Bouzabata *et al.*
Future Journal of Pharmaceutical Sciences (2025) 11:108
https://doi.org/10.1186/s43094-025-00865-9

Future Journal of Pharmaceutical Sciences

RESEARCH Open Access

FactoMineR-based multivariate analysis and SwissADME profiling of medicinal plants against cutaneous leishmaniasis

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Abstract

Background To investigate medicinal plants used in the traditional treatment of cutaneous leishmaniasis using multivariate tests coupled with pharmacokinetic predictions in silico.

Main body Interviews were conducted with 21 herbalists in Annaba and El Tarf provinces. The dataset comprised 26 variables, and multidimensional analyses were applied using the FactoMineR package. Nineteen species were reported in this survey. Among them, the most important family was Lamiaceae, with five species. According to the RFC index, the most famous species were the aerial parts of *Teucrium polium* L. (57.14%).

Second, a data matrix for the species generated showed higher contribution values in the first dimension owing to the lack of the topical administration form, the presence of preparation mode by decoction and cataplasm, and the association of medicinal plants specifically with olive oil and honey, respectively. The analysis of the first dimension demonstrated a high association for the form of administration and the mode of administration, with correlation ratios η^2 of 6.261E-01, 5.501E-01, and 4.772E-01 ($p < 0.05$), respectively. The cluster analysis identified three clusters differentiated by the administration form per *os* with a *p-value* of 7.49E-05 ($p < 0.05$). Later, the ADME profile was tested in silico by identifying the physicochemical properties of the major compounds reported in the literature.

Conclusions The results showed that the major compounds of plants with high RFC showed excellent ADME profiles, with good absorption, low toxicity, and favorable distribution, making them promising candidates for the safe treatment of leishmaniasis.

Keywords ADME, Cluster, Differentiated, FactoMineR, Leishmaniasis

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Background

Leishmaniasis is a significant and devastating public health issue and is ranked top among notifiable parasitic infections [1]. It is caused by flagellate protozoa of the genus *Leishmania*, which are transmitted by phlebotomy insects [2]. Leishmaniasis is widespread in approximately 100 countries, and the at-risk population is estimated to be approximately 350 million [3].

Cutaneous leishmaniasis is the most common clinical manifestation worldwide, affecting 12 million people and causing approximately 2 million new cases annually [4]. Afghanistan, Algeria, Brazil, Iran, Pakistan, Peru, Saudi Arabia, and Syria account for 90% of all cases worldwide [5]. In Algeria, three common species are encountered: *L. infantum*, which causes the CL and VL forms of the disease in the northern part of the country; *L. killicki*, which causes the CL form in Central Southern Algeria (Ghardaïa region); and *L. major*, which is spread in the Central Eastern region of Algeria, with the M'Sila province being the most affected [6]. More than a quarter of a million (252,659) CL cases were registered in the country between 1982 and 2017 in five provinces (Bechar, El Oued, Batna, Biskra, and M'Sila), accounting for > 70% of the total number of cases [6].

Given the epidemiology of leishmaniasis, scarcity of treatment, severe side effects of existing drugs such as amphotericin B and pentamidine, lack of successful vaccines, and lack of interest from major pharmaceutical companies, finding new molecules with leishmanicidal activity has become an urgent challenge [7]. Ethnopharmacological knowledge is a holistic approach that can create better, safer, more accessible, and more sustainable medicines [8, 9]. It is also worth noting that despite numerous published studies over the last decade exploring the diversity of ethnopharmacological research in Algeria [10–13], only three papers have reported on the medicinal plants used for the treatment of cutaneous leishmaniasis in Algeria [14–16]. In addition, several Moroccan and Tunisian medicinal plants have been reported to inhibit the growth of various Leishmania species such as *L. major* (cutaneous leishmaniasis) and *L. infantum* (visceral leishmaniasis) [17–21].

In recent decades, the use of multivariate analyses in various ethnosciences has increased significantly, allowing for quantitative examinations of various topics linked to traditional knowledge and its applications [22]. In 1979, Moerman outlined the first strategy used for Native American medicinal plant utilization [22]. Multivariate approaches are particularly beneficial for understanding the exploitation of biodiversity in ethnomedicinal systems, demonstrating that selecting valuable taxa may be explained by objective criteria rather than being driven by chance [23, 24]. This novel strategy was utilized to determine the specificity of the link between the plant species employed for treating type 2 diabetes by the Cree Nation, the native people of Quebec [25]. There is a constant increase in studies focusing on the use of these methodologies in ethnobotany and ethnopharmacology [26–29].

To the best of our knowledge, no studies have highlighted the multidimensional elements of CL correlating with ethnopharmacology and ethnobotanical data in Algeria. Therefore, there is a clear need to develop a new approach to ethnobotanical and ethnopharmacological research in Algeria.

Furthermore, the exploration of bioactive compounds through in silico methods highlights their potential therapeutic applications, with important considerations regarding their interactions within complex biological systems [30, 31]. The integration of in silico pharmacokinetics (ADME) with ethnobotanical methods represents a transformative approach to drug discovery, particularly in the exploration of bioactive compounds derived from medicinal plants [32].

For instance, the use of in silico tools such as SwissADME has revolutionized the field of pharmacokinetics of medicinal plants based on molecular descriptors to predict properties such as gastrointestinal absorption, blood–brain barrier permeability, and lipophilicity (LogP) [33–35].

Consequently, the objectives of this study were (a) to use multivariate analyses to investigate the association between medicinal plants used by herbalists, (b) to evaluate the most frequently used species, and (c) to investigate factors associated with traditional knowledge of CL in northeastern Algeria. This study also aimed to predict pharmacokinetic parameters using SwissADME, suggesting their potential for drug development.

Materials and methods

Description of the study site

Interviews were held with established herbalists in two districts situated in Northeastern Algeria, namely Annaba and El Tarf, as shown in Fig. 1. Annaba station (36°53′59′′ North, 7°46′00′′ East) is 533 km from Algiers (1439 Km^2 area). The El Tarf station (36°75′58′′ North, 8°22′12′′ East) is 589 km from Algiers (3339 Km^2 area). According to the Köppen and Geiger climate classification, the climate of the two study locations is warm and classified as "Csa" hot-summer Mediterranean climate, with average temperature (A: 18.4 °C, T: 18.3 °C) and average annual rainfall (A: 712 mm, T: 694 mm) [36].

