New tricks for old guys:
recent developments in the chemistry, biochemistry, applications and exploitation of selected species from the Lamiaceae family

Edoardo Napoli, Laura Siracusa, Giuseppe Ruberto*
Istituto del CNR di Chimica Biomolecolare, Via Paolo Gaifami, 18
95126 Catania, Italy
giuseppe.ruberto@icb.cnr.it

In memory of Carmela Spatafora

Abstract

Lamiaceae is one of the largest families of flowering plants comprising about 250 genera and over 7,000 species. The majority of the plants of this family are aromatic and therefore important source of essential oils. Lamiaceae are widely used as culinary herbs and reported as medicinal plants in several folk traditions. In the Mediterranean area oregano, sage, rosemary, thyme and lavender stand out for geographical diffusion and variety of uses. The aim of this review is to provide recent data dealing with the phytochemical and pharmacological studies, and the more recent applications of the essential oils and the non-volatile phytocomplexes. This literature survey suggests how the deeper understanding of biomolecular processes in the health and food sectors as per as pest control bioremediation of cultural heritage, or interaction with human microbiome, fields, leads to the rediscovery and new potential applications of well-known plants.

Keywords: Lamiaceae; essential oils; extracts; phytocomplexes; biological activity.

Contents

1.Introduction

Lamiaceae family belongs to the Lamiales order, also known as mint order, which comprises 24 families, 1,059 genera and more than 23,800 species. The Lamiaceae is the main family of this order together with Verbenaceae, Plantaginaceae, Scrophulariaceae, Orobanchaceae, Acanthaceae, Gesneriaceae, Bignoniaceae, Oleaceae, Pedaliaceae, and the small carnivorous families Lentibulariaceae and Byblidaceae.

Initially this family has been known for long time as Labiatae (*nomen conservandum*) or mint family; only in the 1820 the name was definitely changed into Lamiaceae. Without to deepen the taxonomic aspects, which are outside the aims of this review, the Lamiaceae comprises seven sub-families: Ajugoideae, Lamioideae, Nepetoideae, Prostantheroideae, Scutellarioideae, Symphorematoideae and Viticoideae, which in turn enclose several tribes and sub-tribes. On the whole, the genera belonging to this family are 245, which from a first evaluation lists 22,576 species, but only 7,886 have been accepted as true species removing a great number of synonym uses or wrong attribution. [1] The main genera of this family are *Salvia, Scutellaria, Stachys, Plectranthus, Hyptis, Teucrium, Vitex. Thymus* and *Nepeta* (**Figure 1**).

INSERT FIGURE 1

Lamiaceae is the family with the highest number of aromatic plants, even though these are present in many other families, such as Abietaceae, Apiaceae, Asteraceae, Cupressaceae, Luaraceae, Myrtaceae, Rutaceae, etc. to quote the most important. For aromatic plants we mean those that by a physical process, namely steam distilllation of hydrodistillation, give an essential oil, a lipidic mixture of a high number of different chemical components whose peculiar characteristic is the high volatility and aroma production. Most of the aromatic plants are cultivated and have a growing commercial interest for their fragrance and flavour due to their essential oils, and for their medicinal properties. Despite today more than 3,000 aromatic plants (belonging to the aforesaid families) able to yield an essential oil are known, only three hundred essential oils have a commercial interest. [2]

Furthermore, Lamiaceae is one of the most studied families for the content of a high number of components endowed with a large spectrum of biological activities; as previously mentioned most of the essential oils belong to this category of components, but another consistent portion of not volatile bio-active secondary metabolites is present in this family.

These plants, which enclose the so-called medicinal and aromatic plants, are altogether defined as officinal plants possessing specific sensorial, biological and pharmacological properties. They cannot be classified according to the classic botanic categories, namely herbaceous, arboreous, woody, etc., but the aforesaid characteristics make these plants transversal from the botanic, agronomic and ecological point of views. This large variability accounts for a very wide range of classification producing an estimation ranging between 10,000 and 50,000 botanic species comprehendible in this category. [3]

The term 'officinal', which characterizes these plants, derives from the Latin name "*officina*", namely the back of the medieval chemist's shop, where the plants were subjected to different manufactures (drying, grinding, soaking, essence production, etc.) to obtain several marketable products.

According to a recent survey of World Health Organization issued in 2016, [4] the main human pathologies and the leading causes of deaths were: ischemic heart disease, stroke, obstructive pulmonary disease, respiratory infections, Alzheimer and central nervous system (CNS) diseases, lung cancer, diabetes, road injury, diarrhoeal diseases, tuberculosis. To-day also according to the World Health Organization (WHO) about 3.5 billion of people rely on medicinal plants for their healthcare requirements (WHO Global report 2019). [5] This is particularly true in the developing countries of Asia, South America and mainly Africa, where about 80% of population is based on this practice. [6] Traditional Chinese Medicine (TCM), Ayurvedic medicine (India), South and Central America, Middle East and Asia, as well as many other traditional popular treatments based on medicinal plants in many countries are the expression of the large use of these natural resources and a witness of a cultural heritage, which dates back to several thousands of years.

In these last decades these typologies of medical remedies have assumed an even more important role also in the western population, where the traditional uses of plants have been lost, overshadowed or forgotten. In fact, according to the reports of WHO the global market for herbal medicine raised from US$17 billion in 2000, to US$60 billion in 2003; in particular, only the industry related to TCM in 2012 reached a value of UD$83 billion, [7] a value of US$115 has been estimated for 2020. [8] A little less than 30,000 plants are recorded as medicinal, but only about 4,500 have been phytochemically studied and are used currently used in plant-based medicines. Therefore, a large portion of these plants is still unexplored, representing a very important patrimony of new potential bioactive compounds. [7,9]

As previously mentioned medicinal and aromatic plants, or in general officinal plants, are not ascribable to a particular botanical or agronomic category, being distributed among different orders, families and genera. The **Figure 2** shows the main families in which are present the highest number of medicinal plants. As it can be seen the Fabaceae or Leguminosae family contains the highest number of these species, whereas the Lamiaceae family is in the second position.

INSERT FIGURE 2

Lamiaceae species are distributed nearly worldwide, however, the Mediterranean basin is the region where this family found the best environmental conditions for its development and differentiation. [10,11] The so-called "Mediterranean scrub" is in fact characterized by a large number of Lamiaceae species, which form coastal and mountainous scrublands (garrigues) with rocky and sandy soil, being the typical and unique environmental peculiarity of a large portion of the Mediterranean area.

The discovery of new natural products and the more detailed studies of phytocomplexes, here inetended as a complex mixture of phytochemicals, represent the more promising perspectives of this sector. As previously mentioned also in this family many species have not yet been studied and therefore a lot of work must be still done. However, c*onditio sine qua non* that this knowledge became a shared patrimony is the conservation, the cure and the attention towards the genetic resources and biodiversity. This is strictly connected with the actions of the human beings and with the climate change which already are producing serious problems to the plant survival. A study of some years ago confirmed that this trend based on our incapacity to invert this course and to make the politically correct choices could be the cause of the vulnerability and the serious threat of more than half of species in Europe by 2080. [12]

Plants have 'accompained' the evolution of the human beings supplying an essential portion of foods, and a series of 'tools' able to fight several pathologies or generically speaking many health problems. As previously mentioned to-day a large portion of the world population uses still plants and their derivatives as medicinal remedies, however, it also true that many drugs sold in our pharmacies and used against a large spectrum of pathologies (chronic and/or epidemic), have a natural origin.

In recent years the use (and the abuse) of food supplements has grown exponentially. To these products which can not be classified as food and/or drugs, the term 'nutraceutic' has been associated, while a food containing some of these components has been defined as 'functional food', namely a food able to help an organism to keep a state of well-being, even though it is not generally accepted that such 'functionality', in nutritional and healthy sense, can be associated only to a selected number of foods. [3,5,6]

The Lamiaceae family, object of this review, represents a small portion of the important natural resources that the human beings should have carefully to protect. Besides the classic and still effective studies aimed to the discover of new natural products, several new tools are available helping the fight against the new healthy emergencies of this millennium. One of these is the so-called multi-resistance of several microbial strains towards a large number of antibiotics, which until few years ago were able to contrast many types of infections. Unfortunately, owing to a large abuse of these drugs against microbial strains, these have developed more or less marked resistance making useless or little effective their action in the anti-infections therapies. This problem is particularly acute in the hospitals and for some particular and very dangerous bacterial strains as *Mycobacterium tuberculosis*, the etiological agent of tuberculosis (TB), which in these last years, showed a broad recrudescence becoming one the main cause of death. [13] New strategies such as the use of a multi-components therapy in the hope to exploit synergic and/or additive effects, or the analyses of new and little explored new sources has been taken in consideration. [14-16] Very recently some cyclic heptapseudopeptides have been synthetized taking paradoxically inspiration from a *Staphyloccous aureus* toxin, showing interesting activities against antibiotic-resistant gram-positive and –negative pathogens. [17]

A further and promising tool for the development of the natural products and herbal extracts is the so called "drug repurposing", which has been defined as the "Studying the drugs that are already approved to treat one disease or condition to see if they are safe and effective for treating other diseases" as elaborated by the National Centre for Advancing Translational Sciences (NCATS, Bethesda, Maryland, USA) of the

National Institute of Health (NIH, Bethesda, Maryland, USA). [18] This approach applied in these last years in the pharmaceutical sector has been mainly developed for economic reasons (but not only) because the production of a new drug is a very long (13-15 years) and very expansive (2-3 US$ billion) process, whereas the cost of a pharmaceutical repurposing of an old drug is about 300 million of US$, since in this case the toxicity and clinical studies have been already carried out. As previously mentioned this approach is applied also to natural products and plant extracts, [19,20] and recently it has been supported by several tools such as the Connectivity Map (CMap), the Library Integrated Network based Cellular Signatures (LINCS), the Genome Wide Association Studies (GWAS), the Side Effect Resource (SIDER), and the Directionality Map (DMAP), which have significantly reinforced the drug repurposing applications. [21-25]

These new studies besides to be applied to fight the main pathologies previously described appear particularly promising in the research of therapeutic tools against the so-called rare or orphan diseases, which are often chronic and progressive without an appropriate drug equipment as well as focused pharmaceutical studies.

Aim of this review is to give an up-dated vision of the most recent studies on some selected Lamiaceae plants, such as lavender, oregano, sage, rosemary, and thyme, which characterize the patrimony of the Mediterranean area, with particular attention to southern Italy regions. The increasing cultivation of these species and their growing diffusion as new crops, as well as the evaluation of their new applications of the extracts and essential oils in new sectors of their potential bioactivities will be discussed.

2. Essential oils: very old “guys” with great prospects

Essential oils (EOs) are volatile and complex mixtures of several compounds belonging to different chemical families characterized by strong odor synthetized by aromatic plants as secondary metabolites. These phytocomplexes should be obtained by physical processes involving steam distillation, hydro or dry distillation with the sole exception of *Citrus* EOs which are mechanically obtained by peel expression. [5] After the culinary use as dried or fresh spice, the extraction of EOs is the second main use for rosemary, sage, oregano and thyme, while for lavender the production of the essences is probably the main scope of its cultivation due the additional interest of the cosmetic industry. For the above mentioned reasons several studies were conducted in the recent past with the aim to optimize or increase the yields of EOs using novel techniques in addition or as “pre-treatments” of the traditional way of production. Examples of these novel techniques are microwave-assisted hydrodistillation, [26,27] solvent-free microwave extraction, [28] ultrasounds, [29,30] ultrasonic-microwave assisted preceded by enzymolysis. [31] From these studies, it emerges that the combination of advanced and traditional techniques leads to a variable increase in yields and a significant reduction in times with consequent energy savings. However, this approach also brings with it a further qualitative and quantitative variability of essential oils that is added to that present in nature (conditioned by climatic and environmental factors) with consequent variation of the biological activities of the oils themselves. This parameter must be evaluated every time we want to produce an essential oil that has a particular chemical composition using a combination of extraction techniques.

From the point of view of biological properties and new applications what are the most interesting prospects concerning essential oils and their production with particular reference to the five species of Lamiaceae covered by this review? What emerges from the literature analysis of the last 5-10 years is that the interest on essential oils still remains the exploitation and optimization of the broad-spectrum antimicrobial activity that these phytocomplexes possess. Innovation lies in the application of this activity, which is now declined in the most varied industrial and human and animal health fields. There is also a growing interest in the enhancement of peculiar endemisms and chemotypes capable of enhancing a certain area of production, together with the rationalization of crop management under stress conditions and agronomic techniques able to optimize the productions in terms of biomass and essential oils yields and adapt them even in difficult or extreme environmental conditions. Another aspect of great interest is the research through nanoformulation techniques to overcome the problem of the high volatility and poor solubility in water of essential oils that often limits its potential use at agronomic and industrial level.

Progress has also been made in the knowledge and understanding of the potential of Lamiaceae essential oils as antigerminative and phytotoxic agents capable of being used as an eco-sustainable alternative in the fight against weeds. Finally, there are still numerous studies on the potential repellency and toxicity of these essential oils against the harmful insects of agricultural production or vectors of potential diseases for men or animals. Also in these cases, the combination with nanoformulation techniques seems to be the most promising route.

2.1 Enhancement of endemisms and chemical variations within populations

The chemical variability of essential oils is a peculiar character of these natural matrices being important to understand their biological properties, as well as for their industrialization and commercialization. Owing to their compositional variability the essential oils are able to perform several biological actions, however, at the same time this variability can represent an obstacle for their industrialization processes. This dichotomy has led on the one hand to the search for a rationalization and extremization of the "chemotype" concept, on the other a search for particular endemisms and compositional variations capable of preserving biodiversity and enhancing particular production areas.

An exhaustive treatment of the chemotypes and endemisms of the five Lamiaceae covered by this study is out of the scope of this review. Rather we will try to emphasize the research published in recent years by providing a very general picture of the most recent knowledge in this field.

2.1.1 Lavender

A very interesting dissertation on current lavender and lavender EOs market with an evaluation of the economic impact of these productions in an officinal plants producer country as Turkey was published recently by Giray, [32] concluding that the sector of aromatic and medicinal plants and their essential oils is very promising at the socio-economic level for developing countries. An exhaustive work on the chemistry of *Lavandula* genus was made by Aprotosoaie and colleagues [33] covering the chemistry of 17 species from very different geographical origins. What emerges is that the chemical composition of lavender essential oils have a huge range of variability in terms of volatile constituents, concluding that more research is needed in terms of the knowledge on the genotypic and environmental events that produce the lavender chemical biodiversity, recalling for the standardization of methodology for the analysis and extraction. A complementary list of recent publications is reported in **Table 1**. Among studies on *L. angustifolia*, a recent work of Smigielski et al. [34] compares fresh and dried plant material finding no significant differences in terms of chemical composition of essential oils but rather a higher antioxidant activity in the oil from fresh aerial parts. Recent works [35-38] report a linalool predominance in *L. angustifolia* essential oils from Italy, Croatia, Turkey and Spain respectively. Kivrak and Singh et al., [39-40] report two cases of linalyl acetate chemotypes from Turkey and India respectively, while Behladj et al., [41] reports 1,8-cineole chemotype in Algerian populations.

Some reports on the evaluation of inflorescences, aerial part and whole plant EOs from *L. stoechas* from Spain and Italy, reporting a fenchone chemotype followed by camphor and 1,8-cineole as other main components. [42-44]

L. hybrida (several cultivars) from Italy and Turkey were extensively studied by Pistelli et al., [35] and Kivrak et al., [39] while Robu et al. and Bajalan et al. published analysis of plant material from Romania and Iran, respectively. [45,46] The picture that emerges regarding *L. hybrida* is more varied, from a compositional point of view, than that present for *L. angustifolia*.

Regarding the less studied species of lavender, very interesting is the work of El Hamadoui et al., [47] which report the chemical composition and biological activities of a carvacrol chemotype of *L. mairei*, an endemic and rare species from Morocco. Another two endemic species are *L. pinnata* and *L. pubescens* collected in Spain and Yemen, were studied by Argentieri et al. and Al Badani et al.,. [48-49] Both were carvacrol chemotypes with a variable amount of carvacrol methyl ether and caryophyllene oxide as other main compounds. Finally, an endemic and rare species namely *L. stricta*, was studied by Alizadeh and Aghaee reporting a rare case for this genus of α-pinene chemotype EO. [50]

INSERT TABLE 1

2.1.2 Oregano

A recent work published by Leyva-López et al. [52] provides a broad overview of the major oregano species and their chemical variability, relating them to their biological activities reported in literature. The constituents and concentration of the compounds of the EOs usually vary due to a great diversity of factors such as species, soil conditions, harvest season, geographical location, climatic and growth conditions. A list of recent studies on chemical composition of oregano species EOs is presented in **Table 2**.

Within oregano, *O. vulgare* is probably the more widespread specie worldwide and great attention is still paid by researchers to it. A huge work was focused on the qualitative and quantitative composition of essential oil compounds of European

Origanum vulgare analyzing more than 500 plants from 17 countries. [53] Their work confirms a large variability in terms of yields (0.03-4.60%) and chemical composition, which can be partially explained by different efficiency or activity (up-/down regulation) of the cymyl-, sabinyl- and linalool/linalyl acetate pathway. Their very interesting conclusion is that "the cymyl- and the acyclic pathway were usually active in plants from the Mediterranean climate whereas an active sabinyl-pathway was a characteristic of plants from the Continental climate". The picture is completed by the works of De Mastro et al. and Napoli et al., [54-55] for southern Italy populations reporting the familiar chemical variability and by the carvacrol-chemotypes populations reported for Spanish [56] and Iranian [57] *Origanum vulgare* L. Hatipi et al. report a case of sabinene chemotype *O. vulgare* in Kosovo. [58] Argentinian oregano species were studied by Asensio et al., [59] which reports *trans*-sabinene hydrate as main compound for *Origanum x Majoricum*, *O. vulgare* ssp. *vulgare* and *O. vulgare* ssp. *hyrtum*. Within *O. vulgare* subspecies, *O. vulgare* ssp. *hyrtum* is largely diffused worldwide and is very important under a commercial point of view. It was widely studied by Tuttolomondo, Mancini and collaborators reporting a prevalent thymol chemotype for Italian populations, [60-63] (**Figure 3**) and by Stesevic et al. [64] for populations from Montenegro showing instead a carvacrol chemotype. This differentiation is appreciable at the olfactory and organoleptic level by consumers as shown by a recent comparative study of the chemical composition and sensory analysis of Sicilian oregano and a commercial sample (**Figure 4**). [65] These aspects have positively influenced a large increase of its production (**Figures 5** and **6**) which has been favorably received by the market and consumer.

INSERT TABLE 2

INSERT FIGURES 3-6

Recently, many studies have been carried out to re-evaluate chemical composition of endemic species of oregano in different countries such as *O. compactum*, endemic of Maghreb, [66-68] *O. ehrenbergii* [69] and *O. libanoticum* [70,71] endemic of Lebanon, *O. acutidens* endemic of Turkey, [72] and *O. floribundum* endemic of Algeria. [73]

2.1.3 Rosemary

Among the five Lamiaceae subject of this review, rosemary is the one that has the least chemical variability in terms of the composition of essential oils as confirmed by the results of the bibliographic research of the last 10 years. A list of some of the most significant recent works is shown in **Table 3**, whereas **Figure 7** shows a Sicilian cultivation of this plant.

