, S. (2010): Composition and biological activity of the essential oil from leaves of *Plinia cerrocampanensis*, a new source of α-bisabolol. Bioresource Technology, 101(7):2510-2514.

[19] Fu, Y., Han, G. H., Jung, H. C., Kang, Y., Kim, B. S., Kim, S. K., Kim, S. W., Lee, D. H., Lee, S.-G., Sung, B. H. & Yoon, P. K.-S. (2016): Fermentative production and direct extraction of (−)-α-bisabolol in metabolically engineered Escherichia coli. Microbial Cell Factories, 15(1):185.

[20] Alonso-Gutierrez, J., George, K. W., Keasling, J. D., & Lee, T. S. (2015): Erratum to: Isoprenoid Drugs, Biofuels, and Chemicals - Artemisinin, Farnesene, and Beyond. Advances in Biochemical Engineering/Biotechnology, 148:355-389.

[21] Araújo, F. Y. R. de, Carvalho, A. M. R., Macedo, D. S., Oliveira, G. V. de, Rios, E. R. V., Rocha, N. F. M., Soares, M. G., Sousa, F. C. F. de & Vasconcelos, L. F. (2011): (−)-α-Bisabolol-induced gastroprotection is associated with reduction in lipid peroxidation, superoxide dismutase activity and neutrophil migration. European Journal of Pharmaceutical Sciences, 44(4):455–461.

[22] Achterrath-Tuckermann, U., Flaskamp, E., Kunde, R. & Thiemer, K. (1980): Pharmakologische Untersuchungen von Kamillen-Inhaltsstoffen. Planta Medica, 39(05):38-50.

[23] Isaac, O., Jakovlev, V., Kunde, R. & Thiemer, K. (1979): Pharmakologische Untersuchungen von Kamillen-Inhaltsstoffen. II. Neue Untersuchungen zur antiphlogistischen Wirkung des (-)-α-Bisabolols und der Bisabololoxide. Planta Medica 35:125-140.

[24] Agis, A., Cadórniga, R., Jimenez, M. E., Torrado, S. & Torrado, S. (1995): Effect of dissolution profile and (-)-α-bisabolol on the gastrotoxicity of acetylsalicylic acid. Pharmazie, 50(2):141-3.

[25] Isaac, O. & Thiemer, K. (1975): Biochemical studies on camomile components/III. In vitro studies about the antipeptic activity of (-)-α-bisabolol. Arzneimittelforschung, 25(9):1352-4.

[26] Bezerra, S. B., Campos, A. R., Leal, L. K. A. M. & Nogueira, N. A. P. (2009): Bisabolol-induced gastroprotection against acute gastric lesions: role of prostaglandins, nitric oxide, and K+ATP channels. Journal of Medicinal Food, 12(6):1403-1406.

[27] Bezerra, C.F., Bezerra, M.C.F., Freitas, T.S.d., Honorato, R.d.L., Júnior, J.G.d.A., Lima Sales, D., Santos, A.T.L.d. Silva, J.C.P.d., Silva, T.G.d. … Vieira, T.A.T. (2021): Antifungal effect of liposomal α-bisabolol and when associated with fluconazole. Cosmetics, 8(2):28.

[28] Bhatnagar, D., De Lucca, A. J., Pauli, A., Schilcher, H., Sien, T. & Walsh, T. J. (2011): Fungicidal and bactericidal properties of bisabolol and dragosantol. Journal of Essential Oil Research, 23(3):47-54.

[29] Filippi, A., Forrer, M., Kulik, E. M. & Waltimo, T. (2013): The antimicrobial activity of alpha-bisabolol and tea tree oil against Solobacterium moorei, a Gram-positive bacterium associated with halitosis. Archives of Oral Biology, 58(1):10-16.

[30] Cunha, S., Da Silva, A. P., Da Silva, C. C., De Carvalho, J. E., de Oliveira, C. M. A., Martini, M. V. & Ruiz, A. L. T. G. (2010): Antitumor activity of (−)-α-bisabolol-based thiosemicarbazones against human tumor cell lines. European Journal of Medicinal Chemistry, 45(7):2987-2993.

