Uniciencia Vol. 39(1), pp. 1-12, January-December, 2025
www.revistas.una.ac.cr/uniciencia
revistauniciencia@una.cr
DOI: https://dx.doi.org/10.15359/ru.39-1.11
E-ISSN: 2215-3470

Cephaeline and emetine production and antimicrobial activity of the Ipecac root via optimized maturity-based harvesting and processing

Producción de Cephaelina y Emetina y actividad antimicrobiana de la raíz de Ipecacuana mediante una cosecha y procesamiento optimizados según la Madurez

Produção de cefalina e emetina e atividade antimicrobiana da raiz de ipecacuanha por meio de colheita e processamento otimizados de acordo com a maturidade

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Received: Sep/2/2024 • Accepted: Apr/8/2025 • Published: Nov/30/2025

Abstract

[Objective] This study aimed to determine whether there is an optimal harvest time for cephaeline, emetine, and total alkaloids in Ipecac (*Carapichea ipecacuanha* [Brot.] L. Andersson) production. In addition, the relationship between antibiotic activity and harvest time was tested. Ipeca is an herb with medicinal properties that is grown in northern Costa Rica. The root of this plant is valued based on its alkaloid concentration, which underlies its numerous biological activities. **[Methodology]** Two Ipecac fields from northern Costa Rican producers were sampled every ~2 months for one year. Samples were dried (via sun and oven), ground, extracted, and analyzed using HPLC and titration to evaluate the alkaloid concentration. Antimicrobial activity was also determined using the Kirby-Bauer test. **[Results]** Main findings revealed that there is no significant difference between oven-dried and sun-dried samples. In addition, there is an increase in total alkaloid production in roots during the first 16 months, as well as a variation in alkaloid composition: the cephaeline/emetine ratio increases after 16 months. **[Conclusions]** The highest alkaloid concentration occurs when

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DOI: https://dx.doi.org/10.15359/ru.39-1.11
E-ISSN: 2215-3470

plants are harvested between 16 and 19 months old. Additionally, the antibiotic activity reaches its maximum at 16 months, and the cephaeline/emetine ratio is two at the same harvest time.

Keywords: Antibiotic; *Carapichea ipecacuanha*; cephaeline; emetine; Ipecac.

Resumen

[Objetivo] Este estudio tuvo como objetivo determinar si existe un momento óptimo de cosecha para la producción de emetina, cefaelina y alcaloides totales de Ipecacuana (*Carapichea ipecacuanha* [Brot.] L. Andersson). Además, se probó la relación entre la actividad antibiótica y el momento de la cosecha. La Ipecacuana es una hierba con propiedades medicinales, cultivada en el norte de Costa Rica. La raíz de esta planta se valora, según su concentración de alcaloides, de la que derivan sus numerosas actividades biológicas. **[Metodología]** Se muestrearon dos campos de Ipecac de productores del norte de Costa Rica cada 2 meses durante un año. Las muestras se secaron (al sol y en horno), se molieron, se extrajeron y se analizaron mediante HPLC y titulación para evaluar la concentración de alcaloides. También, se determinó la actividad antimicrobiana utilizando la prueba de Kirbi-Bauer. **[Resultados]** Nuestros principales hallazgos revelaron que no hay una diferencia significativa entre las muestras secadas al horno y las secadas al sol. Asimismo, se observa un aumento en la producción total de alcaloides en las raíces hasta los primeros 16 meses. Igualmente, hay una variación en la composición de alcaloides: la relación cefaelina/emetina aumenta después de 16 meses. **[Conclusiones]** La concentración más alta de alcaloides ocurre cuando las plantas se cosechan entre los 16 y 19 meses de edad. Además, la actividad antibiótica es máxima a los 16 meses, y la relación cefaelina/emetina es de 2 en el mismo momento de la cosecha.

Palabras clave: Antibiótico; *Carapichea ipecacuana*; cefaelina; emetina; Ipecacuana.

