15 April 2011
EMA/HMPC/143183/2010
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Lavandula angustifolia* Mill., aetheroleum and *Lavandula angustifolia* Mill., flos

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

Draft

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Lavandula angustifolia* Mill., aetheroleum; *Lavandula angustifolia* Mill., flos
Herbal preparation(s)	• Lavandulae aetheroleum Essential oil obtained by steam distillation from the flowering tops of *Lavandula angustifolia* Mill. • Lavandulae flos a) Comminuted herbal substance b) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 50-60% v/v
Pharmaceutical forms	• Lavandulae aetheroleum Herbal preparation in liquid dosage form for oral use and as a bath additive. • Lavandulae flos Herbal substance or comminuted herbal substance as herbal tea for oral use. Herbal preparations in liquid dosage form for oral use.

Note: This draft Assessment Report is published to support the release for public consultation of the draft Community herbal monograph on *Lavandula angustifolia* Mill., aetheroleum and of the draft monograph on *Lavandula angustifolia* Mill., flos. It should be noted that this document is a working document, not yet fully edited, and which shall be further developed after the release for consultation of the monographs. Interested parties are welcome to submit comments to the HMPC secretariat,

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which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monographs.

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1. Introduction

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

Lavender flower consists of the dried flowers of *Lavandula angustifolia* Miller (*Lavandula officinalis* Chaix) (European Pharmacopoeia 2008a).

- Herbal preparation(s)

Essential oil obtained by steam distillation from the flowering tops of *Lavandula angustifolia* Miller (*Lavandula officinalis* Chaix) (European Pharmacopoeia 2008b).

The species is regularly confused with other lavender species *L. x intermedia* Emeric. (Lavandin) and *L. latifolia* MEDIK. (Spiklavender). If no detailed quality specifications are mentioned, the herbal substance consists of flowers from different flower species (Hänsel et al. 1993).

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable.

- Constituents

Lavender flower contains not less than 13 ml/kg of essential oil, calculated with reference to the dried drug.

Lavender flower

- Essential oil (1-3%)

- Coumarin derivatives: umbelliferon, herniarine

- Flavonoids

- Sterols (traces): cholesterol, campesterol, stigamsterol, β-sitosterol

- Triterpenes (traces): mictomeric acid, ursolic acid

- Tannins: up to 13% in the herbal substance

- Phenylcarboxylic acids such as rosmarinic acid, ferulic acid, isoferulic acid, α-cumaric acid, p-cumaric acid, gentisinic acid, p-OH-benzoic acid, caffeic acid, melilotic acid, sinapinic acid, sytingic acid, vanillinic acid.

Lavender oil

The main components of the essential oil are monoterpene alcohols (60-65%) such as linalool (20-50% of the fraction), linalyl acetate (25-46% of the fraction).
Others include cis-ocimen (3-7%), terpinene-4-ol (3-5%), limonene, cineole, camphor, lavandulyl acetate, lavandulol and α-terpineol, β-caryophyllene, geraniol, α-pinen.
Non-terpenoid aliphatic components: 3-octanon, 1-octen-3-ol, 1-octen-3-ylacetate, 3-octanol. (ESCOP 2009; Hänsel et al. 1993; Bruneton 1999).

1.2. Information about products on the market in the Member States

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	See composition
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No monopreparations registered
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No monopreparations registered
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only flowers in herbal tea
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered products on the market
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered products on the market
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combined preparations registered
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	See detailed information
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered products on the market
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered products on the market
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered products on the market
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Slovak	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

Member State	Regulatory Status				Comments
Republic					
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered products on the market
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

MA: Marketing Authorisation
TRAD: Traditional Use Registration
Other TRAD: Other national Traditional systems of registration
Other: If known, it should be specified or otherwise add 'Not Known'
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

Composition of preparations

Member State	Regulatory Status	Comments
Austria	**BUCOSEPT Lavendel–Ölbad** 100 g solution contains 5 g essential oil from *Lavandula angustifolia.* Posology For a full bath 30 ml of the solution; duration of bath 15-20 minutes. Indication Supportive in case of exhaustion.	On the market since 1994
Denmark	2 products with Lavandulae herba as one of the components in herbal tea.	On the market since 1999
France	**Aromastress oleocapsule aromatique** (Pranârom–Natessence) Essential oils of *Origanum majorana*, *Lavandula hybrida*, *Citrus reticulata*, *Aloysia triphylla* Indication Stress, nervousness **Climarome voies respiratoires** (Cosbionat) Essential oils of *Lavandula angustifolia*, *Melaleuca viridiflora*, *Pinus sylvestris*, *Mentha arvensis*, *Thymus vulgaris* 33.6% - excipients qsp 100. Indication Prevention of respiratory tract infections. Adults and children ≥3 years: to be applied on tissue for inhalation or to be put on the throat or the thorax. **Perubore spray aromatique** (Mayoli spindler): essential oils of *Thymus vulgaris, Rosmarinus officinalis, Lavandula officinalis, Cinnamomum zeylanicum*. Indication	Capsule as food supplement. >30 years on the market >30 years on the market >30 years on the market

Member State	Regulatory Status	Comments
	Cough, common cold, nose congestion. Adults and children >30 months: vaporise 2 to 3 puffs in the atmosphere or on tissue when the first symptoms of common cold occur. To be repeated several times daily. At nighttime 2 to 3 puffs on the pillow. **Vivalessence** (Motima) Essential oils of *Lavandula, Cinnamomum, Satureja, Eucalyptus* 4.8%, hydroalcoolic extract of *Avena*, ethanol – water qs. ad 100%. Indication Seasonal complaints. Adults, children >7 year: Seasonal complaints: during 15 days 30 to 50 drops daily in a glass of water (in the morning). **Tetesept anti-stress Bad** (Merz Pharma) essential oils of *Lavandula, Melissae indicum, Pinus, Rosmarinus.* Indication No indication mentioned. To be put in a bath. **Tetesept Entspannungs Bad** (Merz Pharma) essential oils of: *Citrus aurantium spp., Cinnamomum, Lavandula* Indication No indication mentioned. To be put in a bath.	>30 years on the market On the market since 1996 On the market since 1983
Germany	**Lavandulae aetheroleum** In soft capsules containing 80 mg Lavandulae aetheroleum Indication For treatment of anxious restlessness or For treatment of restlessness due to anxiety (*…zur Behandlung von Unruhezuständen bei ängstlicher Verstimmung ...*) Posology 1x1 capsule per day For oral use in adults over 18 years Specific information Possible influence on medicinal products, which act via GABA-receptors (barbiturates, benzodiazepine). Clinical data are not available. Adverse events: eructation (7%); nausea (2%) No use in children and adolescents below the age of 18 years. Up to now, there was no need to undertake pharmacovigilance actions. **Lavandulae aetheroleum** All as bath additive Indication Traditionally used to improve feeling in state of exhaustion *(…Traditionell angewendet zur Besserung des Befindens*	Authorized product since 2009 WEU Authorized product at least since 1976 TU

<table>
<tr><th>Member State</th><th>Regulatory Status</th><th>Comments</th></tr>
<tr><td></td><td>bei Erschöpfungszuständen …)
<u>Posology</u>
For use in adults and adolescents over 12 years
1) 15-20 ml bath additive / full bath at 35-38° for 10-20 minutes
7 g Lavandulae aetheroleum / 100 g (= approximately 96 ml) bath additive
2) 15-20 ml bath additive / full bath at 35-38° for 10-20 minutes
7 g Lavandulae aetheroleum / 100 g (=95 ml) bath additive
3) 30 ml bath additive / 150-200 l water at 35-37° for 15-20 minutes
10 g Lavandulae aetheroleum / 100 g bath additive
<u>Specific information</u>
General contraindications to take a bath.
Up to now, there was no need to undertake pharmacovigilance actions.

Combined products
There are 5 authorized products on the market
<table>
<tr><th>number of combination substances</th><th>number of authorized combination products</th></tr>
<tr><td>2-3</td><td>0</td></tr>
<tr><td>4-5</td><td>1</td></tr>
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</td><td>Authorized products</td></tr>
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1.3. Search and assessment methodology

For this assessment report the following sources were used:

- Allied and alternative medicine
- Biosis
- Chemical abstracts (since 1967)
- Current contents search - bibliographic records
- Derwent drug file
- Derwent drug file backfile
- Excerpta Medica
- International pharmaceutical abstracts
- Medline
- Pascal
- PubMed

- Standard reference books

These sources were searched on the following terms (alone or in combination):
Lavandula, *lavender*, *essential oil*, *stress*, *anxiety*, *relaxation*, *sleep*, *sleeping*, *disorder*

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

In the 15th century when the technique of steam distillation was developed, Hildegarde von Bingen and Paracelsus described the use of distilled water saturated with the essential oil of lavender as a sedative. The oil was traditionally used by evaporating it into rooms to calm 'excited' children. Even narcotic effects have been described when high concentrations were used (Guillemain et al. 1989). Rembertus Dodonaeus (1608) mentioned already the use of lavender water as a calming agent, even in case of epileptic seizures. Flowers and essential oil of *Lavandula officinalis* have been used for their sedative activity throughout Europe (Weiss & Fintelmann 1999). Leclerc (1966) has mentioned the use of lavender flowers in phytotherapeutic practice in France.

According to information on marketed products, lavender oil has been marketed for topical use since 1976. Since 2009, soft capsules with lavender oil have been marketed as an authorized product in Germany. This practice has been preceded by a long-standing tradition of administering the essential oil as drops on a piece of sugar (ESCOP 2009; British Herbal Pharmacopoeia 1983, referring to the British Pharmaceutical Codex 1973).

2.2. Information on traditional/current indications and specified substances/preparations

Peroral use

Soft capsules with Lavandulae aetheroleum have been authorized in Germany since 2009.

- Therapeutic indications: WEU
  For treatment of anxious restlessness or for treatment of restlessness due to anxiety.
  (*…zur Behandlung von Unruhezuständen bei ängstlicher Verstimmung ...*)
- Posology
  For adults ≥ 18 years: soft capsules containing 80 mg, 1 capsule per day.

Use as bath additive

Bath additives with Lavandulae aetheroleum have been authorized in Germany since at least 1976.

- Therapeutic indications: TU
  Herbal medicinal product traditionally used to improve feeling in state of exhaustion.
- Posology
  For adults and adolescents over 12 years: 15 to 30 ml bath additive containing 7 to 10% (W/W) Lavandulae aetheroleum per full bath at 35-38°C during 10-20 minutes.

A bath additive with 5% Lavandulae aetheroleum has been on the market in Austria since 1994. The posology is the same as for the preparations in Germany.

