LA FITOTERAPIA CLINICA IN MEDICINA:
tra conoscenza scientifica e tradizione

Sabato 30 aprile 2022 - h. 9.00/14.00
sede OMCEO - Via Manzù 25, Bergamo

La metodologia nella ricerca pre-clinica e clinica in fitoterapia e i percorsi formativi

Marco Biagi
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FITOTERAPIA

Definizione ufficiale

Branca della farmacoterapia che utilizza come principi attivi gli estratti e/o le preparazioni ottenuti dalle piante medicinali (medicinali vegetali o fitoterapici)

OMS, 1980

Prodotti vegetali per la salute

pharmaceuticals

MDPI

Review

Herbal Products in Italy: The Thin Line between Phytotherapy, Nutrition and Parapharmaceuticals; A Normative Overview of the Fastest Growing Market in Europe

Marco Biagi [1,2,*], Rita Pecorari [2], Giovanni Appendino [2,3], Elisabetta Miraldi [1,2], Anna Rosa Magnano [1,2], Paolo Governa [1,2], Giulia Cettolin [1,2] and Daniela Giachetti [1,2]

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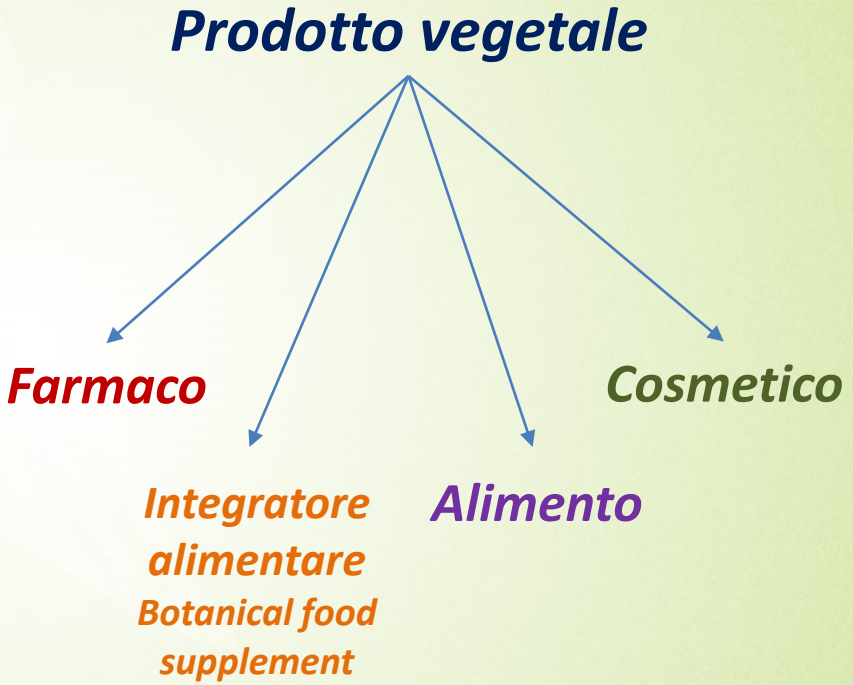
Academic Editor: Dario Donno
Received: 7 September 2016; Accepted: 26 October 2016; Published: 29 October 2016

Abstract: The Italian herbal products market is the most prosperous in Europe. The proof is represented by the use of these products in several marketing categories, ranging from medicine to nutrition and cosmetics. Market and legislation in Italy are at the same time cause and consequence of this peculiar situation. In fact, the legislation on botanical food supplements in Italy is very permissive and at the same time the market shows an overall satisfaction of users and strong feedback in terms of consumption, which brings a widening use of medicinal plants, formerly the prerogative of pharmaceuticals, to other fields such as nutrition. This review summarizes the market and normative panorama of herbal products in Italy, highlighting the blurred boundaries of health indications, marketing authorizations and quality controls between herbal medicines and non pharmaceutical products, such as food supplements, cosmetics and other herbal-based "parapharmaceuticals".



Una stessa specie può trovare collocazione in più settori:

mirtillo nero, ananas, ginseng, molte specie essenziere…

CONTESTO DI INTERVENTO DEI PRODOTTI VEGETALI

PREVENZIONE	SINTOMATOLOGIA LIEVE	CONDIZIONE PATOLOGICA

L’uso dei prodotti vegetali è concentrato molto nella zona di confine tra prevenzione, primi sintomi o sintomi non severi e vengono per questo utilizzati farmaci vegetali e integratori alimentari.

Inquadramento normativo dei prodotti vegetali

FARMACO VEGETALE

Dir. 2001/83/CE

Farmaci registrati in maniera convenzionale

Galenici (magistrali e officinali)

Dir. 2004/24/CE
(emendamento della 2001/83/CE)

Farmaci registrati come THMP

INTEGRATORI ALIMENTARI

Dir. 2002/46/CE

FONTE CONCENTRATA di sostanze nutritive e altre sostanze aventi effetto nutritivo e fisiologico.

Sono ammesse tutte le forme orali di somministrazione (compresse, capsule, sciroppi, soluzioni, polveri….)

Specie ammesse: quelle riportate nell'allegato 1 del DM 04/08/2021

CLAIM SALUTISTICI per adesso ancora ammessi

Oltre 80.000 (ottantamila!) integratori notificati

COSMETICI

Dir. 1223/2009/CE

Qualsiasi sostanza o miscela destinata ad essere applicata sulle superfici esterne del corpo umano (epidermide, sistema pilifero e capelli, unghie, labbra, organi genitali esterni) oppure sui denti e sulle mucose della bocca allo scopo esclusivamente o prevalentemente di pulirli, profumarli, modificarne l'aspetto, proteggerli, mantenerli in buono stato o correggere gli odori corporei.

ALTRE CATEGORIE DOVE SONO PRESENTI I PRODOTTI VEGETALI

- **DISPOSITIVI MEDICI:** **Dir. 2017/745/CE**

- **NOVEL FOOD:** **Dir. 2015/2283/CE**

Come nasce un farmaco vegetale?

Medicina tradizionale

L'uso delle piante medicinali nella sua applicazione più generale è considerata dall'OMS nel contesto delle medicine tradizionali e complementari (MT&C).

- **Accesso a prodotti farmacologicamente attivi da parte delle popolazioni non sviluppate;**
- **Valorizzazione delle tradizioni d'uso e sviluppo delle conoscenze etnobotaniche nei paesi sviluppati.**

Saggi bioguidati e etnobotanica

Studio delle componenti attive su singoli target

L'importanza dell'etnobotanica

Review > Phytother Res. 2000 Nov;14(7):479-88.
doi: 10.1002/1099-1573(200011)14:7<479::aid-ptr958>3.0.co;2-2.

Ethnobotany and its role in drug development

M Heinrich [1]

Affiliations + expand

PMID: 11054835 DOI: 10.1002/1099-1573(200011)14:7<479::aid-ptr958>3.0.co;2-2

Abstract

The botanical collections of early explorers and the later ethnobotany have played important roles in the development of new drugs for many centuries. In the middle of the last century interest in this approach had declined dramatically, but has risen again during its last decade, and new foci have developed. The systematic evaluation of indigenous pharmacopoeias in order to contribute to improved health care in marginalized regions has been placed on the agenda of international and national organizations and of NGOs. In this paper the results of various projects on Mexican Indian ethnobotany and some of the subsequent pharmacological and phytochemical studies are summarized. Medicinal plants are an important element of indigenous medical systems in Mexico. This study uses the medicinal plants in four indigenous groups of Mexican Indians-Maya, Nahua, Zapotec and Mixe-as an example. The relative importance of a medicinal plant within a culture is documented using a quantitative method and the data are compared intra- and interculturally. While the species used by the indigenous groups vary, the data indicate that there exist well-defined criteria specific for each culture, which lead to the selection of a plant as a medicine. For example, a large number of species are used for gastrointestinal illnesses by two or more of the indigenous groups. At least in this case, the multiple transfers of species and their uses within -Mexico seems to be an important reason for the widespread use of a species. Some of the data we gathered in order to evaluate the indigenous claims are also discussed, focusing on the transcription factor NF-kappaB as a molecular target. This led to the identification of sesquiterpene lactones such as parthenolide as potent and relatively specific inhibitors of this transcription factor.

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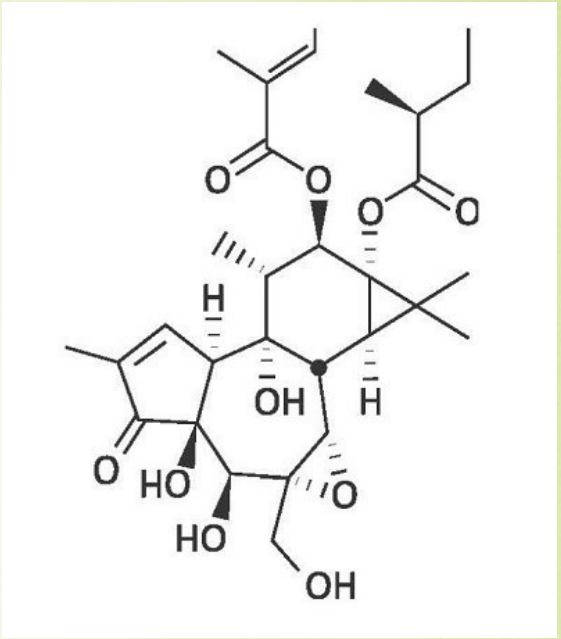

Tiglianolo tiglato
2021, uso veterinario su mastocitoma canino

L'importanza dell'etnobotanica

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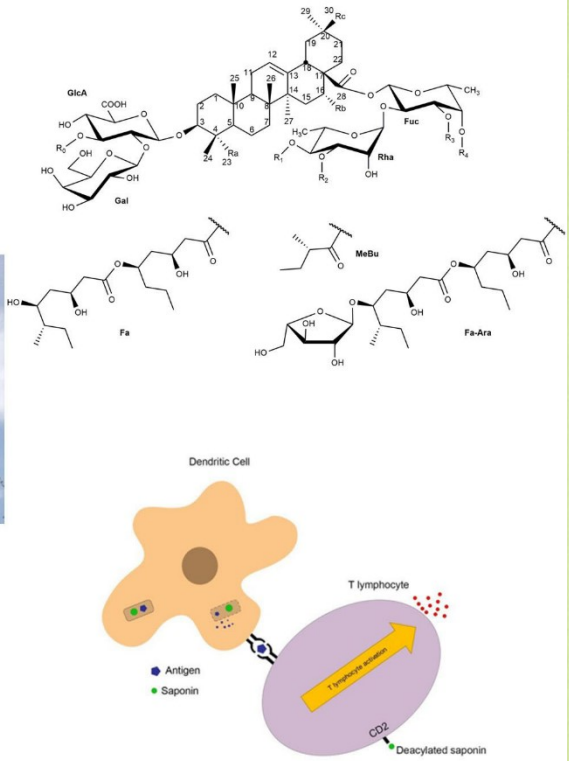
Effetto adiuvante delle saponine di *Quillaja* sp. Nei vaccini COVID-19



Sperimentazione preclinica preliminare

› Phytomedicine. 2020 Nov;78:153307. doi: 10.1016/j.phymed.2020.153307. Epub 2020 Aug 19.

Zingiber officinale Roscoe rhizome extract alleviates neuropathic pain by inhibiting neuroinflammation in mice

Vittoria Borgonetti [1], Paolo Governa [2], Marco Biagi [3], Federica Pellati [4], Nicoletta Galeotti [5]

Affiliations + expand

PMID: 32846405 DOI: 10.1016/j.phymed.2020.153307

Abstract

Background: Current therapies for neuropathic pain are generally symptomatic and possess several side effects, limiting their prolonged usage.

Hypothesis/purpose: Thus, it is urgent to develop novel and safe candidates for the management of this chronical condition. For this purpose, we investigated the analgesic effect of a standardized extract from Zingiber officinale Roscoe rhizomes (ZOE) obtained by CO_2 supercritical extraction, in a mice model of peripheral neuropathy. We also explored the mechanism of action of ZOE and its main constituents using an in vitro model of neuroinflammation.

Methods: Peripheral mono-neuropathy was induced in mice, by spared nerve injury (SNI). The analgesic effect of ZOE after oral administration was assessed by measuring mechanical and thermal allodynia in SNI mice. The mechanism of action of ZOE and its main constituents were investigated using spinal cords samples and in an in vitro model of neuroinflammation by ELISA, western blotting and immunofluorescence techniques.

Results: Oral administration of ZOE 200 mg kg^{-1} ameliorated mechanical and thermal allodynia in SNI mice, with a rapid and a long-lasting effect. ZOE did not alter locomotor activity. In BV2 cells and spinal cord samples, ZOE, 6-gingerol and 6-shogaol reduced pERK levels, whereas ZOE and terpene fraction reduced HDAC1 protein levels, inhibited NF-κB signalling activation and decreased IL-1β, TNF-α and IL-6 release. ZOE and each tested constituent had a positive effect on inflammation-impaired SH-SY5Y cell viability.

Conclusions: The oral administration of ZOE attenuated SNI-induced neuropathic pain symptoms by reducing spinal neuroinflammation, suggesting ZOE as a novel and interesting candidate for the management of neuropathic pain.

