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Article

Variability of the Volatile Organic Compounds of *Achillea millefolium* L. According to the Collection Time, Type of Polyethylene Packaging and Storage Period

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The collection time could be an important target for optimizing technological processes in obtaining essential oils of interest to agribusiness. The objective of this study was to distinguish the time for the collecting of *Achillea millefolium* L. leaves, which provides the highest yield and quality of the essential oil. Also, identify the type of polyethylene packaging and leaf storage period during the one-year period that would maintain the essential oil characteristics. Gas chromatography-mass spectrometry and chemometric studies were performed into two steps trial to detect changes in chemical profile induced by different conditions. First, an analysis of the leaf collection time was performed using chromatographic data from six different gathering times throughout the day. After determining the best time to collect from the leaves, the essential oil was extracted in five storage periods over a year. The highest oil content was observed in leaves harvested between 11 and 15 h, with a maximum of 39 min after 13 h. Therefore, it is recommended to perform extraction in the early afternoon. There was no significant statistical differentiation related to polyethylene packages. In addition, it is recommended that the essential oil can be stored without significant changes for up to six months.

Keywords: metabolomic, phytochemicals, oil essential, GC-MS, chemometrics

Introduction

The *Achillea millefolium* L., commonly named as "yarrow" and "milfoil" is an herbaceous perennial plant widely distributed in Europe, Asia, North Africa, and North America.[1] Traditionally, *A. millefolium* is used for palliative treatments of gastrointestinal,[2] and hepatobiliary disorders.[3] Furthermore, various *in vitro* and *in vivo* studies of *A. millefolium* have reported a broad spectrum of pharmacological and cosmetics activities.

For example, the alcoholic extract of *A. millefolium* shows liver protective,[2] antitumoral,[4] anticholinesterasic,[5] antihypertensive,[6] anxiolytic,[7] and antiparasitic[8] effects. Besides, *ex vivo* and *in vivo* studies performed in the cosmetics area demonstrated the anti-aging potential of *A. millefolium* extract.[9]

A. millefolium's essential oil demonstrates potential as an antioxidant, antimicrobial, anti-inflammatory,[10-13] anticholinesterasic, allelopathic, antibacterial and antifungal,[1] among others.

The diversity and complexity of the chemical composition of *A. millefolium* explain their polyvalent pharmacological activities.[13] In general, the phytochemical profile of the oil of *A. millefolium* is very rich in active compounds, such as monoterpenes,[4,10] lignans,[14] sesquiterpenes,[15] *N*-alkylamides,[2] phenylpropanoids,[13] flavonoids,[16] etc. It has been reported[17] that the chemical profile of the volatile oil is frequently affected by geographical origin. Other environmental conditions such as genetics, plant age, soil purity, vegetation phase, anatomical part of the plant, and harvest season should also be considered as factors affecting chemical profile. Hence, studies on the composition and distribution of these constituents are significantly relevant in many parts of the world, especially for significant metabolites that

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are possibly responsible for the remarkable biological potential.[18]

The *A. millefolium* L. essential oil has a pleasant smell, commercial acceptance, and is still safe in bioactive concentrations.[10] Thus, *A. millefolium* can find applications in the formulation of phytotherapeutics, foodstuffs, and cosmetic products.[13]

According to market analysis, based on calculation of compound annual growth rate performed by Grand View Research,[19] the worldwide essential oils market demand was 226.9 Mkg in 2018 and the expectation is a growth rate at 8.6% from 2019 to 2025. This global trade analysis points out that increased research and development (R&D) activities, coupled with technological innovation in extraction techniques, could bolster market growth in emerging economies such as Brazil, India, and Africa.

A recently released report by Persistence Market Research[20] points out the regional analysis of the yarrow oil market mainly includes the following regions: North America, Latin America, Europe, Asia Pacific, Japan, the Middle East, and Africa. Additionally, yarrow oil is a new product in many countries and has a potential market to grow due to its established reputation for therapeutic properties.

Given the increasing commercial value of *A. millefolium*, this study aimed to identify the collection time, the type of polyethylene packaging and the storage period that simultaneously provided the highest yield and maintained the chemical quality of the essential oil.

Experimental

Plant, transport and storage

The *A. millefolium* L. plants were cultivated at the Lagoa do Ipu Farm in Horizonte, CE, at an altitude of 68 m and 40 km from Fortaleza, CE (4°05'09"S, 38°39'05"W). The climate ranges from hot sub-humid tropical to hot semi-arid mild tropical; the average temperature range varies from 26 to 28 °C, and the average rainfall is 780.7 mm, with the rainy season from January to May. The relief is of the pre-coastal tray type and the soil consists of quartzous sands.

