I terpeni della Cannabis

Caratterizzazione e distribuzione dei terpeni in varietà ad utilizzo medicale e preparazioni galeniche

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UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI MEDICINA VETERINARIA

UNIMONT

Dipartimento di Scienze veterinarie per la Salute la Produzione animale e la Sicurezza alimentare
Vespa

CRC - Gesdimont – UNIMI : centro eccellenza MIUR per le tematiche di sviluppo dei territori montani

UNIMONT

UNIVERSITÀ DEGLI STUDI DI MILANO

MAPPING THE TERRITORY

LANDRACES

NETWORKING

CONSERVATION

Plant roots of Alpine species

TOPICS

VALORISATION

Soil bioengineering
Landraces

Officinal Plants Research Center

Crocus sativus L.
Waldheimia glabra (Decne.) Regel
***Cannabis sativa* L.**
Achillea collina Becker ex Rchb

MEDICINE

PHARMACEUTICS

AGRICULTURE

FOOD

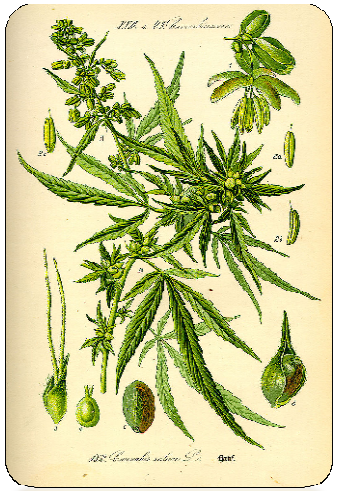
2015

Tesi sperimentale - Scienze e Tecnologie Erboristiche - Università degli Studi di Milano "***Valutazione del contenuto di fitocannabinoidi in cannabis sativa L****. da coltivazione sperimentale del progetto SA.T.I.V.A*."

- **qualità delle preparazioni (tisana/decotto) ad uso terapeutico** che si possono ottenere da fiori e foglie (utilizzo farmaceutico)
- Caratterizzazione qualita' dei **semi** da cui si ricava un olio di eccezionali proprietà benefiche per la salute in termini nutrizionali
- **Oli essenziali –** caratterizzazione terpeni

2017

PROGETTO: caratterizzazione di preparati galenici a base di cannabis ad uso terapeutico



Cannabis sativa L.

Cosa contiene?

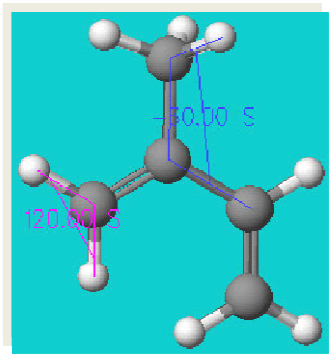
600 composti chimici differenti

Oltre 70
Cannabinoidi naturali
o fitocannabinoidi

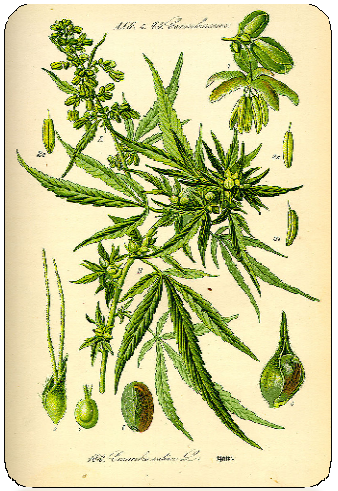
Oltre 100
Terpeni

Flavonoidi

Ma anche...alcani, composti azotati, amminoacidi e proteine, glico-proteine, enzimi, zuccheri, alcoli, chetoni, acidi semplici e acidi grassi, esteri e lattoni, steroidi, fenoli, vitamine e pigmenti



Terpeni



Idrocarburi insaturi negli olii essenziali piante o resine

ISOPRENE (unità costituente)

Classi

Monoterpeni	Sesquiterpeni	Diterpeni	Terpeni ossigenati
2 unità isopreniche	3 unità isopreniche	4 unità isopreniche	1 o più unità isopreniche, con atomi O_2

Monoterpeni
- Limonene
- α-pinene
- Canfene
- δ-3-Carene
- β-Mircene

Sesquiterpeni
- β-Cariofillene
- α-Bergamotene
- α-Umulene
- β-Selinene
- Santalene

Terpeni

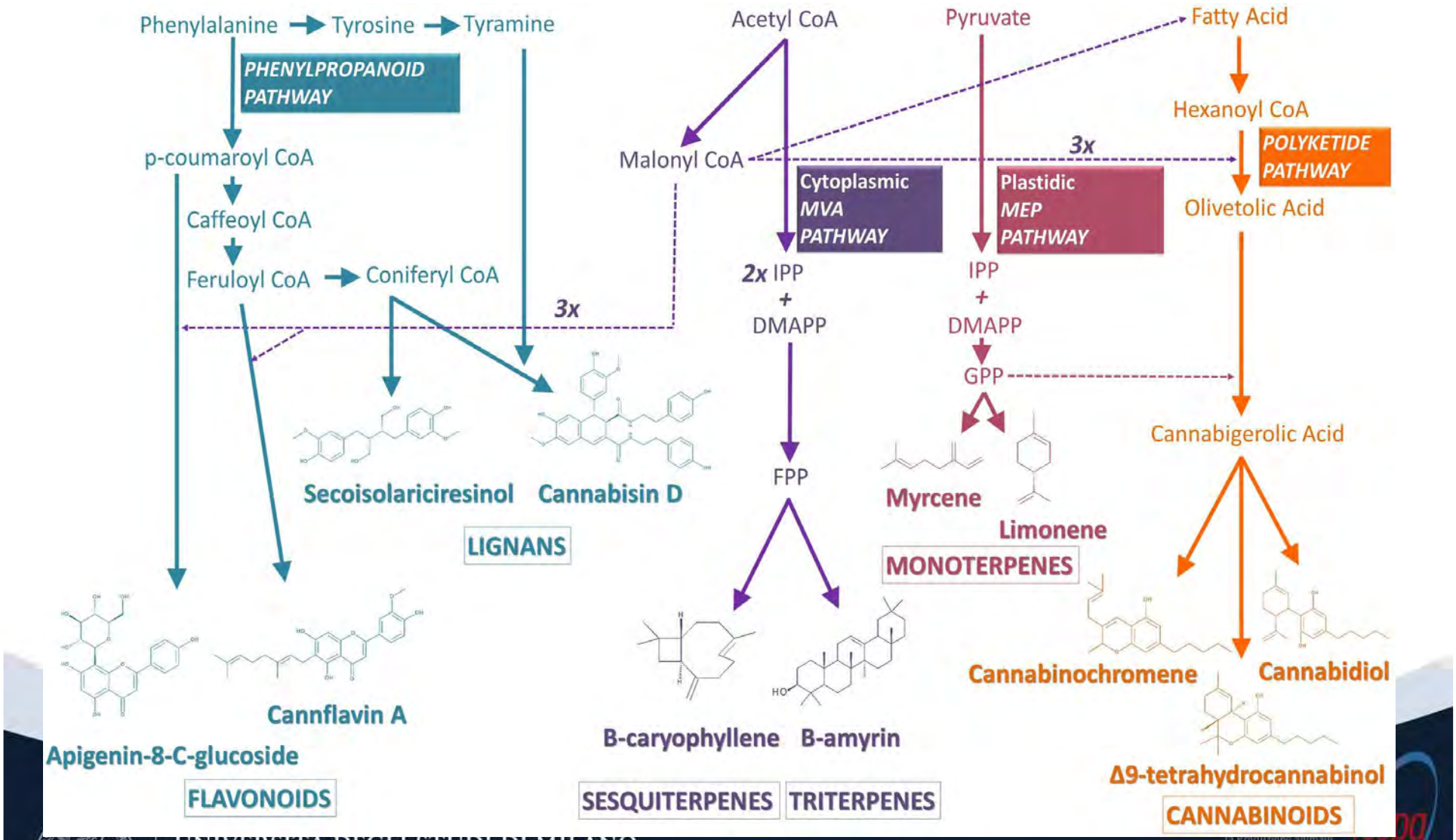
Tricoma (unità anatomica vegetale)

Azione di DIFESA da predatori o ATTRAZIONE per impollinazione

Risposta a stress abiotici (stress idrico, altitudine)

Quantità e qualità sintetizzate dipendono dalla varietà coltivata e dalle tecniche di coltivazione (parametri costanti per produzione flos a **destinazione farmaceutica**)

Terpeni e Pathways biosintesi



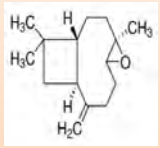
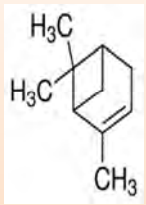
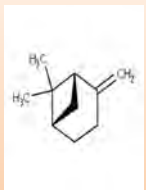
Terpeni – Ruolo

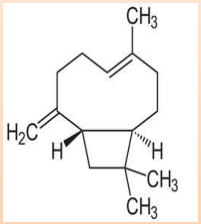
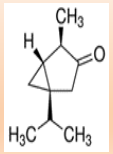
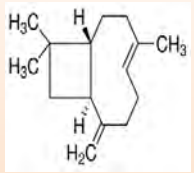
Odore forte e pungente -> contro attacco insetti, funghi e animali erbivori

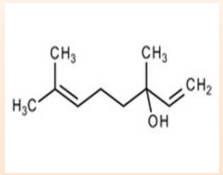
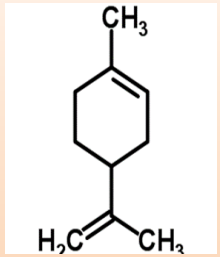
Elementi costitutivi di partenza di molecole complesse e fondamentali per l'organismo (ormoni, vitamine, pigmenti, resine, ecc.)

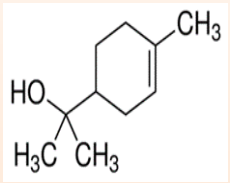
PROPRIETÀ TERAPEUTICHE- studi preliminari

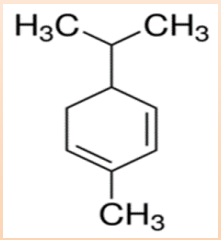
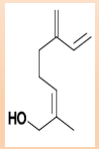
- Effetto gastro-protettivo e **anti-infiammatorio** **β-Cariofillene** (*sapore piccante*, es. Pepe nero)
- Anti-cancerogeno, anti-batterico, anti-depressivo **Limonene** (*odore agrumi*, es. Limone)
- Proprietà **sedative** e anti-ansiolitiche **Linalolo** (*odore lavanda floreale*, es. Lavanda)
- Anti-microbico, analgesico, antiossidante, anti-depressivo e muscolo-rilassante **β-Mircene** (*aroma di chiodi di garofano*, es. Luppolo)
- Aumento concentrazione e **energia** mentale **Pinene** (*odore di erba*, es. Aghi di pino, rosmarino e basilico)

Caryophyllene oxide 	Guava, origano, cinnamomo, chiodi di garofano, pepe nero, melissa eucalypto 	Analgesico Antitumorale Enhancer di principi attivi Antinfiammatorio e antiossidante Battericida e fungicida	A. K. Fidyt, A. Fiedorowicz, L. Strządała, and A. Szumny, "β-caryophyllene and β-caryophyllene oxide—natural compounds of anticancer and analgesic properties," Cancer medicine 5, 3007-3017 (2016). B. S. DI Giacomo, A. DI Sotto, G. Mazzanti, and M. Wink, "Chemosensitizing Properties of beta-Caryophyllene and beta-Caryophyllene Oxide in Combination with Doxorubicin in Human Cancer Cells," Anticancer Res. 37, 1191-1196 (2017). C. S. Sain, P. K Naoghare, S. Saravana Devi, A. Daiwile, K. Krishnamurthi, P. Arrigo, and T. Chakrabarti, "Beta caryophyllene and caryophyllene oxide, isolated from Aegle marmelos, as the potent anti-inflammatory agents against lymphoma and neuroblastoma cells," Anti-Inflammatory & AntiAllergy Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Inflammatory and Anti-Allergy Agents) 13, 45-55 (2014). D. . H. Coté, M. Boucher, A. Pichette, and J. Legault, "Anti-Inflammatory, Antioxidant, Antibiotic, and Cytotoxic Activities of Tanacetum vulgare L. Essential Oil and Its Constituents," Medicines 4, 34 (2017). 68. D. Yang, L. Michel, J. Chaumont, and J. Millet-Clerc, "Use of caryophyllene oxide as an antifungal agent in an in vitro experimental model of onychomycosis," Mycopathologia 148, 79-82 (2000).
α-pinene 	Conifere 	Antitumorale Antiossidante e antinfiammatorio Analgesico Ansiolitico Ipnotico Broncodilatatore	A. A. L. Matsuo, C. R. Figueiredo, D. C. Arruda, F. V. Pereira, J. A. B. Scutti, M. H. Massaoka, L. R. Travassos, P. Sartorelli, and J. H. Lago, "αPinene isolated from Schinus terebinthifolius Raddi (Anacardiaceae) induces apoptosis and confers antimetastatic protection in a melanoma model," Biochem. Biophys. Res. Commun. 411, 449-454 (2011). B. B. W. Q. Chen, B. Xu, J. W. Mao, F. X. Wei, M. Li, T. Liu, X. B. Jin, and L. R. Zhang, "Inhibitory effects of alpha-pinene on hepatoma carcinoma cell proliferation," Asian Pac. J. Cancer. Prev. 15, 3293-3297 (2014). C. M. Porres-Martínez, E. González-Burgos, M. E. Carretero, and M. P. Gómez-Serranillos, "In vitro neuroprotective potential of the monoterpenes α-pinene and 1, 8-cineole against H2O2-induced oxidative stress in PC12 cells," Zeitschrift für Naturforschung C 71, 191-199 (2016). D. M. Porres-Martínez, E. González-Burgos, M. Carretero, and M. Gómez-Serranillos, "Major selected monoterpenes α-pinene and 1, 8-cineole found in Salvia lavandulifolia (Spanish sage) essential oil as regulators of cellular redox balance," Pharm. Biol. 53, 921-929 (2015). E. X. Li, Y. Yang, Y. Li, W. K. Zhang, and H. Tang, "α-Pinene, linalool, and 1-octanol contribute to the topical anti-inflammatory and analgesic activities of frankincense by inhibiting COX-2," J. Ethnopharmacol. 179, 22-26 (2016).
β-pinene 	Conifere 	Antidepressivo Sedativo Antivirale	A.S. Guzmán-Gutiérrez, R. Gómez-Cansino, J. García-Zebadúa, N. Jiménez-Pérez, and R. Reyes-Chilpa, "Antidepressant activity of Litsea glaucescens essential oil: Identification of β-pinene and linalool as active principles," J. Ethnopharmacol. 143, 673-679 (2012). B. S. L. Guzmán-Gutiérrez, H. Bonilla-Jaime, R. Gómez-Cansino, and R. Reyes-Chilpa, "Linalool and β-pinene exert their antidepressant-like activity through the monoaminergic pathway," Life Sci. 128, 24-29 (2015). C. . I. JA Moreira, P. P Menezes, M. R Serafini, A. AS Araújo, L. J Quintans-Júnior, L. R Bonjardim, V. JS Filho, D. BP Júnior, S. L Santos, and W. L Júnior, "Characterization and Antihypertensive Effect of the Complex of (-)-β-pinene in β-cyclodextrin," Curr. Pharm. Biotechnol. 17, 837-845 (2016). 98. A. Astani and P. Schnitzler, "Antiviral activity of monoterpenes beta-pinene and limonene against herpes simplex virus in vitro," Iran. J.