Probably the unique species of rosemary with a great economic interest is *R. officinalis* L. for its use as spice and for the biological properties of its extracts and essential oils with putative health benefits. [86] This is confirmed by the recent work of Borges et al., in which they reviewed studies of *R. officinalis* and its essential oil, giving prominence to its ethnopharmacological importance, phytochemistry, and main biological activities underlying mechanisms of action of its major molecules. [87] Other relevant and recent investigations confirm that EO composition of *R. officinalis* is characterized by the presence of 1,8-cineole, camphor and α-pinene as main compounds although with some differences in terms of relative percentages of each. For the other species of rosemary, the analyses of the essential oils of stems, leaves and flowers of *R. eriocalix*, showed that camphor is the main component in all three parts of the plant examined. [88]

INSERT TABLE 3

FIGURE 7

2.1.4 Sage

Sage is one of the largest genera of the Lamiaceae family. Some species such as *S. officinalis*, *S. sclarea*, *S. lavandulifolia*, *S. miltiorrhiza* and *S. hispanica* are more important under a commercial point of view for their use as food/spices and because of the interest in their essential oils. Through the study of the existing literature, [101] sage shows a high chemical diversity in its secondary metabolites. This diversity and richness has allowed this plant to remain until today one of the most studied plants in search of new bioactive metabolites or to confirm with more current scientific data the evidence of traditional therapeutic use. As for the other medicinal plants, the quantitative yield and the quality of the essential oil, also in the case of sage, is strongly conditioned by the species, the geographical area of origin, the time of harvest and the agronomic techniques used for the its cultivation. A non-exhaustive list of sage species studied in the last 5 years is shown in **Table 4**. From the data examined the confirmation of the thujone/camphor chemotype is obtained for *S. officinalis* from different geographical origin. [102-104]

Some species show high values of caryophyllene and caryophyllene oxide such as *S. hispanica,* [105] Turkish *S. trichoclada* and *S. multicaulis,* [106] *S. montbretii,* [107] Iranian *S. virgate*, *S. reuteriana* and *S. multicaulis*, [108] Iranian *S. nemorosa* [109] and Turkish cultivated *S. forskahlei.* [110] A lot of species have 1,8-cineole as main component such as *S. lavandulifolia, S. buchananii, S. bucharica, S. palaestina, S. ringens* and *S. veneris* from Italy. [111-117] **Figure 7** shows a cultivation of sage in Sicily, and a particular of its inflorescence.

INSERT TABLE 4

2.1.5 Thyme

Thymus is probably the most taxonomically complex genus of the Lamiaceae family. For this reason giving a succinct account of endemisms and chemical variability of its essential oils is particularly difficult. Recently, Salehi et al., [141] provided an overview of the phytochemistry of the EOs of this genus from different locations worldwide confirming the presence of a significant intraspecific chemical diversity in which the two most common chemotypes, thymol and carvacrol, are preponderant. Similar results have been presented within the work of Tohidi et al., [142] in which main *Thymus* species from the Iranian region were studied. Trindade and collaborators [143] addressed the study of terpene synthase genes in the genus *Thymus* by correlating these data to the observed chemotypes, stressing the importance of integrating molecular and biochemical data on chemotype determination. Experimental study of wild samples of *T. capitatus* was made by Napoli et al. and Saija et al., [144,145] giving a broad picture of the chemical composition of thyme populations in Sicily (South Italy) with a predominance of the carvacrol chemotype, as per as Tunisian [146] and Spanish. [147] EOs from Spanish *T. caespititius*, *T. zygis, T. mastichina* and *T. capitatus* flowers and fruits were evaluated by Delgado et al., [148] not showing significant compositional differences between the two parts of the plant. Other examples of studies recently published on *Thymus* endemisms are listed in **Table 5**.

INSERT TABLE 5

2.2 Crops management and agronomic techniques

In recent years, much attention has been paid on the effects that some cultivation techniques may have on the growth of officinal plants and on the quality of their essential oils. Many studies are focused on the growth of these plants in conditions of water and salt stress in order to enhance areas with unfavorable pedoclimatic conditions. Nowadays due the increasing of world demand of high quality essential oil the optimization of the harvesting period is becoming crucial to obtain better yields and better products. New data have been released on the effects of phenological stages or harvesting time on the quality of the essential oils. Collection of *O. vulgare* at pre-flowering time seems to increase the essential oil percentages, [153] while the flowering stage seems to be the best period to increase some biological activities of *O. compactum.* [154] A study conducted on *O. majorana* shows that the harvest time can influence the chemical composition of the essential oil. In fact, the harvest of the herb at full flowering stage allows obtaining an oil containing more *cis*-sabinene hydrate and sabinene than that obtained from the second harvest done at a later time. [155] Moreover, the essential oil of *Origanum vulgare* ssp *glandulosum* from North Africa showed a characteristic and different chemical profile from year to another. [156] Also quantity and quality of *L. angustifolia* EO is positively regulated by temperature and flowering stage development while it was negatively affected by rainfall during flowering period because the remarkable decline of linalool production. [157] Recent studies show that early-summer or summer is the best harvest period for *S. fruticosa* [158] and *S. officinalis,* [159] for which flowering period as best phenological phase is confirmed, [160] as per as for *S. verbenaca*. [161] The seasonal variation showed significant effects in the composition of the essential oils of *R. officinalis* with a greater amount of the oil and the main components in the summer. [162] Very interesting is a recent work evaluating the effect of diurnal variations on chemical composition and biological activities of *S. officinalis* EOs. [163] What is interesting in the discussion on the correct interpretation and assignment of chemotypes is that the results of this study indicate that the EO of plants harvested at 7 am and 12 pm were of α-thujone chemotype while those collected at 5 pm were of camphor chemotype with an important impact on biological activities. The effect of low-light conditions on *S. officinalis* growing in a greenhouse over the winter was studied by Mapes and Xu. [164] Authors concluded that with reduced light intensity, plant height increased whereas leaf size and number decreased. Similar results was obtained for *O. vulgare.* [165] However, growing herbs in northern climates could be a challenge to consider as a new opportunity for our 'old guys'. And in this perspective fits the promising study by Shiwakoti et al., [166] who have grown thyme, oregano and rosemary using plastic tunnels. The ornamental potential and freezing tolerance of six *Thymus* species was studied by Lajayer and collaborators [167] in order to use thyme as ground-covering plants in landscaping, with the results that all the examined species showed valuable ornamental characteristics and freezing stress tolerance.

As already said EOs yields are influenced by various factors, so it is important to keep finding new growing procedures that increase the quantitative content of EOs. The nutrient level in the soil is one of the most investigated aspects of research into aromatic plants with contrasting results, especially when the goal of their cultivation is different from herbage yield. [168] The foliar application of nutrients and abiotic elicitors seems to be a promising technique. Foliar application of 1.5 mg/L of 24-epibrassinolide (a brassinosteroid analogue) on a 8 years old plants of *Lavandula x intermedia* var. Super increase the EO yields from 6.2% to 8.7% (v/w) and also the percentage of linalyl acetate from 27.3% to 30.5% . [169] Negative impact on the quantity and quality of the *O. majorana* EO has been expressed by the application of hydroalcoholic extract of *Zingiber officinale,* [170] while a considerable increment of EO quantity and thymol stabilization of percentage range within analyzed population of *T. vulgaris* was obtained by Pavela et al., [171] with the foliar application of mixed N, P, K and salicylic acid. Again, a recent study on *T. vulgaris* showed that treatment with abiotic elicitors lead to differential up-regulation of genes involved in thymol/carvacrol biosynthesis with the probable consequent increment of the corresponding metabolites. [172] Rosemary tolerance to the salinity stress after foliar treatments with zinc-oxide in common and nano-form was studied by Mehrabani et al.: [173] it seems that zinc foliar spray improved flavonoids, total soluble solids and essential oil contents. Salinity as abiotic stress is a permanent major threat to the agriculture industry worldwide and usually associated with reduced growth and productivity of cultivations. Several approaches had been adopted to control salinity adverse effects on plants and one of the more interesting is the use of salicylic acid. The effects of the use of salicylic acid on *R. officinalis* were studied by El-Esawi and collaborators. [174] Salinity stress caused the reductions in α-pinene, β-pinene, and cineole along with increases in linalool, camphor, borneol, and verbenone. However, salicylic acid applications at 100–300 ppm largely reversed such effects of salinity. Another recent work shows the relationship between EO yields of *R. officinalis* and salinity conditions either alone or in presence of plant growth-promoting rhizobacteria (PGPR). [175] EO yield increases with increasing salinity levels up to 10 g/L NaCl, but decreased with further increases in salinity levels in treatments without using PGPR and being constant in treatment with PGPR. Moderate NaCl salinity was shown to improve the yields of volatile compounds and to modify the relative percentages of main compounds in *S. mirzayanii* and in this process cineole synthase gene is deeply involved. [176,177] *L. angustifolia* grown hydroponically and subjected to salt stress have been studied by Chrysargyris et al., [178] finding that high salinity decreased essential oil yield, while low-moderate salinity levels maintained the volatile oil profile in lavender. The integrated foliar application of K and Zn lighten the presumable detrimental effects of salinity in terms of fresh biomass, antioxidant capacity, and EO yield. Also Mehrabani et al. reached similar conclusions on *L. stoechas*. [179] Additionally increasing salinity of the applied water caused significant decreases in total fresh, total dry and dry leaf yield, total essential oil yield and antioxidant activity values of oregano (*O. onites*). [180]

Sustainable water management has become a global emergency and studies have also multiplied on the cultivation of medicinal plants in conditions of water stress or drought. Oregano can be significantly affected by water stress conditions in terms of herbal yield, essential oil content and composition. *O. vulgare* ssp. *gracile* seems to suffer less than *O. vulgare* ssp. *virens* in terms of EO composition, [181] while the beneficial effects of sprayed chitosan on *T. daenensis* [182] and on the expression increments of stress-related genes in *O. majorana* was demonstrated. [183] Anyway drought stress triggered different responses in the Lamiaceae species as demonstrated by García-Caparrós et al. in their study on six different species. [184] Authors recommend the cultivation of *S. lavandulifolia*, *T. capitatus*, and *T. mastichina* because there are no differences in essential content but if there is a water-saving rate of 30%, while the essential oil content decreased in *L. latifolia* and *S. sclarea* plants under water deficit conditions. EO content and quality of *L. angustifolia* and *S. fruticosa* seemed to increase under water stress conditions in a study of Chrysargyris et al. [185] This behavior is confirmed also for *S. dolomitica* [186], *S. officinalis* [187] and *S. sinaloensis* [188] and some Greek Oregano populations. [189] Foliar application of salicylic acid under water stress conditions increase EO content on *T. kotschyanus*. [190] The importance of water management on this type of cultivations is confirmed by numerous studies on combined variables such as drought/manure or nitrogen application, [191] water stress/arbuscular mycorrhizal fungi, [192,193] water stress/different soil fertility systems, [194] irrigation frequency/manure, [195] irrigation frequency /chitosan application, [196] irrigation frequency/mineral fertilization. [197] An interesting study on the effect of irrigation with secondary-treated effluent, as compared with potable water irrigation, on the composition, biological activities and yield of EO from *O. syriacum* L. var. *syriacum* was conducted by Ali-Shtayeh et al. [198] and their data demonstrate that this kind of water can be successfully utilized for irrigation for essential oil production from *O. syriacum*.

In order to improve plant productivity performance the mycorrhizal inoculation is a promising technology in sustainable agricultural system already investigated also in aromatic herbs and recently some interesting data were published on normal soils [199,200] and industrially polluted soil. [201] Heavy metal contaminated soils due to industrial activities are a major environmental problem that can reduce both the productivity of plants and the safety of plant products. Phytoremediation promoted by aromatic plants could be a promising method for removal of heavy metals from soil due their capability in terms of phytoextraction of metals with a negligible transfer of them to EOs. In this light is very interesting the work of Pistelli and collaborators [202] on some spontaneous species growing in an abandoned mining of Elba island and the work of Stancheva et al., [203] on *Origanum vulgare* L. grown on industrially polluted soil.

2.3 Herbicidal activity, phytotoxic potential and pest control

Interference of weeds with agricultural crops causes huge economic losses to farmers reducing crop quality and quantity, and increasing cost in terms of work and herbicides used to control them. Furthermore, the increasing resistance of weeds has resulted in a dramatic increase in the use of herbicides. Nowadays, the negative effects of synthetic herbicides to human health and environment is regarded as a real problem and trying to solve or mitigate it is a novel priority. Essential oils have been extensively studied in the past as valuable eco-friendly compounds with herbicidal activity and the interest is still high on the possible applications of them in the open field. Phytotoxic potential of *O. vulgare* ssp. *hyrtum* EO has been evaluated on plant model *Arabidopsis thaliana* through a physiological and metabolomic approach by Araniti et al., [204] with the evidence that EOs firstly caused growth reduction and leaf chlorosis, together with a series of interconnected metabolic alterations. Interesting is the work of Atak et al., [205] on the herbicidal effect of *O. onites* and *R. officinalis* EOs on germination and seedling growth of bread wheat and weeds (*Avena sterilis* and *Sinapis avensis*). Authors state that wheat cultivars were less affected compared to weed species suggesting proper dose of essential oils could be used as a bio herbicide for weeds control. These results could be useful for wheat breeders to improve varieties resistant to specific allelochemicals, which kill other weeds causing yield losses. EOs of commercial oregano, marjoram and *T. mastichina* have been compared for their phytotoxicity against *Portulaca oleacea* L., *Lolium multiflorum* Lam. and *Echinochloa crus-galli* (L.) Beauv. in the work of Ibanez and Blazquez. [206] Their results show that Oregano essential oil completely inhibited seed germination and seedling growth at all concentrations assayed, whereas marjoram and *T. mastichina* essential oils only showed significant effects in hypocotyl and/or hypocotyl + radicle length depending on the weed and dose. Among other EOs, *O. vulgare* L. was experimented for their herbicidal activity against *Sinapis avensis* weed at different concentration then compared with commercial herbicides. [207] Although the results are promising about the EOs use as alternative herbicides, the authors propose further studies are required to determine the cost, applicability, safety and phytotoxicity against the cultivated plants. *O. vulgare* EO shows a significant inhibitory effect on *Solidago canadensis* seeds germination in a study where other EOs are ineffectives and significant differences were noted by using different concentrations of single components. [208] EOs chemical composition is affected by plant phenological stages so their biological activity, including phytotoxicity, could be influenced by this factor as stated by Alipour & Saharkhiz in their study on *R. officinalis*. [209]

The encapsulation on a starch matrix of *R. officinalis* EO for phytotoxic purposes has been reported for the first time very recently by Alipour et al., [210] in a study on inhibition effects against *Amaranthus retroflexus* and *Rhaphanus sativus* under greenhouse conditions. A larger study involving 12 EOs *(L. angustifolia*, *S. officinalis* and *T. vulgaris* among the others) and their inhibitory effect on four weeds (*Amaranthus retroflexus*, *Avena fatua*, *Bromus secalinus, Centaurea cyanus*) and three crops (*Avena sativa*, *Brassica napus* and *Zea mays*) was conducted on 2017 [211] and it is worth mentioning that three tested crops were significantly more tolerant then the weeds tested. Synergistic allelopathic potential of *S. officinalis* and *T. vulgaris* EOs was studied by Alexa et al., [212] and the results indicated that the tested EOs alone as well as in combination have allelopathic effect against investigated seeds. Their results revealed significant differences in the inhibitory effect of the investigated EOs on germination capacity of wheat and tomato versus weed species.

The biological activity of essential oils on insects is one of the most studied aspects (**Table 6**). Not only was the toxicity of these substances investigated, but also their potential repellency activity due to volatility and their ability to behave as signal molecules. Despite the good results obtained in many *in vitro* studies, the use of essential oils on a large scale and in the open field for the control of pests has not yet wide diffusion. This is mainly due to outdoor persistence problems and to the difficult dissolution in water with the need to use surfactants to facilitate and homogenize the distribution over large areas. Moreover, much published literature demonstrates a not high selectivity of the insecticidal or repellent action and is often lacking in data on non-target insects and more generally on their impact on the ecosystem.

INSERT TABLE 6.

These findings could improve the industrial formulation (also again with the aid of nano-tecniques) in order to overcome the obstacles that have slowed down the use of essential oils in this field.

2.4 Diet supplement for animals feeding and application for animal health

The use of EOs as diet supplements for farm animals is an interesting application of these phytocomplexes. The aim is to exploit mainly their antimicrobial potential and their interaction with some physiological parameters to improve growth performances, meat quality and animal wellness under stress conditions such as transportation and heat-stress. Another emergent aspect is the potential role of these natural compounds on ruminant fermentation due the increasing concern over their methane emissions and their consequent contribution to global warming. The latest estimates calculate the contribution of ruminants equal to 16-25% to the total greenhouse gases emissions and EOs are recognised as safe a rumen modifier feed additives. [237] Three works of Cobellis and collaborators [238-240] draw a very clear picture of the advantages and disadvantages of using secondary metabolites such as rumen modulators evaluating scientific production in recent years including essential oils. Authors concluded that if on one hand EOs may be promising natural substances to mitigate rumen methane production, improve rumen fermentations, and reduce environmental impact of ruminant production from the other side further research will be required to determine their active compounds/effective doses/mode of action, effect on organoleptic characteristics of animal products in order to evaluate a clear cost–benefit ratio prior to use them as additives at farm level. In addition, a study on *T. vulgaris* and other EOs by Gunal et al. [241] comes to similar conclusions stating that the addition of thyme EO at the high doses resulted in lower methane production but it had negatively affected rumen microbial fermentation. Ruminants are not the only animal category under experimentation in the last years with EOs as food supplement as showed in **Table 7**.

For example a lot of studies were focused on broiler chicken. *L. angustifolia* EO at the dose of 0.4 mL in 1L of drinking water significantly affected some production results as body weight, feed and water conversion ratios. [242] While a supplementation of Oregano EO at the dose of 25 mg/kg to a normal diet promote a better average body weight, feed conversion ratio decreasing mortality. [243] In the same study the composition of the microflora was determined at the day of slaughter. For the oregano supplemented groups significantly higher values of lactic acid and bifidobacteria in ileum and caecum were noted, while, in caecum, reduced counts of coliform bacteria ($P<0.05$) were also recorded compared to control group. A concern about the use of aromatic plants and EOs as food additive in milk-producing farm animals is that their flavors and aromas may make their way into the milk, altering its sensory properties. Two levels of essential oils of caraway and oregano (0.2 and 1.0 g of oil/kg of dry matter) were added to the feed of lactating cows for 24 d in a study of 2016. [244] With this treatment the amount and composition of volatile terpenes were altered in the produced milk, and the sensory properties of the produced milk were altered as well, and milk samples from animals receiving essential oil treatment were perceived as having a fresher aroma and lower stored aroma and flavor. Interesting are the studies on the effects of EOs dietary supplementation on animals under stress conditions. Heat stress, for example, causes dire economic losses in poultry. The *O. syriacum* EO showed some protective effects against heat stress in broilers, [245] while dietary supplementation with *O. vulgare* EO may be superior in alleviating the negative effects of transportation on pigs by improving the pigs' antioxidant status in a comparison study with dietary supplementation of vitamin E. [246] The administration of EO in the diet is becoming an interesting tool also in aquaculture, with the aim of exploiting above all the antimicrobial activity of these phytocomplexes. *O. majorana* EO and its nanocapsules were evaluated recently for their antibacterial activity in silver catfish, *Rhamdia quelen*, infected with *Aeromonas hydrophila*. [247] All treatments improved the survival of infected fish, but authors suggest daily baths containing 20 µL/L EO or 5 µL/L nanoencapsulated EO for five consecutive days because these are the lowest effective concentrations tested which did not interfere with the metabolic parameters of the animals. The *in-vitro* antimicrobial potency against *Aeromonas hydrophila* and other two bacterial fish pathogens *Streptococcus iniae* and *Photobacterium damselae* subspecies *damselae* of four EOs (*Origanum vulgare*, *Eucalyptus globulus*, *Melaleuca alternifolia* and *Lavandula angustifolia*) was evaluated by Gholipourkanani et al. [248] All treatments showed antibacterial activity, and in almost all cases the activity of the nano-emulsions was superior to their essential oil counterparts. Origanum essential oil had a pronounced influence on the innate immunity and increased the *Tilapia zillii* resistance to *Vibrio anguillarum* [249] and dietary supplementation with 0.02% oregano essential oil is a practical prevention strategy for *Ichthyobodo salmonis* and *Trichodina truttae* infection in *Oncorhynchus keta*. [250] Finally, a relevant and promising study on the efficacy of several EOs against *Pseudomonas* spp. isolated from fish was conducted by Kacániová et al., [251] suggesting that the EO may be used as natural compounds with antipseudomonal activity to improve the microbiological quality of freshly caught freshwater fish.

