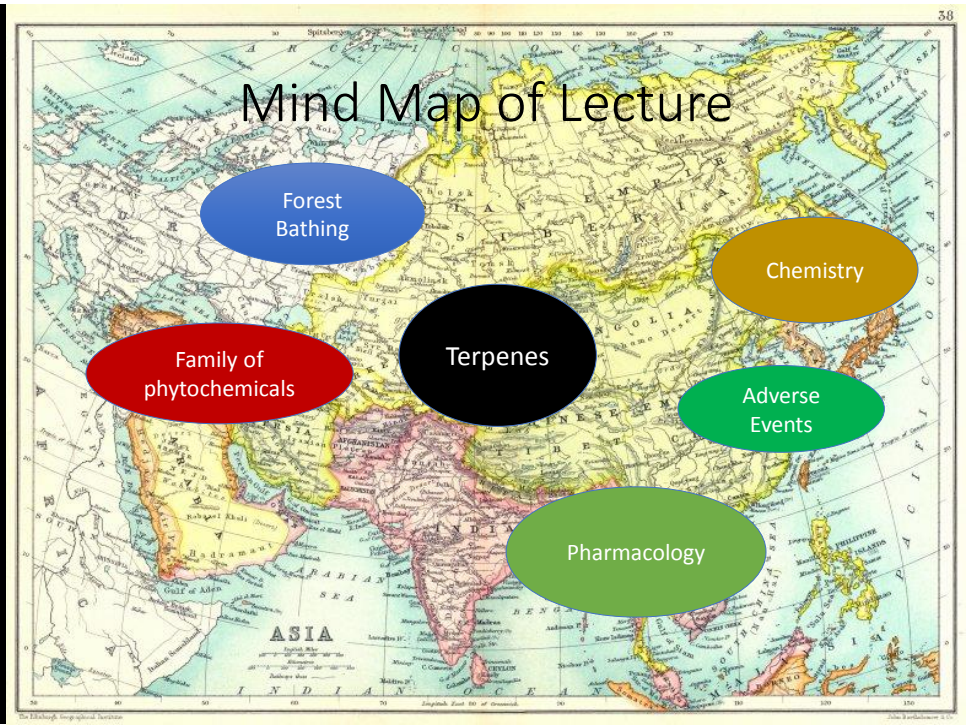
The Terpenes

Kevin Spelman, PhD, MCPP
Health, Education & Research
Ashland, OR



Disclosures

I have been a Natural Products, Pharma and *Cannabis* Industry Consultant, for SOPs, GMPs, Regulatory Issues, Pharmacology, Research Initiatives and Formulation

Forest Bathing

Environ Health Prev Med (2010) 15:9–17
DOI 10.1007/s12199-008-0068-3

SPECIAL FEATURE

The Trends on the Research of Forest Bathing in Japan, Korea and in the World

Effect of forest bathing trips on human immune function

Qing Li

forest bathing trips resulted in an increase in NK activity, which was mediated by increases in the number of NK cells and the levels of intracellular granulysin, perforin, and granzymes A/B

Abstract In Japan, a forest bathing trip, called "Shinrinyoku" in Japanese, is a short, leisurely visit to a forest; it is regarded as being similar to natural aromatherapy. This review focuses on the effects of forest bathing trips on human immune function. Beginning in 2005, adult Japanese individuals, both male and female, participated in a series of studies aimed at investigating the effect of forest bathing trips on human immune function. The subjects experienced a 3-day/2-night trip to forest areas, and blood and urine were sampled on days 2 (the first sampling during each trip) and 3 (the second sampling during each trip), and on days 7 and 30 after the trips. Natural killer (NK) activity, the numbers of NK, granulysin-, perforin-, and granzymes A/B-expressing lymphocytes in the blood, and the concentration of urinary adrenaline were measured. The same measurements were made before the trips on a cells, or the level of intracellular granulysin, perforin, and granzymes A/B. These findings indicate that forest bathing trips resulted in an increase in NK activity, which was mediated by increases in the number of NK cells and the levels of intracellular granulysin, perforin, and granzymes A/B.

Keywords Forest bathing · Granulysin · Granzyme · NK activity · Perforin

Introduction

What is a forest bathing trip?

The forest environment has been enjoyed by humans for a

Morita *et al. BioPsychoSocial Medicine* 2011, **5**:13
http://www.bpsmedicine.com/content/5/1/13

BIOPSYCHOSOCIAL MEDICINE

RESEARCH Open Access

A before and after comparison of the effects of forest walking on the sleep of a community-based sample of people with sleep complaints

Emi Morita[1*], Makoto Imai[2], Masako Okawa[3], Tomiyasu Miyaura[4] and Soichiro Miyazaki[3]

Forest walking improved nocturnal sleep conditions for individuals with sleep complaints

immediate effects of forest walking in a community-based population with sleep complaints.

Methods: Participants were 71 healthy volunteers (43 men and 28 women). Two-hour forest-walking sessions were conducted on 8 different weekend days from September through December 2005. Sleep conditions were compared between the nights before and after walking in a forest by self-administered questionnaire and actigraphy data.

Results: Two hours of forest walking improved sleep characteristics; impacting actual sleep time, immobile minutes, self-rated depth of sleep, and sleep quality. Mean actual sleep time estimated by actigraphy on the night after forest walking was 419.8 ± 128.7 (S.D.) minutes whereas that the night before was 365.9 ± 89.4 minutes (n = 42). Forest walking in the afternoon improved actual sleep time and immobile minutes compared with forest walking in the forenoon. Mean actual sleep times did not increase after forenoon walks (n = 26) (the night before and after forenoon walks, 380.0 ± 99.6 and 385.6 ± 101.7 minutes, respectively), whereas afternoon walks (n = 16) increased mean actual sleep times from 342.9 ± 66.2 to 475.4 ± 150.5 minutes. The trend of mean immobile

Environ Health Prev Med (2010) 15:18–26
DOI 10.1007/s12199-009-0086-9

SPECIAL FEATURE

The Trends on the Research of Forest Bathing in Japan, Korea and in the World

The physiological effects of *Shinrin-yoku* (taking in the forest atmosphere or forest bathing): evidence from field experiments in 24 forests across Japan

Bum Jin Park · Yuko Tsunetsugu · Tamami Kasetani · Takahide Kagawa · Yoshifumi Miyazaki

Received: 18 July 2008 / Accepted: 6 April 2009 / Published online: 2 May 2009

forest environments promote lower concentrations of cortisol, lower pulse rate, lower blood pressure, greater parasympathetic nerve activity, and lower sympathetic nerve activity than do city environments

defined as making contact with and taking in the atmosphere of the forest. In order to clarify the physiological effects of *Shinrin-yoku*, we conducted field experiments in 24 forests across Japan. In each experiment, 12 subjects (280 total; ages 21.7 ± 1.5 year) walked in and viewed a forest or city area. On the first day, six subjects were sent to a forest area, and the others to a city area. On the second day, each group was sent to the other area as a cross-check. Salivary cortisol, blood pressure, pulse rate, and heart rate variability were used as indices. These indices were measured in the morning at the

Keywords Therapeutic effects of forest · Heart rate variability · Salivary cortisol · Blood pressure · Pulse rate

Introduction

The growing interest in environmental stress has been accompanied by a rapid accumulation of evidence indicating that environment can elicit substantial stress in people living in urban environments [1]. Furthermore, it is

Toxicol. Res.
Vol. 33, No. 2, pp. 97-106 (2017)
Open Access https://doi.org/10.5487/TR.2017.33.2.097
pISSN: 1976-8257 eISSN: 2234-2753 **Review Article**

Toxicological Research
Official Journal of Korean Society of Toxicology
Available Online at http://www.ToxicolRes.org

Terpenes from Forests and Human Health

Kyoung Sang Cho[1,2], Young-ran Lim[1], Kyungho Lee[1,2], Jaeseok Lee[1,2], Jang Ho Lee[1] and Im-Soon Lee[1,2]
[1]*Department of Biological Sciences, Konkuk University, Seoul, Korea*
[2]*Research Center for Coupled Human and Natural Systems for Ecowelfare, Konkuk University, Seoul, Korea*

The biological effectiveness of terpenes support the benefits of forest bathing and propose a potential use of terpenes as chemotherapeutic agents for treating various human diseases

easily obtained from forests according to their anti-inflammatory, anti-tumorigenic, or neuroprotective activities. Moreover, potential action mechanisms of the individual terpenes and their effects on such processes, which are described in various *in vivo* and *in vitro* systems, are discussed. In conclusion, the studies that show the biological effectiveness of terpenes support the benefits of forest bathing and propose a potential use of terpenes as chemotherapeutic agents for treating various human diseases.

Key words: Cancer, Forest therapy, Health, Immune function, Neuronal health, Terpene

INTRODUCTION

Exposure to natural environment is beneficial to human health (1). Among environmental exposures, the effects of forest have been emphasized in many studies (2). Recently, it has been shown that a short trip to forest environments

frequently used (6). Kneipp therapy includes five preventive and curative methods created by Sebastian Kneipp, a German priest (5), in which exercise in a forest is one of the five core methods (2). Japan is one of the countries where the forest usage programs for human health are well developed. The Forest Agency of the Japanese government intro-

Forest Bathing

Top 5 terpenes in Forest Bathing exposure

Predominant
- α-pinene
- myrcene
- β-phellandrene
- camphene
- d-limonene

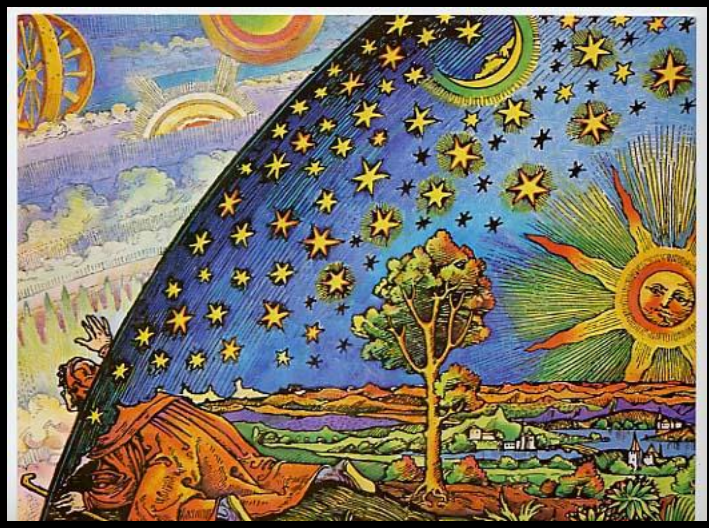
Lesser Concentrations
- alpha-terpinene
- beta-pinene
- caryophyllene

http://download.springer.com/static/pdf/375/art%253A10.1186%252Fs41610-017-0038-z.pdf?originUrl=http%3A%2F%2Fjecoenv.biomedcentral.com%2Farticle%2F10.1186%2Fs41610-017-0038-z&token2=exp=1496678404~acl=%2Fstatic%2Fpdf%2F375%2Fart%25253A10.1186%2

The Terpenes

Nature's Scents

The Magic



Essential oils

Cowan, M. M. (1999). Plant products as antimicrobial agents. *Clin Microbiol Rev* **12**, 564-82.