2.3. Specified strength / posology / route of administration / duration of use for relevant preparations and indications

According to the ESCOP monograph (2009)

- Indications

Mood disturbances such as restlessness, agitation or insomnia

- Posology

- Lavender flower

An infusion is made of 1-2 teaspoons (approximately 0.8 to 1.6 g) in 150 ml of water. The number of doses is not specified.

Tincture (1:5 in 50% v/v ethanol), 60 drops per day

- Lavender oil

1-4 drops (approximately 20-80 mg) e.g. on a sugar cube

According to Blumenthal (2000) (referring to Commission E monographs)

- Indications

Internal use: restlessness or insomnia and nervous stomach irritation, Roehmheld's syndrome (stomach discomfort), meteorism and nervous intestinal discomfort
For balneotherapy: treatment of functional circulatory disorders.

The German standard license for lavender tea lists it for restlessness, sleeplessness, lack of appetite, nervous irritable stomach, meteorism and nervous disorders of the intestines.

- Posology

Infusion: 1-2 teaspoons (approximately 0.8-1.6 g) in 150 ml water
Essential oil: 1-4 drops (approximately 20-80 mg) e.g. on a sugar cube
Bath additive: 20-100 g dried flowers for a 20 liter bath

According to the British Herbal Pharmacopoeia (1979 and the 1983 compilation)

- Posology

Internally as a tea: dried flowers 1-2 g by infusion 3 times daily
Tincture (1:5) in 60% ethanol, 2-4 ml 3 times daily
Lavender oil B.P.C. (1973), 0.06–0.2 ml 3 times daily

According to Leclerc (1966)

Lavandulae flos is used in case of asthma, whooping cough, influenza and laryngitis.
An infusion is made of 5 parts per 100 (W/W) and 4 cups a day are prescribed.

According to Valnet (since 1964)

- Indications

Internal use:

- Irritability, spasms, insomnia

- Fever blasts, infectious diseases

- Neurasthenia, melancholy

- Respiratory diseases: asthma, whooping cough, influenza, bronchitis due to whooping cough

- Oliguria

- Rhumatism

- Instability during childhood

- Atonic stomach or intestinal atony

- Migraine, vertigo, hysteria, sequellae of paralysia

- Typhoid enteritis (diarrhoea)

- Cystitis, blennorrhoea

- Dermal eruptions

- Intestinal parasites

- Metrorrhagia, leucorrhoea

- Hypertension

- Posology

Infusion: 1 teaspoon in a cup of boiled water, infusion during 10 minutes: 3 cups per day between meals.

Alcoholature: 40 drops 4 times daily in water (no detailed composition of alcoholature communicated).

Essential oil: 2-5 drops in honey or in an alcoholic solution. In case of anesthesia: 1 g aids at mentally relaxing, without losing intellectual capacity.

Vaporisation: make a solution of 2% in water. To be vaporised in public rooms.

According to Madaus (1938)

- Indications

Internal use:
Lavender mildly acts on the nervous system, especially in case of migraine. It is used against neurasthenia, vertigo, nervous tachycardia, general nervous tension, hysteria, spasms, weakness and sleeplessness.

Lavender has been used against affections of the stomach like gastritis, against meteorism and edema.

External use:
Lavender flowers are used as a bath additive.

Lavender oil is used for local massage in case of rheumatism, gout, neuralgia, ischias and scabies.

Rinsing fluid is made in case of *fluor albus*.

- Posology

Essential oil: 8 drops (without further specification)

Tincture (strength not given): 10-15 drops

Infusion: 2-3 teaspoons (= 3-4.5 g) daily

3. Non-Clinical Data

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

- *In vitro* studies

Antimicrobial effects

Lavender oil had an antimicrobial activity against *Escherichia coli, Bacillus subtilis, Candida albicans* and *Staphylococcus aureus*, but not against *Pseudomonas aeruginosa*. The model used was the plate diffusion test. No details about the concentrations used are mentioned. Linalool was active against *Streptococcus mutans* with a MIC of 1600 µg/ml which is a rather high concentration (Kubo et al. 1993).

Eight essential oils were examined using the agar dilution method, including *Carum carvi, Citrus aurantium* var. *amara, Foeniculum vulgare dulce, Illicium verum, Lavandula angustifolia, Mentha arvensis, Mentha x piperita,* and *Trachyspermum copticum*. Doubling dilutions of the essential oils were tested against 12 species of intestinal bacteria, which represent the major genera found in the human gastrointestinal tract (GIT). *Carum carvi, Lavandula angustifolia, Trachyspermum copticum,* and *Citrus aurantium* var. *amara* essential oils displayed the greatest degree of selectivity, inhibiting the growth of potential pathogens at concentrations that had no effect on the beneficial bacteria examined. The most promising essential oils for the treatment of intestinal dysbiosis are *Carum carvi, Lavandula angustifolia, Trachyspermum copticum,* and *Citrus aurantium* var. *amara*. The herbs from which these oils are derived have long been used in the treatment of gastrointestinal symptoms and the *in vitro* results of this study suggest that their ingestion will have little detrimental impact on beneficial members of the GIT microflora. More research is needed, however, to investigate tolerability and safety concerns, and verify the selective action of these agents (Hawrelak et al. 2009).

Spasmolytic effects

The ileum of the guinea-pig and the rat uterus and phrenic nerve diaphragm were used as an experimental model. These isolated organs contract when exposed to acetylcholine, histamine or noradrenaline or electrically stimulated (field stimulation). Lavender oil inhibited the contractions of the isolated ileum by about 50%. Pure linalool had similar effects. In contrast with lavender oil, a concentration-effect relationship was studied with linalool: $5x10^{-5}$ to $2x10^{-4}$ g/ml on the diaphragm and $4x10^{-6}$ to $8x10^{-5}$ g/ml was used on the isolated ileum; both organs were electrically stimulated. However no concentration-effect curves were displayed.
The inhibition of the electrically stimulated contractions by lavender of guinea-pig ileum appeared to be postsynaptic and not atropine-like, as lavender inhibited the contractile responses due to acetylcholine and to histamine to a similar degree. The relaxation effect by isoprenaline was potentiated by linalool, which may indicate a phosphodiesterase inhibitory activity (Lis-Balchin & Hart 1997 and 1999).

Experiments were designed to investigate the relaxation mechanism of linalyl acetate as the major ingredient of lavender essential oil in rabbit carotid artery specimens. Linalyl acetate produced

sustained and progressive relaxation during the contraction caused by phenylephrine. The relaxation effect of linalyl acetate at a concentration near the EC_{50} was partially but significantly attenuated by nitroarginine as an inhibitor of nitric oxide synthase, 1H-(1,2,4) oxadiazolo (4,3-a) quinoxaline-1-one as an inhibitor of guanylyl cyclase, or by the denudation of endothelial cells. In specimens without endothelium, the phenylephrine-induced contraction and phosphorylation of myosin light chain (MLC) were significantly attenuated after the pretreatment with linalyl acetate. The relaxation caused by linalyl acetate in the endothelium-denuded specimens was clearly inhibited by calyculin A as an inhibitor of MLC phosphatase, although not by ML-9 as an inhibitor of MLC kinase. Furthermore, suppression of the phenylephrine-induced contraction and MLC phosphorylation with linalyl acetate was canceled by the pretreatment with calyculin A. These results suggest that linalyl acetate relaxes the vascular smooth muscle through partial activation of the nitric oxide/cyclic guanosine monophosphate pathway, and partial MLC dephosphorylation via activating MLC phosphatase (Koto et al. 2006).

Other effects

Cultures of cerebellar granular cells from rat pups were exposed to neurotoxic concentrates of glutamate (10^{-7} M). The neuroprotective effect of a dry aqueous extract from lavender flower (DER approximately 5:1) was tested at concentrations of 10 µg/ml, 100 µg/ml, 1 mg/ml and 10 mg/ml. At 100 µg/ml and 1 mg/ml, the extract significantly reduced glutamate-induced neurotoxicity from 37% to 29% ($p<0.05$) and 21% ($p<0.001$) respectively (Büyükokuroglu et al. 2003).

A study on MCF-7 human breast-cancer cells (positive for oestrogen receptors) demonstrated that lavender oil is weakly oestrogenic in concentrations of 0.01 and 0.03 vol/vol%., treated for 18 hours. In MDA-kb2 cells (positive for androgen receptors) lavender oil was revealed to be weakly anti-androgenic in concentrations between 0.0001 and 0.01 vol/vol% treated for 24 hours (Henley et al. 2007).

Lavender oil concentration-dependently inhibited histamine release from peritoneal mast cells ($p< 0.05$):
- stimulated by compound 48/80 (a synthetic phosphodiesterase and ATP-ase inhibitor) at dilutions of 1:500, 1:100, 1:10, 1:1 and undiluted
- stimulated by anti-dinitrophenyl IgE at dilutions of 1:100, 1:10, 1:1 and undiluted.
It also had a significant inhibitory effect on anti-dinitrophenyl IgE-induced TNFα secretion from peritoneal mast cells at 1:1000, 1:100, 1:10 and undiluted ($p< 0.05$) (Kim & Cho, 1999).

Assessor's comments: the relevance of antimicrobial, spasmolytic as well as other effects is difficult to evaluate, as no detailed information about concentrations as such and concentration-effect relationship is available.

- *In vivo* studies

Anticonvulsive effects

Purpose	Species	Intervention	Outcome
To study the anticonvulsive effects of lavender.	Female and male rats.	Electroshock- and metrazole-induced convulsions.	Electroshock-induced convulsions were inhibited after single intraperitoneal doses of lavender oil at 138 and 140 mg/kg body weight respectively; Metrazole-induced convulsions were also inhibited in 60-70% of

Purpose	Species	Intervention	Outcome
			the animals by intraperitoneal doses of 200-300 mg/kg (Atassanova-Shopova &Roussinov 1970).
To study the anticonvulsive effects of lavender.	Male mice stimulated with pentetrazol, nicotine or strychnine (groups of 3 to 7 mice per convulsive agent).	The anticonvulsive effects of lavender oil inhalation (0.3, 0.5 and 1 ml of lavender oil soaked in cotton, in a glass cylinder) were studied in mice. Convulsions were induced by pentetrazol (50 and 100 mg/kg i,p,), nicotine (7.5 mg/kg i.p,), strychnine (2.5 mg/kg i.p,) or by electroshocks (80V, 0,4 seconds). The convulsive agents or electroshocks were administered after inhalation of lavender oil for 15 minutes.	Compared to controls, lavender oil blocked convulsions induced by the lower dose of pentetrazol and by nicotine. No anticonvulsive effects were observed with strychnine. After electroshocks lavender oil dose-dependently reduced tonic extensions and clonic convulsions (Yamada et al. 1994).