A new vapour phase assay for evaluating the antimicrobial activities of EOs against bovine respiratory pathogens (BRPs) was proposed by Amat and collaborators [252] which have highlighted for *T. zigys* (among the others) vapour phase antimicrobial activity against *M. haemolytica* S1, *H. somni* and *P. multocida*. On the basis of these first results authors declare that future studies are needed to determine whether the application of these EOs as a nasal spray can mitigate BRPs, as alternatives to antibiotics. Antimicrobial activity of *L. berlandieri* and *T. vulgaris* EOs in gaseous phase was studied also by Reyes-Jurado and collaborators [253] with promising results suggesting a potential use also to protect packed food against the growth of microorganisms.

De Aguiar and collaborators [254,255] recently published two works on the antimicrobial potency of several essential oils against one of the major swine pathogens *Streptococcus suis*. In the first study eight EOs were tested against 19 *S. suis* strains isolated from diseased and healthy carrier pigs concluding that the essential oils of oregano, red thyme and common thyme showed a notable *in vitro* bactericidal activity, by vapor and/or direct contact. In the second study, authors changed the approach evaluating the combined interaction of four essential oils or their main components with conventional antimicrobials against 53 resistant *S. suis* strains. The positive interaction observed in their study between conventional antimicrobials and essential oils suggest that combination therapy is a promising alternative for the control of diseases caused by *S. suis* in pig farms. Mastitis is a mammary inflammation and is one of the most economically impacting health events in the dairy cattle industry with high losses due to veterinary and treatment costs and reduced milk production. [256] As alternative to conventional antibiotics, EOs have been evaluated also against mastitis pathogenic agents such as bacteria, fungi and microalgae. EOs from *O. floribundum*, *R. officinalis* and *T. ciliatus* were tested *in-vitro* against *Candida albicans* isolated from bovine clinical mastitis [257] and all essential oils revealed highly effective anticandidal activity. Several essential oils (*Thymus vulgaris* L., *Origanum vulgare* L. and *Origanum majorana* L. among others) were tested also against ten *Prototheca zopfi*i strains that cause inflammation of the mastitis in cows [258]. Results show that the studied essential oils can effectively reduce the growth of *P. zopfii* strains (MIC between 0.25-1.0 µl/ml), including those resistant to antifungal chemotherapeutics used in the treatment of protothecosis. The antimicrobial activity of *L. stoechas* subsp. *luisier*i, *R officinalis* and *T. mastichina* EOs among others was investigated towards *Staphylococcus aureus* and *Staphylococcus epidermidis* isolates from ovine mastitic milk origin. [259] Results of disk diffusion assay revealed that *L. luisieri* and *T. mastichina* EOs are highly active against both *S. aureus* and *S. epidermidis* strains, whereas *R. officinalis* EO is highly active against *S. aureus* strains but inactive against several *S. epidermidis* isolates. Finally the effects of intramammary infusion of sage (*Salvia officinalis*) essential oil on milk somatic cell count, milk composition parameters and selected hematology and serum biochemical parameters in 20 ewes affected with subclinical mastitis were studied by Alekish and collaborators. [260] In this study, the intramammary infusion of sage EO to ewes affected with subclinical mastitis resulted in a significant decrease in milk somatic cells count 24 h and 48 h post treatment. Furthermore, milk fat and lactose were increased in animals that received the EO as well as in those treated with the amoxicillin as reference antibiotic.

INSERT TABLE 7

2.5 Antimicrobial activity

The antimicrobial activity of essential oils is one of the oldest among those attributed to these phytocomplexes and consequently the most studied. It is therefore difficult to extrapolate from such a diverse context, which are actually the most current trends and the most promising prospects. In this section, we will therefore try to give an account of some of the most interesting studies of the last few years, trying to draw at the end of the considerations on the road we are taking. Since the crisis of antibiotics emerged as a global emergency, mainly due to the emergence of bacterial multiresistance, essential oils have represented more than just hope as broad-spectrum antimicrobial agents.

The chemical diversity, the undeniable efficacy *in vitro* and the ability to perform antimicrobial activity not thanks to the presence of only one active ingredient, but to the synergy of several structurally very different molecules have left hope for many years to find the right way to fight less serious infections with natural, less toxic and even inexpensive substances such as EOs. But this hope had to come up against the hydrophobia, the aforementioned chemical variability that limits its standardization, the extreme volatility of these phytocomplexes, the lack of information on mechanism of action, factors that have turned out to be obstacles that have not yet been overcome and that turn into a lack of *in vivo* and clinical data on their effectiveness. Nevertheless, the research continues to produce interesting studies especially with regard to multi-resistant strains and the use of nanotechnologies gives a glimpse of a new era for essential oils in microbiology with an inevitable impact on human and animal health and on other fields of application such as the food industry. All our five Lamiaceae species are largely studied for the antimicrobial activity of their EOs. *In vitro* antibacterial activity of essential oils from *O. vulgare*, *T. vulgaris*, *and L. angustifolia*, against 32 erythromycin-resistant and cell-invasive streptococci isolated from children with pharyngotonsillitis was studied by Magi et al. [279] Thyme and Origanum essential oils demonstrated the highest antimicrobial activity with minimal inhibitory concentration (MIC) ranging from 256 to 512 μg/mL. A synergistic action of the EO main compound carvacrol and erythromycin was detected in 17/23 strains using 24-h time-kill curves. Antimicrobial activity against multiresistant clinical isolates of 11 pathogenic bacteria of a carvacrol chemotype of *Lavandula coronopifolia* was assessed. [280] In a recent study Thyme EO is able to reduce of 59.7-85.0% biofilm biomass formed by methicillin resistant *Staphylococcus aureus* (MRSA) strains, [281] while *L. multifida* L. EO showed anti-MRSA activity since the inhibition diameters reached 27 mm and MICs were lower than 0.1 µg/mL in a study against 14 strains. [282] Sinergistic effects of sub-inhibitory concentrations of *S. officinalis* EO and different antibiotics against MRSA were also evaluated by Milenković et al. [283] Authors highlighted the presence of different interactions between tested oil and antibiotics from synergistic to antagoniistic on different clinical isolates of MRSA suggesting the necessity for systematic *in vitro* studies of interactions of EOs and antibiotics to reveal any undesirable combinations. The antimicrobial activity against multi-drug resistant *Escherichia coli* J53 R1 of *L. angustifolia* EO in combination with piperacillin was also evaluated. [284] Furthermore, their stability against sodium dodecyl sulphate, the scanning electron microscopy analysis and zeta potential measurement revealed that the EO played a role in disrupting the bacterial cell membrane while reduction in light production expression of *E. coli* showed the presence of potential quorum sensing (QS) inhibitors. The crucial role of the membrane disruption in the antimicrobial action of the EO is confirmed by other studies such as the one on *O. vulgare* in which the mode of action of the oil is investigated by using a simple approach which is the estimation of the total proteins in the culture media before and after the addition of increasing concentrations of EO. [285] The conclusion of this study state that oregano EO is effective against clinical pathogens as *E. coli* and *S. aureus* with a mode of action targeting the bacterial membrane permeability or integrity. However, bacteria resistant to chemical antibiotics seem to be capable of overcoming the action of EOs and this is a problem that needs further studies for its resolution.

Can EOs also have any intracellular mechanisms of antibacterial action? It seems so by evaluating results of a study on antimicrobial activity of *O. vulgare*, *T. vulgaris* and *Eugenia caryophyllata* EOs against *Burkholderia cepacia* a complex, opportunistic human pathogens highly resistant to antibiotics. [286] Evaluating the MIC of the EOs alone, with antibiotics or with efflux pump inhibitors, authors conclude that the antimicrobial activity of the six EOs versus *B. cenocepacia* strains might rely on the inactivation of different molecular targets located in the cell cytoplasm rather than at the cell membrane level, even though the latter possibility could be detected at higher concentrations. An intracellular mode of action is confirmed also in a study on the antimicrobial activity of *T. daenensis* and *O. vulgare* EOs against fluoroquinolone-resistant *Streptococcus pneumoniae* clinical isolates [287] in which the tested EOs have a total or partial synergistic effects with ciprofloxacin and ethidium bromide in all strains. Furthermore, MIC/2 concentration of *T. daenensis* and *O. vulgare* EOs caused a significant downregulation of efflux pump gene (pmrA) in seven of eight strains. A further confirmation of the potential plural mode of action of the EO come from a study on *S. sclarea* EO on seven pathogens bacterial strains: it seems that the antimicrobial way of action involves a series of events both on the cell surface and within the cytoplasm. [288] Many concerns are directed to bacterial species capable of forming biofilms, an aggravating factor for the difficult eradication of the bacterial colonization in surfaces (especially in the hospitals and food industries) and human organs (lung for example). Prevention of biofilm formation and anti pre-formed biofilm activity of oregano essential oils was evaluated mainly against *S. aureus* and *P. aeruginosa*, [289,290] with the result that the tested EOs are active in preventing biofilm formation and are effective agents to remove young and mature *S. aureus* biofilms on stainless steel surfaces. Both *O. vulgare* and *S. officinalis* EOs acts as a potent anti-biofilm agent with dual actions, preventing and eradicating the biofilm of *Streptococcus pyogenes* suggesting that these oils can be used in developing potential plant-derived antimicrobial agents in the management of streptococcal pharyngitis. [291] *T. vulgaris* EO is effective against planktonic of *Bacillus cereus* with a significant inhibitory effect on biofilm formation [292] and was found to have a high biofilm eradication ability, causing eradication that ranged from 80.1 to 98.0% at 10 µL/mL against pathogenic *Klebsiella pneumonia*. [293] *O. majorana* and *T. vulgaris* EOs were assessed for their antibiofilm activity against immature and mature biofilms of *E. coli* and *L. monocytogenes* formed on polypropylene surfaces, using the Response Surface Box-Behnken Design to optimize concentration of essential oils, disinfection time and level of pH in the EO-based disinfection solutions. [294] In this study the disinfectant effect of the EO-based natural solutions was in most cases equivalent or better compared to the peracetic acid-based chemical sanitizer used in food industry or to sodium hypochlorite.

The interest on antimicrobial activity of EOs is still high not only for humans/animals pathogens but also for plants pathogens. An *in-vitro* and *in-planta* pathogenic study has been conducted on *O. compactum* and *T. vulgaris* EOs against *Allorhizobium vitis*. The EOs show an interesting MIC, while the *in-planta* experiment conducted with a 1:1 mixture of the two oils at the MIC concentration inoculated into the injured stem of a tomato plant and a grapevine reduced both the number of plants developing gall symptoms and the size of the tumors. [295] *O. rotundifolium* EO was tested against 20 plant pathogenic strains showing a MIC in the range of 7.81 - 62.5 µL/mL. [296] *O. vulgare* and *T. vulgaris* EOs were tested against *Pseudomonas syringae* showing a MIC from 5.8 to 11.6 mg/mL and 1.43 to 11.5 mg/mL respectively with inhibition of biofilm formation in several strains. [297] Finally the potential use of essential oils in the field of the control of oral pathogenic bacteria as active principles of toothpastes and mouthwashes is still of interest. The essential oils of four *Thymus* species in vitro exhibited an antibacterial activity against *S. mutans* and the effects were also confirmed by an interesting in situ method. [298] A higher antibacterial activity was showed by herbal toothpastes after the addition of *O. dubium* EO against *S. mutans*. [299] A similar enhancement of activity against oral pathogens was observed after the addition of a mixture of EOs (*O. vulgare* L. ssp. *hirtum*, *L. nobilis* L., *R. officinalis* L., *S. fruticosa* Mill.) in a percentage between 4.5-9.0% on a mouthwash formulation. [300] As per as antibacterial activity of the EOs, their antifungal activity is largely studied still now. A lot of them are *in-vitro* studies with *Candida albicans* as target strain. *C. albicans* is an important opportunistic pathogen, responsible for the majority of yeast infections in humans. In a study of 2016, 12 EOs (oregano and rosemary among the others) were tested against 30 different vaginal isolated strains of *C. albicans* and the results compared with those of three main used drugs (clotrimazole, fluconazole and itraconazole). [301] Results show that oregano essential oils inhibited both the growth and the activity of *C. albicans* more efficiently than clotrimazole and damages induced by essential oils at the cellular level were stronger than those caused by the reference drug. *Lavandula binadulensis* EO alone or in combination with *Cuminum cyminum* EO shows an interesting antifungal activity against 20 clinical isolates from patients with recurrent vulvovaginal candidiasis, [302] while in another study *L. angustifolia* EO show a similar behavior against 80 clinical isolates with an additional antibiofilm activity against 1 of them. [303] In a huge work of Gucwa and collaborators several EOs including *T. vulgaris* were tested against 183 clinical isolates of *C. albicans* and 76 of *C. glabrata*. The authors also tried to evaluate the mode of action of the EOs concluding that three of the tested EOs (thyme, lemon, and clove) affected cell membranes and all of the tested oils demonstrated the ability to inhibit the transition of yeast to mycelium form. [304] An interesting study was recently conducted by mean of electron paramagnetic resonance (EPR) spectroscopy to evaluate the effect of clary sage oil and its main components, linalool and linalyl acetate, on the plasma membrane of *Candida albicans* [305] confirming that clary sage oil causes membrane perturbations which leads to cell apoptosis process. Recently two studies have been published on the antifungal activity of oregano and thyme EOs [306] and their main compounds thymol and carvacrol [307] against *Cryptococcus neoformans* an emerging and recalcitrant systemic infection occurring in immunocompromised patients and are occasionally being a problem for immunocompetent patients. Their findings highlight the potential EOs effectiveness as natural and cost-effective adjuvants to counteract *Cryptococcus infections* and inhibition of *Cryptococcus* biofilms.

Use of EOs as natural and safer antifungal agents for fruits, [308,309] vegetables and mushrooms [310] also during their postharvest operations [311] it is a very current option and of great interest. According to the study of Bill and collaborators [312] thyme essential oil vapors reduced the anthracnose disease incidence by up-regulation of phenylalanine ammonia-lyase (PAL) gene expression and at the same time led to down-regulation of lipoxygenase (LOX) gene expression of two Avocado fruits variety prior to cold storage. Because all these components are involved in the response to fungal infection, the exposure to thyme oil vapors prior to cold storage is a promising alternative to the use of commercial fungicide. The inhibitory effect of vapor phase of eight EOs from lamiaceae species against seven strains of *Penicillium commune* isolated from moldy milk products was assessed by Tančinová and collaborators [313] founding that essential oils have different effects on individual strains of *P. commune*, and thyme was most effective among the tested essential oil. The potentiality of rosemary EO against two strains of *Fusarium graminearum* isolated from infected cereals was tested founding that the tested one, among others oils, reduce the rate of mycelial growth and showed fungistatic activity. [314] Finally, EOs can be used as alternative to chemical fungicides also in floriculture as showed in a study on the effectiveness of oregano and clove essential oils against *Podosphaera pannosa* and *Botrytis cinerea* affecting two cut rose cultivars in greenhouse. [315]

2.6 Uses of EOs in the food industries

The modern food industry is increasingly oriented towards the production of minimally processed and ready-to-eat products with a particular focus on practices that can guarantee extended refrigerated storage periods. In this logic the major problems are related to lipid oxidation (especially of polyunsaturated fatty acids) and microbial contamination especially for those highly perishable meat and fish products. Nowadays synthetic food additives have been developed to carry out the antioxidant or antimicrobial action remaining safe for public health, cheap and with minimal impact on the sensory qualities of food. Furthermore, improved modern packaging methods have been developed with the use of edible and active coatings or with the use of modified atmosphere packaging techniques. In this context, essential oils can play an important role thanks to their antioxidant [316] and antimicrobial properties, replacing all or part of the synthetic additives to limit both oxidative phenomena and microbial contamination, prolonging, in some cases, the shelf-life of the more perishable products. Up to now some limitations to the use of EOs with this purposes are emerged. First of all the interactions with other food ingredients, which can limit biological activity of the EO. Furthermore compared with synthetic antioxidants EOs are sometimes less effective and more expensive. [317] Finally, the EOs can negatively affect the sensory quality of food and for this reason many studies have been aimed at the possibility of resorting to nanoformulations capable of mitigating the organoleptic impact of EOs. Despite these limitations, studies on the application and effectiveness of EOs in the food industry are continuing and the most studied oils are those of oregano, rosemary and thyme. [318] The main methods through which the biological properties of EOs are transferred to food products are the addition to animal feed (which we have already discussed in paragraph 2.4), direct addition to the food product during production and incorporation into food edible films or coatings.

Oregano essential oil significantly reduced ($p< 0.05$) lipid and protein oxidation, and improved color stability of raw and cooked ground chicken breast meat, showing the strongest effect for all parameters at 400 ppm. [319] A similar study has been conducted with *O. syriacum* L. EO showing 150 ppm as effective dose to delay lipid and protein oxidation. [320] The effects of homogenization of oregano, sage and rosemary EOs with minced beef (2% w/w) with respect to lipid oxidation and color properties during refrigerated storage were evaluated by Unal et al. [321] Thyme and especially oregano EOs show capacity of suppress biogenic amines formation in refrigerated vacuum packed fillets of carp prolonging their shelf-life up to five times than suggested by the manufacturers. [322] In order to extend the shelf-life of food products, the microbial growth is another aspect that must be strongly taken into consideration. EOs are recently considered as powerful antimicrobial agent for food applications as evidenced by the many studies carried out in recent years on the use of oils directly applied on food, on their use as part of active packaging/coating and also in combination with modified atmosphere packaging techniques. The addition of oregano essential oil (0.4% v/w) increased lag phase and decreased growth rates of lactic acid bacteria natural microbiota under isothermal conditions extending shelf-life of vacuum-packed cooked sliced ham. [323] Rosemary EO showed interesting antibacterial activity in several food model experiments conducted on thermally processed chicken meat, [324] ready to eat vegetables [325] and fish. [326] Antimicrobial edible coatings or films acting as a protective barrier can be used to retard food spoilage, thus extending food shelf life. EOs can be active part of the coating as demonstrated by several studies conducted with alginate-based coating on fish or fruits [327,328] and on cooked beef with the confirmation of a high consumers' acceptability. Caseinate-based coating with rosemary oil (0.5%) together with gamma irradiation was evaluated on fish with the result of reduced counts of Enterobacteriaceae, *Staphylococcus aureus*, and *Bacillus cereus*, *Vibrio* spp. and *Salmonella* spp with no adverse effects on the sensory properties. [329] Another way to maintain food quality, freshness and safety of minimally processed food or ready-to-eat fresh food is the use of active packaging. These materials can be made by using polymers with antimicrobial activity themselves or by means direct incorporation of the antimicrobial active ingredients into the polymer. EOs have demonstrated the ability to be incorporated into these materials, becoming useful tools for reducing microbial counts and increasing the shelf-life of food products. Several studies have been conducted in this field sometimes taking into account also the final acceptance of consumers, which remains a fundamental variable for the large-scale application of these materials. Incorporation of oregano EO into polypropylene film gave a material with similar thermal and mechanical properties of polypropylene with a higher antimicrobial activity in a food model of ready-to-eat salad but with 'negative impact on counsumers' purchase intentions. [330] Rosemary oil was incorporated on a packaging film of bilayer structure based on low-density polyethylene for maintaining the freshness and extending the shelf life of packaged shrimps up to 4 days. [331] A polyvinyl alcohol film containing oregano essential oil as an active packaging application for fresh tomatoes without significant changes in the hardness, weight, and color of the product during storage was developed. [332] In addition, biodegradable packaging materials with different percentages of *Origanum* EOs content, which show antimicrobial activity maintaining their biodegradability, can be developed as demonstrated by Ketkaew and collaborators. [333]

EOs can be used in the food industry also in synergy with irradiation and as reinforcement of modified atmosphere packaging techniques. The direct effect of gamma irradiation on EOs is up to now subject of discussion and some data on the impact of this practice on chemical composition and organoleptic descriptors was already published [334,335] and it seems that the irradiation-induced changes in the quality depend on atmosphere during the treatment. However, the combination of irradiation and coating containing EOs is an effective strategy to reduce microbial count in food with minimal impact on sensory properties which is worth investigating in the coming years.