The fragrance of plants is carried in the so called quinta essentia, or essential oil fraction

The Terpenes

- Terpenes are the largest class of naturally occurring organic compounds
  - more than 40,000 structures reported so far

Gershenzon J, Dudareva N. The function of terpene natural products in the natural world. *Nat Chem Biol.* 2007 Jul; 3(7):408-14.
Chappell J. The genetics and molecular genetics of terpene and sterol origami. *Curr Opin Plant Biol.* 2002 Apr; 5(2):151-7.

Terpenes

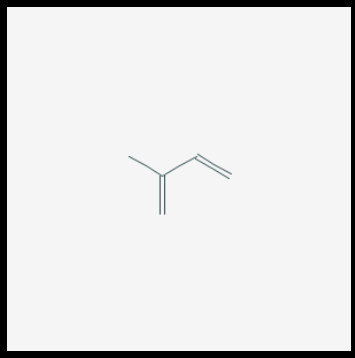
- Compounds classified as terpenes constitute what is arguably the largest and most diverse class of natural products
- A majority of these compounds are found only in plants, but some of the larger and more complex terpenes (e.g. squalene & lanosterol) occur in animals

de las Heras, B., Rodriguez, B., Bosca, L., and Villar, A. M. (2003). Terpenoids: Sources, structure elucidation and therapeutic potential in inflammation. *Curr Top Med Chem* **3**, 171-185.

- According to the number of such C5 units present in the molecule, terpenoids are classified into
  - hemi- (1 unit)
  - mono- (2 units)
  - sesqui- (3 units)
  - di- (4 units)
  - sester- (5 units)
  - tri- (6 units)
  - tetraterpenoids (8 units, carotenoids)

Terpenes

- Monoterpenes
  - In essential oils
  - In Oleoresins
  - Iridoids (monoterpene lactones)
- Sesquiterpenes
  - In essential oils
  - Sesquiterpene lactones
- Diterpenes
- Triterpenes & Steroids
  - Saponins
  - Cardiac glycosides
  - Phytosterols

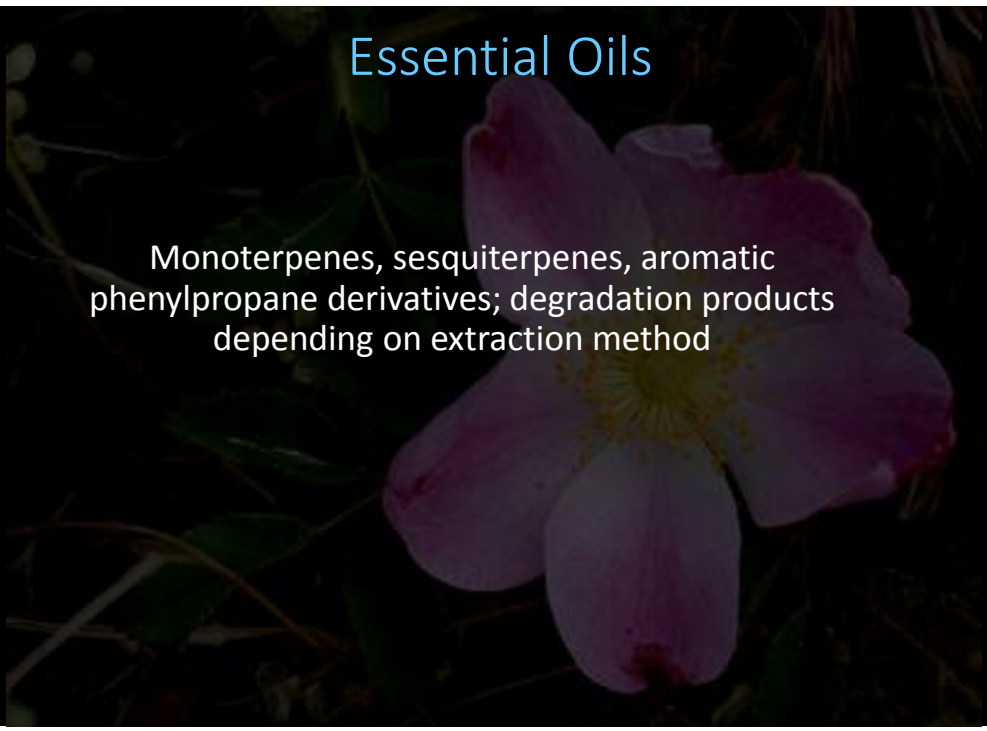


Isoprene, is the structural basis for all of the terpenoids & steroids.

Classification Isoprene Units Carbon

Isoprene itself, a C5H8 gaseous hydrocarbon, is emitted by the leaves of various plants as a natural byproduct of plant metabolism

Essential Oils



Monoterpenes, sesquiterpenes, aromatic phenylpropane derivatives; degradation products depending on extraction method

Essential oils

Cowan, M. M. (1999). Plant products as antimicrobial agents. *Clin Microbiol Rev* **12**, 564-82.

- The fragrance of plants is carried in the so called quinta essentia, or essential oil fraction
- These oils are secondary metabolites that are highly enriched in compounds based on an isoprene structure and/or phenylpropanoids
- Those derived from isoprenes are called terpenes, their general chemical structure is C10H16, and they occur as diterpenes, triterpenes, and tetraterpenes (C20, C30, and C40), as well as hemiterpenes (C5), monoterpenes (C10) and sesquiterpenes (C15)

Essential Oils: Occurrence

- There are ~ 17,500 different species that make essential oils
- Found in all kinds of plant parts: flowers, leaves, fruits, seeds, barks, woods, roots, rhizomes
- Lamiaceae yields many familiar oils: Lavender, Rosemary, Sage, Thyme, Peppermint, Melissa…

Lavender

Garden Sage

Cinnamon bark

ential Oils: Occurrence

Essential oil content varies considerably among different species

- Melissa: 0.05%
- Lemon: 0.1 – 3%
- Wormwood: 0.2 – 0.6%
- Lavender: 0.3 – 1%
- Chamomile: 0.3 – 1.5%
- Bergamot: 0.5%
- Thyme: 0.5 – 2.5%
- Sage: 0.7 – 2.5%
- Rosemary: 1 – 2%
- Peppermint: 1 – 3%
- Eucalyptus: 1 – 3%
- Camphor: 1 – 3%
- Dill: 2.5 – 4%
- Caraway: 3 – 7%

Terpenes in *Cannabis*

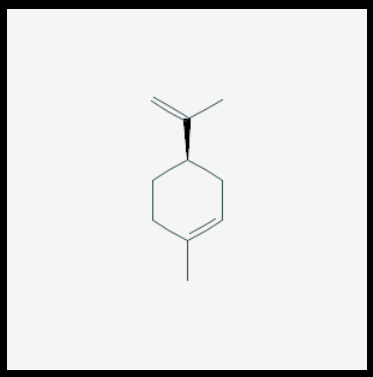
- Unique smell of *Cannabis* derives from terpenes
- Field-cultivated fresh *Cannabis* yields 1.3 L/ton of EO
- *C. sativa* ssp. *indica* more uniform terpene profile
- *C. sativa* ssp. *sativa* terpene profile is more variable

Essential Oils: Antiseptics

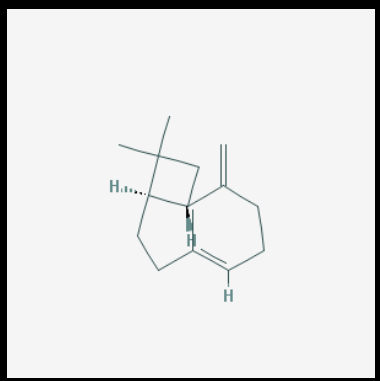
- Plants produce essential oils, in part, to protect themselves from bacterial, fungal, or viral infection
- Levels of essential oil constituents vary as a response to infection: phytoalexins
- Notable antiseptic constituents are found in Thyme, Eucalyptus, Tea Tree, Lavender, Rosemary, Sages (Salvia & Artemisia spp.), Pine spp. & Citrus spp., Clove & Black Pepper and …Cannabis

Monoterpenes & Sesquiterpenes

- Monoterpenes: 10 carbons
- Sesquiterpenes: 15 carbons



Limonene



Caryophyllene

Terpenoids

- When the compounds contain additional elements, usually oxygen, they are termed terpenoids
- Terpenoids share their origins with fatty acids

Cowan, M. M. (1999). Plant products as antimicrobial agents. *Clin Microbiol Rev* **12**, 564-82.

Property	Monoterpenoids	Sesquiterpenoids	Diterpenoids
Analeptic	+	+	−
Anthelmintic	+	+	−
Antibiotic	+	+	+
Anti-epileptic	−	+	−
Anti-inflammatory	+	+	−
Antitumor	+	+	+
Choleretic	−	+	−
Hypotensive	+	+	+
Organoleptic	+	+	+
Sedative	+	+	−
Spasmolytic	+	+	−

Ishida, T. (2005). Biotransformation of terpenoids by mammals, microorganisms, and plant-cultured cells. *Chem Biodiversity* **2**, 569-590.

