



A Review of Recent Phytomedicinal Investigations and the Need for DNA Barcoding of Endemic Plants of Northern Cyprus

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Authors' contributions

This work was carried out in collaboration between both authors. Author DOY designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author MBM managed the analyses of the study and managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: To review the phytomedicinal researches on endemic plants of Northern Cyprus and to assess the plants of their DNA barcoding status.

Study Design: A review.

Methodology: This work reviewed available and accessible original articles in EBSCO, Ovid MEDLINE[®], PubMed[®], ScienceDirect[™], Scopus[®] and Web of Science[™] databases on phytomedicinal investigations and BOLD System, MMDBD version 1.5 and GenBank[®] on DNA barcodes of the endemic plants of Northern Cyprus until May, 2020. Using keywords searches related to phytochemistry, biological activity and DNA barcoding, DNA Sequences and the data obtained evaluated and the information that does not meet the inclusion criteria were excluded. We believe that this information would tentatively help researchers to ethically explore these plants for their Medicinal and Aromatic potentials.

Results: Only 6 of the 20 endemic plants of Northern Cyprus were phytopharmaceutically investigated, while DNA sequences of 5 were found to be deposited in the publicly accessible databases accounting for 30% and 25% of the total plants respectively.

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Conclusion: Endemism is related to uniqueness in features including the phytomedicinal features, thus Northern Cyprus endemic plants hold ample of such. However the results of this review showed that only few were harnessed for their medicinal properties and hence the need for their pharmacological properties and comprehensive barcoding for proper authentication, detection of adulteration, and quality control.

Keywords: Medicinal plants; essential oils; endemics; phytopharmaceuticals; DNA barcoding; Northern Cyprus.

1. INTRODUCTION

Previously, pharmaceutical industries were mostly using synthetic compound libraries as a source of drug discovery however, decrease in the number of new drugs reaching the market revitalizes scientific interest in plant-derived natural product drug discovery. Phytochemistry of plants does not only depend on their identity but also their geographical features [1]. Especially, islands contain unique plant species as a result of being isolated from large landmasses. In time, this isolation triggered the evolutionary forces to cause a development of a distinct genetic reservoir. Formation of these divergent and highly specialized plant species carries entirely new characteristics and they eventually become endemics of these islands. As the third largest Mediterranean island, Cyprus is among the islands with highest percentage endemism of plants in Europe [2]. The Flora of Cyprus consists of 1649 indigenous taxa (species and subspecies), 141 endemic in the whole island; 20 endemic to Northern Cyprus, 33 near-endemic, 244 introduced taxa occurring in the wild, 42 hybrids and 84 species with undetermined status [3]. However, the species in the island are not distributed randomly [4]. 1250 species are documented in Northern Cyprus (representing Botanical Division 4, 5, 6, 7 and 8 see APPENDIX) and about 20 of these species are endemics belonging to 10 families, namely *Allium cupani* subsp. *cypricum* (Amaryllidaceae) [5], *Arabis cyprica* Holmboe (Brassicaceae), *Brassica hilarionis* Post (Brassicaceae), *Delphinium caseyi* B.L.Burt (Ranunculaceae), *Dianthus cypricus* A.K. Jackson et Turrill (Caryophyllaceae), *Ferulago cyprica* H.Wolf (Apiaceae), *Hedysarum cypricum* Boiss. (Fabaceae), *Limonium albidum* (Guss.) Pignatti subsp. *cypricum* Meikle (Plumbaginaceae), *Onosma caespitosum* Kotschy [Boraginaceae], *Origanum syriacum* L. var. *bevanii* (Holmes) Letswaart (Lamiaceae), *Phlomis cyprica* Post var. *cyprica* (Lamiaceae), *Pimpinella cyprica* Boiss., (Apiaceae), *Rosularia cyprica* (Holmboe) Meikle, *Rosularia pallidiflora* (Holmboe) Meikle, *Salvia*

veneris Hedge (Lamiaceae), *Scutellaria sibthorpii* (Benth) Hal. (Lamiaceae), *Sedum lampusae* (Kotschy) Boiss., (Crassulaceae), *Sideritis cyprica* Post (Lamiaceae), *Silene fraudatrix* Meikle (Caryophyllaceae), *Teucrium cypricum* Boiss. subsp. *kyreniae* P.H.Davis. (Lamiaceae) [3,6]. Therefore, flora of Northern Cyprus hosts distinct plants that could open new doors for investigations into their ethnobotanical, nutritional, phytopharmaceutical, and pharmacological values (see Table 1) [7]. While this work encourages for medicinal exploration of these plants, it is important that potential explorers are aware of their IUCN red list category (see Table 1) and promote wise and sustainable uses of medicinal plants based on World Health Organisation (WHO) and European Medicinal Agency (EMA) guidelines.

