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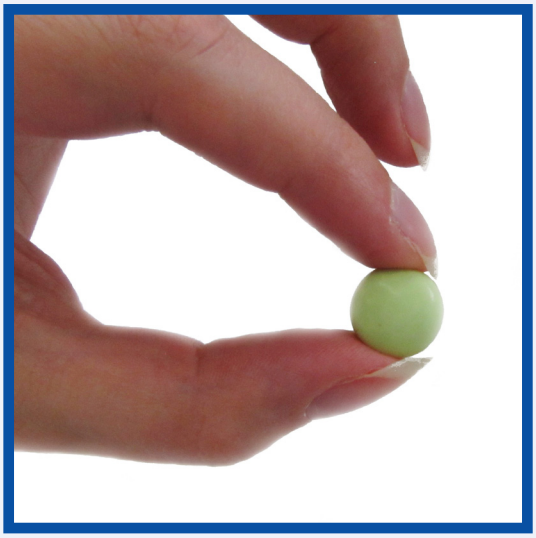
The Scientific Foundation for Herbal Medicinal Products

Caryophylli aetheroleum
Clove Oil

2014



E/S/C/O/P
European Scientific Cooperative On Phytotherapy

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E/S/C/O/P
MONOGRAPHS

***The* Scientific Foundation for**
Herbal Medicinal Products

CARYOPHYLLI AETHEROLEUM
Clove oil

2014

E/S/C/O/P
EUROPEAN SCIENTIFIC COOPERATIVE
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Edited by Simon Mills and Roberta Hutchins
Cover photographs by Simon Mills (*Syzygium aromaticum*)
Cover and text design by Martin Willoughby
Typeset in Optima by Roberta Hutchins

Plant illustrated on the cover: *Syzygium aromaticum*

FOREWORD

It is a great pleasure for me to introduce the online era of ESCOP Monographs. Interest in herbal medicinal products continues to stimulate research on herbal substances and the body of knowledge in this field is steadily growing. ESCOP takes account of this by preparing new monographs and - as the only organisation in the field at the moment - particularly through regular revision of our published monographs. In order to provide readers and authorities with balanced compilations of scientific data as rapidly as possible, ESCOP Monographs will be published online from now on. This contemporary way of publishing adds further momentum to ESCOP's endeavours in the harmonization of European standards for herbal medicinal products.

The Board of ESCOP wishes to express its sincere gratitude to the members of the Scientific Committee, external experts and supervising editors, and to Peter Bradley, the final editor of every monograph published up to March 2011. All have voluntarily contributed their time and scientific expertise to ensure the high standard of the monographs.

Liselotte Krenn
Chair of the Board of ESCOP

PREFACE

Over the 15 years since ESCOP published its first monographs, initially as loose-leaf documents then as two hardback books, ESCOP Monographs have achieved a reputation for well-researched, comprehensive yet concise summaries of available scientific data pertaining to the efficacy and safety of herbal medicinal products. The Second Edition, published in 2003 with a Supplement in 2009, covered a total of 107 herbal substances.

The monograph texts are prepared in the demanding format of the Summary of Product Characteristics (SPC), a standard document required in every application to market a medicinal product for human use within the European Union and ultimately providing information for prescribers and users of individual products.

As a change in style, literature references are now denoted by the name of the first author and year of publication instead of reference numbers; consequently, citations at the end of a monograph are now in alphabetical order. This is intended to give the reader a little more information and perspective when reading the text.

Detailed work in studying the pertinent scientific literature and compiling draft monographs relies to a large extent on the knowledge, skills and dedication of individual project leaders within ESCOP Scientific Committee, as well as invited experts. After discussion and provisional acceptance by the Committee, draft monographs are appraised by an eminent Board of Supervising Editors and all comments are taken into account before final editing and approval. In this way a wide degree of consensus is achieved, but it is a time-consuming process.

To accelerate the publication of new and revised monographs ESCOP has therefore decided to publish them as an online series only, commencing in 2011. We trust that rapid online access will prove helpful and convenient to all users of ESCOP Monographs.

As always, ESCOP is indebted to the many contributors involved in the preparation of monographs, as well as to those who provide administrative assistance and hospitality to keep the enterprise running smoothly; our grateful thanks to them all.

NOTES FOR THE READER

From 2011 new and revised *ESCOP Monographs* are published as an online series only. Earlier monographs are available in two books, *ESCOP Monographs* Second Edition (2003) and the Second Edition *Supplement 2009*, but are not available online for copyright reasons.

After purchase of a single monograph, the specific items to be downloaded are:

Front cover
Title page
Verso
Foreword and Preface
Notes for the Reader
Abbreviations
The monograph text
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Information on the member organizations and people involved in ESCOP's activities can be found on the website (www.escop.com):

Members of ESCOP
Board of Supervising Editors
ESCOP Scientific Committee
Board of Directors of ESCOP

