Chapter 14
Anticholinesterase, Antidiabetic and Anti-inflammatory Activity of Secondary Metabolites of *Teucrium* Species

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Abstract The chapter reviews the data about anticholinesterase, antidiabetic, and anti-inflammatory activity of the active substances from *Teucrium* species. Extracts and essential oils from the species of *Teucrium* genus possess a wide range of secondary metabolites that exhibit biological activity. Discussed examinations are focused on the determination of the qualitative and quantitative composition of the active substances from *Teucrium* species, as well as the anticholinesterase, antidiabetic and anti-inflammatory activity. Many authors state that Alzheimer's disease, diabetes mellitus, and inflammatory diseases correlate because they are precursors of neurodegenerative diseases. Secondary metabolites isolated from plants of the genus *Teucrium* have been shown to be potential inhibitors of acetylcholinesterase. Also, examined metabolites possess antihyperglycemic activity and reduce blood glucose levels. Extracts of the species from the genus *Teucrium* exhibit anti-inflammatory activity in in vitro and in vivo conditions by inhibiting carrageenan-induced inflammation and significantly reduced serum levels of triglyceride and cholesterol. As a result, it has been shown that the species of the genus *Teucrium* are rich in compounds such as flavonoids, phenolic acids and terpenoids that directly contribute to anticholinesterase, antidiabetic and anti-inflammatory activity. Species of the genus *Teucrium* are good candidates for further examination in order to the treatment of the previously mentioned disorders.

Keywords *Teucrium* species · Acetylcholinesterase · Alzheimer's disease · Diabetes mellitus · Inflammation

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Abbreviations

ACh	Acetylcholine
AChE	Acetylcholinesterase
AChI	Acetylcholine iodide
AD	Alzheimer's disease
COX	Cyclooxygenase
DTNB	5,5-dithio-bis-2-nitrobenzoic acid
FDA	Food and drug administration
HLA	Human leukocyte antigen
IC_{50}	Half maximal inhibitory concentration
iNOS	Inducible nitric oxide synthase
LDL	Low density lipoproteins
mRNA	Messenger ribonucleic acid
NO	Nitric oxide
STZ	Single dose streptozotocin
TNB	2-nitro-5-mercaptobenzoic acid

14.1 Introduction

Genus *Teucrium* L. belongs to the family Lamiaceae. Some species belonging to the genus *Teucrium* are known medicinal plants that have wide application. Medicinal species of the genus *Teucrium* are used in the treatment of rheumatism, diabetes, inflammatory and gastrointestinal diseases. The most common groups of secondary metabolites from the *Teucrium* species are flavonoids, phenolic acids, monoterpenes, diterpenes, sesquiterpenes, and others. Due to the specific quantitative and qualitative composition of secondary metabolites, plant species of the genus *Teucrium* exhibit various types of biological activity such as antioxidant, anticancer, anti-inflammatory, antidiabetic, antimicrobial and antiviral activity (Stanković 2012.

This chapter describes the main features of medicinal plants from the genus *Teucrium* on acetylcholinesterase inhibition, diabetes mellitus, and inflammatory processes. Additionally, a brief description of the methods used in the examination of anticholinesterase, antidiabetic and anti-inflammatory activity will be shown.

14.2 Acetylcholinesterase

Acetylcholinesterase (AChE) is serine hydrolysis belonging to the group of enzymes that affect different types of carboxylic esters (Čolović et al. 2013). Acetylcholine is a monomeric molecule consisting of 12 collected beta plates surrounded by 14 alpha helices and possesses a molecular weight of about 60,000. The

acetylcholinesterase molecule consists of several essential parts, peripheral anionic site, the catalytically active site and the aromatic throat (aromatic "gorge"). The peripheral anionic site plays an important role in recognizing the conformation of residues in the aromatic throat and in the catalytic site. The catalytic active site consists of an esterase and anion subunit. Esterase subunit is composed of three amino acids (Ser200, His440, and Glu327). The anionic sub spot plays a role in binding the positively charged quaternary amine of the choline group of acetylcholine (Nađpal 2017).

Acetylcholine (Fig. 14.1) is one of the essential neurotransmitters in the brain. In the central nervous system, it is found in interneurons and some cholinergic nerve fibers. Also, acetylcholine has an important role in the processes of memory and learning, as well as the maintenance of consciousness (Sisodia and Tanzi 2006; Topcu and Kusman 2014). In the peripheral nervous system, acetylcholine participates in the transmission of nerve signals in the motor plate and causes muscle contraction, slows down the pulse, enlarges blood vessels, influences the increased secretion of gastric glands, enhances peristaltic intestines (Takeda et al. 2004).

Science has not yet explained in the best way how choline is brought to the nerve endings, while acetyl groups are fed through the choline acetyltransferase enzyme derived from coenzyme A. Acetylcholine is found in presynaptic nerve endings in a state that can be immediately released or store in the form of surplus (Orhan et al. 2007; Čolović et al. 2013). Depending on whether there is a pulse, it remains unclear how acetylcholine is released from presynaptic endings. Although it is considered that calcium plays a major role in the process. Acetylcholine is released from the presynaptic neuron into the synaptic crack during transmission and binds to acetylcholine receptors (muscarinic and nicotinic) in the postsynaptic membrane, transmitting the neuron signal. The acetylcholine degradation enzyme is called acetylcholinesterase (Takeda et al. 2004; Sisodia and Tanzi 2006; Vladimir-Knežević et al. 2014). The acetylcholinesterase enzyme separates the acetylcholine to the choline an acetate group, which prevents the recurrence of muscular irritation. Released choline is transported to the presynaptic neuron and it is used for the resynthesis of acetylcholine by the activity of choline acetyltransferase enzyme (Čolović et al. 2013). Each molecule of acetylcholinesterase enzyme inhibits an average of 25,000 acetylcholine molecules per second, thereby enzyme having an appreciable catalytic activity. The choline formed in the process of decomposition of acetylcholine is recycled to recover acetylcholine. The main form of acetylcholinesterase is found in the brain and muscles. Acetylcholinesterase is encoded by AChE in humans (Čolović et al. 2013; Nađpal 2017).