Sedative effects

Purpose	Species	Intervention	Outcomes
To study the sleep prolongation.	Rats.	Lavender oil administered IP to rats at 100 mg/kg, anesthetized with hexobarbital sodium (100 mg/kg IP) and alcohol (35%, 3.5 g/kg IP).	The duration of anaesthesia induced by hexobarbital sodium was doubled and anaesthesia induced by alcohol (35%, 3.5 g/kg IP) was prolonged almost two-fold. The duration of the anesthesia by chloral hydrate (300 mg/kg IP) was more than 1.5-fold longer (Atassanova-Shopova & Roussinov 1970).
To study locomotor activity.	Male albino mice.	Lavender oil IP administered during the rotarod motor test.	Lavender oil administered IP at 200-300 mg/kg reduced spontaneous locomotor activity, as well as locomotor activity increased by caffeine-sodium benzoate or amphetamine; in the rotarod test motor coordination was reduced with an ED_{50} of 248 mg/kg (Atassanova-Shopova & Roussinov 1970).
To study locomotor	6-month old female mice.	Exposure to an atmosphere containing the vapour of lavender	Locomotor activity decreased remarkably and time-

Purpose	Species	Intervention	Outcomes
activity.		oil or its constituents linalool and linalyl acetate.	dependently in two studies, after 60 minutes of inhalation, motility was reduced by 43% and 78% with lavender oil, 15% and 73% with linalool, and 35% and 69% with linalyl acetate as compared to controls (Buchbauer et al. 1991; Buchbauer et al. 1993a). An increase in activity of 160% after an injection of caffeine (0.1%, 0.5 ml IP) was reduced to 105%, 126% and 132% respectively by inhalation of the vapour of lavender oil, linalool or linalyl acetate (Buchbauer et al. 1991).
To study stress-induced hyperthermia.	Male Wistar rats. A transmitter was implanted in order to make records of heart rate and body temperature.	Cages with a bedding that had been sprayed with 200 µl of a 0.03% solution of lavender oil, green leaf odour (mixture of hexenol and hexenal), α-pinene or the solvent only (triethyl citrate) as control (n=12 per group, except for the control: n=6).	Following transfer to this novel environment the body temperature of the rats increased by almost 1°C, indicating stress-induced hyperthermia. This was attenuated by green leaf odour and α-pinene, but not by lavender oil or solvent (Akutsu et al. 2002).
To study explorative behaviour and sleeping time.	Mice.	The four plates test with oral administration of lavender oil at 0.4 ml/kg body weight (as a 1:60 dilution in olive oil) daily for 5 days. Pentobarbital-induced sleeping time of 30 minutes. The hole board test and the labyrinth test.	Lavender oil increased in the number of explorations by 68%, indicating an anxiolytic effect. With the same single dose sleeping time was prolonged to 35-59 minutes (Delaveau et al. 1989). In other studies, the same dose of lavender oil did not decrease motility in the hole board test nor increase the number of explorations in the four plates test or number of entries into open arms in the labyrinth test to statistically significant levels (in terms of anxiolytic effects), although modest increases were observed. Pentobarbital-induced

Purpose	Species	Intervention	Outcomes
			sleep latency was significantly shortened ($p < 0.03$) and pentobarbital-induced sleeping time was increased ($p<0.05$) compared to a control group, indicating a sedative effect (Guillemain et al. 1989).
To study locomotor activity.	Mice.	Linalool administered to mice subcutaneously at 25, 50, 75 and 100 mg/kg.	Spontaneous locomotor activity increased by 95% ($p<0.05$ for 75 mg/kg) and 300% ($p<0.0005$ for 100 mg/kg) respectively, whereas 25 mg/kg produced a nonsignificant increase of 15%, and 50 mg/kg a nonsignificant decrease of 34% (Peana et al. 2003).
To investigate the effects of lavender essential oil inhalation on gerbil behaviour.	Male and female gerbils.	Gerbil behaviour in the elevated plus maze test was observed and results compared with the effects of diazepam (1 mg/kg) i.p. after 30 min and 2-week administration. Odour exposure was via an electronic vapouriser and aroma stone, placed into the animal holding room and the experimental suite, but out of reach of the animals, during behavioural testing. Lavender oil was refreshed 3 times daily with 4 drops of the essential oil, to achieve the concentration commonly recommended by aromatherapists.	Traditional measures of open entries showed an increasing trend over the 2 weeks exposure, whereas ethological measures indicative of anxiety (stretch-attend frequency and percentage protected head-dips) were significantly lower. Exploratory behaviour and total head-dip frequency started to increase 24 h after lavender and lasted for the 2 weeks exposure. These results are comparable with diazepam administration. Females showed a significant decrease in protected head-dips compared to both males and to female controls. In conclusion, exposure to lavender oil may have an anxiolytic profile in gerbils similar to that of the anxiolytic diazepam (Bradley et al. 2007).
To study the anticonflict effects of lavender oil and identify its active	ICR mice	Two conflict tests in ICR mice were used and then the active constituents were identified. Lavender oil produced significant anticonflict effects at 800 and 1600 mg/kg in the Geller conflict	Cineol, terpinen-4-ol, alpha-pinene and beta-myrcene did not produce any significant anticonflict effects in the Geller test. Linalyl acetate did not produce any significant

Purpose	Species	Intervention	Outcomes
constituents.		test and at 800 mg/kg in the Vogel conflict test, suggesting that the oil has an anti-anxiety effect. Analysis using GC/MS revealed that lavender oil contains 26 constituents, among which alpha-pinene (ratio, 0.22%), camphene (0.06%), beta-myrcene (5.33%), p-cymene (0.3%), limonene (1.06%), cineol (0.51%), linalool (26.12%), borneol (1.21%), terpinen-4-ol (4.64%), linalyl acetate (26.32%), geranyl acetate (2.14%) and caryophyllene (7.55%) were identified. We examined the effects of linalool, linalyl acetate, borneol, camphene, cineol, terpinen-4-ol, alpha-pinene and beta-myrcene using the Geller and Vogel conflict tests in ICR mice.	anticonflict effects in either test. Both borneol and camphene at 800 mg/kg produced significant anticonflict effects in the Geller, but not in the Vogel conflict test. Linalool, a major constituent of lavender oil, produced significant anticonflict effects at 600 and 400 mg/kg in the Geller and Vogel tests, respectively, findings that were similar to those of lavender oil. Thus, authors concluded that linalool is the major pharmacologically active constituent involved in the anti-anxiety effect of lavender oil (Umezu et al. 2006).
To establish a valid animal model of the effects of olfactory stimuli on anxiety, a series of experiments was conducted using rats in an open- field test.	Rats.	Throughout, effects of lavender oil were compared with the effects of chlordiazepoxide (CDP), as a reference anxiolytic with well-known effects on open-field behaviour. Rats were exposed to lavender oil (0.1-1.0 ml) for 30 min (Experiment 1) or 1 h (Experiment 2) prior to open-field test and in the open field or injected with CDP (10 mg/kg i.p.). In Experiments 3 and 4, various combinations of pre-exposure times and amounts of lavender oil were used.	CDP had predicted effects on behaviour, and the higher doses of lavender oil had some effects on behaviour similar to those of CDP. With sufficient exposure time and quantity of lavender the same effects were obtained as in Experiment 2. Experiment 4 demonstrated that these behavioural effects of lavender could be obtained following pre-exposure, even if no oil was present in the open-field test. In Experiments 2-4, lavender oil increased immobility. Together, these experiments suggest that lavender oil does have anxiolytic effects in the open field, but that a sedative effect can also occur at the highest doses (Shaw et al. 2007).

Anti-inflammatory and analgesic effects

Purpose	Species	Intervention	Outcome
To study local anti-inflammatory activity.	Mice and rats.	Ear swelling induced by the standard compound 48/80 (200 µg/ear intradermally). Pre-treatment with lavender oil (mice). Passive cutaneous anaphylaxis induced by anti-dinitrophenyl IgE (rats) and topical or intradermal lavender oil.	Swelling (ear - mice) was concentration-dependently inhibited by topical or intradermal pre-treatment with lavender oil at concentrations of 1:100, 1:10, 1:1 and undiluted ($p<0.05$). Cutaneous anaphylaxis was also concentration-dependently inhibited following application of lavender oil topically (1:100 non-significant; 1:10; 1:1 and undiluted, $p<0.05$) or intradermally (1:100,1:10 and 1:1 non-significant; undiluted, $p<0.05$) (Kim & Cho 1999).
To study local anti-inflammatory activity.	Mice	Linalool locally applied 30 minutes before the 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced mouse ear oedema test.	2 mg of linalool inhibited oedema by 30% ($p<0.01$) (Yasukawa et al. 1989).
To study systemic anti-inflammatory activity.	Male Wistar rats.	Linalool administered by gavage at 100 and 200 mg/kg three hours before injection of carrageenan (2.5 mg/kg body weight) in the carrageenan-induced paw-oedema test.	Oedema was inhibited by 23 and 24% respectively (Pulla Reddy & Lokesh, 1994).
To study systemic anti-inflammatory activity.	Rats.	The carrageenan-induced rat paw oedema test. Linalool and linalyl acetate perorally administered.	After 3 hours: • (-)-linalool at 25, 50 and 75 mg/kg body weight inhibited oedema by 28, 29 and 33% respectively ($p<0.0l$, $p<0.01$ and $p<0.005$); • (±)-linalool at 50 and 75 mg/kg (but not at 25 mg/kg) inhibited oedema by 51 and 38% ($p<0.05$ and $p<0.05$); • linalyl acetate at 64 and 96 mg/kg (but not at 32 mg/kg) inhibited oedema by 40 and 36% ($p<0.01$ and $p<0.05$). H-linalool is the naturally-

Purpose	Species	Intervention	Outcome
			occurring isomer, but the racemate (±)-linalool may be present in distilled or extracted essential oil (Peana et al. 2002).
To study the anti nociceptive effect.	Mice.	The acetic acid induced writhing test or the hot plate test. Linalool was subcutaneously injected.	In the writhing test, linalool inhibited the response dose-dependently by 38% at 25 mg/kg subcutaneously (p=0.03) and by 52% at 50 mg/kg (p=0.01) and 47% at 75 mg/kg (p=0.03). The effect of linalool at 50 mg/kg was completely reversed by IP-administered naloxone (5 mg/kg) or atropine (5 mg/kg). In the hot plate test, linalool at 100 mg/kg significantly increased reaction time, by 45% after 2 hours (p=0.004) and by 89% after 3 hours (p=0.0001), while lower doses had no effect (Peana et al. 2003).
To study the anti nociceptive effect.	Male Wistar rats.	In the paw withdrawal test, unilateral subplantar injection of carrageenan and L-glutamate induced a hyperalgesic effect (decrease of thermal threshold) on the injection side, while prostaglandin E, induced hyperalgesia on both the injection and the contralateral side. Linalool was administered by abdominal subcutaneous injection 30 minutes before intraplantar injection of the hyperalgesic substances.	In the first test, linalool (50, 100 or 150 mg/kg) significantly reduced withdrawal latencies induced by carrageenan (p<0.05 to p<0.001), with no effect on the contralateral paw. Linalool at the highest dose (200 mg/kg intraplantar) prevented the reduction in paw withdrawal latency induced by L-glutamate (p<0.0005), demonstrating anti hyperalgesic and anti nociceptive effects; an anti nociceptive effect was also apparent in the contralateral paw (p=0.02) compared to the untreated control. In the test with prostaglandin E, linalool at 200 mg/kg antagonized paw withdrawal latency on the side contralateral to the prostaglandin E2 injection (p=0.032), but inhibition of withdrawal latencies on the side