The studies were conducted at Embrapa Agroindústria Tropical, Fortaleza, CE, and consisted of two phases. In the first phase, fresh leaves were harvested at six different times in order to identify the best collection time (7, 9, 11, 13, 15, and 17 h). The experimental design was totally randomized, with four replications.

The leaves of *A. millefolium* used in the storage experiment (second phase) were taken from the same plants used in the first phase, which were harvested at the ideal moment previously determined in the first phase of this experiment. After collection, the damaged leaves were removed, and the sheets were taken to a storage shed. Then, they were placed to dry in the shade in a dryer run by solar energy, located at the Lagoa do Ipu farm (in Ceará State). After drying, 110 g of samples were conditioned in different types of selected packages, which were then sealed by an electric sealer.

The second stage of the study involved the oil extracted from the dried *A. millefolium* leaves after different storage conditions: five different storage periods (0, 3, 6, 9, and 12 months) using three types of low density polyethylene (LDPE) packages (black, silver, and white). These treatments were applied in a 3 × 5 factorial scheme, in a completely randomized experiment with four replications.

Conditions of storage of the plant material

In the first phase, the fresh leaves were used to the extraction of the essential oil. In the second phase, LDPE packages containing the dried leaves were deposited in an environment with air circulation. Packages containing the dried leaves were all accommodated in a steel rack and the samples were stacked according to the type of packaging (white, silver and black). For each storage period, four samples of each packaging type were used, and the samples were randomly selected before analysis.

The three LDPE packages have the following characteristics: low water and gaseous vapor permeability, high chemical resistance to solvents and insulating properties. The melting point for average, commercial, LDPE packages is typically 105 to 115 °C.[21] The samples were stored in low light environment (82 lux). The light intensity recorded within the packages was 43, 21 and 0 lux for the white, silver and black color packages, respectively. The average temperature and relative humidity were 28 °C and 65%, respectively. All temperature, humidity, and light intensity measurements were recorded with a light meter equipment (Lutron LM8000A Combination Instrument).

Analysis of yield of essential oil

For the extraction of the essential oil, 100 g of dried leaves were used; these were placed in 3 L flasks containing 1.5 L of deionized water and the essential oil was extracted by the hydrodistillation method using the closed-circuit Clevenger system,[22] over a period of 7 h. The distilled oils were dried using sodium sulfate and placed in closed vials for further investigations. The collected essential oil yield data were subjected to analysis of variance (ANOVA) and polynomial regression analysis. The means were set

apart at the 5% significance level by the least significant difference test.

The amount of water present in the biomass (100 g) was determined using the cyclohexane solvent distillation method.[23] After extraction of the essential oil, yield analysis was performed based on the dry matter.

Variability of the volatile organic compounds

Gas chromatography-mass spectrometry (GC-MS) analysis was performed in Agilent model GC-7890B/MSD-5977A (quadrupole) equipment, with electron impact at 70 eV, HP-5MS methylpolysiloxane column (30 m × 0.25 mm × 0.25 µm, Agilent), helium carrier gas at flow rate, 1.00 mL min^{-1}; injector temperature, 250 °C; detector temperature, 150 °C; transfer line temperature, 280 °C. Chromatographic oven programming: initial temperature of 70 °C, with a heating ramp of 4 °C min^{-1} to 180 °C and increment of 10 °C min^{-1} to 250 °C at the end of the run (34.5 min).[24] The identification of compounds was performed by analyzing the fragmentation patterns exhibited in the mass spectra with those present in the database provided by the equipment (NIST version 2.0), and from literature data.[25]

The chromatographic data was explored by an unsupervised chemometric analysis known as principal component analysis (PCA). This multivariate analysis was used to understand changes in the organic composition from *A. millefolium* leaves, induced by the three different conditions, performed in triplicate: collecting at six different times of the day (7, 9, 11, 13, 15 and 17 h), four different storage periods of the leaves (3, 6, 9, and 12 months), and 3 packages of different colors (white, silver, and black). Therefore, the chromatograms were converted to American Standard Code for Information Interchange (ASCII) files and exported for PCA evaluation using the Unscrambler X™ program (version 10.4).[26]

The regions of the chromatograms between 2.0 and 34.5 min were used for the analysis. Before the application of the algorithms, noises and imperfect regions were removed, giving two matrices: one for collecting of leaves and the other for storage period and packing color, with dimensionalities of 91,404 (18 samples × 5,078 variables) and 198,042 (39 samples × 5,078 variables) data points, respectively.

