



Pharmacognosy

Chemical composition and antinociceptive activity of volatile fractions of the aerial parts of *Solidago chilensis* (Compositae)

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Abstract

Thirty-six compounds were identified from aerial parts of *Solidago chilensis* cultivated at PAF/FIOCRUZ campus in Rio de Janeiro city (RJ) using solid-phase microextraction (HS-SPME) and gas chromatography-mass spectrometry (GC-MS) analysis. These compounds are mainly non-oxygenated mono and sesquiterpenes. Germacrene D is the major compound of two the essential oil analyzed samples (12 to 23%) and of two of the volatiles samples analyzed by SPME (central stems and dry inflorescences samples). Limonene is the major compound in the fresh inflorescences sample (about 21%). The bornil acetate is present in both volatile fractions (16%) and essential oils (7–8%). All the essential oils samples evaluated shown a great antinociceptive activity, considering the used dose of the samples (1 mg/kg) and the standard substance (50 mg/kg). *Solidago chilensis* is one of Brazil amicas and it is a medicinal plant widely used by the brazilian population. Other plants of the genus *Solidago* are also used in traditional medicine in North America and Europe. This is the first report of SPME analysis from *Solidago* genus and of the antinociceptive effect from *Solidago chilensis* essential oil.

Key words: antinociceptive activity, essential oil, Germacrene D, *Solidago chilensis*, SPME.

Resumo

Trinta e seis compostos foram identificados a partir de partes aéreas de *Solidago chilensis* cultivadas na PAF/FIOCRUZ, na cidade do Rio de Janeiro, usando microextração em fase sólida (MEFS) e analisados por cromatografia gasosa-espectrometria de massa (CG-EM). Estes compostos são principalmente mono terpenos não oxigenados e sesquiterpenos. O Germacrene D é o composto majoritário de duas amostras de óleo essencial analisadas (12 a 23%) e de duas amostras voláteis analisadas por MEFS. Limoneno é o composto majoritário da amostra de inflorescências frescas (cerca de 21%). O acetato de bornila está presente em ambas as frações, voláteis (16%) e óleos essenciais (7–8%). Todas as amostras de óleos essenciais avaliadas apresentaram boa atividade antinociceptiva, considerando a dose utilizada das amostras (1 mg/kg) e a substância padrão (50 mg/kg). *Solidago chilensis* é uma das amicas brasileiras e é uma planta medicinal amplamente utilizada pela população brasileira. Outras plantas do gênero *Solidago* também são utilizadas na medicina tradicional na América do Norte e na Europa. Este é o primeiro relato da análise de MEFS do gênero *Solidago* e do efeito antinociceptivo do óleo essencial de *Solidago chilensis*.

Palavras-chave: atividade antinociceptiva, óleo essencial, Germacrene D, *Solidago chilensis*, MEFS.

Introduction

The *Solidago* genus is the biggest of the Compositae family, and includes about 120 species, most of them occurring in North America. Many members of the *Solidago* genus and of all Compositae family are important as cut flowers and ornamental

crops, as well as being medicinal and aromatic plants, many of which produce essential oils used in folk and modern medicine and in the cosmetics, pharmaceutical industries and as beverages (Abad *et al.* 2013). Species of *Solidago* genus have been reported to possess antibacterial, anti-inflammatory,

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spasmolytic, and carminative properties (Sung *et al.* 1999). *Solidago chilensis* Meyen (also called as *S. microglossa*, *S. odora* (Oliveira *et al.* 1998) is a natural species in Chile, with distribution in South America, including the Northeast, Midwest, Southeast and Southern Brazil. Its use increases based on folk tradition in which its inflorescences and roots are used as anticephalgic in the treatment of injuries, such as anti-inflammatory since the end of the 19th century, after the arrival of the European immigrants, principally the Italians, although its medicinal properties were known since the 13th century. These new settlers called the *Solidago* plants they encountered in Brazil “arnica” due to the similar aromas and medicinal properties to that of *A. montana* L. from Europe (Vieira 1999; Miguel 2007). So, this species has been used by population in place to the hepatotoxic exogenous species *Arnica montana* L. (Digest 2001; Mercandeli *et al.* 2012). Despite of the great use by population, mainly in South America, little is known about the species called “Brazilian arnicas” because very few studies have examined their effectiveness in human health (Silva *et al.* 2010).