Keywords: HDAC; MAPK; Microglia; Neuroinflammation; Neuropathic pain; Zingiber officinale roscoe.

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Sperimentazione preclinica preliminare

› Phytother Res. 2022 Apr 8. doi: 10.1002/ptr.7458. Online ahead of print.

Non-psychotropic Cannabis sativa L. phytocomplex modulates microglial inflammatory response through CB2 receptors-, endocannabinoids-, and NF-κB-mediated signaling

Vittoria Borgonetti [1], Cristina Benatti [2 3], Paolo Governa [4], Giovanni Isoldi [5], Federica Pellati [3], Silvia Alboni [2 3], Fabio Tascedda [2 3 6], Monica Montopoli [7], Nicoletta Galeotti [1], Fabrizio Manetti [4], Elisabetta Miraldi [8], Marco Biagi [8], Giovanna Rigillo [3]

Affiliations + expand

PMID: 35393641 DOI: 10.1002/ptr.7458

Abstract

Cannabis sativa L. is increasingly emerging for its protective role in modulating neuroinflammation, a complex process orchestrated among others by microglia, the resident immune cells of the central nervous system. Phytocannabinoids, especially cannabidiol (CBD), terpenes, and other constituents trigger several upstream and downstream microglial intracellular pathways. Here, we investigated the molecular mechanisms of a CBD- and terpenes-enriched C. sativa extract (CSE) in an in vitro model of neuroinflammation. We evaluated the effect of CSE on the inflammatory response induced by exposure to lipopolysaccharide (LPS) in BV-2 microglial cells, compared with CBD and β-caryophyllene (CAR), CB2 receptors (CB2r) inverse and full agonist, respectively. The LPS-induced upregulation of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α was significantly attenuated by CSE and only partially by CBD, whereas CAR was ineffective. In BV-2 cells, these anti-inflammatory effects exerted by CSE phytocomplex were only partially dependent on CB2r modulation and they were mediated by the regulation of enzymes responsible for the endocannabinoids metabolism, by the inhibition of reactive oxygen species release and the modulation of JNK/p38 cascade with consequent NF-κB p65 nuclear translocation suppression. Our data suggest that C. sativa phytocomplex and its multitarget mechanism could represent a novel therapeutic strategy for neuroinflammatory-related diseases.

Sviluppo delle preparazioni farmaceutiche vegetali

Farmaci vegetali

Dir. 2001/83/CE e Dir. 2004/24/CE

- **Dati chimico farmaceutici**
- **Assicurata conformità GACP**
- **Assicurata conformità GMP**

CONTROLLI DI QUALITÀ SULLE MATERIE PRIME VEGETALI AD USO FARMACEUTICO

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

AIFA
AGENZIA ITALIANA DEL FARMACO

CONTROLLI DI QUALITÀ SULLE MATERIE PRIME VEGETALI AD USO FARMACEUTICO

- ***Controllo dei contaminanti chimici e biologici***
- ***Controllo botanico***

(identificazione botanica, specifica della parte utilizzata, origine geografica)

- ***Controllo dei residui di fertilizzanti***
- ***Metalli pesanti***
- ***Carica microbica***
- ***Sostanze radiattive***
- ***Saggi chimici e titolazione dei principi attivi***

- ***METODI GENERALI DI FARMACOGNOSIA***

MELISSA LEAF

Melissae folium

DEFINITION

Dried leaf of *Melissa officinalis* L.

Content: minimum 4.0 per cent of total hydroxycinnamic derivatives, expressed as rosmarinic acid ($C_{18}H_{16}O_8$; M_r 360.3) (dried drug).

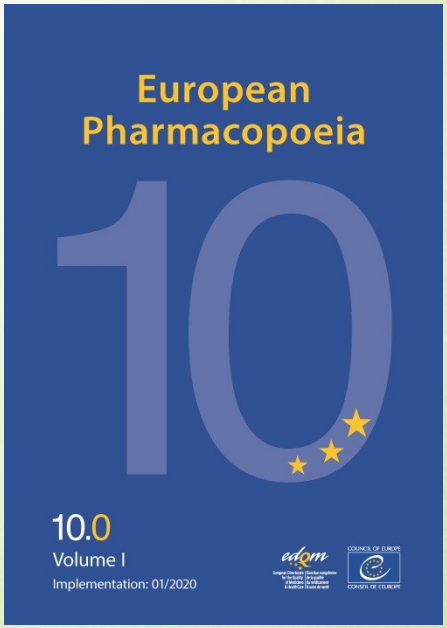
CHARACTERS

Odour reminiscent of lemon.

IDENTIFICATION

A. Melissa leaf has a petiole of varying length and is oval, cordate and up to about 8 cm long and 5 cm wide. The lamina is thin and the under surface has a conspicuous, raised, reticulate venation; the margins are roughly dentate or crenate. The upper surface is bright green and the lower surface is lighter in colour.

Farmacopea Europea
10a edizione



TEA TREE OIL

Melaleucae aetheroleum

DEFINITION

Essential oil obtained by steam distillation from the foliage and terminal branchlets of *Melaleuca alternifolia* (Maiden and Betch) Cheel, *M. linariifolia* Smith, *M. dissitiflora* F. Mueller and/or other species of *Melaleuca*.

CHARACTERS

Appearance: clear, mobile, colourless to pale yellow liquid with a characteristic odour.

Determine the percentage content of these components. The percentages are within the following ranges:

- *α-pinene*: 1.0 per cent to 6.0 per cent,
- *sabinene*: less than 3.5 per cent,
- *α-terpinene*: 5.0 per cent to 13.0 per cent,
- *limonene*: 0.5 per cent to 4.0 per cent,
- *cineole*: less than 15.0 per cent,
- *γ-terpinene*: 10.0 per cent to 28.0 per cent,
- *p-cymene*: 0.5 per cent to 12.0 per cent,
- *terpinolene*: 1.5 per cent to 5.0 per cent,
- *terpinen-4-ol*: minimum 30.0 per cent,
- *aromadendrene*: less than 7.0 per cent,
- *α-terpineol*: 1.5 per cent to 8.0 per cent.

Column:

- *material*: fused silica,
- *size*: *l* = 30 m (a film thickness of 1 µm may be used) to 60 m (a film thickness of 0.2 µm may be used), Ø = 0.25-0.53 mm,
- *stationary phase*: *macrogol 20 000 R*.

Carrier gas: *helium for chromatography R*.

Flow rate: 1.3 ml/min.

Split ratio: 1:50.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 1	50
	1 - 37	50 → 230
	37 - 45	230
Injection port		240
Detector		240

Detection: flame ionisation.

Injection: 1 µl.

Elution order: order indicated in the composition of the reference solution. Record the retention times of these substances.

European Pharmacopoeia 10
10.0 Volume I Implementation: 01/2020

Aesculus hippocastanum L. seme
ippocastano
estratto secco standardizzato

Well-established use

With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC as amended

Aesculus hippocastanum L., semen (horse chestnut seed)

1) Herbal substance
Not applicable

2) Herbal preparations

Dry extracts[2] (40-80% (v/v) ethanol) standardised to contain 16-28% triterpene glycosides, calculated as aescin (photometric method).

Titolazioni e standardizzazione dei prodotti vegetali

Marker chimico

Un marker è un componente o una classe di molecole di una droga o di un prodotto da essa derivato che concorre a definirne:

- le proprietà biologiche
- l'identità
- la specificità
- l'origine
- la genuinità
- la qualità

indipendentemente dalla sua abbondanza

Standardizzazione

La standardizzazione di prodotti di origine vegetale serve a garantire:

- ***la riproducibilità dell'attività biologica e farmacologica***
- ***la costanza di composizione e la sicurezza***

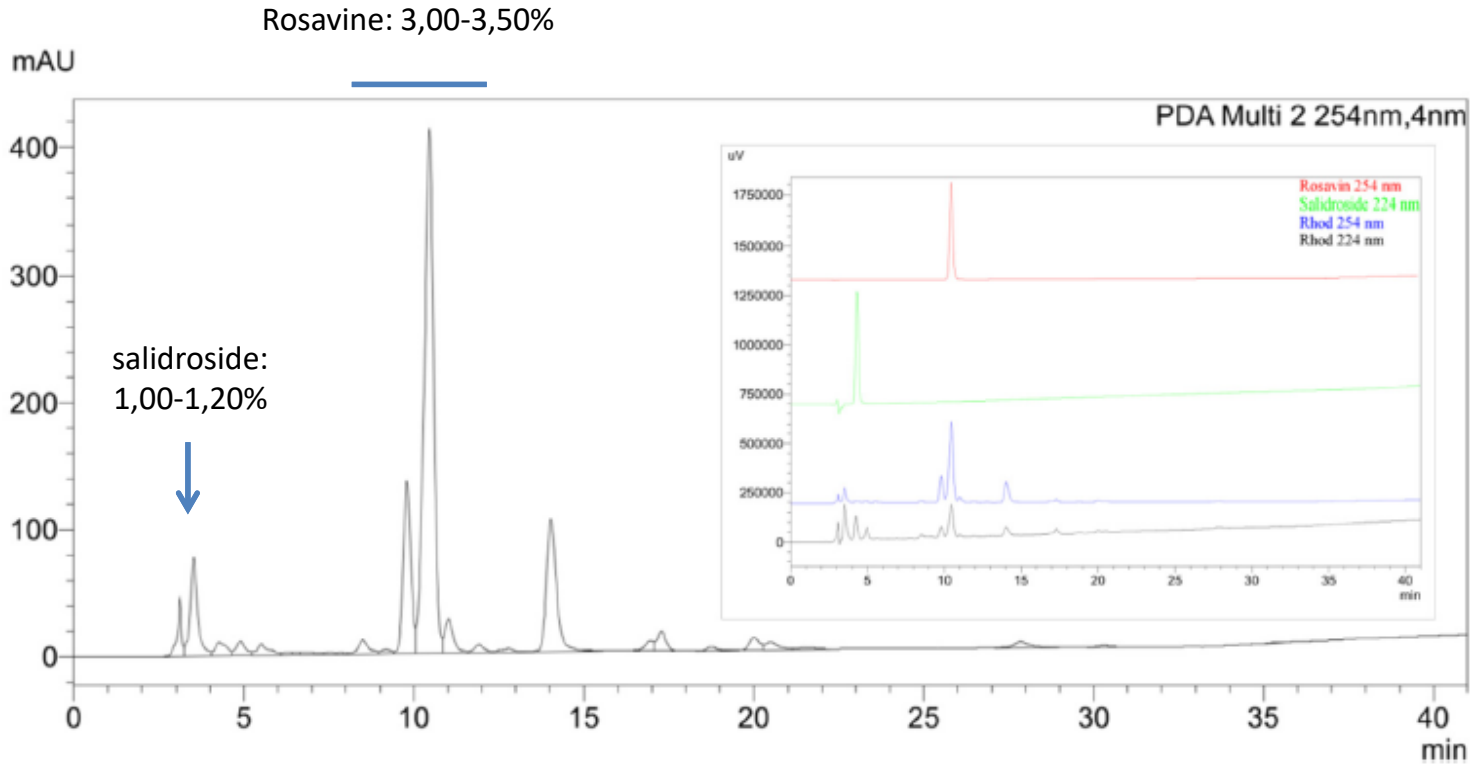
La standardizzazione riguarda l'intero processo di produzione di un estratto, dalla scelta della materia prima alla titolazione chimica.