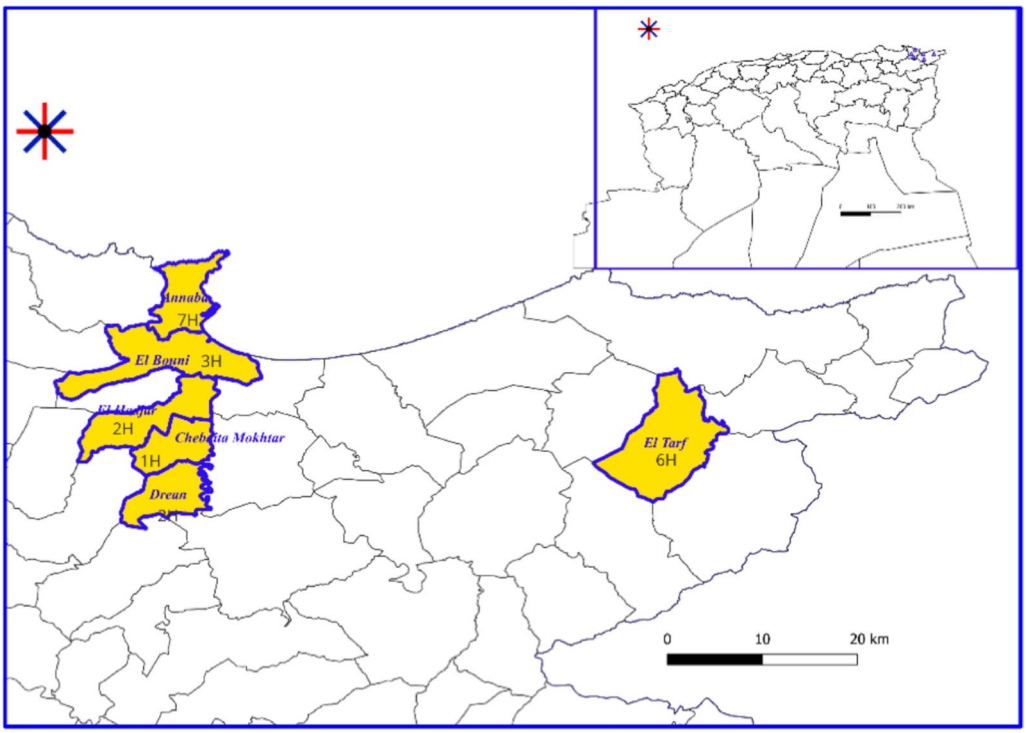


Fig. 1 Geographical position of districts in the study area map. H: herbalists

Data collection

Qualitative variables

The ethnobotanical approach is based on describing the use of traditional treatments. The questionnaire addressed the traditional treatments used in the treatment of CL and included closed questions that required a "yes" or "no" response. Consequently, the questions were semi structured [37]. The interviews were conducted in Arabic language.

The questionnaire was prepared according to the model described by Chassagne et al. (2022) [38]. Due to the absence of an ethics committee in Algeria, the ethical guidelines provided by the International Society of Ethnobiology (http://www.ethnobiology.net/) were strictly followed [39].

The questionnaire focused on five aspects of use: (1) part of the plant used, (2) mode of preparation, (3) form of administration, (4) possibility of association with various natural products, and (5) frequency of use. Each item was subdivided into qualitative variables (25 qualitative variables): 1-a: aerial part, 1-b: bark, 1-c: bulb, 1-d: flower, 1-e: fruit, 1-f: leaves, 1-g: roots, 1-h: resin, and 1-i: seeds; 2-a: decoction; 2-b: infusion; 2-c: cataplasm; 2-d: juice; 2-e: latex; 2-f: powder; and 2-g: oil; 3-a: topical administration or 3-b: oral administration; 4-a: honey, 4-b: olive oil, 4-c: cow's milk, or 4-d: plant; 5-a: once a day, 5-b: twice a day, or 5-c: three times a day.

Quantitative variables

The relative frequency citation (RFC) index indicates the local importance of each plant species based on the number of citations by the informants. Based on the number of citations by informants, the relative frequency citation (RFC) index was used to determine the local relevance of each plant species [40]. This index was calculated by making specific changes to the formula used in previous research.

$$\mathrm{RFC} = \mathrm{FC} \div N \tag{1}$$

$$0 < \mathrm{RFC} < 1$$

where FC indicates the number of citations given by the total number of informants showing the use of each species and N denotes the total number of informants interviewed in the study.

Authentication of medicinal plants

Each voucher specimen was identified by comparing it with the morphological characteristics described for the Algerian flora [41]. The scientific names of each species were checked based on their identification in the international database The Plant List [42].

Multivariate analysis

This research used new statistical methods to evaluate the traditional knowledge for treating CL in North East Algeria. The multivariate analyses were performed with the assistance of R software (4.2.2) [43], an open-source programming language and environment for statistical and graphical techniques, with the assistance of the package "FactoMineR" [44], using the graphical interface "Factoshiny" dedicated to multivariate data analysis, considering the main features: different types of variables, the structure of the data (a partition on the variables and the individuals), and a hierarchical structure of the variables [45].

Multiple correspondence analysis (MCA)

A qualitative matrix was used in MCA to generate two quantitative matrices. The output matrix for "*items*" comprises 19 rows and 25 columns (coordinates against each of the 25 axes), with columns arranged in decreasing order of explained variance from the source matrix. The "*variable*" output matrix has 50 rows (variable modalities) and 19 columns (coordinates against the same 25 axes). Understanding and interpreting the data in the Results section is essential to clarify the distinctions between these parameters.

As a result, the medicinal species identified are considered as individuals, and for one categorical variables we make a one-way analysis with the coordinates of the individuals on the axis explained by the categorical variable [46]. Student's *t-test* was used to compare the category average to the overall average [45].

Hierarchical clustering analysis (HCA)

MCA was applied in the HCA analysis using Ward's minimum variance approach [47].

Ward's linkage method attempts to group observations to reduce cluster variation.

Consequently, an observation is deemed a cluster member if its inclusion in that cluster results in a minimal increase in the error sum of squares [48].

Cluster analysis was used to *(i)* characterize the partition of classes or groups of species used in traditional cutaneous leishmaniasis treatment and *(ii)* characterize the parameters that best describe the partition using the Chi-square test (by increasing the *p*-value) between the qualitative and class variables.

Computational analysis for ADME profile

The first step is to access the PubChem server (https://pubchem.ncbi.nlm.nih.gov accessed on March 19, 2025) to obtain canonical SMILE information. The second stage estimates their ADME profile (absorption, distribution, metabolism, and excretion (ADME) profile) using the online program SwissADME (http://www.swissadme.ch/).

A drug-likeness approach (Lipinski's rule of five) was used to screen the selected compounds. Drug likeness overcomes ADME (absorption, distribution, metabolism, and excretion) constraints, while maintaining an oral bioavailability score greater than 0.50 [49].

Lipinski's rule of five is widely used to assess the drug likeness of small molecules, particularly their potential for oral bioavailability. The rule states that a compound is likely to have poor absorption or permeation if it exceeds one of the following thresholds: molecular weight (MW) $\leq$ 500 Daltons (Da), lipophilicity (logP) $\leq$ 5, number of hydrogen bond donors (HBD) $\leq$ 5, and number of hydrogen bond acceptors (HBA) $\leq$ 10 [50].

Results

Sociodemographic features of informants

A total of 21 herbalists were interviewed, with 57.10% belonging to Annaba and 42.90% from El Tarf Province. The average age of all participants was 53.4 ± 16.7 years old, ranging from 20 to 60 years. The majority of the participants (95.2%) were men. A substantial percentage of participants (76.20%) stated that their

Table 1 Sociodemographic features of interviewees

Characteristics	Frequency	Percentage (%)
Location		
Annaba	12.0	57.1
El Tarf	9.0	42.9
Gender		
Men	20.0	95.2
Women	1.0	4.8
Age (years)		
[20–30[	2.0	9.5
[30–40[	8.0	38.1
[41–60[	10.0	47.6
≥ 60	1.0	4.8
Level education		
Illiterate	8.0	38.1
Primary	5.0	23.8
Secondary	7.0	33.3
University	1.0	4.8
Information source		
Professional experience	16.0	76.2
Internet documentation	5.0	23.8

professional experience made them the most informed about traditional medicine (Table 1).