The singular value decomposition (SVD) algorithm was applied for matrix decomposition after baseline correction using linear fit algorithms over the variables, and mean-centered preprocessing over the samples, because this pretreatment procedure provides more appropriate differences among the samples in the matrices (with a confidence level of 95%) and avoids any negative interference of signal noise.[27]

Results and Discussion

Essential oil yield

The analysis of variance showed that the different times of harvest of *A. millefolium* had a significant effect on the yield of the essential oil. The study of the behavior of these responses at different times revealed a quadratic pattern; higher yield of essential oil at collection times from 11 to 15 h, with the maximum point of the regression curve at 39 min past 13 h (15.14 mL kg^{-1} of dry matter) (Figure 1).

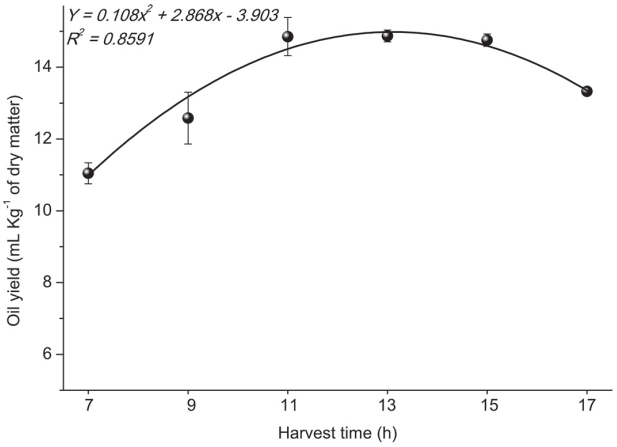

Figure 1. Oil yield of *A. millefolium* L. at different times of harvest in Horizonte (Ceará State). The error bars are related to biological quadruplicate.

This variation of yield as a function of time of harvest is possibly related to increases in temperature[28,29] and light intensity at this time of day,[30] because these factors positively interfere with both the biosynthesis[31] and the integrity of the essential oils.[32]

Determining the best collection time may be crucial for obtaining a higher-quality essential oil. Depending on the species, significant improvements in post-harvest shelf life can be achieved by rescheduling the time for collecting.[33] For example, studies[34] on the essential oil of *Thymbra spicata* L. var. *spicata* displayed a significant diurnal variation of the chemical components. The highest levels of carvacrol (70.87%) and *p*-cymene (6.89%) were obtained at 6 and 21 h, respectively. Thus, it is concluded that the chemical content of the essential oil varies during the day.

The results suggest that the high oil yield associated with carvacrol content varies with temperature and can be optimized by considering the plant's collection time. Seasonal variation has been found for several major chemical constituents in many plants, depending on the time of harvest in the day, such as *Agastache foeniculum*, *Lavandula angustifolia*, *Melissa officinalis*, *Nepeta cataria*,[35]

Pycnocycla spinosa,[36] *Thymus pulegioides*,[37] etc. This fact demonstrated that essential oil synthesis involves species-environment interaction, which cannot be generalized. The establishment of the optimal collection time is necessary for both maximizing yield and oil quality because it exerts a significant influence on the yield of the essential oil of the crops.[38]

Thus, the experiments performed indicate that the appropriate time interval for collecting is from 11 to 15 h. Additionally, the second phase experiments regarding the storage study in LDPE packages were performed with the extracted essential oil in this specific time interval.

Statistical analysis

Table 1 presents the statistical results obtained by ANOVA on the influence of packaging type and storage time on the yield of *A. millefolium* essential oil. Based on the statistical analysis, only the type of packaging ($p > 0.01$) did not significantly influence the yield of the essential oil of one thousand leaves. On the other hand, the storage time ($p < 0.01$) and the interaction of this parameter with the type of packaging ($p < 0.05$) had a significant influence on the yield values obtained for the studied plant material.

Yield of essential oil for plant material in storage

The entire experiment storage profile was conducted with the essential oil extracted from the leaves of *A. millefolium* harvested at 13 h. The yield of the essential oil during the storage period varied according to the color of the packages, showing a linear regression curve for the black LDPE packaging bag with the maximum yield of 10.15 mL kg^{-1} of dry matter after three months of storage. On the other hand, white and silver polyethylene packaging produced polynomial fit with maximum yields of 8.87 and 8.49 mL kg^{-1} of dry matter, respectively, also after three months of storage (Figure 2).