Pharmacology

Monoterpenes and Sesquiterpenes

Thanks to Ethan Russo, MD

Chemical Ecology of Terpenoids
(over 200 reported)

- Insect repellents (pinene, limonene) (Nerio 2010)
- Insecticidal (McPartland 2000):
- "Phytochemical Polymorphism": Aromatic monoterpenes higher in flowers to repel insects, while bitter sesquiterpenoids are higher in leaves to act as anti-feedants for grazing animals (Potter 2009):

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Annals of the New York Academy of Sciences **855**:648-651, 1998

Sensory properties of selected terpenes: Thresholds for odor, nasal pungency, nasal localization, and eye irritation

J. Enrique Cometto-Muñiz[1], William S. Cain[1], Michael H. Abraham[2], and Rachel Kumarsingh[2]

[1]Chemosensory Perception Laboratory, Dept. of Surgery (Otolaryngology), University of California, San Diego, La Jolla, CA 92093-0957, USA

cumene, p-cymene, delta-3-carene, linalool, 1,8-cineole, and geraniol

Odor thresholds ranged between 0.1 & 1.0 ppm
Nasal pungency thresholds lay about three orders of magnitude above odor thresholds

Address for correspondence:
University of California, San Diego
La Jolla, CA 92093-0957

Phone: (619) 622-5832
FAX: (619) 458-9417
e-mail: ecometto@ucsd.edu

HOSTED BY ELSEVIER

CrossMark

Available online at www.sciencedirect.com

ScienceDirect

Food Science and Human Wellness 4 (2015) 9–27

Food Science and Human Wellness

www.elsevier.com/locate/fshw

Tea aroma formation

Chi-Tang Ho[a,*], Xin Zheng[a], Shiming Li[b,**]

[a] *Department of Food Science, Rutgers University, New Brunswick, NJ 08901, USA*
[b] *College of Life Sciences, Huanggang Normal University, Hubei 438000, China*

Geraniol and linalool were detected at 3.2 and 6 ppm, respectively

Abstract

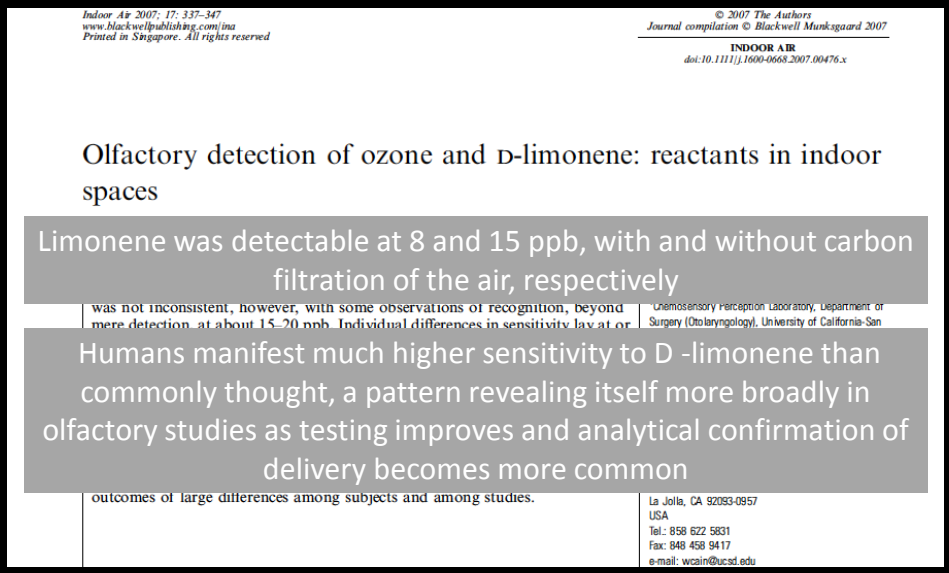
Besides water, tea is one of the most popular beverages around the world. The chemical ingredients and biological activities of tea have been summarized recently. The current review summarizes tea aroma compounds and their formation in green, black, and oolong tea. The flavor of tea can be divided into two categories: taste (non-volatile compounds) and aroma (volatile compounds). All of these aroma molecules are generated from carotenoids, lipids, glycosides, etc. precursors, and also from Maillard reaction. In the current review, we focus on the formation mechanism of main aromas during the tea manufacturing process.

Keywords: Tea; Aroma; Formation; Volatile; Taste

1. Background

Tea is the second most widely consumed beverage around the world after water [1]. The popularity of tea as a global beverage

reaction pathway. To the best of our knowledge, no previous study has provided the details of formation mechanisms for tea aromas. Therefore, in the present study, we review main aromas starting from the manufacturing process, with biological



Indoor Air 2007; 17: 337–347
www.blackwellpublishing.com/ina
Printed in Singapore. All rights reserved

INDOOR AIR
doi:10.1111/j.1600-0668.2007.00476.x

Olfactory detection of ozone and D-limonene: reactants in indoor spaces

Limonene was detectable at 8 and 15 ppb, with and without carbon filtration of the air, respectively

Humans manifest much higher sensitivity to D -limonene than commonly thought, a pattern revealing itself more broadly in olfactory studies as testing improves and analytical confirmation of delivery becomes more common

Chemosensory Perception Laboratory, Department of Surgery (Otolaryngology), University of California-San Diego, La Jolla, CA 92093-0957
USA
Tel.: 858 622 5831
Fax: 848 458 9417
e-mail: wcain@ucsd.edu

Range of Human Detection

15 ppb - 0.1 ppm

low ppb – low ppm

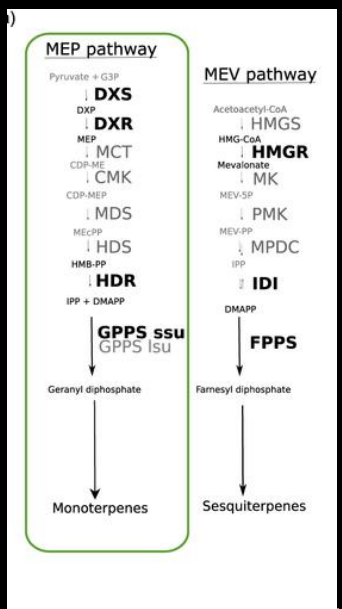
Activity

Compound	% Change Motility	Serum Concentration ng/ml
Linalool	-73.00	4.22
Orange Terpenes (primarily Limonene)	+35.25	Not detectable
α-Pinene	+13.77	Trace
α-Terpineol	-45.00	4.7

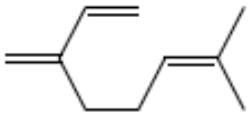
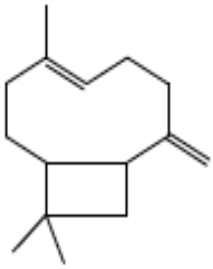
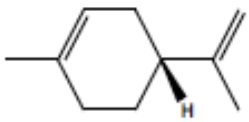
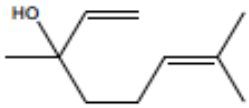
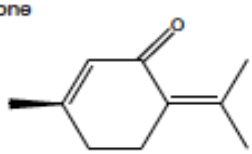
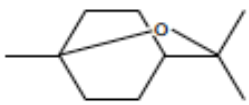
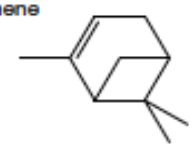
- Mice exposed to terpenoid odors for 1 h in ambient air
- Profound effects noted on activity levels, even at very low serum levels
- Direct pharmacological effect on the brain demonstrated
- Percutaneous absorption also demonstrated (Jäger 1992) (linalool to 100 ng/ml in serum)

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.
Buchbauer G, et al. Fragrance compounds and essential oils with sedative effects upon inhalation. *J Pharm Sci* 1993;82(6):660-4.

Schematic of the plastidial methylerythritol phosphate pathway (MEP) and mevalonic acid pathway (MEV)



Booth JK, Page JE, Bohlmann J (2017) Terpene synthases from Cannabis sativa. PLOS ONE 12(3): e0173911. https://doi.org/10.1371/journal.pone.0173911

Cannabis Constituent Structure*	Concentration†	Boiling Point °C§	Properties
β-myrcene 	0.47%	166-168	Analgesic Antiinflammatory Antibiotic Antimutagenic
β-caryophyllene 	0.05%	119	Antiinflammatory Cytoprotective (gastric mucosa) Antimalarial
d-limonene 	0.14%	177	Cannabinoid agonist? Immune potentiator Antidepressant Antimutagenic
linalool 	0.002%	198	Sedative Antidepressant Anxiolytic Immune potentiator
pulegone 	0.001%	224	Memory booster? AChE inhibitor Sedative Antipyretic
1,8-cineole (eucalyptol) 	> 0.001%	176	AChE inhibitor Increases cerebral blood flow Stimulant Antibiotic Antiviral Antiinflammatory Antinociceptive
α-pinene 	0.04%	156	Antiinflammatory Bronchodilator Stimulant Antibiotic Antineoplastic AChE inhibitor

Chemical Ecology of Terpenoids
(over 200 reported)

- Additive herbicidal properties?
- Strong antibiotic properties

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Other Terpenes

- Diterpenoids = 20 C
  - phytol
- Triterpenoids = 30 C
  - friedelin (roots)

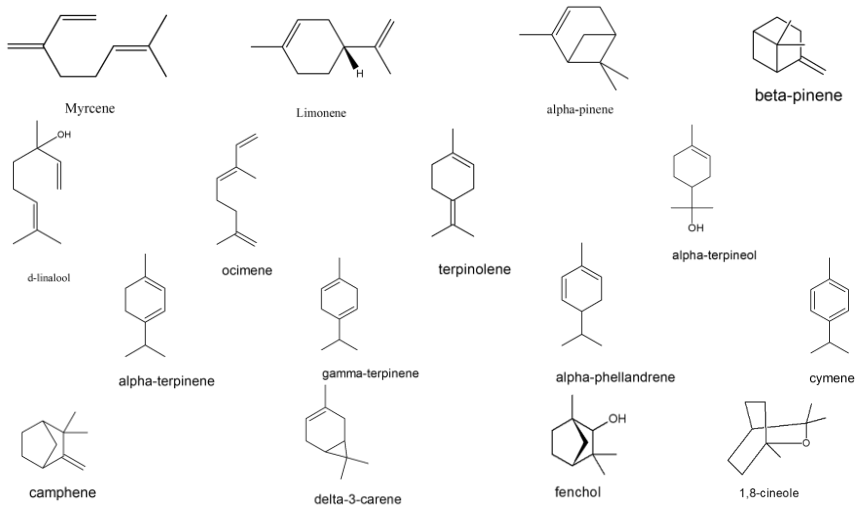
Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Terpenoids

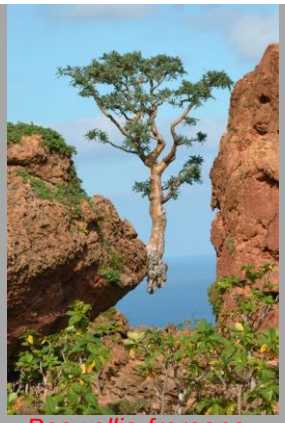
- Monoterpenes usually predominate (limonene, myrcene, pinene: "headspace volatiles") but yields diminish with storage (Ross 1996), and relative quota of sesquiterpenes (esp. caryophyllene) may increase, as they often do in extracts
- All terpenoids discussed are **Generally Recognized As Safe (GRAS)** by FDA, Food and Extract Manufacturers Association (FEMA) or other world regulatory bodies

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

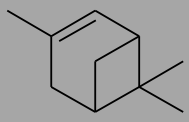
Monoterpenes



Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.