The hydroalcoholic extract of *Solidago chilensis* Meyen has been evaluated and suggested that in oral therapeutic doses (till 100 mg/kg) there is no health risk in the acute toxicity test (Paula-Freire *et al.* 2006). Flavonoids, labdane and clerodane diterpenes, saponins, carotenoids, tannins, essential oil and other substances are chemically and biologically described for the *Solidago* species (Torres 1985; Valverde *et al.* 2013).

Volatile oils typically contain a complex mixture of low boiling components which are composed predominantly of terpenoid compounds derived by the mevalonate pathway or composed predominantly of aromatic substances derived by the shikimate pathway. These oils are widely used in the whole world in aromatherapy, in perfumery, to produce cosmetic (hygiene and health care formulations as toothpastes, mouthwashes) as natural flavouring, as spice blends and as medicines due to their therapeutic properties (generally they have a broad spectrum of bioactivity) due to the presence of several active compounds or they are added on it for its flavouring purposes. Those oils are still used in various human activities including religious ceremonies, adornments, sensory perception and others personal uses (Sangwan *et al.* 2001; Schnaubelt 2005).

The essential oil of the *Solidago* genus have been chemically and biologically previously reported to many species as *S. altissima*, *S. gigantea* (Fujita *et al.* 1979), *S. virgaurea* (Fujita 1991), *S. canadensis*

(Weyerstahl *et al.* 1993; Kasali *et al.* 2002), *S. graminifolia* (Kalemba 1992), *S. virgaurea* (Kalemba 1998), *S. chilensis* (Gressler *et al.* 2003; Duarte *et al.* 2005) and these biological activities described were antifungal and (Gressler *et al.* 2003; Li *et al.* 2011), antimicrobial (Duarte *et al.* 2005). The essential oil from *Solidago canadensis* leaf was tested for cytotoxic activities against three tumor cell lines (Yoshihara *et al.* 1969; Steliopoulos *et al.* 2002). There are no previous reports about the antinociceptive activity neither the SPME analysis of the *Solidago chilensis* Meyen essential oil.

Material and Methods

This is a no human subject research, all experimental protocols used in this work were approved and performed in accordance with the recommendations of Commission of Ethics for Use of Animals (CEUA/FIOCRUZ) under numbers 002/08 and 033/09.

Plant material

Solidago chilensis Meyen was cultivated at Phytomedicine Agroecological Platform (PAF), FIOCRUZ, Rio de Janeiro city, RJ, Brazil (22°93'52.74''S; 43°39'89.16''W). Their inflorescences are collected in the summer, between December and March, when they are produced due to increased sunlight. The central stems were collected from the same producers of inflorescences plants. The species identification was performed by Mariana Reis de Brito, Botany Herbarium of the Department of the Institute of Biology/UFRJ and a voucher specimen was deposited under the code 32689/RFA.

Post-harvest processing

Medicinal plants in post-harvest processing should be dried between 30 and 60 °C, and medicinal plants containing essential oils should be dried at temperatures below 40 °C (Azar *et al.* 2012). Aerial parts of *S. chilensis* were dried in electric oven inflated at 37 °C with air velocity of 0.45 m/s and relative humidity not exceeding 30%, for 48 hours. The mass of *S. chilensis* for essential oil extraction was approximately 310 g of fresh plant or the equivalent when dry. The moisture content in flowers usually varies between 15 and 80%. Were found 40% of moisture content in inflorescences from *S. chilensis*.

Headspace solid phase micro-extraction

An SPME (Solid Phase Micro-Extraction) holder (Supelco, Bellefonte, PA) was used in performing

the experiments. A fused silica fiber coated with a 50/30 μm layer of polydimethylsiloxane (PDMS) was chosen to extract the volatile components from the *S. chilensis*. The fiber was conditioned following the manufacturer's instructions previous to its use. Approximately 1 g of sample was placed in a 4 mL vial closed with a plastic film. Once the desired temperature had been reached in a water bath (60 °C), the vial was placed inside the bath and was allowed to condition for the equilibrium time (no fiber exposition). After the equilibrium time, the fiber was introduced into the vial and exposed to the headspace of the sample during 20 minutes.