Resumo

[Objetivo] O objetivo deste estudo foi determinar se há um momento ideal de colheita para a produção de emetina, cefalina e alcaloides totais da ipeca *(Carapichea ipecacuanha* [Brot.] L.). Andersson). Além disso, foi testada a relação entre a atividade antibiótica e o tempo de colheita. A ipecacuanha é uma erva com propriedades medicinais cultivada no norte da Costa Rica. A raiz dessa planta é valorizada por sua concentração de alcaloides, dos quais derivam suas inúmeras atividades biológicas. **[Metodologia]** Foram amostrados dois campos de Ipeca por produtores no norte da Costa Rica a cada ~2 meses durante um ano. As amostras foram secas (ao sol e no forno), moídas, extraídas e analisadas por HPLC e titulação para avaliar a concentração de alcaloides. Além disso, a atividade antimicrobiana foi determinada usando o teste de Kirbi-Bauer. **[Resultados]** Nossos principais resultados revelaram que não há diferença significativa entre as amostras secas no forno e as secas ao sol. Além disso, observa-se um aumento na produção total de alcaloides nas raízes até os primeiros 16 meses. Há também uma variação na composição de alcaloides: a proporção de cefalina/emetina aumenta após 16 meses. **[Conclusões]** A maior concentração de alcaloides ocorre quando as plantas são colhidas entre 16 e 19 meses de idade. Além disso, a atividade antibiótica é máxima aos 16 meses, e a relação cefalina/emetina é de 2 no momento da colheita.

Palavras-chave: *Carapichea ipecac*; ipeca; emetina; cefalina; antibiótico.

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Introduction

Carapichea ipecacuanha (Brot.) L. Andersson (Ipecac) is a medicinal herb from South and Central America. The syrup prepared with Ipecac extract is used as an expectorant, amebicide, anti-bronchitis, and vomiting inducer (for poisoning treatment) (Patel & Patel, 2021). Alkaloids are responsible for biological activity. Two major alkaloids, emetine and cephaeline, account for 84% of the total alkaloid content of its roots (Smajlović & Dučić, 2021; Uzor, 2016). Additionally, emetine and/or cephaeline have been tested as potential treatments for tumors and viruses (against dengue and SARS-CoV-2) (Bleasel & Peterson, 2020b). Although there is still ongoing debate regarding the use of Ipecac for antiviral purposes, some in vivo evidence supports its bioactivity against certain viruses (Mukhopadhyay *et al*., 2016). Other compounds from Ipecac have been associated with bioactivities as well, e.g., some circular peptides have immunomodulatory effects (Rosales-López *et al*., 2020), and the polyphenols are antioxidants (Ben Hlel *et al*., 2019).

Several commercial formulas contain Ipecac syrup, which have been commercialized in America, India, and Europe since 1762 (García *et al*., 2005). The pharmaceutical industry utilized both syrup and alkaloids, and Ipecac became a major drug during the 1940s in the USA and Europe (Ocampo-Sánchez, 2004). Syrups are prepared from the dried roots of the Ipecac plant. Plants are produced in three central regions: from Nicaragua to northern Colombia (from southern Central America to northern South America), the southwestern Brazilian Amazon, and the rainforest near the Brazilian Atlantic Coast (García *et al*., 2005). Nicaragua and Costa Rica account for 20% and 35% of the global Ipecac market, respectively (Ocampo, 2007). Ipecac root production is a crucial economic activity in the northern Costa Rican and southern Nicaraguan regions. Although *C. ipecacuanha* has been introduced for cultivation in India and various areas in Asia, Costa Rican roots have demonstrated superior quality, with reported alkaloid yields 1.5 to 4.6 times higher than those of Indian and Brazilian counterparts (Han *et al*., 2013; Ocampo-Sánchez, 2004). These facts underscore the importance of preserving the high phytochemical quality of locally cultivated plants through the use of appropriate agronomic and post-harvest practices.

