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Lamiaceae Family Plants as Natural Solutions for Inflammation and Blood Sugar Management

Vasiliki Lagouri
Laboratory of Chemistry, Biochemistry and Cosmetic Science, Department of Biomedical Medicine, University of West Attica, Greece
Perrotis College/ American Farm School, Greece
Sara Oumenoune Tebbi
Laboratoire de Gestion et Valorisation des Ressources Naturelles et Assurance Qualité. Faculté SNVST, Université de Bouira, Algeria
Armando Caseiro
Polytechnic Institute of Coimbra, Coimbra Health School, Biomedical Laboratory Sciences, Portugal
LABINSAÚDE - Research Laboratory for Applied Health Sciences, Polytechnic Institute of Coimbra, Portugal
Molecular Physical-Chemistry R&D Unit, School of Science and Technology, University of Coimbra, Portugal
Maria Trapali
Laboratory of Chemistry, Biochemistry and Cosmetic Science, Department of Biomedical Medicine, University of West Attica, Greece

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Abstract

The *Lamiaceae* family, including common herbs like rosemary and mint, is being investigated for its potential health benefits. In addition to numerous health benefits, research is looking into these plants' anti-inflammatory qualities and potential impacts on blood sugar regulation. More specifically, the Greek endemic Lamiaceae plants are proven to be of great importance, regarding their bioactive compounds and the antioxidant, antidiabetic and anti-inflammatory properties they have. The study's objective was to compile information from the literature regarding the anti-inflammatory, antidiabetic, and antioxidant properties of *Origanum rotundifolium*, *Rosmarinus officinalis*, *Lavendula angustifolia*, and *Thymus serpyllum*. *Lavender angustifolia* is used for many traditional medical and cosmetic products. Several studies demonstrated strong anti-inflammatory mechanisms exhibited by Rosmarinus officinalis. Leukocyte migration was found to be significantly inhibited in vivo by rosemary essential oil and extract. Changes in the gut microbiota induced by essential oils rosemary as prebiotics in mice regulated cardiovascular and metabolic factors, which focus on the potential of these nutraceuticals for reducing Ischemic heart disease risk in patients affected by type-2 diabetes mellitus. A mixture of Origanum majorana and Origanum vulgare plants investigated antidiabetic activities in zebrafish. The *Lamiaceae* family provides a natural source of substances that may be used in functional foods. These functional meals have the potential to improve general health and help manage chronic illnesses. The precise mechanisms of action of these plants and the best doses for use in functional food applications require more investigation.

Keywords: *Lamiaceae* Family, anti-diabetic activity, Antioxidant potential, Anti-inflammatory properties

Introduction

The family Lamiaceae includes semi-shrubs, bracken and herbaceous species. The stem of the species of the family has a square cross-section and bears oil-bearing ducts. The leaves have an opposite arrangement, while the flowers are strongly zygomorphic. They consist of 5 united sepals, 5 petals, of which usually 2 forms the upper lip and 3 the lower lip. Stamens are 4 and carpels are 2. The family includes many aromatic, medicinal and aromatic plants such as oregano, basil, thyme, mountain tea, sage, etc. In Greece the family is represented by over 400 species and subspecies [Dimopoulos et al, 2013], [Dimopoulos et al, 2016]. The *Lamiaceae* belongs to plants that bloom. An abundance of aromatic plants may be found throughout, including common culinary herbs like basil, mint, rosemary, oregano, thyme, and lavender. Certain species are trees, bushes, or infrequently, vines. Since they can be easily grown by stem cuttings, many members of the family are commonly cultivated for their aromatic properties as well as their ease of cultivation [Solomou et al, 2021]. The *Lamiaceae* family, also known as Labiatae, boasts an impressive diversity with over 7,000 species across 250 genera. Some of the largest genera include Salvia, Scutellaria, Stachys, and Thymus. These plants are found throughout the world (cosmopolitan distribution) and thrive in various ecosystems. A hallmark of *Lamiaceae* is their aromatic nature. Most species produce a complex blend of bioactive compounds, contributing to their potent biological activity in both *in-vitro* and

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in-vivo. These secondary metabolites hold promise for their biological properties. Beyond their biological potential, *Lamiaceae* plants offer tremendous value across various industries. From food and cosmetics to flavoring, fragrance, and pharmaceuticals, this family plays a vital role. Their wide range of applications makes them widely cultivated and a crucial source of functional foods. This immense value has spurred extensive research on Lamiaceae species, delving into their biology, ecology, and diverse applications [Uritu et al, 2018].