While it is important to possess a respectable amount of knowledge about the medicinal properties of these plants, this work suggests the use of DNA barcoding as an identification tool for their precise authentication. Not only that this will detect adulteration or substitution, it also has a huge capital importance for pharmacovigilance and illegal trafficking [26]. Therefore, this work reviewed available and accessible original articles in EBSCO, Ovid MEDLINE®, PubMed®, ScienceDirect™, Scopus® and Web of Science™ databases about phytomedicinal investigations and BOLD System, MMDBD version 1.5 and GenBank® about DNA barcodes of the endemic plants of Northern Cyprus until May, 2020. Using keyword searches related to phytochemistry, biological activity and DNA barcoding, the data obtained was evaluated. The information that does not meet the criteria was excluded. The main goal of this work is to acquaint the researchers with this information to help them explore these plants ethically for their pharmacological potentials in the field of pharmacy, phytotherapy, and ethnopharmacy. It is pertinent to note that while considering general researches (Fig. 1) on the endemic plants of this region, pharmacology related study areas represent only 2% of the whole number [27].

Table 1. Status of phytomedicinal investigations on endemic plants of Northern Cyprus

Family	Species	Botanical divisions	Phytochemical constituents	Part used	Biological activity	DNA sequence Reference	IUCN Category*
Amaryllidaceae	<i>Allium cupani</i> subsp. <i>cypricum</i> *	4, 5, 6					
Apiaceae	<i>Pimpinella cypria</i>	7, 8	Essential oil	Aerial	Insecticidal, toxicant, cytotoxic, and antimicrobial activity	[8]	
Boraginaceae	<i>Onosma caespitosun</i>	7				[9]	
Brassicaceae	<i>Brassica hilarionis</i>	7				[10–13]	EN
Campanulaceae	<i>Solenopsis antiphonitis</i> *	7				[14]	EN
Caryophyllaceae	<i>Dianthus cypricus</i>	7, 8					
	<i>Silene fraudatrix</i>	7				[15]	
Crassulaceae	<i>Rosularia cyprica</i>	6,7					
	<i>Rosularia pallidiflora</i>	7					
	<i>Sedum lampusae</i>	6, 7, 8					
Fabaceae	<i>Hedysarum cypricum</i>	4, 5, 6, 7					VU
Lamiaceae	<i>Origanum syriacum</i> var. <i>bevanii</i> *	7	Essential oil			[16] [17]	
		7	Essential oil	Whole	Oxidative stress and nephrotoxicity	[18,19]	
	<i>Phlomis cypria</i> subsp. <i>cyprica</i>	5,7	Essential oil	Leaf and Flower	-	[20]	VU
	<i>Salvia veneris</i>	7,8	Essential oil,	Aerial part	Antimicrobial, enzyme inhibitory, and insecticidal activity	[21]	VU
		7	Rosmarinic acid,	Aerial part	Antioxidant, antimicrobial, and enzyme inhibitory activity	[22]	
	<i>Scutellaria sibthorpii</i>	6,7	Volatile and Essential oil	Leaf	Antimicrobial activity	[23]	
	<i>Sideritis cyprica</i>	7	Essential oil	Leaf and Flower	Antimicrobial activity	[24]	[25] EN
	<i>Teucrium karpasiticum</i> *	8					
	<i>Teucrium cypricum</i> subsp. <i>kyreniae</i>	7					LC

Family	Species	Botanical divisions	Phytochemical constituents	Part used	Biological activity	DNA sequence Reference	IUCN Category*
	<i>Teucrium salaminium*</i>	7,8					
Plumbaginaceae	<i>Limonium albidum</i> subsp. <i>cyprium**</i>	1,3,6,7,8					
	<i>Limonium mucronulatum*</i>	4					CR
Poaceae	<i>Bromus bidentatus*</i>	4					
Ranunculaceae	<i>Delphinium caseyi</i>	7					CR

*CR= Critically Endangered, LC = Least Concern, EN = Endangered, NT = Near Threatened, VU = Vulnerable