Distribution of medicinal plants according to the relative frequency index

Table 2 shows the descriptive analysis of the ethnobotanical data collected from interviews with herbalists in the Annaba and El Tarf districts. Herbalists recommended 19 therapeutic herbs from 13 plant families, of which Lamiaceae was the most abundant species (five), followed by Amaryllidaceae (two species) and Asteraceae (two species).

The species were ranked according to their frequency of citation, and the top two species were *Teucrium polium* L. (57.14%), followed by *Allium sativum* L. (23.80%). Other significant species were *Juniperus phoenicea* L. (14.28%) and *Rosmarinus officinalis* L. (9.52%). The results also showed that 14 medicinal plants [sp1: bulb, sp3: leaves, sp4: leaves, sp5: bark, sp6: fruit, sp7: resin, sp8: fruit, sp10: stem, sp12 seeds, sp13: aerial part, sp14: leaves, sp15: leaves, sp16: aerial part, and sp19: leaves] demonstrated a similar frequency index (4.76%). The most represented parts were the bark, flower, root, resin, and stem, with a similar frequency of occurrence estimated at 18.

Multiple correspondence analysis (MCA)

Regarding the descriptive results and the frequency of responses connected to traditional CL knowledge in Northeastern Algeria, all qualitative variables were chosen for MCA analysis according to the square ratio correlation (η^2).

Distribution of species within variables

A graphical representation of the contribution of individual species on the first two axes is shown in the Fig. 2. The results were visualized using a scatter diagram. The

Table 2 Alphabetical list of antileishmanial species mentioned during the ethnobotanical survey

species	Family	Local Name	Organ	Preparation form	Application	Association	Frequency of use	Informants	RFC (%)
sp1	Amaryllidaceae	*Bsal*	B_O	Cat_MP	Ta_F	No_AS	t2.d_FU	1	4.76
sp2	Amaryllidaceae	*Thoum*	B_O	Cat_MP, Jce_MP	Ta_F	Oo_AS	t2.d_FU	5	23.80
sp3	Aloeaceae	*Sebbae*	L_O	Ltx_MP	Ta_F	No_AS	t2.d_FU	1	4.76
sp4	Asteraceae	*Chih*	L_O	Oil_MP	Ta_F	No_AS	No_FU	1	4.76
sp5	Lauraceae	*Qarfa*	Ba_O	Dec_MP	Oa_F	No_AS	t1.d_FU	1	4.76
sp6	Cucurbitaceae	*Handel*	Fr_O	Cat_MP	Ta_F	Oo_AS Pl_AS	t1.d_FU	1	4.76
sp7	Burseraceae	*El Mour*	Rs_O	Ltx_MP	Ta_F	Oo_AS	t2.d_FU	1	4.76
sp8	Moraceae	*Kartous*	Fr_O	Ltx_MP	Ta_F	No_AS	t1.d_FU	1	4.76
sp9	Cupressaceae	*Aaraar*	L_O, Fr_O	Dec_MP	Ta_F	No_AS	t1.d_FU t2.d_FU t3.d_FU	3	14.28
sp10	Asteraceae	*Oum lbina*	R_O	Ltx_MP	Ta_F	No_AS	t2.d_FU	1	4.76
sp11	Lamiaceae	*Khzama*	Fl_O	Dec_MP	Ta_F	No_AS	t3.d_FU	3	14.28
sp12	Brassicaceae	*Hab rchad*	S_O	Pwd_MP	Ta_F	Cm_AS	t2.d_FU	1	4.76
sp13	Lamiaceae	*Merriouet*	Ap_O	Pwd_MP	Ta_F	No_AS	No_FU	1	4.76
sp14	Apocynaceae	*Defla*	L_O	Pwd_MP	Ta_F	No_AS	t3.d_FU	1	4.76
sp15	Oleaceae	*Zitoun*	L_O	Pwd_MP	Ta_F	Oo_AS	No_FU	1	4.76
sp16	Fabaceae	*Rtem*	Ap_O	Dec_MP	Ta_F	Oo_AS Pl_AS	No_FU	1	4.76
sp17	Lamiaceae	*Iklil djabel*	L_O	Dec_MP	Ta_F	No_AS	t3.d_FU	2	9.52
sp18	Lamiaceae	*El-Khiyata*	Ap_O	Dec_MP, Inf_MP, Cat_MP	Ta_F	No_AS	t2.d_FU t3.d_FU	12	57.14
sp19	Lamiaceae	*Zaatar*	L_O	Dec_MP	Oa_F	H_AS	t2.d_FU	1	4.76

Analyzed of 25 qualitative variables: Ap_O: Aerial part, Ba_O: Bark, B_O: Bulb, Fl_O: Flower, Fr_O: Fruit, L_O: Leaves, R_O: Roots, Rs_O: Resin, S_O: Seeds, Dec_MP: Decoction, Inf_MP: Infusion, Cat_MP: Cataplasm, Jce_MP: Juice, Ltx_MP: Latex, Pwd_MP: Powder, Oil_MP: Oil, Ta_F: Topical administration, Oa_F: Oral administration, H_AS: Honey, Oo_AS: Olive Oil, Cm_AS: Cow's Milk, Pl_AS: Plant. t1.d_FU: once a day, t2.d_FU: twice a day, t3.d_FU: three times a day, No_AS: no association, No_FU: no frequency of use. *Modalities of variables*: Each variable was recoded with a binary code: "No" = "0": or "yes" = "1," RFC: relative frequency citation. The name of each species was checked using the online database "The Plant List.". sp1, *Allium cepa* L.; sp2, *Allium sativum* L.; sp3, *Aloe vera* L.; sp4, *Artemisia herba alba* Asso.; sp5, *Cinnamomum zeylanicum* Blume; sp6, *Citrullus colocynthis* (L.) Schrad., sp7, *Commiphora myrrha* (T. Nees) Engl.; sp8, *Ficus carica* L.; sp9, *Juniperus phoenicea* L.; sp10, *Launaea arborescens* (Batt.). Murb.; sp11, *Lavandula angustifolia* Mill.; sp12, *Lepidium sativum* L.; sp13, *Marrubium vulgare* L.; sp14, *Nerium oleander* L.; sp15, *Olea europaea* L.; sp16, *Retama raetam (*Forssk.) Webb, sp17; *Rosmarinus officinalis* L., sp18; *Teucrium polium* L., sp19; *Thymus vulgaris* L