β-caryophyllene 	Chiodi di garofano, rosmarino, pepe nero, lavanda, luppolo 	Antagonista del recettore CB2 Antitumorale Enhancer di principi attivi Neuroprotettore Antiossidante antinfiammatorio Cura dipendenze (alcol) e disturbi alimentari Antimicrobico	A. J. Gertsch, M. Leonti, S. Raduner, I. Racz, J. Z. Chen, X. Q. Xie, K. H. Altmann, M. Karsak, and A. Zimmer, "Beta-caryophyllene is a dietary cannabinoid," Proc. Natl. Acad. Sci. U. S. A. 105, 9099-9104 (2008). B. . K. Fidyt, A. Fiedorowicz, L. Strządała, and A. Szumny, "β-caryophyllene and β-caryophyllene oxide—natural compounds of anticancer and analgesic properties," Cancer medicine 5, 3007-3017 (2016). C. S. DI Giacomo, A. DI Sotto, G. Mazzanti, and M. Wink, "Chemosensitizing Properties of beta-Caryophyllene and beta-Caryophyllene Oxide in Combination with Doxorubicin in Human Cancer Cells," Anticancer Res. 37, 1191-1196 (2017). D. 35. T. B. Alberti, W. L. R. Barbosa, J. L. F. Vieira, N. R. B. Raposo, and R. C. Dutra, "(−)-β-Caryophyllene, a CB2 Receptor-Selective Phytocannabinoid, Suppresses Motor Paralysis and Neuroinflammation in a Murine Model of Multiple Sclerosis," Int. J. Mol. Sci. 18, 691 (2017). E. Ojha, H. Javed, S. Azimullah, and M. E. Haque, "β-Caryophyllene, a phytocannabinoid attenuates oxidative stress, neuroinflammation, glial activation, and salvages dopaminergic neurons in a rat model of Parkinson disease," Mol. Cell. Biochem. 418, 59-70 (2016). F. 29. M. Aghazadeh Tabrizi, P. G. Baraldi, P. A. Borea, and K. Varani, "Medicinal chemistry, pharmacology, and potential therapeutic benefits of cannabinoid CB2
Thujone 	Assenzio e artemisie 	Antagonista del recettore CB1	A. Meschler, J.P., and A.C. Howlett. 1999. Thujone exhibits low affinity for cannabinoid receptors but fails to evoke cannabimimetic responses. Pharmacol Biochem Behav 62:473-480.
Myrcene 	Citronella, alloro, ylang ylang, timo, prezzemolo, basilico, cardamomo, luppolo 	Analgesico Antinfiammatorio Neuroprotettore Protettore della pelle Antitumorale	A.T. Rufino, M. Ribeiro, C. Sousa, F. Judas, L. Salgueiro, C. Cavaleiro, and A. F. Mendes, "Evaluation of the anti-inflammatory, anti-catabolic and pro-anabolic effects of E-caryophyllene, myrcene and limonene in a cell model of osteoarthritis," Eur. J. Pharmacol. 750, 141-150 (2015). B.22. V. Rao, A. Menezes, and G. Viana, "Effect of myrcene on nociception in mice," J. Pharm. Pharmacol. 42, 877-878 (1990). C.G. B. Burcu, C. Osman, C. Aslı, O. M. Namik, and B. T. Neşe, "The protective cardiac effects of B-myrcene after global cerebral ıschemia/reperfusion in C57BL/J6 mouse," Acta cirurgica brasileira 31, 456-462 (2016). D.O. Ciftci, M. N. Oztanir, and A. Cetin, "Neuroprotective effects of β-myrcene following global cerebral ischemia/reperfusion-mediated oxidative and neuronal damage in a C57BL/J6 mouse," Neurochem. Res. 39, 1717-1723 (2014). E.O. Ciftci, I. Ozdemir, S. Tanyildizi, S. Yildiz, and H. Oguzturk, "Antioxidative effects of curcumin, β-myrcene and 1, 8-cineole against 2, 3, 7, 8tetrachlorodibenzo-p-dioxin-induced oxidative stress in rats liver," Toxicol. Ind. Health 27, 447-453 (2011). F.F. Bonamin, T. M. Moraes, R. C. Dos Santos, H. Kushima, F. M. Faria, M. A. Silva, I. V. Junior, L. Nogueira, T. M. Bauab, and A. R. S. Brito, "The effect of a minor constituent of essential oil from Citrus aurantium: The role of β-myrcene in preventing peptic ulcer disease," Chem. Biol. Interact. 212, 11-19 (2014). G.D. Mitić-Ćulafić, B. Žegura, B. Nikolić, B. Vuković-Gačić, J. Knežević-Vukčević, and M. Filipič, "Protective effect of linalool, myrcene and eucalyptol against t-butyl hydroperoxide

Linalolo 	Lavanda 	Antitumorale Antidepressivo Sedativo Analgesico Antiossidante a Antinfiammatorio Antimicrobico	A. M. Chang and Y. Shen, "Linalool exhibits cytotoxic effects by activating antitumor immunity," Molecules 19, 6694-6706 (2014). B. S. L. Guzmán-Gutiérrez, H. Bonilla-Jaime, R. Gómez-Cansino, and R. Reyes-Chilpa, "Linalool and β-pinene exert their antidepressant-like activity through the monoaminergic pathway," Life Sci. 128, 24-29 (2015). C. . P. A. Batista, M. F. Werner, E. C. Oliveira, L. Burgos, P. Pereira, L. F. Brum, G. M. Story, and A. R. Santos, "The antinociceptive effect of (-)linalool in models of chronic inflammatory and neuropathic hypersensitivity in mice," J. Pain 11, 1222-1229 (2010). D. 117. G. Seol, P. Kang, H. S. Lee, and G. H. Seol, "Antioxidant activity of linalool in patients with carpal tunnel syndrome," BMC neurology 16, 17 (2016). E. S. Çelik and A. Ozkaya, "Effects of intraperitoneally administered lipoic acid, vitamin E, and linalool on the level of total lipid and fatty acids in guinea pig brain with oxidative stress induced by H 2 O 2," BMB Reports 35, 547-552 (2002). F. S. Park, Y. K. Lim, M. O. Freire, E. Cho, D. Jin, and J. Kook, "Antimicrobial effect of linalool and α-terpineol against periodontopathic and cariogenic bacteria," Anaerobe 18, 369-372 (2012). G. ogenic bacteria," Anaerobe 18, 369-372 (2012). 126. M. de Oliveira Lima, A. A. de Medeiros, K. S. Silva, G. Cardoso, E. de Oliveira Lima, and F. de Oliveira Pereira, "Investigation of the antifungal potential of linalool against clinical isolates of fluconazole resistant Trichophyton rubrum," Journal de mycologie medicale 27, 195-202 (2017). H. 127. K. V. Silva, M. I. Lima, G. N. Cardoso, A. S. Santos, G. S. Silva, and F. O. Pereira, "Inibitory effects of linalool on fungal pathogenicity of clinical isolates of Microsporum canis and Microsporum gypseum," Mycoses 60, 387-393 (2017). I. I. Dias, E. Trajano, R. Castro, G. Ferreira, H. Medeiros, and D. Gomes, "Antifungal
Limonene 	Citrus, ajwain, Bupleurum gibraltarium, sedano, ebolo, Coniza canadiensis, coriandolo boliviano, luppolo 	Ansiolitico Antidepressivo Immunostimolante Antitumorale Analgesico Antiossidante antinfiammatorio Anticonvulsivante	A. . E. B. Russo, "Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects," Br. J. Pharmacol. 163, 1344-1364 (2011) B. P. A. d'Alessio, J. Bisson, and M. C. Béné, "Anti-stress effects of d-limonene and its metabolite perillyl alcohol," Rejuvenation research 17, 145-149 (2014). C. P. L. Crowell, A. S. Ayoubi, and Y. D. Burke, "Antitumorigenic effects of limonene and perillyl alcohol against pancreatic and breast cancer," in Dietary Phytochemicals in Cancer Prevention and Treatment, Anonymous (Springer, 1996), pp. 131-136. D. 139. J. F. do Amaral, M. I. G. Silva, de Aquino Neto, Manuel Rufino Aquino, P. F. T. Neto, B. A. Moura, de Melo, Carla Thiciane Vasconcelos, de Araújo, Fernando Luiz Oliveira, D. P. de Sousa, P. F. de Vasconcelos, and de Vasconcelos, Silvânia Maria Mendes, "Antinociceptive effect of the monoterpene R-( )-limonene in mice," Biol. Pharm. Bull. 30, 1217-1220 (2007). E. M. U. Rehman, M. Tahir, A. Q. Khan, R. Khan, Oday-O-Hamiza, A. Lateef, S. K. Hassan, S. Rashid, N. Ali, and M. Zeeshan, "D-limonene suppresses doxorubicin-induced oxidative stress and inflammation via repression of COX-2, iNOS, and NFκB in kidneys of Wistar rats," Exp. Biol. Med. 239, 465-476 (2014). F. H. Rajak, B. S. Thakur, A. Singh, K. Raghuvanshi, A. K. Sah, R. Veerasamy, P. C. Sharma, R. S. Pawar, and M. D. Kharya, "Novel limonene and citral based 2, 5-disubstituted-1, 3, 4-oxadiazoles: a natural product coupled approach to semicarbazones for antiepileptic activity," Bioorg. Med. Chem. Lett. 23, 864-868 (2013).

