Chemodiversity in *Nepeta* spp.: A literature review on comparative germplasm studies with focus on iridoids and other terpenes

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ABSTRACT

Though widely used in the insect repellent, pet toy and essential oil industries, much of the *Nepeta* genus remains underexplored. A few researchers have made efforts to develop elite genotypes, mainly of the *N. cataria* species (catnip), with desired traits that are economically relevant in terms of breeding while enhancing or retaining the desired chemical profile of the plant. One of the fundamental aspects for developing improved genotypes is the study of diverse germplasm and, for aromatic plants, those studies also incorporate phytochemical aspects as part of the phenotypical traits. Because plant secondary metabolism is highly sensitive to environmental influence, it is important that comparative studies standardize growing, harvesting, post-harvest and extraction methods in order to avoid unknown influences in chemodiversity studies. Therefore, the present review aims to discuss comparative inter- and intraspecific studies of the *Nepeta* genus, with focus on terpene metabolites. We start with a brief discussion on the main terpenes produced by plants in the genus and their potential applications and then proceed to discuss literature reports on interspecific comparisons, and intraspecific comparisons among populations, accessions, elite lines and cultivars. The results are discussed in terms of current and potential new uses for *Nepeta* metabolites and the main avenues for research, including the need to standardize the use of breeding terms.

INTRODUCTION

Nepeta is a multiregional genus of the family Lamiaceae, Nepetoideae subfamily and Mentheae tribe which is perhaps most famous because some species, notably *N. cataria* (catnip), have effects on causing euphoria in cats (Bol et al., 2017; Gomes et al., 2020a; Salehi et al., 2018, Sharma et al., 2021). Today catnip is naturalized all over the globe with many species of this genus tracing their origin back to Africa, Asia and Europe (Sharma et al., 2021). In many countries around the world such as India,

Pakistan, China, Nepal and certain regions of Iran and Turkey, *Nepeta* spp. have been used as a part of the country's traditional medicine system as a remedy against a number of ailments such as malaria, tuberculosis, colds, coughs, stomach, and respiratory disorders to name a few (Sharma et al., 2021). Of the many species of *Nepeta* genus, *Nepeta cataria* is one of the most extensively studied (Salehi et al., 2018). The essential oil of *N. cataria* serves as a potent arthropod repellent due to the presence of nepetalactone, a type of iridoid monoterpene (Birkett et al., 2011).

Vector-borne diseases cause at least half a million deaths each year, disproportionately affecting the poor (World Health Organization, 2019). Mosquitoes vector some of the most deadly and debilitating diseases such as malaria, dengue, chikungunya, yellow fever and zika. In the least developed countries, already strained healthcare systems buckle under the strain caused by the influx of patients requiring hospitalization. These infectious diseases make the lives of the survivors even more challenging as those affected are disabled and unable to work and thus provide for their families. This results in exacerbation of poverty and continuation of the cycle of food insecurity, poverty, and mortality (Birkett et al., 2011 and World Health Organization, 2014). Essential oil of *N. cataria* as well as the isolated nepetalactone isomers have shown repellency against the wide range of arthropods such as mosquitoes, house flies, stable flies, ticks, and mites some of which serve as vectors for infectious diseases and cause livestock and crop loss (Bernier et al., 2005; Birkett et al., 2011; Zhu et al., 2009; Zhu et al., 2012; Reichert et al., 2019). Essential oil of *N. cataria* containing nepetalactone isomers and β-caryophyllene, as well as mixtures of isomers with varying ratios showed greater repellency against mosquitoes when compared to the isolated isomers indicating that the presence of the nepetalactone isomers and other compounds contribute to the synergistic activity of the essential oil (Birkett et al., 2011). *Nepeta rtanjensis* and *N. argolica* subsp. *argolica* also possess high contents of nepetalactones. The isolated, pure nepetalactone isomers displayed potent antimicrobial activity against food borne pathogens and were effective in preventing formation of biofilm of a resistant strain of *P. aeruginosa* (Aničić et al., 2021). In addition, various *Nepeta* species have been used for their antioxidant, antimicrobial, anti-inflammatory, carminative, diuretic, anti-asthmatic, antidiabetic, sedative, analgesic, antidepressant, antianxiolytic, antinociceptive, insecticidal and insect repellent properties to name a few (Gomes et al., 2020c; Salehi et al., 2018; Hadi et al., 2017; Azizian et al., 2021).

Despite the popularity of catnip as a source of natural insect repellents and its well-established ethnobotanical use, systematic studies on its horticultural attributes and yield potential are still scarce (Park et al., 2007). Some of the main aspects that still need to be standardized to increase bioactive products' yield in catnip and other *Nepeta* species involve agronomic aspects (such as plant spacing, fertilization and irrigation), harvesting regimes, post-harvest handling (drying and extraction methods for bioactive molecules) and breeding efforts for the development of plant genetic resources with improved yields in terms of quality and quantity of phytochemicals (Park et al., 2007, Gomes et al., 2020a, c).

Efforts to develop highly productive *Nepeta* spp. involve the genetic improvement of current germplasm by incorporating chemical markers in the chemical analysis, which can provide different avenues for domestication, cultivation and development of existing germplasm. In that regard, the comparative studies on chemical composition of different species, populations, accessions, elite lines and cultivars can provide valuable information for breeding programs and domestication efforts as well in the development of new plant-based products. Although many literature reviews have compiled data on chemical composition of *Nepeta* species (Formisano et al., 2011; Gomes et al., 2020c Sharma et al., 2021; Salehi et al., 2018), our intent is to present a literature review with focus on experimental studies that performed direct interspecific and intraspecific chemical comparisons in the genus, and, therefore, used the same agronomic, harvest and post-harvest handling systems for all groups, which, in our understanding,

allows for a more precise isolation of genotype effects (considering less environmental variation) for breeding and domestication purposes.

Therefore, this review aims to discuss the literature on the chemodiversity of germplasm studies in *Nepeta* species at different stages of domestication/breeding programs with focus on terpenes, the main commercial product produced by the genus.

TERPENES PRODUCED BY *Nepeta* spp.

Terpenes are secondary metabolites to which a broad range of biological activities have been reported, including cancer chemopreventive effects, antimicrobial, antifungal, antiviral, antihyperglycemic, anti-inflammatory, and antiparasitic activities (Paduch et al., 2007). In plants, terpenes are largely found as constituents of essential oils and they are mostly hydro-carbons. The building block of terpene molecules is a five-carbon isoprene unit. The simplest terpenes are monoterpenes that contain two isoprene molecules (10 carbons). Sesquiterpenes have three isoprene molecules (15 carbons), diterpenes have four (20 carbons), and triterpenes have 6 (30 carbons) (Aldred, 2009; Buckle, 2015).

In plants, isoprene units are biosynthesized via two main pathways: the mevalonate pathway (occurs in the cytosol) and the methylerythritol phosphate pathway (occurs in the plastids). The methylerythritol phosphate pathway usually supplies precursors for the production of mono- and diterpenes while the mevalonate pathway provides precursors for sesquiterpenes and triterpenes (Yang et al., 2012). For more detailed information on the pathways and the enzymes involved, this information has been excellently reviewed by Karunanithi and Zerbe (2019).

In addition to carbon number, terpenes can be subdivided into cyclic or acyclic, which gives further details on their chemical structure. Acyclic terpenes are linear while cyclic terpenes form a ring. In essential oils, monocyclic, bicyclic, and tricyclic monoterpenes (one, two, or three non-aromatic rings, respectively) have been reported (Buckle, 2015).

In terms of their cyclization, most cyclic terpenes in plants are produced by reactions catalyzed by terpene cyclases. These enzymes are involved in the synthesis of cyclic terpenoids including flavors and fragrances such as menthol and camphor, and even compounds like steroids and lipid soluble vitamins (Starks et al., 1997). However, a different cyclization pathway is known to take place for the production of compounds named iridoids. In this pathway, geranyl-pyrophosphate (product of the condensation of two isoprene units) is converted to geraniol, then hydroxylated to form 8-hydroxygeraniol and subsequently oxidized to 8-oxogeranial. Nepetalactol is then produced from 8-oxogeranial by the enzyme iridoid synthase (ISY) and subsequently an oxyreductase is believed to convert nepetalactol to the lactones in *Nepeta* species (Sherden et al., 2018; Geu-Flores et al., 2012).

Some of the most common iridoid monoterpenes are nepetalactones, characteristic molecules produced by the genus *Nepeta* and main commercial product of species from this genus. While theoretically there could be eight, six stereoisomers of nepetalactone (4aα,7α,7aα; 4aα,7α,7aβ; 4aβ,7α,7aβ; 4aβ,7α,7aα; 4aα,7β,7aβ; and 4aα,7β,7aα) have been reported in the essential oils and extracts from different *Nepeta* species (Sharma et al. 2021) (The structures of the eight possible nepetalactone isomers are presented in Figure 1). Additional iridoid terpenes produced by the *Nepeta* spp. include dihydronepetalactones, nepetalic acid (Handjieva et al.,1996), nepetaside (Xie et al., 1988), nepetanudoside (Takeda et al., 1995), nepetacilicioside (Takeda et al., 1996), nepetalactol (Hallahan et al., 1998), nepetalactam (Chauhan et al. 2014), among others. Figure 2 shows the chemical structures of dihydronepetalactone and nepetalic acid.

Although *Nepeta* species usually produce chemical profiles dominant in nepetalactones, some *Nepeta* spp. can also produce essential oils that are majorly composed of other compounds such as 1,8-cineole (non-iridoid cyclic monoterpene) and compounds related to lemon-like scent such as neral, geranial, citronellol and geraniol (non-iridoid acyclic monoterpenes) (Gomes et al., 2020b; Said-Al Ahl et al., 2018; Kahkeshani, et al., 2018). The structures of

these compounds are presented in Figure 2. The predominance of lemon-like scented compounds in *Nepeta cataria* characterizes a chemotype commonly described as lemon catnip or *N. cataria* var. *citriodora.* Lemon catnip resembles the true catnip morphology and plant architecture, however it does not attract cats since it produces little to no nepetalactones. (Gomes et al., 2020b; Said-Al Ahl et al., 2018; Klimek et al., 2000). This chemotype is reported to be used as a commercial source of citral (neral+geranial) (Kolalite 1998). Some of the predominant compounds in lemon catnip, citronellol and geraniol are also well known arthropod repellents (Müller et al., 2009; Ferreira et al., 2017).

Studies on comparative chemistry have also shown some *Nepeta* species producing sesquiterpenes such as β-caryophyllene, which has demonstrated repellent activity against ticks and mosquitoes and is also an FDA approved food additive, along with its oxidized version, caryophyllene oxide, the latter which is also used in food and cosmetics as a preservative (Tavares et al., 2018; Yang et al., 2000; Galaj et al.,2021). The structures of β-caryophyllene and caryophyllene oxide, the main sesquiterpenes produced by *Nepeta* species are shown in Figure 2.

In addition to the lemon and nepetalactone dominant chemotypes, there is yet another known chemotype for some *Nepeta* species: 1,8-cineole (structure presented in Figure 2). This compound was reported to be the major essential oil constituent (70.06%) of *N. menthoides* from Iran and have also significantly inhibited acetylcholinesterase enzyme activity while showing moderate antimicrobial activity (Kahkeshani, et al., 2018).

While studying 21 populations of *N. kotschyi* from Iran, Hadi et al. (2016) identified 3 chemotypes based on multivariate statistics of essential oil compositions: chemotype 4aα, 7α, 7aα-nepetalactone, chemotype 4aα, 7α, 7aβ-nepetalactone and cubenol and chemotype geranyl acetate and cubenol. The use of advanced statistics can contribute significantly in the identification of new chemotypes, which can, in turn, help develop future plant genetic resources to serve the pharmaceutical and industrial markets.

INTERSPECIFIC COMPARISONS

Relatively little work has been done on comparing species and cultivars for the purposes of breeding. This section focuses on the main findings of studies which evaluated multiple species of *Nepeta*. As of writing this review and to the best knowledge of the authors, fewer than fifty studies have focused on the comparative chemical profiles of members of the *Nepeta* genus with a focus on iridoid and phenolic compounds. Table 1 includes the majority of interspecific comparisons of members of the *Nepeta* genus and the relative phytochemical profiles of the studied species.

The *Nepeta* genus is particularly diverse and complex as members of this genus have been known to hybridize and intrograte frequently (Kaya and Dirmenci, 2008). Some of the morphological diversity of the genus can be observed in Figure 3, obtained from germplasm studies currently being developed by researchers at Rutgers University in New Jersey, United States. Relatively few studies have completed simultaneous comparisons of members of the *Nepeta* genus. This is significant as environment, genotype, and stage of plant growth play a large role in *Nepeta* phytochemistry and chemical yield (Aničić et al., 2020; Schultz et al., 2004; Sefidkon et al., 2003). Additionally, the extraction method of phytochemicals has a significant impact on chemical profile and potential use (Dapkevicius et al., 1998). For instance, essential oils and methanol extracts from the same *Nepeta* accession showed significant different antimicrobial activity (Adiguzel et al., 2009).

