Biosynthesis and Therapeutic Properties of *Lavandula* Essential Oil Constituents

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- Lamiaceae
- *Lavandula angustifolia*
- essential oil
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- linalool

Abstract

Lavenders and their essential oils have been used in alternative medicine for several centuries. The volatile compounds that comprise lavender essential oils, including linalool and linalyl acetate, have demonstrative therapeutic properties, and the relative abundance of these metabolites is greatly influenced by the genetics and environment of the developing plants. With the rapid progress of molecular biology and the genomic sciences, our understanding of essential oil biosynthesis has greatly improved over the past few decades. At the same time, there is a recent surge of interest in the use of natural remedies, including lavender essential oils, in alternative medicine and aromatherapy. This article provides a review of recent developments related to the biosynthesis and medicinal properties of lavender essential oils.

Abbreviations

cAMP:	cyclic adenosine monophosphate
CFVR:	coronary flow velocity reserves
DMAPP:	dimethylallyl diphosphate
DXR:	deoxyxylulose phosphate reductoisomerase
DXS:	1-deoxy-D-xylulose 5-phosphate synthase
EEG:	electroencephalography
EST:	expressed sequence tag
FPP:	farnesyl diphosphate
GABA:	gamma-aminobutyric acid
GPP:	geranyl diphosphate
HMGR:	3-hydroxy-3-methyl-glutaryl-CoA reductase
IPP:	isopentenyl diphosphate
MVA:	mevalonate
MEP:	2-*C*-methyl-D-eryhtritol 4-phosphate

Introduction

Lavender (*Lavandula*) essential oils are complex mixtures of mono- and sesquiterpenoid alcohols, esters, oxides, and ketones. The primary components of these oils are the monoterpenoids linalool, linalyl acetate, 1,8-cineole, *β*-ocimene, terpinen-4-ol, and camphor (**Table 1**). Sesquiterpenoids, such as caryophyllene and nerolidol [1], and other terpenoid compounds, such as perillyl alcohol [2], are also present in trace quantities. A myriad of studies have quantified the medicinal properties of many of these individual terpenoid compounds, in addition to studies of the therapeutic potentials of oils as a whole. The production of these terpenoids is significantly impacted by the genetic milieu of the plant and by environmental factors (such as temperature).

Lavenders belong to the Labiatae (Lamiaceae) family of plants. Most commercially marketed lavender essential oils are obtained from cultivars of two *Lavandula* species, *L. angustifolia* and *L. latifolia*, as well as from lavender hybrids, commonly known as lavandins (see **Table 1**). Other lavender species, such as *L. stoechas* and *L. dentata*, have also been used in folk medicinal practices for their anti-spasmolytic properties [3,4]. With its high linalool/linalyl acetate and low camphor, the essential oils of the species *L. angustifolia* are among the finest and most desired lavender oils in the cosmetic and aroma-therapeutic industries. However, *L. angustifolia* plants produce these valuable oils in relatively low quantities (40 kg per hectare [2]), and cultivation of this species requires hot dry climates at medium altitudes (700–1200 m) in order to produce maximum oil yields [5]. Spike lavender (*L. latifolia*) typically yields 50 kg per hectare and is also commonly grown for its essential oil contents. Since the 1920s, commercial cultivation of lavender hybrids has been employed to increase essential oil yields [6]. Spike lavender is often crossed with

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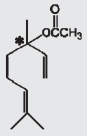
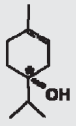
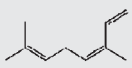
Table 1 The relative abundance of major essential oil constituents in typical *L. angustifolia*, *L. latifolia*, and lavandin (*L. angustifolia* × *L. latifolia*). Values are percentages of total oil yield. Asterisks (*) denote chiral centers.

Compound	Structure	*L. angustifolia*	*L. latifolia*	*Lavandin (L. × intermedia)*
1,8-Cineole		trace	22–27	4–7
Camphor		trace	12–16	6–8
Linalool		25–38	27–41	25–35
Linalyl acetate		25–45	trace	26–38
Terpinen-4-ol		4–5%	trace	trace
β-Ocimene		3–4%	trace	trace

L. angustifolia to produce lavandin (*L.* × *intermedia*), a hybrid lavender species with particularly high oil yields of 120 kg per hectare [2]. Lavandin oils are generally not used in perfumery/therapeutic practices because of the undesirably high levels of camphor. However they are used successfully in antiseptic, antifungal, and antibacterial applications. Growers who cultivate lavenders for their essential oil often assess the trade-offs between yield and terpenoid profiles when targeting different markets.

While most lavenders grow well in a wide range of climactic environments, they generally prefer well-draining soils with a pH range of 7–7.5. Once roots are established, lavenders are xerophytic, and grow best in full sun. In order to generate lavender plants with the highest oil yields, it is necessary to prune woody stocks annually to induce multiple shoots to bloom. As hardy plants, lavenders can tolerate intense heat, wind, and some frost. A limited amount of fertilizer is necessary for developing lavenders with oil rich flowers, but too much fertilizer will result in the production of excessive foliage [2].

The drive to acquire a better understanding of terpene biosynthesis is predicated on our understanding of the pharmacological and clinical properties of lavender oil. In this review, we summarize recent findings related to the medicinal properties of lavender essential oil, and its individual constituents. In particular, the biological activities for the main constituents of lavender oils, including linalool, are discussed.

Therapeutic Properties of Lavender Oils

Lavender essential oils have long been considered to be natural remedies for various ailments. They possess potent calming and sedative effects, making them popular in aroma-therapeutic practices. Furthermore, some studies have shown that several constituents of lavender essential oil possess anticancer and antimutagenic properties. Below, key studies of the therapeutic properties of lavender oils and their various constituents are reviewed. For a summary of the therapeutic research using various constituents of lavender oil discussed in this section, see **Table 2** and **Table 3**.

There are three ways in which essential oils can be absorbed into the human body: 1) though the respiratory system; 2) transdermally via direct contact; and 3) oral ingestion [7]. A developing body of evidence suggests that essential oil absorption into the blood stream, either by inhalation or dermal contact, has salient pharmacological effects in treating pain, anxiety, sleep disorders, and depression [8]. Frey et al. [9], in a landmark study, demonstrated that therapeutic agents can bypass the blood-brain barrier via olfactory uptake in mice. This method of delivery was subsequently confirmed in human subjects [10, 11].