Purpose	Species	Intervention	Outcome
			of the injection were non-significant (Peana et al. 2004a).
To study the anti nociceptive effect.	Male mice and Wistar rats.	The hot plate test with linalool administered subcutaneously. The formalin test.	Linalool significantly increased reaction time in the hot plate test with mice (p=0.005 at 100 mg/kg and p=0.003 at 150 mg/kg). Linalool at 50 and 100 mg/kg s.c. caused a significant reduction in responses (- 42%, p =0.013 and -37%, p=0.04 respectively) in the early acute phase of the formalin test, but not in the late tonic phase (rats). The highest dose (150 mg/kg) caused a significant anti nociceptive effect in both phases (early phase: 35%, p=0.048; late phase: 32%, p=0.0038). The antinociceptive effects of linalool were reduced by pre-treatment with atropine, naloxone, sulpiride and glibenclamide, but not by pirenzepine or SCH-23390 (a dopamine D1 receptor antagonist) (Peana et al. 2004b).
To study local anaesthetic effects.	Male New Zealand rabbits.	The rabbit conjunctival reflex test with lavender oil, linalool and linalyl acetate applied to the conjunctival sac.	Local anaesthetic effects of lavender oil, linalool and linalyl acetate were demonstrated: 30-2500 µg/ml dose-dependently increased the number of stimuli necessary to provoke the reflex (p<0.01) (Ghelardini et al. 1999).

Enzyme-inducing effects

Purpose	Species	Intervention	Outcome
To study the influence on the enzyme content.	Male Wistar albino rats.	Enzyme activity after oral administration of linalool.	Linalool administered at 1.5 g/kg body weight for 5 days caused induction of peroxisomal bifunctional enzyme (2445 ng control protein/µg protein loaded vs. 1069 ng for controls;

Purpose	Species	Intervention	Outcome
			p<0.001) but not of cytochrome P450 IVA1 (1.76% of total P450 vs. 2.43% for controls; non-significant) (Roffey et al. 1990).
To study the influence on liver enzyme content.	Wistar rats (4 week old).	Linalool (500 mg/kg) as a solution in propylene glycol was administered by gavage for 64 days.	Liver weight and relative liver weight were unaffected by linalool (500 mg/kg) up to day 30, but by day 64 there were slight but significant increases in these parameters compared to controls (p<0.05). Microsomal protein concentration was unaffected up to day 14, but had increased by 20%, by day 30 (p<0.02) and remained elevated up to day 64. Cytochrome P450 and cytochrome b concentrations showed a biphasic response, both being depressed on day 7 (p<0.022 in each case) but subsequently increased by 50% on day 30 (p<0.01). Cytochrome P450 remained at this level, whereas cytochrome b, increased further to 70% on day 64 (p<0.002) (Parke et al. 1974).

Other effects

Purpose	Species	Intervention	Outcome
To study the diuretic effect of lavender flower.	Female Wistar rats.	An infusion of lavender flower (40 g/litre) was intragastrically administered.	The infusion exerted significant diuretic effects (p<0.01) in rats 70 and 99 minutes after intragastric administration of 0.03 g/kg body weight. At maximum diuretic response, urinary osmolarity (111 mosmol/kg) was significantly less (p<0.01) than that of the untreated control (195 mosmol/kg) and of the positive control, diosmin (162 mosmol/kg). Sodium excretion was moderate (Elhajili et al.

Purpose	Species	Intervention	Outcome
			2001).

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Species	Intervention	Outcome
Mice.	Exposure of mice to a lavender oil atmosphere.	A time-dependent increase in linalool plasma levels (approximately 0.9 ng/ml after 30 minutes, 2.7 ng/ml after 60 minutes and 2.9 ng/ml after 90 minutes) (Buchbauer et al. 1993).
Mice.	A 1 hour exposure to a medium containing the vapour of lavender oil (37.3% linalool and 41.6% linalyl acetate), linalool or linalyl acetate at 5 mg/liter.	Serum levels were 3 ng/ml for linalool and 11 ng/ml for linalyl acetate. After 1 hour of exposure to linalool, the serum level was 8 g/ml, and after 1 hour of exposure to linalyl acetate the level was 1 ng/ml and the serum linalool level 4 ng/ml (Buchbauer et al. 1993; Jirovetz et al. 1990; Bickers et al. 2003).
Rats.	Oral administration of labelled linalool to rats at 500 mg/kg body weight.	After oral administration of labelled linalool 55% was excreted in the urine as the glucuronic acid conjugate, while 23% was excreted in expired air and 15% in the faeces within 72 hours; only 3% was detected in the tissues (Bickers et al. 2003).

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

Acute toxicity

The acute oral LD_{50} of lavender oil in rats was found to be > 5 g/kg body weight.
Other authors reported the oral LD_{50} in male rats as 6.2 ml/kg and in female rats as 5.0 ml/kg; the oral LD_{50} in male rats as 5 ml/kg and in female rats as 3 ml/kg.
Furthermore an oral LD_{100} in male rats as > 7 ml/kg and in female rats as > 6 ml/kg was reported. In an earlier study the acute oral LD_{50} of lavender oil was determined as 9 g/kg (Buchbauer et al. 1991; Delaveau et al. 1989; von Skramlik 1959).

Acute oral LD_{50} values in rodents have been reported as 2.2-3.9 g/kg body weight for linalool and 5.0-48.8 g/kg for linalyl esters. The dermal LD_{50} of linalool in rabbits exceeded 5 g/kg. No adverse effects were reported from administration of linalool to female mice via a stomach tube at 94, 188 or 375 mg/kg/day for 5 days (Bickers et al. 2003).

Subacute toxicity

In a 90-day chronic dermal toxicity study in rats (20 per group), linalool was applied daily at 250, 1000 and 4000 mg/kg body weight. At 250 mg/kg no changes were observed except decreased activity and transient erythema; at 1000 mg/kg weight gain and activity were reduced; at the highest dose level, 11 animals died (Bickers et al. 2003).

In a 90-day study, a 1:1 mixture of linalool and citronellol was added to the diet of rats to provide an intake of about 50 mg/kg/day of each substance. A slight retardation of body weight gain was observed in the males, but no effects were evident from histopathology, haematology, clinical chemistry or urine analysis at weeks 6 and 12 (Bickers et al. 2003).

Investigations on rats showed that the acute toxicity of essential oil of lavender (OL), given p.o. in olive oil, was relatively low, while when given to mice pharmacological tests demonstrated that it had anxiolytic effects and prolonged sleep induced by i.p. pentobarbital Na (PB, Sanofi), though the latter effect was reduced after repeated p.o. administration. Impaired balance, piloerection and hypersalivation sometimes occurred. The authors concluded that, if its chronic toxicity is also low, OL might be used instead of more active anxiolytics or tranquilizers for minor conditions (Delaveau et al. 1989).

Undiluted lavender oil was not irritant when applied to the backs of hairless mice or pigs, but was slightly irritant on intact or abraded rabbit skin under occlusion for 24 hours (Opdyke 1976).

Undiluted linalool caused slight to severe irritation to guinea pigs and rabbits when applied to open or occluded skin; no irritation was observed at 10% dilution. Undiluted linalyl acetate caused slight to severe irritation in guinea pigs and rabbits; at 5% dilution it was slightly irritating to rabbits (Bickers 2003).

Mutagenicity

Linalool and linalyl acetate showed no mutagenic potential in the Ames mutagenicity test, with or without metabolic activation (Eder et al. 1980; Eder et al. 1982a; Eder et al. 1982b; Ishidate et al. 1984).

In the mouse lymphoma assay, no effects were seen with linalool in the absence of metabolic activation at concentrations up to 300 µg/ml; weak positive effects were observed in the presence of metabolic activation at doses of 200 µg/ml and above (Bickers et al. 2003).

Linalool did not induce chromosomal aberrations when incubated with Chinese hamster fibroblast cells at concentrations up to 0.25 mg/ml (Ishidate et al. 1984) nor with Chinese hamster ovary cells at concentrations up to approximately 300 µg/ml (Bickers et al. 2003).

No induction of unscheduled DNA synthesis in rat hepatocytes was evident at concentrations of linalool up to 50 µg/ml or linalyl acetate up to 300 µg/ml (Bickers et al. 2003).

3.4. Overall conclusions on non-clinical data

Most of the experiments were done with Lavandulae aetheroleum, the herbal preparation that is used in clinical conditions. Lavender flowers were used for investigating a diuretic action.
Experimental pharmacological data point to an activity in the central nervous system: anticonvulsive effects, sleep prolongation, locomotor activity, explorative or anticonflict behaviour and anxiety. Well known inflammatory and nociceptive experimental models were used.
As far as these interventions are concerned, high doses of lavender oil were used to obtain

pharmacological effects. These doses mostly cannot be extrapolated to human conditions. On the other hand, dose-response relationship could be demonstrated in some investigations.
The outcomes are mostly positive. This may be due to a publication bias. The effect on enzyme induction by linalool is difficult to translate to metabolic consequences.

The experimental pharmacokinetic data are limited. Most probably, oil constituents are excreted by the urine as glucuronic conjugates.

Toxicity of lavender oil is not a major concern. Some components like linalool and linalyl acetate are not mutagenic. As the preparations as such have not been tested up to now for genotoxicity, a Community list entry cannot be established for *Lavandula*.