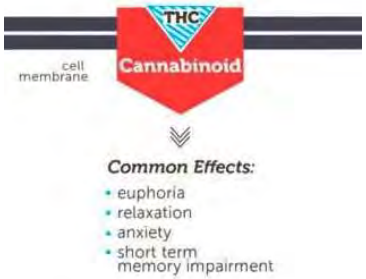
Terpineolo  	tea tree, maleleuca, pino, arancio amaro, lilla, eucalypto, lavanda 	Antitumorale Anticonvulsivante e Antispasmodico Sedativo Neuroprotettore e gastroprotettore Broncodilatatore Antinfiammatorio Antimicrobico	A. S. B. Hassan, H. Gali-Muhtasib, H. Goransson, and R. Larsson, "Alpha terpineol: a potential anticancer agent which acts through suppressing NF-kappaB signalling," Anticancer Res. 30, 1911-1919 (2010). B. F. F. Nobrega, M. G. Salvadori, C. J. Masson, C. F. Mello, T. S. Nascimento, J. H. Leal-Cardoso, D. P. de Sousa, and R. N. Almeida, "Monoterpenoid terpinen-4-ol exhibits anticonvulsant activity in behavioural and electrophysiological studies," Oxid Med. Cell. Longev 2014, 703848 (2014). C. G. Buchbauer, L. Jirovetz, W. Jáger, C. Plank, and H. Dietrich, "Fragrance compounds and essential oils with sedative effects upon inhalation," J. Pharm. Sci. 82, 660-664 (1993). D. A. N. S. Gondim, A. Lara, A. Santos-Miranda, D. Roman-Campos, S. Lauton-Santos, J. E. R. Menezes-Filho, de Vasconcelos, Carla Maria Lins, E. A. Conde-Garcia, S. Guatimosim, and J. S. Cruz, "(-)-Terpinen-4-ol changes intracellular Ca2 handling and induces pacing disturbance in rat hearts," Eur. J. Pharmacol. 807, 56-63 (2017). E. M. Moghimi, S. Parvardeh, T. M. Zanjani, and S. Ghafghazi, "Protective effect of alpha-terpineol against impairment of hippocampal synaptic plasticity and spatial memory following transient cerebral ischemia in rats," Iran. J. Basic Med. Sci. 19, 960-969 (2016). F. R. Souza, M. Cardoso, C. Menezes, J. Silva, D. De Sousa, and J. Batista, "Gastroprotective activity of alpha-terpineol in two experimental models of gastric ulcer in rats," Daru 19, 277-281 (2011). G. W. Zhu, X. Liu, Y. Wang, Y. Tong, and Y. Hu, "Discovery of a novel series of α-terpineol derivatives as promising anti-asthmatic agents: Their design, synthesis, and biological evaluation," Eur. J. Med. Chem. 143, 419-425 (2018). H. gn, synthesis, and biological evaluation," Eur. J. Med. Chem. 143, 419-425 (2018). 217. S. Held, P. Schieberle, and V. Somoza, "Characterization of α-terpineol as an anti-inflammatory component of orange juice by in vitro studies using oral buccal cells," J. Agric. Food Chem. 55, 8040-8046 (2007). I. . H. Trinh, I. Lee, Y. Hyun, and D. Kim, "Artemisia princeps Pamp. Essential oil and its constituents eucalyptol and α-terpineol ameliorate bacterial vaginosis and vulvovaginal candidiasis in mice by inhibiting bacterial growth and NF-κB activation," Planta Med. 77, 1996-2002 (2011). J. . L. Li, C. Shi, Z. Yin, R. Jia, L. Peng, S. Kang, and Z. Li, "Antibacterial activity of α-terpineol may induce morphostructural alterations in Escherichia coli," Brazilian J. Microbiol. 45, 1409-1413 (2014). K. S. Park, Y. K. Lim, M. O. Freire, E. Cho, D. Jin, and J. Kook, "Antimicrobial effect of
α-Terpinene	Tea tree, litsea celanica 	Antiossidante Antimicrobico	A. G. Li and Z. Liu, "Unusual antioxidant behavior of α-and γ-terpinene in protecting methyl linoleate, DNA, and erythrocyte," J. Agric. Food Chem. 57, 3943-3948 (2009). 189 B. M. D. Baldissera, T. H. Grando, C. F. Souza, L. T. Gressler, L. M. Stefani, A. S. da Silva, and S. G. Monteiro, "In vitro and in vivo action of terpinen-4-ol, γ-terpinene, and α-terpinene against Trypanosoma evansi," Exp. Parasitol. 162, 43-48 (2016).

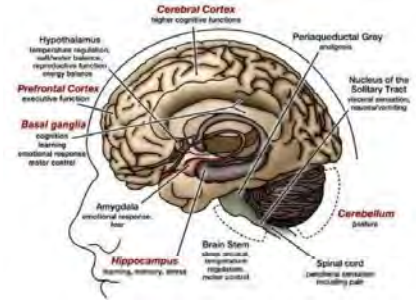
α-Phellandrene 	**Eucalyptus phellandra, water fennel, Schinus terebinthifolius** 	**Immunostimolante** **Antinfiammatorio** **Antidepressivo** **antimicrobico**	A. J. J. Lin, K. W. Lu, Y. S. Ma, N. Y. Tang, P. P. Wu, C. C. Wu, H. F. Lu, J. G. Lin, and J. G. Chung, "Alpha-phellandrene, a natural active monoterpene, influences a murine WEHI-3 leukemia model in vivo by enhancing macrophague phagocytosis and natural killer cell activity," In Vivo 28, 583-588 (2014). B. H. D. S. Siqueira, B. S. Neto, D. P. Sousa, B. S. Gomes, F. V. da Silva, F. V. Cunha, C. W. Wanderley, G. Pinheiro, A. G. Cândido, and D. V. Wong, "α-Phellandrene, a cyclic monoterpene, attenuates inflammatory response through neutrophil migration inhibition and mast cell degranulation," Life Sci. 160, 27-33 (2016) C. D. F. Lima, M. S. Brandão, J. B. Moura, J. M. Leitão, F. A. Carvalho, L. M. Miúra, J. R. Leite, D. P. Sousa, and F. R. Almeida, "Antinociceptive activity of the monoterpene α -phellandrene in rodents: possible mechanisms of action," J. Pharm. Pharmacol. 64, 283-292 (2012) D. ty of the monoterpene α -phellandrene in rodents: possible mechanisms of action," J. Pharm. Pharmacol. 64, 283-292 (2012). 361. J. Zhang, H. Sun, S. Chen, L. Zeng, and T. Wang, "Anti-fungal activity, mechanism studies on α-Phellandrene and Nonanal against Penicillium cyclopium," Botanical studies 58, 13 (2017). E. G. Đşcan, N. Kırımer, F. Demirci, B. Demirci, Y. Noma, and K. Başer, "Biotransformation of (−)-(R)-α-Phellandrene: Antimicrobial Activity of Its Major Metabolite," Chem. Biodiv. 9, 1525-1532 (2012).
Myrcenolo 	**luppolo** 	**Sedativo**	A. H. Aoshima, K. Takeda, Y. Okita, S. J. Hossain, H. Koda, and Y. Kiso, "Effects of beer and hop on ionotropic γ-aminobutyric acid receptors," J. Agric. Food Chem. 54, 2514-2519 (2006)

Terpeni e Cannabinoidi

Recettori dei cannabinoidi:

CB1 (Sistema Nervoso Centrale)
CB2 (Sistema Immunitario)





Effetto "entourage"

Attività farmacologica dei terpeni e sinergia con cannabinoidi

Terpeni agiscono attivamente sui recettori/enzimi cerebrali e sul loro modo di funzionare

⇩

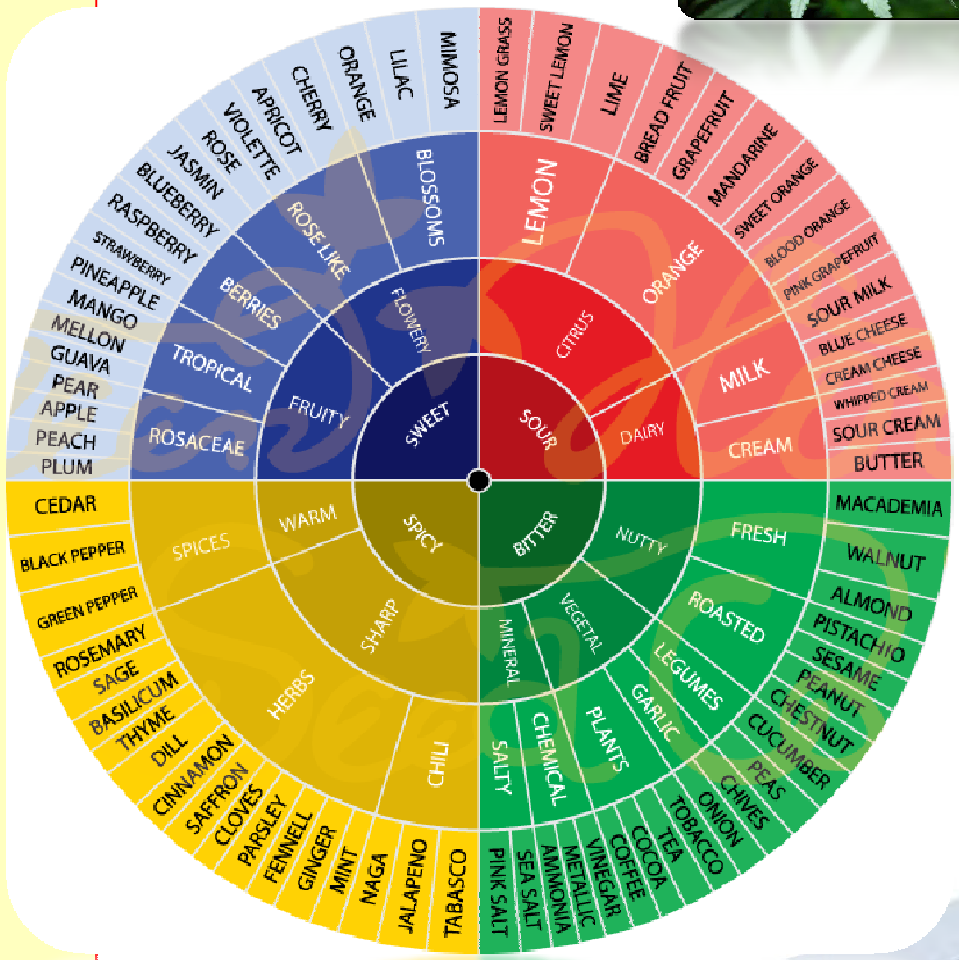
Modificano permeabilità delle cellule modulando transito THC da sangue a cellule neuronali (Russo et al, 2005)

Full spectrum !!!

"High - Δ ^{9} - tetrahydrocannabinol and high-myrcene chemovars dominate markets, these may not be optimal for patients who require distinct chemical profiles to achieve symptomatic relief" *Lewis, Russo 2018 - Planta Medica*

Caratteristiche olfattive di alcuni composti terpenici

α-Pinene	Pungente, di pino
Canfene	Di canfora
Verbenene	Speziato, di menta , canfora
β-Pinene	Fragrante,fresco, di pino
β-Mircene	Fragrante, fresco, di luppolo
2-carene	Dolce , fruttato, pungente
α-Fellandrene	Balsamico, dolce, fresco
β–Fellandrene	Balsamico, dolce, fresco
4-carene	Agrumi e bergamotto
Limonene	Fruttato, di agrumi
β-Ionone	Legnoso, balsamico, floreale, di rosa
Eucaliptolo	Balsamico, fresco , di eucalipto
Fencone	Fresco, canforaceo
Trans-pinocarveolo	Legnoso, balsamico, di finocchio
Tuiolo	Legnoso, di resina
Allocimene	Speziato, erbaceo
Linaloolo	Floreale, di agrumi, legnoso
Fencolo	Limone
α-Farnesene	Delicato,floreale, oleoso
Eugenolo	Forte, speziato, di cannella
α-Terpinene	Legnoso, di agrumi
β-Terpineolo	Floreale, fruttato, di lillà
γ-Terpinene	Di agrumi, legnoso
α-Fenchene	Caldo, dolce
Canfora	Aromatico, legnoso, medicinale



- **S. Panseri**, L.M. Chiesa, N. Nanayakkarawasam M.C. Nanayakkara, M. Mattara, A. Giorgi (2011). "Comparison Of Volatile Compounds Induced By Aphids And Mechanical Damage In *Achillea Collina*". Acta horticulturae, 955:1, pp. 275-280
- **S. Panseri** A. Giorgi,, C. Nanayakkarawasam Masachchige, L. M. Chiesa (2012). "HS-SPME-GC/MS Analysis of the volatile compounds of *Achillea collina*: Evaluation of the emissions fingerprint induced by Myzus persicae infestation" Journal Of Plant Biology 55: 251-260.

Tipologie di assunzione

Galenica: macerati oleosi

-Romano, Hazekamp “Cannabis Oil: chemical evaluation of an upcoming cannabis-based medicine”

-Citti, Cannazza : Medicinal cannabis: Principal cannabinoids concentration and their stability evaluated by a high performance liquid chromatography coupled to diode array and quadrupole time of flight mass spectrometry method

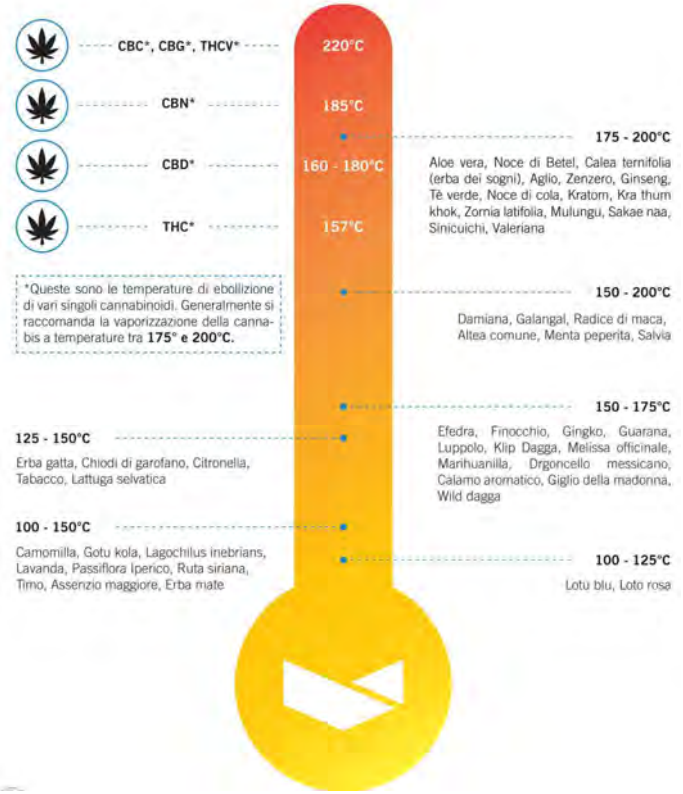
-Calvi et al. Comprehensive quality evaluation of medical Cannabis sativa L. inflorescence and macerated oils based on HS-SPME coupled to GC–MS and LC-HRMS (Q-exactive orbitrap®)

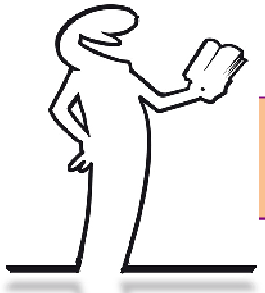
- Casiraghi, et al. Extraction Method and Analysis of Cannabinoids in Cannabis Olive Oil Preparations (SIFAP)

Vaporizzazione inflorescenze

175 - 210°C (Cannabinoidi)

>140 °C (Terpeni)





I terpeni nelle inflorescenze ad uso terapeutico

Inflorescenze ad utilizzo terapeutico – diversi chemotipi

BEDROCAN®

THC 22% | CBD <1.0%
Flos

BEDROBINOL®

THC 13.5% | CBD <1.0%
Flos

BEDIOL®

THC 6.3% | CBD 8%
Granulare

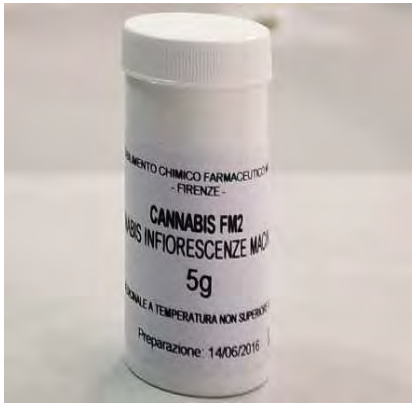
BEDICA®

THC 14% | CBD <1.0%
Granulare

BEDROLITE®

THC <1.0% | CBD 9%
Granulare

Bedrocan



SCFM – Firenze (FM2, FM1)

Pedanios - Aurora (22/1, 1/12)

Fitocomplessi diversi/chemotipi !!