Extraction of essential oil

The aerial parts from *Solidago chilensis* Meyen were separated to steam distillation of the essential oil and they are cut into small pieces. The essential oil extraction was carried out by steam distillation, using the modified apparatus Clevenger adapted to a round bottom flask with 2 liters of capacity. Triplicate samples of portions of 130 g of plant material, were extracted separately by the same technique. The extraction process was performed during 3 hours, maintaining the boiling water. After that, the essential oil has been separated from hydrolate obtained following centrifugation for 10 min, 4,000 rpm, with the aid of Pasteur pipette. The organic phase was filtered through anhydrous sodium sulfate. The samples were stored at -20 °C until analysis.

GC-MS

The chromatographic separation was performed on a column of 30 m \times 0.32 mm and 0.2 mm thick, with 5 % diphenyl 95 % dimethylpolysiloxane as stationary phase. The chromatographic conditions were: linear heating from 30 to 240 °C with a rate of 10 °C/min; gun "split-splitless" rate "split" of 1/100, and flow rate of 1 mL/min. SCAN mode was used for m/z 15 to 300, helium as mobile phase, manual injection and flow rate of 1.00 mL/min. The heating was linear from 40 °C to 300 °C with a rate of 10 °C/min.

Analysis and identification of essential oil by GC/MS

Shimadzu GC/MS QP-2010 (Kyoto, Japan) spectrometer was used in the electron impact (EI) mode for the quantitative analysis. The ionization voltage and temperature of injector and ion source were 70eV, 250 and 280 °C, respectively. The mass spectrometer scanned from 30 to 400 m/z. A DB5 capillary column (30 m \times 0.25 mm; 0.25 μm film thickness) was used for the separation. The oven

temperature was programmed at 60 °C (isothermal for 2 min) which was ramped to 250 °C at 4 °C/min. Helium was used as the carrier gas with a flow rate of 1.0 mL/min with an injector volume of 1 μL using a 1:20 split ratio.

Compounds of interest were identified by comparing their retention times with that of authentic standards injected separately under the same GC-MS conditions and according with literature values (Fig. 1). Peaks compounds were identified by comparing its mass fragmentation pattern with that of standard compounds as well with data available spectral library (Wiley NIST Libraries) of the instrument. All analysis were performed in triplicate and quantification of each constituent obtained by standardization of the areas (%).

Pharmacological assays

Animals

Male Swiss mice and Wistar rats weighing 23–30 and 130–200 g respectively were used. The animals were obtained from the animal-breeding colony at the Oswaldo Cruz Institut Foundation (FIOCRUZ) and maintained in the animal room of the Department of Physiology and Pharmacodynamics, in Oswaldo Cruz Institut (IOC/FIOCRUZ), with free access to pelleted diet and water and a controlled period of light/darkness of 12/12 h. The animals were allowed to adapt to the laboratory for at least 2 hours before testing and were used only once. The experiments in this study received prior approval from the Oswaldo Cruz Institut Foundation's Animal Welfare Committee. The license for use of the animals was granted by Center for the Study of Animal Use (CEUA/FIOCRUZ) under numbers 002/08 and 033/09. After the experimental procedures animals were euthanized in CO₂ chamber.

Antinociceptive effect

The EOCS, EODI and EOFI samples were evaluated for their analgesic activity through Collier's test acetic acid induced writhes in mice to evaluate their antinociceptive effect (Sousa 2011). The amount of contortions was evaluated for 10 minutes, beginning the registers after 5 minutes of the injection of the stimulus. The doses of EOCS, EODI and EOFI (1 mg/Kg), and the control analgesic, diclofenac (50 mg/Kg), were administrated orally (*p.o.*), always an hour after the induction of pain. The control group was treated with saline solution + DMSO (diluent).