The use of EOs as antimicrobial reinforcement of modified atmosphere techniques is an innovative approach to manage microbial contamination of food. Exploiting the synergy between the antimicrobial activity of the essential oil in a packaging atmosphere suitably modified to reduce microbial growth is an interesting approach because it is relatively simple but does not completely resolve the limits already highlighted for the previous methodologies. The modified atmosphere packaging with EOs system could be efficiently used to control the growth of the pathogen when strict temperature control is difficult during the whole shelf life of the product as demonstrated by Mahgoub and collaborators on a ready-to eat product inoculated with *Lysteria monocytogenes*. [336] Boskovic and collaborators [337] with the limitation of the negative effect on sensory properties of the treated food successfully reported the synergistic effect of modified atmosphere and thyme EO against four serovars of *Salmonella* inoculated in minced pork meat. In fact, despite an optimal concentration of 0.9% of EO to obtain the higher antimicrobial activity in combination with the modified atmosphere conditions adopted in the study, only the 0.3 % of EO was considered acceptable by panelists.

2.7 EOs and human health

Since the dawn of modern medicine, essential oils have always been considered as phytocomplexes useful for improving the health of human beings and for maintaining or restoring a state of well-being. Over the centuries, it has gone from magic and superstition to a consolidated use in traditional and popular medicine up to the present day in which the greater awareness about the composition and biological properties of essential oils make them increasingly part of modern alternative and complementary medicine. Surely, this is due to their broad-spectrum antimicrobial activity that in a new era of bacterial antibiotic resistance to synthetic antibiotics puts them at the center of an intense scientific research in order to be able to use them alone or in combination with commercial drugs for a tighter fight to this new health emergency. But the interest in essential oils has also shifted over the years towards their potential use as antiviral and antitumoral agents, not forgetting the growing interest in their interaction with the central nervous system and more generally with the controversial aromatherapy. Unfortunately, this has led to the production of a disproportionate number of *in-vitro* studies that although confirm the potential applicability of these complexes in the human health field, have not translated into adequate *in-vivo* studies able to generate clinical data that confirm the efficacy and selectivity of these substances against human diseases. There are technological limits that have not yet been overcome, even if they have held back the development of these studies. First and foremost, the difficulty of conveying these substances of such a lipophilic nature in aqueous media, a problem that is being faced by resorting to nanoformulations as previously mentioned. However, the main constituents of these essential oils are terpenes and terpenoids, which are small, lipid soluble organic molecules that can be absorbed, through the skin, across nasal mucosa or after ingestion, into the systemic blood circulation producing a systemic effect. Many of them can also cross the blood-brain barrier.

Secondly, the chemical variability of these phytocomplexes that strongly depends on both anthropic and non-anthropic factors. The compositional variability of EOs that often makes it difficult to rationalize the biological activity and discourage from a deepening about their pharmaceutical development. So, the real challenge for these ‘old guys’ is to overcome the above mentioned limitations starting to keep what we have largely promised. All this being stated and considered below we will try to trace a brief state of the art and the most interesting perspectives on the use of essential oils for human health.

Literature data on *in-vitro* cytotoxic activity of EOs are huge and an exhaustive discussion is out of the objectives of this review. A selection of recent publications is summarized in **Table 8**.

What we find most interesting to point out is rather the most recent data on the mechanisms of cytotoxic action of essential oils. Up to now several different mechanisms were hypothesized for their cytotoxic effects. These include mainly the induction of cell death by apoptosis and/or necrosis and cell cycle arrest. Similarly, to what has been demonstrated regarding the mechanism of antimicrobial action of essential oils, the lipophilic nature and low molecular weight of many of their components allows the passage through the cell membrane. Once destabilized, it is no longer able to play its role as a barrier and some of the cytoplasmic content can come out. The physiological consequences of a profoundly altered cellular membrane are many and among these the reduced production of ATP, the alteration of the pH and the loss of the mitochondrial potential can be mentioned. [338] An *in-vitro* and *in-vivo* study on the effect of *L. angustifolia* EO on human prostate cancer cells PC-3 and DU145 demonstrated that this oil is effective in inhibiting tumor growth of human prostate cancer xenografts in nude mice. The use, during the study, of the two main components of the oil linalool and linalyl acetate allow to address the main contribution to the anticancer activity to the former one. [339] A less common EO of lavander (*L. dentata*) was assayed on lung cancer cells Calu-3 in an *in-vitro* model which include both liquid and vapor phases. The oil showed cytotoxic activity in the vapor phase acting by necrotic and apoptotic processes not involving inhibition of P-glycoprotein. [340]

Looking at published data several EOs show antiviral activity against many enveloped RNA and DNA viruses. Among our five EOs, thyme and oregano seems to have more consideration in this field. [341] Only few essential oils, e.g. oregano oil, were also tested against non-enveloped RNA and DNA viruses. [342] Oregano oil and one of its main active component, carvacrol, was assayed against the non envenloped murine norovirus (MNV), a human norovirus surrogate, demonstrating that carvacrol is effective in inactivating MNV within 1 h of exposure by acting directly on the viral capsid and subsequently the RNA. [343]

In a recent screening *in-vitro* study, majoram and clary sage EOs among others exhibited strong anti-influenza A/WS/33 virus activity. Due the relevant presence of linalool in their chemical composition, the antiviral activity appeared to be associated with this compound. [344]

Thymus vulgaris and *Rosmarinus officinalis* EOs were studied for the first time for its possible interference with the Tat/TAR-RNA interaction and with Tat-induced HIV-1 LTR transcription with the result that EOs interfered with Tat function, a feature that was never described before, [345] while *Salvia desoleana* EO and its less polar fraction were here shown to be active against herpes simplex virus HSV-2 inhibiting a step of its replicative cycle that occurs after virus attachment and entry. [346]

Among natural products, essential oils present promising results in the main mechanisms involved in the pathology of inflammation and recently de Lavor and collaborators [347] have published an excellent review of their potential use in this field. In their conclusion authors declare that the main action targets of the EOs for the therapy of chronic inflammations were the reduction in reactive oxygen and nitrogen species and the reduction in NF-κB (nuclear factor kappa-light-enhancer of activated B cells). The anti-inflammatory and immune-modulating activities of essential oils and their bioactive compounds was also linked to cytokine expression showing their potential therapeutic activity for the treatment of asthma. [348] Specifically, for our five essential oils, the antinflammatory activity has been recently reported for oregano essential oil on lipopolysaccharide (LPS)-treated murine macrophage cells. Oregano EO protects against the LPS-induced cell inflammatory response through the NADPH oxidase/ROS pathway. [349] Similarly the results of the anti-inflammatory tests on sage essential oils using murine macrophages indicate that these oils significantly ($p < 0.05$) reduced nitric oxide (NO), and NF-κB production in murine machophages cells. [350] The antinflammatory activity of rosemary EO is mainly attributed to its main compounds 1,8-cineole, α-pinene, and camphor. The anti-inflammatory properties traditionally ascribed to *Thymus carnosus* and *Thymus camphoratus* was recently demonstrated in a study showing inhibitory effects towards nitric oxide production and concomitantly inhibiting the expression of two crucial pro-inflammatory proteins, iNOS and COX-2 in lipopolysaccharide (LPS)-stimulated macrophages. [351] As per as the antinociceptive activity of *Thymus capitatus* essential oil, which acts via peripheral nervous excitability blockade. [352]

In the last few years, essential oil components have been evaluated for their mechanism of action and also to obtain leading compounds active in central nervous system (CNS). Linalool alone as well as the *L. angustifolia* essential oils affect, in a concentration-dependent manner, neural firing activity. [353] *L. angustifolia* EO exerts receptor binding affinities with a relevant activity on the N-methyl-D-aspartate receptor and inhibition of the serotonin transporter. [354] Inhalation and the external application of these oils for the treatment of mental and physical balance are the very basics of aromatherapy in which olfactory nerves from nose to the brain are the site of action for these essential oils. [355] The sense of smell plays an important role in the physiological effects of mood, stress, and working capacity. Electrophysiological studies have revealed that various fragrances affected spontaneous brain activities and cognitive functions. In addition, the electroencephalograph studies clearly revealed that fragrances significantly modulate the activities of different brain waves and are responsible for various states of the brain. [356] Aromatherapy massage with lavender oil increased the sleep quality and reduced the level of anxiety in patients with colorectal surgery in the preoperative period, [357] may reduce the incidence of activities of daily living disability in patients with osteoarthritis of the knee, [358] inhalation aromatherapy can decrease the level of fatigue in the patients undergoing hemodialysis [359] and reduced anxiety and pain suffered during gynecological examination. [360] Rosemary EO inhalation has therapeutic potential against stress-related psychiatric disorders [361] and may improve cognitive function in a model of Alzheimer's type dementia. [362]

INSERT TABLE 8

2.8 Cultural heritage preservation

Cultural heritage is daily attacked by biodeteriogens (fungi and bacteria) which can cause several damages to the materials. All types of materials are subject to biodeterioration from paper, stone materials to paintings. These deteriorations can be chromatic (browning, loss of color, alteration of color due to cellular exudates) or structural (leaching of salts due to rain for example). In some cases, such as molds in historic homes, they can also pose a danger to human health. The use of synthetic products with antifungal and antibacterial activity is today an established practice, but scientific research is increasingly interested in the evaluation and use in this field of natural substances that are effective, ecologically sustainable and safe for cultural heritage and for operators. Essential oils (and hydrolates) seem to have all the requirements to be used in this field. Their broad-spectrum of antimicrobial activity, their safety and their sustainability make them ideal candidates for the replacement of synthetic products in some bioremediation applications. The antifungal activity of *O. vulgare*, *R. officinalis* and *L. angustifolia* essential oils was investigated against fungi isolated from stone (*Bipolaris spicifera* and *Epicoccum nigrum*) and wooden substrata (*Aspergillus niger*, *Aspergillus ochraceus, Penicillium sp*. and *Trichoderma viride*) of cultural heritage objects. Antifungal potential of *O. vulgare* was higher or nearly the same as benzalkonium chloride. [376] Thyme EO was the most effective, among others, against 16 fungal species isolated from three tested archaeological objects (wall painting stone, wooden statue, and pottery coffin) from Saqqara in Egypt. [377] Antimicrobial activity of *T. vulgaris* and *O. vulgare* EOs, have been evaluated in-vitro, ex-situ and in-situ for their antimicrobial activity for the mosaic tesserae of "Casa di Leda" in the Greco - Roman site of Solunto in Sicily. [378] *T. pulegioides* among others EOs was evaluated as antifungal agent in water-damaged buildings of Vilnius Old City, [379] as per as *T. vulgaris* and *T. serpyllum* as antifungal against four mould types isolated from building surfaces. [380] Antifungal activity of *O. vulgare* essential oil as a was tested against fungi causing alterations on the frescoes and facade of the Holy Virgin Church of Gradac Monastery in Serbia highly colonised with cyanobacteria, algae, fungi, lichens, mosses and even higher plants in a long-term ecological succession. [381]

Oregano oil not only was effective against fungi but also prevented their sporulation of them showing in addition a stronger antibacterial activity in a study against 4 strains of fungi and 6 bacterial strains isolated from documents of museal archives. [382] *O. vulgare* L. and *T. vulgaris* L. had antifungal activity against *Scopulariopsis* sp. and *Fusarium* sp. isolated from documentary heritage. [383] The effectiveness of disinfection method with thyme essential oil microatmosphere was compared with silver nanoparticles misting (AgNPs), and low temperature plasma (LTP) by means of culture-dependent method and RNA analysis on paper from historical books with different levels of microbial contamination. [384] Finally, the combined use of gellan and hydrolates seems to be a very promising and eco-friendly system to clean paper artworks. [385]

2.9 Nanotechnologies at the service of essential oils

In the preceding paragraphs we have repeatedly referred to how the biological activities of essential oils suffer the negative effects of hydrophobia and the excessive volatility of these substances. These obstacles can be partly overcome by the use of nanotechnologies, a generic term that includes, in the case of essential oils, nanoemulsions and nanocapsules. These techniques allowing a greater and more uniform distribution of the essential oil in the aqueous medium creates the best conditions for the increase of the contact surface with the target substrates indispensable for the performance of the biological activity. Nano-encapsulations also have the ability to reduce the volatility of EOs by increasing their persistence and reducing their odor, which is an important factor for application in the food sector. Nanoemulsion of EOs is cheap, readily scalable and environment-friendly and comprises mainly three constituents oil phase, aqueous and a surfactant. The size of nanoemulsion droplets ranges from 10 to 100 nm. The surfactant chosen must be able to lower interfacial tension to a very small value to assist dispersion process during the preparation of the nanoemulsion. [386] Its concentration affect emulsions' separation, viscosity, electrical charge (Z-potential) of droplets, and droplet size of the dispersed phase. Several studies demonstrate that low temperatures and long times of homogenization produced systems with small droplet sizes, which promoted the stability of emulsions. [387] Recent comparative studies on antimicrobial efficacy against food-borne bacteria between sage EOs and their nanoformulation with nonionic surfactants demonstrate that the nanoemulsion was up to four-times higher than the bulk oil, more rapid in its action causing extensive bacterial cell membrane damage. [388,389] Droplet growth can be retarded by incorporating water-insoluble oils, known as ripening inhibitors, into the oil phase prior to nanoemulsion formation. The effect of some of these ripening inhibitors on antimicrobial activity of thyme oil nanoemulsion was evaluated by Ryu and collaborators [390] establishing the optimum amount of ripening inhibitor (around 40% of the oil phase) required to maintain antimicrobial activity.

As food consumers are highly interested in products containing more natural ingredients, also surfactant could be chosen among natural compounds as highlighted by Doost and collaborators. [391] In their study Quillaja Saponin was used as a natural surfactant and sucrose monopalmitate (SMP) and octyl modified starch (OMS) as non-petroleum-based ingredients to create a nanoemulsion with *O. compactum* EO. An emulsifier derived from wheat waste (alkyl polypentoside) was successfully used with rosemary EO obtaining monodispersed concentrated emulsions with high physical stability and nanometric sizes [392] and with thyme EO. [393] Whey protein isolate was used by Rashed et al., [394] as a natural-biodegradable polymer wall material to formulate and stabilize Oil-in-Water nanoemulsion of *L. angustifolia* EO with a higher thermal stability. Another example of the use of ecological friendly materials is the nanoencapsulation of oregano EO into ultrathin fibers derived from fruit waste using solution electrospinning in order to obtain films for food packaging with enhanced antimicrobial activity. [395]

The biological activities of EOs nanoemulsion could be further increased trough a co-formulation with synthetic active principles. This approach could be useful mainly in pharmaceutical fields in order to reduce the quantity of the active principle thanking a synergistic action with the EO reducing side-effects. [396] Mainly in the pharmaceutical field the complexation of EOs with cyclodextrins is another way of solving the problems by improving the solubility and stability in water and avoiding the degradation and volatilization of bioactive compounds in the EOs. An excellent review of the *in vitro* and preclinical studies of EOs complexed with different types of cyclodextrins was recently published by de Oliveira-Filho and collaborators. [397] They conclude that both *in vitro* studies and preclinical studies gave evidence that cyclodestrin complexation is able to improve the pharmacological activity of EOs in various animal models with improved efficacy, reducing therapeutic doses and side effects without showing toxicity. Lavander EO incapsulated in hydroxypropyl-beta-cyclodextrin increase its antimicrobial activity up-to three times. [398]

Biological activities of EOs (I.e. antifungal) could be significantly enhanced loading them in chitosan nanocapsules also with the aid of innovative approaches as electrospraying technique, [399] via ionic gelification reaction [400] or in chitosan nanofibers by means of coaxial electrospinning. [401] As per as loading EOs on nanocapsules with biologically active and recognized as safe for human health metal elements (such as copper). [402].

The delivery of EOs could be optimized also by their encapsulation on nanostructured lipid carriers prepared by phase inversion temperature and high pressure homogenization methods, [403] on liposomes prepared using the film hydration method [404] or on nanocochleates based on phosphatidylcholine, cholesterol and calcium ions [405] with interesting increase of their effectiveness and stability. Nanoarchaeosomes made of soybean phosphatidylcholine, polysorbate 80 and total polar archaeolipids extracted from archaebacterial *Halorubrum tebenquichense* and loaded with thyme EO were successfully tested for their anti MRSA biofilm activity opening new ways for the exploitation of these kind of nanovesicles loaded with EOs. [406]

Biodegradable packaging materials has been introduced as a promising solution for the problem of huge amounts of synthetic materials, which cause serious environmental problems. The incorporation of EOs within these materials is a new frontier on the field active packaging. Recently a lot of studies were published with poly (ε-caprolactone), [407] sodium alginate-montmorillonite, [408] soybean polysaccharides [409] and alginate/soy protein. [410]

The sol-gel method to prepare hybrid organic–inorganic silica materials able to encapsulate EOs with a better-controlled release seems to be a promising way for the design of innovative and cheap antibacterial materials. [411,412]

Can EOs based magnetic nanofluid be used in microwave assisted imaging of tissues? A promising study of Dzimitrowicz and collaborators [413] was conducted with *S. hispanica* EO as 'size-definer' for the synthesis of magnetic nanorods which might be used as a contrast agent for microwave-imaging of tissues. In the authors' opinion terpenes-like compounds were likely involved in the green synthesis and surface functionalization of the magnetite nanorods which were susceptible to microwave-excitation.

An innovative approach to exploit the antimicrobial activity of nanoformulated EOs could be the synthesis of antimicrobial textiles able to resist the growth of microorganisms and pathogens causing bad odours and hygienic problems. Thyme essential oil in the presence of second generation of polypropylene Imine dendrimer as a control release agent was investigated. [414] The odour release was measured by electronic nose and the antibacterial activity of the resulting materials was evaluated with encouraging results opening the door to a new generation of composite textile materials.

3. Extracts from selected Lamiaceae herbs: biological activities discovered/assessed during years 2015-2019

Even if not as popular as essential oils, extracts from Lamiaceae herbs (mainly polar, obtained by maceration in alcoholic or hydro-alcoholic mixtures) have always raised interest at some extent, and recent literature confirms this trend. In this paragraph a small survey of the biological activities ascribable to lavender, oregano, rosemary, sage and thyme will be given, as examples from a simple research on one of the most used scientific databases (Scopus).