Studies in human subjects

One of the most common uses of lavender oils is in the enhancement of sleep. It has been demonstrated that lavender aromatics can improve sleep in the elderly [12] and infants [13]. Furthermore, exposure to lavender odors during sleep results in increased duration of deep slow-wave stage sleep [14]. A therapeutic effect that is closely related to sleep is anxiety reduction, and many studies have evaluated the anxiolytic potential of lavender essential oil. Tasev et al. [15] related the sedative and relaxant effect of lavender oils with its effect on the central nervous system delivered via the olfactory system, and Tisserand [16] suggested that *L. angustifolia* odors have a similar action to benzodiazepines in effecting gamma-aminobutyric acid (GABA) neurotransmission. A study on dental patients who were exposed to lavender scents showed significantly reduced anticipatory anxiety [17]. Many of the anxiolytic effects of lavender have been linked to the activity of linalool [18], and Hoferl et al. [19] demonstrated that linalool fragrances alone reversed the psychological parameters produced by stress.

While inhalation of lavender oil and linalool has been shown to impart positive psychopharmacological effects in humans, recent studies have indicated that linalool exposure results in allergenic responses. European legislators have become increasingly aware of the allergenic properties of many common essential oil constituents, and in 2003, the 7th Amendment to the European Cosmetic Directive required that cosmetic products containing any of 26 natural products, including linalool, be labeled as potentially allergenic [20]. While linalool itself may have limited allergenic properties, it can auto-oxidize upon air exposure into a hyperoxide species [21] which can lead to contact allergy responses in mice [22]. In a study of 1511 dermatitis patients, auto-oxidized linalool was shown to induce allergenic responses in 1.3% of those tested, with 1.1% of patients sensitive to the linalool hyperoxide fraction, using patch tests [23]. A follow-up study, again involving 1511 dermatitis patients, showed that exposure to oxidized linalool at concentrations of > 6.0% resulted in allergenic irritation in 5–7% of test subjects [24]. Given the allergenic nature of some of the constituents of lavender essential oil and their breakdown products, as well as an increasing awareness of their presence in cosmetics and aroma-therapeutic products, future

Table 2 Overview of clinical experiments using lavender oil constituents.

Reference	Test subjects	Number of volunteers	Compound	Dosage	Delivery	Method of assessment	Outcome
[12]	Elderly hospitalized for acute care	31	Lavender oil	"One drop" on "a pillow"	Olfactory	Observation	Enhanced sleep
[13]	Healthy infants	30	Lavender oil	Data not shown/aromatic bath oil	Olfactory, transdermal	Observation, salivary cortisol levels	Enhanced sleep, decreased stress
[14]	Healthy adults	31	Lavender oil	Aromatic exposure in 2 minute intervals	Olfactory	Polysomnographic recording	Enhanced sleep
[17]	Healthy adult dental patients	343	Lavender oil	5 Drops of oil in 10 mL diffused by candle	Olfactory	Modified dental anxiety scale, state trait anxiety inventory	Decreased anxiety
[18]	Healthy adults	12 and 24	*R*-(−)- and *S*-(+)-linalool	20 µL of various oil dilutions (between 0.003–30% of air)	Olfactory	Survey, electroencephalographic activity	Increased favorable impressions
[19]	Healthy adults	24	*R*-(−)- and *S*-(+)-linalool	2.7 mg/m^3 (*R*-(−) linalool) and 9.8 mg/m^3 (*S*-(+)-linalool) of air in room	Olfactory	Autonomic and endocrine system parameters including salivary cortisol levels	Decreased anxiety
[23]	Dermatitis patients	1511	Linalool, myrcene, and caryophellene, and oxidation products	0.5–3.9% of oxidized terpenoids, 20% non-oxidized linalool in petrolatum	Transdermal patch test	Observation of skin irritation	Contact allergy to terpenoid oxidation products
[24]	Dermatitis patients	1511	Linalool, oxidized linalool	2–11% Petrolatum (0.80–4.4 mg/cm^2)	Transdermal patch test	Observation according to the International Contact Dermatitis Research Group guidelines	Contact allergy to oxidized linalool
[25]	Elderly hospitalized for dementia	21	Lavender oil	Data not shown	Olfactory, transdermal	Observation of motor behaviours	Decreased agitation
[26]	Elderly hospitalized for dementia	15	Lavender oil	2% of air	Olfactory	Pittsburgh agitation scale	Decreased agitation
[27]	Elderly hospitalized for dementia	36	Lavender oil	3.5% of aqueous solution	Transdermal	Mini-mental state examination	Increased cognition
[29]	Elderly hospitalized in ICU shortterm	122	Lavender oil	1.0% of aqueous solution	Olfactory, transdermal	Behavioral observation, blood pressure, heart rate, breath rate	Increased sedation
[30]	Healthy adult females	96	Lavender oil	Cotton wood soaked with three drops of oil in a jar	Olfactory	Galvanic skin response	Increased relaxation
[31]	Healthy infants	45	Lavender oil	10% v/v	Olfactory	Electroencephalographic activity	Increased positive affect
[32]	Healthy adults	40	Lavender oil	10% v/v	Olfactory	Electroencephalographic activity	Increased positive mood, sedation
[33]	Healthy adult males	30	Lavender oil	"Four oil drops diluted with 20 mL hot water"	Olfactory	Coronary flow velocity reserve	Increased relaxation, coronary circulation
[35]	Adult male	1	Lavender oil	2% in peanut oil	Transdermal	Gas chromatography analysis of blood	Rapid accumulation (peak 20 minutes) and expulsion (90 minutes) of linalool/linalyl acetate
[36]	Healthy adults	4	1,8-Cineole	Air passing over four mL for 20 minutes	Olfactory	Gas chromatography analysis of blood	Accumulation (peak ~ 18 minutes) and expulsion half-life (104.6 minutes) of 1,8 cineole

Table 3 Overview of experiments with model systems using lavender oil constituents.