The primary extraction method reported in the literature for *Nepeta* spp. is hydrodistillation. This is likely due to many of the primary bioactive compounds being present in *Nepeta* essential oil (Formisano et al., 2011), and that aromatic plants are commonly used traditionally for their essential oil (Sharifi-Rad et al., 2017). Various studies have compared the main compounds in the essential oil of different *Nepeta* spp. and have found that plants tend to fall into chemotypes dominated by 1,8-cineole, caryophyllene oxide, and different isomers of nepetalactone (Baser et al., 2000; Formisano et al., 2011; Talebi et al., 2020).

Essential oils are typically analyzed by GC-MS. The second most common evaluation method of *Nepeta spp.* is via methanol extraction and HPLC analysis. This allows for better quantification of phenolic compounds like chlorogenic acid, caffeic acid, ferulic acid, gallic acid, protocatechuic acid, rosmarinic acid, and caffeic acid derivatives along with organic acids such as malic acid and quinic acid. Phenolic compounds along with iridoid terpenes like nepetalactone have been shown to be strong indicators of *Nepeta* chemotypes (Mišić et al., 2015).

From studies that compare different species of *Nepeta*, *N. cataria* and *N. nuda* are the most commonly studied (Figure 4). However, many studies comparing species often compare wild populations and/or different populations growing under different conditions. This is a likely source of variation and hampers the elucidation of true chemotypes from the impacts of the environment. As *Nepeta* spp. have strong breeding potential for medical (Sharma et al., 2021), agronomic (Dmitrović et al., 2015; Mutlu and Atici, 2009), and arthropod repellency (Barrozo et al., 2021; Birkett et al., 2011) applications, having clearer and more accurate comparisons of potential chemotypes is vital (Hadi et al., 2017).

WILD POPULATION COMPARISONS

Wild populations are valuable sources for agriculture and breeding practices and, especially for medicinal plants, the studies on genetic and chemical diversity can consist of strategies for conservation and development of commercially valuable genotypes (Zhou et al., 2021).

Some studies on genetic diversity have been conducted on populations of a few *Nepeta* species. Hadi et al. (2020) studied the genetic diversity in 21 populations of *N. kotschyi*, a *Nepeta* species native to Iran. Cluster analysis showed six genotypic groups and separated 2 varieties, *N. kotschyi* var. *kotschyi* and *N. kotschyi* var. *persica*. The authors also concluded that the genetic diversity pattern corresponds to the geographical distribution of the population and that most of the variance in the germplasm occurred due to intra-population variability (Hadi et al., 2020). Talebi et al. (2021) had similar findings when investigating 34 populations of *Nepeta* spp. from Iran. The authors registered high genetic diversity among the populations of the same species and suggested infraspecific variation should be considered in each taxonomic treatment of the genus (Talebi et al., 2021). Integration of such studies with phytochemical comparisons is fundamental for the selection and improvement of *Nepeta* species for agronomic exploitation and also for ecological studies, since the chemical composition is the main aspect used to determine potential uses and value of medicinal plants and also can shed light on ecophysiological interactions between plant species and the environment.

Nepeta spp. populations have also been studied in terms of morphological aspects. *N. heliotropifolia* populations from different regions of Iran showed significant differences in the chemical composition and content of essential oil and also in trichome density and morphology (Yarmoohammadi et al., 2017). These findings highlight the possibility to establish correlations among plant morphology and chemical diversity in order to provide additional tools for phenotypical characterization and to better understand trichome development associated with their ecological function as specialized structures for the production of secondary metabolites.

In terms of chemical differences between populations, most of the studies in the literature emphasize the chemical composition of essential oils. In Table 2 we summarize the literature reports on chemical comparisons between populations of *Nepeta* spp., showing the essential oil yield and their major compounds. For most of the studies, the major components of populations of *Nepeta* species are nepetalactones, however, 1,8-cineole, caryophyllene oxide, β-caryophyllene and phytol are also frequently reported as dominant in the essential oil of some species. Compounds such as citronellol, geranial, neral and geraniol are not commonly found in high amounts in those studies as the lemon catnip chemotype (*N. cataria* var. *citriodora*) is not commonly included in population comparisons.

Although most of the studies on *N. cataria*, the most important species of the genus for commercial

purposes, show that the species' essential oil is usually dominated by nepetalactones, some populations show a more diverse terpene profile. For instance, in a study with plants collected in different locations in Bulgaria, while the Pirdop *N. cataria* population had 84% of its essential oil composed of nepetalactones (dominated by the 4aα,7a,7aβ-NL isomer), a second population, from Balchik, was shown to have only 35% of its profile composed of these monoterpenes (Handjieva et al.,1996). The Balchick population was composed of considerable amounts (about 25% of the essential oil composition) of dihydronepetalactone and also had small amounts (1.2%) of nepetalic acid (Handjieva et al.,1996). Those compounds, which are also iridoid monoterpenes, have shown promising results in arthropod repellency studies (Feaster et al., 2009; Sengupta et al., 2018). Similarly, in a study comparing 8 populations of *N. cataria* from Iran, although nepetalactones constituted the majority of the essential, copious amounts of compounds such as β-caryophyllene, caryophyllene oxide, β-pinene, and α-pinene were also identified (Baghizadeh et al., 2018). These compounds have also been identified previously as effective insect repellents or insecticides (Cao et al., 2019; Silva et al., 2008; Gunasena et al., 1988) and can be of importance in breeding programs for *Nepeta* spp.

ACCESSION COMPARISONS

Accessions can be defined as a group of related plant materials from a single species that is collected from a specific location and then are given a unique identifier (accession number), used to maintain the information in databases (Ohio State University, 2021). The literature on accessions of *Nepeta* spp. is scarce, especially regarding chemical composition comparisons. Furthermore, the correct identification of the materials utilized in experiments is not always clear due to the interchangeable use of terms such as accessions and populations.

Many of the studies comparing accessions of *Nepeta* spp. are related to genetic diversity. Elkholy et al. (2011) aimed to assess the genetic diversity in 6 accessions of *N. septemcrenata* based on DNA fingerprints as revealed by RAPD-PCR polymorphism. The authors reported that the genetic distance among accessions may be explained by edaphic factors (Elkholy et al., 2011). In a similar study, 31 accessions of different *Nepeta* spp. from the Zagros region in Iran showed high chromosomal diversity, especially for *N. glomerulosa*, *N. fissa*, *N. pungens*, *N. daenensis* and *N. schiraziana* showing that the Zagros region is one of the diversity centers in Iran and can provide evidence of evolutionary trends in the genus (Kharazian et al., 2013). Cytomixis and meiotic abnormalities have also been studied and associated with environmental conditions such as altitude in accessions of *N. govaniana* (Kaur and Singhal, 2014).

In terms of phytochemical comparison of accessions, few studies have been published. Hadi et al. (2017) investigated the phenolic composition of *N. kotschyi*, *N. cataria*, *N. menthoides* and *N. crassifolia* accessions from Iran. *N. kotschyi* stood out by producing high amounts of chlorogenic acid and accessions named N16 and N17 were described as the most suitable for domestication in the environmental conditions (Hadi et al., 2017). Reichert et al. (2018) used a mixture of 10 *N. cataria* accessions to assess phenolic composition and anti-inflammatory activity. Total phenolic contents were found up to the concentration of 12.31 mg/g of dry weight and the extracts also showed promising antioxidant and ant inflammatory effects (Reichert et al., 2018).

Still on phenolics, Mišić et al. (2015) reported rosmarinic acid as one of the major compounds found in accessions of different *Nepeta* species, especially in *N. mussinii* (5.7 mg/g of fresh weight). The authors also emphasized that the studied accession of *N. cataria* was characterized by the presence of both cis, cis- (4aβ,7α,7aβ-) and trans,cis-nepetalactone (4aα,7α,7aβ-) (Mišić et al., 2015). A more complete study on comparative terpene diversity of accessions was performed by Hadi et al. (2018), where 6 accessions of *N. cataria,* 4 accessions of *N. menthoides,* and 2 accessions of *N. crassifolia* from Iran were investigated. For all the accessions of *N. menthoides* 1,8-cineole was the major compound identified in the EO, while for *N. crassifolia* both accessions had 4aα,7α,7aα-

nepetalactone as the major compound of their volatile fraction (Hadi et al., 2018). As for *N. cataria*, the accessions were predominantly composed of 4aα,7α,7aβ-Nepetalactone, with some variations related to the year of collection (Hadi et al., 2018). Study of accessions is one of the first steps to introduce new breeding materials as well as to domesticate plant genetic resources for agronomic purposes. The standardization of identifiers for accessions and proper distinction of the term from other breeding categories seems to be some of the key aspects to be implemented in order to clarify and increase the quality of the studies in chemodiversity in the *Nepeta* genus.

ELITE LINES AND CULTIVARS

There are a few reports on the development of elite breeding lines for the *Nepeta* genus. Much of the *Nepeta* germplasm remains largely unexplored in terms of its horticultural traits, providing substantial opportunities for further development of genotypes as valuable crops that can be used in various industries (Reichert et al., 2016; Hadi et al., 2017). Due to the information on the Indian catnip germplasm being very meager, Srivastava et al. (2021) introduced open pollinated *N.cataria* seeds collected from the Himalayas to the temperate plains of Lucknow. The researchers isolated 19 individual plants for further development based on plant growth and essential oil yield, with nepetalactones dominating the essential oils of the Indian catnip (Srivastava et al., 2021). The composition of *N. cataria* from India showed to be similar to that of the essential oils from USA, UK, France, Turkey and Burundi, due to the high content of 4aα,7α,7aα-nepetalactone isomer (Srivastava et al., 2021). The group's current research involves developing breeding lines to improve yield related traits in catnip (Srivastava et al., 2021).

In a work developed by scientists at Rutgers University, lemon scented *N. cataria* elite lines were studied under the environmental conditions of New Jersey, United States of America (Gomes et al., 2020b). The lines named CN3, CN5, CN6, CL1 and CL2 showed distinct essential oil profiles, with high amounts of citronellol, geraniol, β-caryophyllene and caryophyllene oxide and little to no nepetalactones (Gomes et al., 2020b). The study also demonstrated that there were changes in the essential oil composition as a function of harvests dates, indicating that ecological factors along with growth stages of the plant play a major role in the essential oil composition (Gomes et al., 2020b). The interaction between genotype and environment and its effects on the essential oil profile of *N. cataria* and *N. cataria* var. *citriodora* can help determining best harvest times for optimal production of metabolites of interest and help meeting the industry standards needed to develop the market for specialty crops like these (Gomes et al., 2020b).

One of the main purposes of germplasm evaluation and studies of elite lines is the development of improved cultivars. The development of cultivars represents major contributions to increase the productivity and quality of agricultural products as cultivars usually define the limits of agricultural performance in any environment (Fehr, 1991). In that regard, an excellent report on the main cultivars of *Nepeta* spp. utilized for ornamental purposes was published by Hawke (2007), where characteristics such as flowering habit, color and morphological characteristics are described. However, as for the development of cultivars with focus on terpene productivity the reports are scarce and represent the current limitation on the advance of breeding programs for species in the genus *Nepeta*.

One of the few comparative studies with superior genetic materials of *Nepeta* spp. was authored by Frolova et al. (2019) with lemon catnip (*N. cataria* var. *citriodora*) cultivars from Ukraine. Evaluations of essential oils from cultivars Melody and Peremozhets showed predominance of neral, geranial, nerol, geraniol and citronellol, profiles characteristic of the lemon catnip chemotype (Frolova et al., 2019). For North American conditions, producers identified that the varieties available in the market are difficult to harvest mechanically and produce relatively low amounts of essential oil, with poor overwintering performance (Reichert et al., 2016; Park et al., 2007). As part of the efforts to change this scenario, researchers from

Rutgers University (New Jersey, United States) developed the cultivar CR9, the first *N. cataria* cultivar developed for commercial production of catnip in North America (Reichert et al., 2016). This cultivar has a higher biomass, essential oil yield and a higher Z,E-nepetalactone (4aβ,7α,7aα-) yield than varieties available in the market in addition to an upright growth habit which allows for mechanical harvest (Reichert et al., 2016). Unlike other commercially available varieties, seeds resulting from selfing of CR9 retain all the commercially relevant traits of the plant such as high biomass and essential oil yield. CR9 thus serves as an excellent source of catnip for pet toys and insect repellent industries (Reichert et al., 2016).