ABBREVIATIONS used in ESCOP monographs

AA	arachidonic acid
ABTS	2,2′-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid)
ACE	angiotensin converting enzyme
ADP	adenosine diphosphate
ALAT or ALT	alanine aminotransferase (= SGPT or GPT)
ALP	alkaline phosphatase
anti-IgE	anti-immunoglobulin E
ASA	acetylsalicylic acid
ASAT or AST	aspartate aminotransferase (= SGOT or GOT)
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
BMI	body mass index
BPH	benign prostatic hyperplasia
b.w.	body weight
cAMP	cyclic adenosine monophosphate
CI	confidence interval
C_{max}	maximum concentration of a substance in serum
CNS	central nervous system
CoA	coenzyme A
COX	cyclooxygenase
CSF	colony stimulating factor
CVI	chronic venous insufficiency
CYP	cytochrome P450
d	day
DER	drug-to-extract ratio
DHT	dihydrotestosterone
DNA	deoxyribonucleic acid
DPPH	diphenylpicrylhydrazyl
DSM	Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association)
ECG	electrocardiogram
ED_{50}	effective dose in 50% of cases
EDTA	ethylenediamine tetraacetate
EEG	electroencephalogram
EMA	European Medicines Agency
ENT	ear, nose and throat
ER	oestrogen receptor
ERE	oestrogen-responsive element
FSH	follicle-stimulating hormone
GABA	gamma-aminobutyric acid
Gal	galactose
GFR	glomerular filtration rate
GGTP	gamma-glutamyl transpeptidase
GOT	glutamate oxalacetate transaminase (= SGOT)
GPT	glutamate pyruvate transaminase (= SGPT)
GSH	glutathione (reduced)
GSSG	glutathione (oxidised)
HAMA	Hamilton Anxiety Scale
12-HETE	12-hydroxy-5,8,10,14-eicosatetraenoic acid
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HMPC	Committee on Herbal Medicinal Products (of the EMA)
HPLC	high-performance liquid chromatography
5-HT	5-hydroxytryptamine (= serotonin)
IC_{50}	concentration leading to 50% inhibition
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSD	International Classification of Sleep Disorders
IFN	interferon
IL	interleukin
i.m.	intramuscular
iNOS	inducible nitric oxide synthase
INR	International Normalized Ratio, a measure of blood coagulation (clotting) tendency

i.p.	intraperitoneal
IPSS	International Prostate Symptom Score
i.v.	intravenous
kD	kiloDalton
KM Index	Kuppermann Menopausal Index
kPa	kiloPascal
LC-MS	liquid chromatography-mass spectrometry
LD_{50}	the dose lethal to 50% of animals tested
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LH	luteinizing hormone
5-LOX	5-lipoxygenase
LPS	lipopolysaccharide
LTB_4	leukotriene B_4
M	molar (concentration)
MAO	monoamine oxidase
MBC	minimum bactericidal concentration
MDA	malondialdehyde
MFC	minimum fungicidal concentration
MIC	minimum inhibitory concentration
Mr	molecular
MRS	Menopause Rating Scale
MRSA	methicillin-resistant *Staphylococcus aureus*
MTD	maximum tolerated dose
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MW	molecular weight
NBT	nitro blue tetrazolium
NF-κB	necrosis factor kappa-B
NO	nitric oxide
NOS	nitric oxide synthase
n.s.	not significant
NSAID	non-steroidal anti-inflammatory drug
ovx	ovariectomy or ovariectomized
ORAC	oxygen radical absorbance capacity
PA	pyrrolizidine alkaloid
PAF	platelet activating factor
PCR	polymerase chain reaction
PEG	polyethylene glycol
PGE	prostaglandin E
PHA	phythaemagglutinin
p.o.	per os
POMS	profile of mood states
PVPP	polyvinylpolypyrrolidone
RANKL	receptor activator of nuclear factor kappa-B ligand
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
s.c.	subcutaneous
SCI	spinal cord injury
SERM	selective oestrogen receptor modulator
SGOT or GOT	serum glutamate oxalacetate transaminase (= ASAT or AST)
SGPT or GPT	serum glutamate pyruvate transaminase (= ALAT or ALT)
SHBG	sex hormone binding globulin
SOD	superoxide dismutase
SSRI	selective serotonin reuptake inhibitor
STAI	state-trait anxiety inventory
$t_{1/2}$	elimination half-life
TBARS	thiobarbituric acid reactive substances
TGF-β	transforming growth factor-beta
TNF	tumour necrosis factor
TPA	12-*O*-tetradecanoylphorbol-13-acetate
URT	upper respiratory tract
URTI	upper respiratory tract infection
UTI	urinary tract infection
VAS	visual analogue scale
VLDL	very low density lipoprotein

CARYOPHYLLI AETHEROLEUM 2014

Clove oil

DEFINITION

Clove oil is obtained by steam distillation of the dried flower buds of *Syzygium aromaticum* (L.) Merrill et L.M. Perry (*Eugenia caryophyllata* (C. Spreng., Bull. et Harr.). The material complies with the monograph of the European Pharmacopoeia [Clove oil].

CONSTITUENTS

The main characteristic constituents of the essential oil are β-caryophyllene (5 - 14 %) and phenylpropanoids eugenol (75 - 88 %) and acetyleugenol (4 – 15 % of the oil); minor constituents, less than 1%, are 2-heptanone, ethyl hexanoate, humulenol; sesquiterpenes, α-humulene, α-humulene epoxide, β-humulene, β-caryophyllene oxide, α-cubebene, α-copaene, α-cadinene, δ-cadinene, α-ylangene, calacorene and calamenene [Clove oil; Iwamuro 1983; Gopalakrishnan 1984,1985; Zheng 1992; WHO 2002; Chaieb 2007; Blaschek 2008].

CLINICAL PARTICULARS

Therapeutic indications
In dental healthcare, for short term use, as a local anaesthetic [Leung 1980; Reynolds 1989], as a disinfectant mouthwash [Wichtl 2002; Bradley 2006; Blaschek 2008]. In these treatments the efficacy is plausible on the basis of human experience and longstanding use.