The leaves packaged using silver and white LDPE packages showed a marked reduction in oil content over

Table 1. ANOVA statistics showing the effect of package and time of storage on the essential oil yield of *Achillea millefolium*

Source	Degree of freedom	Sum of squares	Mean square	*F*-Value	*p*-Value probability > *F*
Package (1)	2	1.76	0.88	0.82	0.55004[a]
time (2)	4	145.66	36.41	33.99	0.00001[a]
(1) × (2)	8	21.33	2.67	2.49	0.02483[b]
Residual	45	48.22	1.07		
Total	59	216.96			

[a]$p < 0.01$; [b]$p < 0.05$.

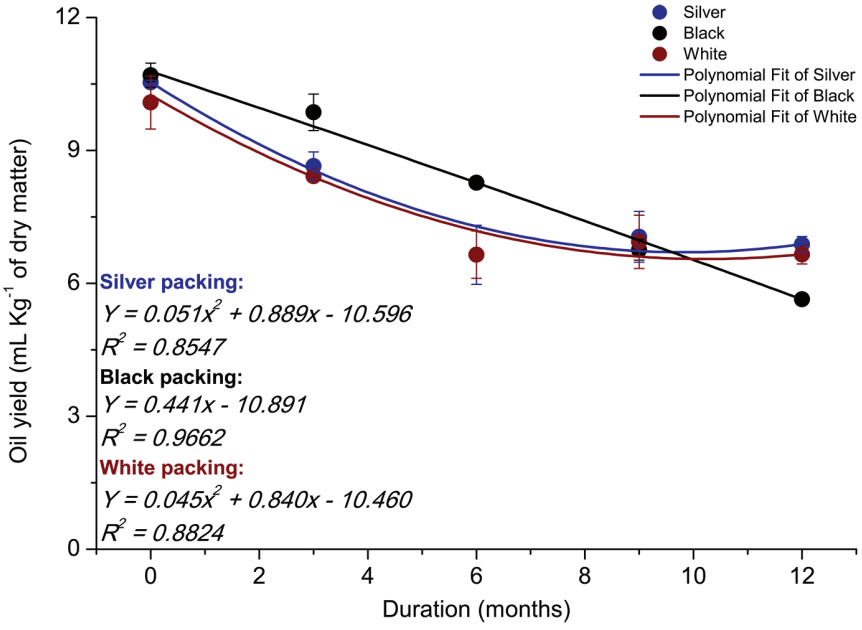

Figure 2. Oil yield of *A. millefolium* L. for 5 different storage periods and 3 types of LDPE packages, in the municipality of Horizonte (Ceará State).

the oil content over the six months. Also, it is noticed the degradation of the *A. millefolium* essential oil was accelerated with increasing time of storage. These results could be related to lower light penetration in the black container because this is the only characteristic that differentiated the packages used herein.

Essential oil quality

To evaluate the variation in the organic composition of *A. millefolium* leaves according to the sampling procedure (collecting, storage period, and packing color), PCA was applied in the resultant matrices. PCA results are presented separately, according to the sample collection (variability of the organic composition using GC-MS data coupled to chemometrics section) and different storage conditions of the leaves (storage period packing color section).

Variability of the organic composition using GC-MS data coupled to chemometrics

The retention times related to the chromatographic peaks are sensitive to minor fluctuations in factors like temperature, pH, flow, and pump operation; this is a valuable feature that must be considered for chemometric analysis. Problems of signals shift among different chromatograms for the same compounds may be solved using different alignment methods, such as correlation optimized warping (COW),[39] or using the bucketing method to reduce the chromatogram dimensionally slicing in equally sized regions.[40,41] For this study, all the chromatogram peaks were aligned using the COW method.

Figure 3 shows the complexity of the data, with several compounds detected in the composition of the *A. millefolium* leaves and the inherent visual similarity among the samples, which makes effective assessment difficult. Therefore, to comprehend the variability of the volatile organic compounds in the leaves according to sample collection, chromatographic data were subjected to PCA (Figure 4).