A second cultivar of *N. cataria*, CR3, was recently patented by Rutgers University scientists and is reported to produce copious amounts of E,Z-nepetalactone (4aα,7α,7aβ-) as well as being adapted to growing conditions of northeastern United States (Simon et al., 2019). Essential oils from both CR9 and CR3 cultivars have been compared for their repellent effects against mosquitoes and bedbugs and showed similar effect, with promising results for the development of commercial products with efficacy compared to synthetic repellents such as DEET (Shi et al., 2021; Reichert et al., 2019).

FUTURE DIRECTIONS AND CONCLUDING REMARKS

Recently, an emerging analytical approach called "metabolomics", which focuses on the study of low molecular weight molecules (<1000 Da), has shown to be an important tool in many areas, especially in the plant sciences (Lyu et al., 2021; Cevallos-Cevallos et al., 2009). Since secondary metabolites are shown to influence the morpho-physiological traits of plants, metabolomics can play a key role in helping understand the link between plant metabolism, morphology, and physiology (Turner et al., 2016). Metabolomics can provide a comprehensive overview of the cellular metabolites that represent the absolute physiological state of the cell, such as small organic compounds that are involved in different cellular events. Metabolomics allows for the detection of metabolites from a single extract, making it an ideal tool for rapidly analyzing a large number of metabolites from a single source (Kumar et al., 2017). However, reports on comprehensive large scale untargeted metabolomics studies in *Nepeta* species appear to not be available to the best of the author's knowledge at the time of the publication of this review. The report on metabolic profiling of *N. cataria* by Nadeem et al., (2021) shows the potential of this technique for the species, but since the report is a preprint and not yet peer reviewed, it has been excluded from this review.

There are, however, reports on targeted analysis of select bioactive compounds that are abundant in catnip to develop chemical markers that, coupled with modern statistical analyses, can be used to evaluate germplasm in a short amount of time. This strategy can assist in plant breeding efforts to develop new cultivars and help create cultivation practices and establish breeding programs (Hadi et al., 2017). A study by Mišić et al., (2015) explores the variation between two major groups of secondary metabolites in the *Nepeta* genus: phenolic compounds and nepetalactones. The authors successfully developed an analytical method that characterize methanolic extracts of select *Nepeta* spp, including *N. cataria*. The results showed that profiling phenolics provided a valuable database of the bioactive compounds, especially flavonoids (flavonols, flavones and flavanones) and phenolic acids (hydroxybenzoic and hydroxycinnamic) (Mišić et al., 2015). Principal component analysis (PCA) and cluster analysis revealed that 10 targeted compounds can serve as chemomarkers for chemotaxonomic studies and this approach has potential to be implemented in quality control of plant materials (Mišić et al., 2015). Previously discussed studies provide a well described methodology for conducting chemotaxonomic studies that can assist in selecting plants for breeding elite genotypes. Future studies could look at untargeted metabolomic studies on a larger scale since a broader more general approach can better help understand the complex secondary metabolite pathways and the components that play key roles in the biosynthesis of economically important secondary metabolites.

As stated, the *Nepeta* genus is a rich source of bioactive compounds and has a long history of traditional uses (Salehi et al., 2018; Sharma et al., 2021). This coupled with the genetic diversity (Kaya and Dirmenci, 2008) makes members of the genus strong candidates for breeding and improvement. Given the potential in preventing malaria alone (Patience et al., 2018), which caused nearly half a million deaths in 2018 (World Health Organization, 2019), the potential for sustainable use cannot be understated. However, as a natural product, much more work is needed to standardize the evaluation of chemical makeup of *Nepeta* secondary metabolites as there are still relatively few studies comparing the many taxa within the genus under the same growing conditions. Evaluating individual plant groups and comparing them to other studies, while useful in seeing qualitative chemical aspects of the species, fails to make a meaningful comparison given the significant variability inherent in growing conditions and potential regional genotypes (Aničić et al., 2020; Schultz et al., 2004; Talebi et al., 2019). Comparing accessions and different taxa under the same conditions has the potential to more efficiently find and produce sustainable production systems for valuable secondary metabolites and natural products (Audoin et al., 2014). Much like other natural products, consistency in product is key in ensuring safe use and consumption (Murch and Saxena, 2006). More studies comparing various *Nepeta* species and accessions simultaneously and under the same conditions are needed for developing clear and meaningful comparison and development of impactful consistent and valuable natural products.

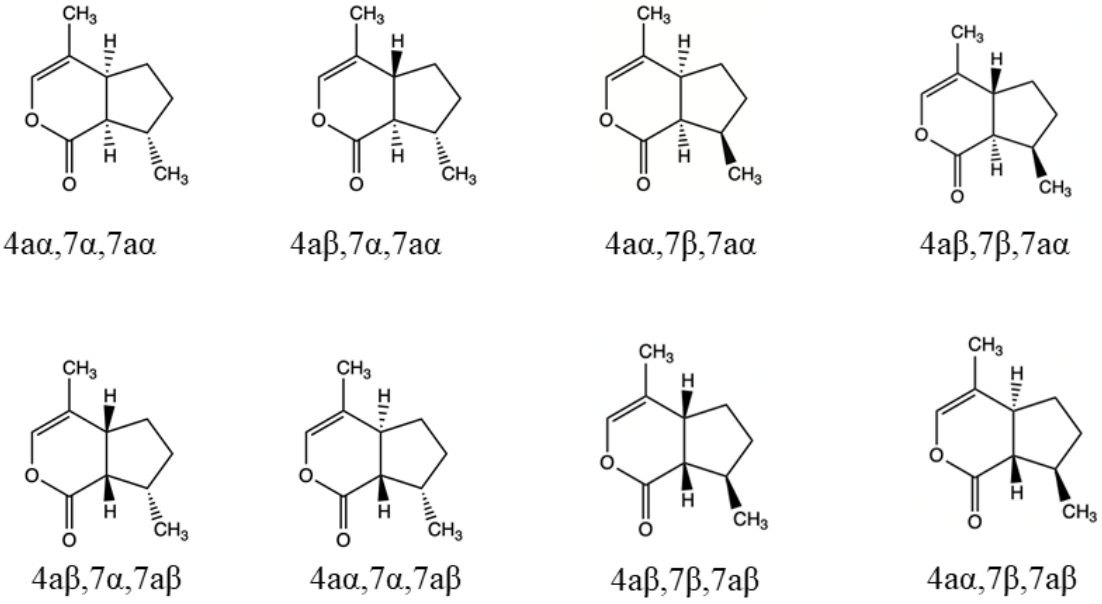

Figure 1. Isomers of nepetalactone produced by *Nepeta* species as reported in the literature.

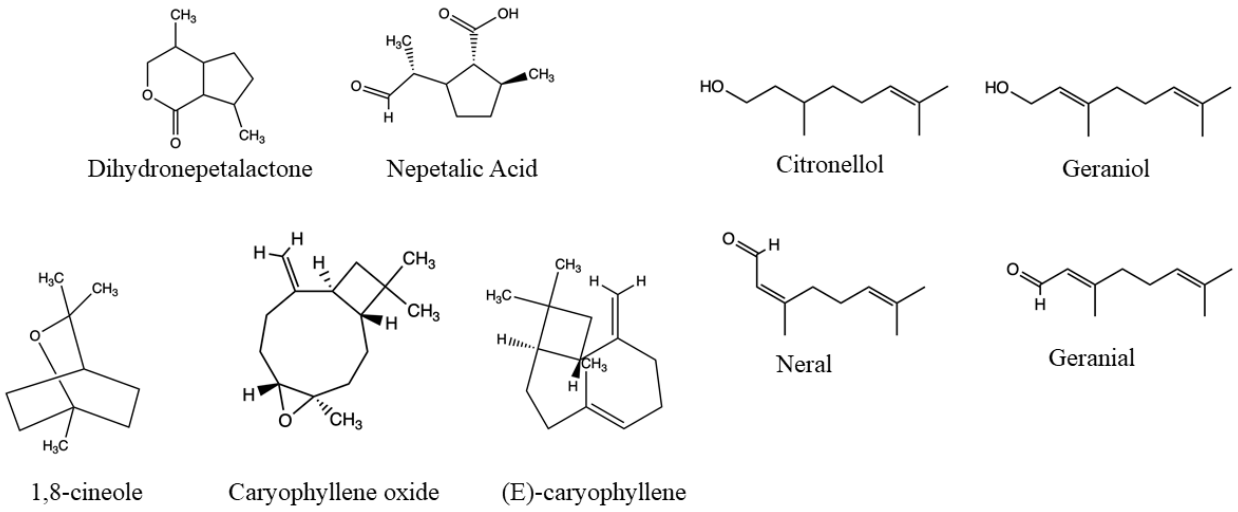

Figure 2. Common bioactive iridoids and terpenes produced by *Nepeta* spp.

Figure 3. Representation of morphological diversity of *Nepeta* species from Rutgers University germplasm studies. Photo: Martin Zorde.

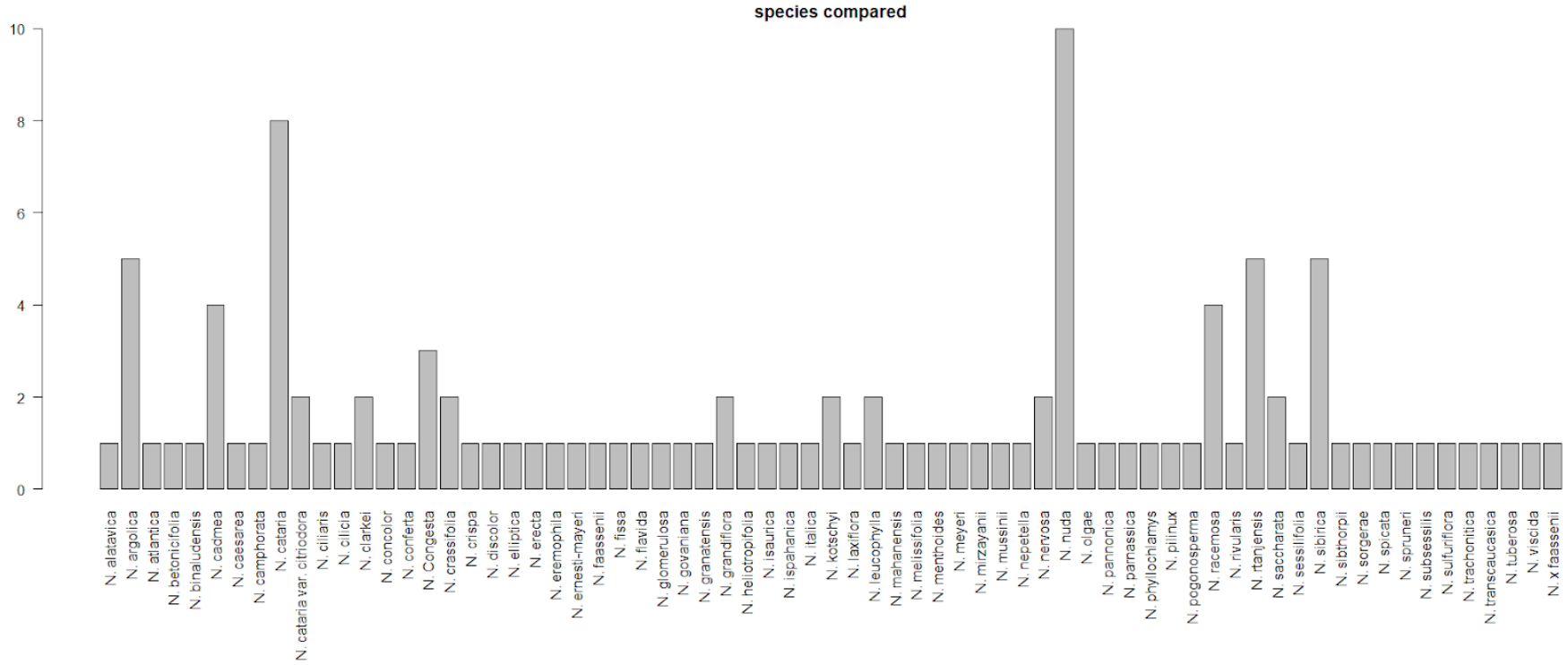

Figure 4. Bar graph of number of each species compared in Table 1. Note this graph has placed sub-species in the same species for simplicity and does not take into account the number of accessions analyzed in and across studies.

Table 1. Interspecific comparisons of the chemical compounds of different *Nepeta* spp.