Statistical analysis

Statistical significance was determined by a one-way analysis of variance, followed by Student's-

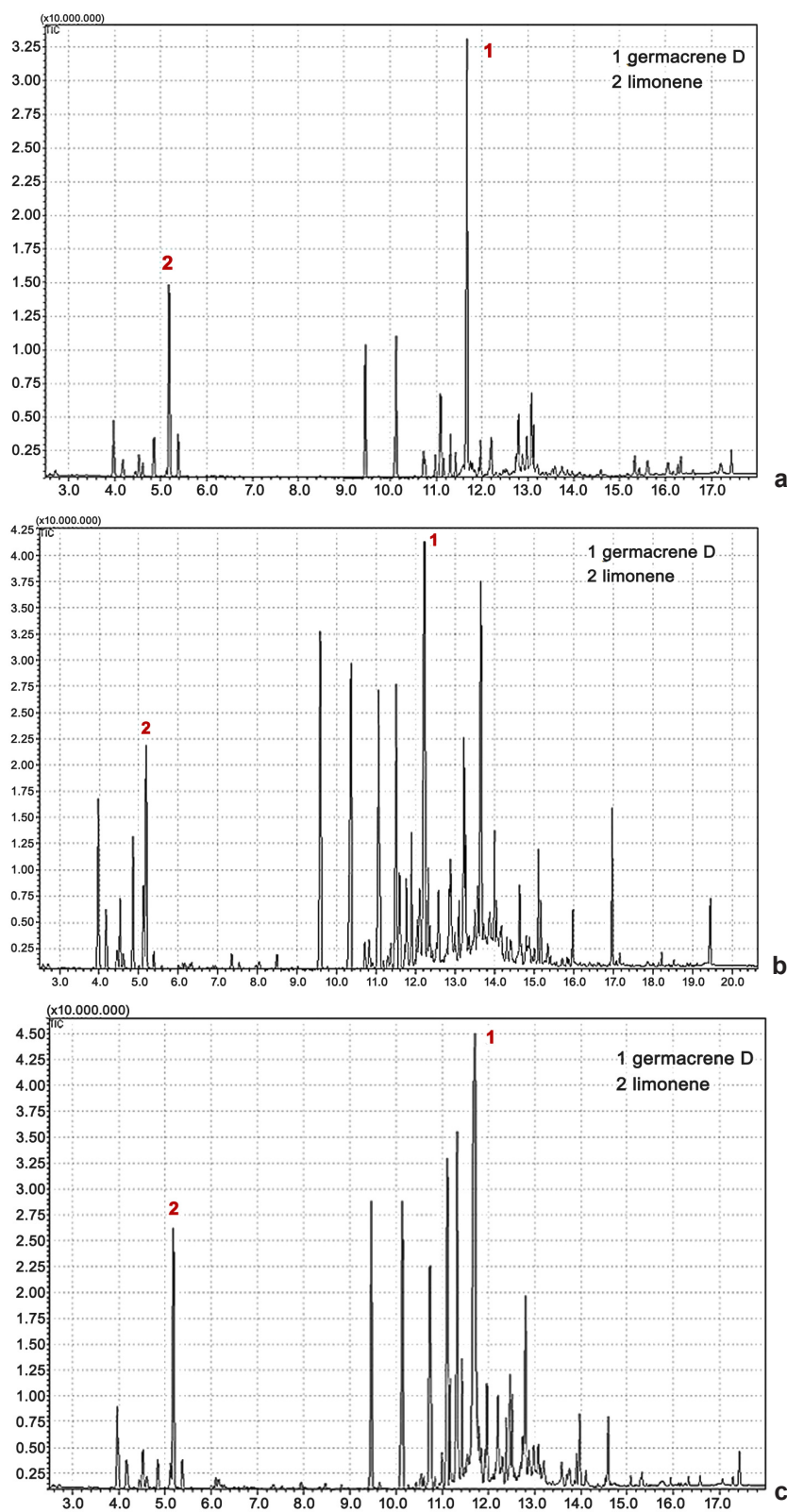


Figure 1 – a-c. Chromatograms of GC analysis of the essential oils from the fresh inflorescences – a. EOFI; b. dry inflorescences, EODI; c. central stem EOCS.