The PCA results show that the central composition variability for this study was retained at first PC, and the subsequent PCs did not produce any relevant results. Figure 4b shows the respective loading graph plotted in lines to illustrate the variables (compounds) responsible for the placement of the samples on the scores graph. Therefore, the leaves sampled in the morning (7 and 9 h) had positives PC1 scores, and leaves tested in the afternoon had negative values of the same PC. The leaves collected at 11 h were located at null values of PC1, and although the leaves sampled at 17 h had negative scores of PC1, the negative influence was lower than those for the leaves tested at 13 and 15 h. Loading evaluation revealed that large amounts of β-cubebene, elixene, α-muurolene, and α-farnesene were observed in the leaves sampled in the morning (7 and 9 h). On the other hand, an opposite

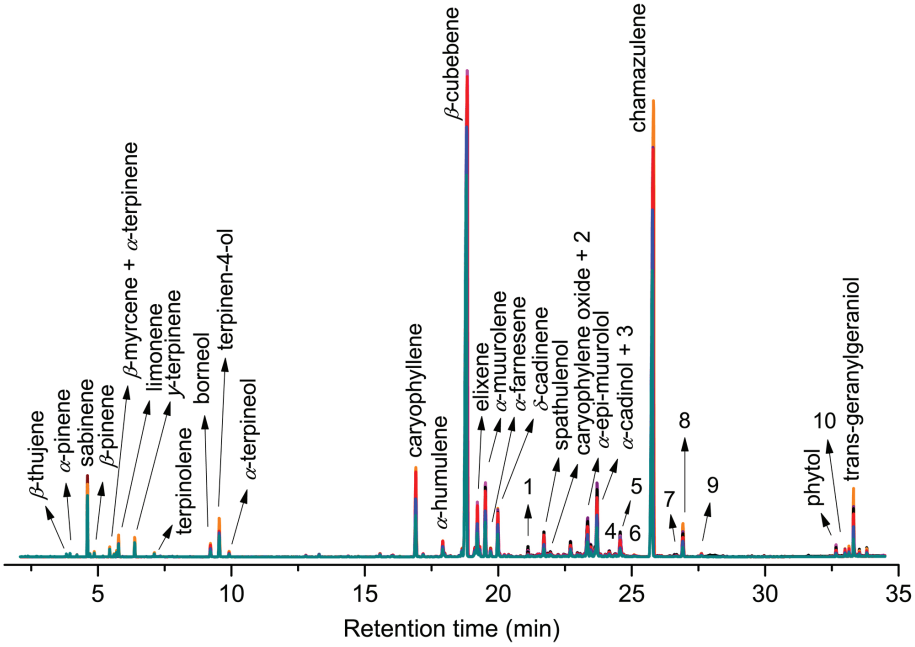

Figure 3. Representative chromatogram from the quadruplicate acquisitions at 6 different sample collection times: 7, 9, 11, 13, 15 and 17 h. **1**: aromadendrene oxide-(2); **2**: aristolene epoxide; **3**: 1*H*-benzocyclohepten-7-ol, 2,3,4,4a,5,6,7,8-octahydro-1,1,4a,7-tetramethyl-, *cis*; **4**: tricyclo[5.2.2.0(1,6)]undecan-3-ol, 2-methylene-6,8,8-trimethyl; **5**: spiro-6-(bicyclo[3.2.1]octane)-2'-(oxirane), 7,8-di(hydroxymethyl)-5-methyl-2-isopropyl; **6**: curlone; **7**: spiro[4.5]decan-7-one, 1,8-dimethyl-8,9-epoxy-4-isopropyl; **8**: 4,4'-dimethylbiphenyl; **9**: aromadendrene oxide-(1); **10**: 9,12,15-octadecatrienoic acid, (*Z*,*Z*,*Z*).