Dipartimento di Scienze veterinarie per la Salute la Produzione animale e la Sicurezza alimentare

Terpeni : approccio analitico moderno

Microestrazione su fase solida accoppiata alla gas-cromatografia e spettrometria di massa (HS-SPME-GC/MS)

HS-SPME-GC/MS

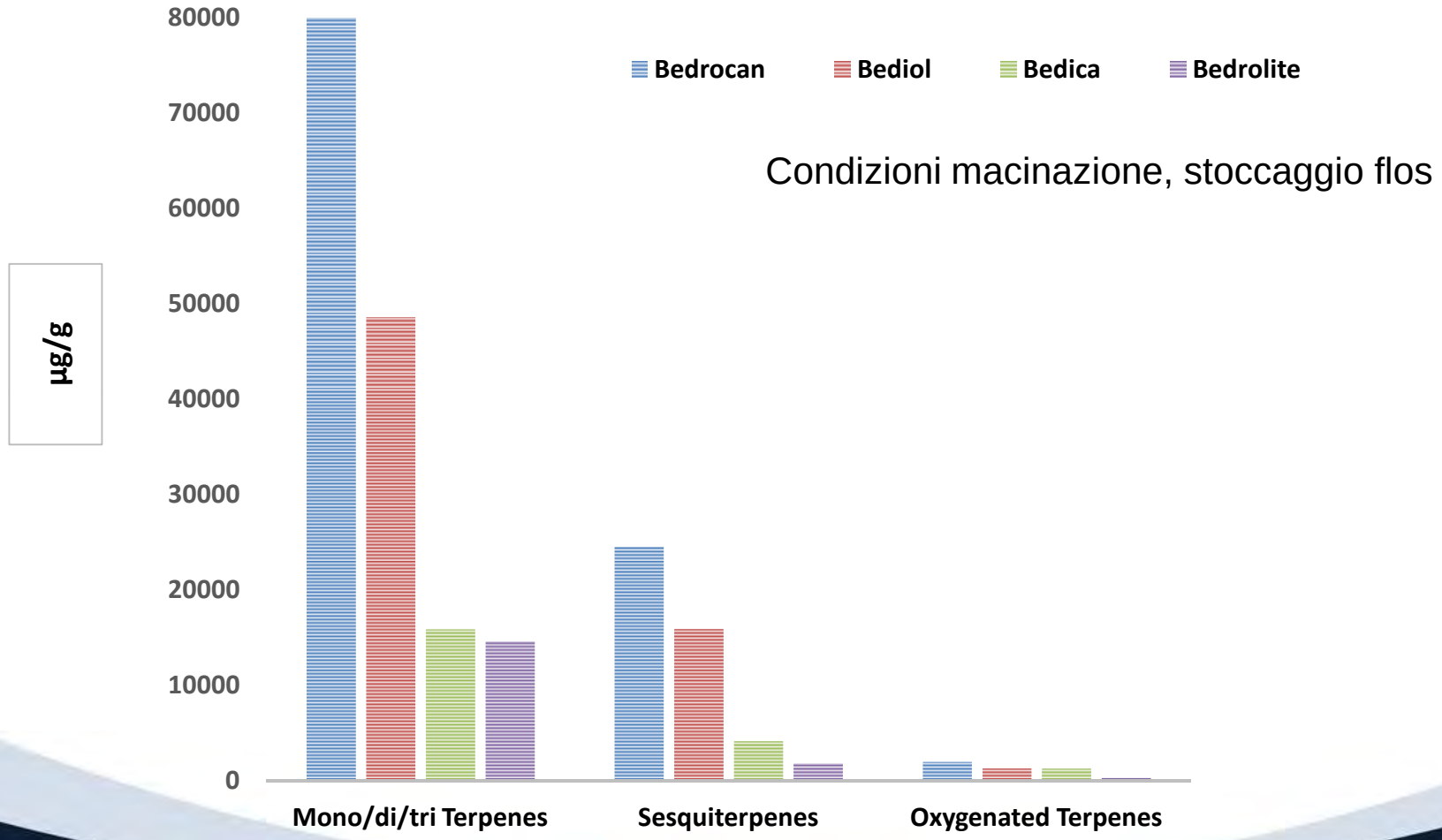
Spazio di testa

Vial con campione
(100 mg Cannabis flos o 1g olio)

Tecnica non distruttiva del campione ---- rilevare le caratteristiche dei terpeni da fitocomplessi (>100 composti flos; >30 composti oli)

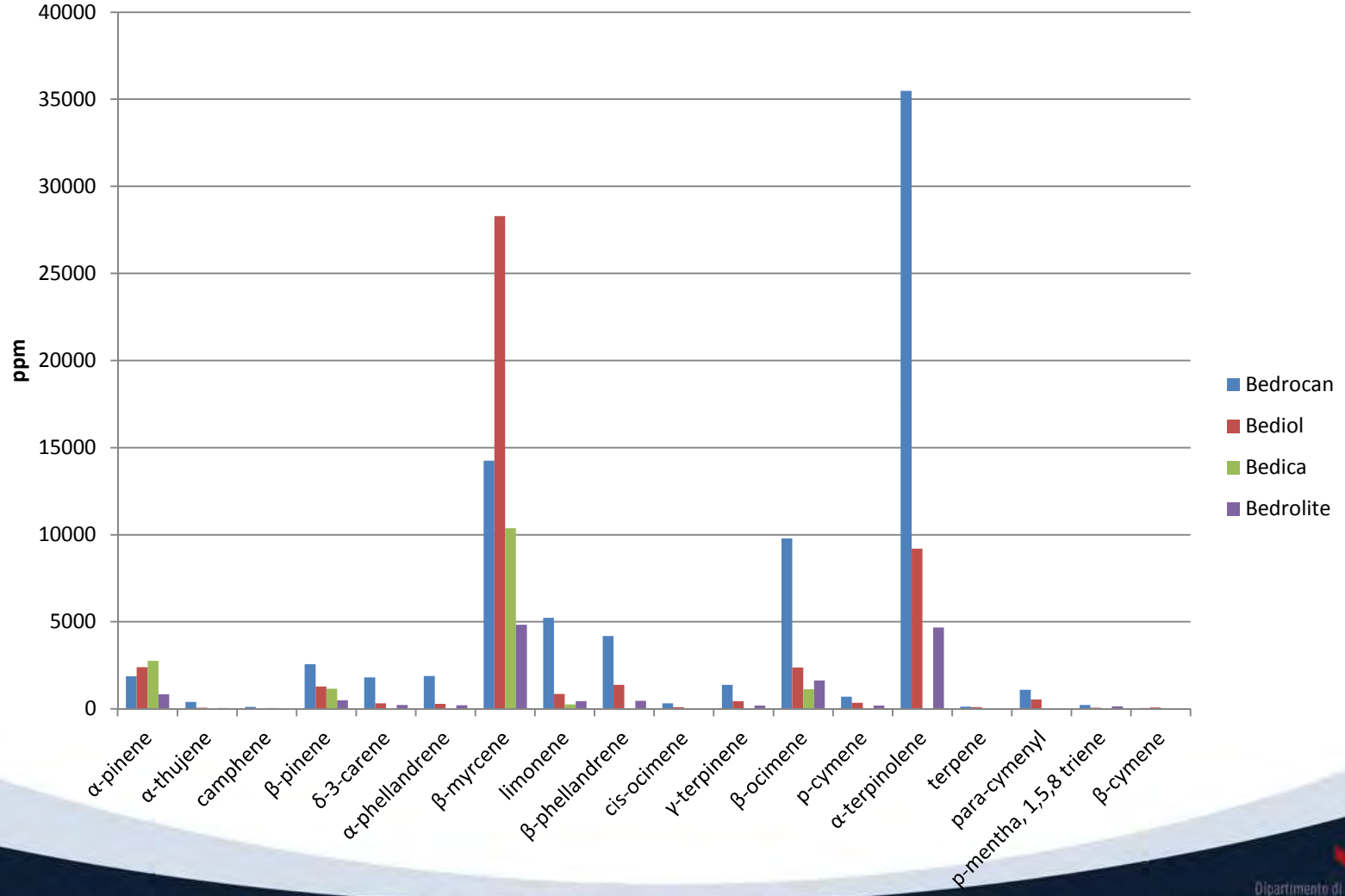
- **S. Panseri**, L.M. Chiesa, N. Nanayakkarawasam M.C. Nanayakkara, M. Mattara, A. Giorgi (2011). "Comparison Of Volatile Compounds Induced By Aphids And Mechanical Damage In *Achillea Collina*". Acta horticulturae, 955:1, pp. 275-280
- **S. Panseri** A. Giorgi,, C. Nanayakkarawasam Masachchige, L. M. Chiesa (2012). "HS-SPME-GC/MS Analysis of the volatile compounds of *Achillea collina*: Evaluation of the emissions fingerprint induced by Myzus persicae infestation" Journal Of Plant Biology 55: 251-260.
- Calvi L., Pentimalli D**., Panseri S.,** Giupponi L., Gelmini F., Beretta G., Vitali D., Bruno M., Zilio E., Pavlovic R., Giorgi A. (2018) Comprehensive quality evaluation of medical Cannabis sativa L. inflorescence and macerated oils based on HS-SPME coupled to GC-MS and LC-HRMS (Q-Exactive Orbitrap®) approach. Journal of Pharmaceutical and Biomedical Analysis 150 (2018) 208–219

Classi di terpeni rappresentativi in Bedrocan, Bediol, Bedica e Bedrolite



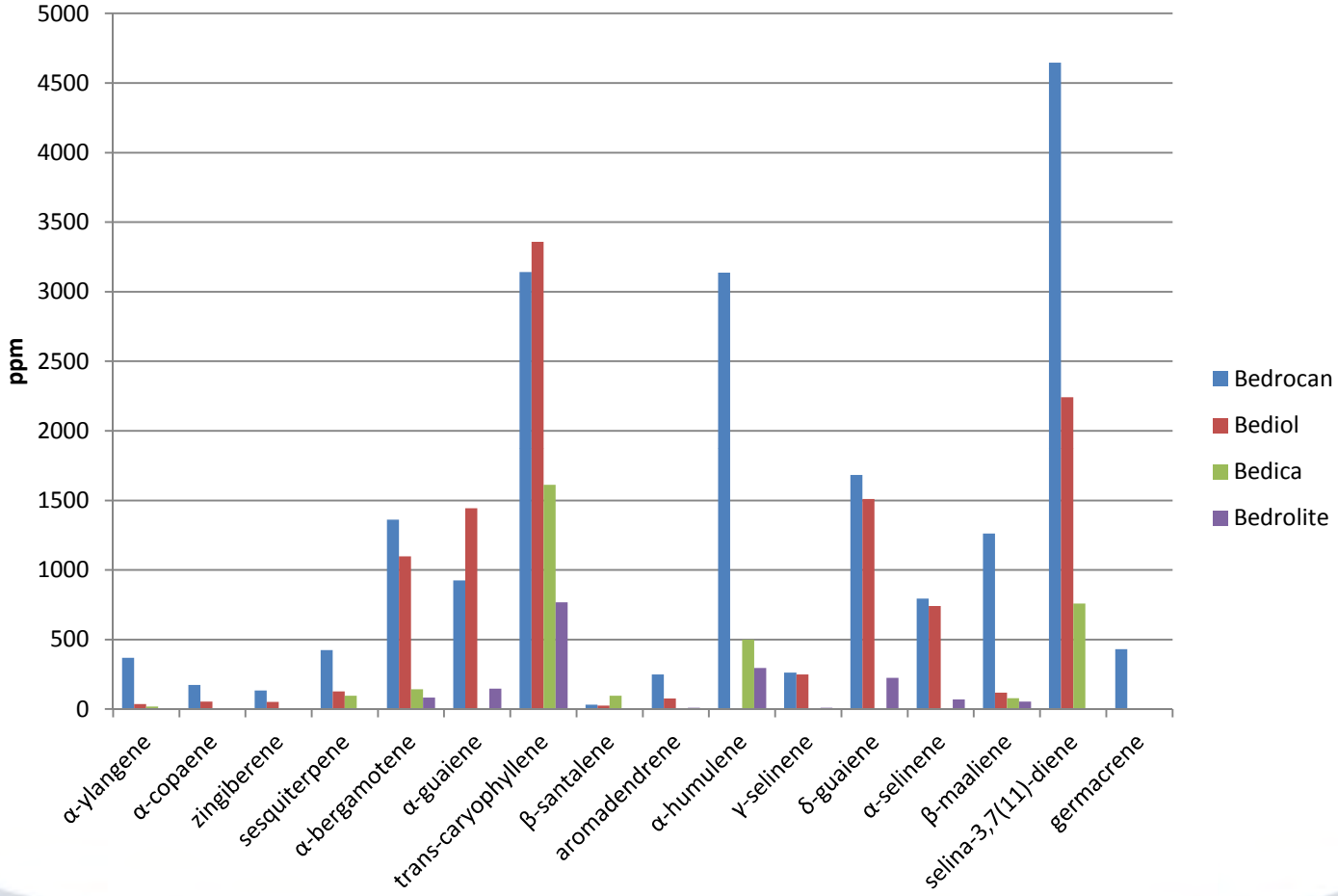
Contenuto di terpeni rappresentativi Bedrocan, Bediol, Bedica e Bedrolite