The final sale price of Ipecac roots depends on the concentration of emetine, cephaeline, and total alkaloids (used as quality parameters). Nonetheless, there is no systematic study of the relationship between the maturity of the plants and the harvest time to optimize the selling price of the final product. Previously, Alvez-García *et al*. (2005) found some dependence of alkaloid content on the morphological characteristics of the root. In addition, there are variations in alkaloid occurrence rates; for example, the emetine-to-cephaeline ratio has been reported to range from 0.6 to 0.7, according to Ocampo (2007), whereas Rosales-López *et al*. (2020) reported a lower value of 0.47. Some of the morphological characteristics could be related to plant maturity and the general production of metabolites.

Costa Rican *C. ipecacuanha* is preferred over other varieties because of its high alkaloid content. The hypothesis in this study is that a specific harvest can be found with optimal alkaloid concentration. This information is relevant to the agricultural production of Ipecac, providing

DOI: https://dx.doi.org/10.15359/ru.39-1.11
E-ISSN: 2215-3470

a better understanding of metabolite production and, ultimately, informing the future evaluation of potential related species. This study aims to determine the optimal maturity and harvest time for alkaloid production in dry Ipecac roots.

Methodology

Sample collection and processing

Plants were harvested from two production fields in La Guaria, San Carlos (Province of Alajuela, Costa Rica). Six samples were taken from each field, approximately 45 days apart, starting one year after sowing. Random samples of *Carapichea ipecacuana*'s roots were taken from each field. Roots were collected, cleaned, and divided into two groups for two different drying procedures: oven-dried (40°C, four days) and sun-dried. The sun-drying procedure is the method used by Ipecac producers, which involves allowing the sample to dry in the sun for several hours until it becomes brittle. After that, samples were ground to 1 mm in a Wiley cutting mill grinder (Thomas Scientific, NJ). Finally, grounded samples were stored under refrigeration at 4°C and used for further analysis.

Total alkaloid determination

Total alkaloids were determined using a previously reported volumetric method (Pharmacopeia, 2014). For this purpose, 3.75 g of dried and powdered Ipecac root samples were added to a flask with 50 mL of ethyl ether and mixed in an orbital shaker at 400 rpm for 5 min. Subsequently, 2.5 mL of 6N ammonium hydroxide was added, and the mixture was shaken at the same speed for an additional hour. A total of 2.5 mL of water was added after agitation, and the flasks were mixed by hand. Flasks were then allowed to settle for a few minutes. The mixture was later filtered using cotton, collecting the organic layer and dumping the aqueous phase. The flask and cotton were washed with 2×15 mL of ethyl ether, and all ether extractions were combined. Ethyl ether was evaporated in a warm water bath (using a hood to extract vapors) until it dried up. The residue was redissolved in 2.5 mL of warm ethanol, allowed to cool, and subsequently mixed with 7.5 mL of a 0.1 N standard solution of sulfuric acid. Alkaloids were back-titrated with 0.1 N sodium hydroxide and a mixture of indicators (1 mg/mL methyl red and 0.5 mg/mL methylene blue, using ethanol as solvent).

Evaluation of extraction conditions

The optimal extraction conditions were assessed. A total of 0.1 g of dry and ground samples was mixed with 0.5 mL of 6N ammonia. Then, each sample from a separate experiment was extracted with 1 to 5 extraction steps. Each extraction step consists of 2 mL of ethyl ether and 10 min in an ultrasonic bath. After each extraction, the mixture was centrifuged for 10 min at 840 x *g*. Then, the other fractions were mixed in a 10 mL volumetric flask and filled with ethyl ether. Finally, 1 mL was transferred to a vial. The solvent was evaporated and then redissolved in 1 mL of methanol for further HPLC analysis. The procedure was repeated three times.

Emetine and cephaeline quantification using HPLC

Main alkaloids were quantified using the procedure reported by Han *et al*. (2013) with minor modifications. Methanolic extracts were analyzed in a UHPLC chromatograph Dionex UltiMate3000 (from Thermo

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Scientific, MA, USA) equipped with an Acclaim™ 120 C18 column, a column oven (kept at 40°C), and a diode array detector. A mobile phase consisting of 0.08% trifluoroacetic acid (TFA, aqueous) and acetonitrile was utilized, following the gradient described in Table 1. The injection volume was 5 µL. Emetine and cephaeline were analyzed at 285 nm, against pure commercial standards (obtained from Sigma-Aldrich).