Many species including *Rosmarinus spp., Micromeria spp., Nepeta spp., Teucrium spp., Scutellaria spp., Satureja spp., Salvia spp., Thymus spp., Origanum spp., Sideritis spp., Mentha spp., Lavandula spp., Stachys spp., Ocimum spp* exist.

Diabetes is a long-term metabolic illness marked by high blood glucose levels. Over time, diabetes can cause significant harm to the heart, blood vessels, kidneys, eyes, nerves, and heart. Approximately 422 million individuals globally suffer from diabetes, with the majority residing in low- and middle-income nations. The disease is also responsible for 1.5 million deaths annually. Over the past few decades, there has been a steady increase in the prevalence of diabetes. [https://www.who.int/health-topics/diabetes]. Type 2 diabetes has been far more common over the last three decades in all nations, regardless of wealth. Insulin-dependent diabetes, or type 1 diabetes, is a chronic condition in which the pancreas produces little to no insulin [Trapali, 2023], [Trapali, 2022], [Trapali, 2021], [Bourkoula et al, 2021]. The human insulin (INS) gene codes for the peptide hormone known as insulin, which is produced by the beta cells of the pancreatic islets. By encouraging the absorption of glucose from the blood into the liver, fat, and skeletal muscle cells, it regulates the metabolism of proteins, lipids, and carbs. Diabetes mellitus is brought on by reduced or absent insulin action. Insulin synthesis and blood secretion are impaired in type 1 diabetes mellitus due to the autoimmune response that destroys beta cells. The loss of beta cells in diabetes mellitus type 2 is not the result of an autoimmune process and is less apparent than in type 1. Although the exact cause of type 2 diabetes is unknown, peripheral tissue insulin resistance, a decline in islet beta cell number, and a drop-in islet beta-cell secretory activity are all factors (Fig.1).

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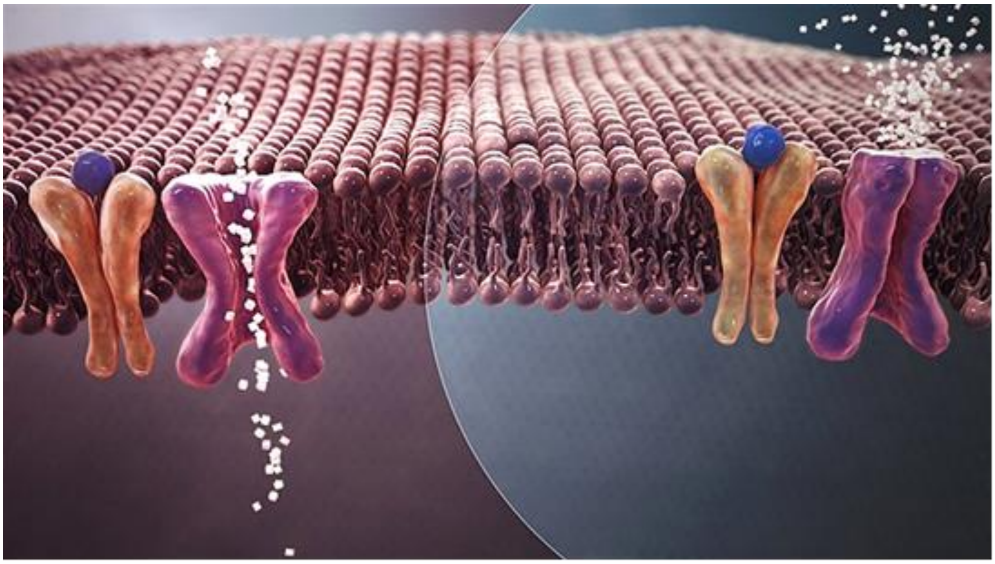