Symptomatic treatment in chronic anal fissure, after diagnosis by a physician [Elwakeel 2007].

Posology and method of administration

Dosage

Adult daily dose
As a mouthwash with 1-3% diluted clove oil, up to three times daily [Tisserand 1995; Wichtl 2002; Bradley 2006; Lis-Balchin 2006; Blaschek 2008].
For anorectal use: clove oil in a 1% cream, applied three times daily [Elwakeel, 2007].

Method of administration
Oromucosal or anorectal applications with liquid or semisolid preparations of clove oil [Markowitz 1992; Wichtl 2002; Elwakeel 2007; Blaschek 2008].

Duration of use
No restrictions. If symptoms persist or worsen medical advice should be sought.

Contraindications
Topical use of clove oil is contraindicated in case of hypersensitivity to clove oil, as well as hypersensitivity to Peru balsam due to possible cross reactivity. Of 78 patients with allergy to Peru balsam, 36 showed a positive reaction to clove powder [Niinimäki 1984]. Four out of 4 patients sensitized to Peru balsam reacted positive to a 1% hexane extract of clove in petrolatum [Bouhlal 1989].

Special warnings and special precautions for use
None required.

Interaction with other medicinal products and other forms of interaction
None reported.

Pregnancy and lactation
No data available. In accordance with general medical practice, the product should not be used during pregnancy and lactation without medical advice.

Effects on ability to drive and use machines
None known.

Undesirable effects
Very rare cases of contact dermatitis and food allergy have been reported for clove oil or eugenol.

Investigations on contact allergy from essential oils were conducted by the Information Network of Departments of Dermatology (IVDK). In patch test results (from the years 2000 to 2008) of 15,682 patients with dermatitis (from 84,716 consulting), there were 637 cases positive for any oil: of these, 1.5% were positive for clove oil [Uter 2010].

In a worldwide, multi-centre investigation of allergy to cosmetics and toiletries, 43 (19%) of 218 subjects with proven contact dermatitis due to fragrance materials tested positive for clove oil (10% solution) in a new patch test [Larsen 2002].

In 589 cases of food allergy, none were allergic to clove [Moneret-Vautrin 2002].

45 patients occupied in stomatological services (dentists, dental surgeons, nurses and dental technicians), presenting with contact dermatitis of various unknown causes, were exposed to 17 potential allergens, including eugenol. Eugenol (1% solution) tested positive in 9% of the cases (3 dentists and 1 dental surgeon) [Berova 1990].

Allergic contact dermatitis was documented during a 5-year investigation. Only 1 of 1000 patients, working with food and diagnosed to have hand dermatitis, was found to be allergic to clove and simultaneously to carrot and allspice [Kanerva 1996]. Occupational allergic contact dermatitis from eugenol, oil of cinnamon and oil of cloves was reported in a physiotherapist [Sanchez-Perez 1999].

A survey of consumer patch-tests to investigate sensitization demonstrated a very low sensitization potential for eugenol. In 11,632 patch tests only 2 positive eugenol tests were detected at a concentration of 0.05 % (induced hypersensitivity) and at 0.09 % (pre-existing sensitization) [Rothenstein 1983].

Overdose, cutaneous and oral
Permanent local anaesthesia and anhidrosis was reported 11 months after an unknown amount of clove oil was spilled on the face of a patient with toothache. The symptoms were considered to be a neurotoxic effect after cutaneous use [Isaacs 1983].

Toxic effects were reported after oral overdoses of clove oil. Two children, that ingested overdoses of clove oil of 1 teaspoon (7 mo. old, corresponding to approx. 0.5 g/kg body weight of eugenol) and 10 ml (2 yr. old), presented with CNS depression and liver failure, respectively; both recovered [Lane 1991; Brown 1992]. After drinking 5-10 ml clove oil a young child presented with coma and acute liver damage, but recovered [Hartnoll 1993]. Fulminant hepatic failure was reported for a 3-month old patient after ingesting less than 8 ml clove oil, and for a 15 month-old boy after ingesting 10-20 ml clove oil. Both were successfully treated with intravenous N-acetylcysteine, according to a standard protocol used for paracetamol (acetaminophen) poisoning [Eisen 2004; Janes 2005].

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

In view of the vast amount of scientific literature on clove oil and eugenol, the selection of literature cited in the following sections is aimed solely at bringing together relevant examples of the possible physiological roles of clove oil and its major constituents eugenol and β-caryophyllene.

Several monographs and reviews have described pharmacological and other properties of clove oil and/or eugenol, its isolated major constituent [Deininger 1991; Markowitz 1992; Tisserand 1995; Lis-Balchin 2006; Chaieb 2007; Edris 2007; Blaschek 2008].

In vitro experiments

Antibacterial activities (Table 1)
Reports on multiple antimicrobial activities of clove oil and other essential oils have been reviewed [Kalemba 2003; Ceylan 2004; Baser 2009]. The antibacterial activity of clove oil compares in magnitude with oils from spices with the highest antibacterial properties, such as the oils of thyme, cinnamon, oregano and rosemary. In direct comparison, clove oil exhibited slightly greater antibacterial activity than that of rosemary oil. For example, *Escherichia coli* was inhibited at 0.125 %V/V (MIC) by clove oil, as compared to 0.250 %V/V (MIC) by rosemary oil [Ceylan 2004; Prabuseenivasan 2006; Fabio 2007; Fu 2007].