Boswellia frereana
42 - 80%

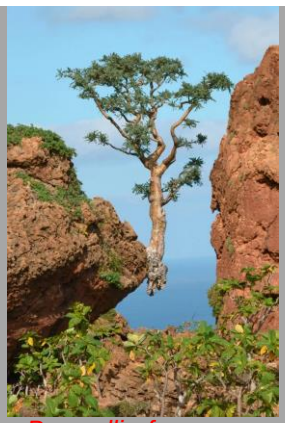


alpha-pinene

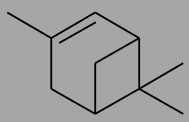
α-Pinene

- A bicyclic monoterpene, the most widely distributed terpenoid in Nature (Noma 2010.
- Anti-inflammatory via PGE-1 (Gil et al., 1989)
- **Bioavailability via inhalation (60%)** with rapid metabolism and redistribution (Falk 1990), with bronchodilation effect in humans.

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.



Boswellia frereana
42 - 80%

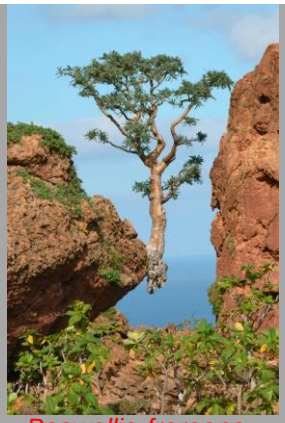


alpha-pinene

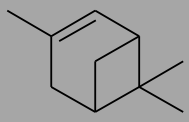
α-Pinene

- **Wide spectrum antibiotic** (Nissen 2010). Equally effective against MRSA and other resistant bacteria as vancomycin (Kose et al., 2010):
- Active versus *P. acnes* and *Staph* spp. (Raman et al., 1995), and for MRSA, *Cryptococcus neoformans Candida albicans* biofilms (Rivas da Silva et al., 2012).

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.



Boswellia frereana
42 - 80%

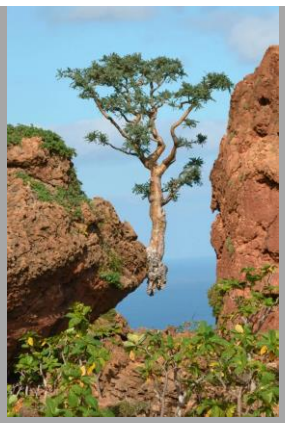


alpha-pinene

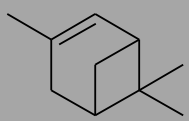
α-Pinene

- Dramatically lowered MIC of ciprofloxacin, erythromycin and triclosan against the gastroenteritis pathogen, *Campylobacter jejuni* (Kovac 2015).
- Beneficial against *Leishmania amazonensis* (Rodrigues 2015), and vectors of malaria, dengue and Japanese encephalitis (Govindarajan et al., 2016).

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.



Boswellia frereana
42 - 80%

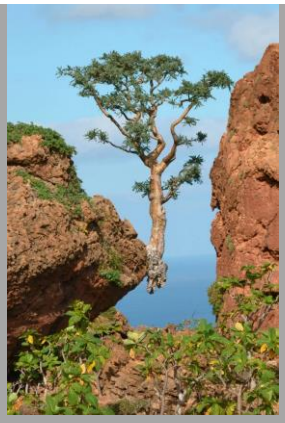


alpha-pinene

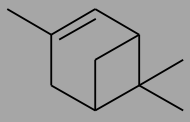
α-Pinene

- **Increased mouse motility after inhalation 13.77%** (Buchbauer 1993). At 10 µL/L concentration **produced an anxiolytic effect in the elevated plus maze**, with general brain distribution (Kasuya 2015). In chronic inhalation over 5 days, anxiolytic effects were maintained (Satou 2014).
- Most notable for **acetylcholinesterase inhibition** (Perry et al., 2000)(Miyazawa 2005), which **serves to reduce or eliminate short-term memory impairment by THC.**

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.



Boswellia frereana
42 - 80%

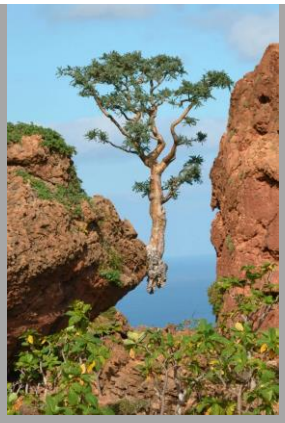


alpha-pinene

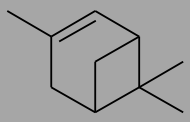
α-Pinene

- **Protected rat astrocytes from H_2O_2 damage by 69%** (Elmann 2008)
- Pinene has also been suggested as **a modulator of THC overdosage** (Russo 2011).
- Chronic exposure led to decreased melanoma growth in mice at 180 ng/L (1 ppm) in ambient air, a dose too low to directly affect tumor (Kusuhara 2012), **a health-promoting effect is known in Japan as "*Shinrin-yoku*" or "forest bathing."**

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.



Boswellia frereana
42 - 80%



alpha-pinene

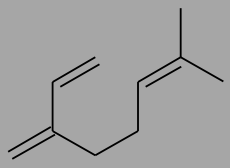
α-Pinene

- A direct synergistic and isobolographic benefit was observed in combination with paclitaxel versus non-small-cell A549 lung carcinoma cells with evidence of apoptosis (Zhang 2015).
- α-Pinene inhibited BEL-7402 human hepatoma cell growth 79.3%, (Chen 2015) equivalent to that from 5-FU.

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

β-Myrcene

Rosmarinus officinalis
19.5 – 52.1%



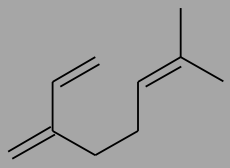
myrcene

- Blocks inflammation via PGE-2 (Lorenzetti et al. 1991)
- Sedating (Wichtl 2004), muscle relaxant and potentiated barbiturate sleep time in mice at high dose (do Vale et al. 2002)
- **Primary "couch-lock" factor in cannabis** (Russo 2011)

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

β-Myrcene

Rosmarinus officinalis
19.5 – 52.1%



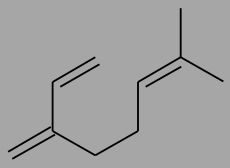
myrcene

- Blocks hepatic carcinogenesis by aflatoxin (de Oliveira et al. 1997)
- **Analgesic in mice, antagonized by naloxone** (Rao et al. 1990).(Paula-Freire 2013) confirmed myrcene 10 mg/kg po reduced pain behavior in both phases of the formalin test for longer that morphine (four hours) ,abrogated by naloxone administration, supporting an opioid mechanism of action.

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

β-Myrcene

Rosmarinus officinalis
19.5 – 52.1%



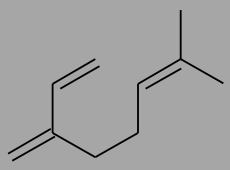
myrcene

- In human chrondrocyte culture, myrcene inhibited NO production (Rufino 2015), suggesting therapeutic application in osteoarthritis.

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

β-Myrcene

Rosmarinus officinalis
19.5 – 52.1%



myrcene

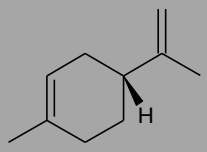
- In rats (Bonamin 2014), oral myrcene 7.5 mg/kg benefited peptic ulcers via multiple
- In mice, 200 mg/kg ip 10 days prevented ischemic/reperfusion oxidative cerebral injury (Ciftci 2014).

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Citrus x sinensis
84 - 96%

D-Limonene

- **Potent antidepressant and immune stimulator in humans via ambient inhalation (Komori et al. 1995), lowering HADS and allowing d/c of AD Rx.**



d-limonene

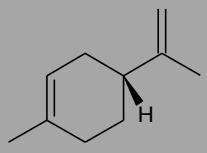
- Lemon EO vapor anxiolytic/AD in mice, with ↑5-HT in PFC, DA in HC, mediated via 5-HT_{1A} (Komiya 1999)

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv*

Citrus x sinensis
84 - 96%

D-Limonene

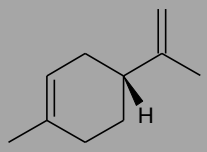
- Citrus EO effective against dermatophytes (Ramadan 1996; Sanguinetti 2007; Singh 2010)
- Human pulmonary uptake 70% (Falk 1990)
- Concentrations of 400 µg/ml inhibited biofilm formation of the pathogen *Streptococcus pyogenes* SF370 and *S. nutans,* which produces dental caries, (Subramenium 2015).



d-limonene

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv*

Citrus x sinensis
84 - 96%



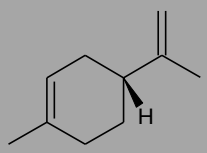
d-limonene

D-Limonene

- **Potent antidepressant and immune stimulator in humans via ambient inhalation (Komori et al. 1995), lowering HADS and allowing d/c of AD Rx.**
- Lemon EO vapor anxiolytic/AD in mice, with ↑5-HT in PFC, DA in HC, mediated via 5-HT_{1A} (Komiya 1999)
- Citrus EO effective against dermatophytes (Ramadan 1996; Sanguinetti 2007; Singh 2010)
- Human pulmonary uptake 70% (Falk 1990)
- Concentrations of 400 µg/ml inhibited biofilm formation of the pathogen *Streptococcus pyogenes* SF370 and *S. nutans,* which produces dental caries, (Subramenium 2015).
- Limonene 10 mg/kg po reduced hyperalgesia in mice induced by intrathecal administration of HIV glycoprotein toxin gp120 (Piccinelli 2016).
- Produced apoptosis of breast cancer cells in Phase II trials (Vigushin et al. 1998)
- In women with pre-operative breast cancer, an oral intake of 2 g of d-limonene a day produced a breast tissue mean concentration of 41.3 µg/g of tissue (Miller 2013).