Reference	Test subjects	Compound	Dosage	Delivery	Method of assessment	Outcome
[21]	Female Dunkin-Hartley albino guinea pigs	Linalool	Linalool, 5.1% w/w, linalool oxides at 1.0, 2.6, 5.1, and 10.3% w/w	Transdermal injection	Freund's complete adjuvant test method	Sensitivity towards linalool oxide exposure, no sensitivity towards linalool
[22]	Female mice	Linalool	1.0–12.7% of linalool and various linalool oxides	Topical application on the dorsum of both ears	Local lymph node assay	Sensitivity towards linalool oxide exposure, no sensitivity towards linalool
[37]	Mice	Linalool	1–12 ng/mL for one hour	Inhalation	Gas chromatography analysis of blood samples	Inhaled linalool is deposited in the blood, linalool partially bound to glucuronic acid
[39]	*Salmonella typhimurium* (TA98 strain)	Lavender oil	0.13–0.80 mg/plate	*In vitro*	Colony counting	Lavender oil antagonized mutagenesis
[40]	Human (human peripheral blood neutrophils)	Lavender oil	0.025–0.2%	*In vitro*	Neutrophil adherence test	Decreased inflammation
[41]	Mouse (male adult albino CF1)	Linalool	1 or 3% of air	Olfactory	Sleep assessment, body temperature, behavioral assessment, locomotor activity, roto-rod locomotor coordination test	Increased sedation, decrease in body temperature, locomotor activity. Locomotor coordination unaffected
[42]	Mouse (female juvenile outbred Swiss)	Linalool, linalyl acetate	Enough to achieve 0.1 ng/mL blood serum	Olfactory	Behavioral assessment, locomotor activity (motility)	Decreased locomotor activity, increased sedation even after agitating stimulus
[43]	Mouse (male adult albino CF1)	Linalool	0.1 to 3.0 mM	*In vitro* - cortical synaptosomes incubated with linalool	Radiolabelled glutamate uptake – scintillation counter	Inhibition of K^+ induced glutamate release increased sedation indicators
[44]	Mouse (male adult albino CF1)	Linalool	25 to 100 mg/kg	*In vivo* - subcutaneous injection	Behavioural assessment – antinociceptive tests (acetic acid writhing test, hot plate) and motility	Antinociception, high doses increase motility
[45]	Mouse (male adult albino CF1) and rat (male juvenile Winstar)	Linalool	50 to 150 mg/kg	*In vivo* - subcutaneous injection	Cholinergic antagonist and agonist, antinociceptive tests (hot plate, formalin test)	Antinociception, stimulation of the cholinergic, opioidergic and dopaminergic systems, local anesthetic activity via blockade of NMDA receptors
[46]	Rat (male juvenile Winstar)	Linalool	50 to 200 mg/kg	*In vivo* - subcutaneous injection	Antinociceptive paw withdrawal test with evoked thermal hyperalgesia (carrageenan, L-glutamate, prostaglandin E2)	Antinociception, anti-inflammation, attenuated inflammation hyperalgesia
[47]	Male juvenile outbred CD1 mice	Linalool	25 to 100 mg/kg	*In vivo* - subcutaneous injection	Antinociceptive paw withdrawal test, injection of A1 and $A2_A$ antagonists	Antinociceptive effect of linalool is mediated by adenosine A1 and $A2_A$
[50]	Human (AJCC stage I-III a breast cancer patients) and rat (adult Sprague-Dawley)	Perillyl alcohol	0.5 g/m^2 (human) and 23 mg/kg (rat) and	Oral ingestion (human) and intravenous (rat)	Gas chromatography, mass spectra	Stable delivery of pharmacological agents
[51]	Bovine	Perillyl alcohol	0.1, 0.5, and 1 mM	*In vitro*	Caspase-3 assay	Induced apoptosis of cancer cells
[52]	Human (leukemia HL-60 cells, Molt 4B cells)	1,8-Cineole	7.5 to 15 µM	*In vitro*	Observation, DNA fragmentation	Induced apoptosis of cancer cells
[53]	Human (M14 melanoma cells, M14 adriamicin-resistant cells)	Terpinen-4-ol	0.42–0.6 µM	*In vitro*	Clonogenic survival test	Induced apoptosis of cancer cells
[54]	Rat (male F344)	Nerolidol	5 mg/g of diet	Oral ingestion	Intestinal neoplasia	Decreased tumor formation

research directed towards understanding the potential allergenic properties of commonly used monoterpenoids, and their breakdown products, is critical to ensure their safe usage.

A multitude of clinical studies have quantified the potential of lavender essential oils in altering the behavior of patients suffering from dementia. Inhalation of lavender oils alone was shown to decrease agitation in dementia patients [25]. In combination with massage therapy, exposure to lavender aromatics was shown to significantly decrease excessive motor behavior in subjects diagnosed with dementia [26]. Over the course of a four-week study, dementia patients showed significant decreases in cognitive impairment after dermal applications (e.g., skin cream) containing lavender oil [27]. While these results support the hypothesis that absorption of lavender essential oils through the nose and skin may assist in promoting mental health, studies involving dementia patients often have many methodological constraints inherent in their experimental design which inhibit cogent interpretations of experimental conclusions. For instance, as Holmes and Ballard [28] report that the signature fragrances of lavender often compromise double-blind studies, that expectation of lavender exposure influences test subjects' responses to treatment, and that patients with severe dementia have likely lost an acute sense of smell. These limitations, in addition to other clinical phenomena such as the Hawthorne effect, are all factors that compromise many studies [28].

The purported aroma-therapeutic properties of lavender in healthy individuals have remained as the most controversial application of this essential oil. Proponents of lavender aromatherapy could cite studies like Dunn et al. [29] which showed that the use of *L. angustifolia* essential oil in aroma-therapeutic practices reduced anxiety in intensive care unit patients. Conversely, Howard and Hughes [30] found that expectancy bias limits the objective study of the efficacy of lavender oils in aroma-therapeutic practices. Such studies often lack adequate placebos and objective measurement of physiological responses [30]. Researchers who study the therapeutic properties of lavender have recently used measurable physiological response parameters, such as electroencephalography (EEG) and coronary flow velocity reserves (CFVR), in attempts to objectively quantify the effects of such treatments. Fernandez et al. [31] showed that infants of depressed mothers had increased left frontal EEG asymmetry (a characteristic response to positive stimuli) after they were exposed to lavender odors. In another study using EEG, Diego et al. [32] found that individuals who received lavender odors during aromatherapy showed increased alpha power in their EEG readings, which is a signature indicator of increased drowsiness. Shiina et al. [33] showed that lavender in aromatherapy resulted in significant increases in test subjects' CFVR, in addition to a decrease in serum cortisol levels, which is indicative of improvement of coronary vessel function and decreased stress, respectively. Taken together, these reports suggest that while there are some potentially positive effects of lavender essential oils in such therapies, interpreting the results of such experiments is often problematic due to the many inherent methodological difficulties.

Human pharmacokinetic data are lacking for many lavender essential oil metabolites [34]. However, one study in humans showed that transdermal applications of lavender oil resulted in the accumulation of monoterpenoids linalool and linalyl acetate in subjects' blood samples [35]. Another common lavender monoterpenoid, 1,8-cineole, was shown to be rapidly absorbed by a human subject via inhalation, with detectible quantities within 5 minutes and peak quantities at ~ 18 minutes of inhalation, followed by a 104.6-minute elimination half-life [36]. In mice, a direct correlation was observed between inhalation of linalool and blood plasma linalool levels [37]. Kohlert et al [38] found that there is little risk in accumulation of these compounds as they likely have a short half-life (hours) in the human body and are quickly eliminated. It was concluded that most of the essential oil constituents are metabolized into carbon dioxide by the body or excreted in conjugated form by the kidneys, with a small fraction of inhaled terpenoids released from the lungs during exhalation [38].

One of the drawbacks in interpreting results of lavender oil treatments in human subjects is the lack of standardization in reporting dosage. In many studies, the precise dosage is reported as percent of oil in solvent for transdermal studies, or as percent of air in a closed chamber in olfactory studies. Furthermore, many studies report essential oil dosages in vague terms, while some lack a discussion of dosage altogether, which limits the implications of such studies. In addition, many studies often lack explicit reporting of the use of Good Clinical Practice or a suitable alternative standard, and authors should be encouraged to report adherence to clinical standards.