Pelargonium sidoides DC. radice

Eps7630

Estratto standardizzato prodotto in GMP

Estratto standardizzato di *Rhodiola rosea* L. radici WS 1375



Sperimentazione sui farmaci vegetali:

Dimostrare l'efficacia e la sicurezza

Sperimentazione preclinica

P. sidoides DC. Radice Eps7630

Meccanismo d'azione nelle infezioni respiratorie

Meccanismo d'azione multitarget esplicata dal fitocomplesso

- **Attività immunomodulante**
- **Attività antivirale**
- **Attività secretomotoria**

P. sidoides radice Eps7630

Attività immunomodulante

PLOS ONE

RESEARCH ARTICLE

The *Pelargonium sidoides* Extract EPs 7630 Drives the Innate Immune Defense by Activating Selected MAP Kinase Pathways in Human Monocytes

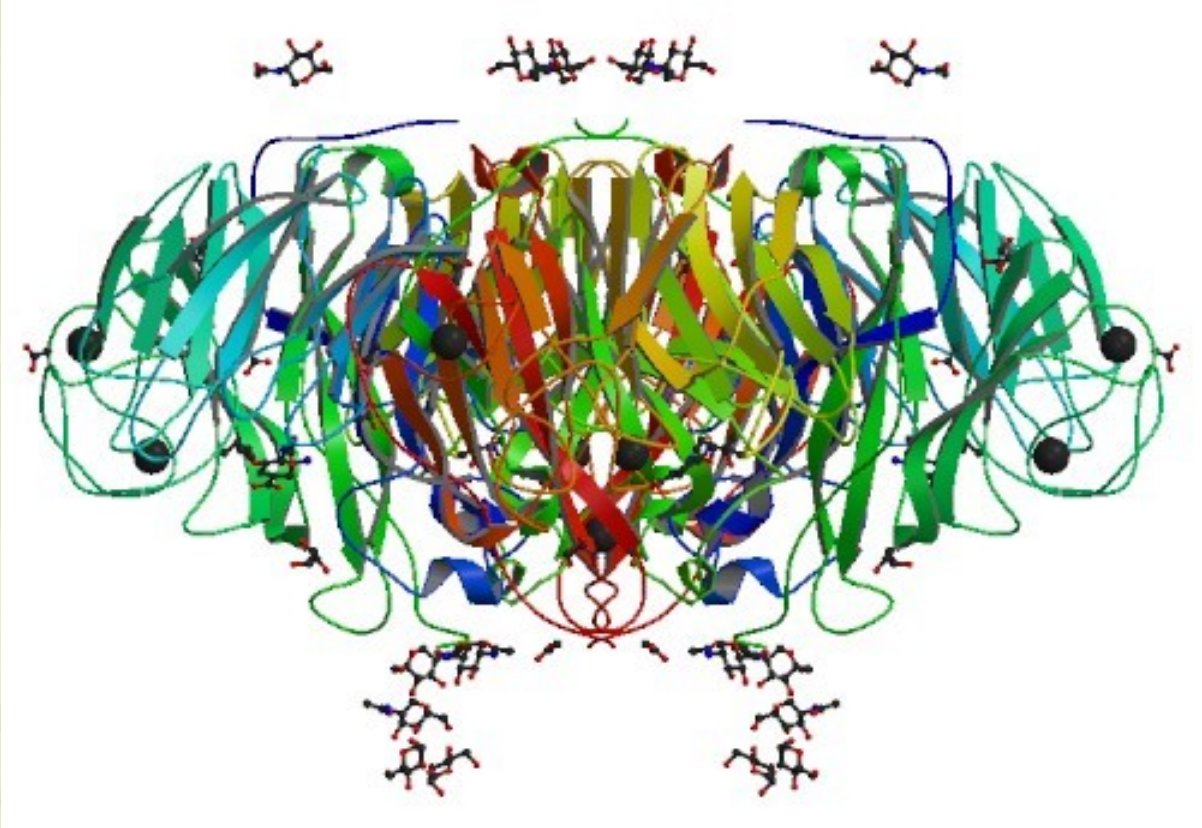
Katrin Witte[1,2], Egon Koch[3], Hans-Dieter Volk[2,4], Kerstin Wolk[1,2,5], Robert Sabat[1,5,6]*

1 Interdisciplinary Group of Molecular Immunopathology, Dermatology/Medical Immunology, University Hospital Charité, Berlin, Germany, **2** Berlin-Brandenburg Center for Regenerative Therapies, University Hospital Charité, Berlin, Germany, **3** Preclinical Research, Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany, **4** Institute of Medical Immunology, University Hospital Charité, Berlin, Germany, **5** Psoriasis Research and Treatment Center, University Hospital Charité, Berlin, Germany, **6** Research Center Immunosciences, University Hospital Charité, Berlin, Germany

* robert.sabat@charite.de

P. sidoides radice Eps7630

Attività antineuraminidasi



PDB CODE: 3TI6

Crystal structure of 2009 pandemic H1N1 neuraminidase complexed with oseltamivir

Software utilizzati:
Pymol
AutoDock 4
LigPlot+

Governa, 2018 unpublished data

P. sidoides radice Eps7630

Attività antineuraminidasi

ligand	binding_energy	ligand_efficiency	inhibition_constant	intermol_energy
oseltamivir	**-5,03**	**-0,25**	**203.89 uM**	**-6,82**
sialic acid	-0,69	-0,03	312.33 mM	-3,67
catechin_2R3S	-4,04	-0,19	1.09 mM	-5,83
catechin_2S3R	**-4,56**	**-0,22**	**451.16 uM**	**-6,35**
epicatechin_2R3R	**-4,93**	**-0,23**	**242.81 uM**	**-6,72**
epicatechin_2S3S	-3,74	-0,18	1.81 mM	-5,53
epigallocatechingallate	**-4,71**	**-0,14**	**351.98 uM**	**-8,29**
gallic_acid	**-2,99**	**-0,25**	**6.47 mM**	**-4,18**

Le catechine e le gallocatechine risultano ligandi adatti all'inibizione di NA.

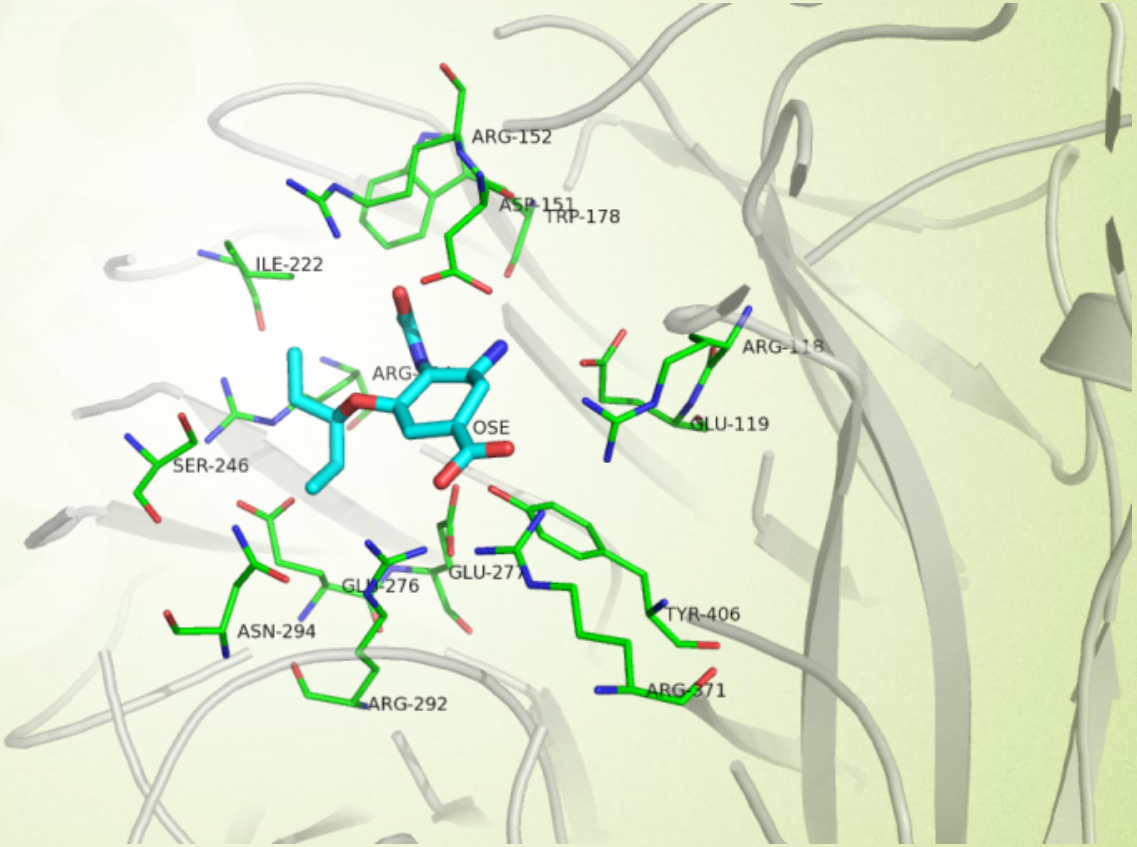
Governa, 2018 unpublished data

P. sidoides radice Eps7630

Attività antineuraminidasi

Oseltamivir

- Interagisce con 13 amminoacidi (5 interazioni polari)
- Le interazioni con ARG292 e GLU119 sono fondamentali per l'inibizione (Marjuki et al., 2015)



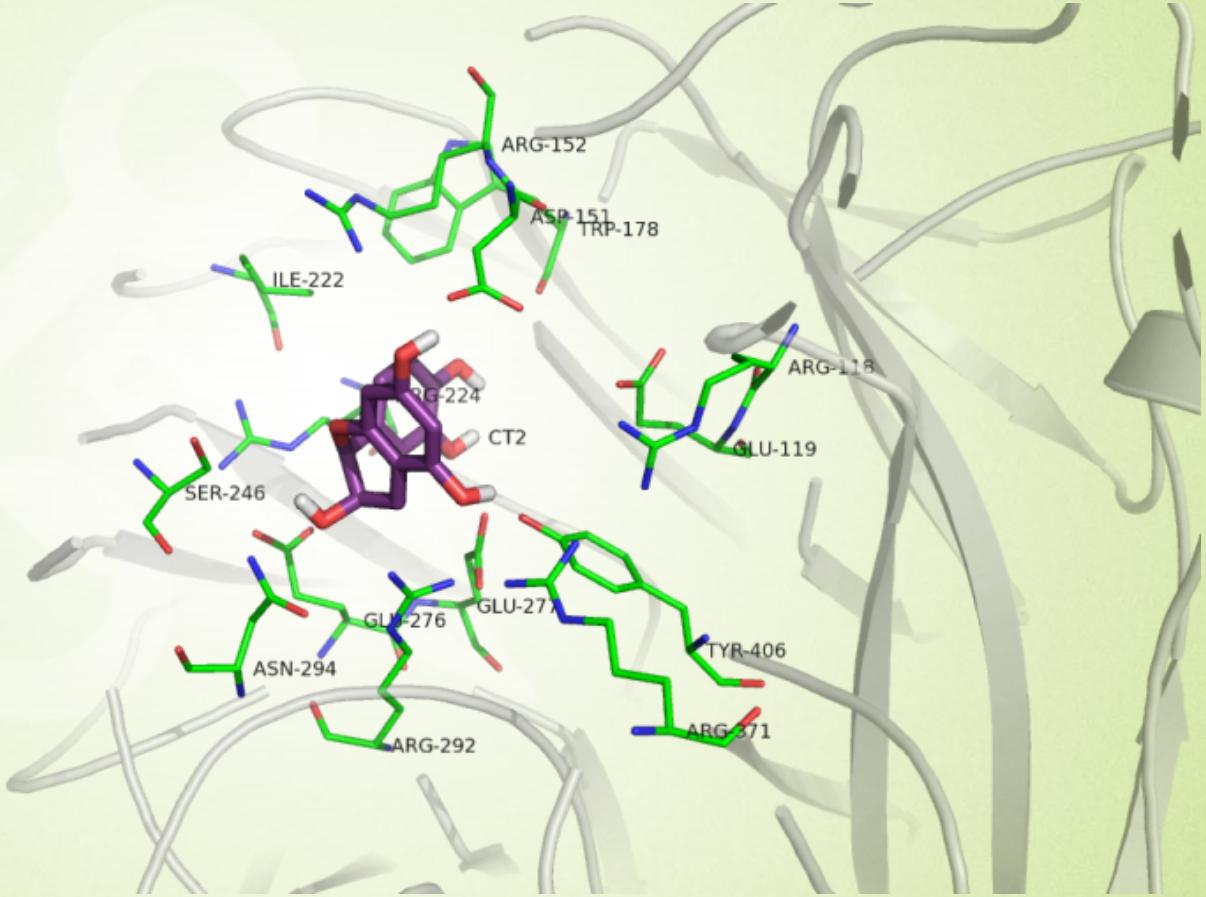
Governa, 2018 unpublished data

P. sidoides radice Eps7630

Attività antineuraminidasi

Catechina 2S3R

- Mantiene quasi tutte le interazioni (1 polari) più 3 polari nuove
- Mantiene l'interazione polare con ARG292