Mono-di-tri terpeni



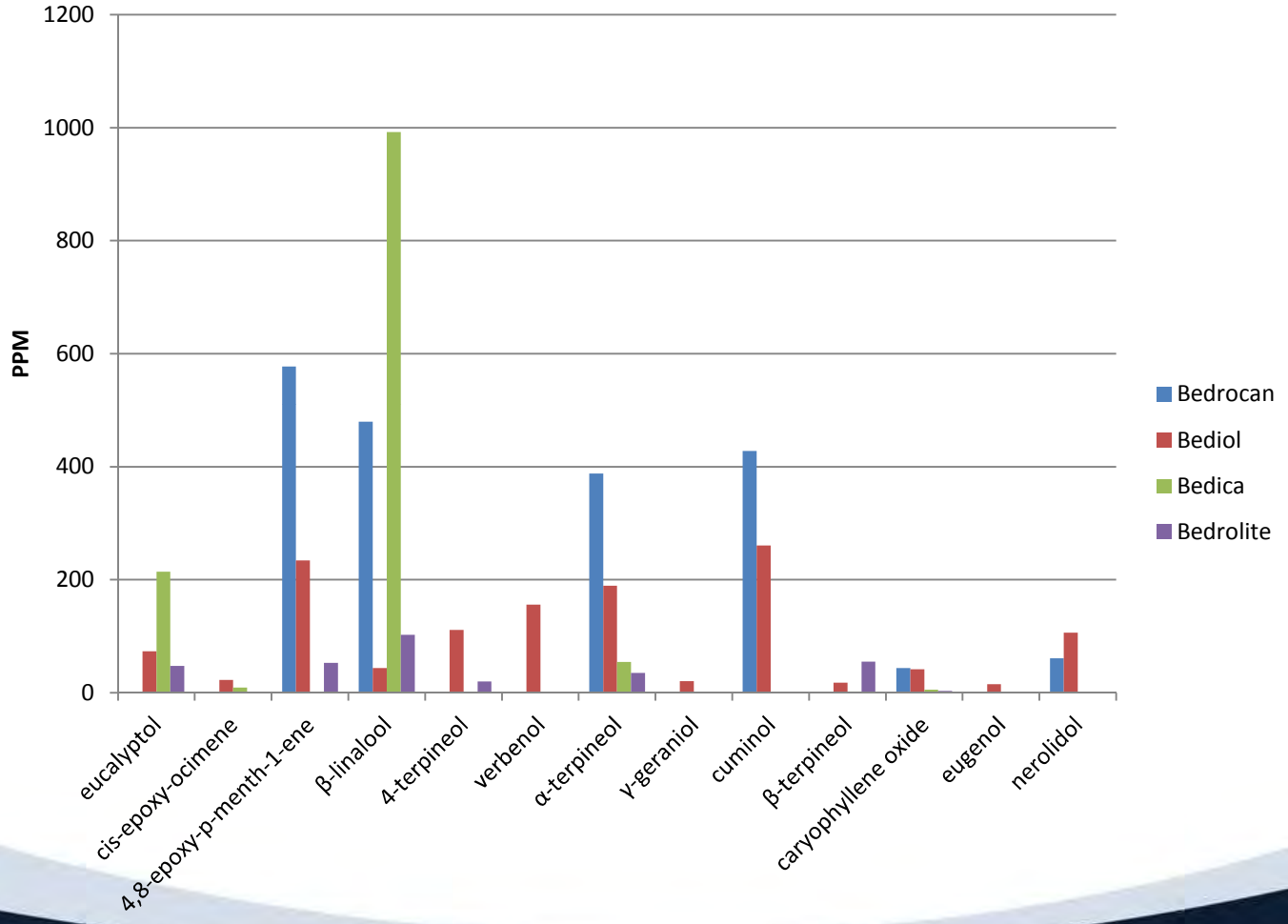
Contenuto di terpeni rappresentativi Bedrocan, Bediol, Bedica e Bedrolite

Sesquiterpeni



Contenuto di terpeni rappresentativi Bedrocan, Bediol, Bedica e Bedrolite

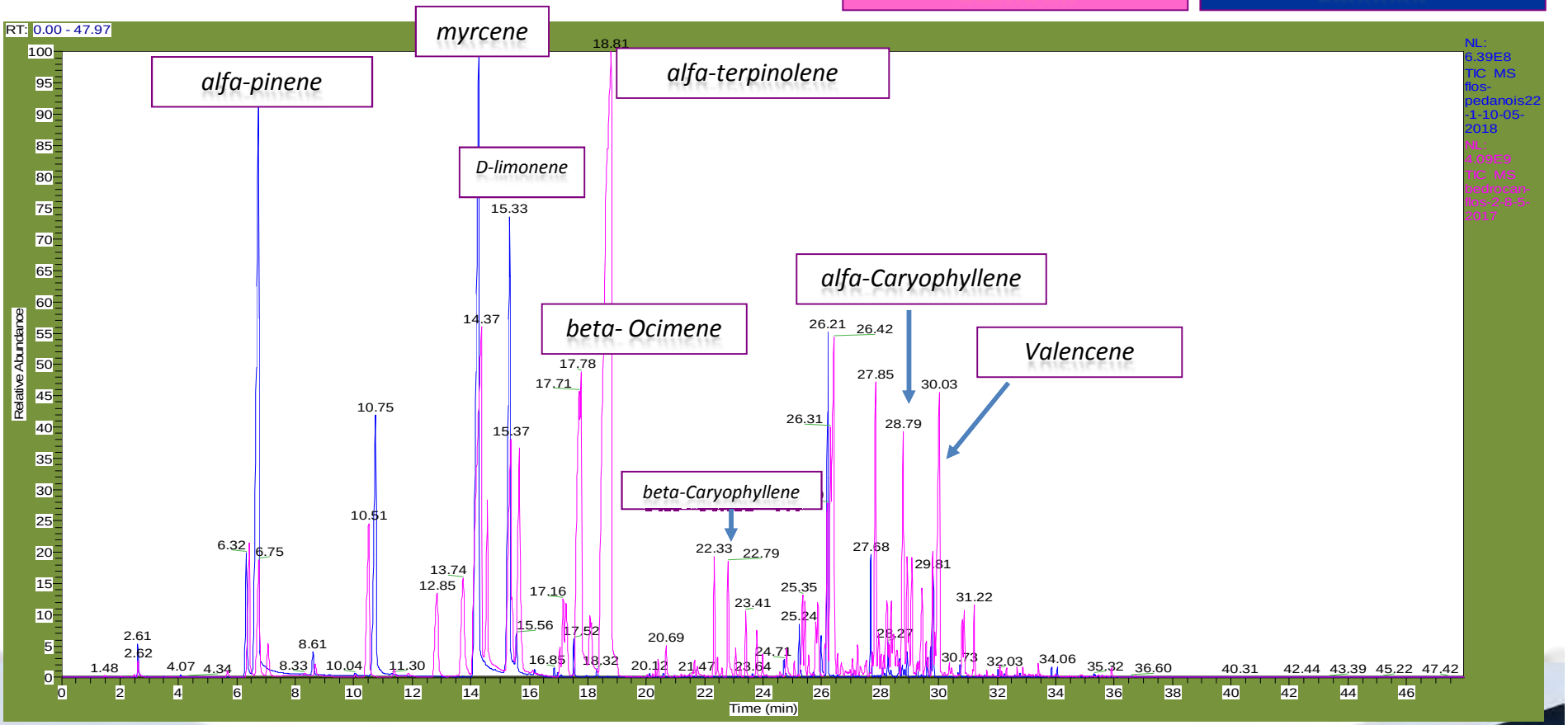
Terpeni ossigenati



Representative terpene profile of Bedrocan and Pedanios 22/1 (TIC-Headspace-SPME and GC/MS)

Alto contenuto THC

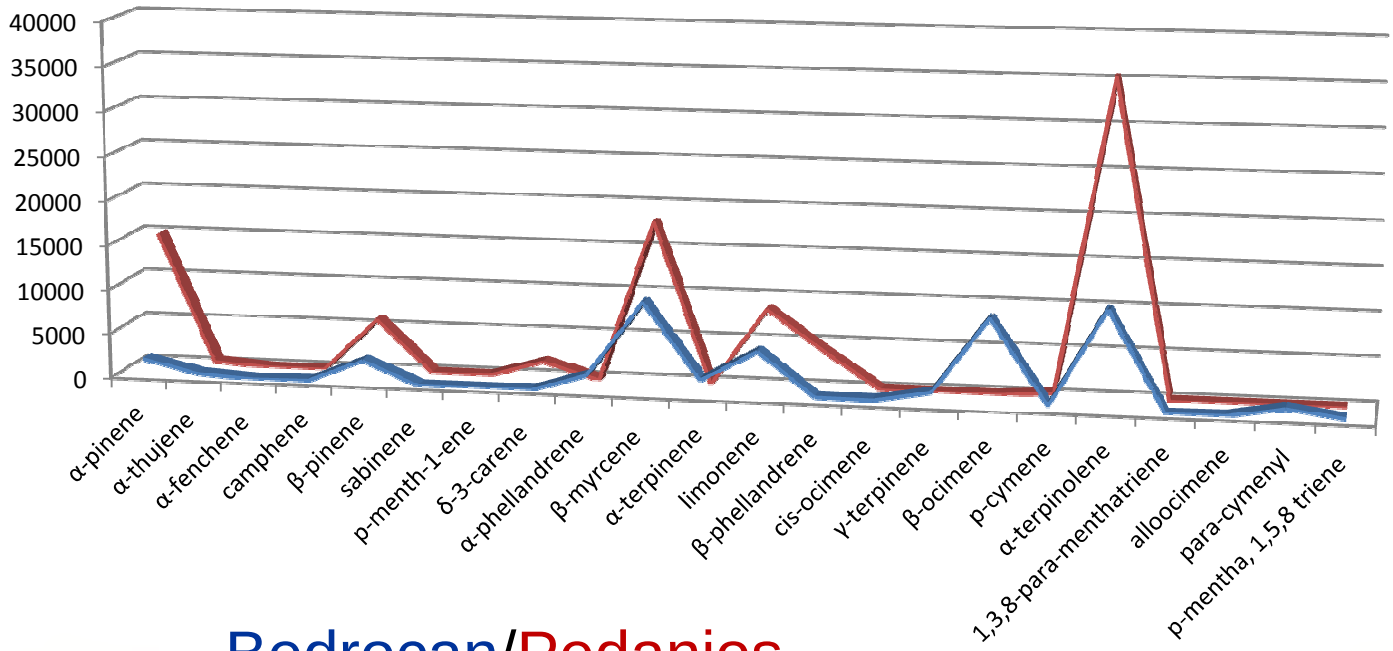
Bedrocan | *Pedanios*



Different concentrations and compounds absent / present in the two chemotypes

Representative terpene profile of Bedrocan and Pedanios 22/1

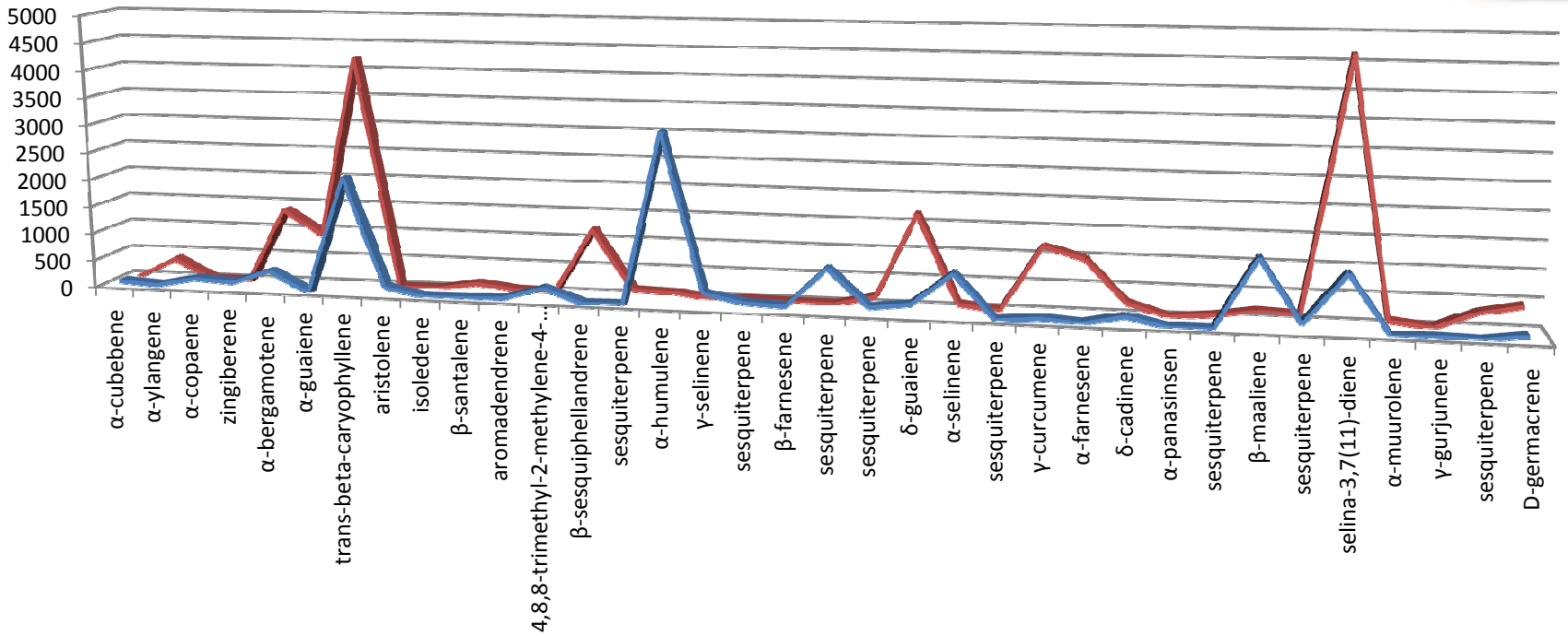
Mono-di-triterpeni (22 composti)