Studies in model species

The use of model species to test lavender oil has led to great progress in our understanding of the pharmacological potential of these natural products. Lavender oil has shown strong antimutagenic activity, as oils from *L. angustifolia* exhibited a significant, concentration-dependent reduction in the mutagenic activity of TA98 bacterial strains exposed to the potent mutagen 2-nitrofluorene [39]. Although weak as compared to other essential oils, lavender oils exerted suppression of tumor necrosis factor alpha-induced neutrophil adherence responses [40]. The antimutagenic properties of lavender make it a promising candidate for new applications in human healthcare, potentially as a topological application to protect skin cancer [39].

Using such models, researchers can identify the action of specific lavender terpenoids *in vivo*. For instance, Linck et al. [41] found that inhalation of linalool by mice resulted in sedative behavior, increased pentobarbital-induced sleeping time, decreased spontaneous activity, and reduced body temperature without a corresponding reduction in motor coordination. In addition, mice that inhaled a combination of linalool and linalyl acetate (another prominent component of lavender oil) exhibited an exposure-dependent decrease in motility [42]. Another experiment conducted on mice suggests that the sedative effects of inhaled linalool may be attributed to the inhibition of glutamate uptake by cortical synaptosomes [43].

Multiple landmark studies on mice have linked the prominent lavender terpenoids linalool and linalyl acetate to antinociceptive activity. Injection of linalool resulted in decreased pain response in mice subjected to thermal hyperalgesia and paw withdrawal challenges [44–46]. The use of selective receptor antagonists in these studies has demonstrated the mechanism of action of linalool to involve muscarinic, opioid, and dopaminergic transmission. Specifically, the antinociceptive effects of linalool maybe mediated through the adenosine A1 and $A2_A$ receptors which are believed to be important in cAMP-dependent neuropathic and spinal pain pathways [47]. While such studies have led to great progress in our understanding of the pharmacological effects of specific terpenoid compounds, the underlying basis of such effects are complex and far from completely understood

[48]. More research is critical in determining the precise mechanisms of action of lavender essential oil compounds.

Many of the studies regarding the anticancer properties of lavender oil constituents have been conducted *in vitro* using rat, bovine, human, and bacterial cell lines. Such investigations have shown that there are compounds found in trace amounts in lavender oils which have potentially significant anticancer activity [49]. One such component, the monoterpenoid perillyl alcohol, has been investigated as a potential component of anticancer treatments [50], and has been shown to inhibit angiogenic cell growth and division *in vitro* [51]. Subsequent studies into the chemoprevention potential of perillyl alcohol were undertaken in National Cancer Institute-sponsored phase I, II, and III trials for prostate, breast, and colon cancers. Other lavender oil constituents, such as 1,8-cineole [52] and terpinen-4-ol [53], also display anticancer properties *in vitro* by inducing apoptosis in tumor cells. Nerolidol, a sesquiterpene found in some lavender essential oils, is also believed to have anticancer potential, as rats fed diets laced with nerolidol showed significantly reduced adenomas and the number of tumors per rat [54].

Biosynthesis of Monoterpenes and Sesquiterpenes

The therapeutic properties of lavender essential oils result from the biological activity of certain oil constituents. In turn, the biosynthesis of essential oil constituents is determined by the genetic makeup of the plant. It should therefore be possible to improve medicinal properties of lavenders by enhancing the production of biologically active essential oil constituents through controlling the expression of related genes. This requires a clear understanding of the biochemical pathways that generate these phytochemicals, and a thorough knowledge of the nature and expression pattern of structural and regulatory genes driving the pathways.

Lavender essential oils are primarily made up of monoterpenes (C_{10}), although trace levels of sesquiterpenoids (C_{15}) can also be present. Like other terpenoids, these low molecular weight biochemicals are derived from condensation of the universal terpene precursors isopentenyl diphosphate (IPP, C_5) and dimethylallyl diphosphate (DMAPP, C_5). The condensation reactions initially form geranyl diphosphate (GPP) and farnesyl diphosphate (FPP), which can be modified by terpene synthases to produce over 1000 monoterpenes and approximately 5000 sesquiterpenes, respectively [55–61]. Monoterpenes are derived from GPP by the action of monoterpene synthases, and sesquiterpene synthases transform FPP to various sesquiterpenes [62]. An overview of the enzymatic reactions resulting in synthesis of major lavender monoterpenoids is shown in **Fig. 1**. Monoterpenes directly derived from GPP may be further modified through the actions of cytochrome P450 hydroxylases, reductases, dehydrogenases, and transferases to produce additional terpenes, which often have unique physical and chemical properties as well as biological activities [63]. For example, linalool is modified by the addition of an acetyl group to form linalyl acetate, although the enzyme responsible for this reaction has not been yet identified.

In plants, IPP and DMAPP are derived from two distinct biochemical pathways: the classical acetate-mevalonate (MVA) pathway, and the more recently discovered 2-*C*-methyl-D-erythritol 4-phosphate (MEP) pathway. Terpene biosynthesis in plants is largely compartmentalized, with sesquiterpenoids primarily being synthesized in the cytosol via the MVA pathway, and with monoterpenoids mainly being derived from the plastidial MEP pathway [64]. However, it has been demonstrated that a considerable amount of cross-talk can occur between the MVA and MEP pathways. For example, Laule et al. [65] demonstrated that *Arabidopsis* plants, in which the MVA pathway was blocked, continued to produce sterols, presumably through the plastidial MEP pathway. Furthermore, in snapdragon, IPP precursors destined for both mono- and sesquiterpene assembly were derived from the MEP pathway [66]. The two biosynthetic pathways can operate in concert, as studies of sesquiterpene production in chamomile, for example, have shown that isoprenoid precursors were derived from both the plastidial and cytosolic terpenoid biosynthetic pathways [67]. In a series of elegant experiments using tobacco cell cultures, radiolabeled precursor metabolites, and protein biochemistry techniques, Hemmerlin et al. [68] described the considerable cross-talk between the MVA and MEP metabolic pathways *in vivo*.