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv*

Citrus x sinensis
84 - 96%



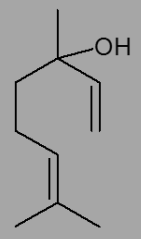
d-limonene

D-Limonene

- **Limonene is an agonist at A_{2A} adenosine receptors (Park) and could synergize activity with both THC (direct activator) and CBD (uptake inhibitor via competition for the nucleotide binding site of the ENT1 transporter) (Carrier 2006)**

- **Limonene 50 µM increased mitochondrial biogenesis**, activated the AMPK energy regulator**, increased brown adipocyte markers PGC-1α UCP1, and induced "browning" of 3T3-L1 adipocytes** by activating β-3-AR and ERK signaling pathway (Lone 2016), **suggesting a putative role in obesity treatment.**

Cinnamomum camphora var. *glavescens* 67-91%



d-linalool

D-Linalool

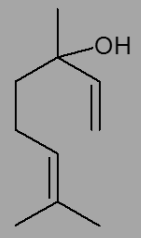
Anti-anxiety (Russo 2001)

Sedative on inhalation in mice (Buchbauer et al. 1993)

- **Local anesthetic** (Re et al 2000), equal to procaine, menthol (Ghelardini 1999)

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Cinnamomum camphora var. *glavescens* 67-91%



d-linalool

D-Linalool

Anticonvulsant/anti-glutamatergic (Elisabetsky et al. 1995

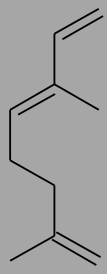
- Produced hot-plate analgesia in mice ($p<0.001$)
- Linalool-incorporated nanoparticles are being explored as a novel anti-cancer agent (Han 2016)

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Commiphora guidottii
33%

Ocimene

- A common component of West Coast (Elzinga 2015) and Dutch chemovars (Fischedick 2010)



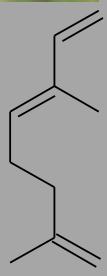
ocimene

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Commiphora guidottii
33%

Ocimene

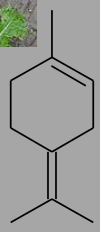
- Associated with EOs with anticonvulsant, antifungal, and anti-tumoral effects, but rarely tested on its own.
- Is a social regulation factor in honeybees (Kennell 2016)



ocimene

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Parsnips 40 - 69%
Pastinaca sativa



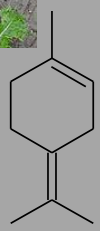
terpinolene

Terpinolene

- Cyclic monoterpene, **a common component of some commercial chemovars**
- **Demonstrated to prevent LDL oxidation (of interest in treatment of atherogenesis and CAD)** (Grassman 2005)
- Concentration of 0.05% markedly reduced AKT1 expression in K562 human CML cells and significantly stimulated apoptosis (Okumura 2012)
- Sedative in mice at 0.1 mg in air, reducing motor activity to 67.8% (Ito 2013)

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Parsnips 40 - 69%
Pastinaca sativa



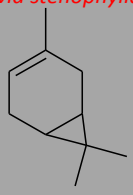
terpinolene

Terpinolene

- **Subjective reports in humans suggest stimulation, possibly attributable to acetylcholinesterase inhibition** (Bonesi 2010)
- Also antifungal, larvicidal (Aydin 2013)
- A subactive antinociceptive/AI dose 3.125 mg/kg po in rats synergized with diclofenac, and reduced hyperalgesia, an effect blocked by ketanserin, suggesting mediation via 5-HT_{2A} (Macedo 2016)

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Salvia stenophylla 38%



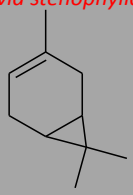
delta-3-carene

Δ^3-Carene

- A bicyclic monoterpenoid alkene
- High-exposure leads to irritation of skin and lungs (Falk 1991), with rapid metabolism and high adipose tissue affinity. Exposure is common in new homes (Krol 2014).
- Carene was rapidly absorbed, distributed and metabolized in human volunteers after oral administration (Schmidt 2015).

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Salvia stenophylla 38%



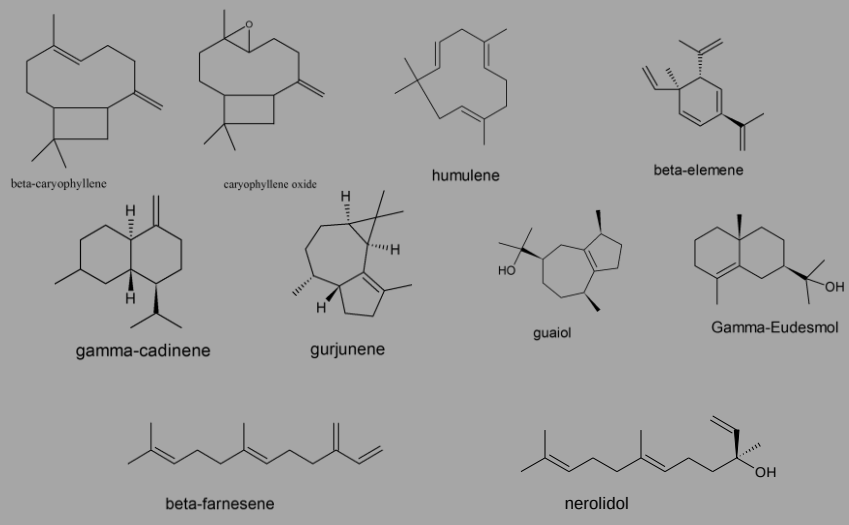
delta-3-carene

Δ^3-Carene

- **A low concentration (5 µM) stimulated mineralization in mouse osteoblastic cells** (Jeong 2008).
- Carene demonstrated larvicidal activity against vectors of malaria, dengue, and filariasis (Govindarajan 2016).
- **Carene content was judged to be a marker of "sativa" cannabis chemovars (**Hazekamp 2016).

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Sesquiterpenoids

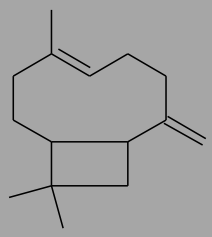


Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Copaifera langsdorfii 25 - 53%

β-Caryophyllene

- **Anti-inflammatory via PGE-1 comparable potency to phenylbutazone** (Basile et al. 1988); EO with BC content = etodolac and indomethacin (Ozturk 2005)



beta-caryophyllene

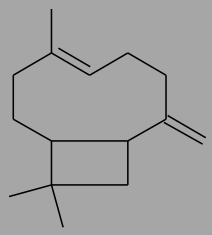
- **Gastric cytoprotective** (Tambe et al. 1996)
- **Selective CB_2 full agonist (100 nM)** (Gertsch 2008a), suggesting dietary use at 5 mg/kg AI (Gertsch 2008b)

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Copaifera langsdorfii 25 - 53%

β-Caryophyllene

- <5 mg/kg po produced AI/analgesic effects in wild-type, but not CB_2 knockout mice (Zimmer 2009)
- Utility in contact dermatitis (Karsak 2007)
- Decreased cocaine administration (Bahi 2014)
- β-Caryophyllene demonstrated larvicidal activity against vectors of malaria, dengue, and Japanese encephalitis (Govindarajan 2016).
- **Broad additional pharmacology** (Sharma 2016)



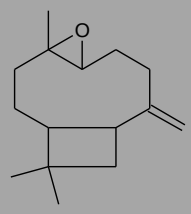
beta-caryophyllene

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Nepeta cataria
6-25%

Caryophyllene oxide

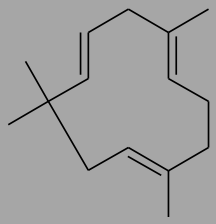
- Sesquiterpenoid oxide
- The cannabis component by which sniffer dogs identify cannabis (Stahl 1973)
- Antifungal in onychomycosis comparable to ciclopiroxolamine and sulconazole (Yang et al. 1999). 8% caryophyllene ox→ onychomycosis cure in 15 days.



caryophyllene oxide

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Hops 37%
Humulus lupulus



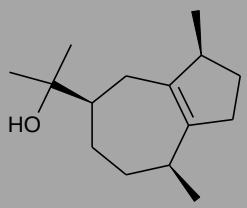
humulene

Humulene

- Very common in North American chemovars, sometimes predominant (Giese 2015)
- Inhibits fruit fly mating (Shelly 2015)
- **Protected rat astrocytes from H_20_2-induced cell death by 50%, and was concentrated 7-fold intracellularly** (Elmann 2009).

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Palo santo 72%
Bulnesia sarmientoi



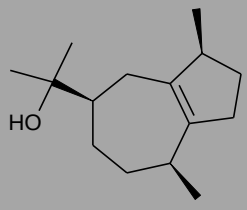
guaiol

Guaiol

- A bicyclic sesquiterpenoid alkene alcohol
- *Bulnesia sarmientoi* essential oil has been employed in aromatherapy to treat arthritis, rheumatoid arthritis and gout.
- Reported actions of the essential oil are: anti-inflammatory, anti-oxidant, anti-rheumatic, antiseptic, diaphoretic, diuretic, laxative.
- Park (2003) demonstrated weak 5-alpha reductase inhibitory effects, possibly helpful in benign prostatic hyperplasia, or male-pattern baldness

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Palo santo 72%
Bulnesia sarmientoi



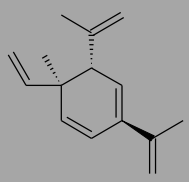
guaiol

Guaiol

- Guaiol inhibited non-small cell lung cancer cells *in vitro,* and *in vivo* in nude mice as effectively as cisplatin at the same 8 mg/kg dose) (Yang 2016)
- Guaiol showed contact toxicity for two moth species and efficacy as a fumigant for *Musca domestica* houseflies with LC50 of 16.9 µL/L (Liu 2013).
- Guiaol demonstrated bite-deterrence index (BDI) against pathogenic mosquitoes comparably to DEET (Ali 2015).
- Guaiol, was said to be a distinguishing factor in Afghan cannabis chemovars (Hillig 2004), with similar claim for "indica" chemovars (Hazekamp 2016).

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Myrrh 9%
Commiphora myrrha



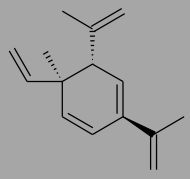
beta-elemene

ℬ-Elemene

- A monocyclic sesquiterpenoid polyalkene
- Elemene injection approved in China since 1993 for treatment of cancer. However, a 2006 Cochrane-style review or 127 RCTs showed poor adherence to CONSORT recommendations and very low Jadad scale scoring (Peng 2006).
- A study in rats at 80 mg/kg IV (equivalent to 13 mg/kg in humans) good passage through the blood-brain barrier and attainment of high brain tissue levels, as well as good tumor inhibition and life extension (Wu 2009).
- A meta-analysis of studies in malignancy (Xu 2013) examined 38 clinical trials. Overall response rate of elemene with chemotherapy was favorable in lung cancer ($p<0.00001$), hepatocarcinoma ($p=0.002$), metastatic brain cancer ($p=0.02$), and leukemia ($p=0.0004$), but not in gastric carcinoma.