Species compared	Extract Type	Iridoid terpenes	Monoterpenes	Sesquiterpenes	Diterpenes	Phenolics and other compounds	Study goals	Reference
N. rtanjensis	ME	4aα,7α,7aβ-NL	NA	NA	NA	NA	Drought stress	(Aničić et al., 2020)
N. argolica ssp. *argolica*	ME	4aα,7α,7aα-NL	NA	NA	NA	NA		
N. rtanjensis	ME	1,5,9-eDLA (3%**); DNL (1.5 %**); 4aα,7α,7aβ-NL (0.5%**)	NA	NA	NA	CHA (0.8%**); CA (0.001%); RA (0.25%**)	Antimicrobial activity	(Aničić et al., 2021)
N. argolica ssp. argolica	ME	1,5,9-eDLA (3%**); 4aα,7α,7aα-NL (2.5%**)	NA	NA	NA	CHA (1.1%**); CA (0.002%**); RA (0.4%**)		
N. nuda ssp. *glandulifera*	EO (0.56% v/w)	NA	1,8-Cineole 1.55% *	Geijerene (61.02%**) Neointermedeol (6.07%**)	NA	NA	Chemical composition and biological activities	(Cengiz Sarikurkcu et al., 2018)
N. cadmea	EO (0.99% v/w)	4aβ,7α,7aβ-NL (70.94% **); 4aα,7α,7aα-NL (3.51%**)	1,8-Cineole 1.18%	NA	NA	NA		
N. nuda ssp. *glandulifera*	ME	NA	NA	NA	NA	CHA (63.52 ± 0.15 #); CA (0.73 ± 0.03a); FA (14.65 ± 0.03 #)	Chemical composition and biological activity	(C. Sarikurkcu et al., 2019)
N. cadmea	ME	NA	NA	NA	NA	CHA (3.30 ± 0.12#); CA (0.47 ± 0.03#); FA (2.76 ± 0.05#) ; RA (nd)		
N. racemosa	EO (0.07% v/w)	NA	1,8-Cineole (51.2%)	Caryophyllene oxide (0.7%)	NA	NA	Chemical composition and *Aedes aegypti* repellency and larvicidal effects	(Ali et al., 2016)
N. sibirica	EO (0.08% v/w)	4aα,7α,7aα-NL (2.6%); 4aα,7α,7aβ-NL (1.7%)	1,8-Cineole (0.2%)	Caryophyllene oxide 4.4%	NA	NA		

N. subsessilis	EO (0.08% (v/w))	4aα,7α,7aα-NL (1.1%); 4aα,7α,7aβ-NL (2.8%)	1,8-Cineole (42.1%); Geraniol (0.2%)	Caryophyllene oxide (5.0%)	NA	NA		
N. faassenii	EO (0.08% v/w)	4aβ,7α,7aβ-NL (0.6%)	1,8-Cineole (2.1%); Geraniol (0.27%)	Caryophyllene oxide (3.4%)	NA	NA		
N. crispa	EO	4aβ,7α,7aα-NL (0.2%); 4aα,7α,7aα-NL (10.3%); 4aβ,7α,7aβ-NL (9.2%)	1,8-Cineole (62.8%); β - pinene (3.6%); α-terpineol (3.3%)	NA	NA	NA	Chemical composition	(Sefidkon et al., 2006)
N. mahanensis	EO	NLU (37.6%)	1,8-Cineole (27.2%); β-pinene (4.3%)	Germacrene D (6.5%); caryophyllene oxide (3.4%)	NA	NA		
N. ispahanica	EO	4aβ,7α,7aα-NL(0.3%); 4aβ,7α,7aβ-NL (0.6%); NLU (2.6%)	1,8-Cineole (71.7%); β-pinene (4.2%)	NA	NA	NA		
N. eremophila	EO	4aα,7α,7aα-NL (2.6%); 4aβ,7α,7aβ-NL (73.3%)	1,8-Cineole (13.1%)	NA	NA	NA		
N. rivularis	EO	4aα,7α,7aα-NL (2.4%); NLU (1.8%)	1,8- Cineole (38.5%); β-pinene (10.7%); -terpinene (5.1%); cis-sabinene hydrate (4.1%); α-terpineol (3.6%)	NA	NA	NA		
N. alatavica	EO (0.5% v/w)	NA	thymol (48.5%); verbenone (7.7%); and carvacrol (7.5%)	NA	NA	NA	Chemical composition and biological activity	(Mamadalieva et al., 2016)
N. nuda	EO (0.3% v/w)	4aα,7β,7aα-NL (21.0%)	1,8-Cineole (24.6%)	germacrene D (13.5%),; β-	NA	NA		

				caryophyllene (12.7%)				
N. olgae	EO (1.3% v/w)	NA	acetylcyclohexene (31.5%); 4-tridecyne (13.2%); 2-methyl cyclopentanone (6.8%); 1,8-cineole (6.0%).	NA	NA	NA		
N. camphorata	EO (0.75 % (v/w))	NA	1,8-Cineole (51.72%); β-pinene (11.98 %); α-terpineol (5.87 %); α-pinene (3.96 %)	NA	NA	NA	Chemical composition and biological activity against *Helicobacter pylori*	(Kalpoutzakis et al., 2001)
N. argolica ssp. *dirphya*	EO (0.73 % (v/w))	4aα,7α,7aβ-NL (58.05%); 4aβ,7α,7aβ-NL (17.00 %)	1,8-Cineole (5.88%); β-pinene (4.53 %); α-terpineol (0.62 %); α-pinene (0.56 %)	NA	NA	NA		
N. leucophylla	EO (0.68%v/w)	Iridodial β-monoenol acetate (25.4%); Dihydroiridodial diacetate (18.2%); Iridodial dienol diacetate (7.8%)	NA	NA	NA	NA	Chemical composition	(Bisht et al., 2010)
N. discolor	EO (0.90%v/w)	NA	1,8-Cineole (25.5%); p-Cymene (9.8%)	β-Caryophyllene (18.6%)	NA	NA		
N. govaniana	EO (0.85%v/w)	Isoiridomyrmecin (35.2%)	NA	Pregeijerene (20.7%)	NA	NA		
N. clarkei	EO (0.70%v/w)	Iridodial β-monoenol acetate diastereomers (25.3%)	NA	β-Sesquiphellandrene (22%); Germacrene D	NA	NA		

				(13%); α-Guaiene (10%)				
N. elliptica	EO (0.92%v/w)	4aβ,7α,7aα-NL (83.4%)	NA	NA	NA	NA		
N. erecta	EO (0.76%v/w)	Isoiridomyrmecin (66.7%)	NA	NA	NA	NA		
N. binaludensis	EO (0.9% v/w)	4aα,7α,7aβ-NL (23.5%)	1,8-Cineole (43.5%); α-terpineol (4.8%); 96erpinene-4-ol (3.1%)	NA	NA	NA	Chemical composition	(Talebi et al., 2020)
N. glomerulosa	EO (0.9% v/w)		1,8- Cineole (23.3%); isobornyl acetate (6%); geraniol (5.4%); 96erpinene-4-ol (5.3%); borneol (4.3%)	NA	NA	NA		
N. kotschyi	EO (0.1% v/w)	4aα,7α,7aα-NL (13.4%)	carvacrol (9.9%), citronellol (8.4%); geranyl acetate (4.8%)	NA	phytol (15.6%)	NA		
N. meyeri	EO (0.2% v/w)	4aα,7β,7aα-NL (83.9%); 4aα,7α,7aβ-NL (7.4%)	2-metoxy-para-cresol (2.6%)	NA	NA	NA		
N. mirzayanii	EO (0.6% v/w)	4aα,7α,7aβ-NL (73.9%); 4aα,7α,7aα-NL (13%)	2–metoxy–para–cresol (3.6%)	Z-β-farnesene (3 %)	NA	NA		
N. pogonosperma	EO (0.4% v/w)	4aα,7α,7aα-NL (6.2%)	1,8-cineole (53.9%); linalool (4.1%); 96erpinene-4-ol (3.8%)	Z-α-bisabolene (5%)	Phytol (0.1%)	NA		
N. racemosa	EO (0.4% v/w)	4aα,7α,7aα-NL (5.3%);	1,8- Cineole (70.9%);	NA	NA	NA		

		4aα,7α,7aβ-NL (3%)	citronellol (4.3%)					
N. saccharata	EO (0.2% v/w)	NA	carvacrol (22.4%);	NA	Phytol (31.2%)	n-hexadecanoic acid (9.3%); dibutyl phthalate (3.3%)		
N. cataria var. *citriodora*	EO (5.94 mg/g pdw)	4aα,7α,7aβ-NL (50.16%); 4aα,7α,7aα-NL (35.64%); 4aα,7β,7aα-NL (1.80%)	citronellol (1.06%)	β-Caryophyllene (3.07%); caryophyllene oxide (1.95%)	NA	NA	Chemical composition and biological activity	(Baranauskienė et al., 2019)
N. transcaucasica	EO (1.75 mg/g pdw)	4aα,7β,7aα-NL (14.34%); 4aα,7α,7aα-NL (2.76%)	citronellol (17.69%); geranial (9.05%); geranyl acetate (8.20%); neral (6.28%); geraniol (5.97%); 1,8-cineole (5.61%)	caryophyllene oxide (5.07%)	NA	NA		
N. melissifolia	EO (1.55 mg/g pdw)	4aα,7α,7aβ-NL (0.97%); 4aα,7β,7aα-NL (0.41%); 4aα,7α,7aα-NL (0.11%)	1,8-Cineole (37.35%)	caryophyllene oxide (22.06%); Spathulenol (3.04%); elemol (2.53%); β-caryophyllene (1.29%)	NA	NA		
N. sibirica	EO (1.32mg/g pdw)	4aα,7α,7aβ-NL (0.57%); 4aα,7β,7aα-NL (0.17%); 4aα,7α,7aα-NL (0.19%)	1,8-Cineole (42.58%)	caryophyllene oxide (20.35%); elemol (2.30%); β-caryophyllene (1.54%)	NA	NA		
N. nuda	EO (0.78 mg/g pdw)	4aα,7α,7aβ-NL (55.72%); 4aα,7α,7aα-NL (6.20%)	nerol (4.79%); geranial (4.03%); neral (2.92%); geraniol (2.64%)	caryophyllene oxide (5.53%)	NA	NA		
N. crassifolia	EO (average	4aβ, 7α, 7aβ-NL (16.46%–	1,8-Cineole (8.15–9.70%)	elemol (14.38–22.14%)	NA	NA	Chemical composition	(Narimani et al., 2017)

	0.65% v/w)	27.45%); 4aα, 7α, 7aβ-NL (13.45%–17.54%)						
N. nuda	EO (average 0.46% v/w)	4aβ, 7α, 7aβ- NL (61–72.21%); 4aα, 7α, 7aβ-NL (8.72–12.63%)	pulegone (7.36%); piperitenone oxide (4.12%)	NA	NA	NA		
N. caesarea	EO	4aα,7α,7aα-NL (91.2%)	NA	NA	NA	NA	Chemical composition	(Baser et al., 2000)
N. cataria	EO	4aα,7α,7aα-NL (89.0%)	NA	NA	NA	NA		
N. cadmea	EO	4aα,7α,7aα-NL (21.7-78.6%)	NA	NA	NA	NA		
N. pilinux	EO	4aα,7α,7aα-NL (66.7%)	NA	NA	NA	NA		
N. racemosa	EO	4aα, 7α, 7aβ-NL (31.5-91.5%)	NA	NA	NA	NA		
N. betonicifolia	EO	NA	NA	Caryophyllene Oxide (39.2%)	NA	NA		
N. cilicia	EO	NA	NA	Caryophyllene Oxide (19.2%)	NA	NA		
N. fissa	EO	NA	NA	Caryophyllene Oxide (36.4%)	NA	NA		
N. nuda L. ssp. *glandulifera*	EO	NA	NA	Caryophyllene Oxide (24.0%-30.7%)	NA	NA		
N. concolor	EO	NA	NA	Caryophyllene Oxide (17.1%)	NA	NA		
N. conferta	EO	NA	NA	Caryophyllene Oxide (15.8%)	NA	NA		
N. isaurica	EO	NA	NA	Caryophyllene Oxide (15.5%)	NA	NA		
N. italica	EO	NA	1,8-Cineole (11.4-51.6%); Linalool (0.4%-61.7%)	NA	NA	NA		
N. sulfuriflora	EO	NA	1,8-Cineole (24.2-46.3%)	NA	NA	NA		