The conversion of IPP/DMAPP to GPP and FPP, and the subsequent transformation of the later precursors to various terpene backbones – catalyzed by terpene synthases – have been extensively studied. Terpene synthases were first identified in tobacco (*Nicotiana tabacum*) [69] and spearmint (*Mentha spicata*) [70], and subsequently in numerous other plants including *Arabidopsis thaliana, Citrus* spp., *Abies grandis*, and *Zea mays* (for a detailed review, see [71]). To date, only three terpene synthase genes (including limonene, linalool, and bergamotene synthases) have been cloned and biochemically characterized in lavender. However, efforts are currently underway to develop genomics re-

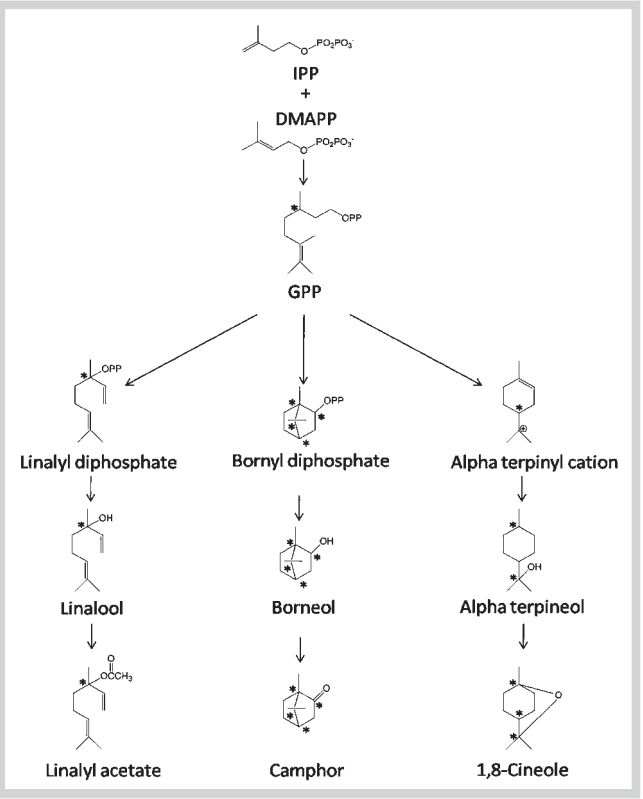


Fig. 1 Enzymatic reactions involved in the synthesis of major lavender monoterpenoids. IPP = isopentenyl diphosphate, DMAPP = dfimethylallaly diphosphate, GPP = geranyl diphosphate. Asterisks (*) denote chiral centers.

sources in lavender to facilitate the discovery of additional structural and regulatory genes that control the production of essential oil constituents in these plants [72].

The discovery and cloning of terpene biosynthetic genes has recently prompted extensive genetic engineering efforts aimed at improving production of mono- and sesquiterpenes in higher plants. These studies have yielded promising results. For instance, over-expression of a key MEP pathway enzyme, 1-deoxy-D-xylulose 5-phosphate *synthase* (DXS), in *Arabidopsis* resulted in increased monoterpene production, as well as increases in quantities of chlorophyll and carotene terpenoids [73]. The relatively slow action of deoxyxylulose phosphate reductoisomerase (DXR), the enzyme that catalyzes the second step of the MEP pathway, was shown to be remediated by the co-overexpression of *DXR* and *DXPS* in *Escherichia coli*, resulting in increased production of lycopene (C_{40}) compared with cells that overexpressed *DXPS* alone [74]. Furthermore, yields of the *p*-menthane monoterpenes have been shown to increase 40–60% via ectopic expression of *DXR* in peppermint (*Mentha* × *piperita*) [75]. These results underscore the potential of genetic engineering to improve the quality of essential oil in plants.

Regulation of Terpenoid Biosynthesis

The biosynthesis of terpenoid compounds is strongly modulated by a myriad of environmental factors, including biotic stress. It is believed that the constitutive induction of volatile compounds is necessary for plants to thwart feeding insects and fungi [76]. Van Poeke and coworkers found that *Arabidopsis* plants infested with herbivorous *Pieris rapae* upregulated terpene synthase genes *AtTPS03* and *AtTPS10*, as well as terpenoids myrcene and *β*-ionone [77]. Increased emission of volatiles [including linalool, *β*-ocimine, and (*E*)-*β*-farnasene] was also observed in cotton exposed to the herbivore *Lygus* [78]. As such, the enhancement of terpenoid biosynthesis may have potentially significant impacts on crop defense.

Abiotic environmental factors also result in the induction of terpene biosynthesis. Leaves from holm oak (*Quercus ilex*) emit monoterpenoids, particularly *cis*-*β*-ocimene and *trans*-*β*-ocimene, in response to heat stress [79]. Seasonal temperature fluctuations were found to elicit volatile emissions from many Mediterranean woody species, including *Arbutus unedo, Erica arborea,* and *Quercus coccifera*, with maximum terpene emission rates in spring [80], and monoterpenoid emission potential was greatest in early summer in Scots pine (*Pinus sylvestris*) [81]. Recent research on lavender has confirmed that volatiles are emitted at various times over the course of plant development, with maximal volatile emissions early in the growing season [82] and that emissions are linked to stages of flower development [83].

Since biosynthesis of terpenoids is believed to be predicated on corresponding terpene synthase gene expression in nature [56], our understanding of terpenoid biosynthesis has been greatly advanced using gene expression analysis and modern genomics techniques (such as microarray), revealing intriguing new insights into the intricacies of plant secondary metabolism. To advance our understanding of terpenoid gene expression, plant researchers have applied powerful web-based software tools, such as Genevestigator (http://www.genevestigator.ethz.ch/), to assess the considerable amounts of new genomics information generated from microarray experiments [84]. For instance, in a comprehensive microarray study, key terpene synthase genes were found to be preferentially expressed in *Arabidopsis* roots, which led to the identification of a tandem-organized pair of genes that were mechanically wound-inducible [85]. Despite these exciting advancements in terpenoid-related gene expression, the key molecular regulators of terpenoid biosynthesis have not been discovered.

Lavender is emerging as a model system for the study of terpenoid-related gene expression. Three lavender terpene synthases were first identified and characterized by Landmann in 2007 [72]. Since then, the first expressed sequence tag (EST) library of *L. angustifolia* has recently been reported [83]. This EST library contains 9453 unigenes, with many coding terpenoid biosynthesis-related enzymes, including terpene synthases, prenyl transfereases, and representatives from both the MVA and MEP terpene biosynthesis pathways [83]. Gene expression studies using this EST library revealed the enrichment of terpene synthase and MEP pathway transcripts in lavender glandular trichomes, in addition to detailing the temporal relationship between terpene synthase gene expression and essential oil accumulation [83]. The association of terpene synthase gene expression and terpene accumulation was also observed in *L. angustifolia* grown under natural conditions [82].

Advancements in genetic engineering protocols optimized for lavender have contributed to our understanding of essential oil production. Using transformation procedures, Munoz-Bertomeu et al. [86] found that over-expression of *DXS*, resulted in significant increases in total essential oil yield in *L. latifolia*. Studies such as these open new possibilities to target and explore terpene metabolism in *Lavandula*, potentially leading to the development of lavender cultivars with exceptional yields of therapeutically crucial terpenoids. Such technologies permit increasing the production of medicinal constituents, and hence developing new and more potent plants.