Table 1. *Solvent gradient utilized for HPLC separation of Ipecac alkaloids*

Run time (min)	Flux (mL/min)	Solvent components (%)	
		TFA 0.08%	Acetonitrile
0.00	0.6	100	0
0.50	0.6	90	10
1.25	0.6	80	20
2.50	0.6	50	50
3.75	0.6	30	70
4.00	0.3	20	80
4.50	0.3	100	0
6.00	0.3	100	0
6.50	0.6	100	0
7.00	0.6	100	0

Note: derived from research.

Antibiotic activity of Ipecac extracts

The antibiotic activity of Ipecac extracts was evaluated against the ESKAPE pathogen group: *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, *Klebsiella pneumoniae* ATCC 13883, *Acinetobacter baumannii* ATCC 19606, *Pseudomonas aeruginosa* ATCC 9027, and *Enterococcus faecium* ATCC 6056.

Modified Kirby-Bauer for agar well diffusion method was utilized (Balouiri *et al*., 2016; Biemer, 1973). For this purpose, 100 µL of *E. coli* suspension (0.5 McFarland scale) in sterile saline solution (0.85% NaCl) was plated into 90 x 15mm Muller-Hinton agar plates (25mL of agar). Then, four 7 mm wells were perforated into each agar plate using sterile Pasteur pipettes (upside down), and the wells were filled with 50 µL of 60 mg/mL extract solution (in methanol). The other two wells were filled with methanol as a negative control and penicillin/streptomycin (1000 µg/mL each) as a positive control. The plates were incubated at 37°C for 18 h. The percentage of relative inhibition (%RI) was calculated according to equation (1).

$$\%RI = \frac{DIZ_{sample} - DIZ_{negative\ control}}{DIZ_{positive\ control}} x100 \quad (1)$$

where DIZ stands for "diameter of inhibition zone".

Statistical analysis

Extraction optimization was evaluated using Minitab®, with α=0.05. Repeated ANOVA measurements for total alkaloids were performed using R-studio. Assumptions of no extreme outliers and normality by the Shapiro-Wilk test were verified by utilizing parametric statistics. Pairwise comparisons were performed using the Bonferroni method to adjust the p-values, α=0.05. Three repetitions were used for drying conditions and total alkaloids. Standard deviations were calculated for emetine and cephaeline concentrations from two fields and six repetitions.

Analysis and results

Evaluation of the sun-drying vs. the oven-drying procedure

Local Ipecac producers utilize a sun-drying method for root drying. Root tissue is relatively easy to dry. The traditional method is inexpensive, requires no technological equipment or trained personnel, and

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DOI: https://dx.doi.org/10.15359/ru.39-1.11
E-ISSN: 2215-3470

is logistically efficient (Belwal *et al*., 2022). However, an unsuccessful drying step will result in lower alkaloid yield and higher transportation costs. Also, long drying times can lead to a decline in the alkaloid concentration because other organisms can contaminate and degrade it (Kamel *et al*., 2013).

The regular oven-drying process and the traditional sun-drying protocol were compared. Results are presented in Fig. 1. Data for plants younger than 13 months were excluded, as preliminary findings revealed high variability and uncertainty, likely due to immature root development. Repeated ANOVA analysis for the average of both fields (Fig. 1 (c)) showed no significant difference between the oven-dried samples and the sun-dried samples. Additionally, 16-month-old plants showed no significant differences. These plants are relevant because they yield the highest titer of total alkaloids. However, some of the samples from the individual fields (Fig. 1(a) and 1(b)) exhibited significant differences during certain months of the test period. For example, some oven-dried samples from Field #2, harvested at 17.5, 19, and 20.5 months, exhibited a total alkaloid content (w/w) approximately 0.1 to 0.5 percentage points higher than their sun-dried counterparts. This difference can be attributed to the fact that older plants have developed stronger structural tissue, making them more challenging to dry. Then, the residual moisture lowers the alkaloid content (Ekeoma *et al*., 2021).