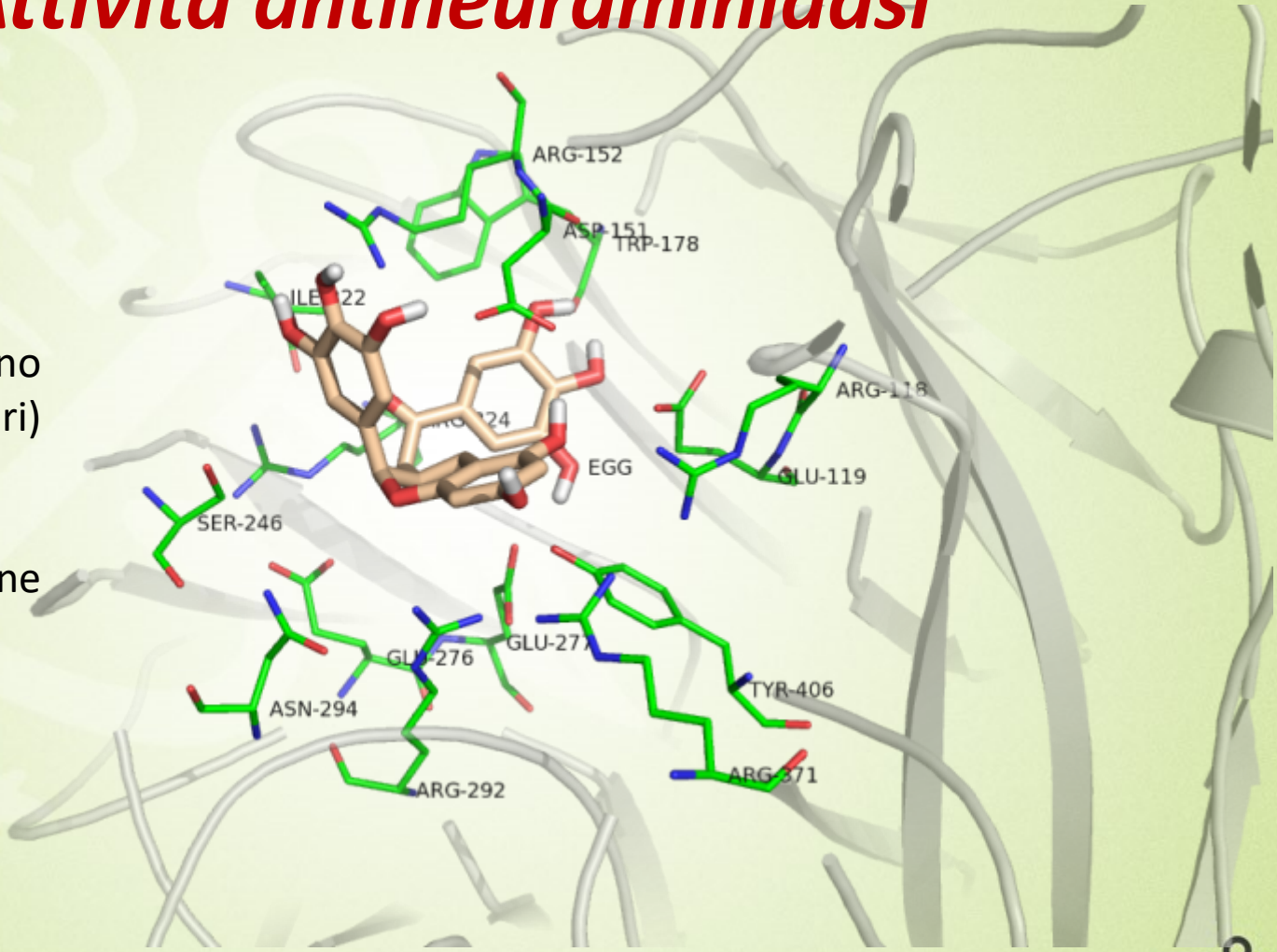
Governa, 2018 unpublished data

P. sidoides radice Eps7630

Attività antineuraminidasi

EGCG

- Mantiene meno interazioni (1 polari) più 2 polari nuove
- Mantiene l'interazione polare con ARG292



Governa, 2018 unpublished data

P. sidoides radice Eps7630

Meccanismo d'azione antinfluenzale

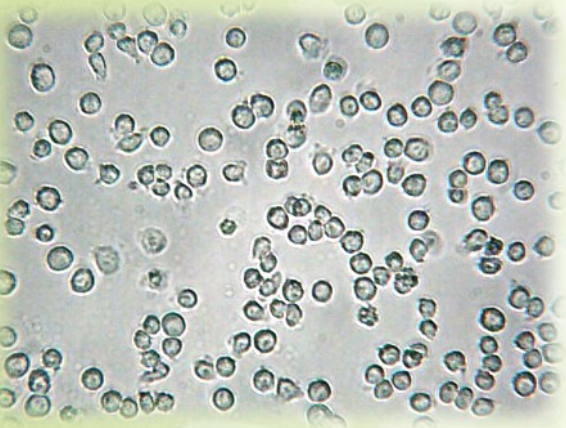
Table 1. IC_{50} values for the inhibition of viral influenza A (H1N1) neuraminidase (H1N1-NA) and bacterial *Vibrio cholerae* neuraminidase (VCNA) by flavan-3-ols.

Test Substance	IC_{50} (Viral) µg/mL	µM	IC_{50} (Bacterial) µg/mL	µM
Positive control				
oseltamivir carboxylate	2.9 ± 0.2 (1)	0.01 ± 0.001	41 ± 1	144 ± 1
zanamivir	3.7 ± 0.4 (1)	0.01 ± 0.001	17 ± 1	52 ± 2
Flavan-3-ols				
catechin	312 ± 21	1076 ± 75	595 ± 25	2050 ± 87
gallocatechin	547 ± 23	1787 ± 74	603 ± 61	1969 ± 199
catechin-3-*O*-gallate	862 ± 2	1949 ± 4	24 ± 2	55 ± 4
gallocatechin-3-*O*-gallate	181 ± 3	396 ± 7	11 ± 1	25 ± 2
epicatechin	305 ± 19	1053 ± 64	670 ± 29	2186 ± 99
epigallocatechin	532 ± 41	1739 ± 135	598 ± 57	1955 ± 185
epicatechin-3-*O*-gallate	845 ± 24	1910 ± 55	93 ± 8	211 ± 19
epigallocatechin-3-*O*-gallate	717 ± 63	1565 ± 137	29 ± 1	64 ± 3

IC_{50} values are expressed as mean ± standard deviation (SD) (n = 3–6 independent experiments); (1) data are in ng/mL.

Eps7630: IC_{50} viral: 61±2 microg/ml

Rhodiola rosea L.: meccanismo di azione



BV2
Cellule microgliali murine

Estratto
WS1375®

Phytomedicine 68 (2020) 153143

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Original Article

Rhodiola rosea L. modulates inflammatory processes in a CRH-activated BV2 cell model

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ARTICLE INFO

Keywords:
Rhodiola rosea L.
microglia
CRH
HSP70
MAPK
NF-κB

ABSTRACT

Background: *Rhodiola rosea* L. (Crassulaceae) has been used for years in the traditional medicine of several countries as an adaptogen drug, able to preserve homeostasis in response to stress stimuli. Currently *R. rosea* roots and rhizome are classified as a traditional herbal medicinal product for temporary relief of symptoms of stress, such as fatigue and sensation of weakness by the European Medicines Agency.

Hypothesis/Purpose: Increasing evidences suggest the involvement of neuroinflammation in response to stress. However, whether the modulation of neuroinflammatory parameters could be involved in the anti-stress effect of *R. rosea* has been barely studied. Thus, the aim of this work is to investigate the possible modulation of molecular inflammatory processes elicited by a *R. rosea* roots and rhizome ethanolic extract in an *in vitro* model of corticotropin releasing hormone (CRH)-stimulated BV2 microglial cells.

Methods: BV2 cells were stimulated with CRH 100 nM and changes in cell viability, cytokines production and heat shock protein 70 (HSP70) levels were evaluated. Intracellular pathways related to inflammation, such as nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) nuclear translocation and mitogen-activated protein kinases (MAPK) activation were also analyzed.

Results: We found that *R. rosea* extract (2.7% m/m rosavin and 1% m/m salidroside) 20 μg/ml was able to counteract the neuroinflammatory effect of CRH by inhibiting NF-κB nuclear translocation with a mechanism of action involving the modulation of mitogen-activated protein kinase-activated protein kinase 2 (MKK2), extracellular signal-regulated kinase 1/2 (ERK 1/2) and c-Jun n-terminal kinase (JNK), resulting in a reduction of HSP70 expression.

Conclusion: This work expands the knowledge of the intracellular mechanisms involved in *R. rosea* anti-stress activity and may be useful for the study of other adaptogen drugs.

Rhodiola rosea L.: meccanismo di azione

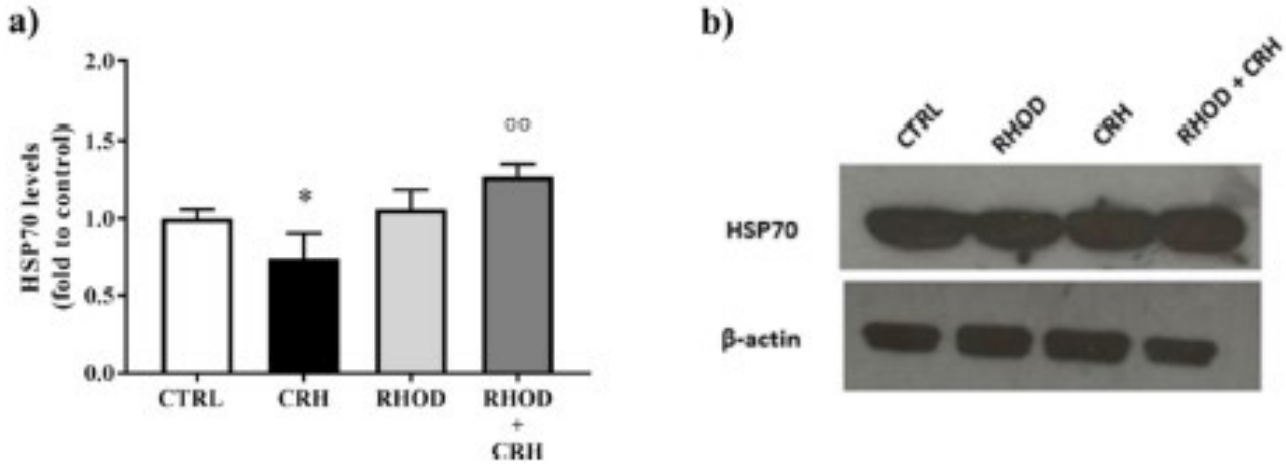
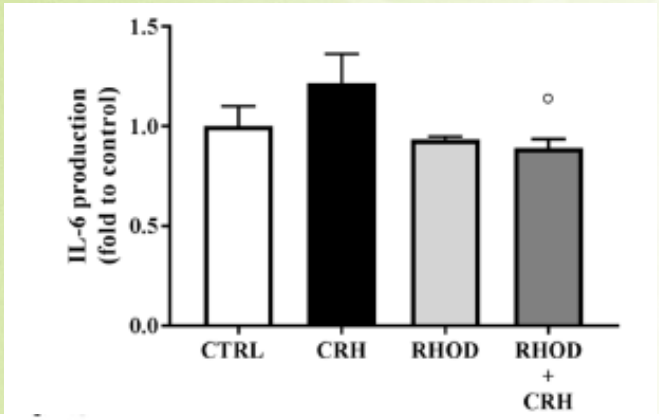


Fig. 6. Relative protein quantification, normalized to β-actin (a) and representative western blot bands (b) of HSP70. * $p < 0.05$ *vs.* control; ° $p < 0.01$ *vs.* stimulus.

- ***Modulazione del rilascio di HSP70***

Rhodiola rosea L.: meccanismo di azione



- *Modulazione del rilascio di IL-6*

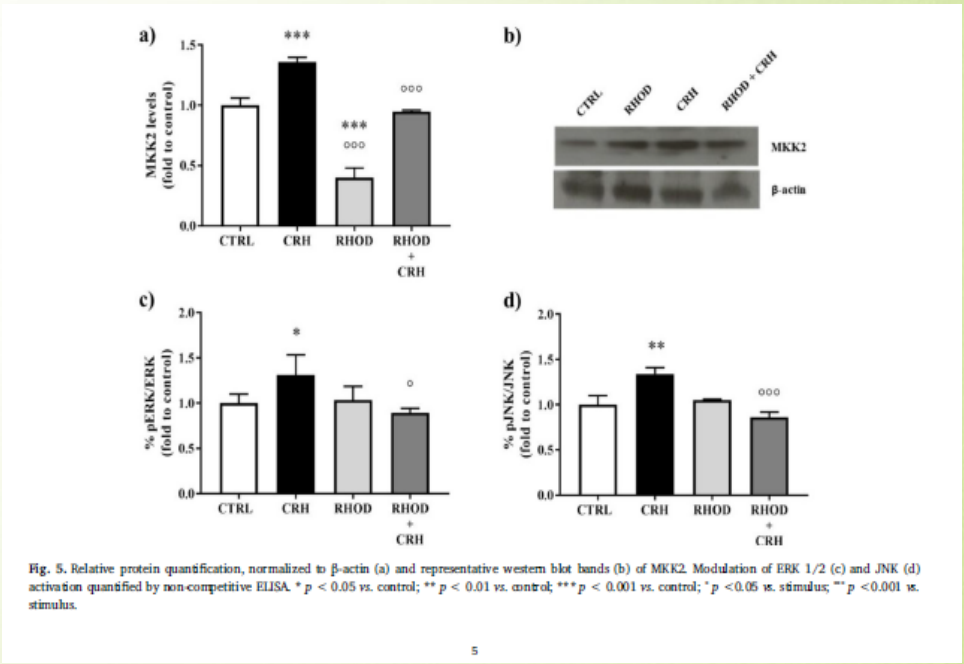
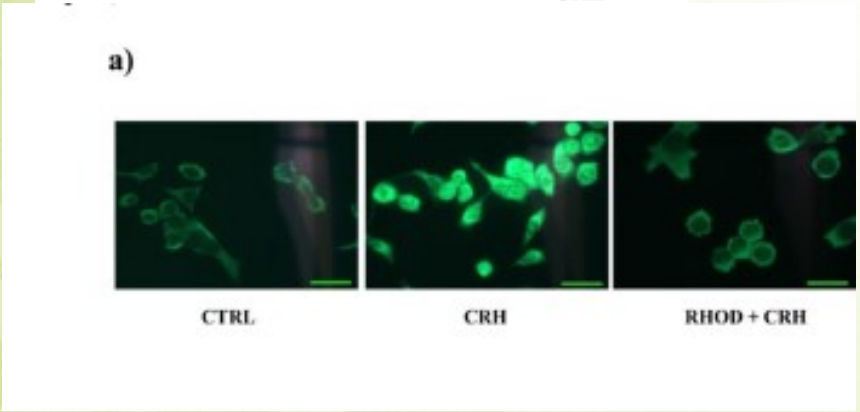


Fig. 5. Relative protein quantification, normalized to β-actin (a) and representative western blot bands (b) of MKK2. Modulation of ERK 1/2 (c) and JNK (d) activation quantified by non-competitive ELISA. * $p < 0.05$ *vs.* control; ** $p < 0.01$ *vs.* control; *** $p < 0.001$ *vs.* control; ° $p < 0.05$ *vs.* stimulus; °°° $p < 0.001$ *vs.* stimulus.