Conclusions and Future Directions

A recent increase in the popularity of alternative medicine and "natural products" has renewed interest in lavenders and their essential oils as potential natural remedies. This surge has provided an exciting marketplace for lavenders with novel properties and applications, and future research is vital to better develop our understanding and production of lavender oils. Many discreet compounds in lavender oils have shown a myriad of potential therapeutic applications, and researchers continue to seek novel therapies to various ailments. Given that some of the most potent oil constituents (e.g., perillyl alcohol) are not highly abundant, our rapidly developing knowledge of terpenoid metabolic pathways will pave the way for improving the production of these compounds in lavenders through traditional breeding, or through modern plant biotechnology.

References

1 *Aqil M, Ahad A, Sultana Y, Ali A.* Status of terpenes as skin penetration enhancers. Drug Discov Today 2007; 12: 1061–1067
2 *Lis-Balchin M.* Lavender: the genus *Lavandula*. London: CRC Press; 2002: 208–209
3 *Gilani AH, Aziz N, Khan MA, Shaheen F, Jabeen Q, Siddiqui BS.* Ethnopharmacological evaluation of the anticonvulsant, sedative and antispasmodic activities of *Lavandula stoechas* L. J Ethnopharmacol 2000; 71: 161–167
4 *Khalil AM, Ashy MA, El-Tawil BAH, Tawfiq NI.* Constituents of local plants: 5. The coumarin and triterpenoid constituents of *Lavandula dentata* L. plant. Pharmazie 1979; 34: 564–565

5 *National Non-Food Crops Centre.* Available at http://www.nnfcc.co.uk/metadot/index. Accessed February 1, 2010
6 *Wyckoff L, Sievers A.* Lavender growing in America. Am Perfumer 1935; 31: 67–70
7 *Perry N, Perry E.* Aromatherapy in the management of psychiatric disorders clinical and neuropharmacological perspectives. CNS Drugs 2006; 20: 257–280
8 *Heuberger E, Hongratanaworakit T, Böhm C, Weber R, Buchbauer G.* Effects of chiral fragrances on human autonomic nervous system parameters and self-evaluation. Chem Senses 2001; 26: 281–292
9 *Frey WH.* Bypassing the blood-brain barrier to deliver therapeutic agents to the brain and spinal cord. Drug Deliv Technol 2002; 2: 46–49
10 *Born J, Lange T, Kern W, McGregor GP, Bickel U, Fehm HL.* Sniffing neuropeptides: a transnasal approach to the human brain. Nat Neurosci 2002; 5: 514–516
11 *Hallschmid M, Benedict C, Born J, Fehm H-L, Kern W.* Manipulating central nervous mechanisms of food intake and body weight regulation by intranasal administration of neuropeptides in man. Physiol Behav 2004; 83: 55–64
12 *Hudson R.* The value of lavender for rest and activity in the elderly patient. Complement Ther Med 1996; 4: 52–57
13 *Field T, Field T, Cullen C, Largie S, Diego M, Schanberg S, Kuhn C.* Lavender bath oil reduces stress and crying and enhances sleep in very young infants. Early Hum Dev 2008; 84: 399–401
14 *Goel N, Kim H, Lao RP.* An olfactory stimulus modifies nighttime sleep in young men and women. Chronobiol Int 2005; 22: 889–904
15 *Tasev T, Toléva P, Balabanova V.* Neurophysical effect of Bulgarian essential oils from rose, lavender and geranium. Folia Med (Plovdiv) 1969; 11: 307–317
16 *Tisserand R.* The essential oil safety data manual. Brighton: Tisserand Aromatherapy Institute; 1988
17 *Kritsidima M, Newton T, Asimakopoulou K.* The effects of lavender scent on dental patient anxiety levels: a cluster randomised-controlled trial. Community Dent Oral Epidemiol 2009; 38: 83–87
18 *Sugawara Y, Hara C, Tamura K, Fujii T, Nakamura K, Masujima M, Aoki T.* Sedative effect on humans of inhalation of essential oil of linalool: sensory evaluation and physiological measurements using optically active linalools. Anal Chim Acta 1998; 365: 293–299
19 *Hoferl M, Krist S, Buchbauer G.* Chirality influences the effects of linalool on physiological parameters of stress. Planta Med 2006; 72: 1188–1192
20 *European Parliament and of the Council of 27 February 2003.* Amending council directive 76/768/EEC on the approximation of the laws of the member states relating to cosmetic products. Off J Eur Union 2003; L66: 26–35
21 *Sköld M, Börje A, Matura M, Karlberg A-T.* Studies on the autoxidation and sensitizing capacity of the fragrance chemical linalool, identifying a linalool hydroperoxide. Contact Dermatitis 2002; 46: 267–272
22 *Sköld M, Börje A, Harambasic E, Karlberg A-T.* Contact allergens formed on air exposure of linalool. Identification and quantification of primary and secondary oxidation products and the effect on skin sensitization. Chem Res Toxicol 2004; 17: 1697–1705
23 *Matura M, Sköld M, Börje A, Andersen K, Bruze M, Frosch P, Goossens A, Johansen J, Svedman C, White I, Karlberg A-T.* Selected oxidized fragrance terpenes are common contact allergens. Contact Dermatitis 2005; 52: 320–328
24 *Christensson JB, Matura M, Gruvberger B, Bruze M, Karlberg A-T.* Linalool – a significant contact sensitizer after air exposure. Contact Dermatitis 2010; 62: 32–41
25 *Smallwood J, Brown R, Coulter F, Irvine E, Copland C.* Aromatherapy and behaviour disturbances in dementia: a randomized controlled trial. Int J Geriatr Psychiatry 2001; 16: 1010–1013
26 *Holmes C, Hopkins V, Hensford C, MacLaughlin V, Wilkinson D, Rosenvinge H.* Lavender oil as a treatment for agitated behaviour in severe dementia: a placebo controlled study. Int Geriatr Psychiatry 2002; 17: 305–308
27 *Bowles EJ, Griffiths DM, Quirk L, Brownrigg A, Croot K.* Effects of essential oils and touch on resistance to nursing care procedures and other dementia-related behaviours in a residential care facility. Int J Aromather 2002; 12: 1–8
28 *Holmes C, Ballard C.* Aromatherapy in dementia. Adv Psychiatric Treat 2004; 10: 296–300
29 *Dunn C, Sleep J, Collett D.* Sensing an improvement: an experimental study to evaluate the use of aromatherapy, massage and periods of rest in an intensive care unit. J Adv Nurs 1995; 21: 34–40
30 *Howard S, Hughes BM.* Expectancies, not aroma, explain impact of lavender aromatherapy on psychophysiological indices of relaxation in young healthy women. Br J Health Psychol 2008; 13: 603–617
31 *Fernandez M, Hernandez-Reif M, Field T, Diego M, Sanders C, Roca A.* EEG during lavender and rosemary exposure in infants of depressed and non-depressed mothers. Infant Behav Dev 2004; 27: 91–100
32 *Diego MA, Jones NA, Field T, Hernandez-Reif M, Schanberg S, Kuhn C, McAdam V, Galamaga R, Galamaga M.* Aromatherapy positively affects mood, EEG patterns of alertness and math computations. Int J Neurosci 1998; 96: 217–224
33 *Shiina Y, Funabashi N, Lee K, Toyoda T, Sekine T, Honjo S, Hasegawa, Kawata T, Wakatsuki Y, Hayashi S, Murakami S, Koike K, Daimon M, Komuro I.* Relaxation effects of lavender aromatherapy improve coronary flow velocity reserve in healthy men evaluated by transthoracic Doppler echocardiography. Int J Cardiol 2008; 129: 193–197
34 *Ravizza R, Gariboldi MB, Molteni R, Monti E.* Linalool, a plant-derived monoterpene alcohol, reverses doxorubicin resistance in human breast adenocarcinoma cells. Oncol Rep 2008; 20: 625–630
35 *Jager W, Buchbauer G, Jirovetz L, Fritzer M.* Percutaneous absorption of lavender oil from massage oil. J Soc Cosmet Chem 1992; 4: 49–54
36 *Jager W, Nasel B, Nasel C, Binder R, Stimpfl T, Vycudilik W, Buchbauer G.* Pharmacokinetic studies of the fragrance compound 1,8-cineol in humans during inhalation. Chem Senses 1996; 21: 477–480
37 *Jirovetz L, Buchbauer G, Jager W, Raverdino V, Nikiforov A.* Determination of lavender oil fragrance compounds in blood samples. Fresenius J Anal Chem 1990; 338: 922–923
38 *Kohlert C, van Rensen I, März R, Schindler G, Graefe UE, Veit M.* Bioavailability and pharmacokinetics of natural volatile terpenes in animals and humans. Planta Med 2000; 66: 495–505
39 *Evandri MG, Battinelli L, Daniele C, Mastrangelo S, Bolle P, Mazzanti G.* The antimutagenic activity of *Lavandula angustifolia* (lavender) essential oil in the bacterial reverse mutation assay. Food Chem Toxicol 2005; 43: 1381–1387
40 *Abe S, Maruyama N, Hayama K, Ishibashi H, Inoue S, Oshima H, Yamaguchi H.* Suppression of tumor necrosis factor-alpha-induced neutrophil adherence responses by essential oils. Mediators Inflamm 2003; 12: 323–328
41 *Linck VM, da Silva AL, Figueiró M, Piato AL, Herrmann AP, Birck DF, Caramão E, Nunes DS, Moreno PRH, Elisabetsky E.* Inhaled linalool-induced sedation in mice. Phytomedicine 2009; 16: 303–307
42 *Buchbauer G, Jirovetz L, Jäger W, Plank C, Dietrich H.* Fragrance compounds and essential oils with sedative effects upon inhalation. J Pharm Sci 1993; 82: 660–664
43 *Silva Brum LF, Emanuelli T, Souza DO, Elisabetsky E.* Effects of linalool on glutamate release and uptake in mouse cortical synaptosomes. Neurochem Res 2001; 26: 191–194
44 *Peana AT, D'Aquila PS, Chessa ML, Moretti MDL, Serra G, Pippia P.* (−)-Linalool produces antinociception in two experimental models of pain. Eur J Pharmacol 2003; 403: 37–41
45 *Peana AT, De Montis MG, Nieddu E, Spano MT, D'Aquila PS, Pippia P.* Profile of spinal and supra-spinal antinociception of (−)-linalool. Eur J Pharmacol 2004; 485: 165–174
46 *Peana AT, De Montis MG, Sechi S, Sircana G, D'Aquila PS, Pippia P.* Effects of (−)-linalool in the acute hyperalgesia induced by carrageenan, l-glutamate and prostaglandin E2. Eur J Pharmacol 2004; 497: 279–284
47 *Peana AT, Rubattu P, Piga GG, Fumagalli S, Boatto G, Pippia P, De Montis MG.* Involvement of adenosine A1 and A2A receptors in (−)-linalool-induced antinociception. Life Sci 2006; 78: 2471–2474
48 *Komiya M, Takeuchi T, Harada E.* Lemon oil vapor causes an anti-stress effect via modulating the 5-HT and DA activities in mice. Behav Brain Res 2006; 172: 240–249
49 *Buchbauer G, Jager W, Jirovetz L, Ilmberger J, Dietrich H.* Therapeutic properties of essential oils and fragrances. Bioactive volatile compounds from plants. Washington DC: American Chemical Society; 1993: 159–165
50 *Zhang Z, Chen H, Chan K, Budd T, Ganapathi R.* Gas chromatographic mass-spectrometric analysis of perillyl alcohol and metabolites in plasma. J Chromatogr B Biomed Sci Appl 1999; 728: 85–95
51 *Loutrari H, Hatziapostolou M, Skouridou V, Papadimitriou E, Roussos C, Kolisis FN, Papapetropoulos A.* Perillyl alcohol is an angiogenesis inhibitor. J Pharmacol Exp Ther 2004; 311: 568–575
52 *Moteki H, Hibasami H, Yamada Y, Katsuzaki H, Imai K, Komiya T.* Specific induction of apoptosis by 1,8-cineole in two human leukemia cell lines, but not a in human stomach cancer cell line. Oncol Rep 2002; 9: 757–760