Neuman-Keuls test (Prism 4, GraphPad, La Jolla, CA, USA). The results were considered significant for values of $P \leq .05$.

Results and Discussion

In order to identify the largest possible number of volatile compounds of the *S. chilensis* by HS-SPME (Headspace Solid Phase Microextraction) the PDMS (Polydimethylsiloxane) fiber was chosen. The PDMS fiber is more suitable for the analysis of low molecular weight polar and non polar compounds. Table 1 lists the volatiles, obtained by SPME, of the analyzed samples CSV (Central Stem Volatiles), DIV (Dry Inflorescences Volatiles) and FIV (Fresh Inflorescences Volatiles) of *S. chilensis*.

Germacrene D is the major constituent of the CSV and DIV volatiles samples, and it represents 12% of the CSV and 23%, of the DIV. In spite of FIV sample Germacrene D has been

found in large amounts (20.8%), limonene is the compound with the highest concentration of 20.95%. This hydrocarbon is a widely distributed metabolic compound in *S. chilensis* plant species and it is considered to be a key intermediate in the biosynthesis of many sesquiterpenes from farnesyl diphosphate (Bülow *et al.* 2000; Steliopoulos *et al.* 2002; Shah *et al.* 2012). According to Vila and Gressler (Vila *et al.* 2002; Gressler *et al.* 2003), the pumiloxide, a labdane diterpene, was found as the major compound in the essential oil from leaves and inflorescences of *Solidago chilensis* Meyen collected in Pérez (Rosario, Argentina). In the *S. chilensis* cultivated at Phytomedicine Agroecological Platform (PAF), FIOCRUZ/RJ, there was no pumiloxide found. The diterpene compounds found were phytol and solidagenone (also a labdane diterpene) (Tab. 2) The difference in concentration of germacrene D can be explained

Table 1 – Identified compounds by GC-MS in volatiles from different plant material¹ by HS-SPME (PDMS) of *Solidago chilensis* Meyen.

Compound ²	Linear retention index ³	Electron impact mass spectrometric data	Relative content (%)		
	sample		CSV	DIV	FIV
α -pinene	942	93; 91; 92; 77; 121; 136	4.62	3.23	5.59
camphene	953	93; 121; 79; 107; 136	-	1.28	2.36
β -pinene	983	93; 41; 69; 91; 136	1.78	1.79	3.41
β -myrcene	992	93; 41; 69; 91; 136	-	-	2.29
α -phellandrene	1007	93; 91; 77; 92; 136	2.6	1.5	4.42
o-cymene	1025	119; 134; 91; 117	1.38	1.27	-
β -phellandrene	1033	93; 77; 91; 136	-	-	1.26
limonene	1034	68; 67; 93; 79; 121; 136	6.77	7.54	20.95
(Z)- β -ocimene	1040	93; 91; 79; 77; 41; 136	-	1.3	6.08
bornyl acetate	1284	95; 43; 93; 136; 121; 196	12.95	9.03	16.72
α -cubebene	1353	119; 105; 161	1.85	-	-
copaene	1378	161; 91; 105; 119; 133	3.84	3.21	1.92
β -bourbonene	1385	81; 29; 80; 123; 161; 204	11.87	7.58	2.1
isocaryophyllene	1411	69; 161; 93; 41; 93; 105; 204	4.18	-	-
β -caryophyllene	1420	93; 133; 91; 41; 79; 69; 204	10.91	10.72	4.94
γ -elemene	1434	93; 81; 67; 41; 107; 147; 161	11.68	8.14	5.97
α -humulene	1443	93; 80; 121; 41; 204	3.58	3.68	1.32
(Z)- β -farnesene	1445	119; 93; 41; 91; 204	-	11.82	1.42
γ -muurolene	1479	161; 93; 105; 119; 204	1.31	-	-
germacrene D	1482	161; 105; 91; 119; 79; 204	19.35	22.43	20.8

¹ CSV = central stem volatiles; DIV = inflorescences volatiles; FIV = fresh inflorescences.