3.1 Lavender

Lavender (*Lavandula* spp.) aerial parts, either in the form of mostly essential oil or different forms of extracts have been traditionally used as therapeutics since ancient times. Nevertheless, data showing that the effects of lavender polar extracts are limited. In a study conducted over 10 years, Soheili and Salami [415] demonstrated that the aqueous extract of lavender improves the impaired learning and memory, positively affect the synaptic transmission in an animal model of Alzheimer's disease (AD), clears the amyloid beta (Aβ) plaques from the hippocampus of these animals , and dose dependently inhibits the formation of Aβ aggregate, caffeic acid (**1**) and luteolin (**5**) were characacterized as components of the aqueous extract. Alexa and coworkers [416] investigated the *in vitro* antimicrobial effect against *Staphylococcus aureus* and the antiproliferative activity against two cancerous cell lines (A375 human melanoma and MDA-MB-231 breast carcinoma) of *Mentha piperita* L. and *Lavandula angustifolia* Mill. extracts prepared using “aromatic” water (obtained after hydrodistillation and separation of the corresponding essential oil) as extraction medium and apple vinegar to acidify the solution at pH 4. A mixture of hydroxycinnamic acids (HCAs) have been detected in both aromatic plants and in particular caffeic (**1**), *p*-coumaric (**2**), ferulic (**3**), and rosmarinic (**4**) acids. Unfortunately, the results obtained were only moderately positive. Regarding antioxidant activity, a lavender (*L. latifolia*) extract obtained by sequential cold maceration with dichloromethane, ethyl acetate and methanol was tested *in vitro* (DPPH, ABTS, FRAP, TPC assays) and *in vivo* (*Caenorhabditis elegans* model) together with extracts from *Melissa officinalis* and *Origanum vulgare* as potential antioxidants for functional food formulations, giving promising results. The novelty in this case is represented by the *in vivo* model used: the nematode *Caenorhabditis elegans*, which in contrast to cellular models allows to study whole organisms with many different organs and tissues and increases the chance of identifying synergistic and/or off-target effects. [417] As in the previous cases the main components were coumaric (**2**), ferulic (**3**) and rosmarinic (**4**) acids together with luteolin (**5**). Finally, methanolic extracts from several Portuguese lavenders (*Lavandula stoechas* ssp. *luisieri* and *L. pedunculata*) with well known antioxidant activity, being rich in polyphenols and in particular of flavonoids and rosmarinic acid (**4**), were selected for encapsulation in polymeric poly (lactic-co-glycolic) acid (PLGA) nanoparticles in order to improve their stability and provide a better efficiency for treatment of cutaneous diseases. The authors obtained promising results especially in term of low risks of toxicity of the produced nanoparticles. [418]

3.2 Oregano

The most recent findings on the biological activities ascribable to *O. vulgare* mainly deal with its anticancer, antibacterial and cytotoxic potential. As example Rubin and coworkers [419] analysed for the first time a crude extract of oregano in 2 tumour cell lines, SW13 and H295R cells, the only available for adrenocortical tumors, finding out that this extract showed promising effects. The anti-mycobacterial and anti-inflammatory activities of *Origanum vulgare* L. ssp. *hirtum* in innate immune cells were assessed by De Santis et al. [420] The authors run the experiments using eight different fractions of a hydroalcoholic extract (50% aqueous ethanol) from this plant; the results obtained showed that the capability to activate antimicrobial and anti-inflammatory response is shared by different fractions, suggesting that different molecules take part in the process and that oregano may be exploitable as phytocomplex for novel therapeutic approaches. Still on anti-myco-bacterial and anti-mycotoxin properties of oregano, Ponzilacqua and co-authors [421] evaluate the ability of an aqueous extract from this herb for its ability to degrade aflatoxin B1 *in vitro*, together with extracts from sweet passion fruit (*Passiflora alata*), araçá (*Psidium cattleianum*) and rosemary. A significant decrease in AFB1 levels was observed in the aqueous extracts of all plants, with rosemary extract having the highest percentage of AFB1 reduction, followed by oregano. With these data the authors demonstrated that these plant extracts are interesting alternatives for the control of aflatoxins in food. Finally, recent applications of oregano involve veterinary research, where extracts/infusions of this herb were used as food supplement in the diet of cows in the transition period [422] and to fight avian infectious bronchitis virus with very promising results *in vitro*. [423]

An exhaustive study of the chemical composition of a large sampling of Sicilian *O. vulgare* ssp. *hirtum* carried out some years ago allowed to establish the chemical composition of ethyl acetate and ethanol extracts: four flavanones [eriodictyol 7-*O* rutinoside (**6**), aromadendrin (**7**), eriodictyol (**8**) and naringenin (**9**)], seven flavones [luteolin (**5**), sorbifolin (**10**), cirsiliol (**11**), apigenin (**12**), cirsilineol (**13**), cirsimaritin (**14**) and xanthomycol (**15**)], and two organic acids [(caffeic (**1**) and rosmarinic (**4**)] have been detected and quantified. The antioxidant effectiveness of the extracts, obtained with different methods (ABTS, DPPH, FRAP, ORAC, β-carotene bleaching test to quote the most applied), was quite significant and of course associate with the polyphenols content previously described. [59]

O. vulgare is one of the main species of this genus and then the most studied, however, other minor species show interesting chemical composition associated with biological activities, for example a study of the chemical characterization and the evaluation of antimicrobial, enzyme inhibitory, and antioxidant activities of methanol and water extracts of Turkish *O. onites* has been recently reported. [424] In total 28 components belonging to polyphenols, flavonoids, terpenoids, organic acids and esters have been identified: 3-*O*-(4-coumaroyl)-quinic acid (**16**), acacetin (**17**), cirsimaritin (**14**), naringenin (**9**), tuberonic acid glucoside (**18**), ferulic acid (**3**), apigenin-7,4'-dimethyl ether (**19**), azelaic acid (**20**), baicalin (**21**), casticin (**22**), cirsiliol (**11**), dihydrorobinetin (**23**), gardenin B (**24**), genkwanin (**25**), isoferulic acid (**26**), kaempferol (**27**), nevadensin (**28**), oroxylin A 7-*O*-glucuronide (**29**), quercetin (**30**), rosmarinic acid methyl ester (**31**), sakuranetin (**32**) and salvigenin (**33**).

O. dictamus collected in Greece showed a simpler polyphenol profile, [425] with vicenin-2 (**34**), apigenin 7-*O*-glucuronide (**35**), luteolin (**5**), chlorogenic (**36**) and rosmarinic acids (**4**) among the main components.

3.3 Rosemary

Among the herbs belonging to the Lamiaceae family, rosemary (*Rosmarinus officinalis* L.) is by far the one to which the highest number of biological activities have been ascribed. In the latest five years, the *in-vivo* hepato- and hepato-renal protective effects of rosemary have been extensively studied; as example Hegazy and coworkers [426] investigated the preventive effect of the aqueous extract of this herb on the gentamicin-induced hepatotoxicity in rats with promising result connecting these activities with the presence in the extract of catechin (**37**), coumarin (**38**), cinnamic acid (**39**), rutin (**40**), sinapic acid (**41**) and oleuropein (**42**), whilst Mohamed et al. [427] studied the protection of rosemary ethanolic extract on lead acetate hepato- and nephro-toxicity in male albino rabbits. The authors found that pre-treatment with rosemary extract significantly suppressed levels of hepatic and renal damage products as well as lipid peroxidation.

Furthermore, the extract preserved blood cells and their structure and renal and hepatic architecture. An ethanolic extract from rosemary is also capable of attenuate pulmonary fibrosis induced by the use of the chemotherapeutic bleomycin, as reported by Hosseini et al. [428] in a recent review. Wen et al. [429] reported the synergic action of carnosic acid in combination with cisplatin in the treatment of mouse Lewis lung cancer. Carnosic acid, together with carnosol (**43**) and rosmanol (**44**), are diterpenoids belonging to the metabolic pool of rosemary, responsible for the majority of its biological activities. In a recent survey of Sicilian *R. officinalis* the ethyl acetate and ethanol extracts showed the presence of several polyphenols subdivided in organic acids: caffeic (**1**) and rosmarinic (**4**), flavonoids: luteolin (**5**), luteolin glucuronide (**45**), 6-hydroxy luteolin glucoside (**46**), scutellarin (**47**) and scutellarin 7-O-glucoside (**48**), cirsimaritin (**14**), genkwanin (**25**), salvigenin (**33**), and diterpenes: carnosol (**43**), carnosic acid (**49**) and methyl carnosoate (**50**). Rosmarinic and carnosic acids were largely the main components contributing to the antioxidant properties of the extracts. [95] Another compound with recognized biological activities is rosmarinic acid (**4**), which can be considered as a sort of "family marker" for Lamiaceae. Rahbardar and co-workers [430] investigated the anti-inflammatory effects of an ethanolic extract from *R. officinalis* and rosmarinic acid (**4**) in a rat model of sciatic nerve chronic constriction injury (CCI)-induced neuropathic pain to verify usage of rosemary in folk medicine. Their data supported the traditional use of this herb as an effective remedy for pain relief and inflammatory disorders, and also suggested that the ethanolic extract of *R. officinalis* and rosmarinic acid might be potential candidates in treating different neurological disorders associated with inflammation.

3.4 Sage

Salvia officinalis L. (common sage) is a very popular herb frequently used in many countries as spice and as a folk remedy. Nevertheless, the molecular mechanism beyond sage extracts' biological activity has not yet been fully understood. Horváthová and coworkers [431] investigated the antioxidant potential of sage in rat liver cells in search for evidences of a hepatoprotective potential of this herb. The authors found out that, after only two weeks of drinking extracts, not only the level of DNA damage induced by oxidants was decreased, but sage extract was able to start up the antioxidant protection expressed by increased content of glutathione. More recently, El Gabbas et al. [432] evaluated the anxiolytic and antidepressant-like effects of a methanolic extract from

Salvia officinalis; the same extract was also studied for its potential to enhance rat's memory using conditioned learning test. The administration of sage extract showed a significant anxiolytic effect in marble burying test. In the case of conditioned learning paradigm, memory enhancement was observed in sage treated group, which indicates a cognition improvement. These are to be ascribed to the phytochemicals characterized in the extract of *S. officinalis*, namely caffeic acid (**1**), *p*-coumaric acid (**2**), rutin (**40**), rosmarinic acid (**4**), quercetin (**30**), luteolin (**5**), apigenin (**12**), carnosol (**43**) and carnosic acid (**49**).

3.5 Thyme

The antibacterial potential of thyme is well recognized and documented; recently, Cheurfa and Allem [433] tested the aqueous and hydro-alcoholic extracts prepared from *Thymus vulgaris* and other vegetable matrices (*Aloysia triphylla*, *Pistacia lentiscus*, *Olea europaea* leaves and *Trigonella foenum-graecum* seeds) on a collection of pathogenic bacteria responsible for gastroenteritis, where some of them isolated from clinical samples (*Escherichia coli, Staphylococcus aureus, Citrobacter freundii, Pseudomonas aeruginosa, Proteus mirabilis, Proteus vulgaris* and *Salmonella typhimurium*), thus obtaining encouraging results against all the strains. The antidiabetic effect, measured as *in vitro* antiglycation activity (ability of the extracts to inhibit the methyl glyoxal mediated development of fluorescence of bovine serum albumin BSA) of a 80% acetone extract from *Thymus vulgaris* (thyme) was studied by Kazeem and others [434] obtaining excellent results as the extract of this herb had a high antiglycation effect with 50% inhibitory concentration (IC50) of 0.02 mg/mL. As already stated for essential oils (see previous paragraphs), the use of nano-constructs can modulate and even ameliorate the bioactivities of vegetable matrices; Proks and coworkers [435] conducted an experiment on 4 different cancer cell lines: non-melanoma skin cancer (A431 cell line), melanoma skin cancer (A375cell line), hormone dependent breast cancer (MCF-7 cell line), and non-hormone dependent breast cancer (MDA-MB-231 cell line). The authors compared anticancer activities of thyme aqueous extract alone and silver nanoparticles prepared with thyme aqueous extract. The extract tested at various concentrations (10-1000 mg/mL) exhibited a pronounced effect only on MCF-7 cells whilst the biosynthesized silver nanoparticles the effect can be noted even at 1 M, thus indicating a pronounced effect of silver nanoparticles, in a dose-dependent manner, on the viability of hormone dependent breast cancer cells. The composition of the tested *T. vulgaris* aqueous extracts revealed the presence of several polyphenols: *p*-hydroxybenzoic (**51**), caffeic (**1**) rosmarinic (**4**) acids, catechin (**37**), eriocitrin (**6**), luteolin 7-*O*-rutinoside (**52**), luteolin 7-*O*-glucuronide (**45**), luteolin (**5**), apigenin 7-*O*-glucoside (**53**), apigenin (**12**), quercetin (**30**) and phloridzin (**54**).

As regarding uncommon thyme varieties, Khouya and others [436] evaluated the anti-inflammatory, anticoagulant and antioxidant effects of aqueous extracts from *Thymus atlanticus*, *T. satureioides* and *T. zygis*. All varieties were found to possess considerable antioxidant activity and potent anti-inflammatory activity. Administration of aqueous extracts of two varieties (*T. zygis* and *T. atlanticus*) reduced significantly the carrageenan-induced paw edema similar to non-steroidal anti-inflammatory drug (indomethacin). In partial thromboplastin time and prothrombin time tests, *T. atlanticus* and *T. zygis* extracts showed the strongest anticoagulant activity, while *T. satureioides* did not show the anticoagulant activity in these tests. The observed activities of the aforesaid thyme species can be ascribed to the presence (in the aqueous extracts) of caffeic (**1**) and rosmarinic acids (**4**), quercetin (**30**), hesperitin (**55**) and luteolin-7-*O*-glycoside (**56**).

In south Italy and in particular in Sicily *Thymus capitatus* (syn. *Coridothymus capitatus* and *Thymbra capitata*) is the main wild species belonging to this genus. Also in this case the ethyl acetate and ethanol extracts of several samples collected in the Sicilian territory showed the presence of several polyphenols: caffeic (**1**) and rosmarinic (**4**) acids were the main organic acids, all others components were flavonoid derivatives: vicenin-2 (**34**), luteolin rutinoside (**53**), 6-hydroxy luteolin (**57**), 6-hydroxy luteolin glucoside (**46**), taxifolin di-*O*-glucoside (**58**), apigenin (**12**), apigenin 7-*O*-rutinoside (**59**), apigenin 7-*O*-glucuronide (**35**), gardenin B glucoside (**60**), eriodictyol (**8**), genkwanin (**25**), thymusin (**61**), naringenin (**9**), cirsilineol (**13**), and chrysoeriol (**62**). [145]

Figure 8 shows the molecular formulas of the currently known Lamiaceae components, whereas **Figure 9** reports some typical HPLC profiles of the extracts of some Lamiaceae

INSERT FIGURE 8

INSERT FIGURE 9

4. Extracts from *Lamiaceae* in the food preservation sector: food additives, edible coatings & films, active and intelligent packaging

4.1 Background

The quality and acceptability of food products is seriously limited by oxidation phenomena, usually initiated by free radicals; oxidation affects attributes such as taste, color, texture and nutritional value as oxidative chain reactions are associated with oxygen reaction with lipids, pigments, proteins and vitamins. [437] Synthetic and natural food additives with antioxidant properties have been developed to limit and control lipid oxidation and formation of the unpleasant byproducts in foods. In this context, spices and herbs have been always used in foods for their flavor; they have also been proven to contain high concentrations of components able to counteract oxidative reactions: phenolic compounds, carotenoids, and tocopherols just to cite a few. [438] As previously stated, nowadays EOs are widely used in the food industry for their ability to inhibit pathogen growth and retarding the food spoilage, thus improving food organoleptic quality. [439] Plant polyphenols can be definitely offered as alternatives to EOs; the plant extracts obtained from different sources such as fruits, vegetables, herbs, and spices have been in fact proven to possess strong antioxidant activity because of their high content of phenolic compounds. [440]

The extracts have been prepared from the plant materials by using different solvents and extraction methods, both conventional or green. [441] In order to decrease or inhibit oxidative reactions in foods, antioxidants are usually used at an average level. Higher concentration may cause various side effects through pro-oxidative action. [442]

4.2 Food additives

The simplest way to employ an antioxidant compound (synthetic or natural) in food to preserve its nutritional and quality features is to add it to the food matrix before storage. One class of additives that could be replaced with natural extracts (spices, fruits and vegetable residues) are the antioxidants used in meat products. These compounds increase the shelf life of foods to which they are added by inhibiting the oxidation of lipids, proteins and pigments, preserving attributes such as color, texture, aroma, taste and the overall quality of the product. [443] As regarding the object of this review, the herbs from the Lamiaceae family, numerous papers present in literature report the use of sage, rosemary and oregano in the quality preservation of meat, fish and bread. Examples include the use of a sage extract to reduce the lipid oxidation in pork preparations [444] and oregano extracts employed to inhibit the spoilage of tilapia meat; anyhow the most popular herb in the food preservation sector seems to be rosemary, which was successfully tested as additive in the extension of the shelf life of carp, [445] pork meat [446] and chicken, [447] or in combination with thyme to preserve the quality of the already mentioned Nile tilapia. [448] The antioxidant properties of these extracts are due to the presence of phenolic acids caffeic and rosmarinic (**4**) and phenolic diterpenes, such as carnosic acid and carnosol. [60,95] Another serious problem related with food shelf life and storage is the spoilage caused by bacteria, yeast and molds as in fruits, vegetables and bakery products, mainly bread. The most critical factors controlling the growth of fungi on foodstuffs are again oxygen, but also temperature, pH, and water activity. Mold spoilage is particularly dangerous for consumer health as fungi are also responsible for the generation of mycotoxins and off-flavors, which are usually produced before fungal growth is visible. [449] In order to counteract these kind of contaminants in foodstuff physical methods like ultraviolet light, infrared radiation, microwave heating or ultra-high pressure treatments have been developed; however, the consumer-preferred solution is to replace traditionally used chemical preservatives with environmental friendly, “green” alternatives such as natural extracts bearing antifungal activity for the so called “biopreservation”. [450] As example, methanolic extract from oregano was employed in shelf life prolongation of “Rocha” pears via reduction of mold spoilage. [451]. Finally, extract from oregano has been proven to act as antibacterial agent against *Listeria monocytogenes*, *Staphylococcus aureus*, and *Salmonella enterica* in cheese at room temperature; treatments with this extract also increased the stability of cheese against lipid peroxidation. [452]

4.3 Edible coatings and films

Rather than adding the additive directly to the food matrix, the use of edible coatings is one of the most important methods applied for preserving food quality. Edible films and coatings are promising systems to be used in the prolongation of food shelf life; as they can be consider both a packaging and a food component, they should have good sensory attributes, peculiar mechanical properties, biochemical, physicochemical, and microbial stability, safety, non-polluting nature, simple technology and low raw material and processing cost. These coatings are useful to improve food appearance and to delay transmission of moisture and oxygen (which cause oxidative degradation) but also of aroma and solutes during storage, thus enhancing product shelf life; furthermore, they can retard food spoilage and maintain food security by inhibiting the growth of microorganisms, usually due to the incorporation of antimicrobial compounds such as plant-derived matrices (single molecules, extracts or essential oils). The most famous edible coatings are made of proteins or polysaccharides, so they are considered environmentally friendly. In the "antimicrobial version", the phytochemicals are gradually released on the food surface over time, maintaining a proper concentration of active components during the storage thus allowing the use of smaller amounts of active compounds compared with direct application (see previous paragraph). The controlled release of phytochemicals into the food matrix to preserve *via* edible coating depends on several factors: interaction between the antimicrobial agent and the polymer, osmosis, and environmental conditions (temperature, humidity, pH). [453] As already stated aromatic herbs from Lamiaceae have been used for centuries to improve the sensory characteristics and to prolong the shelf life of food due to the antimicrobial and antioxidants properties of their essential oils and extracts. [454] Examples reported in literature on edible films incorporating antioxidant/antimicrobial extract from Lamiaceae herbs include edible cassava starch film containing rosemary extracts having antioxidant activity, [455] rosemary and oregano extracts-enriched gelatin films, [456,457] again rosemary as additive in chitosan -based edible biopolymers for the preservation of beef burgers [458] and the reduction of lipid oxidation and microbial spoilage in fish. [459] Finally, rosemary in association with olive oleoresin in chitosan edible polymers has been proven to improve antioxidant protection and to prevent browning reaction in butternut squash (*Cucurbita moschata* Duch) and Romaine lettuce. [460]

4.4 Active and intelligent packaging

Edible films and coatings are just a subset in the broader scenario of the use of technology to increase food shelf life and food security in the design, creation and employment of the so called active and intelligent (smart) packaging. An active package was firstly defined by Rooney [461] as a material that "performs a role other than an inert barrier to the outside environment". Nowadays an "active" packaging is defined as a "packaging in which subsidiary constituents have been deliberately included in or on either the packaging material or the package headspace to enhance the performance of the package system", while the current definition of “intelligent packaging is “packaging that contains an external or internal indicator to provide information about aspects of the history of the package and/or the quality of the food”, respectively. In contrast to traditional packaging, active and intelligent packaging may change the composition and organoleptic characteristics of food, provided that the changes are consistent with the provisions for food. [462] The principles behind active packaging are based either on the intrinsic properties of the polymer used as packaging material itself or on the introduction of specific substances inside the polymer, such as plant extracts. Packaging may be called “active” when it performs some desired role in food preservation other than providing an inert barrier to external conditions. [463] Intelligent packaging gives useful information to the consumer based on its ability to sense, detect, or record external or internal changes in the food products’ environment. There are two types of intelligent packaging: one based on measuring the condition of the package on the outside, the other measuring directly the quality of the food product inside the packaging. [464] On the other hand, active packaging includes additives capable of scavenging, absorbing or releasing gasses such as oxygen, carbon dioxide and ethylene but also moisture, ethanol, antioxidants and antimicrobials. The main advantages of using active packaging for the application of natural antimicrobials in foods are the controlled release of the bioactive compounds into the product during storage time and the lower possibility of development of undesirable flavors than the direct addition into food could cause. [465] Plant or fruit extracts having antioxidant and/or antimicrobial activities can be used in the packaging with the aim of i) having an action in the packaging or ii) with the intention of being released into the food to avoid its oxidation and spoilage. Rosemary extract is one of the plant extracts that has already been successfully incorporated into food packaging. Rosemary contains several flavones (apigenin, genkwanin, hesperetin and cirsimaritin), phenolic diterpenes (carnosic acid, carnosol, rosmadial, epirrosmanol, rosmanol) and phenolic acids (caffeic acid and rosmarinic acid, the latest being the main compound in polar extract from this herb). [95] Carnosic acid and rosmarinic acid are considered as the compounds responsible for rosemary’s activities. According to numerous papers found in literature, rosemary extracts are effective in delaying the lipid oxidation in meat when immobilized on polypropylene films [466] or in contrasting oxidation and browning in fresh-cut pears. [467] An ethanolic extract from rosemary was also successfully tested as antimicrobial agent on cooked ready-to-eat vacuum-packaged shrimps. Another herb from the Lamiaceae family that has been incorporated into food packaging is oregano, which again contains rosmarinic acid as one of principal compounds in its polar extracts. [60] Camo and others [468] studied the prolongation of the shelf life of beef when packaged with a film containing oregano extract in various concentrations. Bentayeb and co-authors [469] have confirmed the effectiveness of the film with oregano extract when comparing the antioxidant capacity of various natural extracts incorporated in active packaging.