53 *Calcabrini A, Stringaro A, Toccacieli L, Meschini S, Marra M, Colone M, Salvatore G, Mondello F, Arancia G, Molinari A.* Terpinen-4-ol, the main component of *Melaleuca alternifolia* (tea tree) oil inhibits the *in vitro* growth of human melanoma cells. J Invest Dermatol 2004; 122: 349–360

54 *Wattenberg LW.* Inhibition of azoxymethane-induced neoplasia of the large bowel by 3-hydroxy-3,7,11-trimethyl-l,6,10-dodecatriene (nerolidol). Carcinogen 1991; 12: 151–152

55 *McGarvey DJ, Croteau R.* Terpenoid metabolism. Plant Cell 1995; 7: 1015–1026

56 *Mahmoud SS, Croteau RB.* Metabolic engineering of essential oil yield and composition in mint by altering expression of deoxyxylulose phosphate reductoisomerase and menthofuran synthase. Proc Natl Acad Sci USA 2001; 98: 8915–8920

57 *Chappell J.* Biochemistry and molecular biology of the isoprenoid biosynthetic pathway in plants. Annu Rev Plant Biol 1995; 46: 521–547

58 *Chappell J, Wolf F, Proulx J, Cuellar R, Saunders C.* Is the reaction catalyzed by 3-hydroxy-3-methylglutaryl coenzyme A reductase a rate-limiting step for isoprenoid biosynthesis in plants? Plant Physiol 1995; 109: 1337–1343