[31] Martín-Sánchez, J., Morales-Yuste, M., Morillas-Márquez, F., Navarro-Moll, M. C. & Valero-López, A. (2010): Activity of (-) α-bisabolol against Leishmania infantum promastigotes. Phytomedicine, 17(3-4):279-281.

[32] Araruna, M. K. A., Campos, A. R., da Costa, J. G. M., de Menezes, I. R. A., Leite, G. de O., Leite, L. H. I. & Sampaio, R. de S. (2011): (−)-α-Bisabolol attenuates visceral nociception and inflammation in mice. Fitoterapia, 82(2):208-211.

[33] Luqman, S. & Srivastava, S. (2011): Protective effect of α-(-)-bisabolol on markers of oxidative stress in erythrocytes subjected to oxidative insult. Planta Med. 77(12*)*.

[34] De-Oliveira, A. C. A. X., Dias, D. M. M., Gomes-Carneiro, M. R. & Paumgartten, F. J. R. (2005): Evaluation of mutagenic and antimutagenic activities of α-bisabolol in the Salmonella/microsome assay. Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 585(1-2):105-112.

[35] Coimbra, M.A., Maraschin, M., Petronilho, S. & Rocha S.M. (2012): In vitro and in vivo studies of natural products: A challenge for their valuation. The case study of chamomile (Matricaria recutita L.). Ind. Crops Prod.,40:1-12.

[36] Andersen, F. A. (1999): Final report on the safety assessment of bisabolol. International Journal of Toxicology, 18(3):33-40.

[37] Beck, M.H., Hausen, B.M. & Wilkinson, S.M. (1995): Allergic contact dermatitis from plant extracts in a cosmetic. Contact Dermatitis, 33:58-9.

[38] Mataix, J., Pastor, N., Silvestre, J.F., et al. (2008): Contact cheilitis from bisabolol and polyvinylpyrrolidone/hexadecane copolymer in lipstick. Contact Dermatitis. 58:178-9.

[39] Hsu, J. W. & Jacob, S. E. (2010): Reactions to Aquaphor®: Is bisabolol the culprit? Pediatric Dermatology, 27(1):103–104.

[40] Herro, E.M., Jacob, S.E. & Matiz, C. (2011): Compositae-associated allergic contact dermatitis from bisabolol. Dermatitis, 22(2):102-5.

[41] Sarre, M. E., Guérin-Moreau, M., Lepoittevin, J.P., Martin, L. & Avenel-Audran, M. (2014): Allergic contact cheilitis caused by polysilicone-15 (Parsol® SLX) in a lipcare balm. Contact Dermatitis, 70(2):119–121.

[42] Api, A.M.; Belsito, D.; Biserta, S.; Botelho, D.; Bruze, M.; Burton, G.A.; Buschmann, J.; Cancellieri, M.A.; Dagli, M.L.; Date, M.; Dekant, W.; Deodhar, C.; Fryer, A.D.; Gadhia, S.; Jones, L.; Joshi, K.; Lapczynski, A.; Lavelle, M.; Liebler, D.C.; Na, M.; O'Brien, D.; Patel, A.; Penning, T.M.; Ritacco, G.; Rodriguez-Ropero, F.; Romine, J.; Sadekar, N.; Salvito, D.; Schultz, T.W.; Siddiqi, F.; Sipes, I.G.; Sullivan, G.; Thakkar, Y.; Tokura, Y.; Tsang, S. (2020): RIFM fragrance ingredient safety assessment, α-bisabolol, CAS registry number 515-69-5. Food and Chemical Toxicology, 149(1):112047.

[43] Legault, J., Gauthier, C., Pichette, A. & Piochon, M. (2009): Synthesis and cytotoxicity evaluation of natural α-bisabolol β-d-fucopyranoside and analogues. Phytochemistry, 70(2):228–236.

[44] Api, A. M., Bhatia, S. P., Letizia, C. S. & McGinty, D. (2008): Fragrance material review on α-bisabolol. Food and Chemical Toxicology, 46(11):72–76.