Figure 1: Mechanism of normal Blood Sugar (white crystals) uptake (Left) Vs. insulin resistance in Type 2 Diabetes (Right).
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Inflammation is a complex reaction of body tissues to harmful stimuli including infections, damaged cells, or irritants. Inflammation serves to remove the initial source of cell damage, remove necrotic cells and tissues that have been harmed by the first insult, and start the healing process for injured tissue. Acute inflammation is caused by an increase in the circulation's flow of plasma and leukocytes, particularly granulocytes, into the injured tissues [Ma et al, 2016]. A series of biochemical events involving the immune system, the local vascular system, and other cells in the injured tissue promote the inflammatory response. The simultaneous inflammatory process-induced tissue death and healing characterizes chronic inflammation. Additionally, it consistently alters the types of cells, including mononuclear cells, that are present at the site of inflammation [Ma et al, 2016]. Moreover, Type 1 and Type 2 inflammation have been identified according to the helper T cell (Th1 and Th2) and cytokine types involved (Fig. 2). Oxidative stress is an imbalance of free radicals and antioxidants in the body, which can lead to cell and tissue damage. Free radicals, including reactive oxygen species, are molecules with one or more unpaired electron like: superoxide, hydroxyl radical, nitric oxide radical When the body has more free radicals than antioxidants can neutralize, the free radicals can begin causing damage to proteins, DNA, and fatty tissues (Fig.3). This can eventually result in a wide range of disorders like cancer, Alzheimer's disease, diabetes, cardiovascular conditions such as high blood pressure, atherosclerosis, and stroke,

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inflammatory disorders, chronic fatigue syndrome, asthma male infertility [Pizzino et al, 2018].

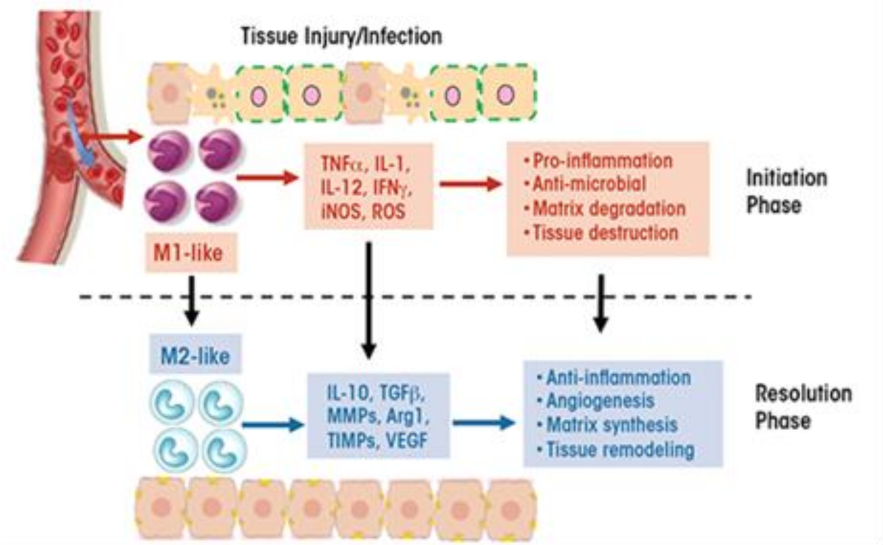

Figure 2: Diagram illustrating the role of macrophage plasticity in tissue damage https://commons.wikimedia.org/w/index.php?search=cytokines+in+inflammation&title=Special:MediaSearch&go=Go&type=image

TNFα, interleukin (IL)-1 and -12, interferon γ (IFNγ), an enzyme that produces nitric oxide (iNOS), reactive oxygen species (ROS), and other pro-inflammatory and stress mediators are produced by macrophages that are recruited to the site of an injury or infection during the initiation phase of the inflammatory reaction. Changing their phenotype from M1 to M2, during the resolution phase of the injury, they appear anti-inflammatory effects and promote blood-vessel formation, matrix synthesis, and tissue remodeling.