Bedrocan/Pedanios

Representative terpene profile of Bedrocan and Pedanios 22/1

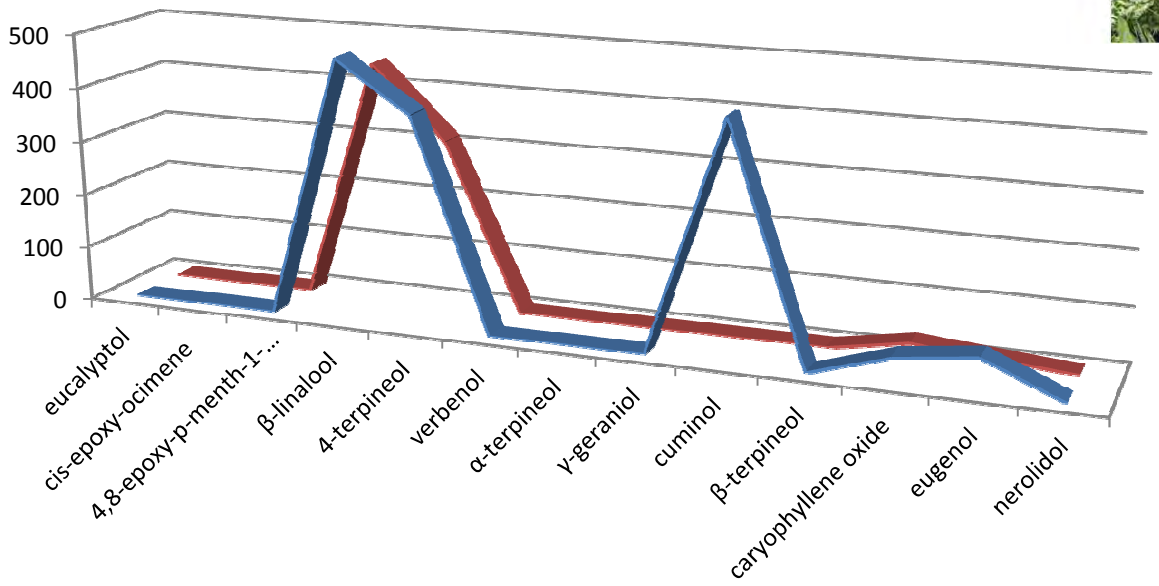
Sesquiterpeni (35 composti)



Bedrocan/Pedanios

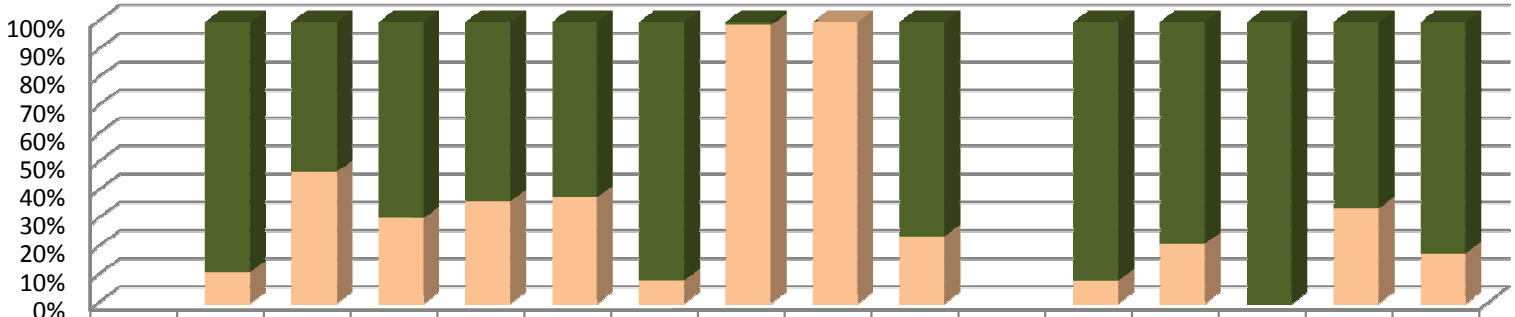
Representative terpene profile of Bedrocan and Pedanios 22/1

Terpeni ossigenati (13 composti)



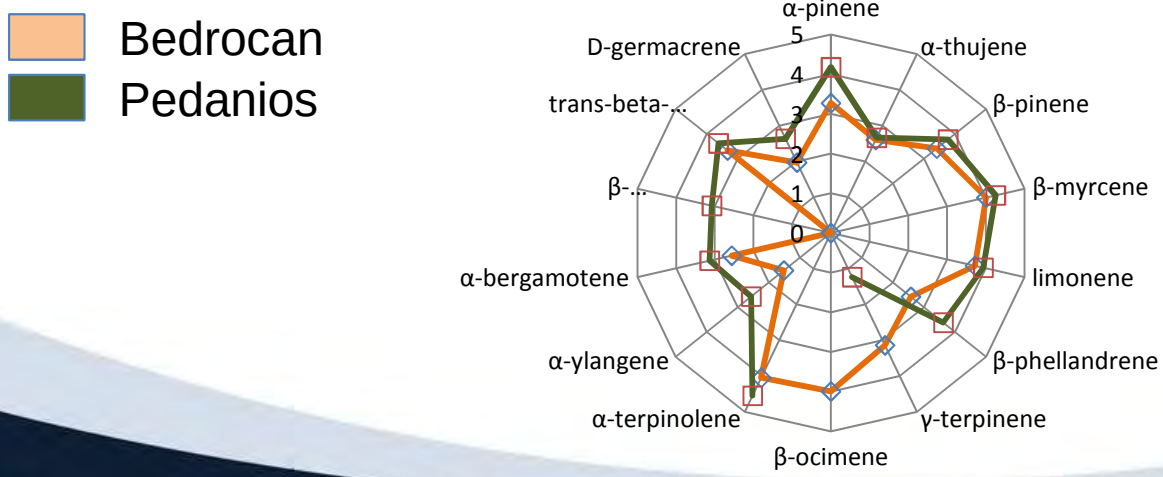
Bedrocan/Pedanios

Dominants terpenes identified in *Cannabis* flos chemotypes



ppm	Mono/di/tri Terpenes	α-pinene	α-thujene	β-pinene	β-myrcene	limonene	β-phellandrene	γ-terpinene	β-ocimene	α-terpinolene	Sesquiterpenes	α-ylangene	α-bergamotene	β-sesquiphellandrene	trans-beta-caryophyllene	D-germacrene
Pedanois22-1		14980.16	459.63	5929.94	18064.19	8657.14	4189.05	17.09	0	35473.43		369.53	1362.06	1195.19	4209.05	431.58
Bedrocan		1865.59	401.58	2567.45	10244.99	5223.87	376.19	1378.16	9793.13	11176.42		32.78	365.98	0	2141.13	93.11

Radar distribution of representative terpenes in *Cannabis* varieties (log_{10})

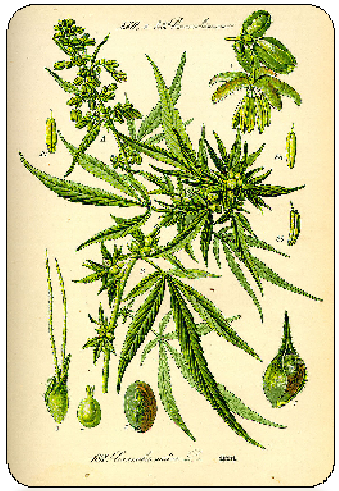


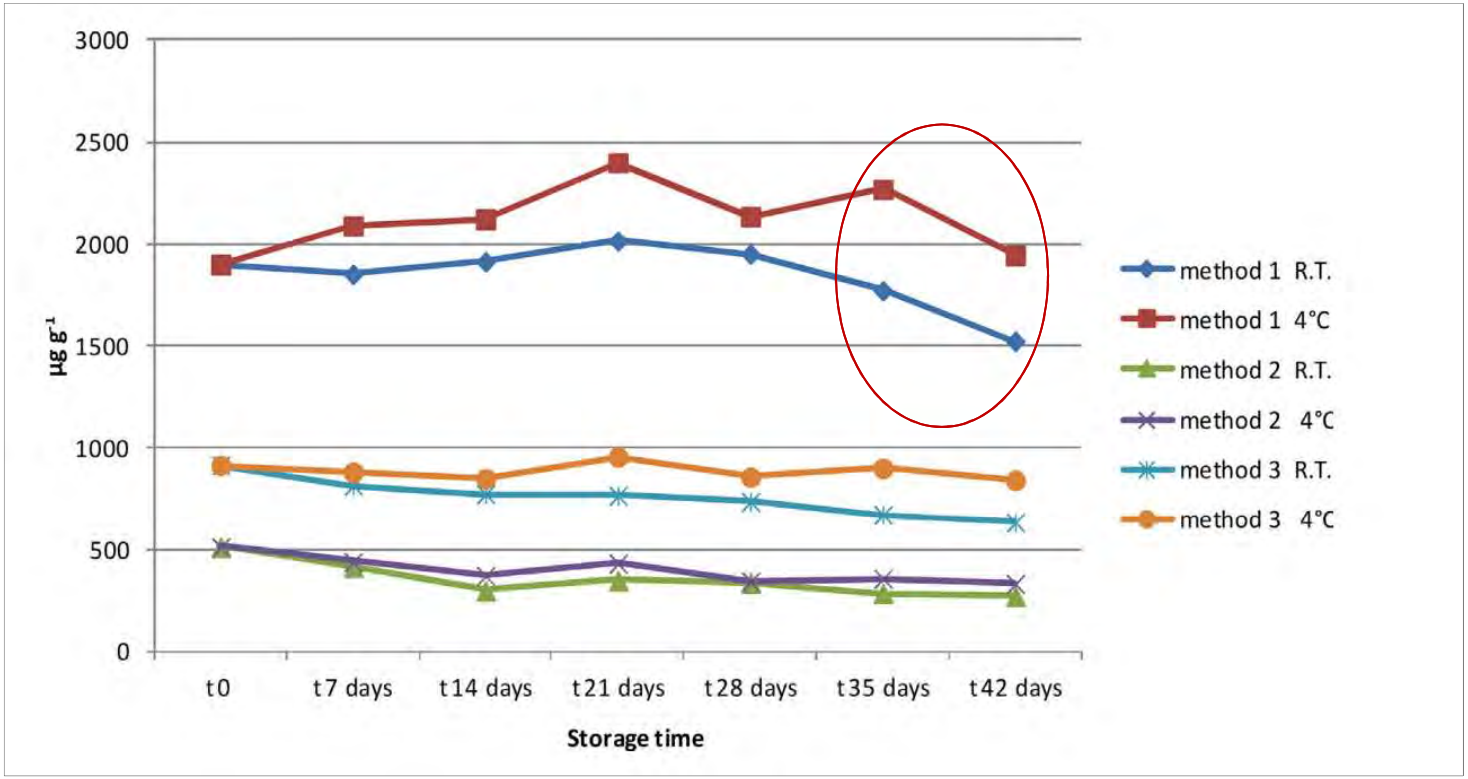
I terpeni nei macerati oleosi (preparati galenici)

Qualita’

Sicurezza

Macerati oleosi galenici: terpeni – differenti metodi estrazione – shelf life 42 gg





Bediol

- Non lavori letteratura su forme acide cannabinoidi ed evidenze cliniche

- Maggior stabilita' 4°C

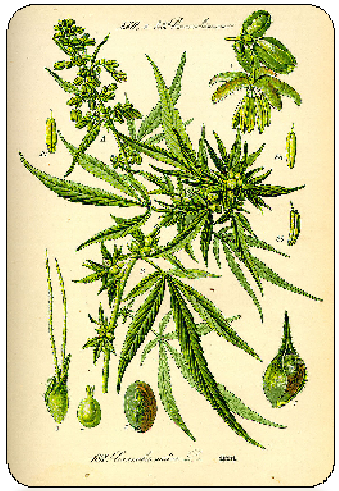
- Maggior concentrazione: metodo RH senza decarbossilazione