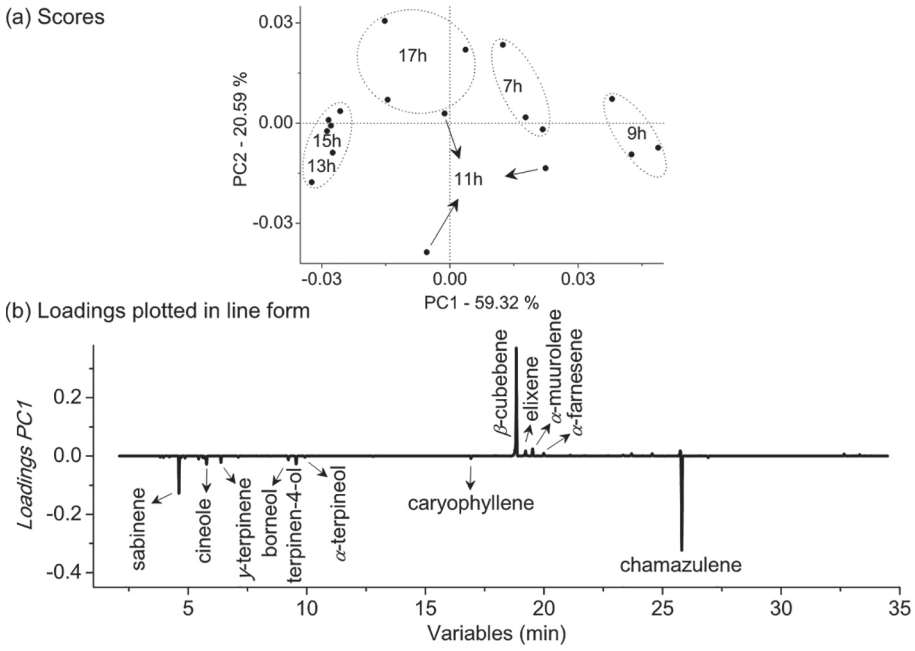

Figure 4. PC1 × PC2 scores of the coordinate system (a) and respective loadings plotted in lines (b) for the *A. millefolium* leaves based on sample collection at 7, 9, 11, 13, 15, and 17 h.

behavior was found in the composition of leaves tested in the afternoon according to cineole, y-terpinene, borneol, terpinene-4-ol, α-terpineol, caryophyllene, sabinene, and chamazulene, along with a smaller decrease in the amount of these compounds at 17 h compared to the samples obtained in the afternoon. In particular, the first periods of the afternoon (13 and 15 h) had the most considerable influence on the increased amount of chamazulene.

Storage period packing color

Similar to Figure 3, Figure 5 illustrated the high complexity of visual evaluation due to the similarity among the samples (chromatograms) and the increased concentration of detected compounds. Therefore, to understand the variability of the composition of *A. millefolium* leaves according to the storage period (0, 3, 6, 9, and 12 months) and color of packaging (white, silver, and black), the resultant matrix was evaluated by PCA, and the results are presented in Figure 6. Important separation tendencies were observed on the scores graph (Figure 6a) concerning the first two principal components (PC1 and PC2), with the total variance being 73.75%. Figure 6b shows the respective PC1 and PC2 loading graphs plotted in lines to demonstrate the most important variables (compounds) for the separation of the leaves.

A clear clustering of the control leaves at positive PC1 scores and negative PC2 scores was detected; the leaves after storage gave negative PC1 values independent of the period and package color. The PC1 loadings showed the main variables (compounds) responsible for the scores placement: control leaves with highest levels of β-cubebene, elixene, α-muurolene, and α-farnesene, and the leaves after storage with highest concentrations of cineole, y-terpinene, borneol, terpinene-4-ol, α-terpineol, and caryophyllene. The compounds sabinene and chamazulene only presented significant information according to PC2 loadings, while the control leaves showed higher concentration of chamazulene and increased the amount of sabinene in the leaves after storage, independent of the storage period or packaging color.

A detailed PCA was performed to investigate the effect of the storage period and packaging color on the variability of the composition of the leaves. Figure 7 presents the scores (a) and loadings (b) of the coordinate system, with a total variance of 73.75% in the first two principal components. The scores graph showed a tendency of the samples to be separated according to the PC1 axis: leaves after smaller storage periods (3 and 6 months) and using white packaging were located in positive scores, while leaves after more extended storage periods (9 and 12 months), and using silver and black packaging were located in negative scores. Loadings graph illustrated that chamazulene is the main compound responsible for the placement of the samples at the positive scores of PC1 and its degradation during longer storage periods (more than 6 months). In addition, the positive values of PC1 show that sabinene, cineole, y-terpinene, borneol, terpinen-4-ol, α-terpineol, and caryophyllene were more susceptible to degradation when white packaging was used.