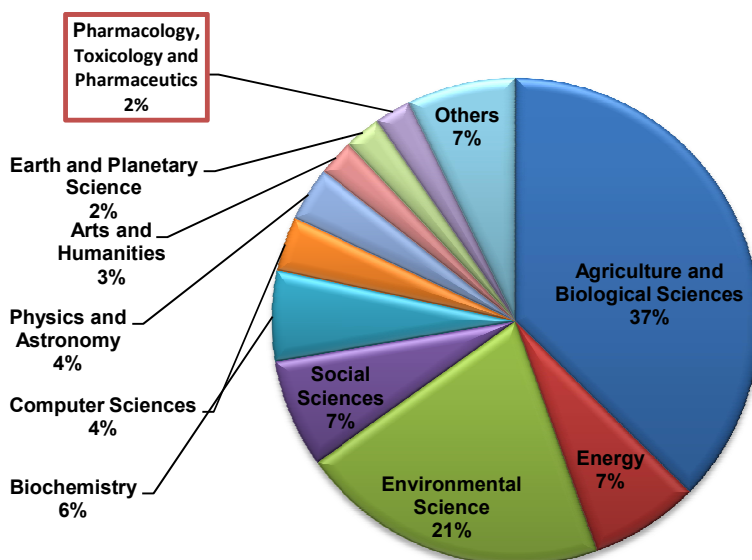


Fig. 1. A pie chart showing research on endemic plants of Northern Cyprus by subject area

2. RECENT PHYTOMEDICINAL INVESTIGATIONS OF ENDEMICS OF NORTHERN CYPRUS

Most recent investigations on endemic plant taxa of Northern Cyprus were floristic [3,28], palynological [6], cytological [29,30] or systematics [5]. Despite the potentials of these endemic plants, only 6 were investigated for phytomedicinal values. For example, the aerial parts of *Allium cupani* subsp. *cypricum* and *Salvia veneris* were studied for presence of essential oils and their antioxidant, antimicrobial, enzyme inhibitory, toxicant and cytotoxic activities [8,17,22] whereas the leaves and flowers of *Phlomis cypria* subsp. *cypria* and *Sideritis cypria* were investigated for presence of essential oils and their antimicrobial effects [20,24]. And *Origanum syriacum* L. subsp. *bevanii* (Holmes) Letswaart was evaluated [16] for comparative presence of different essential oils and phenolic compounds (see Table 1 and Fig. 2). This indicates that only six (30%) of the twenty endemic plants were scientifically investigated for medicinal potentials signifying the dearth for further investigation.

3. NEED FOR DNA BARCODING OF THE ENDEMIC POTENTIAL MEDICINAL PLANTS OF NORTHERN CYPRUS

Although the micromorphological and macromorphological features of the endemic

plants are diagnostically important and have been described [5,30,31], it is quite difficult to identify capsulated or small powdered pieces of leaf with precision and detect their presence, adulteration and/or substitution. As a matter of fact, it was reported that one of the endemics, *Salvia veneris*, was substituted for the medicinal herb tea of *S. fruticosa* [22], as they are quite hard to be separated by naked eye. Traditionally, and even empirically, an expert is definitely required for an on-time correct identification. Yet, this can be easily detected by using DNA barcoding method [32]. DNA barcoding in plants refers to a botanical identification method using short portions (barcodes) of their Deoxyribonucleic Acid [33,34]. This is important because only few laymen can easily identify endemic plants from the similar and relative species. Pieces of recorded evidence have shown that incorrect identification and adulteration of pharmaceutically important medicinal plants had their effects on consumers [35–37]. Although the available research data is quite limited, the frequency of product mislabelling in herbal drugs has been estimated to be in the range from 14% to 33% [38]. There are legitimate health concerns from consumers due to lack of confidence in the availability of safe and high quality herbal products. Consumers' confidence could be built knowing that drugs used are identified unambiguously authenticated in standard procedures. Therefore, DNA barcoding method for the identification of

medicinal plants, especially the endemics, is called for. Achieving this on-site easy identification method is highly recommended. Traditional methods used to authenticate herbal materials primarily include morphological, microscopic, and chemical identification, but these methods have some problems in distinguishing the medicinal plants from their close relatives, inferior substitutes, adulterants, and counterfeits and present a challenge to the large number and variety of medicinal plants species, which can end up in threatening the patient safety and herbal efficacy.

More recently, a universal and publicly available DNA barcoding system for identifying plants including herbal materials has been established based on the *ITS2*, *rbcL*, *matK*, and *psbA-trnH* barcodes [33,39,40]. The sequences of these regions generated are deposited as a reference barcodes. Presently, the Barcode of Life Data System (<http://v3.boldsystems.org/>) is the workbench for accessing and use of DNA barcoding data for animals (COI), plant (*matK+rbcL*) and fungi (ITS) [41]. Chen and colleagues constructed an online DNA barcoding database for traditional medicines