N. congesta Fisch. & Mey. var. *cryptantha*	EO	NA	1,8-Cineole (40%)	NA	NA	NA		
N. flavida	EO	NA	1,8-Cineole (22.7%); Linalool (37.7%)	NA	NA	NA		
N. nuda L. ssp. *nuda*	EO	NA	1,8-Cineole (14.9%)	NA	NA	NA		
N. nuda L. spp. *albiflora*	EO	NA	1,8-Cineole (10.6%)	NA	NA	NA		
N. phyllochlamys	EO	NA	β-Pinene (16.3%)	NA	NA	NA		
N. viscida	EO	NA	α-Terpineol (18.7%)	NA	NA	NA		
N. sorgerae	EO	NA	NA	Germacrene-D (45.0%)	NA	NA		
N. trachonitica	EO	NA	NA	Spathulenol (22.1%)	NA	NA		
N. argolica ssp. malacotrichos	EO (0.9% v/w)	NA	1,8-Cineole (30.9%); Myrtenol (6.8%); trans-Pinocarveol (3.2%)	Caryophyllene oxide (23.9%)	NA	NA	Chemical composition	(Hanlidou et al., 2012)
N. argolica ssp. vourinensis	EO (0.9% v/w)	NA	1,8-Cineole (55.6%); Myrtenol (4.8%); trans-Pinocarveol (8.6%)	Caryophyllene oxide (6.0%)	NA	NA		
N. spruneri	EO (0.5-1.2% v/w)	Only present in 2out of 6 populations 4aα,7α,7aα-NL (5.0% , 11.5%); 4aα, 7α, 7aβ-NL (12.4%, 29%)	1,8-Cineole (1.6 -16.5%); Myrtenol (5.1-11.9%); Camphor (2.4-10.1%); trans-Pinocarveol (1.9-6.9%)	Caryophyllene oxide (11.7-19.8%); Ledol (1.9-10.7%)	NA	NA		
N. rtanjensis	EO	4aα,7β,7aα-NL (72.03%);	α-Pinene (2.99%)	NA	NA	NA	Chemical composition and	(Dmitrović et al., 2015)

		4aα,7α,7aα-NL (16.31%)					biological activity on Ambrosia artemisiiflolia	
N. cataria	EO	4aα,7α,7aα-NL (72.03%)	NA	Caryophyllene oxide (4.8%); Spathulenol (4.26%)	Neophytadiene (1.89%)			
N. cataria	EO (Control group data presented)	NLU (37.19%)	Geraniol (40.33%): Citronellol (8.985); Geranial (5.78%); Neral (4.22%); Citronellal (0.59%); Myristicin (0.16%)	Caryophyllene (1.09%);	NA	NA	Chemical Content and yield in response to potassium humate treatment	(Mohamed et al., 2018)
N. cataria var. *citriodora*	EO (Control group data presented)	NA	Geraniol (51.16%): Citronellol (16.45%); Geranial (7.54%); Neral (6.78%); Citronellal (1.24%); Myristicin (6.09%)	Caryophyllene (1.24%);	NA	NA		
N. grandiflora	EO (Control group data presented)	NA	o-Cymene (10.01%); c-Terpinene (16.45%); p-Cymene (45.13%); Carvacrol (11.05%)	Caryophyllene (2.38%);	NA	NA		
N. leucophylla	EO	iridodial b-monoenol Acetate (9.8%)	NA	Caryophyllene oxide (26.3%),	NA	NA	Chemical composition and fungicidal effect	(Kumar et al., 2014)
N. ciliaris	EO	NA	NA	b-Caryophyllene	NA	NA		

				(18.0%); b-sesquiphellandrene (15.0%)				
N. clarkei	EO	actinidine (10.0%)	NA	b-Sesquiphellandrene (22.0%); germacrene D (8.0%)	NA	NA		
N. rtanjensis	ME	4aα,7α,7aβ-NL (present but unquantified)	NA	NA	NA	NA	Nepetalactone content and antimicrobial activity	(Nestorović et al., 2010)
N. sibirica	ME	4aα,7α,7aα-NL (present but unquantified)	NA	NA	NA	NA		
N. nervosa	ME	NA	NA	NA	NA	NA		
N. nuda ssp. *glandulifera*	Soxhlet-ME (content expressed as mg/g extract)	NA	NA	NA	NA	PA (0.44 mg/g); CHA (3.30mg/g); CA (0.47mg/g); FA (2.76mg/g); Rutin (1.41mg/g); Apigenin (0.22mg/g)	Chemical composition and biological activity	(Sarikurkcu et al., 2019)
N. cadmea	Soxhlet-ME (content expressed as mg/g extract)	NA	NA	NA	NA	PA (0.15mg/g); CHA (63.52mg/g); CA (0.73mg/g); FA (14.65mg/g); Apigenin (0.44mg/g)		
N. kotschyi	ME	NA	NA	NA	NA	CHA1(1790 µg g−1*); CHA2(1200 µg g−1*); UCAD(1590µg g−1*); RA(800 µg g−1*)	Chemical composition	(Hadi et al., 2017)
N. menthoides	ME	NA	NA	NA	NA	CHA1(550 µg g−1*); CHA2 (190 µg g−1*); UCAD (390 µg g−1*); RA (1400 µg g−1*)		
N. crassifolia	ME	NA	NA	NA	NA	CHA1(420 µg g−1*); CHA2(190 µg g−1*);		

						UCAD(100 µg g−1*); RA(1180 µg g−1*)		
N. cataria	ME	NA	NA	NA	NA	UCAD (400 µg g−1*); RA (1000 µg g−1*)		
N. racemosa	EO (1.76 % v/w) and ME	4aα,7α,7aα -NL (0.1%); 4aα,7α,7aβ -NL (91.0%); 4aβ,7α,7aβ -NL (1.5%)	1,8-Cineole (0.3%);	Germacrene D (0.9%); €-Caryophyllene (trace); β-Bourbonene (3.3%); Spathulenol (0.2%)	NA	Top three presented: CHA (2.06 g kg-1*); CA (0.82 g kg-1*); FA (8.03 g kg-1*);	Chemical composition and biological activity	(Azizian et al., 2021)
N. saccharata	EO (0.6% v/w) and ME	4aβ,7α,7aα -NL (9.2%); 4aα,7α,7aα -NL (7.8%); 4aα,7α,7aβ -NL (75.4%); 4aβ,7α,7aβ -NL (2.4%)	1,8-Cineole (1.9%);	Germacrene D (0.1%); (E)-Caryophyllene (trace); β-Bourbonene (trace);	NA	Top three presented: CHA (2.20 g kg-1*); CA (0.89 g kg-1*); FA (18.28 g kg-1*);		
N. congesta	EO (0.31% v/w) and ME	4aβ,7α,7aα -NL (1.5%); 4aα,7α,7aβ -NL (2.0%);	1,8-Cineole (25.4%); β-Pinene (7.9%); Sabinene (4.3%); p-Cymene (9.3%)	Germacrene D (21.4%); €-Caryophyllene (7.4%); Bicyclogermacrene (4.9%); β-Bourbonene (3.9%); Spathulenol (2.8%)	NA	Top three presented:CHA (1.02 g kg-1*); CA (0.77 g kg-1*); FA (9.30 g kg-1*);		
N. cataria	EO (0.7%v/w) and ME	4aα,7α,7aα -NL (4.2%); 4aα,7α,7aβ -NL (81.3%); 4aβ,7α,7aβ -NL (1.2%)	1,8-Cineole (2.5%);	Germacrene D (0.8%); (E)-Caryophyllene (1.8%); β-Bourbonene (0.3%); Spathulenol (2.2%)	NA	Top three presented:CHA (9.18 g kg-1*); CA (1.23 g kg-1*); FA (26.08 g kg-1*);		

N. heliotropifolia	EO (0.5%v/w) and ME	No NL detected	β-Pinene (1.5%); Sabinene (0.8%); Eucalyptol (4.0%)	Germacrene D (36.7 %); Caryophyllene (3.3%); tau-Cadinol(2.3%); α-Copaene (3.8%); β-Bourbonene (6.4%); Spathulenol (5.7%); β-Elemene (3.4%); γ-Elemene (5.0%)	Phytol (1.6%)	Apigetrin (174.44µg/g extract); CA(10.34µg/g extract); CHA (15.65 µg/g extract); FA (2.85 µg/g extract); MA (1104 µg/g extract); RA (138.61 µg/g extract)	Chemical composition and biological activity	(Akdeniz et al., 2020)
N. congesta ssp. *cryptantha*	EO (0.4%v/w) and ME	No NL detected	β-Pinene (1.6%); D-Limonene (4.5%); Sabinene (1.0%); Eucalyptol (6.1%)	Germacrene D (38.5 %); Caryophyllene (trace); tau-Cadinol(1.6%); α-Copaene (0.8%); β-Bourbonene (6.0%); Spathulenol (5.1%); β-Elemene (2.1%); γ-Elemene (8.9%)	Phytol (2.0%)	Apigetrin (126.57 µg/g extract); CA(15.67µg/g extract); CHA (15.65 µg/g extract); FA (9.87 µg/g extract); MA (514.97 µg/g extract); QA (179.43µg/g extract); RA (417.96 µg/g extract)		
N. cataria	ME	4aβ,7α,7aβ-NL (5.80 mg/g **)	NA	NA	NA	NA	Chemical Composition	(Mišić et al., 2015)
N. ernesti-mayeri	ME	NA	NA	NA	NA	UCAD(14 mg/g fw); 3-O-caffeoylquinic acid (1.7 mg/g **)		
N. grandiflora	ME	NA	NA	NA	NA			
*N. mussinii (*syn. *racemosa)*	ME	4aβ,7α,7aβ-NL (7.39 mg/g **)	NA	NA	NA	RA(~5.7 mg/g**)		
N. nervosa	ME	NA	NA	NA	NA	UCAN (0.005 mg/g **)		

N. pannonica (syn. *nuda) L.*	ME	NA	NA	NA	NA	NA		
N. parnassica Heldr. & Sart.	ME	DHL (13.16 mg/g **)	NA	NA	NA	NA		
N. rtanjensis	ME	DHL (32.96 mg/g **)	NA	NA	NA	NA		
N. sibirica	ME	4aα,7α,7aα-NL (5.80 mg/g **)	NA	NA	NA	NA		
N. sibthorpii	ME	NA	NA	NA	NA	NA		
N. spicata	ME	NA	NA	NA	NA	NA		
N. laxiflora	EO (0.17% v/w)	NA	a-pinene (19.07 %); 1,8-cineol (11.80%)	a-bisabolol (6.92%); germacrene-D-4-ol (6.24%)	NA	NA	Chemical composition and biological activity	(Safaei-Ghomi et al., 2011)
N. sessilifolia	EO (0.65% v/w)	NA	lavandulyl acetate (16.70%); limonene (6.44%) genaryl acetate (4.17%)	spathulenol (25.75%);	NA	NA		
N. cataria	EO	4aα,7α,7aα-NL(91.1%a ; 70.1%b); 4aα,7α,7aβ-NL(0.1%a; 20.0%b); 4aβ,7α,7aβ-NL(1.0%a; 1.0%b); 4aβ,7α,7aα-NL (0a; 0.1%b); DNL(0.1%a; 0b)	NA	b-Caryophyllene (4.6%a; 4.2%b)	NA	NA	Chemical comp and chemotaxonomy of two accessions per species (content displayed as ‘a’ and ‘b’ in yields)	(De Pooter et al., 1988)
N. x faassenii	EO	4aα,7α,7aα-NL(73.4%a ; 15.0%b); 4aβ,7α,7aβ-NL(5.0%a; 1.2%b); DiNL	NA	trans-β-Ocimene (0a; 17%b); b-Caryophyllene (0a; 2.9%b); β-Farnesene (0a; 4.1%b);	NA	NA		

		(2.5%a; 0b); DNL(0.1%a; 0b)		Germacrene D (0a; 26.9%b)				
N. nepetella	EO	4aα,7α,7aα-NL(86.3%a ; 76.5%b); 4aα,7α,7aβ-NL(0.4%a; 0.6%b); 4aβ,7α,7aβ-NL(0.6%a; 0b); DiNL (0a; 1.6%b);	NA	b-Caryophyllene (5.3%a; 7.0%b); β-Farnesene (3.3%a; 2.8%b); Germacrene D (1.6%a; 2.4%b)	NA	NA		
N. sibirica	EO	4aα,7α,7aα-NL(84.7%); 4aα,7α,7aβ-NL(1.6%); DiNL (0.1%); DNL(0.1%)	NA	b-Caryophyllene (1.6%); β-Farnesene (2.0%); Germacrene D (3.4%)	NA	NA		
N. nuda	EO	4aα,7α,7aα-NL(6.0%a ; 6.0%b); 4aα,7α,7aβ-NL(36.0%a; 26.5%b); 4aβ,7α,7aβ-NL(1.7%a; 3.2%b); 4aβ,7α,7aα-NL (18.4%a; 3.4%b); DNL(0.2%a trace b)	1,8- Cineole (11.0%a; 22.9%b)	Germacrene D (4.9%a; 13.5%b); b-Caryophyllene (4.6%a; 4.2%b); β-Bourbonene (4.5%a; 0.7%b);	NA	NA		
N. atlantica	EO (1.04% v/w)	4aα,7α,7aβ-NL(71.4%); DiNL (3.1%)	NA	B-caryophyllene (8.2%)	NA	Farnesol (2.5%)	Chemical composition and Antimicrobial activity	(Zenasni et al., 2008)
N. tuberosa L. ssp. *reticulata*	EO (1.2%v/w)	4aα,7α,7aβ-NL(76.8%); DiNL (5.9%)	α-pinene1.3%; Menthol (1.6%)	NA	NA	NA		

N. cataria	EO (1.02% v/w)	4aα,7α,7aβ-NL(77.4%); DiNL (5.0%)	Terpinene (4.2%); limonene (4.1)	NA	NA	NA		
N. granatensis	EO (0.96% v/w)	4aα,7α,7aβ-NL(39.4%); DiNL (2.8%)	Eucalyptol (24.0%); α-Phellandrene (5.0%)	NA	NA	NA		

ME = Methanol Extracted; **EO**= essential oil; **NLU**= Unidentified nepetalactone isomer **1,5,9-eDLA** = 1,5,9-epideoxyloganic acid; **DNL** = Dehydronepetalactone; **DiNL** Dihydronepetalactone; ***= dry weight; ****= fresh weight; **#** = mg/g extract; **pdw** = plant dry weight; **CHA**= Chlorogenic acid; **CHA1** = 3-O-caffeoylquinic acid; **CHA2** = 4-O-caffeoylquinic acid; **CA**= Caffeic acid; **FA** = Ferulic acid; **GA**= Gallic acid; **MA** = Malic Acid; **PA** = Protocatechuic acid; **QA** = Quinic acid; **RA** = Rosmarinic Acid; **UCAD** = unidentified caffeic acid derivative; **NA=** not assessed.