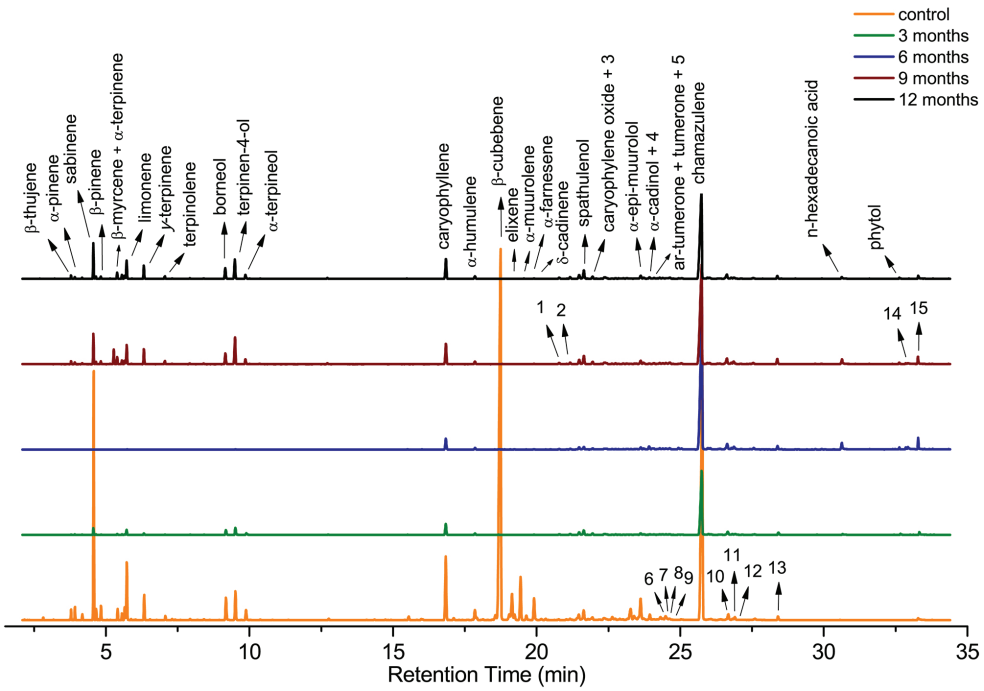

Figure 5. Chromatograms from the triplicate acquisition from 11 samples: control leaf, and leaves stored for 4 different periods using 3 different packages. **1**: 2-butenal, 2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl); **2**: aromadendrene oxide-(2); **3**: aristolene epoxide; **4**: 1*H*-benzocyclohepten-7-ol, 2,3,4,4a,5,6,7,8-octahydro-1,1,4a,7-tetramethyl-, *cis*; **5**: (6,8-bis-hydroxymethyl-4-isopropyl-7-methylene-bicyclo[3.2.1]oct-1-yl)-methanol; **6**: alloaromadendrene oxide-(1); **7**: tricyclo[5.2.2.0(1,6)]undecan-3-ol, 2-methylene-6,8,8-trimethyl; **8**: spiro-6-(bicycle[3.2.1]octane)-2'-(oxirane), 7,8-di(hydroxymethyl)-5-methyl-2-isopropyl; **9**: curlone; **10**: spiro[4.5]decan-7-one, 1,8-dimethyl-8,9-epoxy-4-isopropyl; **11**: 4,4'-dimethylbiphenyl; **12**: aromadendrene oxide-(1); **13**: 2-butenal, 2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl); **14**: 9,12,15-octadecatrienoic acid, (*Z*,*Z*,*Z*); **15**: *trans*-geranylgeraniol.