Mechanism of antibacterial action
Eugenol at 1% V/V (MIC of 0.0125%) increased permeability of the bacterial cell membrane of *Salmonella typhi* and caused disruption of the cytoplasmic membrane [Devi 2010]. Clove oil had an antibacterial effect on *Propionibacterium acnes* (MBC/MIC 0.31 mg/mL). Loss of the bacterial membrane integrity, i.e. ruptured cell walls and membranes, resulted at 0.031-0.62 mg/mL clove oil, measured by flow cytometry [Fu 2009].

Antibiotic–resistant bacteria in hospital isolates
Clove oil was shown to be effective against hospital-acquired isolates of Methicillin-resistant *Staphylococcus aureus* (MRSA) and was proposed, together with other essential oils, for antiseptic topical treatment [Warnke 2009]. Inhibition zones of 26 multi-resistant *Staphylococcus epidermidis* strains, isolated from dialysis biomaterial in the hospital, were in the range of 11-15 mm, five strains had zones >16 mm [Chaieb 2007]. Eugenol was active against the antibiotic-resistant bacteria, *Klebsiella pneumonia*, *Shigella ssp.* and *Proteus ssp.* [Nascimento 2000].

Synergistic and additive antibacterial effects
Synergistic interactions of eugenol with antibiotics against Gram-negative bacteria were reported in a model for antibiotic-resistant bacteria [Hemaiswarya 2009]. Combinations of clove oil and rosemary oil have produced mostly additive and rarely synergistic or even antagonistic effects [Fu 2007].

A selection of reported antibacterial activities of clove oil and eugenol against a series of oral, respiratory and antibiotic-resistant pathogens, Gram-positive as well as Gram-negative bacteria, is presented in Table 1. For the MIC values shown, those representing a strong antibacterial effect are in the range of 0.01% - 0.25% V/V.

Antifungal activities (Table 2)
Selected information about antifungal properties of clove oil is presented in Table 2. 48 h-Biofilms of *Candida albicans* were inhibited by eugenol treatment at 0.047 % V/V (IC_{50}) and at 0.188 % V/V (IC_{80}), using the tetrazolium salt reduction assay [He 2007].

Clove oil exhibited, in comparison, a slightly higher antifungal activity than rosemary oil. For example, *Candida albicans* was inhibited at 0.125 %V/V (MIC) by clove oil, as compared

TABLE 1 In vitro antibacterial activities of clove oil and eugenol

Author Year	Material Method	Bacteria	MIC* (%V/V)	MBC* (%V/V)
Saeki 1989	Oil and eugenol Oral bacteria	*Streptococcus species* *Actinomyces species* *Propionibacterium acnes* *Actinobacillus species* *Bacteroides species* *Capnocytophaga gingivalis* *Eikenella corrodens*	0.1 % 0.1 % 0.1 % 0.01 % 0.01 % 0.01 % 0.01 %	
Smith-Palmer 1998	Oil	*Escherichia coli* *Staphylococcus aureus* *Listeria monocytogenes* *Salmonella enteridis* *Campylobacter jejuni*	0.04 % 0.04 % 0.03 % 0.04 % 0.05 %	0.1 % 0.04 % 0.04 % 0.075 % 1 %
Nascimento 2000	Eugenol acts on antibiotic-resistant bacteria	*Klebsiella pneumoniae* *Shigella ssp.* *Proteus ssp.*	1.89 % 0.94 % 0.94 %	
Rhayour 2003	Oil and eugenol	*Escherichia coli* *Bacillus subtilis*	0.050 % 0.033 %	0.100 % 0.050 %
Prabuseenivasan 2006	Oil	*Staphylococcus aureus* *Bacillus subtilis* *Klebsiella pneumoniae* *Proteus vulgaris* *Pseudomonas aeruginosa* *Escherichia coli*	< 0.61 % < 0.30 % < 0.61 % < 0.30 % < 0.15 % < 0.15 %	
Fabio 2007	Oil Bacteria from respiratory infections	*Streptococcus pyogenes* *Streptococcus agalactiae* *Streptococcus pneumoniae* *Staphylococcus aureus* *Haemophilus influenzae* *Klebsiella pneumoniae* *Stenotrophomonas maltophilia*	1.25 % 1.25 % 1.25 % 1.25 % 1.25 % 5.00 % 1.25 %	
Fu 2007	Oil 3 Gram- positive and 3 Gram-negative bacteria	*Staphylococcus epidermidis* *Staphylococcus aureus* *Bacillus subtilis* *Escherichia coli* *Proteus vulgaris* *Pseudomonas aeruginosa*	0.250 % 0.125 % 0.125 % 0.125 % 0.125 % 0.500 %	0.250 % 0.250 % 0.250 % 0.125 % 0.250.% 0.500 %

* MIC = minimal inhibitory concentration; MBC = minimal bactericidal concentration;
For unit conversion to %V/V: density of clove oil =1.04 g/cm^3; of eugenol =1.06 g/cm^3.

to 0.250 %V/V (MIC) by rosemary oil [Fu 2007]. Clove oil was effective against isolates from hospitalised patients with antimycotic-resistant *Candida* species, *C. albicans* and *C. krusei* [Warnke 2009].