59 *Mahmoud SS, Croteau RB.* Menthofuran regulates essential oil biosynthesis in peppermint by controlling a downstream monoterpene reductase. Proc Natl Acad Sci USA 2003; 100: 14481–14486

60 *Mahmoud SS, Williams M, Croteau R.* Cosuppression of limonene-3-hydroxylase in peppermint promotes accumulation of limonene in the essential oil. Phytochemistry 2004; 65: 547–554

61 *McConkey ME, Gershenzon J, Croteau RB.* Developmental regulation of monoterpene biosynthesis in the glandular trichomes of peppermint. Plant Physiol 2000; 122: 215–223

62 *Schilmiller AL, Schauvinhold I, Larson M, Xu R, Charbonneau AL, Schmidt A, Wilkerson C, Last RL, Pichersky E.* Monoterpenes in the glandular trichomes of tomato are synthesized from a neryl diphosphate precursor rather than geranyl diphosphate. Proc Natl Acad Sci USA 2009; 106: 10865–10870

63 *Aharoni A, Giri AP, Deuerlein S, Griepink F, de Kogel WJ, Verstappen FW, Verhoeven HA, Jongsma MA, Schwab W, Bouwmeester HJ.* Terpenoid metabolism in wild-type and transgenic *Arabidopsis* plants. Plant Cell 2003; 15: 2866–2884

64 *McCaskill D, Croteau R.* Monoterpene and sesquiterpene biosynthesis in glandular trichomes of peppermint (*Mentha* × *piperita*) rely exclusively on plastid-derived isopentenyl diphosphate. Planta 1995; 197: 49–56

65 *Laule O, Furholz A, Chang HS, Zhu T, Wang X, Heifetz PB, Gruissem W, Lange M.* Crosstalk between cytosolic and plastidial pathways of isoprenoid biosynthesis in *Arabidopsis thaliana*. Proc Natl Acad Sci USA 2003; 100: 6866–6871

66 *Dudareva N, Andersson S, Orlova I, Gatto N, Reichelt M, Rhodes D, Boland W, Gershenzon J.* The nonmevalonate pathway supports both monoterpene and sesquiterpene formation in snapdragon flowers. Proc Natl Acad Sci USA 2005; 102: 933–938

67 *Adam KP, Zapp J.* Biosynthesis of the isoprene units of chamomile sesquiterpenes. Phytochemistry 1998; 48: 953–959

68 *Hemmerlin A, Hoeffler JF, Meyer O, Tritsch D, Kagan IA, Grosdemange-Billiard C, Rohmer M, Bach TJ.* Cross-talk between the cytosolic mevalonate and the plastidial methylerythritol phosphate pathways in tobacco bright yellow-2 cells. J Biol Chem 2003; 278: 26666–26676

69 *Facchini PJ, Chappell J.* Gene family for an elicitor-induced sesquiterpene cyclase in tobacco. Proc Natl Acad Sci USA 1992; 89: 11088–11092

70 *Colby SM, Alonso WR, Katahira EJ, McGarvey DJ, Croteau R.* 4S-limonene synthase from the oil glands of spearmint (*Mentha spicata*). cDNA isolation, characterization, and bacterial expression of the catalytically active monoterpene cyclase. J Biol Chem 1993; 268: 23016–23024

71 *Degenhardt J, Köllner TG, Gershenzon J.* Monoterpene and sesquiterpene synthases and the origin of terpene skeletal diversity in plants. Phytochemistry 2009; 70: 1621–1637

72 *Landmann C, Fink B, Festner M, Dregus M, Engel KH, Schwab W.* Cloning and functional characterization of three terpene synthases from lavender (*Lavandula angustifolia*). Arch Biochem Biophys 2007; 465: 417–429

73 *Estevez J, Cantero A, Reindl A, Reichler S, León P.* 1-Deoxy-d-xylulose-5-phosphate synthase, a limiting enzyme for plastidic isoprenoid biosynthesis in plants. J Biol Chem 2001; 276: 22901–22909

74 *Kim SW, Keasling JD.* Metabolic engineering of the nonmevalonate isopentenyl diphosphate synthesis pathway in *Escherichia coli* enhances lycopene production. Biotechnol Bioeng 2001; 72: 408–415

75 *Mahmoud SS, Croteau RB.* Strategies for transgenic manipulation of monoterpene biosynthesis in plants. Trends Plant Sci 2002; 7: 366–373

76 *Phillips MA, Croteau R.* Resin based defenses in conifers. Trends Plant Sci 1999; 4: 184–190

77 *Van Poecke RMP, Posthumus MA, Dicke M.* Herbivore-induced volatile production by *Arabidopsis thaliana* leads to attraction of the parasitoid *Cotesia rubecula*: chemical, behavioral, and gene-expression analysis. J Chem Ecol 2001; 27: 1911–1928

78 *Rodriguez-Saona C, Crafts-Brandner SJ, Williams III L, Pare P. Lygus hesperus* feeding and salivary gland extracts induce volatile emissions in plants. J Chem Ecol 2002; 28: 1733–1747

79 *Staudt M, Bertin N.* Light and temperature dependence of the emission of cyclic and acyclic monoterpenes from holm oak (*Quercus ilex* L.) leaves. Plant Cell Environ 1998; 21: 385–395

80 *Llusià J, Peñuelas J.* Seasonal patterns of terpene content and emission from seven Mediterranean woody species in field conditions. Am J Bot 2000; 87: 133–140

81 *Hakola H, Tarvainen V, Bäck J, Ranta H, Bonn B, Rinne J, Kulmala M.* Seasonal variation of mono- and sesquiterpene emission rates of Scots pine. Biogeoscience 2006; 2: 1697–1717

82 *Guitton Y, Nicolè F, Moja S, Valot N, Legrand S, Jullien F, Legendre F.* Differential accumulation of volatile terpene and terpene synthase mRNAs during lavender (*Lavandula angustifolia* and *L.* X *intermedia*) inflorescence development. Physiol Plant 2010; 138: 150–163

83 *Lane A, Boeckelmann A, Woronuk G, Sarker L, Mahmoud S.* Genomics resource for investigating regulation of essential oil production in *Lavandula angustifolia*. Planta 2010; 231: 835–845

84 *Zwenger S, Basu C. In silico* analysis of terpene synthase genes in *Arabidopsis thaliana*. EXCLI J 2007; 6: 203–211

85 *Godard KA, White R, Bohlmann J.* Monoterpene-induced molecular responses in *Arabidopsis thaliana*. Phytochemistry 2008; 69: 1838–1849

86 *Munoz-Bertomeu J, Arrillaga I, Ros R, Segura J.* Up-regulation of 1-deoxy-D-xylulose-5-phosphate synthase enhances production of essential oils in transgenic spike lavender. Plant Physiol 2006; 142: 890–900