5. A novel key to understanding bioactivity: interactions between Lamiaceae herbs and human microbiota

5.1 Symbiotic (commensal) bacteria: the human microbiota

We are all inhabited by complex communities of microorganisms known as the microbiota, which reside in most surfaces of the human body. It is estimated that there is up to 100 trillion bacteria in the same individual, which is around 10-fold greater than the number of human cells. [470] The majority of the human commensal bacteria (10–100 trillion) can be found in the gastrointestinal tract and particularly in the distal intestine, where they have many beneficial functions such as fermentation of indigestible dietary residues, production of vitamins, control of intestinal epithelial cell proliferation and differentiation, and the creation of a protective barrier against pathogens; [471] the gastrointestinal tract microbiota also contributes to the development and differentiation of the mammalian immune system. The composition of the microbiota affects immune responses, susceptibility to infection and development of allergic and inflammatory diseases. Antibiotic administration usually perturbs microbial communities and decreases host resistance to antibiotic resistant microbes. Following perturbations by antibiotics, diet, immune deficiency, or infection, this ecosystem can shift to a state of dysbiosis, a state that may be deleterious to the host. Recent evidence suggests that there is a link between the human gut microbiome and the development various illnesses such as obesity, cardiovascular disease, and metabolic syndromes. Similarly, there is increasing evidence for dysbiotic microbiota in carcinogenesis. Also a panel of gastrointestinal complaints, including functional and inflammatory gastrointestinal diseases, are obviously associated with altered gut microbiota. [472] A deeper understanding of the mechanisms correlating changes in microbiota composition (dysbiosis) with disease states is needed to improve our knowledge. [473]

5.2 Interactions between vegetable dietary components, phytochemicals and human gut microbiota: still a lot to investigate

Numerous papers in literature suggests that dietary components, including phytochemicals, can interact with microbial populations in the human host and have the potential to modify them. Phytochemicals are compounds present in our diet having a wide range of recognized effects including anti-inflammatory, anti- cancer, anti-oxidant, and other beneficial properties both *in vivo* and *in vitro*. Understanding how diet can interact with microbiota will contribute to developing personalized nutrition to manage diseases. Interactions between the gut microbiome and the diet are complex and dynamic, as diet is the primary determinant in the development of the microbiota colonization pattern from the first stages of life. [474] Not all the phytochemicals orally ingested via plant-based food or herbal medicinal products get into contact with colonic microorganisms, but only those that remain unaltered in the upper intestinal tract. For these molecules, interactions with gut microbiota are dual and reciprocal: plant constituents are metabolized by gut microbial populations, leading to the formation of bacterial catabolites with altered bioactivity profile, and on the other hand, plant constituents can initiate changes in microbial community composition and function. Thumann et al. [475] recently surveyed nearly 50 plants traditionally used for gastrointestinal diseases, concluding that only a very limited portion of them has been investigated so far with regard to potential interactions with gut microbiota. As example, constituents present in some of these plants like curcumin (curcuma), shogaol (ginger), and rosmarinic acid (Lamiaceae herbs) have been shown to be metabolized by human gut microbiota, and preliminary data also indicate potential gut microbiome modulatory effects. Rosmarinic acid can be considered a “family marker” for Lamiaceae herbs, being present in polar extracts from the aerials of all family members; it has been shown to be readily degraded by gut microbiota *in vitro*, as well as after oral intake in experimental animals and in humans [476] producing caffeic acid and other several hydroxypropionic acid as catabolites. In a recent paper, Madureira et al. demonstrated that in turn rosmarinic acid affected microbiome composition. [477] The interaction of herbs and their components, phytochemicals, with gut microbiota is still therefore not fully investigated offering an open field for future research.

6. Conclusions

Plants have ‘accompained’ the evolution of the human beings supplying an essential portion of foods, and a series of ‘tools’ able to fight several pathologies or generically speaking many health problems.

The species belonging to the Lamiaceae family represents a small portion of this large resource that the humanity would do well to protect and safeguard, through concerted and targeted efforts of public and private institutions, and the reasearch sectors.

To-day, alongside the classic and still effective methods of analyses aimed to the discover of new compounds and phytocomplexes, are available new tools, for example in the health sector but not only, to fight the medical emergencies of this millenium.

With this in mind, the here reported limited survey on the Lamiaceae family shows as the phytochemical studies of these species (as well as of other plants) are still essential being the main phytochemical components, represented by the essential oils and not volatile exctracts, an invaluable and fundamental help for all of us.

Their biological activities are continuously confirmed by new studies, carried out with more sophisticated models and more suited to new applications and technological needs. The potential use of medicinal plants in arid and with difficult climatic conditions areas has continued to promote the identification and study of new endemisms.

In particular, concerning the essential oils one of the most interesting development regards their antimicrobial studies, while still in the health field, they seem to slow down the progress in their application as anticancer and antiviral. Moreover, the best prospects are currently concentrated in the food industry thanks to the synergy with nanotechnologies. Very early and interesting are the first results of application of essential oils in the field of cultural heritage preservation.

Regarding the extracts from the plants of this family they are not so popular and known as the essentials oils, however, from the studies performed in these last years they have showed a large plethora of bioactivities, thank also to the ethnopharmacology and ethnobotanical surveys of their uses in many countries. The phytochemical studies, as reported in this review, showed that the main components characterized in the various types of extracts belong to the polyphenols family, and these components are considered the main actors for the anticancer, antibacterial, anti-inflammatory, and cytotoxic and others activities of several phytocomplexes.

In conclusion taking into account all the aspects reported in this review it is possible to affirm that the species of this family seem to behave like those great classics of literature, for which even if time passes they always remain current. The next big challenges probably concern an increase of their production possibly correlated to a sustainable management, the development of alternative and green technological processes requiring high energy consumption, and an ecological and rationale treatment of the waste products.

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Author Contribution Statement

G. R. conceived and designed the structure of the work. E. N. organized and wrote the section of the essential oils, L. S. carried out the organization and the writing of the section dealing with the extracts. G. R. assembled all sections and wrote the final version with the contribution from all co-authors. All authors participated in literature analysis, reviewed and approved the final version of the manuscript.

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Table 1. Extract of the main recent publications on endemisms of Lavender and chemical variability of its essential oils

Species	Plant material	Origin	Yield (%)	Main components	Ref.
L. hybrida	Whole plant	Romania	N.R.	linalyl acetate (23%), linalool (22%), terpinene-4-ol (17%)	[45]
L. hybrida ‘Budrovka’	Leaves	Croatia	3.3	linalool (57%), linalyl acetate (10%), 1,8-cineole (8%)	[36]
L. hybrida	Aerial parts	Iran	0.5-1.5	1,8-cineole (32-48%), borneol (17-26%), camphor (8-13%)	[46]
L. hybrida ‘Grosso’	Aerial parts	Italy	8.2-8.5	linalool (34-43%), linalyl acetate (15-17%), 1,8-cineole (8%)	[35]
L. hybrida ‘ SuperA’	Whole plant	Italy	8.8-9.3	linalool (34-39%), linalyl acetate (16-21%), 1,8- cineole (6-8%)	[35]
L. hybrida ‘SuperA’	Aerial parts	Turkey	N.R.	linalool (37%), linalyl acetate (33%), camphor (5%)	[39]
L. hybrida ‘ Sumiens’	Whole plant	Italy	6.4-6.9	linalool (40-41%), 1,8-cineole (16%), borneol (4%)	[41]
L. hybrida “Grey hedge”	Aerial parts	Turkey	N.R.	linalool (29%), 1,8-cineole (16%), borneol (8%)	[39]
L. angustifolia	Aerial parts	Algeria	2.0	1,8-cineole (29%), camphor (25%), borneol (4%)	[41]
L. angustifolia	Aerial parts	India	0.55	linalyl acetate (39%), linalool (30%), terpinene-4-ol (4%)	[40]
L. angustifolia	Inflorescens	Croatia	0.9	linalool (54%), linalyl acetate (12%), lavandulol (7%)	[36]
L. angustifolia	Inflorescens	Turkey	3.5-6.0	linalool (32-50%), linalyl acetate (2-18%)	[37]
L. angustifolia	Whole plant	Turkey	N.R.	linalyl acetate (29-47%), linalool (28-36%)	[39]
L. angustifolia	Whole plant	Spain	N.R.	linalool (37-54%), linalyl acetate (21- 36%), (*E*)-caryophyllene (1-3%)	[38]
L. angustifolia	Inflorescens	Poland	N.R.	linalool (fresh and dried 35%), linalyl acetate (fresh 23%, dried 20%)	[34]
L. angustifolia	Aerial parts	Poland	N.R.	linalool (fresh 31%, dried 27%), linalyl acetate (fresh and dried 23%)	[34]
L. angustifolia ‘mailette’	Aerial parts	Italy	4.5-5.1	linalool (46-48%), linalyl acetate (26%), α-terpineol (7-57%)	[35]
L. mairei (w)	Aerial parts	Morocco	1.0	carvacrol (78%), terpinolene (3%), octen-3-ol (2%)	[47]
L. mairei (w)	Aerial parts	Morocco	1.2	carvacrol (77%), terpinolene (3%), octen-3-ol (2%)	[47]
L. pinnata	Inflorescens	Spain	N.R.	carvacrol (68%), caryophyllene oxide (15%), spathulenol (12%)	[48]
L. pinnata	Leaves	Spain	N.R.	carvacrol (84%), carvacrol methyl ether (3%)	[48]
L. pubescens	Aerial parts	Yemen	1.3	carvacrol (73%), carvacrol methyl ether (7%), caryophyllene oxide (6%)	[49]
L. stricta	Aerial parts	Iran	0.2-0.4	α-pinene (58-63%), linalool (9%), 3-methyl-2-methyl butanoate (7-8%)	[50]
L. stoechas	Whole plant	Spain	0.3-1.0	fenchone (33-37%), camphor (16-24%), 1,8-cineole (17-18%)	[42]
L. stoechas	Aerial parts	Italy	0.7-1.1	fenchone (45-60%), camphor (8-2%), 1,8-cineole (1-16%)	[43]
L. stoechas	Inflorescens	Italy	0.4-0.5	fenchone (53-71%), camphor (7-12%), 1,8-cineole (1-13%)	[44]
L. stoechas	Aerial parts	Algeria	1.5	fenchone (50%), camphor (14%), bornyl acetate (6%)	[51]
L. latifolia	Whole plant	Spain	N.R.	linalool (35-51%), 1,8-cineole (26-32%), camphor (10-18%)	[38]

(w) = wild; N.R. = not reported

Table 2. Extract of the main recent publications on endemisms of Oregano and chemical variability of its essential oils

Species	**Plant material**	**Origin**	**Yield (%)**	**Main components**	**Ref.**
O. acutidens	Aerial parts	Turkey	0.5	carvacrol (62%), *p*-cymene (16%), thymol (13%)	[72]
O. compactum	Aerial parts	Morocco	1.2-4.4	carvacrol (2-64%), *p*-cymene (7-43%), thymol (<1-42.%)	[67]
O. compactum	Aerial parts	Morocco	0.6-2.9	carvacrol (2-79%), thymol (<1-56%), *p*-cymene (4-48%)	[68]
Origanum x majoricum	Aerial parts	Argentina	N.R.	*trans*-sabinene hydrate (24-28%), thymol (12-17%), γ-terpinene (7-8%)	[59]
O. vulgare	Aerial parts	Kosovo	0.4-0.8	sabinene (2-12%), 1,8- cineole (1-14%), caryophyllene oxide (<1-38%)	[58]
O. vulgare (w)	Aerial parts	Italy	2.1-6.2	thymol (21-63%), γ-terpinene (6-24%), *p*-cymene (4-12%)	[55]
O. vulgare	Aerial parts	Iran	0.1-1.8	carvacrol (<1-47%), linalyl acetate (<1-44%), *Z*-β-bisabolene (nd-40%)	[57]
O. vulgare	Aerial parts	Spain	0.8-2.0	carvacrol (59-77%), γ-terpinene (2-11%), *p*-cymene (4-8%)	[56]
O. vulgare ssp. *vulgare*	Aerial parts	Argentina	N.R.	*trans*-sabinene-hydrate (23-27%), thymol (14-17%), terpinene-4-ol (8-11%)	[59]
O. vulgare ssp. *vulgare*	Aerial parts	Poland	0.3-0.9	sabinene (2-25%), 1,8-cineole (<1-15%), linalool (3-32%)	[74]
O. vulgare ssp. *vulgare*(w)	Aerial parts	Montenegro	0.7-1.2	germacrene D (16-28%), α-terpineol (15-18%), (*E*)-caryophyllene (8-15%)	[64]
O. vulgare ssp. *vulgare*(w)	Aerial parts	India	0.2-2.1	thymol (14-86%), carvacrol (nd-63%)	[75]
O. vulgare ssp. *hirtum*	Aerial parts	Argentina	N.R.	*trans*-sabinene hydrate (18-23%), thymol (17-19%), γ-terpinene (7-8%)	[59]
O. vulgare ssp. *hirtum*	Aerial parts	Italy	2.3-6.2	thymol (24-54%), γ-terpinene (10- 31%*), p*-cymene (5-19%)	[61-62]
O. vulgare ssp. *hirtum*	Aerial parts	Italy	1.8-6.4	thymol (11-54%), *p*-cymene (3-19%), γ-terpinene (8-53%)	[60]
O. vulgare ssp. *hirtum*	Aerial parts	Italy	1.0-2.7	thymol/carvacrol (65-85%), linalool (<1-3%)	[63]
O. vulgare ssp. *hirtum* (w)	Aerial parts	Montenegro	3.0	carvacrol (74%), *p*-cymene (8%), γ-terpinene (7%)	[64]
O. vulgare ssp. *gracile*	Aerial parts	Turkey	0.2-0.5	thymol (8-33%), *p*-cymene (3-24%), γ-terpinene (9-30%)	[76]
O. vulgare ssp. *gracile*	Leaves	Iran	1.4	carvacrol (47%), γ-terpinene (14%), *p*-cymene (14%)	[77]
O. vulgare ssp. *gracile*	Flowers	Iran	2.4	carvacrol (61%), γ-terpinene (17%), *p*-cimene (7%)	[77]
O. dictamnus	Aerial parts	Greece	1.2	*p*-cymene (33%), carvacrol (15%), linalool (7%)	[71]
O. microphyllum	Aerial parts	Greece	0.3	terpinen-4-ol (16%), carvacrol (13%), sabinene (8%)	[71]
O. libanoticum	Aerial parts	Lebanon	0.16	hexadecanoic acid (11%), linalool (9%), 3-methyl-2-methyl butanoate (7-8%)	[50]

O. libanoticum	Aerial parts	Lebanon	0.16	(*E*)-caryophyllene (27%), caryophyllene oxide (23%), germacrene D (17%)	[70]
O. dubium	Aerial parts	Turkey	8.0-11.1	carvarcrol (82-91%), γ-terpinene (2-6%), *p*-cymene (2-4%)	[78]
O. ehrenbergii	Aerial parts	Lebanon	3.8-4.5	carvacrol (48-90%), *p*-cymene (1-21%), γ-terpinene (<1-7%)	[69]
O. ehrenbergii	Aerial parts	Lebanon	3.2	carvacrol (79%), *p*-cymene (4%), γ-terpinene (3%)	[70]
O. floribundum	Aerial parts	Algeria	2.5-5.8	carvacrol (32-61%), γ-terpinene (3-26%), *p*-cymene (9-43%)	[73]
O. syriacum	Aerial parts	Lebanon	1.6	carvacrol (61%), *p*-cymene (8%), γ-terpinene (8%)	[70]
O. syriacum (w)	Whole plant	Egypt	4.6	thymol (32%), γ-terpinene (14%), linalool (9%)	[79]
O. syriacum	Whole plant	Egypt	5.5	carvacrol (81%), *p*-cymene (9%), γ-terpinene (2%)	[79]
O. hypericifolium	Aerial parts	Turkey	1.5	*p*-cymene (33%), thymol (23%), γ-terpinene (15%)	[80]
O. sypleum	Aerial parts	Turkey	1.1	*p*-cymene (13%), carvacrol (13%), α-pinene (11%)	[80]
O. majorana	Aerial parts	Turkey	1.9	linalool (38%), thymol (26%), γ-terpinene (12%)	[80]
O. majorana	Aerial parts	Tunisia	1.8	terpinen-4-ol (23%), *cis*-sabinene hydrate (18%), γ-terpinene (11%)	[81]
O. majorana	Leaves	Egypt	2.3-2.6	*cis*-sabinene hydrate (15-34%), γ-terpinene (9-29%), terpinen-4-ol (14-35%)	[82]
O. onites	Aerial parts	Turkey	2.0	thymol (42%), linalool (14%), carvacrol (9%)	[80]
O. onites	Inflorescens	Greece	3.0-7.0	carvacrol (69-93%), *p*-cymene (nd-10%), γ-terpinene (nd-8%)	[83]
O. minutiflorum	Aerial parts	Turkey	1.1	carvacrol (91%), linalool (3%), (*E*)-caryophyllene (1%)	[84]
O. rotundifolium	Aerial parts	Turkey	1.0	carvacrol (57%), *p*-cymene (13%), (*Z*)-β-ocimene (5%)	[85]