² Compounds are listed in order of their elution from a DB-5 column.

³ RI = retention indices relative to C8 – C28 *n*-alkanes.

Table 2 – Chemical composition of the volatile compounds detected from the essential oil from *Solidago chilensis* Meyen¹.

Compound ²	Linear retention index ³	Electron impact mass spectrometric data	Relative content ^a (%)		
	sample		EOCS	EODI	EOFI
α -pinene	940	93; 91; 92; 77; 121; 136	3.89	2.24	3.1
camphene	951	93; 121; 79; 107; 136	-	-	0.98
β -pinene	982	93; 41; 69; 91; 136	1.39	0.9	1.2
β -myrcene	994	93; 41; 69; 91; 136	-	-	0.76
α -phellandrene	1005	93; 91; 77; 92; 136	2.67	-	2.07
o-cymene	1023	119; 134; 91; 117	1.69	-	-
limonene	1032	68; 67; 93; 79; 121; 136	4.41	5.745	10.07
(Z)- β -ocimene	1043	93; 91; 79; 77; 41; 136	-	0.6	2.13
bornyl acetate	1284	95; 43; 93; 136; 121; 196	8.19	6.9	7.06
α -cubebene	1352	119; 105; 161	1.2	2.18	-
copaene	1379	161; 91; 105; 119; 133	1.85	2.23	1.27
β -bourbonene	1383	81; 29; 80; 123; 161; 204	7.32	6.39	2.03
Isolongifolene	1388	131; 187; 91; 146; 202	2.24	1.84	1.62
β -cubebene	1389	161; 105; 119; 91; 204	-	0.69	2.69
α -gurjunene	1412	105; 161; 204; 119; 91	1.19	1.16	-
β -caryophyllene	1419	93; 133; 91; 41; 79; 69; 204	6.87	9.03	5.51
γ -elemene	1428	93; 81; 67; 41; 107; 161	8.40	7.54	7.78
aromadendrene	1439	145; 159; 202; 131; 105; 204	2.93	1.86	2.34
α -guaiane	1440	105; 107; 93; 147; 204	3.81	2.3	-
α -humulene	1441	93; 80; 121; 41; 204	2.52	2.69	1.28
(Z)- β -farnesene	1443	119; 93; 41; 91; 204	2.17	9.69	2.64
γ -muurolene	1480	161; 93; 105; 119; 204	-	0.74	-
germacrene D	1483	161; 105; 91; 119; 79; 204	12.11	22.01	23.3
α -bisabolene	1507	93; 119; 41; 105; 204	-	0.83	-
δ -cadinene	1526	161; 134; 105; 119; 204	-	0.91	-
δ -calacorene	1540	157; 142; 141; 200; 183	1.79	-	-
germacrene B	1563	121; 93; 41; 107; 204	-	1.51	-
spathulenol	1573	43; 41; 205; 119; 220	7.93	3.38	3.52
caryophyllene oxide	1583	91; 67; 41; 109; 121; 138	1.88	1.54	0.66
δ -cadinol	1638	161; 43; 119; 105; 41; 204; 222	-	0.7	1.72
cedren-13-ol	1644	119; 41; 91; 105; 220	1.02	0.65	1.58
α -cadinol	1656	43; 95; 121; 41; 204; 222	-	1.04	2.61
acorenone	1685	220; 41; 159; 91; 191; 105	2	1.56	-
(E)-phytol	1945	71; 57; 43; 123; 295	2.33	-	0.81
solidagenone	2385	82; 81; 41; 111; 95; 316	0.9	0.67	1.85

¹ EOCS = central stem; EODI = inflorescences; EOFI = fresh inflorescences.² Compounds are listed in order of their elution from a DB-5 column.³ RI = retention indices relative to C8 – C28 *n*-alkanes.

by the fact that the sesquiterpene be precursor for the biosynthesis of several other sesquiterpenes (Tab. 2) (Him *et al.* 2008). Some of the identified compounds of the essential oil samples have been reported for their antinociceptive activity such as

δ -cadinene, α -pinene, myrcene, germacrene D, limonene and caryophyllene oxide (Collier *et al.* 1968; Him *et al.* 2008). The comparison of the major compounds in the analyzed samples from *S. chilensis* is showed in Table 3.