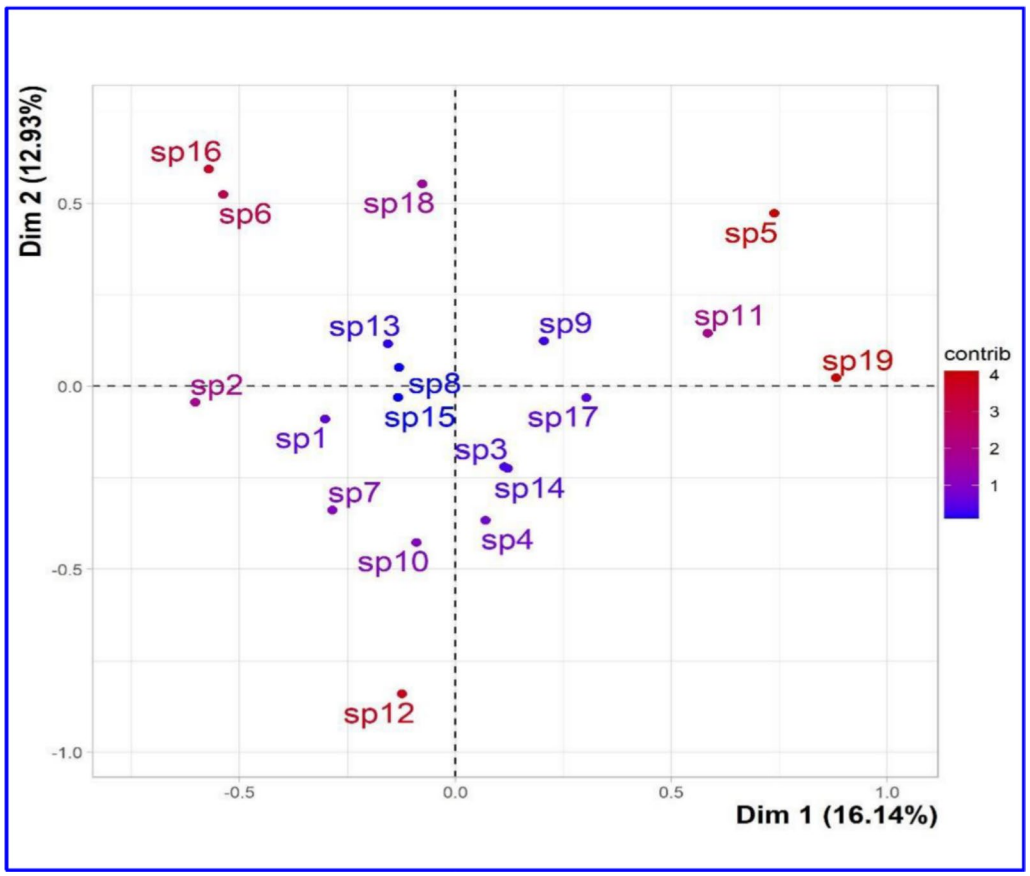


Fig. 2 Scatter plot of plant species according to their contribution to the two first dimensions. The labeled individuals (species in red) are those with the higher contribution to the plane construction

variability or similarity of the species identified in this study was described according to the descriptors used.

The first dimension opposed species characterized by a higher contribution value with positive coordinates on the x-axis [sp5: ctr = 17.738, x = 0.723, sp11: ctr = 11.128, x = 0.573, sp19: ctr = 25.292, x = 0.864] to species with negative coordinate values on the x-axis [sp 2: ctr = 11.869, x = -0.592, sp6: ctr = 9.425, x = -0.527, sp16: ctr = 10.633, x = -0.560). Concerning the first dimension, the second axis opposes similarities with a strongly positive coordinate on the y-axis [sp16: ctr = 14.363, y = 0.582, sp6: ctr = 11.221, y = 0.515, and sp18: ctr = 12.497, y = 0.543] to species [sp12, sp10 and sp7] characterized by a negative coordinate value [ctr = 28.727/y = − 0.824, ctr = 7.376/y = − 0.417, ctr = 4.635/ y = − 0,331].

Figure 3 shows a graphical depiction of each variable coordinate based on the square correlation ratios (η^2) between the variable and the coordinates of the individuals on the first and second axes, respectively.

Thus, the first dimension showed a higher correlation with the Ta_F variable, with the squared correlation ratio (η^2) estimated as 0.626 *(p < 0.05)*. This correlation with the first dimension was followed by two variables, Oa_F and Dec_MP, with values of η^2:0.550 and 0.477 *(p < 0.05)*. In parallel, frequency of use (t1_FU) showed a higher correlation with the second dimension, with a η^2 value estimated of 0.509.

A common method for visually depicting a category on a graph of people is to place the category at the barycenter, which refers to the average location of the individuals who possess it in their response [51] (Fig. 4).

Here, for example, the categories Ta_F_no, Oa_F_yes, and Dec_MP_yes are superimposed as they are chosen by the same species [sp5, sp19, and sp11, sp9, sp17]. Moreover, the modalities Cat_MP_yes, Pl_AS_yes, and Oo_AS_yes were closely associated with the species [sp16, sp6, sp2, and sp18]. Table 3 lists the main features and their correlation ratios for the first two dimensions (1 and 2).

Cluster analysis

Cluster characterization

The Chi-square test was performed between the categorical variable and the cluster variable, and the *p*-value

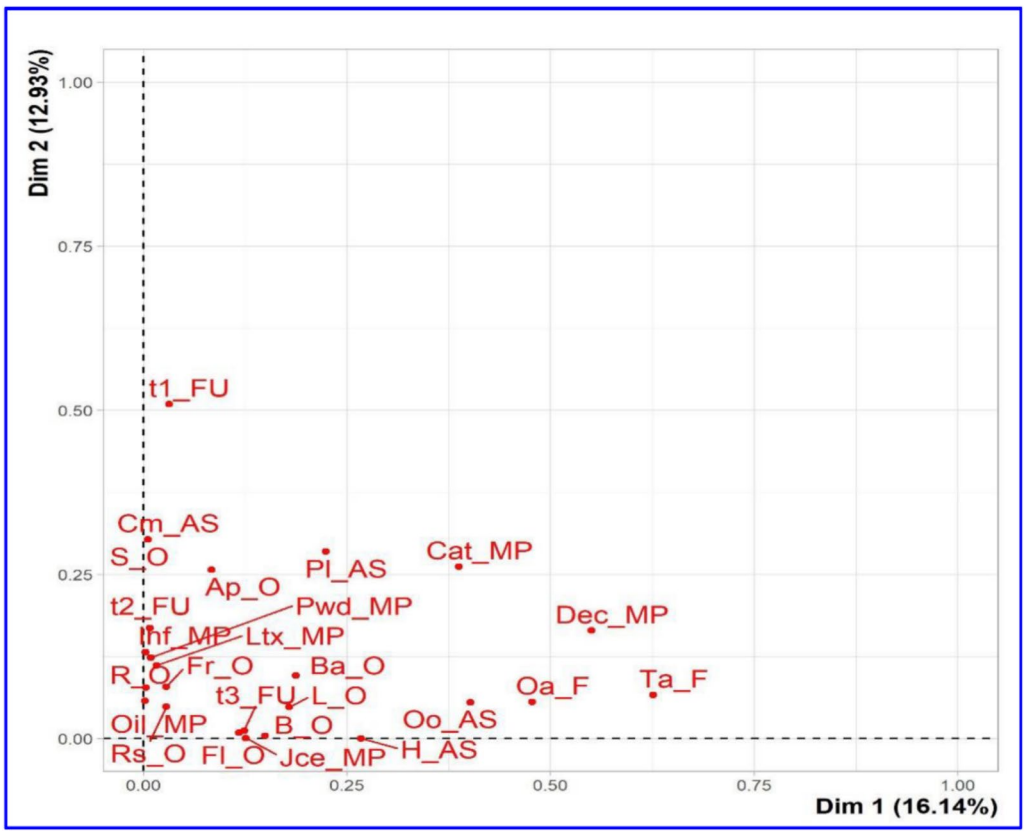


Fig. 3 Square correlation ratios of the twenty-five qualitative variables on the two first dimensions. Dim: Dimension