4. Clinical Data

4.1. Clinical Pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Effects on the central nervous system and neuronal activity

Clinical question	Patients	Intervention	Outcome
To what extent can lavender oil influence indicators for mood status?	Healthy adults (n=20).	Subjects were exposed to lavender oil (10% in grape seed oil, 3 drops on a cotton swab held 8 cm from the participant's nose for 3 minutes).	As compared to baseline, beta power in the EEG increased, suggesting increased drowsiness. Significantly lower scores were obtained for depressed mood (assessed by the Profile of Mood States: -56% p<0.01) and anxiety (assessed bv the State Trait Anxiety Inventorv: -9%, p<0.05). The volunteers reported feeling more relaxed (tense/relaxed and drowsy/alert visual analogue mood scales: + 25.9%, p<0.001) and performed mathematical computations faster and more accurately (von Skramlik 1959). Further data analysis revealed significant EEG shift (p<0.05) with greater left frontal EEG activation (associated with extrovert behaviour and less depressed mood) (Sanders et al. 2002).
What is the	24 healthy	The acute sedative effects of p.o.	Diazepam, Valerian and

Clinical question	Patients	Intervention	Outcome
possible influence of a.o. lavender oil on the EEG-pattern?	females.	extracts of *Valeriana officinalis*, *Lavandula angustifolia*, *Passiflora incarnata*, *Kava-kava*, *Melissa officinalis*, *Eschscholzia californica*, *Hypericum perforatum* and *Ginkgo biloba* (all Lichtwer) were compared to those of diazepam using quantitative EEG recordings. Studies followed a double-blind, randomized, crossover design.	*Lavandula* were sedative on a self-rating of tiredness. Diazepam increased power in the beta frequency band of the EEG and decreased power in the alpha and sub-alpha bands. Valerian increased power in the delta, theta and alpha1 bands. *Lavandula* had a minimal effect on power. Quantitative EEGs are a sensitive means of describing drug-induced CNS activity changes, but do not constitute a good screening method for potential sedatives (Schulz et al. 1998).
How does lavender oil influence EEG-patterns?	Healthy female volunteers (n=13).	EEG recordings made during and after inhalation of lavender oil for 90 seconds (diffuser fixed on the chest; no details on concentration given).	Alpha I frequencies (8-10 Hz) in parietal and posterior temporal regions significantly decreased soon after the onset of inhalation ($p<0.01$). This was associated with a comfortable feeling in the subjects (Masago et al. 2000).
How does lavender oil influence EEG and behaviour of newborn babies?	Newborn babies (n=20).	The effects were evaluated of inhalation of lavender oil (10% V/V in grape seed oil, 3 drops on a cotton swab held 15 cm from the nose for 2 minutes) on the behaviour of 20 newborn babies.	Infants of depressed mothers showed increased relative left frontal EEG asymmetry from baseline during the odour exposure phase ($p<0.01$). In contrast, infants of non-depressed mothers showed no change in frontal EEG-asymmetry from baseline during the odour exposure phase. Among the behaviours recorded (negative affect, head turns, lip licking, and nose wrinkling), the only differences were that infants of depressed mothers showed increased head turning during exposure to the odour ($p<0.05$) (Fernandez et al. 2004).
To what extent does	Healthy women	In a randomized single-blind study, the effect of a lavender oil	"Positive" effects of bathing - irrespective of whether or not

Clinical question	Patients	Intervention	Outcome
lavender oil influence mood and positive behaviour towards future events?	(n=40).	bath (3 ml/bath) on psychological well-being was evaluated. The participants, randomly assigned to use either grape seed oil or 20% lavender oil in grape seed oil in their bath for 14 days, assessed their well-being with the Mood Adjective Checklist of the University of Wales Institute of Science and Technology. In a further study a similar design and assessment by the Macleod and Byrne Future Events procedure was done.	lavender oil was added to the bath - were evident with respect to energetic arousal, tense arousal and hedonic tone, while anger-frustration was selectively reduced by lavender oil. In the further study using the Macleod and Byrne Future Events procedure, no effect was observed on the rate of positive responses to possible future events but negative responses were reduced after lavender oil baths (Morris 2002).
To what extent does lavender oil influence cognitive functions?	Healthy volunteers (n=144).	Participants were assigned to one of three independent groups and subsequently performed the Cognitive Drug Research computerized cognitive assessment battery in a cubicle containing the odour of lavender oil or rosemary oil (from 4 drops on a diffuser pad, placed under a bench in the testing cubicles) or no odour (as a control). Visual analogue mood questionnaires were completed prior to exposure to the odour and after completion of the test battery.	Compared to controls, lavender odour caused significant impairment in performance of working memory ($p<0.05$) and impaired reaction times for both memory and attention based tasks (working memory subfactor, speed of memory factor, speed of attention factor, alertness and contentedness) (Moss et al. 2003).
What influence has lavender oil on arousal and mental stress?	Healthy volunteers (n=42).	The effect of lavender oil (from a diffuser on the floor of the experimental room for 20 minutes) was assessed by a Japanese version of Cox and Mackay's stress/arousal adjective checklist in three groups of healthy volunteers. Stress was induced by waiting in a soundproofed small room for 20 minutes. One group of 14 was placed in the room without exposure to the oil, a group of 15 was exposed to lavender oil, and a group of 13 did not have to wait	Analysis suggested that lavender odour was associated with reduced mental stress and increased arousal rate ($p<0.01$) (Motomura et al. 2001).

Clinical question	Patients	Intervention	Outcome
		in the soundproofed room.	
To what extent does lavender oil influence pain sensation?	Healthy volunteers (13 men and 13 women).	The effects of inhalation of lavender oil (5 drops on cotton gauze placed 30 cm below the nose for 10 minutes), rosemary oil or water (as a control) on sensory and affective responses to experimentally-induced pain were studied in 13 men and 13 women in a randomized cross-over design. Pre- and post-treatment scores were documented for quantitative sensory ratings of contact heat pain (thermode placed on the forearm), pressure pain (pressure algometer applied to the trapezius and masseter) and ischaemic pain (submaximal effort tourniquet procedure: elevating the arm above heart level for 30 seconds, occlusion of circulation with a standard blood pressure cuff, hand-grip exercises with lowered arm). Subjective ratings of treatment-related changes in pain intensity and pain unpleasantness were obtained for each condition using a visual analogue scale.	Quantitative pain sensitivity ratings were unchanged in both groups. Retrospectively, however, subjective ratings of both perceived pain intensity and perceived pain unpleasantness were significantly less after treatment with lavender ($p<0.01$) (Gedney et al. 2004).
What is the influence of lavender on sustained attention?	Healthy volunteers (n=7; aged 20-24 years).	Exposure to volatile oil vapours, an odour delivery system passed air at a standard rate through sample bottles and presented, in randomized order, dispersions of lavender oil (0.29 mg per liter of air), eucalyptus oil (4.8 mg per liter of air) and a no-odour control to a point exactly 10 cm below the nose.	During 30-minute vigilance tasks, involving selection responses in relation to numbers changing every second on a computer screen, the gradual increase in reaction time was found to be significantly lower with lavender oil odour than with the control ($p<0.001$). The results suggested that the odour of lavender oil helped to maintain sustained attention during the long-term task (Shimizu et al. 2008).
What is the	Healthy	Aromatherapy given to subjects	• The State Anxiety scores

Clinical question	Patients	Intervention	Outcome
influence of lavender on EEG activity, alertness and mood?	volunteers (n=40; mean age 31y).	seated in a special massage chair. Lavender or rosemary oil (3 drops) diluted with a 10% concentration in grape seed oil were placed on a dental swab and presented in a 100 ml plastic vial which the subjects held about 3 inches from their nose for a period of 3 minutes.	decreased in both groups ($p<0.05$); • Only the lavender group had a significantly better mood on the POMS (= Profile Of Mood States) ($p< 0.01$); • Both groups felt more relaxed ($p< 0.001$); • The accuracy scores improved significantly ($p< 0.05$). • Frontal alpha power increased after lavender, suggesting increased drowsiness (Diego et al. 1998).
What is the influence of lavender oil on neuropsychic activity?	Healthy medical students (n=48; 22-23 y), subdivided in groups of 16 subjects, receiving lavender, rose or geranium oil.	Inhalation of lavender oil (50 ml of a 1% solution nebulized in a room of 176 m^3). Assessment of neuropsychic activity by the Pauli-test (assessing concentration, working efficiency, reaction and attention).	The lavender oil stimulated neuropsychic activity, but results are difficult to interpret by differentiation of parameters (Tašev T et al. 1969).
To what extent does lavender oil influence reaction time?	Healthy volunteers (n=10).	Computer-based reaction-time tests (parts of the Munich Attention Test) were performed while inhaling air or lavender oil vapour in 6 daily sessions.	Increases in reaction time were observed on days 4 and 6 when the subjects performed the tests while inhaling lavender oil vapour (Buchbauer et al. 1993b).

Cardiovascular system

Clinical question	Patients	Intervention	Outcome
It was examined whether the power spectral analysis of heart rate variability	Healthy young women (n=10; 23+/-3 years)	Continuous electrocardiographic (ECG) monitoring before and after (10, 20, 30 minutes) a stimulus with lavender oil. Lavender oil was topically administered by a commercially available plaster for aroma therapy ('Lavender girl',	Increases in the parasympathetic tone were observed after the lavender oil seen as increases in the HF component and decreases in the LF/HF. Additional measurement with positron emission

Clinical question	Patients	Intervention	Outcome
(HRV) could detect changes in autonomic tone following a treatment with Lavandula essential oil.		Teikoku Pharmaceuticals, Tokyo, Japan). No information was given on the dose. HRV was expressed by three indices: low (0.04-0.15 Hz) and high (0.15-0.40 Hz) frequency components (nLF and nHF respectively) as well as LF/HF ratio.	tomography (PET) demonstrated the regional metabolic activation in the orbitofrontal, posterior cingulate gyrus, brainstem, thalamus and cerebellum, as well as the reductions in the pre/post-central gyrus and frontal eye field. These results suggested that lavender aromatic treatment induced not only relaxation but also increased arousal level in these subjects (Duan et al. 2007).
To what extent does lavender oil influence blood flow and nerve activity when taken as a footbath?	Healthy young women (n=10; 19-21y).	In a randomized cross-over study subjects took a hot footbath for 10 minutes with and without lavender oil (2 ml to 4 liters of water; 0.05%). Effects on the autonomic nervous system were recorded on an electrocardiogram and by finger tip blood flow and respiratory rate. Autonomic function was evaluated using spectral analysis of heart rate variability.	A significant increase in finger tip blood flow (34.8 to 40.1 ml/min/100g; no change without lavender oil) was recorded. Parasympathetic nerve activity increased significantly ($p<0.05$) during both types of footbath. With lavender oil, delayed changes in the balance of autonomic activity were observed, suggesting relaxation. No changes were observed in heart or respiratory rates (Saeki 2000).
To what extent does lavender oil influence cardiovascular parameters after exercise?	Healthy volunteers (n=20).	After performing moderate physical exercise for 2 minutes, subjects rested for 10 minutes. During this time they were randomly exposed to an atmosphere with or without lavender oil (10 drops in water, nebulized).	Compared to the controls, the volunteers exposed to lavender oil had lower diastolic (- 6.1 mmHg) and systolic blood pressure (- 15.1 mmHg), and lower arterial pressure (- 8.5 mmHg) and heart rate (- 15 beats/minute), although the differences were not statistically significant (Romine et al. 1999).