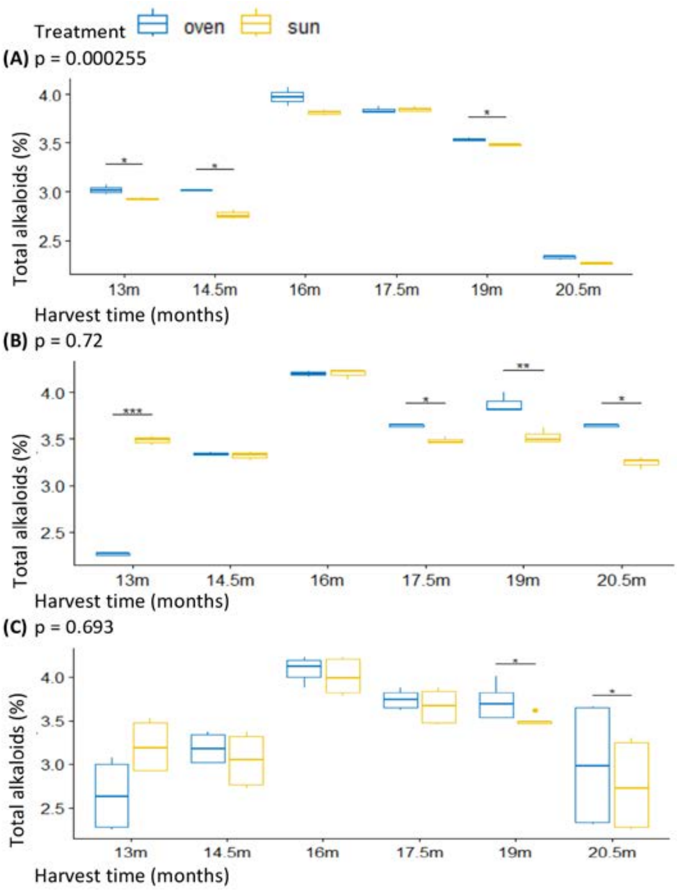

Figure 1. *Boxplot graph of the effect of drying treatment on final alkaloid concentration. (a) field #1, (b) field #2, (c) both fields combined.*

*Note: Boxes represent the t-test for pairwise comparison between sun-drying and oven-drying (Two-way ANOVA). The p-value above each graph represents the pairwise comparison between treatment groups. Significance codes for pairwise boxes are: 0.001 ´**´ and 0.01´*´. The p-adjust utilized is Bonferroni.*

Note: derived from research.

Effect of the plant maturity on total alkaloid production

Fig. 1(c) shows the average concentration of alkaloid production in the combined samples of both fields included in this study. Clearly, the best results are obtained when plants are between 16 and 19 months old, with the maximum at 16 months. Previously, Yonjan (1988) found *that C. ipecacuanha increases its alkaloid concentration during the warmer months of the Indian summer, with the maximum increment occurring*

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DOI: https://dx.doi.org/10.15359/ru.39-1.11
E-ISSN: 2215-3470

at the beginning of the summer. The increment in the total alkaloid concentration is claimed to be related to the post-reproductive phases. Samples from the 16th-old Ipecac roots included in this study were taken during December, the beginning of the dry season (December to March). After the 16th month, the alkaloid concentration begins to decrease. Therefore, climate conditions can impact alkaloid production. In the Northern zone, average temperatures range from 21 to 30 °C (Solano, 2023). Seasonal temperature variations between the dry and rainy periods (April to November) are minimal (±3°C) and are unlikely to significantly affect alkaloid production. Consequently, they were not considered in this study. However, previous studies (Hüther *et al*., 2024) have shown that larger temperature differences can influence alkaloid levels, although their impact appears to be less significant than that of shading. Precipitation may have some influence over alkaloid concentration, although it was not considered a factor in this study.

Other variables, such as explant hardening and lower altitude, are reported to increase the total alkaloid concentration (Chatterjee *et al*., 1986).