5



- *Inibizione della traslocazione di NF-kB e della fosforilazione delle MAPK*

Sperimentazione clinica

Rhodiola rosea L.

A selected pharmacological profile of adaptogens, clinical efficacy in humans relative to CNS.

	Pathophysiological condition	***Rhodiola***	***Eleutherococcus***	***Schisandra***
Neuro-endocrine system	Physical fatigue	+	+	++
	Mental fatigue (declined attention)	++	+	+
	Stress induced chronic fatigue	+	+	
	Depression	+		

Panossian e Wikman, 2010

Rodiola è l'adattogeno più studiato e risultato maggiormente efficace nel ridurre lo stress mentale

Rhodiola rosea L.

› Neuropsychiatr Dis Treat. 2017 Mar 22;13:889-898. doi: 10.2147/NDT.S120113. eCollection 2017.

Multicenter, open-label, exploratory clinical trial with *Rhodiola rosea* extract in patients suffering from burnout symptoms

Siegfried Kasper [1], Angelika Dienel [2]

Affiliations + expand

PMID: 28367055 PMCID: PMC5370380 DOI: 10.2147/NDT.S120113

Free PMC article

Abstract

Purpose: This study is the first clinical trial aiming to explore the clinical outcomes in burnout patients treated with *Rhodiola rosea*. The reported capacity of *R. rosea* to strengthen the organism against stress and its good tolerability offer a promising approach in the treatment of stress-related burnout. The aim of the treatment was to increase stress resistance, thus addressing the source rather than the symptoms of the syndrome and preventing subsequent diseases associated with a history of burnout. The objective of the trial was to provide the exploratory data required for planning future randomized trials in burnout patients in order to investigate the clinical outcomes of treatment with *R. rosea* dry extract in this target group.

Methods: The study was planned as an exploratory, open-label, multicenter, single-arm trial. A wide range of rating scales were assessed and evaluated in an exploratory data analysis to generate hypotheses regarding clinical courses and to provide a basis for the planning of subsequent studies. A total of 118 outpatients were enrolled. A daily dose of 400 mg *R. rosea* extract (WS® 1375, Rosalin) was administered over 12 weeks. Clinical outcomes were assessed by the German version of the Maslach Burnout Inventory, Burnout Screening Scales I and II, Sheehan Disability Scale, Perceived Stress Questionnaire, Number Connection Test, Multidimensional Mood State Questionnaire, Numerical Analogue Scales for different stress symptoms and impairment of sexual life, Patient Sexual Function Questionnaire, and the Clinical Global Impression Scales.

Results: The majority of the outcome measures showed clear improvement over time. Several parameters had already improved after 1 week of treatment and continued to improve further up to the end of the study. The incidence of adverse events was low with 0.015 events per observation day.

Discussion: The trial reported here was the first to investigate clinical outcomes in patients suffering from burnout symptoms when treated with *R. rosea*. During administration of the study drug over the course of 12 weeks, a wide range of outcome measures associated with the syndrome clearly

Estratto secco standardizzato WS1375 utilizzato al dosaggio di 2 x 200 mg/die per 12 settimane.

118 soggetti con sintomi da esaurimento da stress (burnout)

Misura dei parametri di stress.

Risultati positivi negli score già dopo una settimana.

Effetti avversi minimi e non correlati a rodiola.

Rhodiola rosea L.

Neuropsychiatr Dis Treat. 2017 Mar 22;13:889-898. doi: 10.2147/NDT.S120113. eCollection 2017.

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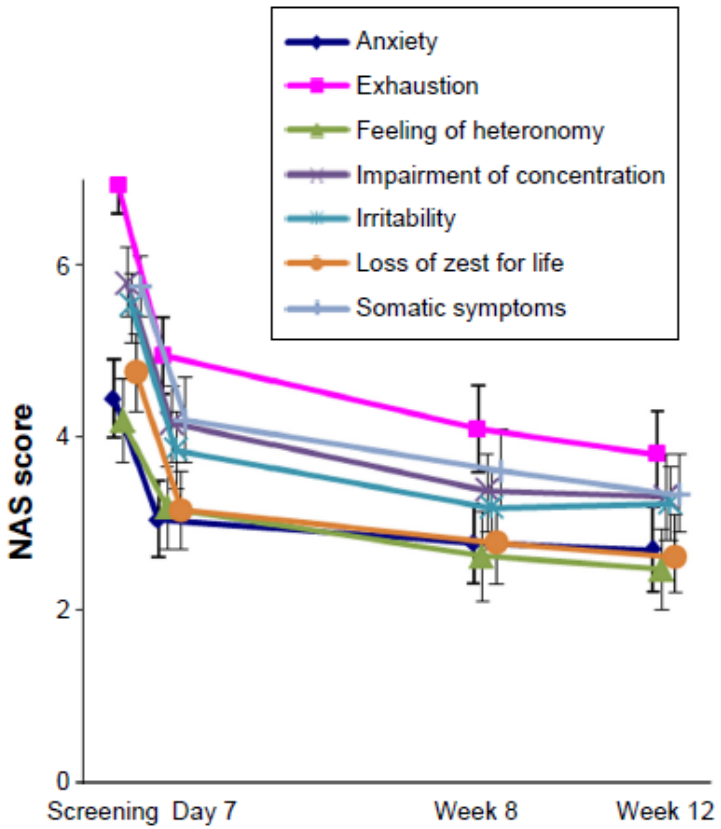


Figure 2 NAS for subjective stress symptoms.
Note: N=117, mean ±95% confidence interval, FAS.
Abbreviations: NAS, Numerical Analogue Scale; FAS, full analysis set.

Rhodiola rosea L.

Clinical Trial > Planta Med. 2009 Feb;75(2):105-12. doi: 10.1055/s-0028-1088346.
Epub 2008 Nov 18.

A randomised, double-blind, placebo-controlled, parallel-group study of the standardised extract shr-5 of the roots of Rhodiola rosea in the treatment of subjects with stress-related fatigue

Erik M Olsson [1], Bo von Schéele, Alexander G Panossian

Affiliations + expand

PMID: 19016404 DOI: 10.1055/s-0028-1088346

Abstract

The aim of the study was to assess the efficacy of the standardised extract SHR-5 of roots of Rhodiola Rosea L. in the treatment of individuals suffering from stress-related fatigue. The phase III clinical trial took the form of a randomised, double-blind, placebo-controlled study with parallel groups. Participants, males and females aged between 20 and 55 years, were selected according to the Swedish National Board of Health and Welfare diagnostic criteria for fatigue syndrome. A total of 60 individuals were randomised into two groups, one (N = 30) of which received four tablets daily of SHR-5 extract (576 mg extract/day), while a second (N = 30) received four placebo tablets daily. The effects of the extract with respect to quality of life (SF-36 questionnaire), symptoms of fatigue (Pines' burnout scale), depression (Montgomery -Asberg depression rating scale - MADRS), attention (Conners' computerised continuous performance test II - CCPT II), and saliva cortisol response to awakening were assessed on day 1 and after 28 days of medication. Data were analysed by between-within analyses of variance. No serious side effects that could be attributed to the extract were reported. Significant post-treatment improvements were observed for both groups (placebo effect) in Pines' burnout scale, mental health (SF-36), and MADRS and in several CCPT II indices of attention, namely, omissions, commissions, and Hit RT SE. When the two groups were compared, however, significant effects of the SHR-5 extract in comparison with the placebo were observed in Pines' burnout scale and the CCPT II indices omissions, Hit RT SE, and variability. Pre- VERSUS post-treatment cortisol responses to awakening stress were significantly different in the treatment group compared with the control group. It is concluded that repeated administration of R. ROSEA extract SHR-5 exerts an anti-fatigue effect that increases mental performance, particularly the ability to concentrate, and decreases cortisol response to awakening stress in burnout patients with fatigue syndrome.

Estratto secco standardizzato SHR-5 utilizzato al dosaggio di 576 mg/die per 4 settimane.

60 soggetti con sintomi da affaticamento da stress. Studio in doppio cieco.

Misura dei parametri di stress e cortisolo salivare

- Risultati positivi e migliori del placebo negli score della scala di burnout di Pines e indici di performance mentale CCPT.

- Riduzione del cortisolo salivare al mattino

Effetti avversi minimi e non correlati a rodiola.

Rhodiola rosea L.

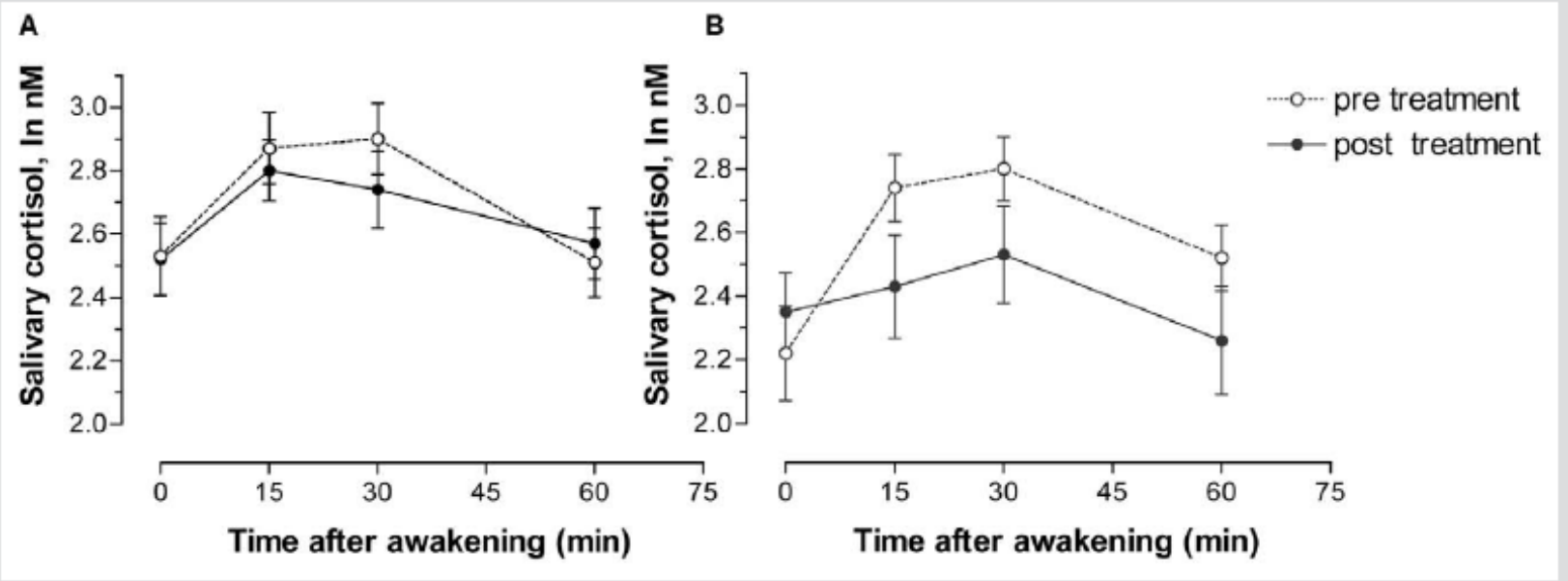


Fig. 1 Cortisol response to awakening in patients with fatigue syndrome showing pre- and post-treatment logarithmised mean values of salivary cortisol with respect to time after awakening for (A) placebo group ($n = 25$) and (B) group treated with *R. rosea* extract SHR-5 ($n = 21$) over a period of 28 days. Vertical bars denote standard deviations.

Riduzione dei livelli di cortisolo mattutino

Metanalisi

Lavandula angustifolia Mill.

Meta-Analysis > Phytomedicine. 2019 Dec;65:153099. doi: 10.1016/j.phymed.2019.153099. Epub 2019 Sep 26.