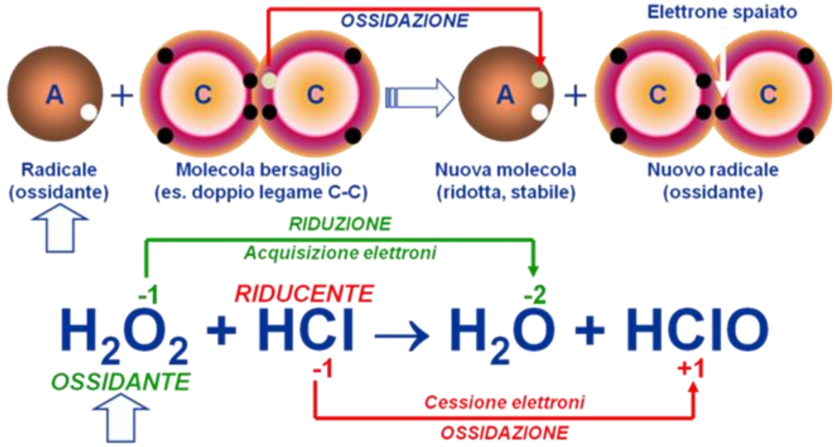

Figure 3: Oxidative stress process https://commons.wikimedia.org/w/index.php?search=Oxidative+stress+process+&title=Special:MediaSearch&go=Go&type=image

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Objective

The study's objective was to compile information from the literature regarding the anti-inflammatory, antidiabetic, and antioxidant properties of *Origanum rotundifolium*, *Rosmarinus officinalis*, *Lavendula angustifolia*, and *Thymus serpyllum*.

Results

1. Lavendula Angustifolia known by several names, including medicinal lavender, and common lavender. This plant is a perennial evergreen one (*Lavandula vera*, *Lavandula angustifolia* and, *Lavandula officinalis*) (Fig.4).

Fig 4. Lavender (Lavendula Angustifolia)
https://commons.wikimedia.org/w/index.php?search=Lavender+%28Lavendula+Angustifolia&title=Special:MediaSearch&go=Go&type=image

The latin verbs "*lavo*" and "*lavare*," which means "wash" or "clean" are the source of the term lavender. For a very long time, lavender has been used as a bath additive, as formulating soaps and perfumes, food additives and as a remedy for several diseases. Lavender species contain more than 100 molecules including essential oil, anthocyanins, phytosterols, sugars, minerals, tannins and coumarins [Letsiou et al, 2023], [Letsiou et al, 2023], [Tebbi et al, 2023], [Habán et al, 2023]. Significant antioxidant potential is present in lavender, though the exact potential varies greatly among species. In the food industry, safe-to-eat antioxidants are essential because oxidative lipid breakdown lowers food quality and flavor. This disintegration could be the consequence of heating techniques like microwave heating or storing. By adding spike lavender essential oil (EO), one can stabilize the lipids, stop the formation of unwanted secondary oxidation products, and preserve the vitamin content [Hajhashemi et al, 2023].