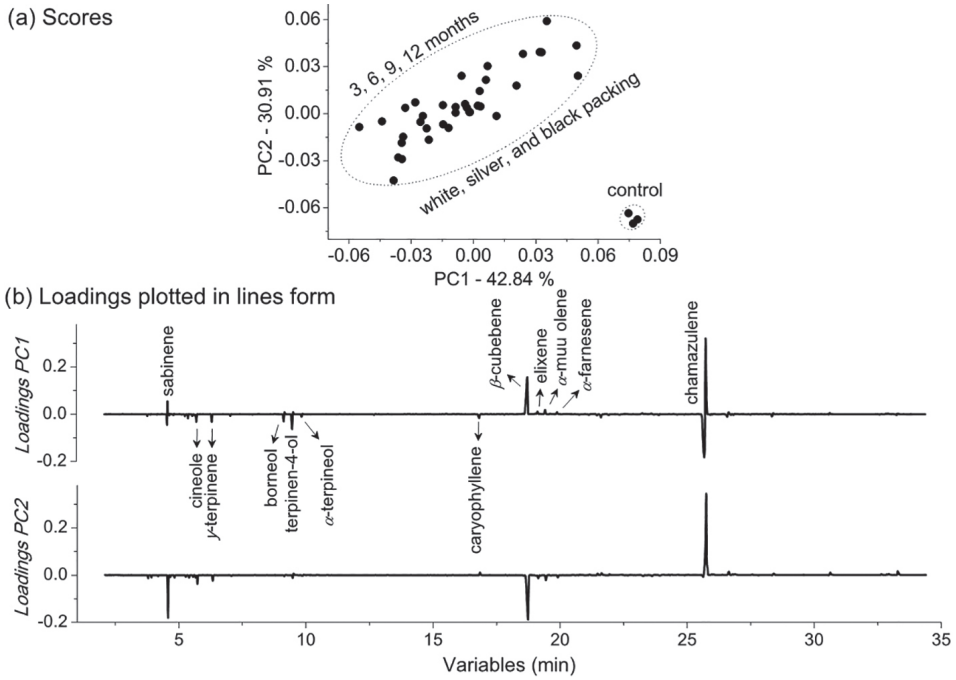

Figure 6. PC1 × PC2 scores of the coordinate system (a) and respective loadings plotted in lines (b) for the control *A. millefolium* L. leaves, and the sampled leaves after different storage periods and for packages of different colors, and the control sample.

Conclusions

The GC-MS study of leaves from *Achillea millefolium* L. indicates that significant metabolites are mainly chamazulene, β-cubebene, and sabinene. Besides, chemometric analysis applied to discriminate the chemical

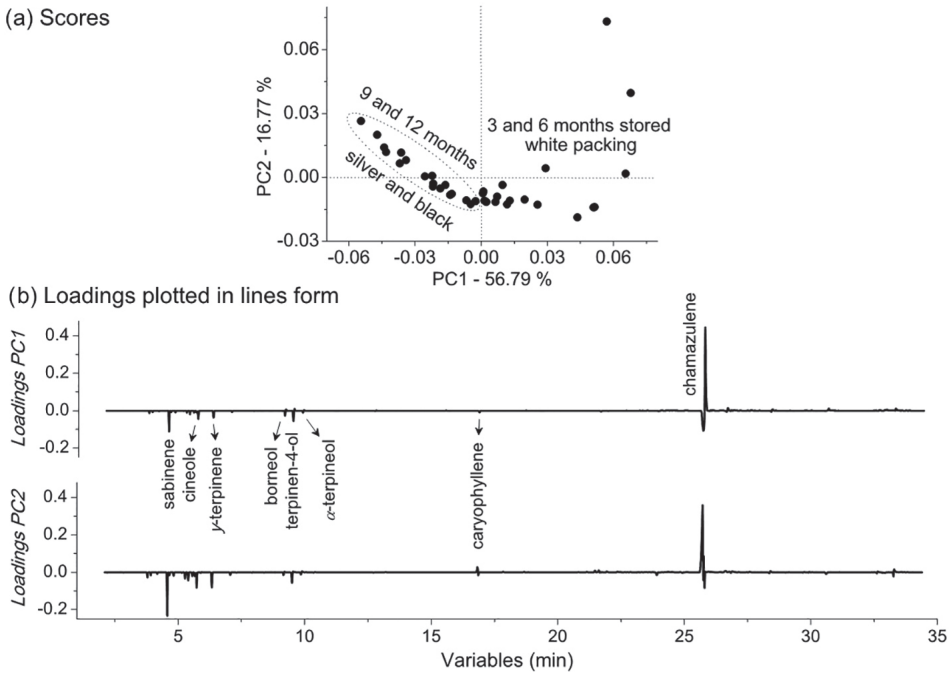

Figure 7. PC1 × PC2 scores of the coordinate system (a) and respective loadings plotted in lines (b) for the *Achillea millefolium* leaves for different periods of storage and packaging colors.

profile of essential oil from leaves of the *Achillea millefolium* evidenced the metabolic differentiation as a function of the collecting schedule and type of packaging for storage.

Accordingly, considering the changes in the chemical profile observed in the study based on collection time, it is concluded that *A. millefolium* plants should be harvested between 11 and 15 h, and also should be extracted shortly after harvest.

Based on the chemical variability, the essential oil of *A. millefolium* lost quality during the storage, and therefore, the procedure using LDPE packages under the conditions used is not recommended for this species.

Although the essential oil content decreased over time in all packages studied at the beginning of storage, the degradation of the metabolites was lower and higher in the black and white containers, respectively.

Additionally, the study indicates that although there is a loss of biomass over time compared to the initial time (t_0), it is possible to store the essential oil without significant losses up to six months. Finally, based on the chromatographic analysis under all conditions of collection and storage, it was observed that chamazulene was the most stable metabolite.

Our study guided by the metabolic changes associated with collection time coupled with chemometric techniques contributes to the optimization of post-harvest handling involving mainly harvest during the day and improvement of its quality and shelf-life.

Acknowledgments

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