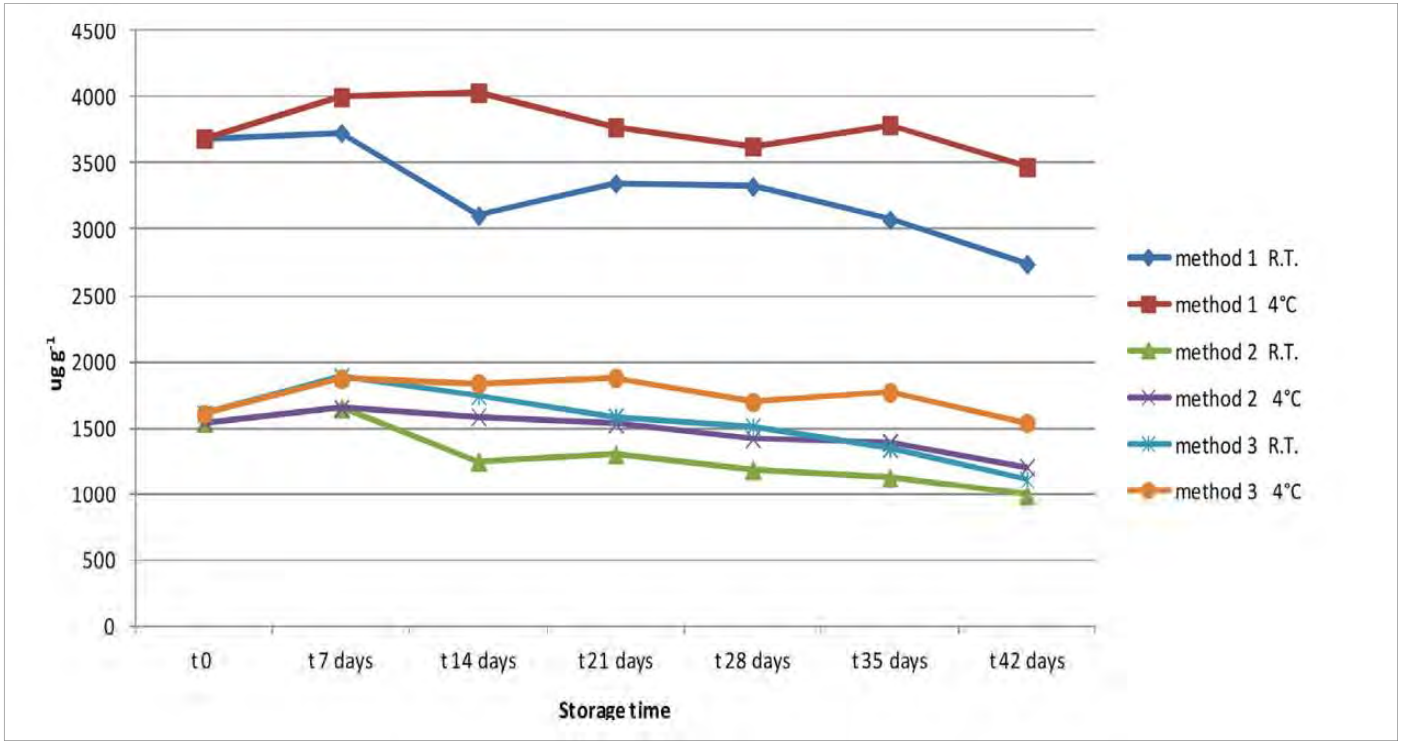
Comprehensive quality evaluation of medical *Cannabis sativa* L. inflorescence and macerated oils based on HS-SPME coupled to GC–MS and LC-HRMS (q-exactive orbitrap®) approach

Lorenzo Calvi[a,b], Daniela Pentimalli[c], Sara Panseri[a,*], Luca Giupponi[c], Fabrizio Gelmini[d], Giangiacomo Beretta[e], Davide Vitali[a], Massimo Bruno[a], Emanuela Zilio[c], Radmila Pavlovic[a], Annamaria Giorgi[b,c]

Dipartimento di Scienze veterinarie per la Salute la Produzione animale e la Sicurezza alimentare
Vespa

Macerati oleosi galenici: terpeni – differenti metodi estrazione – shelf life 42 gg





Bedrocan

Comprehensive quality evaluation of medical *Cannabis sativa* L. inflorescence and macerated oils based on HS-SPME coupled to GC–MS and LC-HRMS (q-exactive orbitrap®) approach

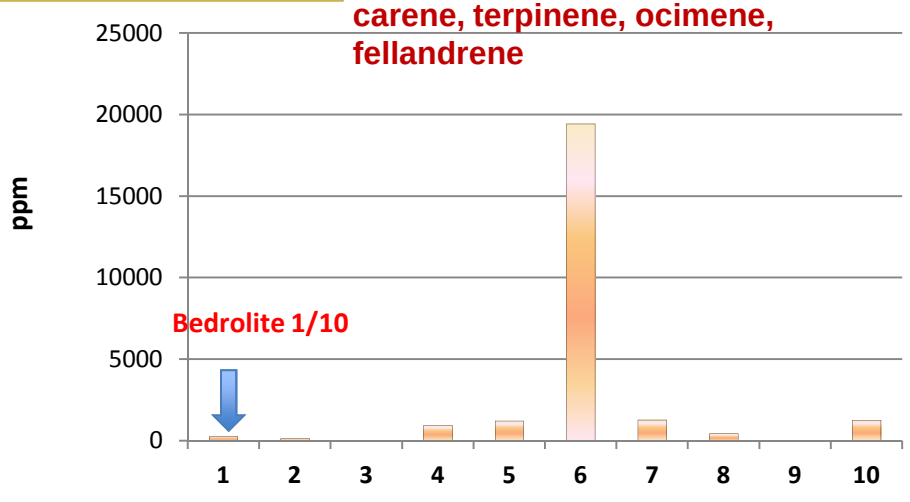
Lorenzo Calvi[a,b], Daniela Pentimalli[c], Sara Panseri[a,*], Luca Giupponi[c], Fabrizio Gelmini[d], Giangiacomo Beretta[e], Davide Vitali[a], Massimo Bruno[a], Emanuela Zilio[c], Radmila Pavlovic[a], Annamaria Giorgi[b,c]

Dipartimento di Scienze veterinarie per la Salute la Produzione animale e la Sicurezza alimentare

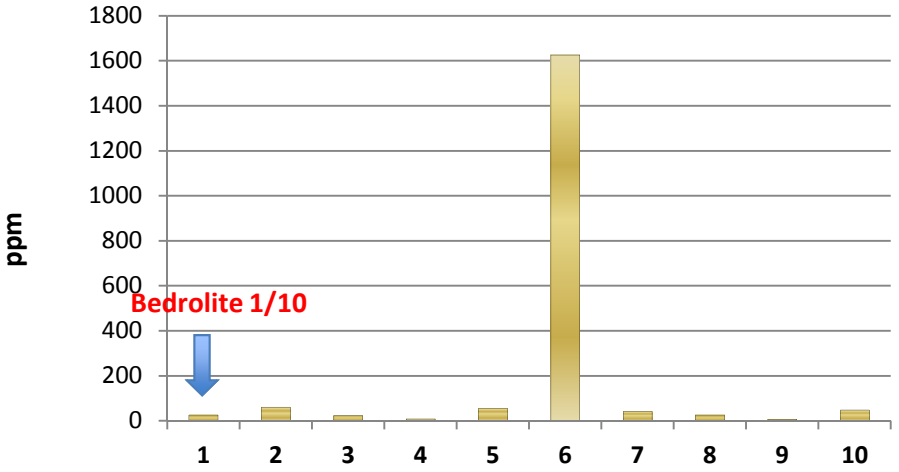
Vespa

Terpeni identificati in macerati oleosi a base di cannabidiolo (CBD oils)

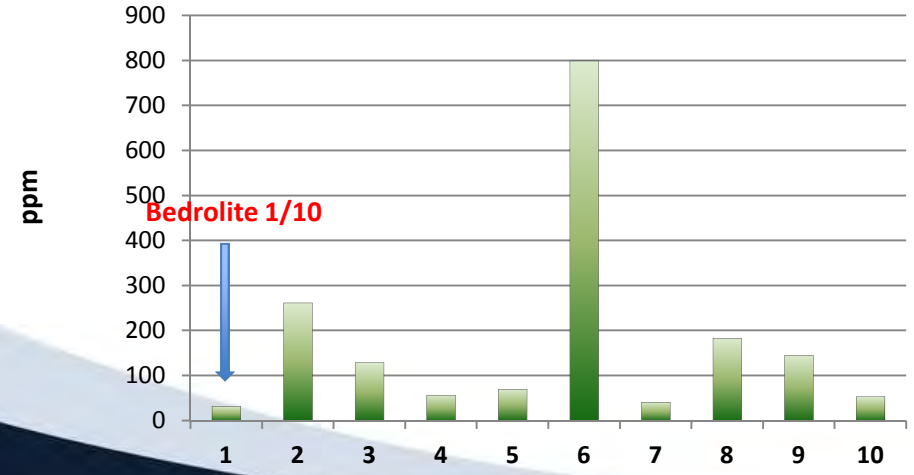
Mono/di/tri Terpenes **Alfa-beta pinene, limonene, mricene, carene, terpinene, ocimene, fellandrene**



Oxygenated Terpenes **Linalolo, pinocarveolo, mentadienolo, eucaliptolo,**



Sesquiterpenes **Alfa-beta-cariofillene, bergamottene**



-metodo/processo di estrazione (bagnomaria, CO_2 supercritica, ultrasuoni)

-Tipologia fonte lipidica (olive oil, hemp seed oil, MCT): influenza notevole su stabilita' durante lo stoccaggio

-presenza pesticidi, micotossine, metalli pesanti

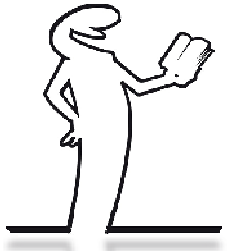
Sicurezza !!

molecules

Article

Quality Traits of "Cannabidiol Oils": Cannabinoids Content, Terpene Fingerprint and Oxidation Stability of European Commercially Available Preparations

DEGLI STUDI DI MILANO
EDICINA VETERINARIA



I terpeni nella Cannabis vaporizzata e combusta (fumo)

Vaporizzazione sperimentale: *Bediol, Bedica, Bedrocan*

- 200 mg flos

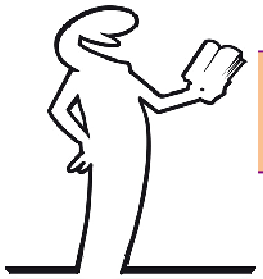
-Temperature di vaporizzazione :

-Tempo standardizzato : 15 min; campionamento: 45 min SPME, bag 30 cm

CANNABINOID conference 2017 IACM 9th Conference on Cannabinoids in Medicine Maritim Hotel Cologne, Germany, 29-30 September 2017

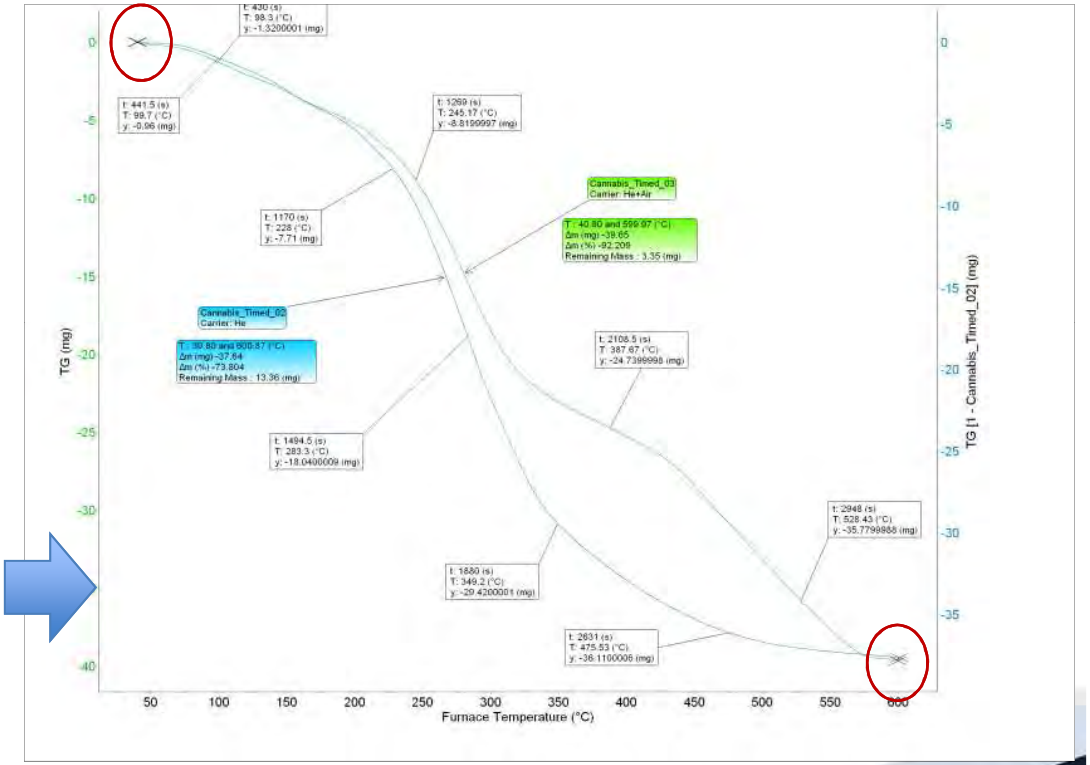
Dipartimento di

Calvi L., Panseri S ., Pentimalli D., Giupponi L, Pavlovic R[a], Giorgi A**HS-SPME AND GC-MS FOR THE COMPREHENSIVE STUDY OF TERPENES AND CANNABINOIDS EMITTED FROM MEDICAL CANNABIS SATIVA FLOS DURING VAPORISATION BY USING A MEDICAL DISPOSAL**