Mechanism of antifungal action
Clove oil and eugenol both exhibited antifungal activity towards various *Candida*, *Aspergillus* and dermatophyte species, and against fluconazole-resistant strains (MFC's ranged at 0.32-1.25 µl/mL and MIC's at 0.16-1.25 µl/mL). The fungicidal effect at concentrations just above the MIC values, measured by penetration of propidium iodide, resulted in extensive lesions of the fungal cell membrane and reduced ergosterol in the membrane [Pinto 2009].

The mode of action for the antifungal effects of clove oil and eugenol on the fungal virulence of *Aspergillus niger* and *Trichophyton rubrum* was investigated by measuring elastase and keratinase activitiy. Eugenol and clove oil inhibited fungal elastase by up to 78% and 68% respectively. Keratinase was slightly inhibited by both. Since proteinases contribute to fungal virulence by destroying host tissues and digesting immunologically important proteins, such as antibodies and complement factors, the anti-proteinase activity may reduce the pathogenesis of fungi [Khan 2011].

Antiviral activity
The lipid envelope of *Herpes simplex* virus type 1 and Newcastle disease virus has been destroyed by clove oil (1/500 dilution;0.2 %V/V) and replication inhibited. Non-enveloped viruses (*adenovirus*-3 and *poliovirus*-S) were not affected by clove oil [Siddiqui 1996]. Antiviral activity was exhibited by eugenol at 149.5 µg/ml (0.016 % V/V) for 2 isolated strains of *Herpes simplex* virus-1, however this concentration did not inactivate a standard HSV-1 strain. Eugenol reduced virus HSV-2 replication by 16.5 -100 % [Tragoolpua 2007].

Anti-inflammatory properties
A scintillation proximity-based assay demonstrated inhibition of COX-2 by eugenol (IC_{50} = 129 µM) [Huss, 2002]. COX-2 gene

TABLE 2 In vitro antifungal activities of clove oil and eugenol

Author Year	Material Method	Fungi	MIC* (% V/V)	MFC* (% V/V)
el-Naghy 1992	Oil 10 dermatophytes isolated from patients with dermatomycosis	*Trichophyton simii* *Trichophyton kyryngei* *Trichophyton rubrum* *Trichophyton equinum* *Chrysosporium keratinophilum* *Microsporum audouinii* *Microsporum canis* *Candida albicans* *Candida tropicalis* *Epidermophyton floccosum*	0.1 % 0.1 % 0.1 % 0.1 % 0.1 % 0.1 % 0.1 % 0.1 % 0.1 % 0.1 %	
Sinha 1993	Oil Aflatoxin formation	*Aspergillus flavus*	0.014 %	
Martini 1996	Eugenol	*Cladosporium herbarum* *Penicillium glabrum*	0.002 % 0.014 %	
Hussein 2000	Eugenol Aquatic molds	*Saprolegnia spp.myc* *Achlya klebsiana* *Aphanomyces piscicida*	0.047 % 0.024 % 0.012 %	0.094 % 0.047 % 0.024 %
Beg 2002	Oil	*Alternaria alternata*	0.05%	
Juglal 2002	Oil Mycotoxin, aflatoxin formation	*Aspergillus parasiticus* *Fusarium moniliforme*	0.01 % 0.05 %	
Bennis 2004	Eugenol	*Saccharomyces cerevisiae*	0.033 %	0.055 %
Ahmad 2005	Oil Isolate from vaginal candidiasis	*Candida albicans*	0.005 %	
Chami 2005a	Oil Surface alteration	*Saccharomyces cerevisiae*	0.033 %	0.05 %
Chami 2005b	Eugenol	*Candida albicans*	0.2 %	
Gayoso 2005	Oil and eugenol Fungi from onychomycosis	3 *Candida ssp.* *Trichophyton rubrum* *Trichophyton mentagrophytes* *Geotrichum candidum*	2% / 4% 2% / 4% 2% / 4% 2% / 4%	
He 2007	Eugenol	*Candida albicans*	IC50:0.04 7%	
Fu 2007	Oil	*Candida albicans* *Aspergillus niger*	0.125 % 0.062 %	0.250 % 0.125 %

* MIC = minimal inhibitory (fungostatic) concentration; MFC = minimal fungicidal concentration; For unit conversion to %V/V: density of clove oil =1.04 g/cm^3; of eugenol =1.06 g/cm^3; MW eugenol=197.

expression and PGE_2 production were inhibited by eugenol (IC_{50} = 0.37 µM) in mouse macrophages [Kim SS, 2003]. Eugenol inhibited 5-lipoxygenase activity (IC_{50} = 26 µM) and leukotriene C_4 formation (IC_{50} = 30 µM) by stimulated Human PMN (polymorphonuclear neutrophils) [Raghavenra 2006].

Induction of apoptosis
Reactive oxygen species-mediated apoptosis was induced by eugenol at 40 µM in HL-60 leukemia cells. Eugenol (at 700µM for 50% loss of viability) was also reported to induce apoptosis in mast cells, an indication of its anti-allergic potential. It is suggested that eugenol induces apoptosis *in vitro* by depleting intracellular thiols [Park 2005; Yoo 2005].

In vivo experiments

Clove oil, and its major constituents eugenol and β-caryophyllene, have been investigated for their local anaesthetic, antibacterial, antifungal, antioxidant, immunomodulatory, anti-allergic and insect repellent activities.

Antibacterial activity
Bacterial (*Klebsiella pneumonia*) colonization of the lungs was decreased ($p<0.01$) after 15 days of feeding with clove oil (0.5 mL of 1% w/v oil, once daily), when compared to control mice given saline 0.5 mL [Saini 2009].