Effects of lavender on anxiety: A systematic review and meta-analysis

Davide Donelli [1], Michele Antonelli [2], Caterina Bellinazzi [3], Gian Franco Gensini [4], Fabio Firenzuoli [5]

Affiliations + expand

PMID: 31655395 DOI: 10.1016/j.phymed.2019.153099

Free article

Abstract

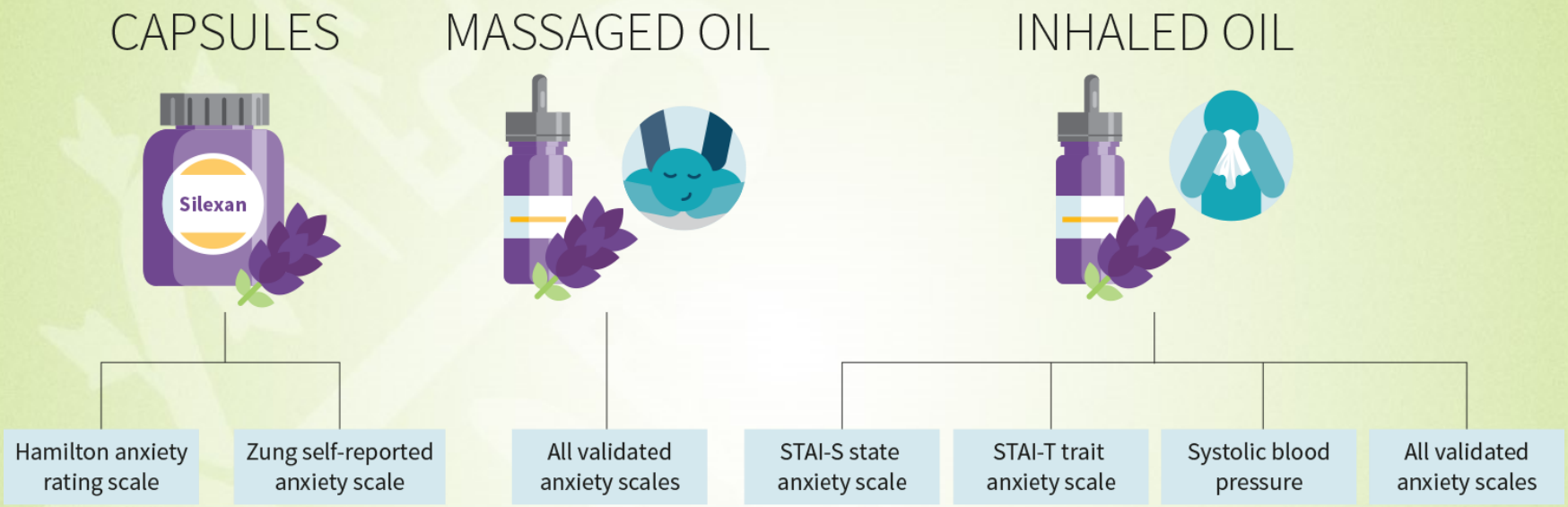
Background: Anxiety is one of the uprising psychiatric disorders of the last decades and lavender administration has been traditionally suggested as a possible treatment. The objective of this review is to assess the efficacy of lavender, in any form and way of administration, on anxiety and anxiety-related conditions.

Methods: The PRISMA guidelines were followed. Retrieved data were qualitatively and quantitatively synthesized. Randomized Controlled Trials (RCTs) and Non-Randomized Studies (NRSs) which investigated the efficacy of lavender, in any form and way of administration, on patients with anxiety, involved in anxiety-inducing settings or undergoing anxiety-inducing activities, compared to any type of control, without language restrictions, were identified through electronic database searches. Medline via PubMed, Scopus, Web of Science, Cochrane Library, EMBASE, and Google Scholar were systematically searched. All databases were screened up to November 2018. Risk of bias was assessed with the Cochrane risk-of-bias tool and the following domains were considered: randomization, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting, and other biases.

Results: 65 RCTs (7993 participants) and 25 NRSs (1200 participants) were included in the qualitative synthesis and 37 RCTs (3964 participants) were included in the quantitative synthesis. Overall, the qualitative synthesis indicated that 54 RCTs and 17 NRSs reported at least a significant result in favor of lavender use for anxiety. The quantitative synthesis showed that lavender inhalation can significantly reduce anxiety levels measured with any validated scale (Hedges' g = -0.73 [95% CI -1.00 to -0.46], p < 0.00001, 1682 participants), as well as state anxiety (Spielberger's state-trait anxiety inventory (STAI)-State mean difference = -5.99 [95% CI -9.39 to -2.59], p < 0.001, 901 participants) and trait anxiety (STAI-Trait mean difference = -8.14 [95% CI -14.44 to -1.84], p < 0.05, 196 participants). Lavender inhalation did not show a significant effect in reducing systolic blood pressure as a physiological parameter of anxiety. A significant effect in diminishing anxiety levels was also found in favor of the use of oral Silexan® 80 mg/die for at least 6 weeks (Hamilton Anxiety Scale mean difference = -2.90 [95% CI -4.86 to -0.95], p = 0.004, 1173 participants; Zung Self-rating Anxiety Scale mean difference = -2.62 [95% CI -4.84 to -0.39], p < 0.05, 451 participants) or of the administration of massage with lavender oil (Hedges' g = -0.66 [95% CI -0.97 to -0.35], p < 0.0001, 448 participants).

Discussion: The most important limitation of this review is the low average quality of available studies on the topic. The majority of included RCTs were characterized by a high overall risk of bias. Another limitation regards the heterogeneity of study designs, especially with regard to non-oral ways of administration. Overall, oral administration of lavender essential oil proves to be effective in the treatment of anxiety, whereas for inhalation there is only an indication of an effect of reasonable size, due to the heterogeneity of available studies. Lavender essential oil administered through massage appears effective, but available studies are not sufficient to determine whether the benefit is due to a specific effect of lavender. Further high-quality RCTs with more homogeneous study designs are needed to confirm these findings. Available information outlines a safe profile for lavender-based interventions, although more attention should be paid to the collection and reporting of safety data in future studies. Considering these findings, since treatments with lavender essential oil generally seem safe, and, in the case of inhalation, also simple and inexpensive, they are a therapeutic option which may be considered in some clinical contexts.

Lavandula angustifolia Mill.



Inalazione, bagno o massaggio con olio essenziale di lavanda risultano essere buoni trattamenti a breve termine per l'ansia.

L'assunzione di 20-80 mg/die di o.e. *per os* è la modalità di somministrazione più indicata per trattamenti prolungati per ansia moderata e disturbi dell'umore.

Come viene registrato un farmaco vegetale?

FARMACO VEGETALE

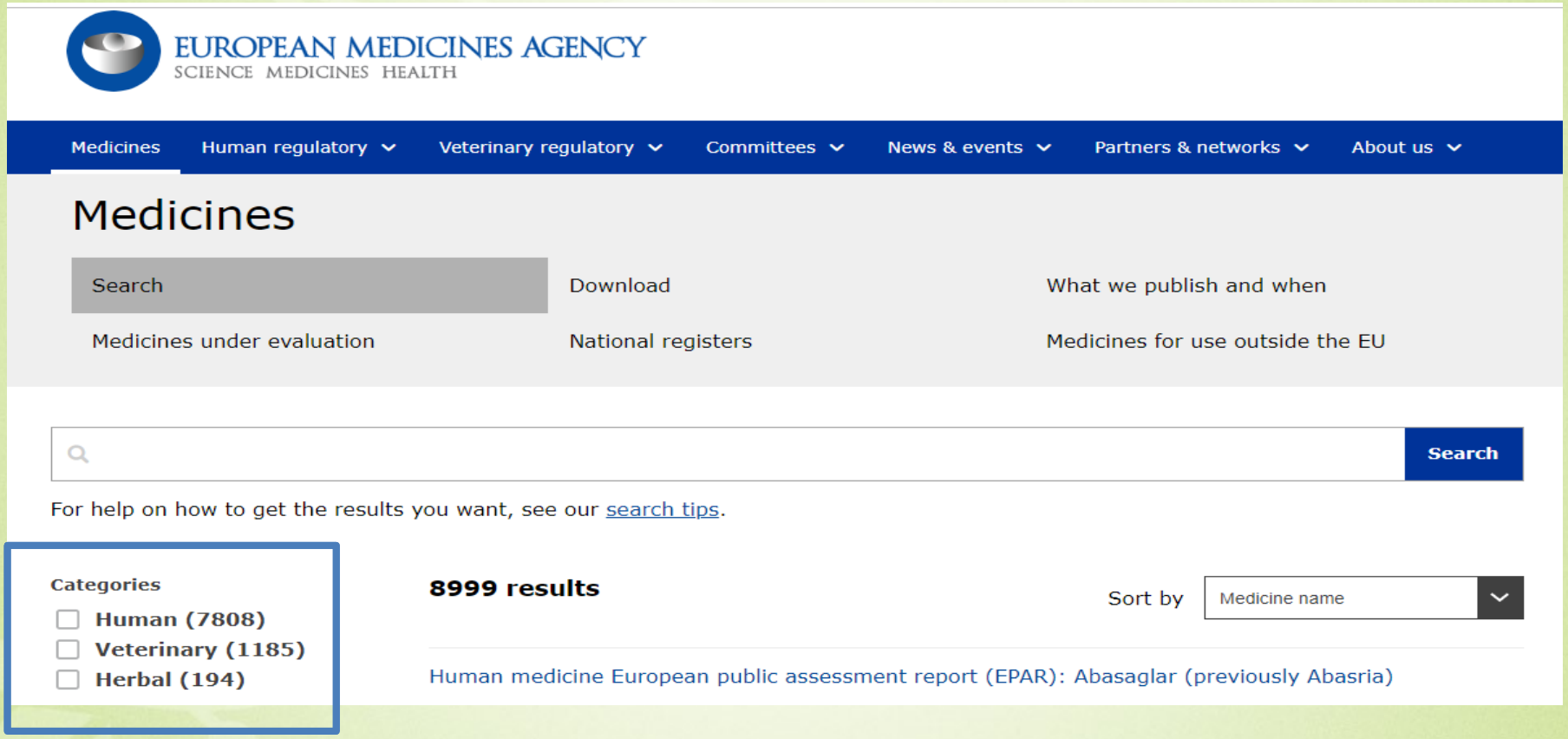
Dir. 2001/83/CE

Farmaci registrati in maniera convenzionale

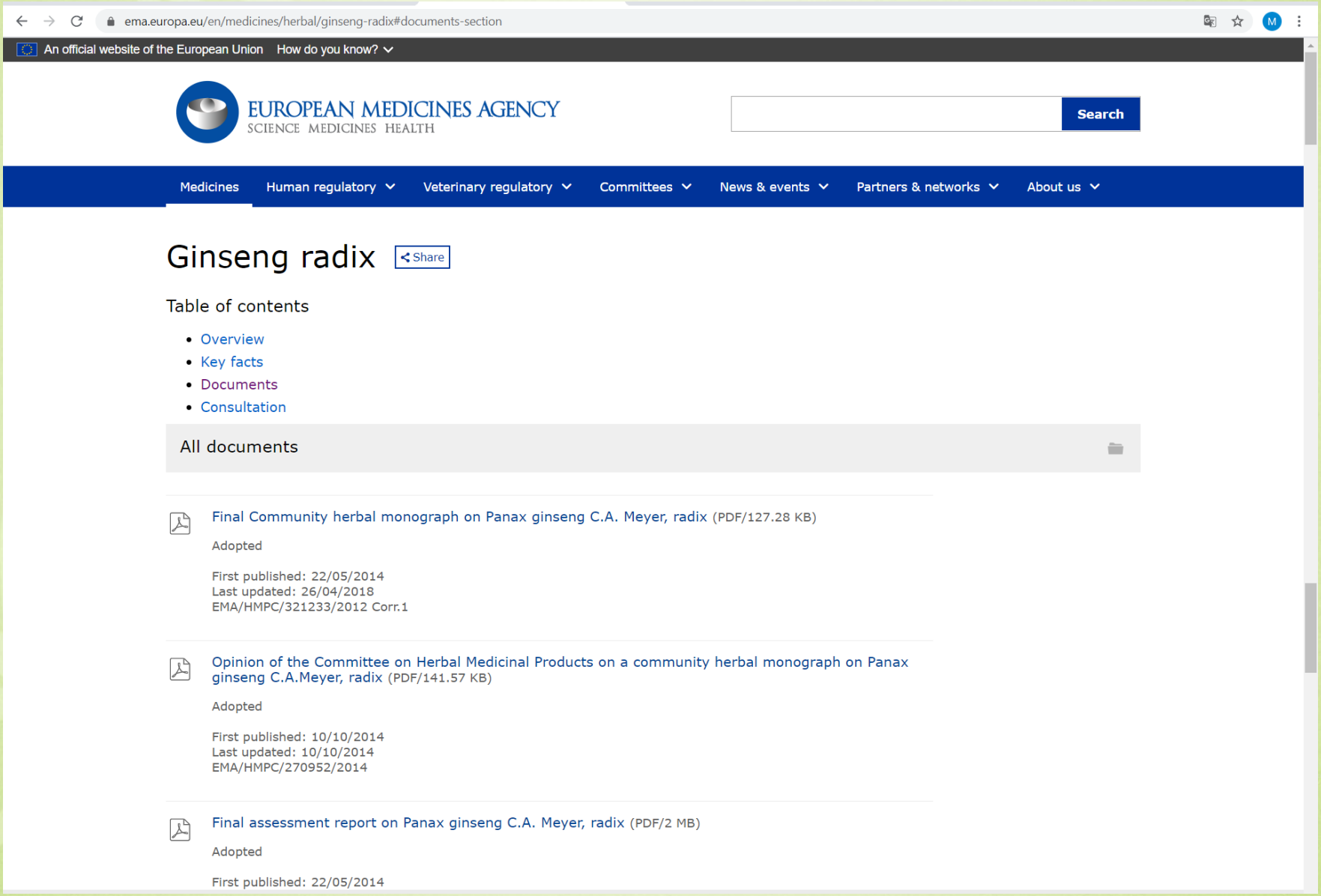
Dir. 2004/24/CE
(emendamento della 2001/83/CE)

Farmaci registrati come THMP

www.ema.europa.eu



www.ema.europa.eu



MONOGRAFIA EMA DI UN FARMACO VEGETALE

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05 June 2018
EMA/HMPC/444244/2015
Committee on Herbal Medicinal Products (HMPC)

European Union herbal monograph on ***Pelargonium sidoides*** DC and/or ***Pelargonium reniforme*** Curt., radix

Final

3. Pharmaceutical form

Well-established use	Traditional use
	Herbal preparations in liquid or solid dosage forms for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.