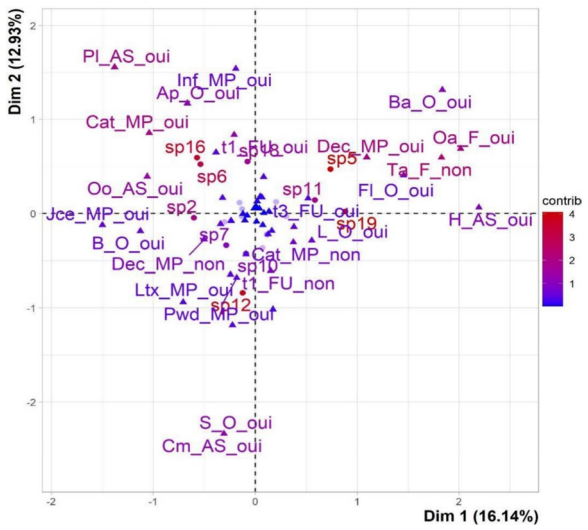


Fig. 4 Two-dimensional MCA plot. Correlation between species and the category of each variable

Table 3 Square correlation ratios of main features with modalities

Modalities	η^2	*p*-value
Dimension 1		
sTa_F_no	0.435	5.467E-05
Oa_F_yes	0.452	1.058E-03
Dec_MP_yes	0.320	2.780E-04
Cat_MP_yes	0.283	4.442E-03
Pl_AS_no	0.309	4.070E-02
Oo_AS_no	0.289	3.573E-03
Dimension 2		
t1_FU_yes	0.259	6.004E-04
Cm_AS_no	0.443	1.455E-02
S_O_no	0.443	1.455E-02
Pl_AS_yes	0.312	1.859E-02
Cat_MP_yes	0.209	2.506E-02
Ap_O_yes	0.250	2.660E-02

η^2: squared correlation ratio is an indicator used in the ANOVA model to test the relationship between a qualitative variable and quantitative variable (coordinate value of the qualitative variable on the axis)

was less than 0.05, indicating that the categorical variable was linked to the cluster variable [51]. Indeed, the most characteristic variables affecting the partition of the clusters were Oa_F, t3_FU, Dec_ MP, and Ta_F with respective *p*-values 7.48E-05, 5.44E-04, 3.95E-03, and 1.87E-03 (*p*-values < *0.05*).

The dendrogram suggests the existence of three clusters (Fig. 5). Cluster 1 includes ten species, sp1, sp2, sp10, sp7, sp15, sp13, sp8, sp6, sp16, and sp12), while cluster 2 contained seven species (sp17, sp9, sp11, sp3, sp4, sp14, and sp18). In addition, cluster 3 included two species, sp5 and sp19.

Link between the cluster variable and the categorical variables

The characteristic variables for the partition were determined by the difference between the values of the model of the nominal variable related to the cluster and the overall values. The modality is considered characteristic if its abundance in the cluster is significantly higher than expected given its presence in the population. This was measured using a criterion known as the *test value* [52]. The test value is a criterion used

Table 4 Link between the cluster variable and the significant categorical variables (Chi-square test)

Categorical variable	*p*. value	*v*. test
Cluster 1		
t3_FU = t3_FU_no	3.09E-03	+ 2.95
Dec_MP = Dec_MP_no	3.09E-03	+ 2.95
Cluster 2		
t3_FU = t3_FU_yes	2.57E-04	+ 3.65
t3_FU = t3_FU_no	2.57E-04	− 3.65
Cluster 3		
Oa_F = Oa_F_yes	5.84E-03	+ 2.75
Ta_F = Ta_F_no	1.75-E02	+ 2.37

The sign of the v. test indicates that the mean of the cluster is lower (−) or greater (+) than the overall mean [51]

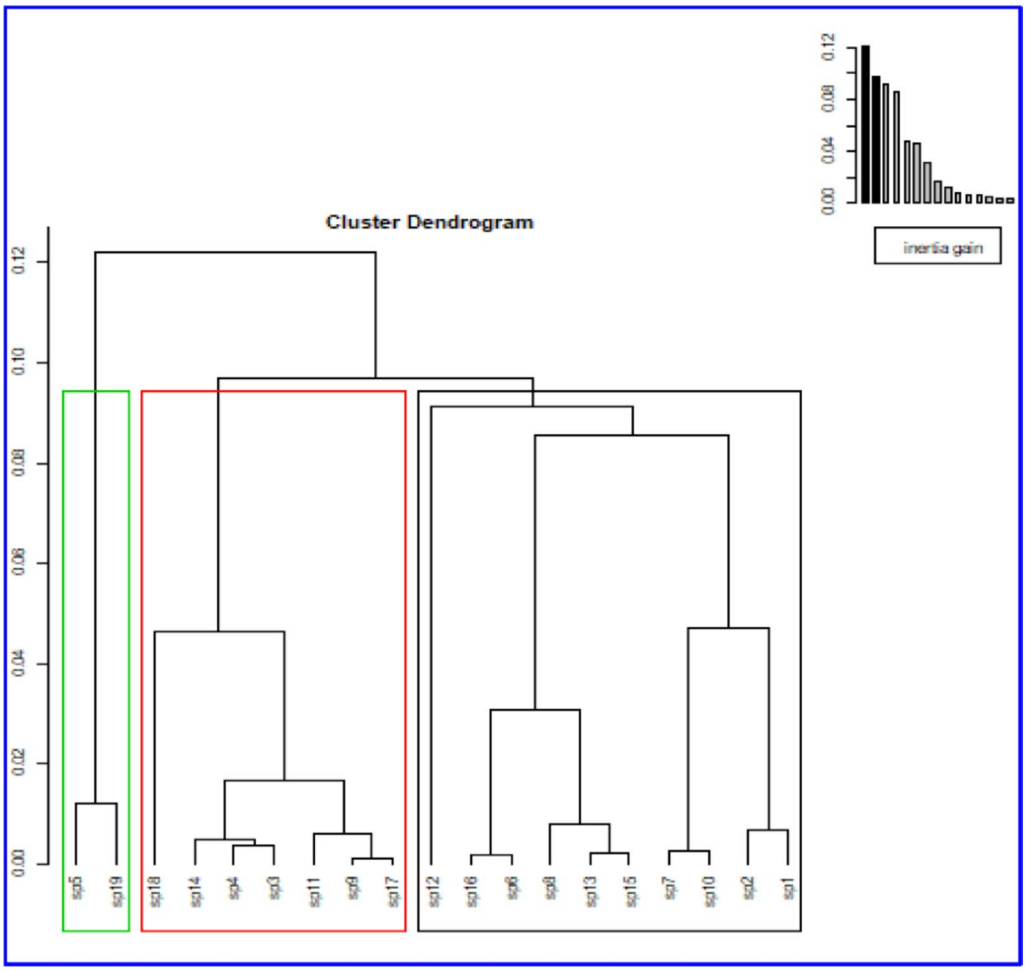


Fig. 5 Dendrogram of plant species based on Elucidean distances of 25 variables

to assess the significant position of a modality or category of the variable. A significant position was considered when the test value was greater than 2 in absolute value, corresponding to approximately the 5% threshold [53]. Table 4 defines the categories of variables most related to the cluster variables with the test value.