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A protective reaction to a variety of chemical, physical, and biological agents is inflammation. Every one of these things sets off a defensive response in the body. Acute and chronic are the two types, and each has a distinct set of effects. The immune system's overactive response, which releases inflammatory cells like neutrophils, lymphocytes, and macrophages, is linked to inflammation. Inflammatory mediator expression is linked to the immune system's critical function. Furthermore, a number of animal experimental models are used to test anti-inflammatory activity, including the paw edema in mice and rats caused by carrageenan, the mice formalin test, the mice ear edema caused by croton oil, the mice ear edema caused by TPA, and the LPS-stimulated cell line [Dobros et al, 2022]. Studies have shown that the anti-inflammatory properties of lavender stem from the existence of non-volatile terpenoids, polyphenols, and components of essential oils. Numerous studies have demonstrated that lavender oil inhibits important inflammation-related enzymes, including cyclooxygenase (COX), nitric oxide synthase (iNOS), and lipoxygenase (LOX) [Dobros et al, 2022]. Intraperitoneal administration of lavender oil to experimental animals significantly improved oxidative stress parameters and pro-inflammatory cytokine levels [But et al,2023]. In THP-1 single cell culture lavender essential oil extracted at the beginning of flowering period is a potent inhibitor of pro-inflammatory cytokines IL-6, IL-8, IL-β and TNFα [Pandur et al, 2021].

Lavender angustifolia is used for many traditional medical and cosmetic products. Coumarin compounds in lavender exhibit many biological properties, antimicrobial, antibacterial, antifungal, antioxidant, anticancer, anti-HIV, antihypertensive, anticoagulant, anticancer, antiviral, anti-inflammatory, analgesic, antidiabetic, antidepressant and other bioactive properties [Bhattarai et al, 2021].

Lavender has also been recognized as having healing potential in the treatment of type 2 diabetes, and tests are currently being undertaken on it. The possible application of methanol extracts in the management of diabetic dyslipidemia has been studied. The results demonstrated that L. angustifolia decreased the in vitro activity of hormone-sensitive lipase (HSL) and pancreatic lipase (PL). The presence of gallic acid (10,1 and 14,5 g/mL IC50s for PL and HSL, respectively) and rosmarinic (RA) acid (125,2 and 51,5 g/mL IC50s for PL and HSL, respectively) may be linked to these inhibitory effects [Batiha et al, 2023], [Issa et al, 2011].

The result of biotechnologically produced cell suspension extract of Lavandula angustifolia high in RA content as therapeutics for psoriasis-associated inflammation in human keratinocytes has been studied. RA inhibited the JAK2/STAT1 signaling pathway determining psoriasis-like inflammation in human keratinocytes [Koycheva et al, 2021], [Naghdi et al, 2018], [Perra et al, 2022]. The JAK/STAT pathway is associated with stem

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cell supporting, hematopoiesis, inflammatory feedback and transmits signals from cytokines, interleukins and growth factors which act through transmembrane receptors. In a clinical trial including fifty-two patients with type II diabetes mellitus (DM) and insomnia, inhaled lavender ameliorated sleep quality and emotional state in diabetic patients being distressed from insomnia with no remarkable effect on metabolic status [Lari et al, 2020].

2. Rosmarinus Officinalis Known by its common name, rosemary, Rosmarinus officinalis (RO) L. belongs to the Lamiaceae family. In addition to its culinary applications owing to its distinct scent, this plant is extensively utilized by native communities in areas where it grows naturally. RO is a woody, perennial herb with flowers that can be white, pink, purple, or blue. Its leaves are evergreen and fragrant (Fig.5). This is a strong herb from the Mediterranean region. The Latin words "ros" (dew) and "marinus" (sea) are the source of the phrase "dew of the sea". Forms vary in height from 1.5 m to 2 m, with upright forms rarely reaching this height. The evergreen leaves measure 2-4 cm in length and 2.5 mm in width. They are green on top and white underneath, with dense, short, wooly hair [Akshay et al, 2019].

Fig 5. Rosmarinus officinalis
https://commons.wikimedia.org/w/index.php?search=Rosmarinus+officinalis+&title=Special:MediaSearch&go=Go&type=image

The chemical compounds that make up its composition are what give it its antioxidant qualities. Historically, studies have demonstrated the potential benefits of rosemary oil in the treatment or management of a wide range of illnesses, including diabetes mellitus and inflammatory diseases.