4. Clinical particulars

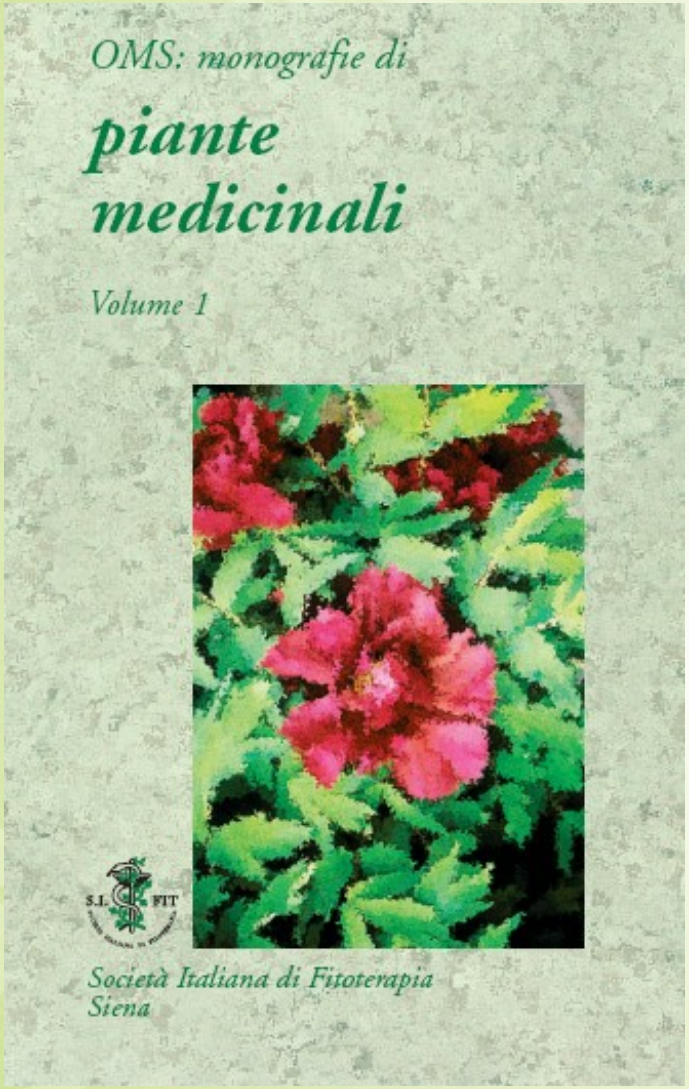
4.1. Therapeutic indications

Well-established use	Traditional use
	Traditional herbal medicinal product for the symptomatic treatment of common cold. The product is a traditional herbal medicinal

4.2. Posology and method of administration

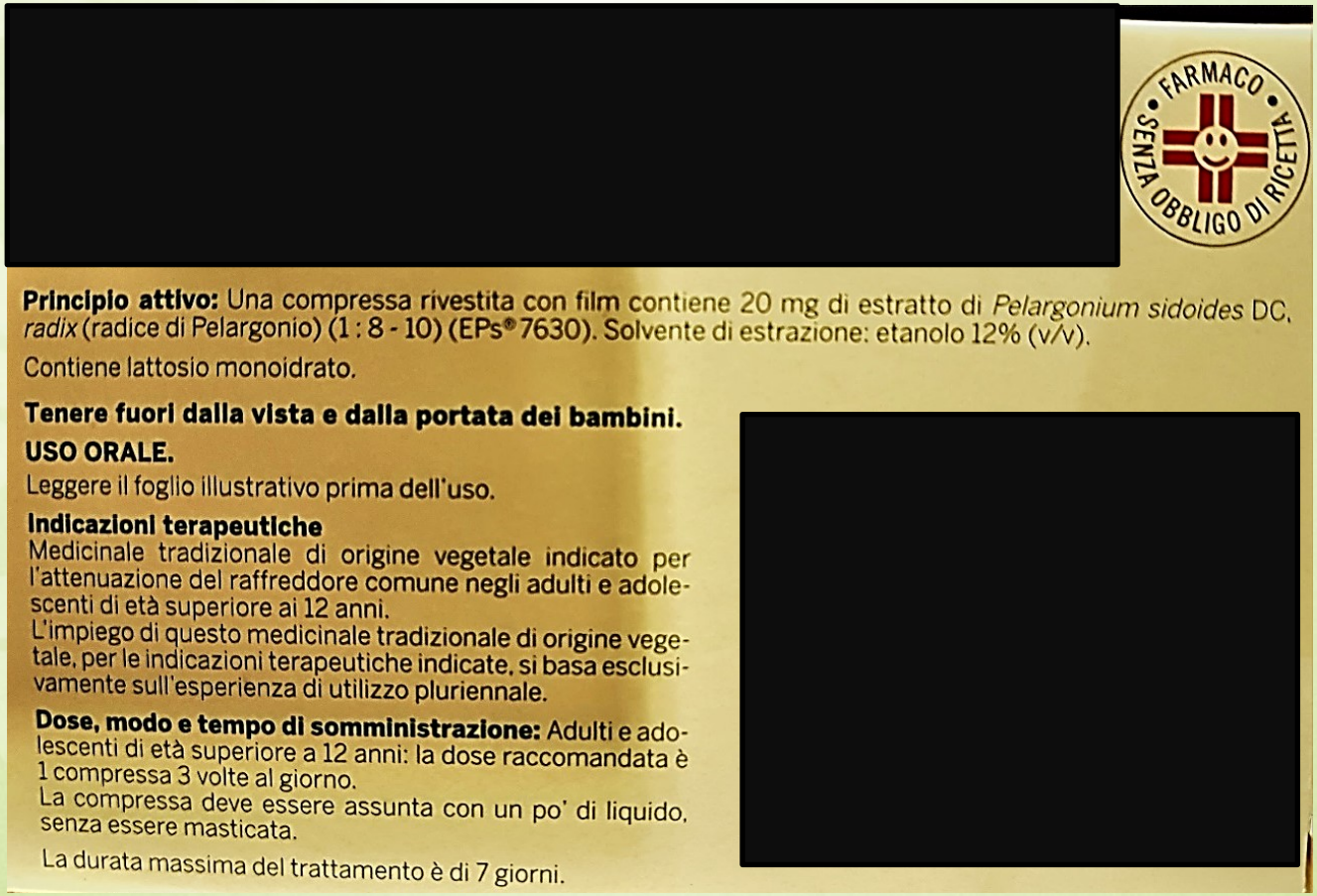
Well-established use	Traditional use
	Posology Single dose ***Adolescents over the age of 12 years, adults and elderly*** a) Liquid extract: 1.19-1.25 ml, 3 times daily. b) Dry extract: 20 mg, 3 times daily. ***Children between 6-12 years*** a) Liquid extract: 0.79-0.83 ml, 3 times daily. b) Dry extract: 20 mg, 2 times daily.

Monografie di Piante Medicinali WHO



Monografie (in ordine alfabetico secondo il nome della pianta)

COME RICONOSCERE E CONOSCERE UN FARMACO VEGETALE

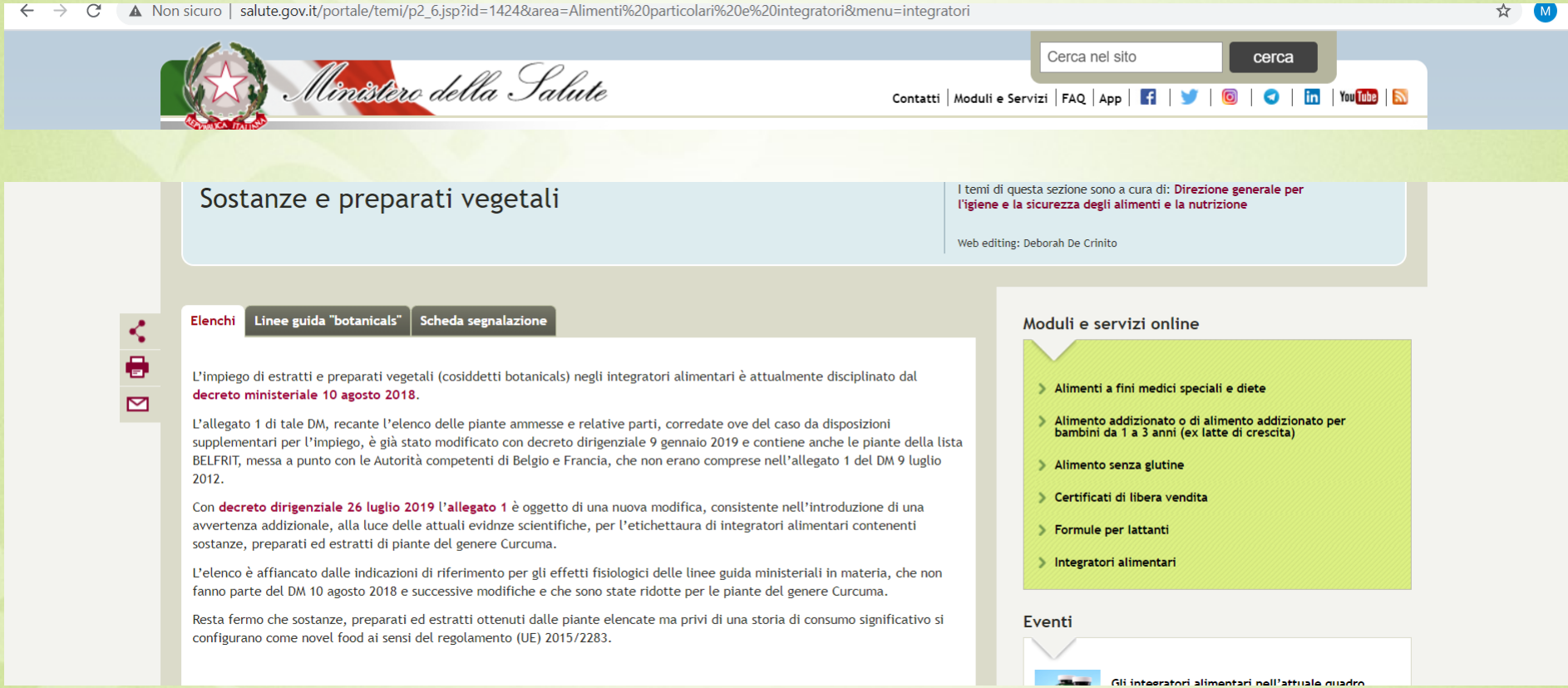


RAZIONALE E SVILUPPO DI UN INTEGRATORE ALIMENTARE VEGETALE

Razionale di uso dell'integratore alimentare

- ***Prodotti pensati realmente per avere un effetto salutistico e di mantenimento della salute;***
- ***Uso di estratti «nuovi», ancora non utilizzabili nel mondo farmaceutico;***
- ***Formulazioni innovative non presenti nei farmaci.***

www.salute.gov.it



INFORMAZIONI PER I PRODOTTI VEGETALI UTILIZZATI IN CONTESTO NON FARMACEUTICO

efsa
European Food Safety Authority

Ministero della Salute

Il documento riporta:
→ l'Allegato 1 al DM 10 agosto 2018 sulla disciplina dell'impiego negli integratori alimentari di Sostanze e preparati vegetali come aggiornato con Decreto 9 gennaio 2018 e da ultimo con Decreto 26 luglio 2019.

→ nell'ultima colonna le "Linee guida ministeriali di riferimento per gli effetti fisiologici" che non fanno parte integrante del predetto DM. Tali effetti, impiegabili in attesa della definizione dei claims sui botanicals, sono volti ad ottimizzare le funzioni dell'organismo nell'ambito dell'omeostasi secondo il modello definito dal Consiglio d'Europa (Homeostasis, a model to distinguish between food, including food supplements, and medicinal products, 07/02/2008)

CLAIMS DEI BOTANICALS IN UN INTEGRATORE ALIMENTARE

ALLEGATO 1- BOTANICALS						
***Passiflora caerulea* L.**	Passifloraceae		**folium, flos**			
***Passiflora edulis* Sims**	Passifloraceae		**fructus, herba**			herba: Antiossidante. Contrasto dei disturbi del ciclo mestruale. Contrasto dei disturbi della menopausa. Funzionalità articolare. Rilassamento (sonno). Funzionalità del sistema digerente.
***Passiflora incarnata* L.**	Passifloraceae		**folium, flos, herba cum floribus**			folium, herba cum floribus : Rilassamento (sonno; in caso di stress). Benessere mentale. Regolare motilità gastrointestinale ed eliminazione dei gas.