[45] Costa, M. dos S., da Silva Rocha, K. A., De Meireles, A. L. P. & Gusevskaya, E. V. (2015): Heteropoly acid catalyzed cyclization of nerolidol and farnesol: Synthesis of α-bisabolol. Applied Catalysis A: General, 502:271–275.

[46] Fiume, M. M. (2017): Bisabolol. International Journal of Toxicology, 36(5_suppl2):24S–25S.

[47] Hahn B., Hölzl J. (1987): Absorption, distribution and metabolism of [14C]-levomenol in the skin. Arzneimittel-Forschung 37(6):716-720.

[48] Fernández, I.D., Hammond, G.B., Maldonado, H., Marçalo, A., Martin, J., Vaisberg, A.J. & Villegas, L. F. (2001): (+)- epi-α-bisabolol is the wound-healing principle of *Peperomia galioides*: Investigation of the in vivo wound-healing activity of related terpenoids. Journal of Natural Products, 64(10):1357–1359.

[49] Isaac, O. (1979): Pharmacological investigations with compounds of chamomile i. on the pharmacology of (-)-alpha-bisabolol and bisabolol oxides. Planta Med., 35: 118-124.

[50] Capparé, G., De Ascentii, A., Mattana, P., Solovăstru, L. G., Stîncanu, A. & Vâţă, D. (2015): Randomized, controlled study of innovative spray formulation containing ozonated oil and α-bisabolol in the topical treatment of chronic venous leg ulcers. Advances in Skin & Wound Care, 28(9):406–409.

[51] Bawankule, D.U., Dubey, V., Luqman, S., Mautya, A.K., Singh, M. & Srivastava, S. (2014): (-)-α-Bisabolol reduces pro-inflammatory cytokine production and ameliorates skin inflammation. Curr. Pharm. Biotechnol.,15:173–181.

[52] Han, F., Lee, I.-S. & Park, J. (2022): Biotransformation of ()-α-bisabolol by Absidia coerulea. Molecules, 27:881.

[53] Arenberger, P., Arenbergerová, M., Drozenová, H., Hladíková, M., & Holcová, S. (2011): Effect of topical heparin and levomenol on atopic dermatitis: a randomized four-arm, placebo-controlled, double-blind clinical study. Journal of the European Academy of Dermatology and Venereology, 25(6):688–694.

[54] INCI Decorder, https://incidecoder.com/ingredients/bisabolol (accessed on 12 February 2022)

[55] Ha, J., Jun, H., Jung, E., Lee, J. & Park, D. (2010): Whitening effect of α-bisabolol in Asian women subjects. International Journal of Cosmetic Science, 32(4):299–303.

[56] Byun, S. Y., Huh, S., Jung, E., Kim, S., Lee, J., Lee, J., Park, D. & Park, J.-O. (2008): Mechanisms of depigmentation by α-bisabolol. Journal of Dermatological Science, 52(3):219–222.

[57] Ahada, A., Ali, A., Aqil, M. & Sultanaa, Y. (2007): Status of terpenes as skin penetration enhancers. Drug Discovery Today, 12:1061–1067.

[58] Garrison, J., Guy, R.H., Kalia, Y.N. & Naik, A. (2007): Iontophoretic drug delivery. Advanced Drug Delivery Reviews, 56:619–658.

[59] Barry B. W. & Williams AC. (1991): Terpenes and the lipid-protein-partitioning theory of skin penetration enhancement. Pharmaceutical Research, 8:17–24.

[60] Galli-Angeli, D., Giannaccini, B., Monti, D. & Saettone, M. F. (1995): Enhancement of transdermal penetration of dapiprazole through hairless mouse skin. Journal of Control Release, 33:71–77.

[61] Braun, N., Garbe, B., Heinrich, U., Herling, M., Theek, C., Tronnier, H. & Werner, M. (2017): Determination of the Influence of the Antiphlogistic Ingredients Panthenol and Bisabolol on the SPF Value in vivo. Skin Pharmacology and Physiology, 30(6):284–291.

[62] Sarkic, A. & Stappen, I. (2018): Essential oils and their single compounds in cosmetics - a critical review. Cosmetics, 5:11.