It should come as no surprise that Rosmarinus officinalis (RO) has been identified in numerous studies as a potent anti-diabetic agent. RO antioxidant qualities carry out a number of anti-diabetic and anti-

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hyperglycemic actions. In one study, rosemary extract lowered the blood glucose levels of normoglycemic, hyperglycemic, and diabetic rabbits [Bakirel et al, 2008], [Abu-Al-Basai et al, 2010]. The extract also increased insulin secretion by promoting antioxidant enzyme activation and lipid peroxidation inhibition [Bakirel et al, 2008]. Additionally, it was discovered that rosemary relieved delayed wound healing, a significant consequence of diabetes. Following the administration of rosemary, the body's improved antioxidant status is responsible for these anti-diabetic effects [Khalil et al, 2012], [de Oliveira et al, 2019].

Moreover, several studies demonstrated strong anti-inflammatory mechanisms exhibited by Rosmarinus officinalis. Leukocyte migration was found to be significantly inhibited in vivo by rosemary essential oil and extract. An anti-inflammatory response was produced as a result of the decrease in leukocytes at the site of inflammation. Additionally, pro-inflammatory compounds like nitric oxide and genes linked to inflammation were inhibited by rosemary extract [Mengoni et al, 2011], [Benincá et al, 2011], [Gaya et al, 2013]. The effect of rosemary addition on Barbarine rams and dogs was studied and the results showed decrease in blood glucose and enhancement of the spermatic quality and the hormonal status regulating the testicular function [Khnissi et al, 2023], [Abdelrahman et al, 2020]. A daily dose of 400 mg/kg for 21 days, via gavage of Rosmarinus officinalis in animal models showed anti-inflammatory activity lowering the levels of SOD, TNFα, CAT, IL6 and IL10[Gonçalves et al, 2022], [Ahmed et al, 2020].

Changes in the gut microbiota induced by essential oils rosemary as prebiotics in mice, regulated cardiovascular and metabolic factors, which focus on the potential of these nutraceuticals for reducing Ischemic heart disease risk in patients affected by type-2 diabetes mellitus [Sánchez-Quintero et al, 2022].

3. **Thymus Serpyllum** a genus that belongs to the *Lamiaceae* family. It comprises approximately 250 taxa worldwide, comprising 214 species and 36 sub-species. The Thymus genus originated in the Mediterranean area, especially in the Iberian Peninsula and North-West Africa (Fig.6).

From there, it extended to Asia, Europe, Greenland, North America, and Abyssinia. Because of its delicious flavor, healthful qualities, and medicinal qualities, plants in the Thymus genus are widely employed in the food, cosmetic, perfume, and pharmaceutical industries. Some species, such T. pulegioides L. (big thyme), T. serpyllum L. (wild thyme), and T. zygis L. (Spain thyme), are important commercial types grown around the world.

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Fig 6. Thymus Serpyllum
https://commons.wikimedia.org/w/index.php?search=Thymus+Serpyllum&title=Special:MediaSearch&go=Go&type=image

Plants in the Thymus genus have extracts and characteristic monomer components that have been shown to be effective natural antioxidants that reduce oxidative stress, especially in the liver and heart. *Thymus Serpillum* (TS) essential oil (EO) showed the highest radical scavenging activity (EC50:0.94 g/mL). followed by oils of *Thymus algeiensis* (TA) (EC50: 1.64 g/mL) and *Thymus vulgaris* (TV) (EC50: 4.80 g/mL) which was confirmed by previous studies regarding the EOs of this plant [Salaria et al, 2023].