(w) = wild; nd = not detected; N.R. = not reported

Table 3. Extract of the main recent publications on endemism of Rosemary and chemical variability of its essential oils

Species	Plant material	Origin	Yield (%)	Main components	Ref.
R. eriocalix	Stems	Algeria	0.02	camphor (41%), camphene (10%), α-pinene (8%)	[87]
R. eriocalix	Leaves	Algeria	0.7	camphor (37%), α-pinene (18%), camphene (16%)	[87]
R. eriocalix	Flowers	Algeria	0.9	camphor (30%), α-pinene (15%), camphene (13%)	[87]
R. officinals (w)	Aerial parts	Italy	0.8-3.6	α-pinene (10-46%), 1,8-cineole (<1-67%), camphor (<1-27%)	[88]
R. officinalis	Aerial parts	Jordan	0.7	1,8-cineole (31%), α-pinene (17%), camphor (12%)	[89]
R. officinalis	Aerial parts	Italy	0.1-0.9	α-pinene (14-34%), 1,8-cineole (11-28%)	[90]
R. officinals (w)	Aerial parts	Tunisia	0.7-1.7	α-pinene (7-10%), 1,8-cineole (23-53%), camphor (7-28%)	[91]
R. officinals (w)	Aerial parts	Tunisia	1.5-2.1	1,8-cineole (29-60%), camphor (6-28%), α-pinene (7-13%)	[92]
R. officinals (w)	Aerial parts	Algeria	0.7-1.9	1,8-cineole (2-48%), camphor (3-41%), α-pinene (14-29%)	[93]
R. officinals (w)	Aerial parts	Italy	0.7-2.8	1,8-cineole (<1-63%), α-pinene (12-40%), camphor (3-31%)	[94]
R. officinalis	Leaves	Iran	0.5-2.6	1,8-cineole (5-28%), camphor (2-25%), α-pinene (14-21%)	[95]
R. officinals (w)	Leaves	Iran	0.6-2.3	1,8-cineole (6-27%), camphor (2-25%), α-pinene (15-21%)	[96]
R. officinals (w)	Aerial parts	Italy	0.8-2.3	1,8-cineole (8-59%), α-pinene (14-27%), camphor (3-15%)	[97]
R. officinals (w)	Aerial parts	Italy	N.R.	1,8-cineole (nd-48%), α-pinene (9-44%), camphor (<1-23%)	[98]
R. officinalis	Aerial parts	Tunisia	N.R.	1,8-cineole (24%), camphene (13%), camphor (13%)	[99]
R. officinalis	Aerial parts	Italy	N.R.	1,8-cineole (2-48%), α-pinene (9-44%), camphor (1-13%)	[100]

(w) = wild; nd = not detected; N.R. = not reported

Table 4. Extract of the main recent publications on endemism of Sage and chemical variability of its essential oils

Species	Plant material	Origin	Yield (%)	Main components	Ref.
S. algeriensis	Leaves	Algeria	0.8	benzaldehyde (10%), eugenol (9%), phenylethyl alcohol (8%)	[118]
S. algeriensis	Flowers	Algeria	1.5	viridiflorol (71%), globulol (9%), α-cadinene (3%)	[118]
S. fruticos ssp. *thomasii*	Aerial parts	Italy	0.2	1,8-cineole (11-26%), β-pinene (13-14%), camphor (8-9%)	[111]
S. hispanica	Aerial parts	Italy	0.05	(*Z*)-caryophyllene (12%), (*E*)-caryophyllene (11%), humulene (5%)	[105]
S. trichoclada	Aerial parts	Turkey	N.R.	caryophyllene oxide (25%), spathulenol (15%), β-pinene(12%)	[106]
S. virgate	Aerial parts	Turkey	N.R.	1,8-cineole (20%), α-copaene (19%), germacrene D (18%)	[106]
S. virgate	Aerial parts	Iran	0.03	(*E*)-caryophyllene (34-38%), caryophyllene oxide (26-29%), β-farnesene (9-10%)	[109]
S. ceratophilla	Aerial parts	Turkey	N.R.	germacrene D (24%), α- copaene (19%), 1,8-cineole (8%)	[106]
S. multicaulis	Aerial parts	Turkey	N.R.	caryophyllene oxide (23%), spathulenol (13%), β-pinene (8%)	[106]
S. multicaulis	Aerial parts	Iran	0.2-0.5	(*E*)-caryophyllene (11-35%), α-pinene (12-17%), linalyl acetate (10-14%)	[108]
S. multicaulis	Aerial parts	Lebanon	0.7-1.3	*trans*-nerolidol (nd-12%), 1,8-cineole (7-16%), δ-cadinene (2-5%)	[119]
S. lavandulifolia	Aerial parts	Spain	N.R.	1,8-cineole (19%), camphor (11%), α-pinene (10%)	[112]
S. nemorosa	Aerial parts	Iran	N.R.	caryophyllene oxide (11-35%), spathulenol (4-37%), (*E*)-caryophyllene (2-27%)	[109]
S. officinalis	Aerial parts	Ethiopia	1.0-1.2	α-thujone (20-26%), 1,8-cineole (17-22%), camphor (13-18%)	[102]
S. officinalis	Aerial parts	Montenegro	1.8-2.8	α-thujone (17-40%), camphor (13-35%), 1,8-cineole (6-12%)	[103]
S. officinalis	Aerial parts	Spain	0.8-1.5	α-thujone (23-42%), camphor (11-20%), 1,8-cineole (5-16%)	[104]
S. reuteriana	Aerial parts	Iran	0.2-0.4	α-gurjunene (5-14%), β-elemene (5-14%), germacrene D (3-7%)	[120]
S. reuteriana	Aerial parts	Iran	0.1-0.3	caryophyllene oxide (30-52%), spathulenol (12-15%), (*E*)-caryophyllene (5-10%)	[108]
S. sclarea	Flowers	Iran	0.08	germacrene D (21%), α-bulnesene (12%), limonene (12%)	[121]
S. sclarea	Leaves	Iran	0.05	germacrene D (21%), caryophyllene (17%), caryophyllene oxide (10%)	[121]
S. syriaca	Aerial parts	Iran	0.1	germacrene B (26-36%), germacrene D (18-24%), bicyclogermacrene (9-15%)	[108]
S. tomentosa	Aerial parts	Greece	1.1-3.3	β-pinene (1-30%), α-pinene (11-25%), α-thujone (nd-24%)	[122]
S. sericeo-tomentosa	Aerial parts	Turkey	N.R.	sabinyl acetate (80%), α-pinene (3-4%)	[123]
S. adenophylla	Aerial parts	Turkey	0.28	α-pinene (16%), β-pinene (14%)	[124]
S. viscosa	Aerial parts	Turkey	0.16	β-pinene (25%), myrcene (9%), humulene (8%)	[124]
S. argentea	Aerial parts	Italy	0.27	14-hydroxy-α-humulene (40%), 1,3,8-*p*-menthatriene (12%)	[125]

S. aristata	Aerial parts	Iran	0.02	carvacrol (23%), 1,8-cineole (8%), α-pinene (7%)	[126]
S. aucheri spp. *blancoana*	Aerial parts	Morocco	1.4	camphor (27%), camphene (22%), α-pinene (21%)	[127]
S. aucheri spp. *blancoana*(w)	Aerial parts	Morocco	1.2	camphor (57%), camphene (6%), (*E*)-caryophyllene (5%)	[127]
S. bicolor	Aerial parts	Egypt	0.3	α-pinene (25%), α-thujone (13%), (*E*)-caryophyllene (7%)	[128]
S. broussonetti	Aerial parts	Italy	<0.01	α-gurjunene (6-16%), α-pinene (11-15%), germacrene D (7-14%)	[129]
S. buchananii	Aerial parts	Algeria	0.9	1,8-cineole (23%), α-pinene (20%), camphene (17%)	[113]
S. bucharica	Aerial parts	Pakistan	0.17	1,8-cineole (26%), camphor (16%), (*E*)-caryophyllene (11%)	[114]
S. chudaei	Aerial parts	Algeria	0.55	bornyl acetate (21%), β-eudesmol (14%), (*E*)-caryophyllene (11%)	[130]
S. desoleana	Aerial parts	Italy	N.R.	germacrene D (4-26%), linalyl acetate (<1-38%), 1,8-cineole (8-11%)	[131]
S. forskahlei(w)	Aerial parts	Turkey	0.1	germacrene D (19%), δ-cadinene (13%), neophytadiene (13%)	[110]
S. forskahlei	Aerial parts	Turkey	0.01	(*E*)-caryophyllene (24%), α-selinene (13%), naphtalene (11%)	[110]
S. hypoeuca	Inflorescens	Iran	0.1-0.8	bicyclogermacrene (2-37%), (*E*)-caryophyllene (2-22%)	[132]
S. kiangsiensis	Leaves	China	0.1	epimanool (46%), globulol (6%), α-guaiene (4%)	[133]
S. lachnocalyx	Aerial parts	Iran	N.R.	bicyclogermacrene (41%), (*E*)-caryophyllene (11%), spathulenol (9%)	[134]
S. lachnocalyx	Aerial parts	Iran	N.R.	bicyclogermacrene (18%), α-pinene (15%), β-pinene (14%)	[134]
S. leriifolia	Aerial parts	Iran	0.4	β-pinene (14%), 1,8-cineole (14%), α-pinene (10%)	[135]
S. limbata	Aerial parts	Iran	0.4	caryophyllene oxide (12%), terpinen-4-ol (9%), sabinene (8%)	[136]
S. montbretti	Aerial parts	Turkey	<0.1	(*E*)-caryophyllene (33%), β-pinene (10%), humulene (8%)	[107]
S. palaestina	Leaves	Palestine	0.1-0.7	1,8-cineole (52-63%), camphor (1-9%), (*E*)-caryophyllene (1-5%)	[115]
S. ringens	Aerial parts	Macedonia	0.2	1,8-cineole (32%), camphene (17%), borneol (12%)	[116]
S. sahendica	Aerial parts	Iran	1.5-1.8	α-pinene (14-15%), β-pinene (11-13%), germacrene D (3-8%)	[137]
S. santolinifolia	Aerial parts	Iran	1.6	α-pinene (49%), β-eudesmol (20%), camphene (8%)	[138]
S. sclareopsis	Leaves	Iran	N.R.	viridiflorol (24 %), humulene (18 %), α-muurolene (9%)	[139]
S. sclareopsis	Stems	Iran	N.R.	octadecane (21%), caryophyllene oxide (8%), nonanal (6%)	[139]
S. sclareopsis	Flowers	Iran	N.R.	linalool (28%), hexyl 2-methyl butyrate (5%), *n*-hexyl acetate (5%)	[139]
S. sharifi	Aerial parts	Iran	0.2	germacrene D (30%), bicyclogermacrene (16%), β-caryophyllene (12%)	[140]
S. veneris	Aerial parts	Cyprus	2.0	1,8-cineole (51%), camphor (9%), camphene (6%).	[117]

(w) = wild; nd = not detected; N.R. = not reported

Table 5. Extract of the main recent publications on endemisms of Thyme and chemical variability of its essential oils

Species	Plant material	Origin	Yield (%)	Main components	Ref.
T. mastichina	Aerial parts	Spain	N.R.	1,8-cineole (59-68%), linalool (1-10%), β-pinene (4-5%)	[112]
T. mastichina	Flowers	Spain	N.R.	limonene+1,8-cineole (71%), myrcene (10%)	[148]
T. mastichina	Fruits	Spain	N.R.	limonene+1,8-cineole (78%), myrcene (6%)	[148]
T. capitata	Aerial parts	Italy	1.4-5.6	carvacrol (3-83%), *p*-cymene (4-40%), γ-terpinene (<1-10%)	[144]
T. capitata	Aerial parts	Spain	2.8-5.6	carvacrol (69-76%), γ-terpinene (7-8%), *p*-cymene (7%)	[147]
T. capitata	Flowers	Spain	N.R.	carvacrol (76%), *p*-cymene (7%), γ-terpinene (5%)	[148]
T. capitata	Fruits	Spain	N.R.	carvacrol (74%), *p*-cymene (9%), γ-terpinene (4%)	[148]
T. capitata	Aerial parts	Tunisia	1.4-2.4	carvacrol (73-76%), *p*-cymene (5-13%), γ-terpinene (1-8%)	[146]
T. capitata	Aerial parts	Italy	4.2-8.1	carvacrol (62-81%), *p*-cymene (5-11%), γ-terpinene (2-9%)	[145]
T. caespititius	Flowers	Spain	N.R.	α-terpineol (42%), *p*-cymene (11%), γ-terpinene (6%)	[147]
T. caespititius	Fruits	Spain	N.R.	α-terpineol (53%), *p*-cymene (10%), γ-terpinene (4%)	[147]
T. zygis	Flowers	Spain	N.R.	thymol (45%), *p*-cymene (23%), γ-terpinene (11%)	[147]
T. zygis	Fruits	Spain	N.R.	thymol (53%), *p*-cymene (30%), γ-terpinene (5%)	[147]
T. spicata	Aerial parts	Greece	2.4-4.8	carvacrol (67-88%), *p*-cymene (1-17%), γ-terpinene (<1-7%)	[149]
T. serpyllum	Aerial parts	Poland	0.2-1.0	geranyl acetate <1-23%), α-terpineol (5-22%), myrcene (1-16%)	[150]
T. serrulatus	Aerial parts	Ethiopia	N.R.	carvacrol (7-81%), thymol (7-66%)	[151]
T. schimperi	Aerial parts	Ethiopia	N.R.	carvacrol (35-72%), thymol (16-54%)	[151]
T. pannonicus	Aerial parts	Serbia	0.3-1.3	geranial (29-46%), neral (23-36%)	[152]

(w) = wild; nd = not detected; N.R. = not reported

Table 6. Recent studies on repellent and insecticidal activity of essential oils

Essential oil	Target insect	Evaluated parameters	Ref.
L. dentata	*Culiseta longiareolata*	Larvicidal activity	[213]
L. dentata	*Culex pipiens*	Larvicidal activity	[213]
L. luisieri	*Hyalomma lusitanucum*	Larivicidal actvity	[214]
L. angustifolia	*Lucilla sericata*	Toxicity and oviposition deterrence	[215]
L. angustifolia	*Plodia interpunctella*	Toxicity	[216]
L. angustifolia	*Plutella xylostella*	Toxicity	[217]
L. angustifolia	*Sitophilus granarius*	Contact/fumigant toxicity, repellent, antifeedant and nutritional effects	[218]
L. stoechas	*Orgyia trigotephras*	Toxicity	[219]
Lavandin	*Spodoptera littoralis*	Biocidal	[220]
Several	*Hyalomma scupense*	Acaricidal activity (adults and larvae)	[221]
O. vulgare	*Tribolium confusum*	Repellence	[222]
O. vulgare	*Sitophilus oryzae*	Repellence	[222]
O. onites	*Amblyomma americanum*	Repellence	[223]
O. onites	*Aedes aegypti*	Repellence	[223]
Origanum	*Aedes albopictus*	Larvicidal effects and repellence	[224]
O. syriacum	*Spodoptera littoralis*	Insecticidal	[225]
O. syriacum	*Myzus persicae*	Insecticidal	[225]
O. syriacum	*Musca domestica*	Insecticidal	[225]
O. scabrum	*Mosquito vectors*	Insecticidal, ovicidal	[226]
O. elongatum	*Varroa destructor*	Acaricidal	[227]
R. officinalis	*Tribolium castaneum*	Fumigant and contact toxicity	[228]
S. officinalis	*Varroa destructor*	Acaricidal	[229]
S. officinalis	*Aedes aegypti*	Larvicidal	[230]
S. plebeian	*Aedes aegypti*	Larvicidal	[231]
S. lavandulifolia	*Synanthropic mites*	Acaricidal	[232]
S. mirzayanii	*Oligonychus afrasiaticus*	Acaricidal	[233]
S. veneris	*Spodoptera exigua*	Insecticidal	[234]
S. ballotiflora	*Spodoptera frugiperda*	Insectistatic and insecticidal	[235]
T. satureioides	*Varroa desctructor*	Acaricidal	[227]
T. vulgaris	*Macrosiphum rosae*	Insecticidal	[236]

Table 7. Use of essential oils in animal feeding

Essential oil	Target animal	Way of aministration	Evaluated parameters	Ref.
L. angustifolia	Broiler chickens	Drinking water	Production, blood biochemical paraameters, ileal microflora	[242]
L. graveolens	Pigs	Food supplement	Carcass yield, sensory and acceptance of meat	[261]
O. vulgare	Calves	Oral administration	Neonatal diarrhea	[262]
O. vulgare	Lambs	Food supplement	Performance, carcass characteristics, blood parameters	[263]
O. vulgare	Lambs	Food supplement	Growth	[264]
O. vulgare	Broiler chickens	Food supplement	Growth, intestinal microflora, gut integrity	[243]
O. vulgare	Pigs	Food supplement	Meat quality, fatty acid composition, oxidative stability of *Longissimus thoracis* muscle	[265]
O. vulgare	Nile tilapia	Food supplemet	Growth, behavioral, stress response	[266]
O. vulgare	Cows	Food supplement	Sensory properties and production levels of milk, feed consumption, methane emission	[244]
O. vulgare	Goats	Food supplement	Rumen fermentation, enzyme profile	[267]
O. onites	Rainbow trout	Food supplement	Growth, lysozyme, antioxidant activity	[268]
O. syriacum	Broiler chickens	Food supplement	Blood parameters	[245]
R. officinalis	Goats	Food supplement	Milk production	[269]
R. officinalis	Hens	Food supplement	Performances, egg quality, blood parameters	[270]
R. officinalis	Japanes quail	Food supplement	Heat stress-induced testes, structural and functional damage	[271]
R. officinalis	Dairy ewes, lambs	Food supplement	Digestion, colostrum production of dairy ewes, lambs mortality anf growth	[272]
R. officinalis	Lambs	Food supplement	Meat quality	[273]
R. officinalis	Sheeps	Food supplement	Ruminal fermentation	[274]
T. vulgaris	Broiler chickens	Food supplement	Growth performances, blood parameters	[275]
T. vulgaris	Japanese quail	Food supplement	Performance, organs weight, intestinal morphology, serum lipids	[276]
T. vulgaris	Nile tilapia	Food supplement	Hemato-immunological indices, intestinal morphology, microbiota	[277]
T. vulgaris	Rabbits	Food supplement	Productive performance, carcass criteria and meat quality	[278]

Table 8. Selection of recent *in-vitro* studies on citotoxicity of essential oil[a]

Essential oil	**Cell lines**	**Test**	**Ref.**
L. stoechas	RD, L20B, RD	MTT	[363]
L. angustifolia	Caco-2	Microscopic evaluation of cell monolayers	[364]
O. vulgare	AGS	MTT, inverted phase- miscroscope	[366]
O. vulgare	MCF-7, HT-29	Sulforhodamine B assay	[367]
O. vulgare	HepG2, HEK293	MTT, inverted phase-contrast microscope	[368]
O. acutidens	HAT-29, HeLa	Real time cell analysis	[369]
R. officinalis	RDL20B, RD	MTT	[363]
R. officinalis	A549, H1299, MCF-7, HUVEC	MTT	[365]
S. officinalis	MCF.7, LNCaP, HeLa	MTT	[370]
S. officinalis	A549, NCl-H226	MTT	[371]
S. verbenacea	M14	MTT, LGD, COMET, Caspase colorimetric	[372]
S. sclarea	HeLa	MTT, RT-PCR	[373]
S. aurea	DU-145	MTT, LDH, Comet, Caspase colorimetric	[374]
S. judaica	DU-145	MTT, LDH, Comet, Caspase colorimetric	[374]
S. viscosa	DU-145	MTT, LDH, Comet, Caspase colorimetric	[374]
T. capitatus	MCF-7	Sulforhodamine B assay	[375]

[a] MTT: tetrazolium dye MTT 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide colorimetric assay; LGD: Lowest genotoxic dose assay; RT-PCR: Reverse transcriptase-Polymerase Chain Reaction; LDH: Lactate dehydrogenase cytotoxicity assay.