Antioxidative activity

Clinical question	Patients	Intervention	Outcome
How does the smelling of lavender and	22 healthy volunteers.	They sniffed aroma for 5 min, and each subject's saliva was collected immediately. FRSA was	Various physiologically active substances in saliva such as cortisol, secretory IgA, and

Clinical question	Patients	Intervention	Outcome
rosemary essential oil influence the total salivary FRSA (Free Radical Scavenging Activity)?		measured using 1.1- diphenyl-2-picrylhydrazyl.	alpha-amylase activity were found to be correlated with aroma-induced FRSA. The FRSA values were increased by stimulation with low concentrations (1000 times dilution) of lavender or by high-concentrations (10 times dilution) of rosemary. In contrast, both lavender and rosemary stimulations decreased cortisol levels. A significant inverse correlation was observed between the FRSA values and the cortisol levels with each concentration of rosemary stimulation. No significant changes were noted in sIgA or alpha-amylase. These findings clarify that lavender and rosemary enhance FRSA and decrease the stress hormone, cortisol, which protects the body from oxidative stress. The body possesses various antioxidative systems (FRSA) for preventing oxidative stress, and saliva contains such activity (Atsumi & Tonosaki 2007).

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Patient	Intervention	Outcome
Male volunteer.	A massage oil containing 2% of lavender oil (approximately 25% linalool and 30% linalyl acetate) was gently massaged on to the abdomen for 10 minutes.	Trace amounts of both linalool and linalyl acetate were detected in the blood within 5 minutes of finishing the massage, and peak plasma concentrations of 121 ng/ml for linalool and 100 ng/ml for linalyl acetate were reached after 19 minutes. Most of the linalool and linalyl acetate disappeared from the blood within 90 minutes, both having a biological half-life of approximately 14 minutes (Jäger et al. 1992).

4.2. Clinical Efficacy

4.2.1. Dose response studies

Not applicable.

4.2.2. Clinical studies (case studies and clinical trials)

Anxiety

Purpose	Patients	Intervention	Outcome
To evaluate possible anxiolytic effects of lavender oil.	Healthy volunteers (n=97; 57 females, 39 males; aged between 18 and 74 years). Participants refrained from alcohol, tea and coffee 24 hours prior to the study.	Orally administered lavender capsules (placebo, 100, 200 µl) were tested in a randomised between-subjects double-blind study. Film clips were used to elicit anxiety. Measures included anxiety, State Trait Anxiety Inventory (STAI), mood, positive and negative affect scale (PANAS), heart rate (HR), galvanic skin response (GSR), and heart rate variation (HRV). Following baseline measurements, capsules were administered. Participants viewed a neutral film clip, then an anxiety-provoking and light-hearted recovery film clip.	For the 200 µl lavender dose during the neutral film clip there was a trend towards reduced state anxiety, GSR and HR and increased HRV. In the anxiety-eliciting film, lavender was mildly beneficial in females but only on HRV measures. In males sympathetic arousal increased during the anxiety film (GSR). HRV significantly increased at 200 µl during all three film clips in females, suggesting decreased anxiety. These findings suggest that lavender has anxiolytic effects in humans under conditions of low anxiety, but these effects may not extend to conditions of high anxiety (Bradley et al. 2009).
To investigate the effect of lavender oil in general anxiety disorder (GAD).	Patients (n=77; 18 to 65 years) with primary diagnosis of GAD according to the DSM-IV criteria and outpatient treatment by a general practitioner were selected. In order to be eligible for study inclusion, all	A double-blind, randomized, double dummy, controlled clinical study was performed to evaluate the efficacy of silexan (80 mg lavender oil), a new oral lavender oil capsule preparation, versus a benzodiazepine. In this study, the efficacy of a 6-week intake of silexan compared to lorazepam (0.5 mg) was investigated in adults with GAD. The primary target variable was the change in the Hamilton Anxiety Rating Scale (HAM-A-total score) as an objective measurement of the severity of anxiety between baseline and week 6.	The results suggest that silexan effectively ameliorates generalized anxiety comparable to a common benzodiazepine (lorazepam). The mean of the HAM-A-total score (primary parameter) decreased clearly and to a similar extent in both groups (by 11.3 $\pm$ 6.7 points (45%) in the silexan group and by 11.6 $\pm$ 6.6 points (46%) in the lorazepam group, from 25 $\pm$ 4 points at baseline in both groups). During the active treatment period, the two HAM-A subscores "somatic anxiety" (HAM-A subscore I) and "psychic anxiety" (HAM-A subscore II)

Purpose	Patients	Intervention	Outcome
	patients were required to have a Hamilton Anxiety (HAM-A) total score of ≥ 18 and item 1 'anxious mood' ≥ 2 and item 2 'tension' ≥ 2. Before being included, patients underwent a one-week screening phase to ensure wash-out of any other drugs. Patients with a decrease of 25% or more of the HAM-A total score during this phase were to be excluded.		also decreased clearly and to a similar extent in both groups. The changes in other subscores measured during the study, such as the SAS (Self-rating Anxiety Scale), PSWQ-PW (Penn State Worry Questionnaire), SF 36 Health survey Questionnaire and Clinical Global Impressions of severity of disorder (CGI item 1, CGI item 2, CGI item 3), and the results of the sleep diary demonstrated comparable positive effects of the two compounds. The results demonstrate that silexan is as effective as lorazepam in adults with GAD. The safety of silexan was also demonstrated. Since lavender oil showed no sedative effects in the study and has no potential for drug abuse, silexan appears to be an effective and well tolerated alternative to benzodiazepines for amelioration of generalised anxiety, according to the authors (Woelk and Schläfke 2010).
To review the effect of lavender scent on anticipatory anxiety in dental consultations.	Dental patients in ambulatory practice (n=340).	In a cluster randomized-controlled trial, patients' anxiety was assessed while waiting for a scheduled dental appointment, either under the odour of lavender or with no odour. Current anxiety, assessed by the brief State Trait Anxiety Indicator (STAI-6), and generalized dental anxiety, assessed by the Modified Dental Anxiety Scale (MDAS) were examined.	Analyses of variance (anovas) showed that although both groups showed similar, moderate levels of generalized dental anxiety (MDAS $F=2.17$, $p>0.05$) the lavender group reported significantly lower current anxiety (STAI: $F=74.69$, $p<0.001$) than the control group. Although anxiety about future dental visits seems to be unaffected, lavender scent reduces state anxiety in dental patients (Kritsidima et al. 2010)
To investigate the effects of	Korean elderly women	A quasi-experimental, control group, pretest-posttest design	The intervention produced significant differences in the

Purpose	Patients	Intervention	Outcome
aromatherapy massage on the anxiety and self-esteem.	(n=36)	was used: 16 patients in the experimental group and 20 in the control group. Aromatherapy massage using lavender, chamomile, rosemary and lemon was given to the experimental group only. Each massage session lasted 20 min, and was performed 3 times per week for two 3-week periods with an intervening 1-week break.	anxiety and self-esteem and no significant differences in blood pressure or pulse rate between the two groups. These results suggest that aromatherapy massage exerts positive effects on anxiety and self-esteem. More objective, clinical measures should be applied in a future study with a randomized placebo-controlled design (Rho et al. 2006).
The purpose of this study was to evaluate the use of aromatherapy to reduce anxiety prior to a scheduled colonoscopy or esophago gastroduode noscopy.	A controlled, prospective study was done on a convenience sample of 118 patients (mean age 52y, range 24-57y, 50% male). There was no difference between the experimental and control group in enjoyment of scent (p=0.94).	The state component of the State Trait anxiety Inventory (STAI) was used to evaluate patients' anxiety levels pre- and post-aromatherapy. The control group was given inert oil (placebo) for inhalation, and the experimental group was given lavender oil for inhalation.	The STAI state anxiety raw score revealed that patients were at the 99th (women) and 96th (men) percentiles for anxiety. The intervention group and the control group had similar levels of state anxiety prior to the beginning of the study (p=0.64). There was no difference in state anxiety levels between pre-and post-placebo inhalation in the control group (p=0.63). There was no statistical difference in state anxiety levels between pre- and post-lavender inhalation in the experimental group (p=0.47). Although this study did not show aromatherapy to be effective based on statistical analysis, patients did generally report the lavender scent to be pleasant. Lavender is an inexpensive and popular technique for relaxation that can be offered to patients as an opportunity to promote preprocedural stress reduction in a hospital setting (Muzzarelli et al. 2006).

Depression

Clinical question	Patients	Intervention	Outcome

Clinical question	Patients	Intervention	Outcome
To what extent does a lavender flower tincture influence the status of depressed patients as compared to imipramine?	Patients who met the DSM criteria for major depression (based on the structured clinical interview for DSM IV) and had a baseline score of at least 18 on the Hamilton Rating Scale for Depression (HAM-D) (n=45).	Patients were assigned to the following daily oral treatments for 4 weeks: • Group A: lavender flower tincture (60 drops/day) + a placebo tablet; • Group B: an imipramine tablet (100 mg/day) + placebo drops; • Group C: lavender flower tincture (60 drops/day) + 1 imipramine tablet (100 mg/day).	Highly significant improvements in HAM-D scores ($p<0.0001$) were observed in groups A (approximately 19 to 12) and B (approximately 19 to 9), although lavender tincture at this dosage was less effective than imipramine ($p=0.0001$). In group C the combination of lavender tincture and imipramine was more effective than imipramine alone (approximately 19 to 5 versus 19 to 9; $p<0.0001$) (Akhondzadeh et al. 2003).

Analgesia

Purpose	Patients	Intervention	Outcome
To investigate the analgesic efficacy of postoperative lavender oil aromatherapy	Patients undergoing breast biopsy surgery (n=50).	25 patients received supplemental oxygen through a face mask with two drops of 2% lavender oil postoperatively. The remainder of the patients received supplemental oxygen through a face mask with no lavender oil. Outcome variables included pain scores (a numeric rating scale from 0 to 10) at 5, 30, and 60 minutes postoperatively, narcotic requirements in the postanesthesia care unit (PACU), patient satisfaction with pain control, as well as time to discharge from the PACU.	There were no significant differences in narcotic requirements and recovery room discharge times between the two groups. Postoperative lavender oil aromatherapy did not significantly affect pain scores. However, patients in the lavender group reported a higher satisfaction rate with pain control than patients in the control group ($p=0.0001$) (Kim et al. 2006).
To assess the efficacy of acupressure using lavender oil.	Adults (32 patients enrolled of which 28 completed the	An add-on treatment for pain relief and enhancing physical functional activities. Experimental study design: the Telehealth clinic and the community centre, Hong	A panel 8 experts in the musculoskeletal field verified the content validity of the outcome measures (inter-raters reliability=0.98). The baseline

Purpose	Patients	Intervention	Outcome
	study; mean age 51.2y ± 7.6) with sub-acute non-specific neck pain.	Kong. A course of 8-session manual acupressure with lavender oil over a 3 week period. Changes from baseline to the end of treatment were assessed on neck pain intensity (by Visual Analogue Scale (VAS)); stiffness level; stress level; neck lateral flexion, forward flexion and extension in cm, and interference with daily activities.	VAS score of neck pain intensity (primary outcome) for the intervention and control groups were 5.12 and 4.91 out of 10, respectively (p=0.72). One month after the end of treatment, compared to the control group, the manual acupressure group had 23% reduced pain intensity (p=0.02), 23% reduced neck stiffness (p=0.001), 39% reduced stress level (p=0.0001), improved neck flexion (p=0.02), neck lateral flexion (p=0.02), and neck extension (p=0.01). However, improvements in functional disability level were found in both the manual acupressure group (p=0.001) and control group (p=0.02). Our results show that eight sessions of acupressure with aromatic lavender oil were an effective method for short-term neck pain relief (Yip & Tse 2006).