Considering the partition of the categorical variable for each cluster, cluster 1 is characterized by two modalities: the mode of preparation via decoction [Dec_MP_no] and the frequency of use [t3_FU_no]. More species were not used by decoction and a frequency of three times per day in this cluster than in others. Indeed, 76.92% of species related to t3_FU_no/Dec_MP_no belonged to cluster 1, and 100% of species in cluster 1 were cited with t3_FU_no/Dec_MP_no considered as significant modalities, with test values estimated to be 2.95. In contrast, 100% of the species used with a frequency of use of t3_FU_yes belonged to cluster 2 (v. test = 3.65). The modality Oa_F_yes was significant and characterized 100% of the species in cluster 3, with the test value estimated as 2.75.

The analysis of the clustering partition and the phylogenetic relationship demonstrated the disorders of the distribution of the botanical family coupled with the traditional use of the antileishmanial species. This was justified by the occurrence of the Lamiaceae family in three clusters: cluster 1 (sp_13_*Marrubium vulgare* L.), cluster 2 (sp_17_*Rosmarinus officinalis* L., sp_11_*Lavandula angustifolia* Mill., and sp_18_*Teucrium polium* L.), and cluster 3 (sp_19_*Thymus vulgaris* L.).

However, the partition of the species belonging to the Asteraceae family was noticeable for cluster 1 (sp10_*Launaea arborescens* (Batt.) Murb) and 2 (sp4_*Artemisia herba alba* Asso). The applicability of the cluster analysis to the study of plant taxonomy in the context of ethnopharmacology was performed by Leduc et al., 2006, who reported the limitations of the classification within phylogenetic relationships [40].

ADME profile of major phytoconstituents of the five top species

In the first step, the chemical composition of the top five species classified in the traditional medicine of cutaneous leishmaniasis according to the literature data specified in three geographical sectors in Algeria (Table 5). In the second step, canonical SMILE information was obtained from the PubChem database.

To assess whether molecules can be selected as potential drugs, we calculated their pharmacokinetic properties [49]. The molecules used in this study were subjected to the calculation of their absorption, distribution, metabolism, and excretion (ADME). Furthermore, physicochemical properties such as molecular hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), weight (MW), topological polar surface area (TPSA), rotatable bond count (RB), octanol/water partition coefficient (LogP), and molar refractivity (MR) were calculated using the SwissADME webserver. The ADME profiles of the major compounds selected are shown in Fig. 6 and Table 7.

Discussion

Considering the ethnobotanical research carried out in North Africa, it was found that 42% of the species were not previously reported for the traditional treatment of cutaneous leishmaniasis. Among them, three species were reported for the first time: *Retama raetam (*Forssk.) Webb, *Ficus carica* L., *Launaea arborescens* (Batt.) Murb.

Moreover, traditional healers in the Ain Sekhouna region (western Algeria) cited the predominant species: *Haloxylon scoparium* Pomel (Chenopodiaceae, 73%)

Table 5 Major compounds of the top five medicinal plants used in the traditional treatment of CL

Species	Origin	Extract: organ	Major compound (%)	Source
T. polium L	M'sila [C]	EO: FAP	ß-pinene [32.3%]	[54]
A.sativum L	Western Alg [W]	EO: bulb	Allyl trisulfide [45.0%] Diallyl disulfide [22.0%[	[55]
J. phoenicea L	Bouira [SEA]	EO: AP	α-pinene [34.4%]	[56]
L. angustifolia L	Batna [E]	EO: FF	1,8-cineole [29.4%] camphor [24.6%]	[57]]
	Kabylie region [C]	EO: AP	1,8-cineole [37.80%] ß-caryophyllene [20.90%]	[58]
R. officinalis L	Bordj Bou Arreridj [EA]	EO: EAP	1,8-cineole [52.4%] camphor [12.6%]	[59]

EO: essential oil; FAP: flowering aerial parts; Alg: Algeria; SEA: Southeast Algiers; EA: East Algiers; AP: aerial parts; FF: Fresh flowering; E: East, C: Center, W: West; n.p: not precise/determined; EAP: External aerial parts (flowers, leaves, and small stems)

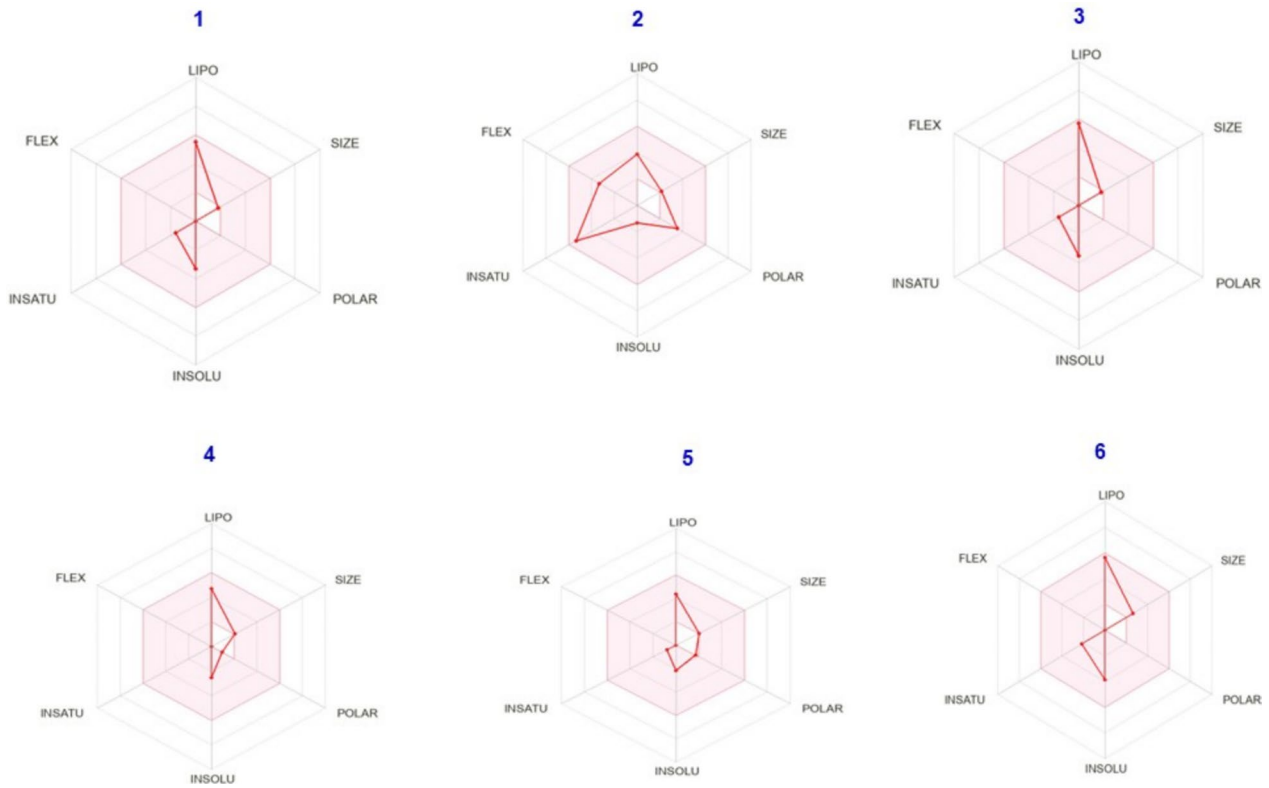


Fig. 6 Bioavailability radar plot representations of six physicochemical properties for the six major compound. The shaded area represents the range of properties to be considered drug-like