Controlli di qualità di un integratore alimentare

CONTROLLI DI QUALITA' DEGLI INTEGRATORI ALIMENTARI

- *Controllo botanico*
- *Metalli pesanti*
- *Carica microbica*
- *Sostanze radiattive*
- *Pesticidi*

CONTROLLI DI QUALITA' PER LA SICUREZZA DI IMPIEGO

L'importanza della titolazione dei marker in un integratore alimentare

Negli integratori alimentari vegetali il primo requisito di qualità non obbligatorio, ma fondamentale, è la titolazione degli estratti, cioè la quantificazione dei marker chimici.

Un marker è un componente o una classe di molecole di una droga o di un prodotto da essa derivato che concorre a definirne:

- ***le proprietà biologiche***
- ***l'identità***
- ***la specificità***
- ***l'origine***
- ***la genuinità***
- ***la qualità***

indipendentemente dalla sua abbondanza

TABELLA NUTRIZIONALE	PER BUSTA	% VNR*
Echinacea e.s.	200 mg	**
Acerola e.s.	90 mg	**

CONTENUTI MEDI	per 15 ml	per 100 ml
Miele di Manuka	750 mg	5 g
Propolis e.s. tit 12%	120 mg	0,8 g
flavonoidi tot. come galangina	14,4 mg	0,096 g
Echinacea purpurea e.s. tit. 4%	60 mg	0,4 g
polifenoli totali	2,4 mg	0,016 g
Echinacea purpurea e.s. tit. 2%	30 mg	0,2 g
acido cicorico	0,6 mg	0,004 g

Sperimentazione di una formulazione "nutraceutica"

Nutrients **2020**, *12*, 1803; doi:10.3390/nu12061803

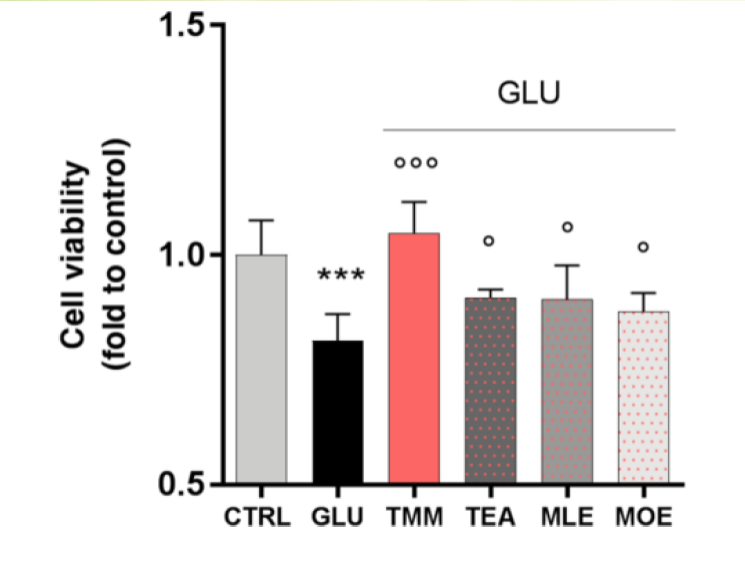
Article

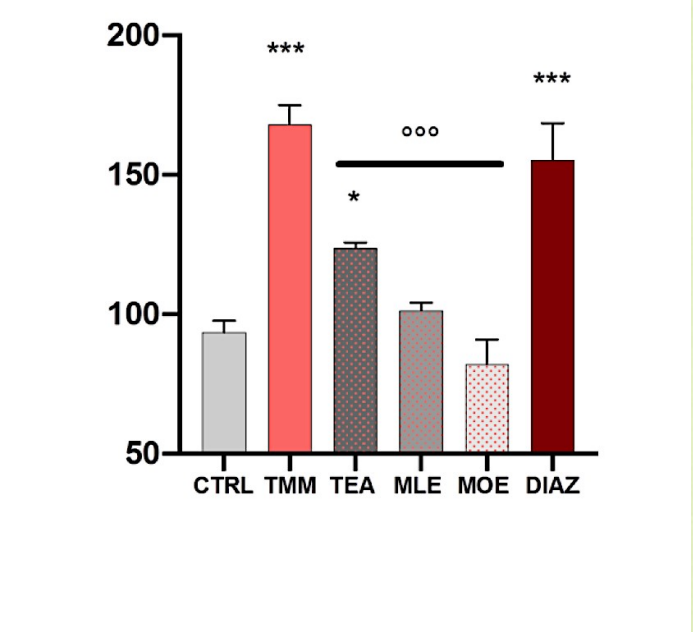
Novel Therapeutic Approach for the Management of Mood Disorders: In Vivo and In Vitro Effect of a Combination of L-Theanine, *Melissa officinalis* L. and *Magnolia officinalis* Rehder & E.H. Wilson

Vittoria Borgonetti [1,†], Paolo Governa [2,†], Marco Biagi [3] and Nicoletta Galeotti [1,*]

Abstract: Mood disorders represent one of the most prevalent and costly psychiatric diseases worldwide. The current therapies are generally characterized by several well-known side effects which limit their prolonged use. The use of herbal medicine for the management of several psychiatric conditions is becoming more established, as it is considered a safer support to conventional pharmacotherapy. The aim of this study was to investigate the possible anxiolytic and antidepressant activity of a fixed combination of L-theanine, *Magnolia officinalis*, and *Melissa officinalis* (TMM) in an attempt to evaluate how the multiple modulations of different physiological systems may contribute to reducing mood disorders. TMM showed an anxiolytic-like and antidepressant-like activity in vivo, which was related to a neuroprotective effect in an in vitro model of excitotoxicity. The effect of TMM was not altered by the presence of flumazenil, thus suggesting a non-benzodiazepine-like mechanism of action. On the contrary, a significant reduction in the effect was observed in animals and neuronal cells co-treated with AM251, a cannabinoid receptor type 1 (CB1) antagonist, suggesting that the endocannabinoid system may be involved in the TMM mechanism of action. In conclusion, TMM may represent a useful and safe candidate for the management of mood disorders with an innovative mechanism of action, particularly as an adjuvant to conventional therapies.

Sperimentazione di una formulazione "nutraceutica"





TMM: *Associazione* MOE: *Magnolia officinalis* MLE: *Melissa officinalis* TEA: *L-theanine*

Effetto ansiolitico su modello animale simile qualitativamente a quello del diazepam.
Sinergia *in vitro* e *in vivo* dei costituenti.

Sperimentazione di una formulazione "nutraceutica"

Review > J Herb Med. 2021 Aug;28:100451. doi: 10.1016/j.hermed.2021.100451. Epub 2021 Mar 26.

Appropriate use of essential oils and their components in the management of upper respiratory tract symptoms in patients with COVID-19

Marco Valussi [1], Michele Antonelli [2], Davide Donelli [2 3], Fabio Firenzuoli [3]

Review > Minerva Gastroenterol (Torino). 2021 Jun;67(2):190-195. doi: 10.23736/S2724-5985.20.02771-3. Epub 2020 Oct 5.

Quercetin Phytosome® as a potential candidate for managing COVID-19

Francesco DI Pierro [1], Amjad Khan [2], Alexander Bertuccioli [3], Pamela Maffioli [4], Giuseppe Derosa [4 5], Saeed Khan [6], Bilal A Khan [6], Roohi Nigar [7], Ikram Ujjan [8], Bikha R Devrajani [9]

Sicurezza degli integratori alimentari

Review > J Med Food. 2022 Jan;25(1):1-11. doi: 10.1089/jmf.2021.0062. Epub 2021 Nov 17.

A Practical Perspective on the Use of Botanicals During the COVID-19 Pandemic: From Proven to Potential Interactions

Alexander Bertuccioli [1], Marco Cardinali [2], Francesco Di Pierro [3 4], Simone Magi [5], Giordano Zonzini [5]

Review > Phytother Res. 2022 Mar;36(3):1093-1102. doi: 10.1002/ptr.7373. Epub 2022 Jan 17.

Anthraquinone laxatives use and colorectal cancer: A systematic review and meta-analysis of observational studies

Niccolò Lombardi [1 2], Giada Crescioli [1 2], Valentina Maggini [1 3], Raffaele Bellezza [1], Iacopo Landi [1], Alessandra Bettiol [4], Francesca Menniti-Ippolito [5], Ilaria Ippoliti [5], Gabriela Mazzanti [6], Annabella Vitalone [6], Eugenia Gallo [3 4], Francesco Sivelli [3], Francesco Sofi [4], Gian Franco Gensini [7], Alfredo Vannacci [1 2], Fabio Firenzuoli [3]

I percorsi formativi in fitoterapia

LA FITOTERAPIA: A CAVALLO TRA CONVENZIONALE E NON CONVENZIONALE

Convenzionale:

Branca della farmacoterapia convenzionale che prevede **l'utilizzo di farmaci vegetali.**

Non convenzionale:

Utilizzo di prodotti vegetali tradizionali (MTC, Ayurveda, Unani…)

Utilizzo di prodotti non farmaceutici (integratori, cosmetici…) per condizioni patologiche.

DISCIPLINA DELLA FITOTERAPIA IN ITALIA

In Italia la fitoterapia è considerata una delle tre discipline complementari (non convenzionali!) riconosciute, insieme a agopuntura e omeopatia.

La formazione dei medici chirurghi ed odontoiatri che esercitano la fitoterapia fa riferimento all'Accordo Stato-Regioni del 2013 e le successive leggi regionali.

L'accordo prevede che ogni Ordine provinciale disponga di elenchi speciali di «esperti» delle medicine complementari.

TITOLI RICHIESTI PER L'ISCRIZIONE NEGLI ELENCHI SPECIALI DEGLI ESPERTI IN FITOTERAPIA

Ai fini dell'iscrizione agli elenchi istituiti presso gli Ordini professionali provinciali dei Medici Chirurghi e degli Odontoiatri, **il percorso formativo dei professionisti che esercitano l'Agopuntura, la Fitoterapia, l'Omeopatia, l'Omotossicologia, l'Antroposofia, l'Ayurvedica e la Medicina Tradizionale Cinese deve essere effettuato, presso soggetti pubblici o privati accreditati alla formazione.**

TITOLI RICHIESTI PER L'ISCRIZIONE NEGLI ELENCHI SPECIALI DEGLI ESPERTI IN FITOTERAPIA

Il percorso formativo in Agopuntura, Fitoterapia, Omeopatia, Omotossicologia, Antroposofia, Ayurvedica e Medicina Tradizionale Cinese, deve corrispondere ai seguenti requisiti:

- ***durata di almeno 400 ore di formazione teorica, cui si aggiungono 100 ore di pratica clinica, di cui almeno il 50% di tirocinio pratico supervisionato da un medico esperto della disciplina in oggetto. A tale monte orario vanno sommati lo studio individuale e la formazione guidata.***

- ***Master universitari, ovvero corsi di formazione triennali.***

- frequenza minima all'80% delle lezioni sia teoriche che pratiche

- il percorso formativo accreditato prevede il superamento di un esame teorico-pratico al termine di ciascuno degli anni di corso previsti, nonché la discussione finale di una tesi.

- al termine del percorso formativo, verrà rilasciato dai soggetti pubblici e privati accreditati alla formazione un attestato in conformità ai requisiti richiesti, che consentirà l'iscrizione del professionista agli elenchi delle singole discipline.
- gli insegnamenti di tipo generale, non riferiti specificamente alla disciplina in oggetto, non dovranno superare il 20% del monte ore complessivo di formazione teorica.
- la Formazione a distanza (FAD) eventualmente inserita nella programmazione didattica non dovrà superare il 30% delle ore di formazione teorica e dovrà essere realizzata in conformità alla normativa vigente.

Master Universitari in fitoterapia

Note conclusive

Le piante medicinali, se ben conosciute e razionalmente utilizzate, hanno una solida evidenza scientifica di utilizzo in medicina.

Elementi favorevoli:

- **Meccanismo d'azione aspecifico e multitarget**
- **Profilo di sicurezza**

Elementi da tenere in considerazione:

- **Intenzione d'uso (trattamento o prevenzione)**
- **Diversità dei prodotti in commercio**
- **Titolazione e qualità dei preparati**
- **Dosaggi delle formulazioni**

Note conclusive

I percorsi formativi in fitoterapia sono post-lauream e in alcuni casi sono istituiti dalle Università come Master (DM 509/99) secondo i requisiti dell'Accordo Stato-Regioni per la formazione degli esperti in medicine complementari…

In attesa che la formazione parta dal curriculum del medico durante il corso di laurea, secondo i canoni di una medicina basata sull'evidenza in cui la fitoterapia non può mancare.