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Myrrh 9%
Commiphora myrrha



beta-elemene

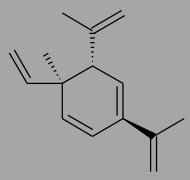
ℬ-Elemene

- Elemene prevented human umbilical vein endothelial cell (HUVEC) damage by hydrogen peroxide *in vitro*, inhibited smooth muscle proliferation and migration, and neointima formation after vessel injury in rats (Wu 2011). In subsequent work (Liu 2015), elemene also decreased reactive oxygen species and mitogen-activated protein kinase signaling in HUVECS, and suggesting utility in atherosclerosis treatment

- In a rat model of hepatic fibrosis, elemene downregulated plasma endotoxins, serum TNF-α and expression of CD14, the co-receptor for bacterial lipopolysaccharide detection (Liu 2011)

Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Myrrh 9%
Commiphora myrrha



beta-elemene

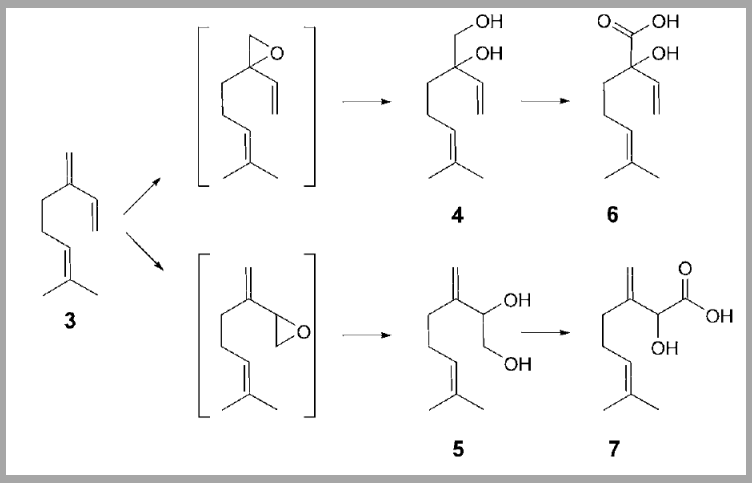
ℬ-Elemene

- Elemene 12.5-50 µg/ml inhibited osteogenic differentiation from cultured human hip joint capsule fibroblasts via inhibition of the BMP/SMADs pathway, suggesting its ability to reduce ectopic ossification in ankylosing spondylitis (Zhou 2015).

- Elemene 10-200 µg/ml also reduced viability and increased apoptosis of rheumatoid arthritis fibroblast-like synoviocytes via induction of ROS and p38 MAPK activation, implying therapeutic potential in that disorder (Zou 2016).

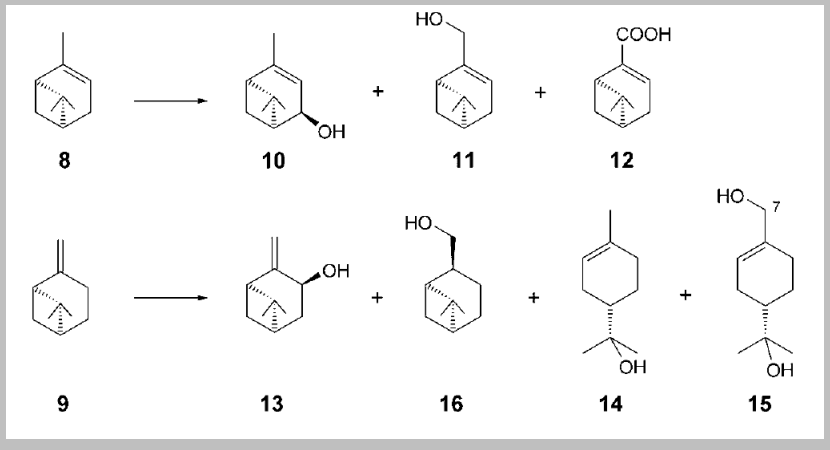
Russo EB, Marcu J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* 2017;80:67-134.

Phase I metabolism of myrcene



Ishida, T. (2005). Biotransformation of terpenoids by mammals, microorganisms, and plant-cultured cells. *Chem Biodiversity* **2**, 569-590.

Phase I metabolism of α-pinene and β-pinene



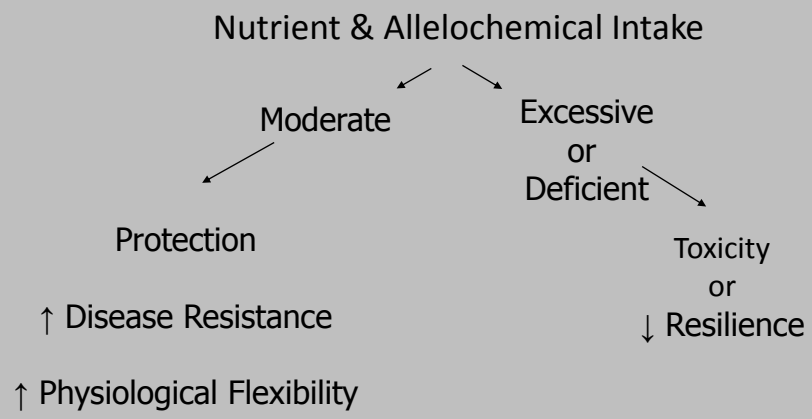
Ishida, T. (2005). Biotransformation of terpenoids by mammals, microorganisms, and plant-cultured cells. *Chem Biodiversity* **2**, 569-590.

Terpene Adverse Events

If one is good is not two better?

In a word, NO!

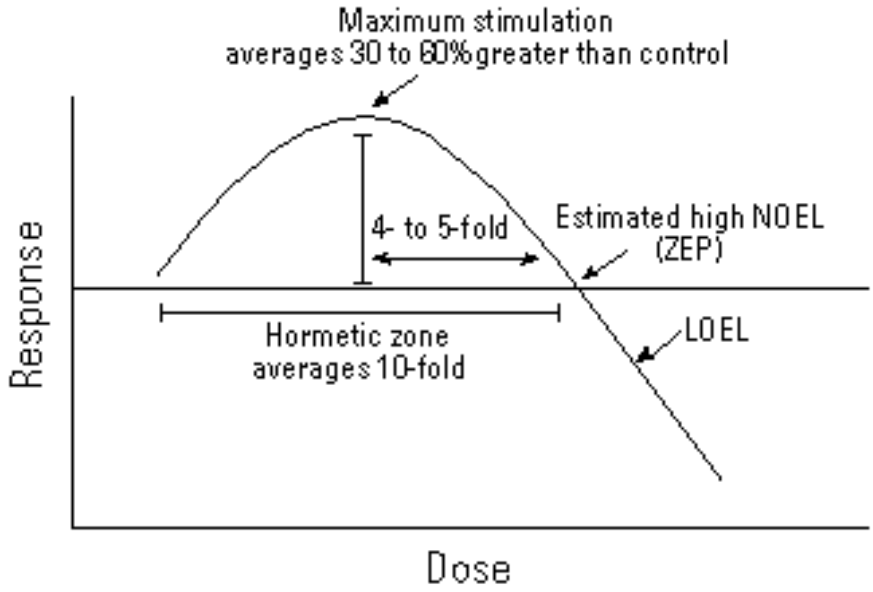
Humans and Plants



Hormesis Defined

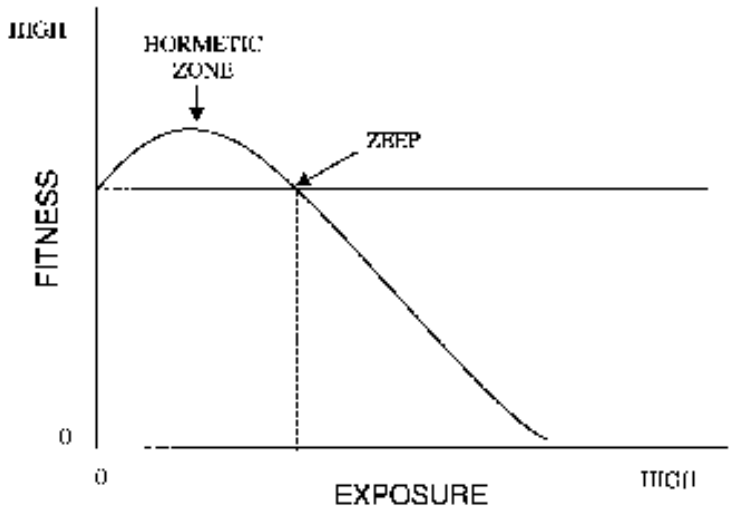
Trewavas A. & Stewart D. 2003. *Curr Opin Plant Biol* 6(2):185-90

A paradoxical effect of a toxic chemical or of radiation at low doses



The most common form of hormesis follows the widely recognized ß-curve

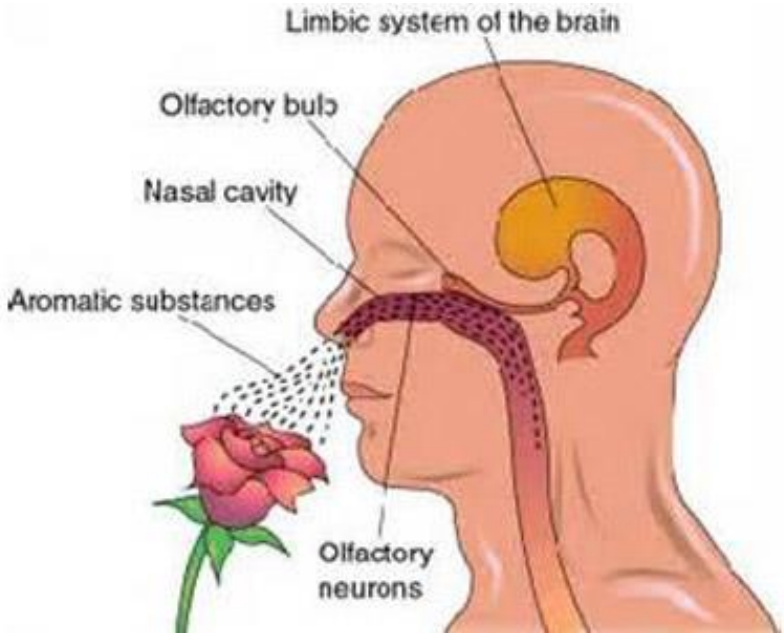
Calabrese EJ, Baldwin LA. 1998. Hormesis as a Biological Hypothesis. *Enviro Health Perspect* 106(S1).