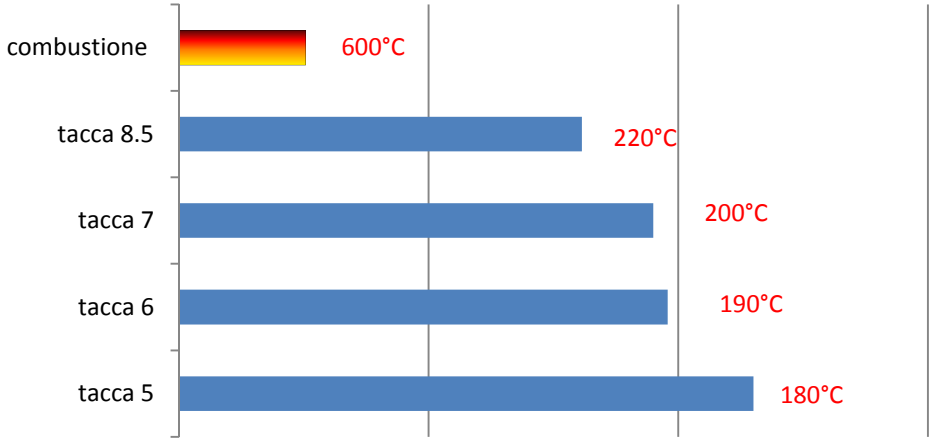


I terpeni nella Cannabis vaporizzata e combusta (fumo)

Termogravimetria – GC/MS (50 °C → 600 °C)

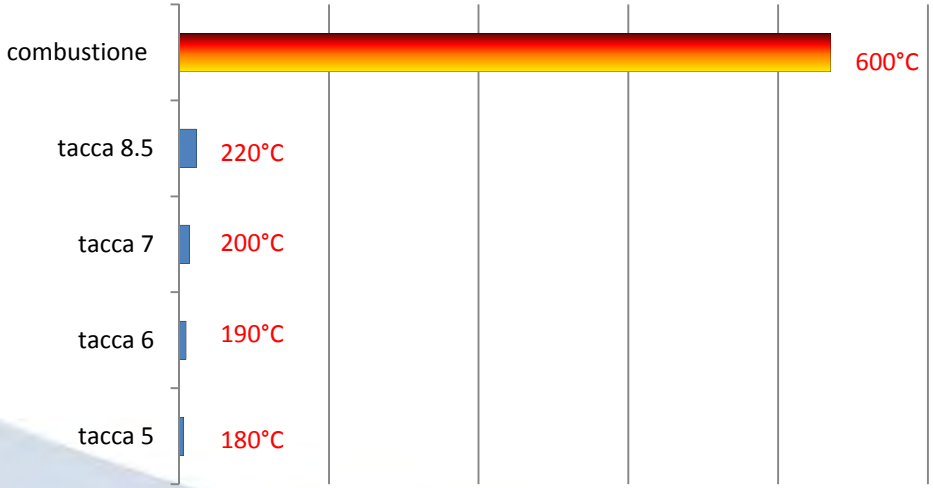


Analisi comparativa 200 mg flos Bediol (vaporizzazione vs combustione)



Terpeni

Influenza della temperatura sulla degradazione (combustione degrada > 40% terpeni)



Pirazine

Composti della combustione dannosi (stress ossidativo cellulare e/o possibili cancerogeni (IARC – 2B)

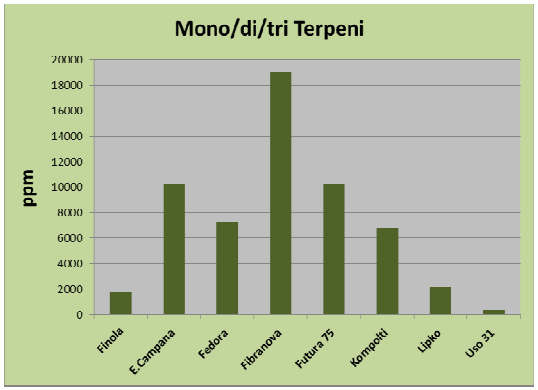
- Patologie sclerosi multipla (si sconsiglia fumo)

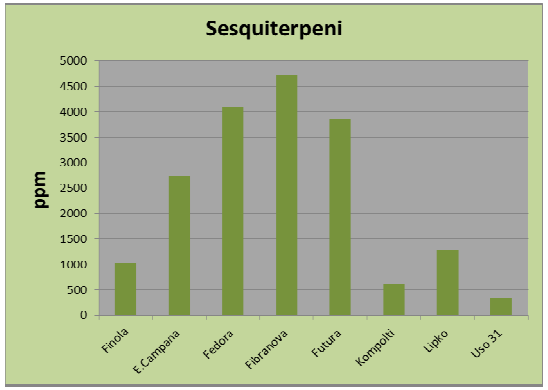
He et al., TG–GC–MS study of volatile products from Shengli lignite pyrolysis- Fuel 156 (2015) 121–128

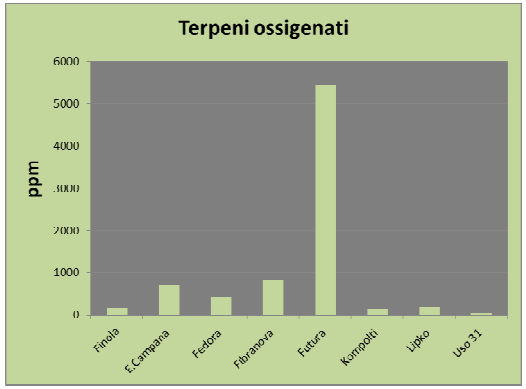
Fingerprint –Terpeni (Cannabis sativa di varietà ad uso agricolo)

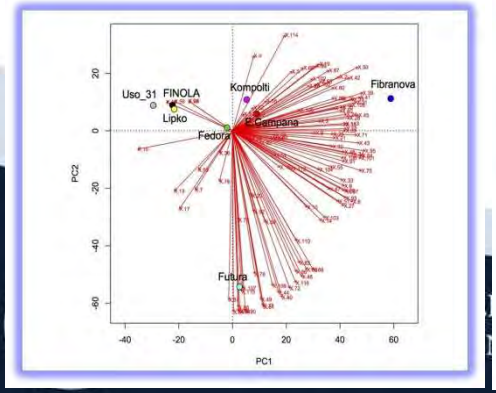
Fingerprint terpenico costituito da più di <u>100</u> composti volatili

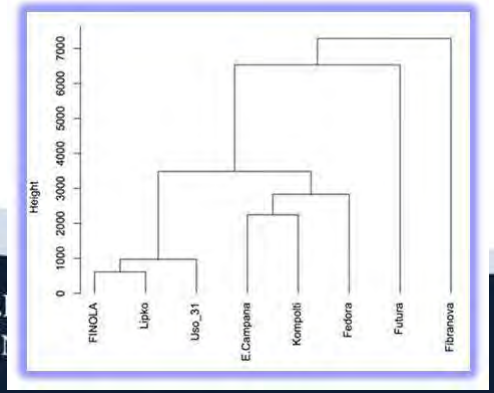
Futura 75, Fibranova e E. Campana > ***mono/di/ tri terpeni***
Futura 75, Fibranova, Fedora e E. Campana> ***sesquiterpeni***
Futura 75 > ***terpeni ossigenati***











Livello differenze varietà *Cannabis sativa*
L. rispetto al contenuto terpenico (cluster)

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Necessita' ed approcci futuri

- Ruolo chiave come "indicatori" di buona preservazione fitocomplesso durante le fasi di preparazione (*es.* macerati oleosi)

- Terpeni agiscono attivamente sui recettori/enzimi cerebrali : necessita' di studi mirati per evidenziarne la specifica efficacia a livello clinico

- Indagare le proprieta' complessive dei fitocomplessi di chemotipi ad utilizzo terapeutico: quantificare i composti terpenici caratteristici --- diversi chemotipi utilizzabili

Approccio ad oggi di cautela nell'addizionare terpeni a preparazioni e/o estrazioni (es cariofillene , mircene in oli a base di cannabidiolo) – ruolo irritativo ossidante

Journal of Pharmaceutical and Biomedical Analysis 150 (2018) 208–219

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

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ARTICLE INFO

Article history:
Received 6 October 2017
Received in revised form
28 November 2017
Accepted 28 November 2017

Keywords:
HS-SPME
GC–MS
LC-Orbitrap
Cannabis sativa L.
Bedrocan®
Bediol®
Terpenes
Cannabinoids

ABSTRACT

There are at least 554 identified compounds in *C. sativa* L., among them 113 phytocannabinoids and 120 terpenes. Phytocomplex composition differences between the pharmaceutical properties of different medical cannabis chemotype have been attributed to strict interactions, defined as 'entourage effect', between ca
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Article

Quality Traits of "Cannabidiol Oils": Cannabinoids Content, Terpene Fingerprint and Oxidation Stability of European Commercially Available Preparations

Radmila Pavlovic [1,2], Giorgio Nenna [3], Lorenzo Calvi [2], Sara Panseri [4,*], Gigliola Borgonovo [5], Luca Giupponi [1,2], Giuseppe Cannazza [6] and Annamaria Giorgi [1,2]

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Received: 21 April 2018; Accepted: 15 May 2018; Published: 20 May 2018

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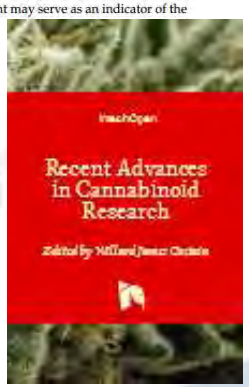
Abstract: Cannabidiol (CBD)-based oil preparations are becoming extremely popular, as CBD has been shown to have beneficial effects on human health. CBD-based oil preparations are not unambiguously regulated under the European legislation, as CBD is not considered as a controlled substance. This means that companies can produce and distribute CBD products derived from non-psychoactive hemp varieties, providing an easy access to this extremely advantageous cannabinoid. This leaves consumers with no legal quality guarantees. The objective of this project was to assess the quality of 14 CBD oils commercially available in European countries. An in-depth chemical profiling of cannabinoids, terpenes and oxidation products was conducted by means of GC-MS and HPLC-Q-Exactive-Orbitrap-MS in order to improve knowledge regarding the characteristics of CBD oils. Nine out of the 14 samples studied had concentrations that differed notably from the declared amount, while the remaining five preserved CBD within optimal limits. Our results highlighted a wide variability in cannabinoids profile that justifies the need for strict and standardized regulations. In addition, the terpenes fingerprint may serve as an indicator of the

Book title: Recent Advances in Cannabinoid Research

Chapter title: Quality traits of Medical *Cannabis sativa* L. inflorescences and derived products based on comprehensive mass-spectrometry analytical investigation

Authors: Lorenzo Calvi [1], Radmila Pavlovic [1,2], Sara Panseri [3*], Luca Giupponi [1,2], Valeria Leoni [1,2], and Annamaria Giorgi [1,2]



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Vespa

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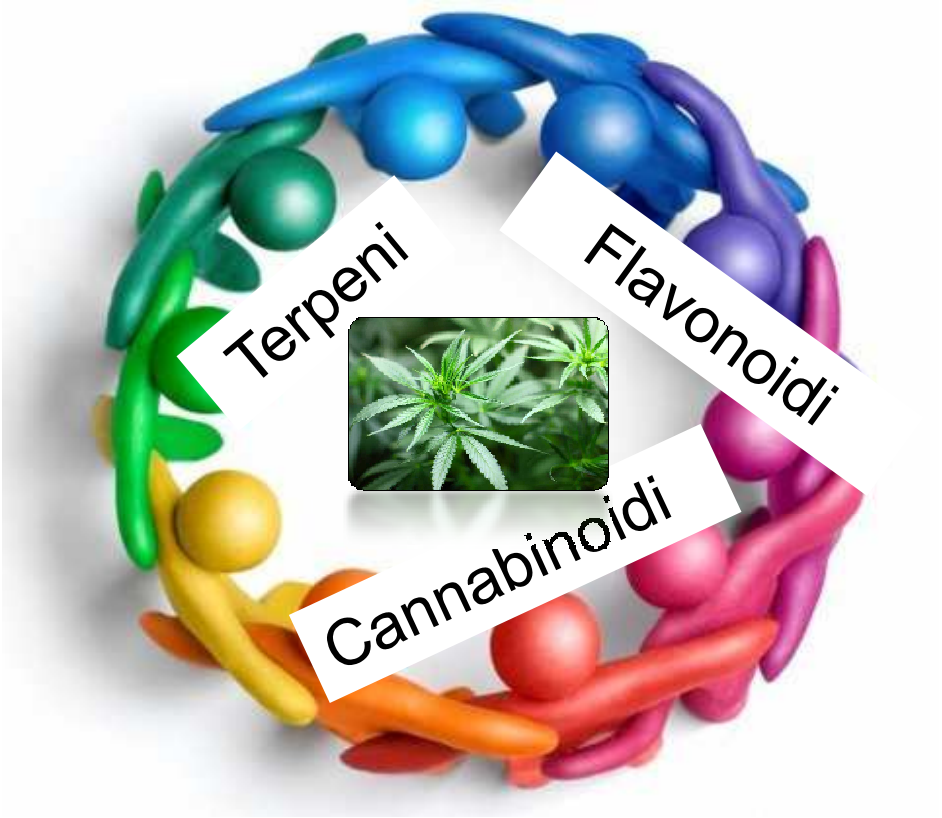
L’unione fa la forza del fitocomplesso



Grazie per l’attenzione