Captions of figures

Figure 1.
The main genera of the Lamiaceae family.

Figure 2.
Number of medicinal plants in different plant families [7-9].

Figure 3.
Comparison between the average content of the main components of the Sicilian oregano essential oils (A) and a commercial (B) sample.

Figure 4.
Spider diagram of the sensory profile of the a Sicilian oregano and a commercial oregano sample.

Figure 5.
The photo on the left shows the typical rows of an oregano cultivation, the photo on the right shows a particular of oregano flowers.

Figure 6.
The photo on the left shows the mechanical harvesting of oregano, in the photo on the right the machinery for the preparation of the bunches of oregano

Figure 7.
The photo on the left shows alternate rows of rosemary and sage cultivation, the photo on the right shows a particular of sage inflorescens.

Figure 8.
Selection of compounds isolated from Lamiaceae species (glc=glucoside, glu=glucuronide, rhm=rhamnoside).

Figure 9.
Typical HPLC profiles of oregano (**A**), rosemary (**B**), sage (**C**), and thyme (**D**) ethyl acetate extracts.

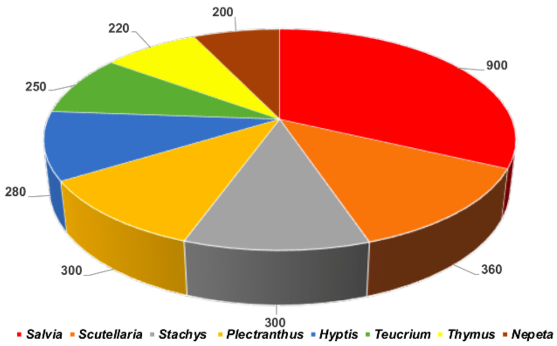


Figure 1.

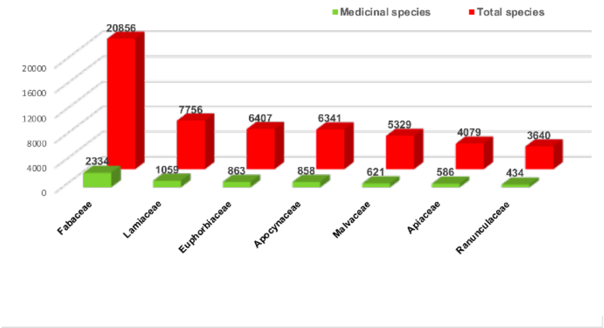


Figure 2.

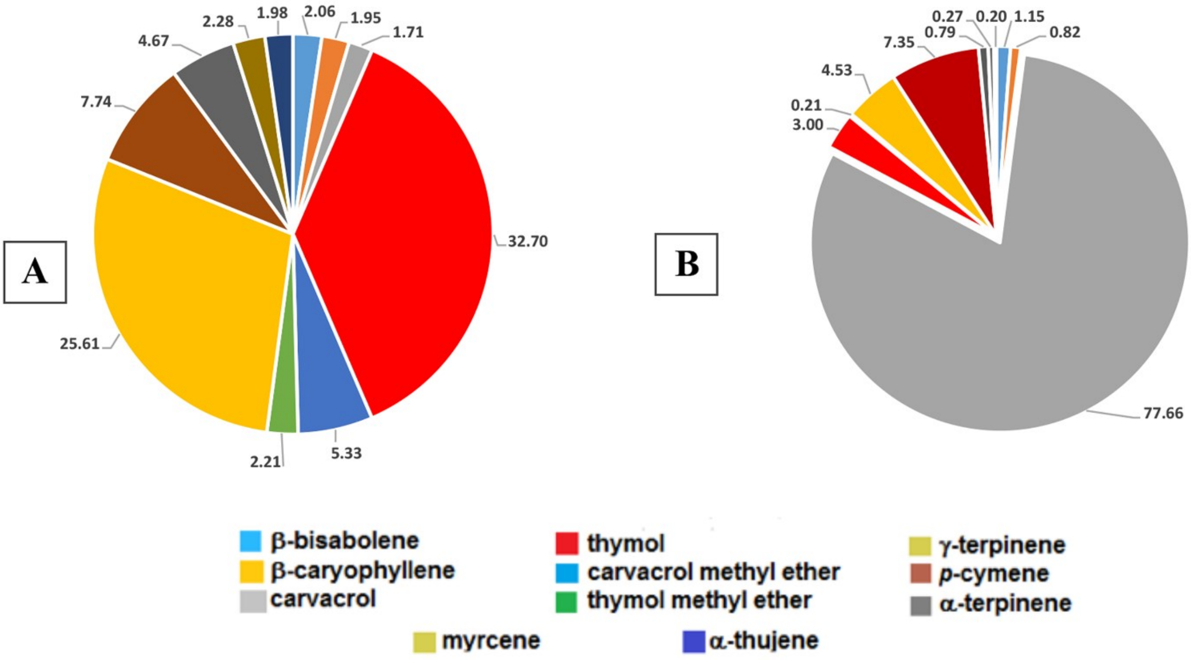


Figure 3.

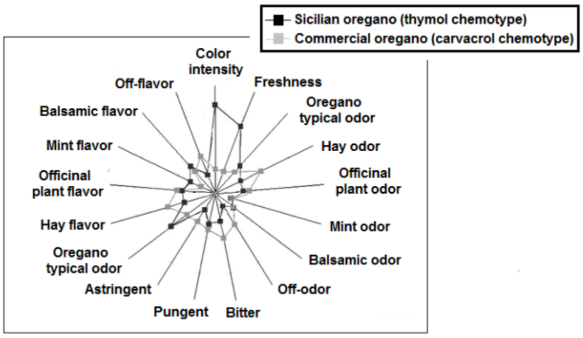
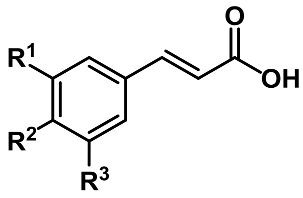


Figure 4.

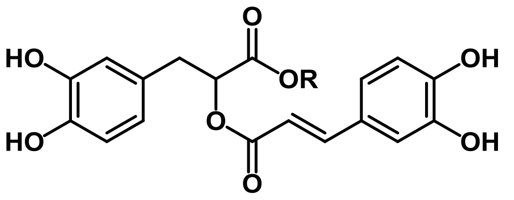
Figure 5.

Figure 6.

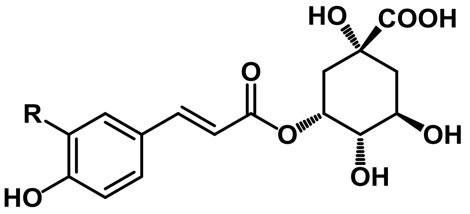
Figure 7.



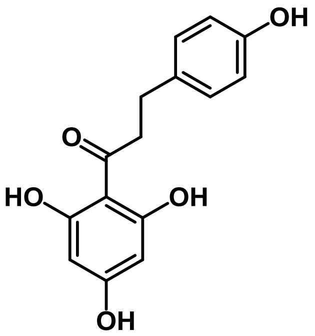
Cinnamic acid (**39**) $R^1=R^2=R^3=H$
p-Coumaric acid (**2**) $R^1=R^3=H$, $R^2=OH$
Caffeic acid (**1**) $R^1=R^2=OH$, $R^3=H$
Ferulic acid (**3**) $R^1=OCH_3$, $R^2=OH$, $R^3=H$
iso-Ferulic acid (**26**) $R^1=OH$, $R^2=OCH_3$, $R^3=H$
Sinapic acid (**41**) $R^1=R^3=OCH_3$, $R^2=OH$



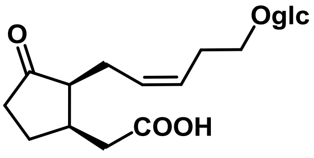
Rosmarinic acid (**4**) (R=H)
Rosmarinic acid methyl ester (**31**) ($R=CH_3$)



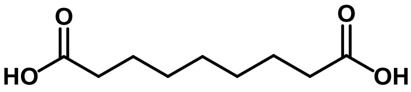
3-*O*-4-Coumaroylquinic acid (**16**) (R=H)
Chlorogenic acid (**36**) (R=OH)



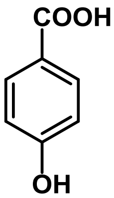
Phloridzin (**54**)



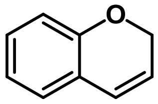
Tuberonic acid glucoside (**18**)



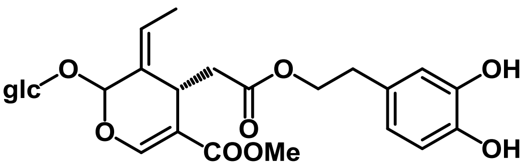
Azelaic acid (**20**)



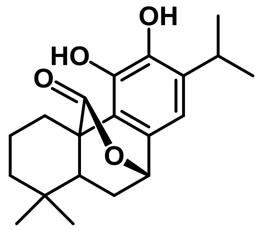
p-hydroxybenzoic acid (**51**)



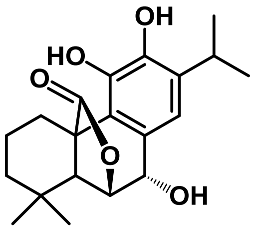
Coumarin (**38**)



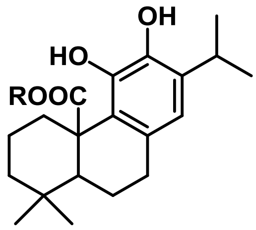
Oleuropein (**42**)



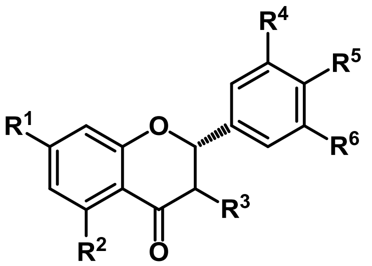
Carnosol (**43**)



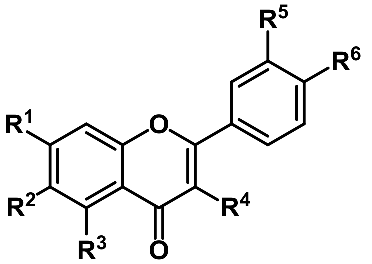
Rosmanol (**44**)



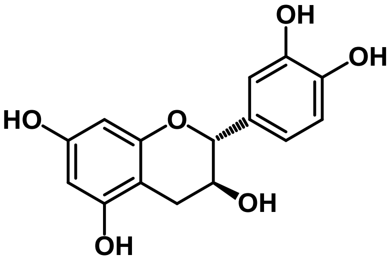
Carnosic acid (**49**) (R=H)
Methyl carnosoate (**50**) ($R=CH_3$)



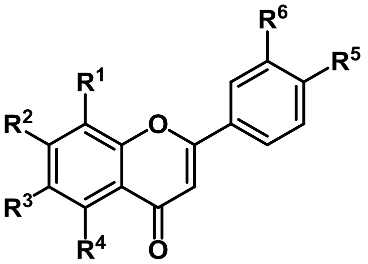
Aromadendrin (**7**)	$R^1=R^2=R^3=R^5=OH$, $R^4=R^6=H$
Dihydrorobinetin (**23**)	$R^1=R^3=R^4=R^5=R^6=OH$, $R^2=H$
Eriodictyol (**8**)	$R^1=R^2=R^4=R^5=OH$, $R^3=R^6=H$
Eriodictyol 7-*O*-rutinoside (**6**)	$R^1=Orut$, $R^2=R^4=R^5=OH$, $R^3=R^6=H$
Hesperetin (**55**)	$R^1=R^2=R^4=OH$, $R^3=R^6=H$, $R^5=OCH_3$
Naringenin (**9**)	$R^1=R^2=R^5=OH$, $R^3=R^4=R^6=H$
Sakuranetin (**32**)	$R^1=OCH_3$, $R^2=R^5=OH$, $R^3=R^4=R^6=H$
Taxifolin (**58**)	$R^1=R^2=R^4=R^5=OH$, $R^3=R^6=H$



Casticin (**22**)	$R^1=R^2=R^4=R^6=OCH_3$, $R^3=R^5=OH$
Kaempferol (**27**)	$R^1=R^3=R^4=R^6=OH$, $R^2=R^5=H$
Quercetin (**30**)	$R^1=R^3=R^4=R^5=R^6=OH$, $R^2=H$
Rutin (**40**)	$R^1=R^3=R^5=R^6=OH$, $R^2=H$, $R^4=Orut$

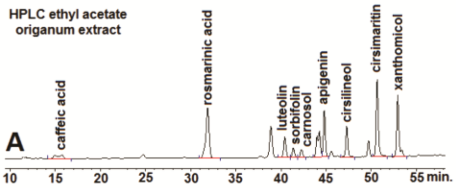


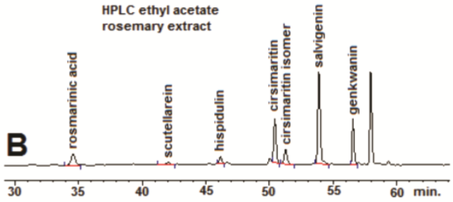
Catechin (**37**)

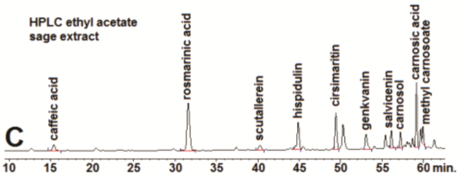


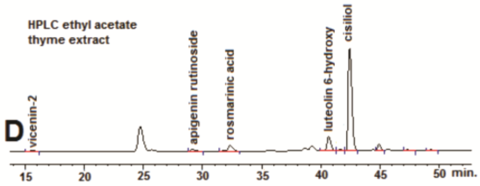
Acacetin (**17**)	R^1=R^3=R^6=H, R^2=R^4=OH, R^5=OCH_3
Apigenin (**12**)	R^1=R^3=R^6=H, R^2=R^4=R^5=OH
Apigenin 7,4'-dimethyl ether (**19**)	R^1=R^3=R^6=H, R^4 =OH, R^2=R^5=OCH_3
Apigenin 7-*O*-glucuronide (**35**)	R^1=R^3=R^6=H, R^2=Oglu, R^4=R^5=OH
Apigenin 7-*O*-glucoside (**53**)	R^1=R^3=R^6=H, R^2=Oglc, R^4=R^5=OH
Apigenin 7-*O*-rutinoside (**59**)	R^1=R^3=R^6=H, R^2=Orut, R^4=R^5=OH
Baicalin (**21**)	R^1=R^5=R^6=H, R^2=Oglu, R^3=R^4=OH
Cirsiliol (**11**)	R^1=H, R^2=R^3=OCH_3, R^4=R^5=R^6=OH
Cirsilineol (**13**)	R^1=H, R^2=R^3=R^6=OCH_3, R^4=R^5=OH
Cirsimaritin (**14**)	R^1=R^6=H, R^2=R^3=OCH_3, R^4=R^5=OH
Chrysoeriol (**62**)	R^1=R^3=H, R^2=R^4=R^5=OH, R^6=OCH_3
Gardenin B (**24**)	R^1=R^2=R^3=R^5=OCH_3, R^4=OH, R^6=H
Gardenin B glucoside (**60**)	R^1=R^2=R^3=R^5=OCH_3, R^4=Oglc, R^6=H
Genkwanin (**25**)	R^1=R^3=R^6=H, R^2=OCH_3, R^4=R^5=OH
Luteolin (**5**)	R^1=R^3=H, R^2=R^4=R^5=R^6=OH
Luteolin 7-*O*-glucoside (**56**)	R^1=R^3=H, R^2=Oglc, R^4=R^5=R^6=OH
Luteoilin 7-*O*-glucuronide (**45**)	R^1=R^3=H, R^2=Oglu, R^4=R^5=R^6=OH
Luteolin 6-hydroxy (**57**)	R^1=H, R^2=R^3=R^4=R^5=R^6=OH
Luteolin 6-hydroxy-7-*O*-glucoside (**46**)	R^1=H, R^2=Oglc, R^3=R^4=R^5=R^6=OH
Luteolin 7-*O*-rutinoside (**52**)	R^1=R^3=H, R^2=Orut, R^4=R^5=R^6=OH
Nevadensin (**28**)	R^1=R^3=R^5=OCH_3, R^2=R^4=OH, R^6=H
Oroxylin 7-*O*-glucoside (**29**)	R^1=R^5=R^6=H, R^2=OCH_3, R^3=R^4=OH
Salvigenin (**33**)	R^1=R^6=H, R^2=R^3=R^5=OCH_3, R^4=OH
Scutallarin (**47**)	R^1=R^6=H, R^2=Oglu, R^3=R^4=R^5=OH
Scutallarein 7-*O*-glucoside (**48**)	R^1=R^6=H, R^2=Oglc, R^3=R^4=R^5=OH
Sorbifolin (**10**)	R^1=R^6=H, R^2=Orhm, R^3=R^4=R^5=OH
Vicenin-2 (**34**)	R^1=R^3=*C*-glc; R^2=R^4=R^5=OH, R^6=H
Thymusin (**61**)	R^1=R^2=OCH_3, R^3=R^4=R^6=OH
Xanthomicol (**15**)	R^1=R^2=OCH_3, R^3=R^4=R^5=OH, R^6=H

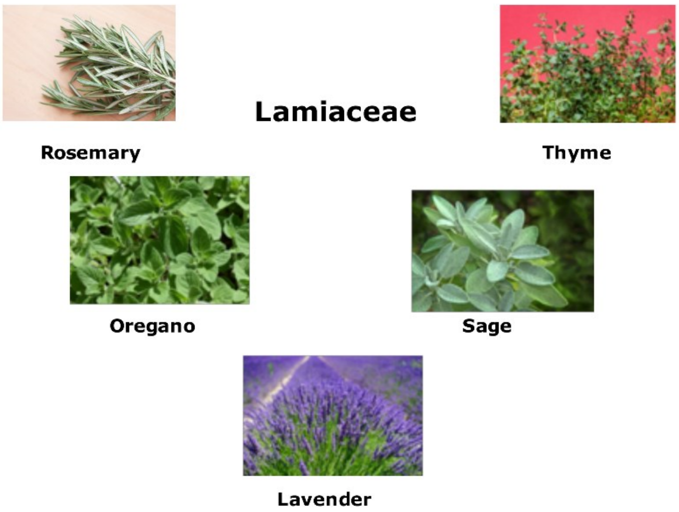
Figure 8. Selection of compounds isolated from Lamiaceae species (glc=glucoside, glu=glucuronide, rhm=rhamnoside).


HPLC ethyl acetate
origanum extract
A
caffeic acid
rosmarinic acid
luteolin
sorbifolin
carnosol
apigenin
cirsilineol
cirsimaritin
xanthomicol
10
15
20
25
30
35
40
45
50
55 min.


HPLC ethyl acetate
rosemary extract
B
rosmarinic acid
scutellarein
hispidulin
cirsimaritin
cirsimaritin isomer
salvigenin
genkwanin
30
35
40
45
50
55
60 min.


HPLC ethyl acetate
sage extract
C
caffeic acid
rosmarinic acid
scutallerein
hispidulin
cirsimaritin
genkvanin
salvigenin
carnosol
carnosic acid
methyl carnosoate
10
15
20
25
30
35
40
45
50
55
60 min.


HPLC ethyl acetate
thyme extract
D
vicenin-2
apigenin rutinoside
rosmarinic acid
luteolin 6-hydroxy
cisiliol
15
20
25
30
35
40
45
50 min.



Graphical Abstract