Antifungal activity
To immunosuppressed rats with artificial vaginal candidiasis, 500 µL eugenol (equivalent to 2-fold MIC; approx. 20 mg/kg per day) was applied twice daily by topical intravaginal route (as prophylactic treatment, from 2 days before until 3 days after inoculation with *C. albicans*) and was compared to the effect of nystatin and further controls. Prophylactic eugenol reduced the colony count of *C. albicans* in vaginas of infected rats by 98.9% 10 days after inoculation, with negative culture results in 2/9 rats and significantly lower levels in 7/9 rats compared to control. In a second experiment, treatment with 500 µL eugenol

began 3 days after inoculation and was continued for 7 days. Two of 9 rats were cured completely and 7/9 showed an 84% reduction of the *C. albicans* colony count in the vagina. The positive control, nystatin, used at 10-fold MIC, confirmed the validity of the rat model [Chami 2004].

In the immunosuppressed (dexamethasone/tetracycline treated) rat model of experimental oral candidiasis, topical treatment in the oral cavity, twice daily with 0.5 mL of 0.4% eugenol dispersed in viscous 0.8% agar solution (20µg/kg/d), was started 3 days post-infection and continued for 8 days. Eugenol significantly ($p<0.05$) reduced the number of colonies sampled from the oral cavity, compared to the number of colonies in untreated rats. Nystatin was similarly effective and confirmed the fungicidal effect of eugenol [Chami, Bennis 2005].

Mice with an artificial urogenital infection were treated successfully with clove oil. Vaginal administration of a liposome preparation of clove oil, on days 2, 4, 6 and 8 after intra-vaginal inoculation with *Candida albicans*, was nearly as effective as a liposome preparation of nystatin in eliminating the fungal infection. Both the clove oil and nystatin formulations reduced the vaginal titre of *C. albicans* in vaginal lavage fluid significantly, when tested on day 10 against a negative control ($p<0.001$). At 14 days post-infection topical clove oil had completely eliminated the fungal burden in treated mice [Ahmad 2005].

Anti-anaphylactic, anti-allergic potential and immunomodulatory activity
Intraperitoneal treatment with eugenol at 50-100 mg/kg provided protection against PAF-induced shock from i.v. carrageenan-induced rat paw oedema in rabbits ($p\leq0.001$) [Saeed 1995].

In rats with chemically-induced anaphylactic shock, eugenol was anti-anaphylactic at an intraperitoneal dose of 10 mg/kg b.w. Accordingly, in rat peritoneal mast cells, histamine release and TNF-α production were reduced *in vitro* by eugenol at 10µg/mL [Kim 1997].

Immunomodulatory functions of clove oil were tested in mice (previously immunized with sheep red blood cells) after oral treatment once daily for 7 days with 100, 200 and 400 mg/kg clove oil. The oil increased the white blood cell count and also enhanced delayed-type hypersensitivity significantly ($p<0.001$ for all doses). It restored cellular and humoral immune reponses in cyclophosphamide-immunosuppressed mice in a dose-dependent manner ($p<0.001$ for 200 and 400 mg/kg) [Carrasco 2009].

Eugenol (at 700µM and at 10 µg/kg b.w.) was considered to exhibit an anti-allergic potential, resulting from induction of apoptosis in mast cells of rats (*in vitro* and *in vivo* respectively) [Park 2005].

Antioxidant activity in an aflatoxicosis rat model
Rats fed an aflatoxin-contaminated diet were either treated orally with clove oil (5 mg/kg b.w.) or untreated, for 30 days. Resulting haematological and biochemical changes were typical for aflatoxicosis. Clove oil treatment resulted in protection against aflatoxicosis, i.e. significantly restored ($p<0.05$) parameters that were altered by aflatoxin in rats [Abdel-Wahhab 2005].

Anaesthetic use
In the rabbit conjunctival reflex test, local β-caryophyllene treatment, by drops into the conjunctival sac, permitted a concentration-dependent increase of the number of stimuli necessary to provoke the reflex during 5-15 minutes after application, at 10-1000 µg/mL. In a comparative test, chemically related caryophyllene oxide, at 3-1000 µg/mL was ineffective. Thus β-caryophyllene acted as a specific local anaesthetic to the rabbit eye [Ghelardini 2001].

Eugenol produced reversible dose-dependent (i.v. administration of single doses at 5-60 mg/kg) anaesthesia. The anaesthetic level was determined using the withdrawal reflex test by pinching the rats until the return of a positive response. Eugenol-induced loss of consciousness, in a dose–dependent manner, showed a mean recovery time of 167 +/- 42 sec at the highest dose level [Guenette 2006]. Induced thermal hypersensitivity was attenuated in rats treated with 40 mg/kg eugenol for 5 days ($p<0.01$) [Guenette 2007].

Gastroprotective activity
Clove oil and eugenol both displayed anti-ulcer activity. Gastroprotective effects were observed after intraduodenal administration of clove oil and eugenol (100 and 250 mg/kg) in rat models of indomethacin- and ethanol-induced ulcers. At the same doses, eugenol and clove oil also stimulated the production of mucus ($p<0.01$), an important gastro-protective factor [Santin 2011].

Insect repellent activity
Tick nymphs (*Ixodes ricinus*) were exposed to clove oil on filter paper discs (0.5 mL, undiluted). Clove oil acted as a long lasting repellent (from 4h to 8h) for 68% to 78% of the nymphs, compared to 0% repellency observed for the controls [Thorsell 2006].