Cephaeline and emetine production

Chromatographic determination was performed using standards for the main alkaloids, as shown in Fig. 2. Cephaeline has a retention time of approximately 5.3, while emetine has a retention time of around 5.8. Chromatographic separation was successful.

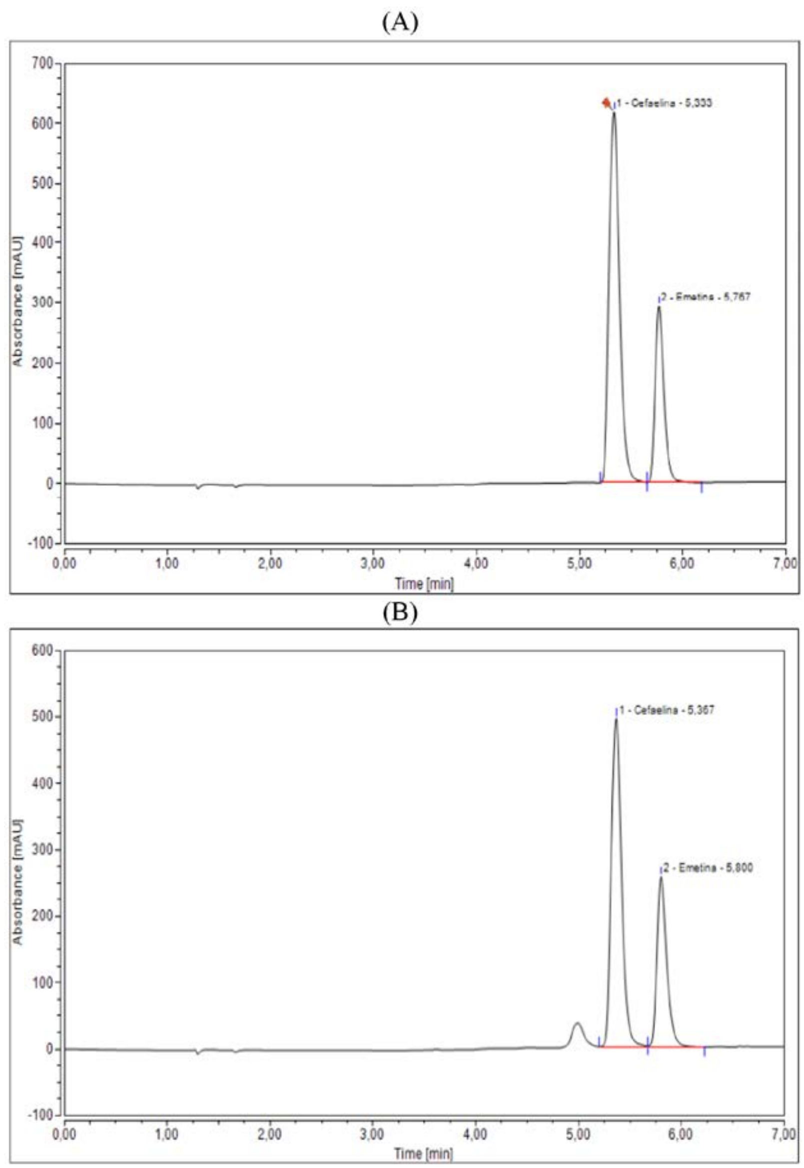

Figure 2. *UPLC chromatographs for alkaloids determination (A) a mixture of emetine and cephaeline standards. (B) Ipecac roots sample. Note: derived from research.*

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Fig. 3(A) shows the emetine and cephaeline concentrations of Ipecac roots during maturity. Results are consistent with total alkaloid production, showing a maximum cephaeline concentration between 16 and 19 months old (3.2-3.7%) and an emetine maximum titer between 14.5 and 19 months (1.4-1.7%). Additionally, the cephaeline/emetine (C/E) ratio is approximately 2 in plants ranging from 13 to 17.5 months old, and then it increases to approximately three at 20.5 months (Fig. 3(B)). According to the US Pharmacopeia, oral formulations containing Ipecac extracts should not exceed a 2.5 C/E ratio (Bleasel & Peterson, 2020a). Emetine's highest titer is reached earlier (around 6 months), while cephaeline's top concentration is reached at 19 months. The trend of C/E ratios increased at 19 months, despite a decrease in the concentration of both alkaloids. All this data suggests the same conclusion: optimal harvest time is around 16 months.