Table 2. Comparative chemodiversity studies in populations of *Nepeta* species, with focus on terpene metabolites.

spp.	**Populations**	**Type of extract (yield)**	**Major compound (% of extract)**				**Experimental goal**	**Reference**
			Terpenes					
			Iridoid	**Monoterpenes**	**Sesquiterpenes**	**Diterpenes**		
N. crassifolia	Razey (Iran)	EO (0.56%)	4aβ, 7α, 7aβ-NL (23.27%)	-	-	-	Comparative chemical composition	Narimani et al. (2017)
	Namin (Iran)	EO (0.74%)	4aβ, 7α, 7aβ-NL (27.45%)	-	-	-		
	Heyran (Iran)	EO (0.66%)	-	-	Elemol (19.21%)	-		
N. nuda	Meshkin (Iran)	EO (0.34%)	4aβ, 7α, 7aβ-NL (61%)	-	-	-	Comparative chemical composition	
	Heris (Iran)	EO (0.58%)	4aβ, 7α, 7aβ-NL (70.71%)	-	-	-		
	Maragheh (Iran)	EO (0.32%)	4aβ, 7α, 7aβ-NL (68.8%)	-	-	-		
	Meshkin-Heris (Iran)	EO (0.60%)	4aβ, 7α, 7aβ-NL (72.21%)	-	-	-		
N. argolica	Peloponnisos (Greece)	EO (0.27%)	-	1,8-Cineole (39.79%)	-	-	Comparative chemical composition	Skaltsa et al. (2000)
	Sterea Ellas (Greece)	EO (0.66%)	4aβ, 7α, 7aα-NL (29.38%)	-	-	-		
N. argolica	Aoos Gorge (Greece)	EO (0.09%)	-	1,8-Cineole (30.9%)	-	-	Comparative chemical composition	Hanlidou et al. (2012)

	Xirolivado (Greece)	EO (0.09%)	-	1,8-Cineole (55.6%)	-	-		
N. spruneri	Aoos Gorge (Greece)	EO (0.06%)	-	-	Caryophyllene oxide (19.8%)	-	Comparative chemical composition	Hanlidou et al. (2012)
	Vikos Gorge 1 (Greece)	EO (0.08%)	-	-	Caryophyllene oxide (14.6%)	-		
	Vikos Gorge 2 (Greece)	EO (0.1%)	-	-	Caryophyllene oxide (17.9%)	-		
	Mt Timfi 1 (Greece)	EO (0.12%)	4aα, 7α, 7aβ-NL (29%)	-	-	-		
	Mt Timfi 2 (Greece)	EO (0.05%)	-	-	Caryophyllene oxide (17.3%)	-		
	Mt Timfi 3 (Greece)	EO (0.06%)	-	1,8-Cineole (16.5%)	-	-		
N. heliotropifolia	Sefidkhani (Iran)	EO (0.09%)	-	-	Caryophyllene oxide (14.17%)	-	Comparative chemical composition and plant morphology (Trichomes)	Yarmoohammadi et al. (2017)
	Qazvin (Iran)	EO (0.2%)	-	-	-	Phytol (12.79%)		
N. cataria	Balchik (Bulgary)	EO (0.4%)	4aα,7a,7aβ-NL (24%)	-	-	-	Comparative chemical composition	Handjieva et al. (1996)
	Pirdop (Bulgary)	EO (0.3%)	4aα,7a,7aβ-NL (78%)	-	-	-		
N. fissa	Polor (Iran)	EO (N.A)	-	-	-	Phytol (20.01%)	Comparative chemical composition	Talebi et al. (2017)
	Dizin (Iran)	EO (0.2%)	-	1,8-Cineole (55.9%)	-	-		
N. asterotricha	Darreh shir (Iran)	EO (2.4%)	4aα,7β,7aα-NL (31.7%)	-	-	-	Comparative chemical composition, antibacterial, anti-Candida, and antioxidant activity	Goldansaz et al. (2019)
	Deh Bala (Iran)	EO (2.9%)	4aα,7β,7aα-NL (27.1%)	-	-	-		
	Khames Abad (Iran)	EO (1.9%)	4aα,7β,7aα-NL (34.4%)	-	-	-		
	Manshad (Iran)	EO (2.2%)	4aα,7β,7aα-NL (35.8%)	-	-	-		
	Sanij (Iran)	EO (2.7%)	4aα,7β,7aα-NL (25.4%)	-	-	-		
	Taghi Abad (Iran)	EO (2.9%)	4aα,7β,7aα-NL (20.6%)	-	-	-		

	Tezerjan (Iran)	EO (2.5%)	4aα,7β,7aα-NL (29.4%)	-	-	-		
	Zardein (Iran)	EO (3.2%)	4aα,7β,7aα-NL (35.1%)	-	-	-		
N. heliotropifolia	Vidar 1 (Iran)	EO (0.2%)	-	1,8-Cineole (20.1%)	-	-	Comparative chemical composition and plant morphology (Trichomes)	Talebi et al. (2019)
	Vidar 2 (Iran)	EO (0.25%)	-	-	β-Caryophyllene (18.8%)	-		
N. sessilifolia	Arak 1 (Iran)	EO (0.1%)	-	-	Spathulenol (14.2%)	-		
	Arak 2 (Iran)	EO (0.15%)	-	-	-	Phytol (32.8%)		
N. fissa	Sangak 1 (Iran)	EO (0.2%)	-	-	β-Caryophyllene (33.1%)	-		
	Sangak 2 (Iran)	EO (0.2%)	-	-	Caryophyllene oxide (21.5%)	-		
N. depauperata	Shiraz (Iran)	EO (N.A)	-	-	Caryophyllene oxide (37.4%)	-	Comparative chemical composition, Chemotaxonomic studies	Javidnia et al. (2011)
	Chenar (Iran)	EO (N.A)		α-Pinene (41%)	-	-		
	Abad (Iran)	EO (N.A)	-	-	β-Caryophyllene (7.8%)	-		
N. oxyodonta	Derak mountain (Iran)	EO (N.A)	4aα,7β,7aα-NL (69.9%)	-	-	-		
	Shiraz (Iran)	EO (N.A)	-	-	Caryophyllene oxide (34.5%)	-		
	Abadeh Tashk (Iran)	EO (N.A)	-	-	Caryophyllene oxide (42.6%)	-		
N. curviflora	Salt (Jordan)	EO (0.57%)	4aα,7α,7aα-NL (89.95%)	-	-	-	Comparative chemical composition and extraction methods	Barhoumi et al. (2017)
	Irbid (Jordan)	EO (0.57%)	4aα,7α,7aα-NL (85.74%)	-	-	-		

EO: Essential oil; NL: nepetalactone

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REFERENCES

Adiguzel, A., Ozer, H., Sokmen, M., Gulluce, M., Sokmen, A., Kilic, H., Sahin, F., and Baris, O. 2009. Antimicrobial and antioxidant activity of the essential oil and methanol extract of *Nepeta cataria*. Polish Journal of Microbiology 58: 69–76.

Akdeniz, M., Ertas, A., Yener, I., Firat, M., and Kolak, U. 2020. Phytochemical and biological investigations on two *Nepeta* species: *Nepeta heliotropifolia* and *N. congesta* subsp. *cryptantha*. Journal of Food Biochemistry 44: e13124.

Aldred, E.M. 2009. *Pharmacology, A Handbook for Complementary Healthcare Professionals*. Elsevier Churchill Livingstone, London, UK. 376 pp

Ali, A., Tabanca, N., Demirci, B., Blythe, E.K., Husnu Can Baser, K., and Khan, I.A. 2016. Chemical Composition and Biological Activity of Essential Oils from Four *Nepeta* Species and Hybrids against *Aedes aegypti* (L.) (Diptera: Culicidae). Records of Natural Products 10: 137–147.

Aničić, N., Matekalo, D., Skorić, M., Živković, J.N., Petrović, L., Dragićević, M., Dmitrović, S., and Mišić, D. 2020. Alterations in nepetalactone metabolism during polyethylene glycol (PEG)-induced dehydration stress in two *Nepeta* species. Phytochemistry 174: 112340.

Aničić, N., Gašić, U., Lu, F., Ćirić, A., Ivanov, M., Jevtić, B., Dimitrijević, M., Anđelković, B., Skorić, M., Živković, J.N., Mao, Y., Liu, J., Tang, C., Soković, M., Ye, Y., and Mišić, D. 2021. Antimicrobial and immunomodulating activities of two endemic *Nepeta* species and their major iridoids isolated from natural sources. Pharmaceuticals 14: 414-436.

Audoin, C., Cocandeau, V., Thomas, O.P., Bruschini, A., Holderith, S., and Genta-Jouve, G. 2014. Metabolome consistency: additional parazoanthines from the mediterranean zoanthid parazoanthus axinellae. Metabolites 4: 421–432.

Azizian, T., Alirezalu, A., Hassani, A., Bahadori, S., and Sonboli, A. 2021. Phytochemical analysis of selected *Nepeta* species by HPLC-ESI-MS/MS and GC–MS methods and exploring their antioxidant and antifungal potentials. Journal of Food Measurement and Characterization 15: 2417–2429.

Baghizadeh, A., Mashayekhi, Z., and Ebrahimi, M.A. 2018. Investigation of genetic and phytochemical diversity of some catnip (*Nepeta cataria* L.) populations by RAPD molecular marker and GC/MS method. Iranian Journal of Medicinal and Aromatic Plants 34: 1–14.

Baranauskienė, R., Bendžiuvienė, V., Ragažinskienė, O., and Venskutonis, P.R. 2019. Essential oil composition of five *Nepeta* species cultivated in Lithuania and evaluation of their bioactivities, toxicity and antioxidant potential of hydrodistillation residues. Food and Chemical Toxicology 129: 269–280.

Barhoumi, L.M., Al-Jaber, H.I., and Abu-Zarga, M.H. 2017. Volatile organic compounds and essential oil composition of selected organs of *Nepeta curviflora* collected from two regions in Jordan. Jordan Journal of Chemistry 12: 101-112.

Barrozo, M.M., Zeringóta, V., Borges, L.M.F., Moraes, N., Benz, K., Farr, A., and Zhu, J.J. 2021. Repellent and acaricidal activity of coconut oil fatty acids and their derivative compounds and catnip oil against *Amblyomma sculptum*. Veterinary Parasitology 300: 109591.

Baser, K.H.C., Kirimer, N., Kurkcuoglu, U., and Demirci, B. 2000. Essential oils of *Nepeta* species growing in Turkey. Chemistry of Natural Compounds 36: 356–359.

Bernier, U.R., Furman, K.D., Kline, D.L., Allan, S.A., and Barnard, D.R. 2005. Comparison of contact and spatial repellency of catnip oil and N, N-diethyl-3-methylbenzamide (DEET) against mosquitoes. Journal of Medical Entomology 42: 306–311.

Birkett, M.A., Hassanali, A., Hoglund, S., Pettersson, J., and Pickett, J.A. 2011. Repellent activity of catmint, *Nepeta cataria*, and iridoid nepetalactone isomers against Afro-tropical mosquitoes, ixodid ticks and red poultry mites. Phytochemistry 72: 109–114.

Bisht, D., Padalia, R., Singh, L., Pande, V., Lal, P., and Mathela, C. 2010. Constituents and antimicrobial activity of the essential oils of six Himalayan *Nepeta* species. Journal of the Serbian Chemical Society 75: 739–747.

Bol, S., Caspers, J., Buckingham, L., Anderson-Shelton, G.D., Ridgway, C., Buffington, C.T., Schulz, S., and Bunnik, E.M. 2017. Responsiveness of cats (Felidae) to silver vine (*Actinidia polygama*), Tatarian honeysuckle (*Lonicera tatarica*), valerian (*Valeriana officinalis*) and catnip (*Nepeta cataria*). BMC Veterinary Research 13: 1-16.