Pharmacological studies in humans

Studies in humans as insect repellent
Clove oil (in 25% - 100% preparations) administered to the skin of 2 human subjects was investigated as a repellent for the prevention of bites from 2 mosquito species (*Anopheles albimanus* and *Aedes aegypti*). These applications provided protection from 1.5h up to 3.5h, in a dose-dependent manner. From a group of 15 essential oils clove oil was the only one that could selectively prevent bites of *Anopheles albimanus*. Clove oil, in the dilution range of 25% - 100%, was 7 times more effective compared to a synthetic repellent (25% Deet, N,N-diethyl-3-methylbenzamide) [Barnard 1999].

A controlled study investigating clove oil application to the skin (4 groups: 10%, 50%, undiluted oil and solvent controls) was conducted in 3 human subjects (who agreed to be test objects) for prevention of mosquito bites. The undiluted oil fully prevented bites for 2 to 4 hours in 3 mosquito species (*Aedes aegypti*, *Anopheles dirus* and *Culex quinquefasciatus*). Dose dependency was shown, 50% oil prevented bites for 1.5h [Trongtokit 2005].

Clinical studies

A randomized, single-blind, controlled, comparative clinical trial was conducted for 6 weeks. Clove oil (as a 1% cream) was applied anorectally 3 times daily, and tested against a positive control (5% lignocaine cream), in 55 patients with chronic anal fissure (clove oil n=30; lignocaine n=25). After a 3-month follow-up, significantly more of the clove oil group (60%) than the lignocaine control group (12%) were symptom-free ($p<0.001$). Significant decreases in anal sphincter pressures were also reported for the clove oil patients. The majority of clove oil patients did not require additional systemic analgesics during the study, presumably because of the anaesthetic effect of 1% clove oil. This demonstrated a further advantage when compared to the control group who had received the traditional treatment of stool softeners and the topical anaesthetic 5% lignocaine cream [Elwakeel 2007].

Pharmacokinetic properties

Pharmacokinetics in animals

Absorption, metabolism, elimination
Pharmacokinetics of orally administered eugenol were assessed in rats following administration by gavage of 40 mg/kg for 5 successive days. Blood samples were collected over 24h. Eugenol in blood peaked rapidly, but mean $T_{1/2}$ values of eugenol in plasma and blood were quite long, at 14.0 h and 18.3 h respectively, suggesting a potential accumulation following repeated administration [Guenette 2007].

Eugenol is rapidly metabolized and excreted. Over 70% of an oral dose was excreted in the urine of rabbits. Eugenol had little or no effect on microsomal enzyme induction [Opdyke 1975b].

Blood and urinary samples from rats given a single intravenous dose of 20 mg/kg eugenol were collected over 1h for pharmacokinetic assessment. Mean systemic clearance from plasma and blood was 157 and 204 ml/min/kg respectively. Glucuronide and sulphate conjugate metabolites were identified in urine [Guenette 2006].

Pharmacokinetics in humans

Absorption, metabolism, elimination
Eugenol was rapidly absorbed and metabolized after oral administration to male and female healthy volunteers with 95% of the dose recovered in the urine within 24h. Most were phenolic conjugates (99%), plus nine metabolites of eugenol [Fischer 1990].

Dental healthcare/ anaesthetic
In vivo drug release studies were conducted with 6 healthy human volunteers using a eugenol-containing mucoadhesive layer (200 mg tablet contained 10 mg eugenol) stuck to the gums. The tablets remained on the gums up to 8h. Eugenol was completely released at 6h in 1 of 3 tested formulations [Jadhav 2004].

Preclinical safety data for clove oil and eugenol

Clove oil

Acute toxicity
In rats, the acute oral LD_{50} value of clove oil was 2.65-3.72 g/kg. In rabbits, the acute dermal LD_{50} was reported as 5g/kg [Opdyke 1975a].

There were no signs of toxicity, or alterations in food and water consumption, in rats during the 14 day period following a single oral dose of clove oil (2000 mg/kg b.w.).

Repeated dose and chronic toxicity studies
Rats tolerated daily oral doses of 35-70 mg clove oil well for 8 weeks. Higher doses led to inactivity and weight loss [Opdyke 1975a].

An estimated acceptable daily intake of eugenol up to 2.5 mg/kg b.w. for humans was established at the 26th and confirmed at the 65th Joint FAO/WHO Committee on Food Additives [Reynolds 1989].

Irritation of animal skin: Applied undiluted to backs of mice, clove oil was not irritating. Applied undiluted to abraded rabbit skin for 24h under occlusion it was mildly irritating [Opdyke 1975a].

Irritation of human skin: In 2 of 25 normal subjects, 20% clove oil in vaseline caused erythema in a closed-patch test on the skin. In 30 normal subjects tested at 2%, and in 35 subjects with dermatoses tested at 0.2%, no reaction was evoked. Tested at 5% in vaseline it produced no irritation after a 48h closed-patch test in humans [Opdyke 1975a].

Sensitization (human test): In a maximization test, clove oil at 5% in vaseline produced no sensitization reactions in 25 volunteers. In another study sensitization caused by clove oil was attributed to eugenol [Opdyke 1975a].

Human dental pulp: A zinc oxide-clove oil paste damaged the dental pulp in human dental cavities [Opdyke 1975a].