Clinical question	Patients	Intervention	Outcome
To what extent does lavender oil improve low back pain?	Adult patients with sub-acute or chronic non-specific low back pain (number that completed the study: intervention group=27; control group=24).	In a randomized controlled study, the effect on pain relief and enhancement of physical functional activities of acupoint stimulation with electrodes combined with acupressure using lavender oil (in addition to conventional treatment) was assessed. Over a 3-week period the patients had 8 sessions of relaxation acupoint stimulation, each of 35-40 minutes, followed by acupressure massage with 3% lavender oil in grape seed oil using light to medium finger pressure on 8 fixed acupoints for 2 minutes each. Patients in the	Baseline VAS scores for the intervention and control groups were 6.38 and 5.70 respectively (p=0.24). One week after the end of treatment the intervention group reported 39% greater reduction in pain intensity than the control group (p=0.0001) and had improved walking time (p=0.05) and greater lateral spine flexibility (p=0.01) (Yip & Tse 2004).

Clinical question	Patients	Intervention	Outcome
		control group received conventional treatment only. Outcome measures were changes in pain intensity scores (10 cm VAS) and duration from baseline to end of treatment, lateral fingertip-to-ground distance, walking time (to cover 15 meter) and interference with daily activities.	
To what extent can lavender oil alleviate postoperative pain?	Morbidly obese patients who had undergone surgery for laparoscopic adjustable gastric banding (n=54).	In a randomized, placebo controlled study patients were treated, upon arrival at the post-anaesthesia care unit, by application of either lavender oil or non-scented baby oil to the oxygen face mask. The two groups were comparable with regard to patient characteristics, intra-operative drug use and surgical time. Postoperative pain was treated with morphine and the level of pain was assessed at 5, 30 and 60 minutes from numerical rating scores (0-1 0).	Patients in the lavender group required significantly less morphine postoperatively than those in the placebo group: 2.38 mg vs 4.26 mg (p=0.04). Furthermore, significantly more patients in the placebo group (22/27, 82%) than in the lavender group (12/26, 46%) required analgesics for postoperative pain (p=0.007) (Kim et al. 2007).
To what extent does lavender oil influence pain perception?	Patients with vascular wounds requiring frequent painful dressing changes (n=8).	In a pilot, the effects were assessed of diffusion of 15-20 drops of lavender oil by means of an aroma stream diffuser during the dressing change (in addition to conventional analgesics). Pain perception was assessed by two measures from the McGill Pain Questionnaire, the Visual Analogue Scale (VAS) and the Present Pain Inventory; a Sleep Questionnaire and the Spielberger State Trait Anxiety Inventory were also used. During five dressing changes the patients received, in random order, two odor therapies (lavender or lemon), music therapy of two types, or no treatment.	Lavender oil diffusion did not reduce pain intensity during dressing changes, but at post-dressing change assessments of lavender therapy a significant reduction in pain intensity was evident from VAS scores (p<0.05) (Kane et al. 2004).

Sleeping disorders

Purpose	Patients	Intervention	Outcome
To test the hypotheses that Essential Oil of Lavender has a sedative effect and that the resultant sleep promotes therapeutic activity.	Acutely ill elderly people and long-term patients.	A pilot study was arranged, followed by a more detailed trial with long-term patients.	The results show a positive trend towards improvement with lavender (Hudson 1996).
To study the hypnotic effects of lavender oil.	12 mid-life women with sleep disturbances (56y range 50-59y): mean sleep time 6.5 hours.	A cross-over placebo-controlled study. Patients received a dose of 0.86 g (3 drops) lavender oil, jasmine oil or base oil (placebo) on their pillow on 3 separate occasions (for 2 nights in a balanced, placebo-controlled cross-over design).	*Lavandula angustifolia* oil was mild hypnotic and jasmine oil a stimulant. In contrast to jasmine oil, lavender oil significantly increased actual sleep time by a mean of 69 minutes ($p<0.05$). Perceived changes in self-rated sedation and residual side-effects did not reveal any significant subjective impairment. In comparison to jasmine oil, ease of getting to sleep and quality of sleep was positively improved with the lavender oil. Mean trends indicated that in comparison to jasmine, awakening was also positively improved with lavender oil, whilst jasmine decreased sleep in contrast to the placebo. Lavender oil may be of value as a mild hypnotic whilst jasmine, having an opposite effect, may be helpful in counteracting daytime sleepiness (Austin & Alford 1997).
To explore the effects of the lavender fragrance on sleep and depression in	42 women college students who complained of insomnia.	Patients were studied during a four-week protocol (control treatment week, 60% lavender fragrance treatment week, washout week, 100% lavender fragrance treatment week). All	Among sleep variables, length of time taken to fall asleep, severity of insomnia, and self satisfaction with sleep were improved for the 60% ($p<0.001$, $p<0.001$, $p<0.001$) and 100%

Purpose	Patients	Intervention	Outcome
women college students.		subjects were in the department of nursing in a college and the study was a single blind repeated measurements experiment. For the duration of the study, weekly evaluations of sleep, patterns of sleep disturbance, severity of insomnia scale, self satisfaction with sleep, and severity of depression were performed.	($p<0.001$, $p<0.001$, $p<0.001$) week while the severity of depression was improved only for the 100% ($p=0.002$) week. According to the study results, it can be concluded that the lavender fragrance had a beneficial effect on insomnia and depression in women college students. Repeated studies are needed to confirm effective proportions of lavender oil and carrier oil for insomnia and depression (Lee & Lee 2006).

Malignant diseases

Clinical question	Patients	Intervention	Outcome
To what extent lavender oil could be useful as an adjuvant in cancer therapy?	The study population consisted of 17 still conscious and oriented in-home hospice patients. The abstract of the article categorizes them as 'cancer' patients without further specification. There are also no details given about age and gender.	Patients were evaluated for the effects of exposure to a lavender oil atmosphere on levels of pain, anxiety, depression and perceived sense of well-being. On three different days, prior to and after a 60-minute session involving no intervention (as a control), exposure to an atmosphere humidified with water (as a control) or to an atmosphere humidified with 3% lavender oil vapour, each patient was evaluated using 11-point verbal analogue scales and vital signs were also measured.	Compared to the no-intervention control small non significant decreases in blood pressure and heart rate, and decreases in pain and anxiety, as well as an improvement in sense of well-being, were observed after both water humidification and lavender oil treatment (Louis & Kowalski 2002).

Cardiovascular effects

Clinical question	Patients	Intervention	Outcome

Clinical question	Patients	Intervention	Outcome
To identify the effects of aromatherapy on blood pressure and stress responses of clients with essential hypertension.	Patients (n=52) with essential hypertension at random assigned to an essential oil group, a placebo group and a control group.	The application of aromatherapy was the inhalation method of blending oils with lavender, ylang-ylang, and bergamot once daily for 4 weeks. To evaluate the effects of aromatherapy, blood pressure and pulse were measured two times a week and serum cortisol levels, catecholamine levels, subjective stress and state anxiety were measured before and after treatment in the three groups.	The blood pressure, pulse, subjective stress state anxiety and serum cortisol levels among the three groups were significantly statistically different. The differences of catecholamine among the three groups were not significant statistically. The results suggest that the inhalation method using essential oils can be considered an effective nursing intervention that reduces psychological stress responses and serum cortisol levels, as well as the blood pressure of clients with essential hypertension (Hwang 2006).

4.2.3. Clinical studies in special populations (e.g. elderly and children)

Purpose	Patients	Intervention	Outcome
To study the influence of lavender oil on stress in newborns.	Five-day-old human infants' responses to heelstick stress (n=83).	Infants were assessed with behavioural and physiological indices. The subjects were divided randomly into three groups: the LAV group, who were presented with artificial odour of lavender during the heelstick; the MILK group, who were presented with artificial odour of milk during the heelstick; and the CONT group, who were presented with no special odours.	The CONT group showed more adrenocortisol release in saliva than the other groups ($p<0.05$), but there were no differences between the two odours (lavender and milk) (Kawakami et al. 1997).
To study the influence of lavender oil on autistic behaviour in children.	Twelve children with autism and learning difficulties (2 girls and 10 boys aged between 12 years 2 months to 15 years 7	A within subjects repeated measures design: 3 nights when the children were given aromatherapy massage with lavender oil were compared with 14 nights when it was not given. The children were checked every 30 min throughout the night to determine the time taken for the children to settle to sleep, the number of awakenings and the	Repeated measures analysis revealed no differences in any of the sleep measures between the nights when the children were given aromatherapy massage and nights when the children were not given aromatherapy massage. The results suggest that the use of aromatherapy massage with lavender oil has no beneficial effect on the sleep

Purpose	Patients	Intervention	Outcome
	months) in a residential school.	sleep duration. One boy's data was not analyzed owing to lengthy absence.	patterns of children with autism attending a residential school. It is possible that there are greater effects in the home environment or with longer-term interventions (Williams 2006).
To examine the effectiveness of an aromatherapy intervention on the reduction of children's distress in a perianesthesia setting.	The sample included children with and without developmental disabilities who underwent (mostly orthopaedic) surgery (n=94: age: 7-17). Other surgery included phenol or Botox injections, skin surgery, neurosurgery or cranofacial surgery.	Randomized, controlled, blinded design. Subjects in the intervention group received an aromatherapy intervention of lavender and ginger essential oils as a comfort measure. A drop of essential oil was placed on a cotton ball and then taped to the subject's hospital gown approximately 12 inches from the face. A drop of essential oil was also placed over a pulse point and then covered with a small non-occlusive adhesive dressing. The dressing marked the application site and also prevented inadvertent removal of the oil by surgery or anaesthesia department staff. The essential oils were reapplied postoperatively if the subject was in the operating room for longer than 3 hours. The control group received a placebo intervention of jojoba oil. Distress was measured at two times: before induction and in the post anaesthesia care unit (stay of 15 to 75 minutes) using the Faces, Legs, Arms, Cry and Consolability (FLACC) scale. All subjects received standard care, which included pharmacologic treatment for postoperative pain, anxiety, nausea and vomiting.	The mean distress level was lower for the children in the essential oil group, but the effect was not statistically significant (p=.055). Parents' responses to survey questions about satisfaction with aromatherapy did not differ between groups, although open-ended comments indicated a more positive opinion of the benefits of the intervention in the aromatherapy group (Nord & Belew 2009).
To investigate the effects of lavender oil for insomnia, on the	4 psycho-geriatric patients, 3 of whom were receiving	The hours of sleep of the patients were measured for 2 weeks, then measured for another 2 weeks period after medication withdrawal, and then measured	The amount of time spent asleep was significantly reduced after withdrawal of medication, but that amount of time asleep returned to the same level with