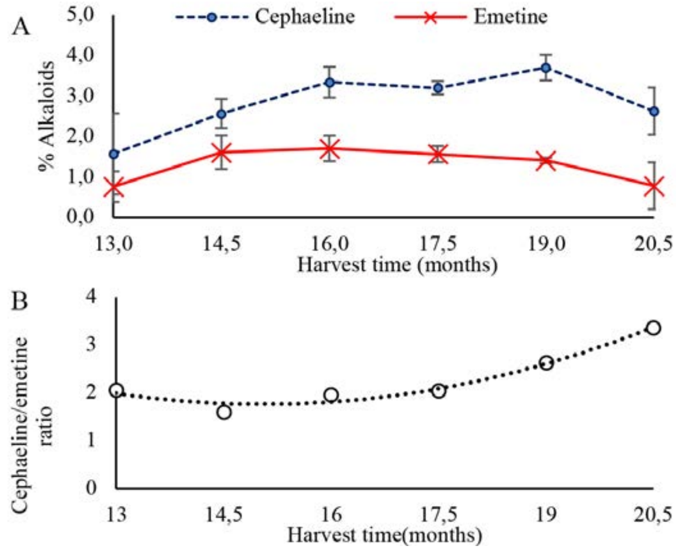

Figure 3. *Main alkaloids in C. ipecacuanha roots. (A) Cephaeline and emetine concentration in dried roots vs. maturity time. Error bars represent standard deviation. (B) Cephaeline/emetine ratio during maturity. The dotted line represents the trend of the ratio.*
Note: derived from research.

Cephaeline and emetine are monoterpenoid-isoquinoline alkaloids. The biosynthetic pathway comprises the transformation of loganin → deacetylisoipicoside → protoemetine → cephaeline → emetine (Jha *et al.*, 1991). Many of the present alkaloids only differ in the O-methylation of some of the phenolic residues regulated by O-methyltransferases (OMT). The conversion of cephaeline to emetine is catalyzed by ipeOMT1 (Nomura & Kutchan, 2010). Therefore, it is reasonable to hypothesize that the C/E ratio is influenced by changes in *ipeOMT1* expression at different growth stages; however, further experimentation is required to validate this hypothesis.

Antibiotic activity of Ipecac extracts

Given that Alkaloids are also known for their antimicrobial properties (Cushnie *et al.*, 2014), the properties of the Ipecac extracts and how they change with the harvest time were explored. Fig. 4 summarizes antibiogram results for the antimicrobial activity *of C. ipecacuanha* against six bacterial strains. All the extracts showed antimicrobial properties, with at least half the activity of penicillin/streptomycin (54-94%). Interestingly, the antimicrobial activity remains unchanged in the presence of Gram-positive bacteria. Moreover, the activity of the extracts against *E. faecium* is almost as vast as the positive control (penicillin-streptomycin), which is remarkable since this bacterium is one of the most problematic intra-hospital microbes due to its high capacity to generate resistance to antibiotics (Miller *et al.*, 2014).

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Antibiotic activity is probably related to alkaloid concentration. Then, the extracts from plants harvested at 16 months old are the most active, as expected, due to the high alkaloid concentration (Cushnie *et al*., 2014).

Antimicrobial properties against *A. baumannii*, one of the most common multidrug-resistant pathogens (Shi *et al*., 2024), demonstrated significant inhibition, even when our positive control (penicillin-streptomycin 1000 µg/mL) failed to inhibit bacterial growth. The primary mechanisms of action against eukaryotic cells (e.g., antiparasitic activity) and viruses involve the inhibition of protein synthesis and DNA replication. However, the exact antimicrobial mode of action remains unclear (Abookleesh *et al*., 2022).