and *Artemisia herba-alba* Asso. (Asteraceae, 18%), and *Camellia sinensis* L. (Theaceae, 9%) were prepared as powdered extracts mixed with butter or olive oil for topical application as poultices [16]. In addition, 61 Tafilalet oasis species have been documented by 272 herbalists with 96% external treatments such as cataplasms and ointments [60]. Additionally, 16 species were identified in Sefrou city with a major frequency index for *Lavandula dentata* L. (93.75%), *Cistus salviifolius* L. (87.5%), *Crataegus oxyacantha* L. (81.25%), *Ephedra altissima* Desf. (75%), and *Rosmarinus officinalis* L. (62.5%) [61]. Table 6 describes the pharmacological data of antileishmanial medicinal plants. In this fact, three species have demonstrated an effective activity against *L. major* for *Erica arborea* L. (IC_{50} = 43.98 µg/mL) and *Marrubium vulgare* L. against *L. infantum* (IC_{50} = 35.63 µg/mL). Three antimicrobial agents were tested against two parasitic agents (*L. infantum* and *L. major*): Amphotericin, SbIII and Glucantime®, a highest activity was observed for Amphotericin B with a similar value of IC50 (0.2 µg /mL) [44]. Globally, Passero et al. (2011) reviewed 292 plants for leishmaniasis treatment and indicated that most families used by traditional communities were Fabaceae, with 27 species. Notably, 74.6% of the species were applied topically [7]. These insights underscore the critical role of ethnobotanical knowledge in identifying medicinal plants for CL therapies, and constitute a rigorous scientific validation to bridge traditional practices and modern medicine.

Furthermore, 30 medicinal plants have been reported in traditional Iranian medicine [74]. The greatest effect was observed for the genera Artemisia and Tagetes (Asteraceae). In addition, two forms of administration have been documented for the treatment of leishmaniasis: oral administration and topical application of crude plant extracts [75]. In this fact, the topical administration of hydroalcoolic extract of *Thymus vulgaris* L. is more effective than Glucantime for the treatment of cutaneous leishmaniasis in BALB/c mice with a mean ulcer size of 36.09%, *v.s* 43.77% [76]. Moreover, the MTT assay for leishmanicidal effect of *Cinnamomum zeylanicum* Blume essential oil (CZEO) [with 62.04% cinnamaldehyde] against *L. major* and *L. tropica* showed half-maximal inhibitory concentrations (IC50) of 16.53 and 7.56 µg/mL. In addition, the formulation of a nanoemulsion prepared with 0.5% of (CZEO) demonstrated potential antileishmanial activity with a significant reduction in viability to 0% [77]. The mechanism of action of the major

Table 6 Ethnopharmacological and experimental data of antileishmanial plants

Species	Family	Part used	origin	Extract	Parasitic Strain	IC_{50} value	Reference
Teucrium polium L	Lamiaceae	Aerial Part	Tunisia	EO	*L. infantum* *L. major*	0.09 ± 0.02 µg/mL 0.15 ± 0.09 µg/mL	[19]
Allium sativum L	Amaryllidaceae	Bulb	Iran	AGE AGE	*L. major*	37 µg/mL 37 mg/mL (MTT assay)	[62] [63, 64]
		Bulb	Sudan	MGE	*L. major*	4.94 µg/mL	[65]
		Bulb	Iran	AGE MGE	*L. tropica*	19.2 ± 2.51 µg/mL 12.3 ± 1.15 µg/mL	[66]
		Bulb	India	MGE	*L. donovani* Promastigotes *L. donovani* Amastigotes	89 ± 7 µg/mL 67 ± 5 µg/mL	[67]
		Bulb	Not specified	MGE	*L. major* Promastigotes *L. donovani* Promastigotes	34.22 µg/mL 37.41 µg/mL	[68]
		Bulb	Not specified	DCE	*L. tarentolae*	2.89 ± 0.4 µg/mL	[69]
		Bulb	Hadley, MA	Fresh bulb	*L. mexicana* *L. chagasi*	105 µg/mL 76 µg/m	[70]
		Bulb	Kenya	AGE	*L. major*	575.75 µg/mL	[71]
Juniperus phoenicea L	Cupressaceae	Berries	Saudi Arabia	HXE	*L. donovani*	4.4 µg/mL	[72]
Rosmarinus officinalis L	Lamiaceae	Not precise	Iran	EO EO NE	*L. infantum* *L. tropica* *L. major* *L. major*	1.20 ± 0.36 µg/mL 3.50 ± 0.83 µg/mL 2.60 ± 0.64 µg/mL 0.26 µl/mL 0.08 µl/mL	[21] [73]
Lanvandula angustifolia L	Lamiaceae	Not precise		EO	*L. major*	0.11 µl/mL	[74]

AGE: Aqueous Garlic Extract, MGE: Methanolic Garlic Extract, DCE: Dichloromethane Extract, HXE: Hexane Extract, EO: Essential Oil, NE: Nanoemulsion formulated: the oil-in-water (o/w) nanoemulsions of Lavender and Rosemary essential oils were prepared using essential oil (1% w/w) and Span 60 (0.5% w/w) as the oil phase, and a mixture of Tween 80 (1% w/w) in deionized water as the aqueous phase, IC_{50}: concentration of drug that causes 50% growth inhibition of amastigote and promastigote forms of *Leishmania* spp

Table 7 ADME molecular descriptors of the six major compounds in the five top species

N°	Compound	Predicted ADME properties					Lipophilicity
		MW (g/mol)	MR	HBA	HBD	TPSA (A^{o2})	LogP
1	ß-pinene	136,23	45.22	0	0	0	3.42
2	Allicin	162,27	45.88	1	0	61,58	1.61
3	α-pinene	136,23	45.22	0	0	0	3.44
4	1,8-Cineole	154,25	47.12	1	0	9,23	2.67
5	Camphor	152,23	45.64	1	0	17,07	2.37
6	ß-caryophyllene	204,35	68.78	0	0	0	4.24

N°	Lipophilicity	Water solubility		Pharmacokinetics			Bioavailability score	Synthetic accessibility
	LogP	ESOL LogS	ESOL class	GI absorption	BBB	P-gG		
1	3.42	−3,31	Soluble	Low	Yes	No	0.55	3.73
2	1.61	−1,34	Very soluble	High	Yes	No	0.55	3.60
3	3.44	−3,51	Soluble	Low	Yes	No	0.55	4.44
4	2.67	−2,52	Soluble	High	Yes	No	0.55	3.65
5	2.37	−2,16	Soluble	High	Yes	No	0.55	3.22
6	4.24	−3,87	Soluble	Low	No	No	0.55	4.51

MW: molecular weight (g/mol); MR, molar refractivity (m^3/mol); HBA: hydrogen bond acceptor; HBD: hydrogen bond donor; LogP: octanol/water partition coefficient; ESOL LogS: log of solubility (insoluble < −10 < poorly < −6 < moderately < −4 < soluble < −2 very < 0 < highly), TPSA: topological polar surface area ($Å^2$), GI absorption: gastrointestinal absorption, BBB: blood–brain barrier penetration, P-gG: Permeability glycoprotein, Synth. Acce: synthetic accessibility

component was previously reported, affecting intracellular granulations, cell shrinkage, membrane fragility, multiflagellated cells, condensation of nuclear chromatin, decreased nucleus, and loss of motility of *L. major* [78]. However, the synergistic effect of other compounds in (CZEO) affect positively affected the leishmanicidal effect of cinnmaldehyde [79].