Purpose	Patients	Intervention	Outcome
duration of sleep of psycho-geriatric patients.	hypnotics or tranquilizers.	for a final 2 weeks, during which lavender oil was diffused into the ward.	lavender oil as that under medication. (Number References: 4) (Hardy et al. 1995).
To determine whether smelling lavender oil decreases the frequency of agitated behaviour in patients with dementia.	7 agitated nursing home residents with advanced dementia.	The study design was within-subjects ABCBA (A = lavender oil, B = thyme oil, C = unscented grape seed oil): 4 weeks of baseline measurement, 2 weeks for each of the five treatment conditions (10-week total intervention time), and 2 weeks of postintervention measurement. Oil was placed every 3 hours on an absorbent fabric sachet pinned near the collarbone of each participant's shirt. The study was performed in a long-term care facility specifically for persons with dementia. Agitation was assessed every 2 days using a modified Cohen-Mansfield Agitation Inventory. Olfactory functioning was assessed with structured olfactory identification and discrimination tasks and with qualitative behavioural observation during those tasks.	Split-middle analyses conducted separately for each patient revealed no treatment effects specific to lavender, no treatment effects nonspecific to pleasant smelling substances, and no treatment effects dependent on order of treatment administration. There were no differences between participants with more and less intact olfactory abilities. There is significant evidence in the neurologic and neuropsychologic literature that persons with dementia have impaired olfactory abilities. Concordant with this literature, this study found no support for the use of a purely olfactory form of aromatherapy to decrease agitation in severely demented patients. Cutaneous application of the essential oil may be necessary to achieve the effects reported in previous controlled studies (Snow 2004).

Clinical question	Patients	Intervention	Outcome
To what extent lavender oil affects agitation in psycho-geriatric patients?	Patients (mean age 79 $\pm$ 6.3y) meeting ICD-10 diagnostic criteria for severe dementia and suffering from agitated	Patients were included in a placebo-controlled study. During a total of 10 daily treatment sessions a stream of 2% lavender oil vapour, alternated every other day with placebo (water) was diffused into the community area of a long-stay psychogeriatric ward for a 2-hour period. For each subject 10 PAS scores were	Compared to placebo, 9 patients (60%) showed improvement during exposure to lavender oil, 5 (33%) showed no change and agitated behaviour worsened in 1 patient (7%). Group median PAS scores showed that lavender oil therapy produced a modest improvement in agitated behaviour compared to placebo

Clinical question	Patients	Intervention	Outcome
	behaviour (minimum score of 3 points on the Pittsburgh Agitation Scale, PAS) (n=15).	obtained: 5 during treatment and 5 during placebo periods.	(p=0.016) (Holmes et al. 2002).
To what extent does lavender oil influence postnatal discomfort in childbearing mothers?	Mothers (total n=635) after normal child birth.	Mothers (total n=635) used 6 drops of pure lavender oil (n=217) or a synthetic lavender oil (n=213) or an inert substance (205) as an additive to their daily bath for 10 days in a randomized single-blind study. Analysis of daily VAS scores for perineal discomfort was recorded. A power calculation was made on the level of significance.	VAS scores revealed no significant differences between groups. However, there was a trend between the 3rd and 5th days, those women using lavender oil reporting lower mean scores for perineal discomfort (Dale & Cornwell 1994).
To what extent lavender oil improves the mood and anxiety in hospital stress?	Patients admitted to an intensive care unit (n=122). The youngest patient was 2 years old and the oldest 92.	Patients were randomly allocated to receive either massage, massage with lavender oil (1%) or a period of rest.	Patients who received lavender oil massage reported significantly greater improvement in their mood and perceived levels of anxiety (p=0.05). The patients used a 4-point scale to score their level of anxiety, their mood and their ability to cope with the present situation. A pilot study was conducted to test the reliability and the validity of the final assessment tool (Dunn et al. 1995).
To what extent can lavender aroma therapy be beneficial in the treatment of behavioural and psychological symptoms of dementia	28 patients with moderate to severe dementia (nine men and 19 women; mean 1 standard deviation [SD], 78 +/- 10 years; MMSE 9 +/-	Patients with BPSD were divided into two groups. One was treated with lavender aromatherapy and another group was not.	Overall conclusions on clinical pharmacology and efficacy: these conclusions should include an assessment of the plausibility of efficacy of the medicinal product on the basis of long-standing use and experience (Fujii et al. 2008).

Clinical question	Patients	Intervention	Outcome
(BPSD)?	8).		

4.3. Overall conclusions on clinical pharmacology and efficacy

The anxiolytic activity of lavender oil has been studied in different conditions. Patients can be considered as representative for ambulatory practice. The number of patients per study is low, although in some trials a critical mass is obtained. Lavender oil is administered in dosage forms or nebulised as aromatherapy. The former is more reliable as compared to the latter. Independently from the form administered, lavender oil seems to positively influence anxiety and stress-related restlessness. In one of the most recent studies (Woelk & Schläfke, 2010) patients with general anxiety disorder are included. The study is organised according to good clinical practice. Patients are well characterised, capsules with lavender oil are directly compared with lorazepam, and primary and secondary outcomes are clearly distinguished. Before entering there was a one-week screening phase. Results were calculated using the full analysis set (Intention to treat or ITT) as well as per protocol (PP). However the number of patients is low and no power calculation is made. Furthermore no placebo arm was included. Therefore it is not possible to grant a well-established use for lavender.

Lavender oil has been studied in special populations like newborn children, children with autistic behaviour, psychogeriatric patients and hospitalised patients with positive outcomes. However the study populations are small and might be too diverse.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

In clinical studies involving patients treated orally with a lavender flower tincture (Buchbauer et al. 1993b), and patients or healthy volunteers treated with lavender oil either topically (Dale & Cornwell 1994; Yip & Tse 2004; Dunn et al. 1995) or by inhalation of the odour (Diego et al. 1998; Louis & Kowalski 2002; Kane et al. 2004), only a few mild adverse events have been reported.

At a concentration of 16% in petrolatum, lavender oil did not produce any irritation after 48 hours in the closed-patch test and produced no sensitization reactions in the maximization test (Opdyke 1976).

From evaluation of linalool and linalyl acetate for skin irritation in male volunteers no irritation was observed with 20% linalool or up to 32% linalyl acetate, while mild irritation was observed with 32% linalool. No sensitization reactions were observed in the human maximization test with linalool at concentrations of 8% or 20% in 50 volunteers, nor with 10% linalyl acetate in 131 volunteers. With linalyl acetate at 12% and 20% no reactions were observed in 25 subjects (Bickers et al. 2003).

In very rare cases allergic reactions have been reported due to contact with lavender oil. Coulson & Khan (1999) describe two case reports of mild facial 'pillow' dermatitis due to lavender oil allergy. Lavender oil does not seem to be a major sensitizing substance (Hausen & Vieluf 1997).
A case of allergic reactions have been reported in young students (20 years). When an aromatherapy student started massaging the feet of a client with a mixture of *Lavandula*, Origanum and Juniperus oil, her hands started to tingle and became swollen with redness to her arms and throat area. Shortness of breath occurred within 3 minutes of exposure. The symptoms were reversible upon cleaning the skin of lavender oil (Maddocks-Jennings 2004).

Another case of contact dermatitis was reported after rubbing the face with hands that were not cleaned from a massage gel, containing 5% benzylamine and lavender fragrance. Erythema, followed by acute vesicular dermatitis developed (Rademaker 1994).
Three cases of gynecomastia in prepubertal boys were seen after topical application of products that contained lavender and tea tree oils. The boys were between 4 and 10 years old. Exposure was as a 'healing balm' with lavender on the skin, styling gel containing lavender on hair and scalp and the use of lavender-scented soap. Gynecomastia resolved after discontinuing of the therapy. No re-application is mentioned. Nevertheless, causality was accepted between the topical use of the plant species mentioned and the gynecomastia (Henley et al. 2007).

5.2. Patient exposure

Lavender flowers and essential oil have been used for centuries. Exact exposure data related to the use of registered preparations have not been retrieved.

5.3. Adverse events and serious adverse events and deaths

There have been reports of contact dermatitis associated with lavender oil in shampoo, and facial dermatitis after application of the oil to pillows for its sedative properties (Sweetman 2009).

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

No data available.

5.6. Overall conclusions on clinical safety

There is no major concern about human toxicity due to lavender essential oil or lavender flowers. Contact dermatitis may be possible in rare cases.

6. Overall conclusions

Lavender essential oil as well as the dried lavender flowers can be considered as safe. There is no major concern about the quality of the herbal substance and the herbal preparation thereof.

Experimental as well as clinical evidence converge to central nervous effects, more particularly related to anxiety. There are many small- and larger-scale studies available with a patient population representative for ambulatory practice, including children and elderly. Some criticism can be given to the doses and the method of administration. Especially inhalation is difficult to quantify, although the substances will be more directly delivered to the circulation. There are no major concerns on the safety of lavender flowers or essential oil.

Lavender oil and flowers have been used for more than 30 years in the EU. A well established use cannot be proposed for lavender flowers and oil in the treatment of general anxiety disorders (cf. ICD-10 F 41.1). Although the quality of the studies increases with the time, the number of patients treated with essential oil of lavender in RCTs is too low. No structured clinical research has been done on the cutaneous use of *Lavandula* preparations. The use as bath additive of the oil has to be considered as traditional.

The regulatory position of lavender flowers was discussed. There is a long-standing use of the flowers, in a very wide range of therapeutic indications. Moreover, no authorized preparations with flowers were reported in the EU countries. However, the effects for the relief of mild symptoms of mental stress and exhaustion and to aid sleep are plausible on the basis of long-standing use and tradition, thus a monograph could be established.

As the genotoxicity of lavender flowers and total essential oil was not appropriately tested, a Community list entry cannot be established.

Annex

List of references