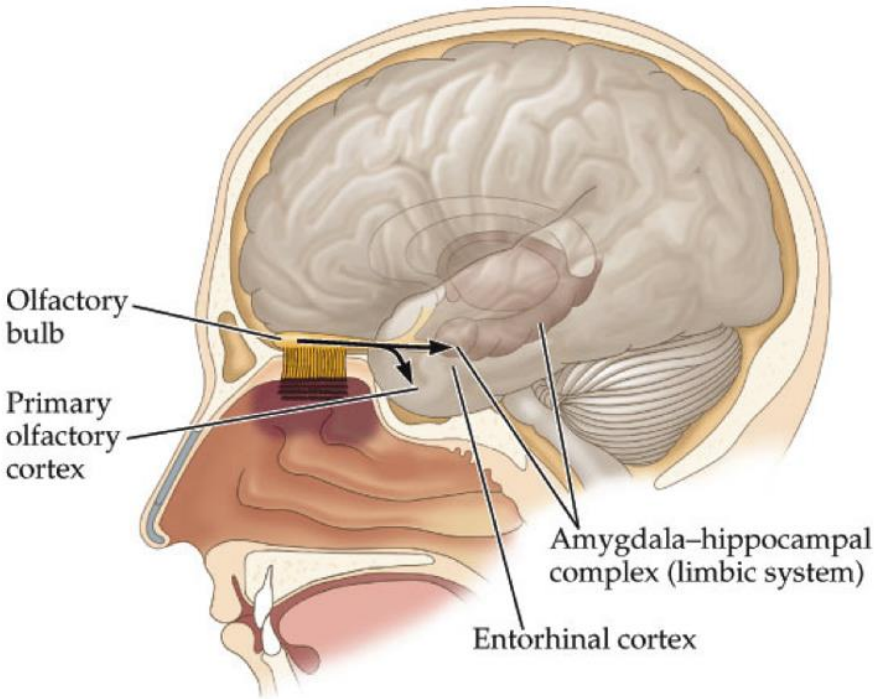


Hormesis Defined

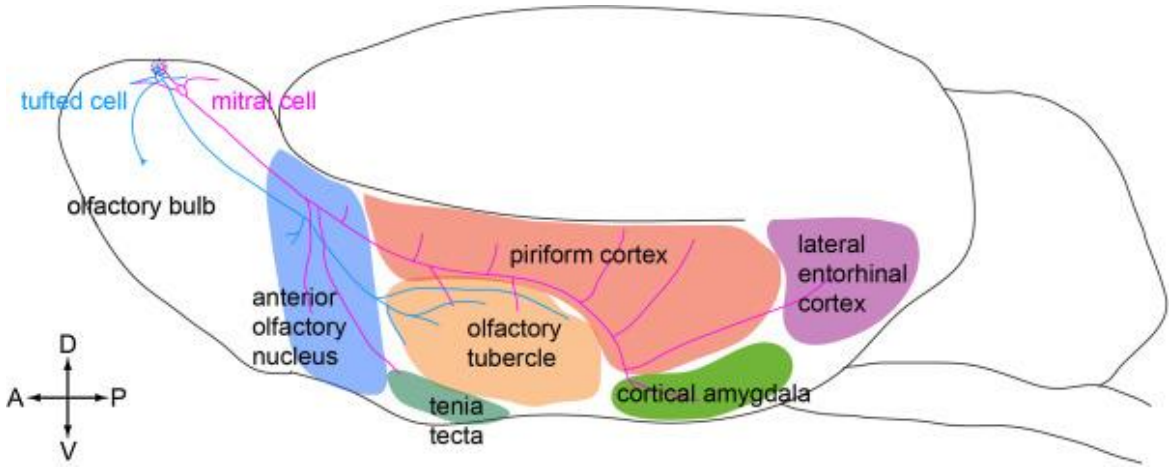
Stebbing ARD. 1982. Hormesis—the stimulation of growth by low levels of inhibitors. *Sci Total Environ* 22:213-234.

Low-dose stimulation followed by higher-dose inhibition


Limbic system of the brain
Olfactory bulb
Nasal cavity
Aromatic substances
Olfactory neurons


Olfactory bulb
Primary olfactory cortex
Amygdala–hippocampal complex (limbic system)
Entorhinal cortex

Piriform Complex Articulates with Amgydala



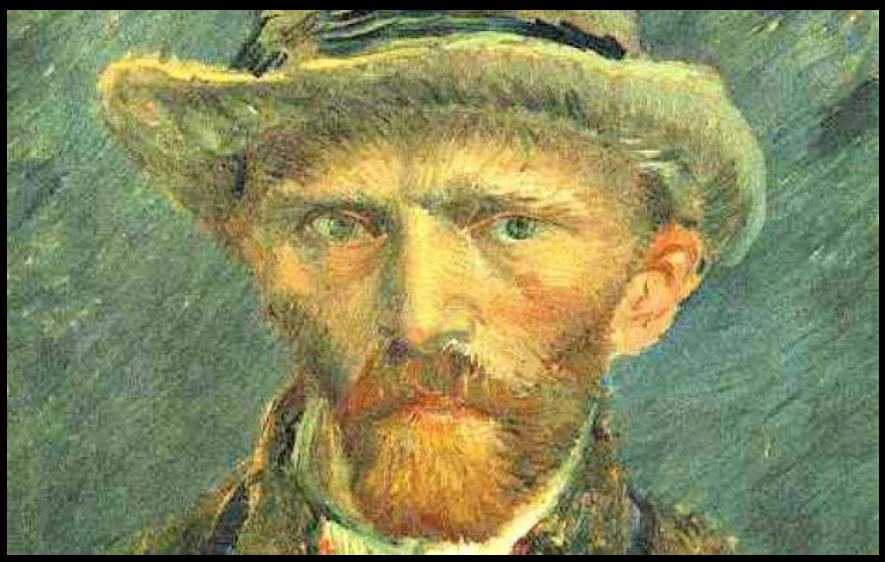
It has been shown that VOCs, pesticides, and other toxins can disturb the cell membrane, allowing Ca++ and Na+ into the cell. When the Ca++ combines with protein kinases A and C and is phosphorylated, it can increase sensitivity by a factor of 1000.

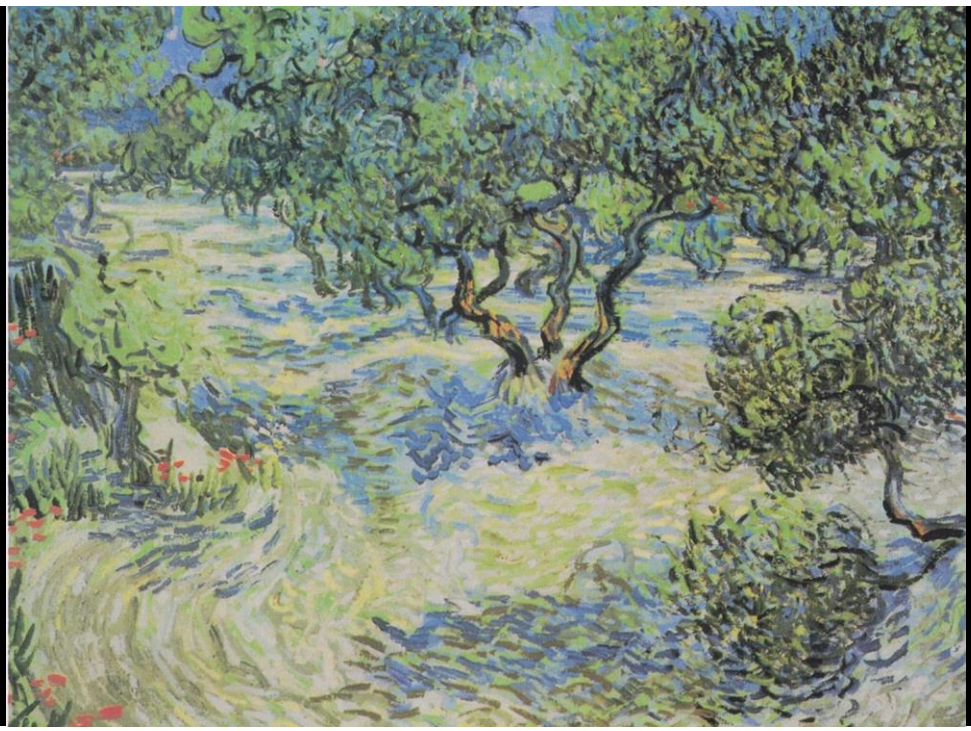
There is evidence that some essential oils interfere with GABA-gated chloride channels.

Guenther A, Karl T, Harley P, Wiedinmyer C, Palmer PI, Geron C. Estimates ofglobal terrestrial isoprene emissions using MEGAN (Model of Emissions of Gases and Aerosols from Nature). *Atmos Chem Phys*. 2006;6(11):3181-3210.

Weterings E, Verkaik NS, Brüggenwirth HT, Hoeijmakers JHJ, and van Gent DC. The role of DNA dependent protein kinase in synapsis of DNA ends. *Nucleic Acids Res*. 2003;31(24):7238-7246.

Koul O, Walia S, Dhaliwal GS. Essentail oils as green pesticides: potentials and constraints. *Biopestic Int* 2008; 4(1):63–84.





ELSEVIER

Biochemical Pharmacology

Volume 43, Issue 11, 9 June 1992, Pages 2359-2368

Porphyrogenic properties of the terpenes camphor, pinene, and thujone: (with a note on historic implications for absinthe and the illness of vincent van gogh)

Herbert L. Bonkovsky [1], Edward E. Cable [1], Julia W. Cable [1], Susan E. Donohue [1], Emily C. White [1], Yvonne

In the presence of any of the three terpenes, the major product that accumulated was protoporphyrin 5-20 fold. The present results indicate that the terpenes tested are porphyrogenic and hazardous to patients with underlying defects in hepatic heme synthesis.