On the other hand, the assessment of drug likeness on the basis of the evaluation of physicochemical properties (Table 7) demonstrated that the molecular weights (MW) of compounds 1–6 ranged from 136.23 to 204.35 Da, which is significantly below the 500 Da threshold set for oral bioavailability reported by Lipinski et al. (2001) [49], an essential criterion in pharmaceutical development [80].

Compounds 1–5, which possess MWs ≤ 162.27 Da, demonstrate compact molecular structures that facilitate the infiltration of host macrophages, the cellular milieu in which Leishmania amastigotes are sequestered. Additionally, compound 6, with its molecular weight of 204.35 Da and 15 heavy atoms, is approaching the "lead-like" threshold (< 250 Da), signifying a possible trade-off between efficacy and pharmacokinetic flexibility.

Fraction Csp3 (0.33–1.0) reflects structural saturation, with molecules 1, 3, 4, and 5 (0.8–1.0) showing high values indicative of improved aqueous solubility and conformational adaptability, which is key for CL drugs requiring dermal penetration or systemic exposure.

Molecule 2, with a lower Fraction Csp3 (0.33) and five rotatable bonds, offers greater flexibility but risks metabolic instability, as specified by Veber et al. (2002) in their study of bioavailability constraints [81]. This variation emphasizes the need for customized optimization according to the administration route.

Lipinski's criteria for hydrogen bond donors (0–1) and acceptors (0–1), with the exception of molecules 1, 3, and 6, exhibit an absence of both features, thereby reducing polarity and enhancing lipophilicity. The topological polar surface area (TPSA) of 0.0 $Å^2$ indicates limited solubility but high membrane permeability, which is beneficial for the targeting of intracellular parasites. In contrast, molecules 2, 4, and 5 exhibited TPSA values of 61.58 $Å^2$, 9.23 $Å^2$, and 17.07 $Å^2$, respectively.

The consensus Log P (1.61–4.24) indicates a range of moderate to high lipophilicity, with molecule 6 (4.24) near the upper threshold of drug-like properties (≤ 5). The solubility parameter, which serves as a fundamental aspect of bioavailability, exhibits variability across different predictive models (ESOL, Ali, Silicos-IT). Molecules 2, 4, and 5 demonstrate the achievement of ESOL solubility values ranging from 0.463 to 7.39 mg/ml ("soluble" to "very soluble"), thereby implying a degree of versatility for both oral and topical administration. Molecule 2, which demonstrated a notable solubility of 3.24 mg/ml (Silicos-IT). Conversely, molecules 1, 3, and 6 (0.0278–0.0674 mg/ml) exhibited reduced solubility, approaching the classification of "moderately soluble," which is likely attributable to their nonpolar characteristics.

Gastrointestinal absorption was higher for molecules 2, 4, and 5. These results correlate with the solubility and total polar surface area (TPSA). In contrast, molecules 1, 3, and 6 exhibited low absorption, likely because of their higher lipophilicity. This profile contributes to the optimization of favorable topical delivery to support a promising cutaneous liberation strategy that targets localized cutaneous lesions by avoiding systemic metabolism through dermal delivery.

Drug-likeness assessments have revealed one violation for the Lipinski rule (molecules 1,3, 6) [49] and one violation for the Ghose rule [82] (for all molecules except for molecule 6). In addition, molecule 1,3,4 and 5 have shown two violations of the Muegge rule [83] as well as one violation for molecules 2 and 6 driven by lipophilicity or solubility deficits. Moreover, the bioavailability score was calculated as 0.55 persists across all.

Conclusions

This is the first study to employ a quantitative ethnobotanical technique to investigate the traditional usage of antileishmanial medicinal plants from Northeastern Algeria combined with in silico pharmacokinetic studies (ADME). Although this survey reported 19 species ranked according to their relative frequency index, practically none of the cited species has been described in prior studies on Algerian antileishmanial plants. For the first time, three species have been documented for their traditional use in the treatment of CL.

Multivariate tests revealed that the traditional usage of antileishmanial species is distinguished by two factors: the mode of administration and the mode of preparation.

The ADME profiles suggest promising antileishmanial leads, particularly for topical applications. However, future studies should validate these predictions using in vitro and in vivo assays based on their drug likeness, pharmacokinetic behavior, and suitability for CL therapy, offering a foundation for further drug optimization. It is also necessary to highlight the need to identify the exact metabolite profile and biological activity to establish a global matrix for a potential candidate plant. Selected clinical research studies should be conducted to determine their safety and efficacy against certain strains of leishmaniasis.

Regarding the limitations of this study, SwissADME provides predictions of absorption, distribution, metabolism, and excretion (ADME), which constitute

theoretical data and require experimental validation. This limitation suggests a gap in the understanding of the efficacy of these compounds in vitro and in vivo, which is crucial for clinical applications. In addition, computational tools can significantly accelerate the identification of promising compounds and, when combined with experimental validation, can lead to the development of new therapies. However, researchers must be cautious when interpreting computational predictions and ensuring that they are complemented by robust experimental data. This balanced approach can help overcome some inherent limitations and pave the way for innovative treatments for leishmaniasis.

Abbreviations

MCA	Multiple correspondence analysis
HCA	Hierarchical clustering analysis
RFC	Relative frequency citation
CL	Cutaneous leishmaniasis
VL	Visceral leishmaniasis
MCL	Mucocutaneous leishmaniasis
Csa	Hot-summer mediterranean climate
p	Eigenvalue
ctr	Contribution
η^2	Square ratio correlation.
ANOVA	Analysis of variance
PCA	Principal component analysis
v. test	Test value
FI	Frequency index
IC_{50}	Half-maximal inhibitory concentration
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay
ADME	Absorption, distribution, metabolism and excretion

Acknowledgements
The authors extend their appreciation to the Northern Border University, Arar, KSA, for funding this research "work through the project number" (NBU-CRP-2025-249).

Author contributions
A.B. was involved in investigation, methodology, supervision, and writing—reviewing and editing. M.L.A. was responsible for conceptualization, data curation, formal analysis, methodology, and writing—original draft. L.B. took part in investigation, methodology, formal analysis, and writing—reviewing and editing. E.R.E. and Z.B. participated in data curation, funding acquisition, supervision, and writing—reviewing and editing. A.Gu. took care of conceptualization, funding acquisition, supervision, and writing—reviewing and editing. A.Gr. helped with conceptualization, data curation, formal analysis, investigation, methodology, and writing—original draft. G.A.C. assisted with validation and writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

Funding
The authors extend their appreciation to the Northern Border University, Arar, KSA, for funding this research "work through the project number" (NBU-CRP-2025–249).

Availability of data and material
All the data are available in the manuscript and further data could be given by the authors upon request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 14 May 2025 Accepted: 3 August 2025
Published online: 14 August 2025

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