Buckle, J. 2015. Basic plant taxonomy, basic essential oil chemistry, extraction, biosynthesis, and analysis. In: J. Buckle, ed, *Clinical Aromatherapy*. Elsevier, London.

Cao, J.Q., Pang, X., Guo, S.S., Wang, Y., Geng, Z.F., Sang, Y. L., Guo, P.J., and Du, S.S. 2019. Pinene-rich essential oils from *Haplophyllum dauricum* (L.) G. Don display anti-insect activity on two stored-product insects. International Biodeterioration & Biodegradation, 140: 1-8.

Cevallos-Cevallos, J.M., Reyes-De-Corcuera, J.I., Etxeberria, E., Danyluk, M.D., and Rodrick, G.E. 2009. Metabolomic analysis in food science: a review. Trends in Food Science & Technology 20: 557-566.

Chauhan, K.R., Khanna, H., Bathini, N.B., Le, T.C., and Grieco, J. 2014. Biobased lactams as novel arthropod repellents. Natural Product Communications 9: 1671–1672.

Dapkevicius, A., Venskutonis, R., van Beek, T.A., and Linssen, J.P.H. 1998. Antioxidant activity of extracts obtained by different isolation procedures from some aromatic herbs grown in Lithuania. Journal of the Science of Food and Agriculture 77: 140–146.

De Pooter, H.L., Nicolai, B., De Laet, J., De Buyck, L.F., Schamp, N.M., and Goetghebeur, P. 1988. The essential oils of five *Nepeta* Species. A preliminary evaluation of their use in chemotaxonomy by cluster analysis. Flavour and Fragrance Journal 3: 155–159.

Dmitrović, S., Perišić, M., Stojić, A., Živković, S., Boljević, J., Živković, J.N., Aničić, N., Ristić, M., and Mišić, D. 2015. Essential oils of two *Nepeta* species inhibit growth and induce oxidative stress in ragweed (*Ambrosia artemisiifolia* L.) shoots *in vitro*. Acta Physiologiae Plantarum 37: 1–15.

Elkholy, M.A., Mansour, M., and Omar, K. 2011. Genetic variability of *Nepeta septemcrenata* Benth.(Lamiaceae) assessed by RAPD Markers. New York Science Journal 4: 97–105.

Feaster, J.E., Scialdone, M.A., Todd, R.G., Gonzalez, Y.I., Foster, J.P., and Hallahan, D.L. 2009. Dihydronepetalactones deter feeding activity by mosquitoes, stable flies, and deer ticks. Journal of Medical Entomology 46: 832–840.

Fehr, W. R. 1991. *Principles of cultivar development: Theory and technique*. Macmillan, Ames, Iowa. 550 p.

Ferreira, L.L., de Oliveira Filho, J.G., Mascarin, G.M., de León, A.A.P., and Borges, L.M.F. 2017. *In vitro* repellency of DEET and β-citronellol against the ticks *Rhipicephalus sanguineus* sensu lato and *Amblyomma sculptum*. Veterinary Parasitology 239: 42–45.

Formisano, C., Rigano, D., and Senatore, F. 2011. Chemical constituents and biological activities of *Nepeta* species. Chemistry & Biodiversity 8: 1783–1818.

Frolova, N., Ukrainets, A., Korablova, O., and

Voitsekhivskyi, V. 2019. Plants of *Nepeta cataria* var. *citriodora* Beck. and essential oils from them for food industry. Slovak Journal of Food Sciences, 13: 449–455.

Galaj, E., Bi, G.H., Moore, A., Chen, K., He, Y., Gardner, E., and Xi, Z.X. 2021. Beta-caryophyllene inhibits cocaine addiction-related behavior by activation of PPARα and PPARγ: repurposing a FDA-approved food additive for cocaine use disorder. Neuropsychopharmacology 46: 860–870.

Geu-Flores, F., Sherden, N.H., Courdavault, V., Burlat, V., Glenn, W.S., Wu, C., and O'Connor, S.E. 2012. An alternative route to cyclic terpenes by reductive cyclization in iridoid biosynthesis. Nature, 492: 138–142.

Goldansaz, S.M., Jafarian Jeloudar, Z., Safaeian, R., and Sonboli, A. 2019. Comparison of the chemical constitutions, antibacterial, anti-Candida, and antioxidant activity of *Nepeta asterotricha* Rech. f. essential oil. American Journal of Essential Oils and Natural Products 7: 15–22.

Gomes, E.N., Allen, K., Jaworski, K., Zorde, M., Lockhart, A., Besancon, T., and Simon, J.E. 2020a. Catnip (*Nepeta cataria* L.): Recent Advances in Botany, Horticulture and Production. In: Á Máthé, ed, *Medicinal and Aromatic Plants of North America*. Springer, Cham

Gomes, E.N., Reichert, W., Vasilatis, A.A., Allen, K.A., Wu, Q., and Simon, J.E. 2020b. Essential Oil Yield and Aromatic Profile of Lemon Catnip and Lemon-Scented Catnip Selections at Different Harvesting Times. *Journal of Medicinally Active Plants*, 9: 21–33.

Gomes, E.N., Allen, K. A., Zorde, M., Wu, Q., and Simon, J.E. 2020c. Ethnobotany, Chemistry, and Pharmacology of African Nepeta Species. In: H.R. Juliani, J.E. Simon, and C.T. Ho, eds, *African Natural Plant Products*, *Volume III*: *Discoveries and Innovations in Chemistry, Bioactivity, and Applications*. American Chemical Society, Washington DC.

Gunasena, G.H., Vinson, S.B., Williams, H.J., and Stipanovic, R.D. 1988. Effects of caryophyllene, caryophyllene oxide, and their interaction with gossypol on the growth and development of *Heliothis virescens* (F.) (Lepidoptera: Noctuidae). Journal of Economic Entomology 81: 93-97

Hadi, N., Sefidkon, F., Shojaeiyan, A., and Jafari, A. A. 2016. Essential oil diversity of 21 populations from Iranian endemic species *Nepeta kotschyi* Boiss. Iranian Journal of Medicinal and Aromatic Plants 32: 189-201.

Hadi, N., Sefidkon, F., Shojaeiyan, A., Šiler, B., Jafari, A.-A., Aničić, N., and Mišić, D. 2017. Phenolics' composition in four endemic *Nepeta* species from Iran cultivated under experimental field conditions: The possibility of the exploitation of *Nepeta* germplasm. Industrial Crops and Products 95: 475–484.

Hadi, N., Shojaeiyan, A., Sefidkon, F., and Jafari, A.A. 2018. Quantitative and qualitative study of essential oil in some accessions of *Nepeta spp.* and determination of essential oil components capability in intra and inter-specific relationships analysis. Iranian Journal of Horticultural Science 49: 601-612.

Hadi, N., Shojaeiyan, A., Sefidkon, F., Jafari, A.A., Mišić, D., Banjanac, T., and Šiler, B. 2020. Assessment of infraspecific genetic diversity in *Nepeta kotschyi* Boiss., a native Iranian medicinal plant. Journal of Agricultural Science and Technology 22: 1327-1342.

Hallahan, D.L., West, J.M., Smiley, D.W., and Pickett, J.A. 1998. Nepetalactol oxidoreductase in trichomes of the catmint *Nepeta racemosa*. Phytochemistry 48: 421-427.

Handjieva, N.V., Popov, S.S., and Evstatieva, L.N. 1996. Constituents of Essential Oils from *Nepeta cataria* L., *N. grandiflora* MB and *N. nuda* L. Journal of Essential Oil Research 8: 639-643.

Hanlidou, E., Karousou, R., and Lazari, D. 2012. Essential oils of three taxa of the *Nepeta argolica* aggregate from Greece. Chemistry and Biodiversity 9: 1559–1566.

Hawke, R.G. 2007. A Comparative Study of Cultivated Catmints. Chicago Botanical Garden 29: 1-4.

Javidnia, K., Mehdipour, A. R., Hemmateenejad, B., Rezazadeh, S.R., Soltani, M., Khosravi, A.R., and Miri, R. 2011. Nepetalactones as chemotaxonomic markers in the essential oils of *Nepeta* species. Chemistry of Natural Compounds 47: 843-847.

Kahkeshani, N., Hadjiakhoondi, A., Navidpour, L., Akbarzadeh, T., Safavi, M., Karimpour-Razkenari, E., and Khanavi, M. 2018. Chemodiversity of *Nepeta menthoides* Boiss. and Bohse. essential oil from Iran and antimicrobial, acetylcholinesterase inhibitory and cytotoxic properties of 1,8-cineole chemotype. Natural Product Research 32: 2745-2748.

Kalpoutzakis, E., Aligiannis, N., Mentis, A., Mitaku, S., and Charvala, C. 2001. Composition of the essential oil of two *Nepeta* species and *in vitro* evaluation of their activity against *Helicobacter pylori*. Planta Medica 67: 880–883.

Karunanithi, P.S., and Zerbe, P. 2019. Terpene synthases as metabolic gatekeepers in the evolution of plant terpenoid chemical diversity. Frontiers in Plant Science 10: 1-23.

Kaur, M., and Singhal, V.K. 2014. First report of cytomixis and meiotic abnormalities in *Nepeta govaniana* from Solang Valley, Kullu District, Himachal Pradesh. Cytologia 79: 227-233.

Kaya, A., and Dirmenci, T. 2008. Nutlet Surface Micromorphology of the Genus *Nepeta* L. (Lamiaceae) in Turkey. Turkish Journal of Botany 32: 103–112.

Kharazian, N., Shourabi, S. Z., and Yousefi, M. 2013. Chromosome count and karyotype study of eleven Nepeta L. Lamiaceae species from Iran. Biyolojik Çeşitlilik ve Koruma 6: 76-87.

Klimek, B., Majda, T., Góra, J., and Patora, J. 2000. Investigation of the essential oil from lemon catnip (*Nepeta cataria* L. var *citriodora*) in comparison to the oil from lemon balm (*Melissa officinalis* L.). Herba Polonica 46: 226-234.

Kolalite, M.R. 1998. Comparative analysis of ultrastructure of glandular trichomes in two *Nepeta cataria* chemotypes (*N. cataria* and *N. cataria* var. *citriodora*). Nordic Journal of Botany 18: 589-598.

Kumar, V., Mathela, C.S., Tewari, A.K., and Bisht, K. S. 2014. *In vitro* inhibition activity of essential oils from some Lamiaceae species against phytopathogenic fungi. Pesticide Biochemistry and Physiology 114: 67–71.

Kumar, R., Bohra, A., Pandey, A.K., Pandey, M.K., and Kumar, A. 2017. Metabolomics for plant improvement: status and prospects. Frontiers in Pant Science 8: 1-27.

Lyu, W., Yuan, B., Liu, S., Simon, J.E., and Wu, Q. 2021. Assessment of lemon juice adulteration by targeted screening using LC-UV-MS and untargeted screening using UHPLC-QTOF/MS with machine learning. Food Chemistry 373: 1-11.

Mamadalieva, N.Z., Sharopov, F.S., Satyal, P., Azimova, S.S., and Wink, M. 2016. Chemical Composition of the Essential Oils of Some Central Asian *Nepeta* Species (Lamiaceae) by GLC-MS. Natural Product Communications 11: 1891–1893.

Mišić, D., Siler, B., Gašić, U., Avramov, S., Zivković, S., Živković, J., Milutinović, M., and Tešić, Z. 2015. Simultaneous UHPLC/DAD/(+/-)HESI-MS/MS analysis of phenolic acids and nepetalactones in methanol extracts of *Nepeta* species: a possible application in chemotaxonomic studies. Phytochemical Analysis 26: 72–85.

Mohamed, H.F.Y., Mahmoud, A.A., Alatawi, A., Hegazy, M.H., Astatkie, T., and Said-Al Ahl, H.A. 2018. Growth and essential oil responses of *Nepeta* species to potassium humate and harvest time. Acta Physiologiae Plantarum 40: 1-8.

Murch, S.J., and Saxena, P.K. 2006. St. John's wort (*Hypericum perforatum* L.): Challenges and strategies for production of chemically-consistent plants. Canadian Journal of Plant Science 86: 765–771.

Mutlu, S., and Atici, Ö. 2009. Allelopathic effect of *Nepeta meyeri* Benth. extracts on seed germination and seedling growth of some crop plants. Acta Physiologiae Plantarum. 31: 89–93

Müller, G.C., Junnila, A., Butler, J., Kravchenko,

V.D., Revay, E.E., Weiss, R.W., and Schlein, Y. 2009. Efficacy of the botanical repellents geraniol, linalool, and citronella against mosquitoes. Journal of Vector Ecology 34: 2-8.

Nadeem, A., Ahmed, B., Shahzad, H., Craker, L.E., and Muntean, T. 2021. *Verbascum thapsus* (Mullein) Versatile Polarity Extracts: GC-MS Analysis, Phytochemical Profiling, Anti-bacterial Potential and Anti-oxidant Activity. Pharmacognosy Journal 13: 1488–1497.