Abstract

Camphor, α-pinene (the major component of turpentine), and thujone (a constituent in

There are also implications for the illness of Vincent van Gogh and the once popular, but now banned liqueur, called absinthe.

which inhibits heme synthesis and thereby mimics the effect of the block associated with acute porphyria), the terpenes enhanced porphyrin accumulation 5- to 20-fold. They also induced synthesis of the rate-controlling enzyme for the pathway, 5-aminolevulinic acid

Proceedings: Indoor Air 2002

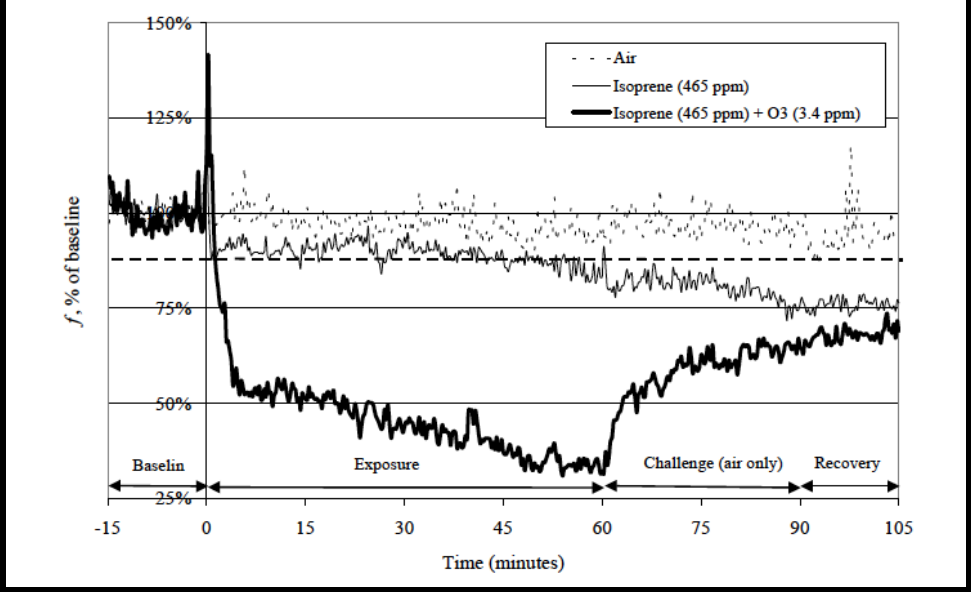
UPPER AIRWAY AND PULMONARY EFFECTS OF TERPENE OXIDATION PRODUCTS IN BALB/C MICE

AC Rohr[1*], CK Wilkins[2], PA Clausen[2], M Hammer[2], GD Nielsen[2], JD Spengler[3], and P Wolkoff[2]

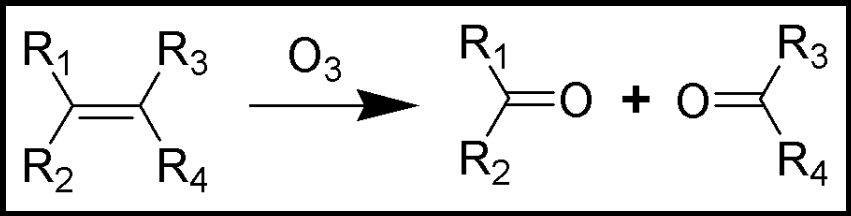
[1]EPRI, Palo Alto, CA, USA
[2]National Institute of Occupational Health, Copenhagen, Denmark
[3]Harvard School of Public Health, Department of Environmental Health, Boston, MA, USA

ABSTRACT

Terpene oxidation products (OPs) have previously been shown to cause upper airway irritation in mice during 30-minute exposures. This study evaluated the effects of the OPs of *d*-limonene, (+)-α-pinene, and isoprene on the upper airways, conducting airways, and lungs over a longer 60-minute exposure period. Respiratory parameters in male BALB/c mice were monitored via head-out plethysmography during exposure to reaction mixtures comprised of 3.4 ppm ozone with 47 ppm α-pinene, 51 ppm *d*-limonene, or 465 ppm isoprene. Upper airway irritation was a prominent effect; however, over the longer exposure period we further observed the development of airflow limitation that persisted for at least 45 minutes post-exposure. These findings suggest that terpene OPs may have moderate-lasting adverse effects on both the upper airways and pulmonary regions, which may be important in the context of lower airway symptoms in office and sawmill workers, or of occupational asthma in cleaning personnel.



Ozonolysis



Journal of Veterinary Emergency and Critical Care

Retrospective Study

Journal of Veterinary Emergency and Critical Care 22(4) 2012, pp 470–475
doi: 10.1111/j.1476-4431.2012.00780.x

Adverse reactions from essential oil-containing natural flea products exempted from Environmental Protection Agency regulations in dogs and cats

Allison G. Genovese, DVM; Mary Kay McLean, MS and Safdar A. Khan, DVM, MS, PhD, DABVT

Dogs and cats can experience significant adverse effects when exposed to plant-derived flea preventatives even when used according to label directions.

plant-derived flea preventatives containing mixtures of essential oils.
Design – Retrospective study from 2006 to 2008.

The number of reports of exposure in cats was higher than dogs, but the frequency of reported adverse effects was similar between the 2 species. Agitation and hypersalivation were common in cats, whereas lethargy and vomiting were common in dogs.

more adverse effects. The frequency of adverse effects in dogs ($n = 8$; 89%) and cats (n = 36; 92%) was similar. Onset time of adverse effects in 39 of 44 animals occurred within 24 hours. The duration of signs in 24 animals ranged from 30 minutes to 149 hours. The products were used as per label in 77% animals ($n = 37$). Of 28 animals with known outcome, 50% ($n = 14$) recovered with bathing alone while others received intravenous fluids, muscle relaxants, and anticonvulsive medications. Death (1 cat; $n = 1/28$; 4%) or euthanasia (1 cat and 1 dog; $n = 2/28$; 7%) was reported in 3 animals.
Conclusion – Dogs and cats can experience significant adverse effects when exposed to plant-derived flea preventatives even when used according to label directions. The number of reports of exposure in cats was higher than dogs, but the frequency of reported adverse effects was similar between the 2 species. Agitation and hypersalivation were common in cats, whereas lethargy and vomiting were common in dogs.

Journal of Veterinary Emergency and Critical Care

Retrospective Study

Journal of Veterinary Emergency and Critical Care 22(4) 2012, pp 470–475
doi: 10.1111/j.1476-4431.2012.00780.x

Clinical signs	Total incidents (48 animals)	Cat incidents (39 cats[a])	Dog incidents (9 dogs[a])
Agitation	10	9 (23%)	1 (11%)
Hypersalivation	8	7 (18%)	1 (11%)
Seizures	7	6 (15%)	1 (11%)
Vocalization	6	6 (15%)	0
Hiding	5	5 (13%)	0
Lethargy	7	5 (13%)	2 (22%)
Tremors	4	4 (10%)	0
Vomiting	4	2 (5%)	2 (22%)
Panting	4	3 (8%)	1 (11%)
Anorexia	3	3 (8%)	0
Ataxia	3	3 (8%)	0
Erythema	3	2 (5%)	1 (11%)
Fasciculation	3	3 (8%)	0
Hyperactivity	3	3 (8%)	0
Hyperthermia	3	1 (3%)	2 (22%)
Hypothermia	3	3 (8%)	0
Weakness	3	2 (5%)	1 (11%)

ORIGINAL RESEARCH

Terpenes and Terpenoids in Chemical Sensitivity

William J. Rea, MD, FACS, FAAEM; Carolina Restrepo, MD; Yaqin Pan, MD

Of 45 chemically sensitive patients, 43 demonstrated sensitivity to terpenes.

targeted by terpenes and terpenoids, resulting in a triggering of symptoms and pathology. Often patients

of the toxics in the order of parts per billion (PPB) and parts per million (PPM). These toxics included formaldehyde

Physicians report terpene responses included spontaneous bruising, petechia,
edema, acne, or inability to walk a straight line with eyes open or closed.

the patients in part 1, followed by a second set of challenges to determine each patient's concurrent sensitivity to terpenes and terpenoids in part 2. In all of the challenges, normal saline was used as a control. A case report illustrates the history of 1 patient and describes the

symptoms 30 min before and at 15-min intervals for 2 h postchallenge. Intradermal challenges recorded wheal size and the provocation of signs and symptoms.

Results • Different numbers of patients were tested for each terpenes source because of time-related factors or the

ACS OMEGA

Article

http://pubs.acs.org/journal/acsodf

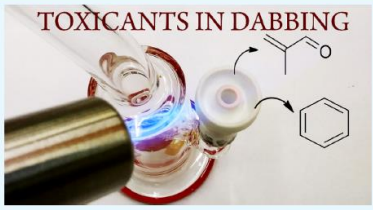
Toxicant Formation in Dabbing: The Terpene Story

Jiries Meehan-Atrash, Wentai Luo, and Robert M. Strongin*

Department of Chemistry, Portland State University, 1719 SW 10th Avenue, Portland, Oregon 97201, United States

Supporting Information

ABSTRACT: Inhalable, noncombustible cannabis products are playing a central role in the expansion of the medical and recreational use of cannabis. In particular, the practice of "dabbing" with butane hash oil has emerged with great popularity in states that have legalized cannabis. Despite their growing popularity, the degradation product profiles of these new products have not been extensively investigated. The study herein focuses on the chemistry of myrcene and other common terpenes found in cannabis extracts. Methacrolein, benzene, and several other products of concern to human health were formed under the conditions that simulated real-world dabbing. The terpene degradation products observed are consistent with those reported in the atmospheric chemistry literature.



INTRODUCTION

Terpenes and terpenoids are present in such a wide diversity of environments (nature, food, cosmetics, pharmaceuticals, and drugs) that their consequences for inhalation toxicology cannot be ignored. Additionally, their inclusion in flavored electronic cigarettes[1] and ubiquitous presence in inhalable cannabis

The principal extract used in dabbing is butane hash oil (BHO). BHO is a resinous, nonpolar extract of the cannabis made using butane as a solvent.[10] BHO has active ingredient (tetrahydrocannabinol (THC) or cannabidiol) contents ranging between 50 and 90%,[8,11] with terpene content ranging from 0.1 to 34% (unpublished). Myrcene is unequivocally the most

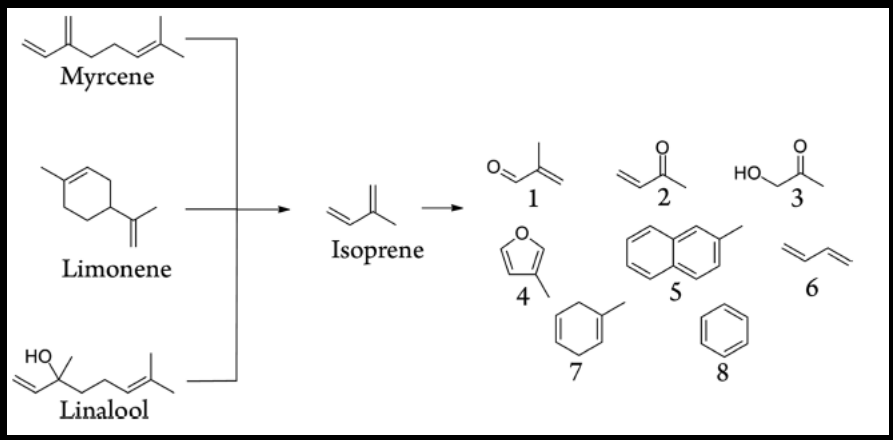
Dabbing

Dabbing

- Terpene content ranging from 0.1 to 34%
  - Myrcene
  - Limonene
  - Linalool
  - Pinene
  - Caryophyllene
  - Humulene

Meehan-Atrash J, Luo W, Strongin RM. Toxicant Formation in Dabbing: The Terpene Story. *ACS Omega* 2017, 2, 6112−6117.

By Products



Acknowledgements

- Ethan Russo, MD – Sharing materials
- Jeff Raber, PhD – use of his study
- Betsy Costillo, MS – research assistant