Table 3 – Comparison of major volatile compounds in the analyzed samples from *S. chilensis* aerial parts detected/extracted by SPME and hydrodistillation.

Aerial part	Major compounds	Method of detection/extraction
Central stems	Germacrene D, bornyl acetate, γ -elemene, β -caryophyllene, limonene	SPME
	Germacrene D, γ -elemene, bornyl acetate, spathulenol, β -caryophyllene	hydrodistillation
Dry inflorescences	Germacrene D, (Z)- β -farnesene, β -caryophyllene, bornyl acetate	SPME
	Germacrene D, β -caryophyllene, γ -elemene, bornyl acetate	hydrodistillation
Fresh inflorescences	Limonene, germacrene D, bornyl acetate	SPME
	Germacrene D, limonene, γ -elemene, β -caryophyllene	hydrodistillation

The antinociceptive effect was observed in the three oils samples, the EOCS have inhibited about 35% of number of writhings (29.42 ± 4.6), the EOFI have inhibited about 53% of number of writhings (21.25 ± 4.2), EODI have inhibited about 49% of number of writhings (23.08 ± 1.4) and the standard substance diclofenac have inhibited about 67% of number of writhings (14.83 ± 3.1). A difference in the antinociceptive activity of about 6% between dry and fresh inflorescences was observed (Tab. 4). Chemically, there was the loss of the most volatile substances in the dry sample due to their evaporation of the some monoterpenes as camphene, β -mircene, α -phellandrene that are present only in the EOFI and

limonene, (Z)- β -ocimene, β -cubebene, cedren-13-ol and α -cadinol which are present in only one half of the EODI sample concentration.

Conclusions

Germacrene D is also previously reported as the main compound of many species of the *Solidago* genus. The limonene, that is widely used as pharmaceutical ingredient in industry to produce bath products as soap and room sprays due to their pleasant smell, comprises about 10% of the essential oil of fresh inflorescences. The antinociceptive activity of many terpenes present in essential oils, combined with the chemical complexity of these

Table 4 – Antinociceptive effect of EOCS¹, EODI¹ and EOFI¹.

Treatment	Dose (mg/Kg)	Number of writhings ²	% Inhibition
Saline	-	45.14 ± 3.3	0%
EOCS	1	29.42 ± 4.6	34.84**
EOI	1	23.08 ± 1.4	48.86**
EOFI	1	21.25 ± 4.2	52.93***
Diclofenac	50	14.83 ± 3.1	67.14

¹ EOCS = central stem *S. chilensis* essential oil; EODI = inflorescences of *S. chilensis* essential oil; EOFI = fresh inflorescences of *S. chilensis* essential oil; n = 12.

² Values represent mean \pm S.E.M.; **P < 0.01; ***P < 0.001.

oils, shows the synergistic potential that the *Solidago chilensis* essential oil could exert, acting through different mechanisms of action, in addition to their potential in developing new topical analgesics, even as adjuvants in pharmaceutical formulations. This is the first report about the SPME analysis and about the pharmacological activity of the *Solidago chilensis* Meyen essential oil.

Acknowledgments

The authors are grateful to Pharmaceutical Technology Institute (Farmanguinhos), Military Institute of Engineering (IME) and Oswaldo Cruz Institute (IOC), for infrastructural support; Agroecological Phytomedicine Platform (PAF/Fiocruz), for the identification, cultivation and supply of *Solidago chilensis*; Foundation for Scientific and Technological Development in Health (FIOTEC), Coordination for the Improvement of Higher Education Personnel (CAPES) and National Council for Scientific and Technological Development (CNPq), for financial support and scholarships.

Conflicts of interest

The authors declare no conflict of interest.

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Sample Availability: samples of the essential oils of *Solidago chilensis* Meyen are available from the authors.

Area Editor: Dr. Leopoldo Baratto

Received in June 24, 2019. Accepted in October 29, 2019.



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