Narimani, R., Moghaddam, M., Ghasemi Pirbalouti, A., and Mojarab, S. 2017. Essential oil composition of seven populations belonging to two *Nepeta* species from Northwestern Iran. International Journal of Food Properties 20: 2272-2279.

Nestorović, J., Misić, D., Siler, B., Soković, M., Glamoclija, J., Cirić, A., Maksimović, V., and Grubisić, D. 2010. Nepetalactone content in shoot cultures of three endemic *Nepeta* species and the evaluation of their antimicrobial activity. Fitoterapia 81: 621–626.

Ohio State University 2021. Ornamental Plant Germplasm Center: What is an accession? Available at: https://opgc.osu.edu/node/88, accessed on November 30, 2021.

Paduch, R., Kandefer-Szerszeń, M., Trytek, M., and Fiedurek, J. 2007. Terpenes: substances useful in human healthcare. Archivum Immunologiae et Therapiae Experimentalis 55: 315-327.

Park, C.H., Tannous, P., Juliani, H.R., Wu, Q.L., Sciarappa, W.J., VanVranken, R., Dalponte, D., and Simon, J.E. 2007. Catnip as a source of essential oils. New Crops And New Uses 1: 311-315

Patience, G.S., Karirekinyana, G., Galli, F., Patience, N.A., Kubwabo, C., Collin, G., Bizimana, J.C., and Boffito, D.C. 2018. Sustainable manufacture of insect repellents derived from *Nepeta cataria*. Scientific Reports 8: 22-35.

Reichert,W., Park, H.C., Juliani, H.R., and Simon, J.E. 2016. 'CR9': A New Highly Aromatic Catnip *Nepeta cataria* L. Cultivar Rich in Z, E-Nepetalactone. HortScience 51:588-591.

Reichert, W., Villani, T., Pan MH., Ho CT., Simon, J.E., and Wu, QL. 2018. Phytochemical analysis and anti-inflammatory activity of *Nepeta cataria* accessions. Journal of Medicinally Active Plants 7:19–27

Reichert, W., Ejercito, J., Guda, T., Dong, X., Wu, Q., Ray, A., and Simon, J.E. 2019. Repellency assessment of *Nepeta cataria* essential oils and isolated Nepetalactones on *Aedes aegypti*. Scientific Reports 9:1-9.

Safaei-Ghomi, J., Nahavandi, S., and Batooli, H. 2011. Studies on the antioxidant activity of the volatile oil and methanol extracts of *Nepeta laxiflora* benth. and *Nepeta sessilifolia* bunge. from Iran. Journal of Food Biochemistry 35:1486–1492.

Said-Al Ahl, H., Naguib, N.Y., and Hussein, M.S. 2018. Evaluation growth and essential oil content of catmint and lemon catnip plants as new cultivated medicinal plants in Egypt. Annals of Agricultural Sciences 63:201-205.

Salehi, B., Valussi, M., Jugran, A.K., Martorell, M., Ramírez-Alarcón, K., Stojanović-Radić, Z.Z., Antolak, H., Kręgiel, D., Mileski, K.S., Sharifi-Rad, M., Setzer, W.N., Cádiz-Gurrea, M., de la Luz Cádiz-Gurrea, M., Segura-Carretero, A., Şener, B., and Sharifi-Rad, J. 2018. *Nepeta* species: From farm to food applications and phytotherapy. Trends in Food Science & Technology 80:104–122.

Sarikurkcu, C., Ceylan, O., Targan, S., and Zeljković, S.Ć. 2018. Chemical composition and biological activities of the essential oils of two endemic *Nepeta* species. Industrial Crops and Products 125:5–8

Sarikurkcu, C., Eskici, M., Karanfil, A., and Tepe, B. 2019. Phenolic profile, enzyme inhibitory and antioxidant activities of two endemic *Nepeta* species: *Nepeta nuda* subsp. *glandulifera* and *N. cadmea*. South African Journal of Botany 120:298–301.

Schultz, G., Simbro, E., Belden, J., Zhu, J., and Coats, J. 2004. Catnip, *Nepeta cataria* (Lamiales: Lamiaceae)—A closer look: Seasonal occurrence of nepetalactone isomers and comparative repellency of three terpenoids to insects. Environmental Entomology 33:1562–

1569
Sefidkon, F., Kalvandi, R., and Mirza, M. 2003. Chemical variation of the essential oil of *Nepeta heliotropifolia* in different stage of plant growth. Iranian Journal of Medicinal and Aromatic Plants 19:255–267.
Sefidkon, F., Jamzad, Z., and Mirza, M. 2006. Chemical composition of the essential oil of five Iranian *Nepeta* species (*N. crispa, N. mahanensis, N. ispahanica, N. eremophila and N. rivularis*). Flavour and Fragrance Journal 21:764–767.
Sengupta, S.K., Hutchenson, K.W., Hallahan, D.L., Gonzalez, Y.I., Manzer, L.E., Jackson, S.C., Scialdone, M.A., and Kou, B. 2018. Hydrogenation of naturally-derived nepetalactone as a topical insect repellent. ACS Sustainable Chemistry & Engineering 6:9628–9639.
Sharifi-Rad, J., Sureda, A., Tenore, G.C., Daglia, M., Sharifi-Rad, M., Valussi, M., Tundis, R., Sharifi-Rad, M., Loizzo, M.R., Ademiluyi, A.O., Sharifi-Rad, R., Ayatollahi, S.A., and Iriti, M. 2017. Biological activities of essential oils: From plant chemoecology to traditional healing systems. Molecules 22:70.
Sharma, A., Cooper, R., Bhardwaj, G., and Cannoo, D.S. 2021. The genus *Nepeta*: Traditional uses, phytochemicals and pharmacological properties. Journal of Ethnopharmacology 268:113679.
Sharma, A., Nayik, G.A., and Cannoo, D.S. 2019. Pharmacology and toxicology of *Nepeta cataria* (Catmint) species of genus *Nepeta*: A review. Plant and Human Health 3:285-299.
Sherden, N.H., Lichman, B., Caputi, L., Zhao, D., Kamileen, M.O., Buell, C.R., and O'Connor, S.E. 2018. Identification of iridoid synthases from *Nepeta* species: Iridoid cyclization does not determine nepetalactone stereochemistry. Phytochemistry145:48-56.
Shi, X., Wang, C., Simon, J.E., Reichert, W., and Wu, QL. 2021. Repellency of novel catnip oils against the bed bug (*Hemiptera:* Cimicidae). Journal of Medical Entomology 58:528-534.
Silva, W.J., Dória, G.A.A., Maia, R.T., Nunes, R.S., Carvalho, G.A., Blank, A.F., and Cavalcanti, S.C.H. 2008. Effects of essential oils on *Aedes aegypti* larvae: Alternatives to environmentally safe insecticides. Bioresource Technology 99:3251-3255.
Simon, J. E., Reichert, W., and Wu, QL 2019. Catnip cultivar 'CR3'. U.S. patent 10,512,231B2
Skaltsa, H.D., Lazari, D.M., Loukis, A.E., and Constantinidis, T. 2000. Essential oil analysis of *Nepeta argolica* Bory & Chaub. subsp. *argolica* (Lamiaceae) growing wild in Greece. Flavour and Fragrance Journal 15:96-99.
Srivastava, A., Gupta, S., Singh, S., Verma, R.S., Srivastava, R.K., Gupta, A.K., and Lal, R.K. 2021. Genetic variability and elite line selection for high essential oil and nepetalactone content in catmint (*Nepeta cataria* L.). American Journal of Plant Sciences 12:1135-1154.
Starks, C.M., Back, K., Chappell, J., and Noel, J.P. 1997. Structural basis for cyclic terpene biosynthesis by tobacco 5-epi-aristolochene synthase. Science 277:1815-1820.
Takeda, Y., Matsumoto, T., Ooiso, Y., Honda, G., Tabata, M., Fujita, T., Otsuka, H., Sezik, E., and Yesilada, E. 1996. Nepetacilicioside, a new iridoid glucoside from *Nepeta cilicia*. Journal of Natural Products 59:518-519.
Takeda, Y., Morimoto, Y., Matsumoto, T., Honda, G., Tabata, M., Fujita, T., Otsuka, H., Sezik, E and Yesilada, E. 1995. Nepetanudoside, an iridoid glucoside with an unusual stereostructure from *Nepeta nuda* ssp. *albiflora*. Journal of Natural Products 58:1217-1221.
Talebi, S.M., Nohooji, M.G., and Yarmohammadi, M. 2017. Infraspecific variations in essential oil compositions of *Nepeta fissa* from Iran. Nusantara Bioscience 9:318-321.
Talebi, S.M., Nohooji, M.G., Yarmohammadi, M., Khani, M., and Matsyura, A. 2019. Effect of altitude on essential oil composition and on glandular trichome density in three *Nepeta* species (*N. sessilifolia, N. heliotropifolia* and *N. fissa*). Mediterranean Botany 40:81-93.
Talebi, S.M., Nohooji, M.G., and Yarmohammadi, M. 2020. Essential oil analysis of eight "*Nepeta*" taxa in Iran. In Mediterranean Botany

41:43–53.
Talebi, S.M., Tabaripour, R., and Matsyura, A. 2021. Genetic diversity and population structure of diverse Iranian *Nepeta* L. taxa. Genetic Resources and Crop Evolution 1-12.
Tavares, M., da Silva, M.R.M., de Siqueira, L.B.D.O., Rodrigues, R.A.S., Bodjolle-d'Almeida, L., Dos Santos, E.P., and Ricci-Júnior, E. 2018. Trends in insect repellent formulations: a review. International Journal of Pharmaceutics 539:190-209.
Turner, M.F., Heuberger, A.L., Kirkwood, J.S., Collins, C.C., Wolfrum, E.J., Broeckling, C.D., Prenni, J.E., and Jahn, C.E. 2016. Non-targeted metabolomics in diverse sorghum breeding lines indicates primary and secondary metabolite profiles are associated with plant biomass accumulation and photosynthesis. Frontiers in Plant Science 7:953.
Xie, S., Uesato, S., Inouye, H., Fujita, T., Murai, F., Tagawa, M., and Shingu, T. 1988. Absolute structure of nepetaside, a new iridoid glucoside from *Nepeta cataria*. Phytochemistry 27:469-472.
World Health Organization. 2014. A global brief on vector-borne diseases. Accessed November 30, 2021,https://apps.who.int/iris/bitstream/handle/10665/111008/WHO_DCO?sequence=1
World Health Organization. 2019. A global brief on vector-borne diseases. Accessed November 30, 2021,https://www.who.int/publications/i/item/9789241565721
Yang, D., Michel, L., Chaumont, J.P., and Millet-Clerc, J. 2000. Use of caryophyllene oxide as an antifungal agent in an in vitro experimental model of onychomycosis. Mycopathologia 148:79-82.
Yang, D., Du, X., Liang, X., Han, R., Liang, Z., Liu, Y., Liu, F., and Zhao, J. 2012. Different Roles of the Mevalonate and Methylerythritol Phosphate Pathways in Cell Growth and Tanshinone Production of *Salvia miltiorrhiza* Hairy Roots. PLoS ONE 7:e46797.
Yarmoohammadi, M., Talebi, S.M., and Nohooji, M.G. 2017. Infraspecific variations in essential oil and glandular trichomes in *Nepeta heliotropifolia*. Biodiversitas Journal of Biological Diversity 18:964-970.
Zenasni, L., Bouidida, H., Hancali, A., Boudhane, A., Amzal, H., Idrissi, A.I., El Aouad, R., Bakri, Y., and Benjouad, A. 2008. The essentials oils and antimicrobial activity of four *Nepeta* species from Morocco. Journal of Medicinal Plants Research 2:111-114.
Zhou, X., Zhang, Z.C., Huang, Y.B., Xiao, H.W., Wu, J. J., Qi, Z.C., and Wei, Y.K. 2021. Conservation genomics of wild Red Sage (*Salvia miltiorrhiza*) and its endangered relatives in China: Population structure and interspecific relationships revealed from 2b-RAD Data. Frontiers In Genetics 12:707.
Zhu, J.J., Zeng, X.P., Berkebile, D., Du, H.J., TONG, Y., and Qian, K. 2009. Efficacy and safety of catnip (*Nepeta cataria*) as a novel filth fly repellent. Medical and Veterinary Entomology 23:209-216.
Zhu, J.J., Berkebile, D.R., Dunlap, C.A., Zhang, A., Boxler, D., Tangtrakulwanich, K., Behle R.W., Baxendale, F., and Brewer, G. 2012. Nepetalactones from essential oil of *Nepeta cataria* represent a stable fly feeding and oviposition repellent. Medical and Veterinary Entomology 26:131-138.