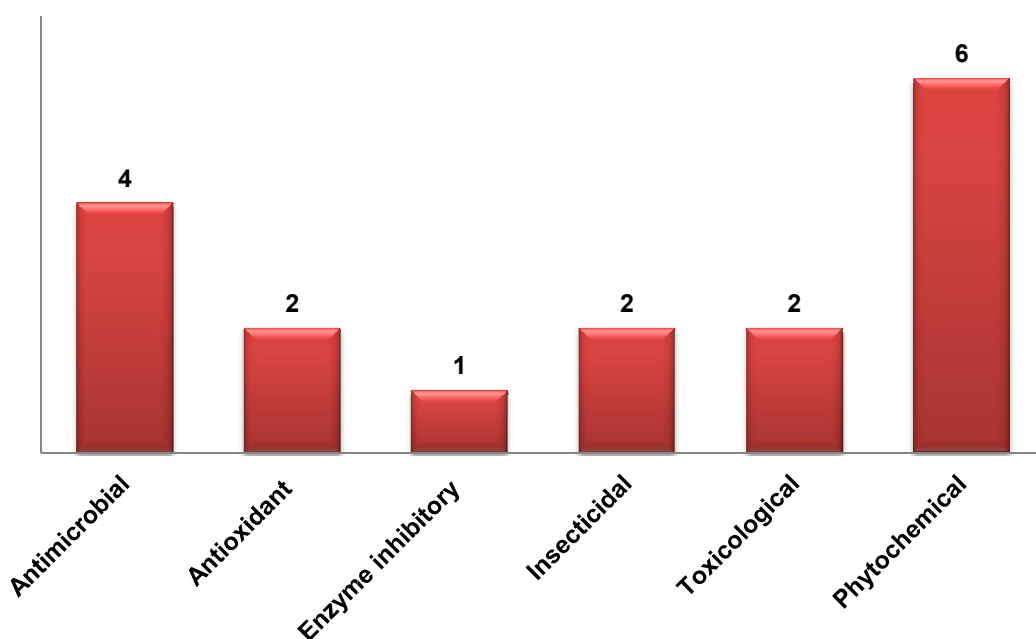


Fig. 2. Number of endemic plants of Northern Cyprus studied for biological activities

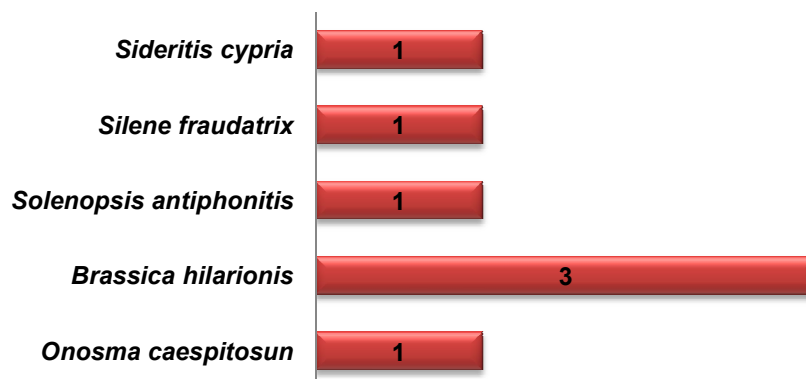


Fig. 3. Number of DNA sequence studies on endemic plants of Northern Cyprus

(<http://www.tcmbarcode.cn/en/>) that selected ITS2 and psbA–trnH for medicinal plants and COI for medicinal animals. The enhanced Medicinal Materials DNA Barcode Database MMDBD version 1.5 (<http://rdccm.cuhk.edu.hk/mherbsdb/>), for a web-based, one-stop platform that included access to sequences, sequence similarity search, multiple sequence alignment and primer design [42,43]. DNA barcode identification can be applied to a wide range of phytopharmaceutical materials from the field, commercial trade, and hospital pharmacy for authentication. However within the limit of this review, only DNA sequences of *Onosma caespitosun* [9], *Brassica hilarionis* [10–13], *Sideritis cypria* [15], *Solenopsis antiphonitis* [14] and *Sideritis cypria* [25] were found in the publicly accessible databases (Fig. 3).

4. CONCLUSION

DNA barcoding technology has a wide-reaching potential in the phytomedicinal industry, especially to help ensure that herbal ingredients, are correct and not contaminated or substituted. This could be applied not only to medicinal endemic plants of Northern Cyprus, but also to all the plants of the island to avoid health effects that could arise as a result of misidentification, substitution and/or adulteration drugs from these plants. On the basis of this review, it is pertinent that there is dearth in pharmacological and molecular finger printing of endemics of the Northern Cyprus.

DISCLAIMER

The products used for this research are commonly and predominantly used products in our area of research and country. Since there is absolutely no conflict of interest between the authors and producers of the products, there is no intention of using these products as an avenue for any litigation, but only for the advancement of knowledge. Furthermore, the research was not funded by the producing company; it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX



Botanical Division of Cyprus (in Fincham, 2013)

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