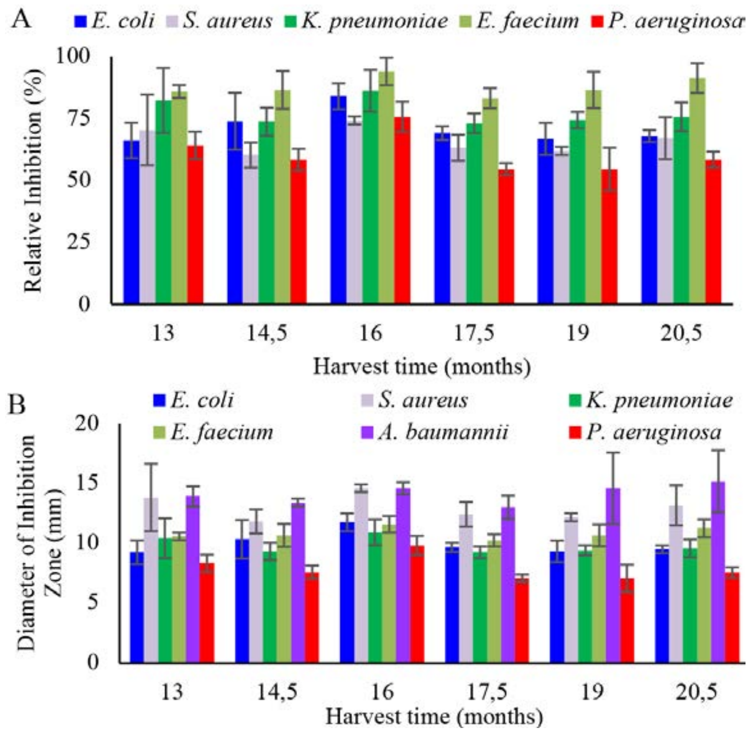

Figure 4. *Antibiotic activity of Ipecac extracts vs. harvest time. Error bars represent the standard deviation. (A) Percent of relative inhibition using penicillin-streptomycin 1000 µg/mL as positive control. A. baumannii was excluded because it was not inhibited by the positive control. (B) Diameter of inhibition zones in antibiograms.*
Note: derived from research.

Conclusions

The concentrations of emetine, cephaeline, and total alkaloids in *Carapichea ipecacuanha* are influenced by harvest time. Roots harvested at 16 months of age are considered optimal due to their elevated levels of total alkaloids, including emetine and cephaeline, as well as a favorable emetine-to-cephaeline (E/C) ratio. Notably, these samples exhibit significant antibiotic activity, in some cases comparable to that of conventional antibiotics. This antimicrobial effect is likely associated with the high alkaloid content.

Funding

This project was supported by the Office of the Vice-Rector for Research through the Fund for the Dissemination of Knowledge Generated at the National University, Costa Rica, 2025.

Acknowledgements

The authors thank the local Ipecac producers for providing the samples and Mr. Adrián Cerdas for proofreading the document.

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DOI: https://dx.doi.org/10.15359/ru.39-1.11
E-ISSN: 2215-3470

Conflict of Interest

The authors declare no competing interests.

Author contribution statement

All the authors declare that the final version of this paper was read and approved.

Authors and CRediT Roles: V. A. V., R. S. L., & G. R. R.: Conceptualization, and Supervision; M. A. R. V., and J. A. R. R. Methodology, Data Curation, and Formal Analysis; P. J. B. Validation, Writing - Original Draft, Writing – Review.

The total contribution percentage for this paper was as follows: M.A.V.R., 40 %., R. S. L. 10 %, J. A. R. R. 10 %, G. R. R. 15 %, V.A.V. 15%, P. J. B. 10 %.

Data availability statement

The data supporting the results of this study will be made available by the corresponding author, **V. A. V.,** upon reasonable request.

Preprint

A Preprint version of this paper was deposited in: http://hdl.handle.net/11056/28798

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DOI: https://dx.doi.org/10.15359/ru.39-1.11
E-ISSN: 2215-3470
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