TS ability to inhibit diabetes mellitus was studied previously and the results showed that it targets 91 genes and contains 21 constituents as active ingredients, with scutellarein (producing the lowest concentration of Ca^{2+}) acting as the hub gene and most active ingredient, respectively. The main mechanism of TS against diabetes is the inactivation of the advanced glycation end products (AGE), Receptor for AGE (RAGE) signaling (oxidative stress induced) pathway, which may help to prevent diabetes-related comorbidities and disease progression. The mechanisms of TS against diabetes have been linked to 26 signaling pathways [Alamgeer et al, 2014]. When Diabetes was induced in BALB/c mice fed with a high-fat diet, oral administration of aqueous extract of Thymus serpyllum attenuated hyperglycemia in their liver muscle via AMPK and IRS1 upregulation. AMP-activated protein kinase (AMPK) plays a critical role both in sensing and regulating cellular energy state. In experimental animals, its activation has been shown to reduce the risk of obesity and diabetes-related co-morbidities such as insulin resistance, metabolic syndrome and atherosclerotic cardiovascular disease [Azhar et al,.2022], [Wahab et al, 2022].

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4. Origanum rotundifolium, Another member of the *Lamiaceae* family is oregano. Since this plant grows at heights of 400–1800 m and in sunny locations, its name, Origanum, originates from the Greek name όρίγνον (origanon), which in turn comes from the words Ͻρος (oros = mountain) and γάνος (ganos = brightness). (Fig.7). Greece and Turkey are home to the most of Origanum species, which are found in the Mediterranean. Certain species of Origanum are annual or perennial herbs with small, round, oval-shaped leaves that can have toothed edges and pointed, obtuse tips. The flowers are grouped in spikes and may be white, pink, or purple in color [Picos-Salas et al, 2021].

Fig 7. Origanum rotundifolium
https://commons.wikimedia.org/w/index.php?search=Origanum+rotundifolium+&title=Special:MediaSearch&go=Go&type=image

Origanum rotundifolium extract contained a number of flavones such as: xanthomicrol (5,4′-dihidroxy-6,7,8-trimethoxyflavone), luteolin-7-O-diglucuronide, apigenin-7-O-triglucuronide, luteolin-7-O-rutinoside, vitexin, 6,8-di-C-hexosylapigenin. The most often found flavones, are derivatives of luteolin and apigenin, which have demonstrated antioxidant, anti-cancer, and anti-inflammatory effects [Picos-Salas et al ,2021], [Maietta et al, 2018]. Vitexin also disclosed antiproliferative activity against HeLa, HT29, C6 and Vero cells lines [Erenler et al, 2017].

Furthermore, research on plants in the *Lamiaceae* family has linked the anti-diabetic qualities of Origanum essential oil to its primary constituents, carvacrol and thymol. This suggests that the mechanism of action of EOs may differ based on their composition [Leyva-López et al, 2017], [Aras et al, 2017]. Mixture of Cinnamomum verum (CV), Origanum majorana (OM), and Origanum vulgare (OV) plants investigated promising antidiabetic activities on glucose-induced-diabetic zebrafish [Gutiérrez et al, 2021], while OV

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extract inhibited α-glucosidase activity, upgraded glucose uptake, restrained glycosylation and alleviated oxidative stress In vitro assays [Yu et al, 2021].

Conclusion

This study emphasizes the possible health advantages of numerous *Lamiaceae* plants, such as oregano, thyme, lavender, and rosemary. Plants of the *Lamiaceae* family have a lot of antioxidant-producing chemicals, these antioxidants can aid in lowering the body's oxidative stress, which has been connected to a number of chronic illnesses. These plants may ameliorate insulin activity and blood sugar regulation. Plants of the *Lamiaceae* family may have anti-inflammatory qualities that could lessen the symptoms of inflammatory diseases, which can be found in functional meals, and may provide a natural way to manage inflammation. The *Lamiaceae* family provides a natural source of substances that may be used in functional foods. These functional meals have the potential to improve general health and help manage chronic illnesses. The precise mechanisms of action of these plants and the best doses for use in functional food applications require more investigation. To confirm the effectiveness and safety of functional foods based on the *Lamiaceae* family, clinical trials are required. It is imperative to look at how these functional foods interact with prescription drugs. These plants have the power to transform the functional food market and advance health by overcoming these obstacles and conducting additional research.

Conflict of Interest: The authors reported no conflict of interest.

Data Availability: All data are included in the content of the paper.

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