Mutagenicity and carcinogenicity
Clove oil was cytotoxic for HEP-2 cells (human carcinoma-derived) at ID_{50} = 7.31 µg/ml [Saenz 1996]. Clove oil and eugenol were both found to be cytotoxic to human fibroblasts and to a human transformed dermal endothelial cell line at concentrations as low as 0.03%V/V and 0.06%V/V, respectively. β-caryophyllene was not cytotoxic to these cells [Prashar 2006].

Reproductive toxicity
Motility and viability of human spermatozoa were investigated *in vitro*. Clove oil tested for immediate spermicidal activity was minimally effective at a concentration of 0.5 % V/V. Eugenol had a similar minimal effect at 0.33 %V/V [Buch 1988]. Female mating mice on a diet with additional 0.25% clove oil for 2 weeks, exhibited a slight but significant increase in embryo cell death at 0.8%, compared to control mice at 0.3% ($p<.0.01$) on day 4 of pregnancy [Domaracky, 2007].

Eugenol

Acute toxicity
Oral LD_{50} of eugenol in rats was 2.68 g/kg; in mice 3.00 g/kg; in guinea pigs 2.13 g/kg. Minor liver damage occurred in rats given oral doses of 900 mg/kg 4 times daily. The highest *no effect oral dose* in dogs was 200 mg/kg b.w. [Opdyke 1975b].

There were no signs of toxicity, or alterations in food and water consumption, in rats during the 14 day period following a single oral dose of eugenol (2000 mg/kg b.w.).

Repeated dose and chronic toxicity studies
After repeated application of a 5% eugenol emulsion to the mucosa of Heidenhain's pouch (mucous membranes) in dogs, the gastric mucous barrier showed degenerative and reparative changes [Opdyke 1975b].

Short term toxicity in rats: feeding male and female rats for 19 wk (0%, 0.1% and 1% eugenol in the diet, 3 groups of 20 rats) exerted no effect on growth, haematology or organ weights and histology [Opdyke 1975b].

The effect of one drop of topically applied, undiluted eugenol, when administered to a round 3mm diameter area of rat oral/labial mucosa for 1 minute, was observed by histological procedures after periods of 15 minutes up to 6 hours. This treatment resulted in denaturation of cytoplasmic proteins, loss of staining capacity of the epithelium, loss of cell boundaries, swelling and cell necrosis. In addition, vesicle formation, edema in the corium and striated muscle dissolution were observed. It was concluded that undiluted eugenol is injurious to labial mucous membranes [Kozam 1978].

Irritation of human skin: Mild irritation was observed in a study involving 25 human subjects topically treated with 8% eugenol

in vaseline for 48 h in a closed-patch test. A patch test using undiluted eugenol for 24h produced no reaction in 20 human subjects [Opdyke 1975b].

Sensitization (human test) by eugenol was tested in 25 human volunteers: a maximization test with 8% eugenol in vaseline, applied topically, produced no sensitization reactions [Opdyke 1975b].

Mutagenicity and carcinogenicity
Carcinogen (diethyl-nitrosamine)-induced microsomal degranulation of rat liver microsomes could be protected by 3mM eugenol [Selvi 1998]. Eugenol acted as an anti-mutagen in the *Salmonella typh*. mutagen-induced SOS response test (mutagen furylfuramide and others). Eugenol suppressed 29.9% of the SOS-inducing activity at 0.60 µM/ml [Miyazawa 2001]. Eugenol at 2500 µM induced chromosomal aberrations in V79 chinese hamster cells (3.5% aberrant cells). In the presence of biotransformation mix S9, aberrations increased dose-dependently to 15%. An increase of endoreduplicated cells was observed (up to 5% at 2000 µM eugenol) [Maralhas 2006].

Cell viability
Eugenol was metabolized by isolated myeloperoxidase and inhibited the oxidative burst in phorbol-stimulated human polymorphonuclear neutrophils. Intracellular glutathione levels decreased by 90% when the cells were exposed to 100 µM eugenol [Thompson 1989]. A review discussing the clinical use of eugenol, in dental materials, suggests that prolonged exposure to concentrations of 0.001 mol/L eugenol and higher may be toxic to mammalian cells, as well as to vital dental tissue, and should be avoided [Markowitz 1992]. Rat liver mitochondria membrane potential was decreased to 50% at 7.5 µmoles/mg protein for eugenol. Mitochondrial NADH oxidase was inhibited by eugenol in a dose dependent fashion [Usta 2002].

Clinical safety data
The total number of human patients, subjects and volunteers in studies, where either clove oil or eugenol were administered by cutaneous, oromucosal or anorectal route, is 276. In these studies no adverse reactions were reported, except for mild skin irritations by 8% eugenol and erythema caused by 20% clove oil [Opdyke 1975a; Opdyke 1975b; Fischer 1990; Jadhav 2004; Barnard 1999; Trongtokit 2005 and Elwakeel 2007].

A double-dummy, controlled, randomized clinical study involving 73 human subjects was conducted in 2 groups. The clove bud group consisted of 37 healthy volunteers; clove bud powder (containing 15-20% clove oil) was administered topically and investigated for its effect as an anaesthetic on the buccal mucosa. The positive control group (36 volunteers) received a benzocaine gel (20%). Treatments were on both sides of the mouth (dummy-placebo and active agent in each subject). Adverse effects were observed only in the clove bud group; 4 of 37 clove patients developed aphthous-like ulcers at the application site of the clove bud preparation. This adverse event could not be directly attributed to the clove oil content of the clove bud powder [Alqareer 2006].

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