A neurodegenerative disease such as Alzheimer's disease indicates a condition where neurons of the spinal cord and brain collapse (Mattson 2004). This leads to a loss of muscular coordination and cognitive dysfunction. Alzheimer's disease (AD), first described by neuropsychiatrist Alois Alzheimer in 1906, is a progressive

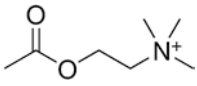

Fig. 14.1 Chemical structure of acetylcholine (ACh)

degeneration, which most often affects the elderly in developed countries (Nađpal 2017). The disease is recognized by the loss of short-term memory and disorientation (Akhondzadeh et al. 2003; Topcu and Kusman 2014). In morphological terms, Alzheimer's disease is characterized by the appearance of D-amyloid deposits and neurofibrillary loops produced by hyperphosphorylated τ-proteins (Adewusi et al. 2011). Neurochemical is characterized by loss of activity of cholinergic neurotransmitters, primarily acetylcholine (ACh) in the cerebral cortex (Orhan et al. 2007).

In people suffering from Alzheimer's disease, choline-acetyltransferase has been significantly reduced in the central nervous system. The loss of choline acetyltransferase is particularly pronounced in brain regions where the areas responsible for memory are located, i.e. in the cortex and hippocampus of the brain. Treatment of people suffering from Alzheimer's disease implied the use of acetylcholine, but such attempts to treat the disease have not shown great success (Nađpal 2017). Today's attempts to treat affected people are aimed at increasing cholinergic transmission by blocking the activity of acetylcholinesterase that degrades acetylcholine in synaptic cracks. Also, there are acetylcholinesterase inhibitors that are used in medicine but with varying degrees of efficacy in treatment (Mattson 2004).

14.2.1 Inhibition of Acetylcholinesterase

Pharmacological inhibitors of acetylcholinesterase are very important in the context of diseases where reduced neurotransmission activity mediates acetylcholine. In a disease such as Alzheimer's, there is a loss of cholinergic neurons in the brain, while some autoimmune diseases of the antibody lead to loss of nicotine acetylcholine receptors in the motor plate (Čolović et al. 2013). Alzheimer's disease is one of the most common forms of dementia, where there is a significant loss of brain mass. Despite numerous findings, it is still not known what causes Alzheimer's disease. It is considered that disease is developed by decreasing holing-acetyltransferase activity and inhibition of acetylcholinesterase enzyme is important for the treatment of the disease. The inhibition of acetylcholine increases its concentration in the synapses, which allows long-term stimulation of the receptors and the control of the disease (Soreq and Seidman 2001).

Depending on the mode of action, acetylcholine inhibitors are divided into irreversible and reversible. Reversible inhibitors are protagonists in the treatment of Alzheimer's disease symptoms. In the treatment of Alzheimer's disease, drugs that compensate for ACh deficiency, including ACh precursors, muscarinic and nicotinic receptor antagonists, and AChE inhibitors (Akhondzadeh et al. 2003). Inhibition of AChE is one of the most widely used treatment models for Alzheimer's disease (Akhondzadeh et al. 2003; Orhan et al. 2007). Some of the synthetic and natural remedies, such as galanthamine (Razadyne®, Reminyl®) donepezil (Aricept®), rivastigmine (Exelon®), and tacrine (Cognex®) are approved by the Food and Drug Administration, FDA) (Topcu and Kusman 2014; Nađpal 2017).

These drugs respond by enhancing the transmission of cholinergic neurons in the frontal region of the brain and compensating the loss of functional brain cells. Additionally, the treatment of Alzheimer's disease by drugs are used in the treatment of symptoms of neurological disorders such as Parkinson's disease, dementia with Levi's bodies and Myasthenia gravis. Irreversible acetylcholine inhibitors have a toxic activity whose function is reflected in the accumulation of acetylcholine in synaptic cracks, resulting in disorders in neurotransmission (Čolović et al. 2013). Synthetic acetylcholinesterase inhibitors exhibit side effects. Side effects are detected in the disorder of the gastrointestinal tract and hepatoxicity. There is still no answer in the science of developing acetylcholine inhibitors that manage in the brain without effect on other organs.

Commercially common inhibitors of acetylcholinesterase enzymes such as donepezil, tacrine, and rivastigmine have a damaging effect on human health, and now trying to find alternative substances of plant origin that will replace synthetic drugs. Tacrine has a short-acting time, unlike other drugs, and tablets should be taken several times a day, although it has been shown that taking this drug causes headache, muscle pain, loss of aptitude, nausea, diarrhea, etc. Rivastigmine and donepezil have similar effects because they are reversible acetylcholinesterase inhibitors, but their effect is reduced after prolonged usage (Martorana et al. 2010; Nađpal 2017).

14.2.2 Plants as Natural Sources of Anticholinesterase Agents

Nowadays, science is focused on the testing of plant extracts of certain species in order to inhibit acetylcholine and treat neurodegenerative diseases (Dastmalchi et al. 2007; Zhao et al. 2013). Galantamine is one of the most effective acetylcholinesterase inhibitors isolated from plant extracts of *Galanthus nivalis*. Galantamine does not exhibit adverse effects such as synthetic inhibitors and is used for clinical purposes. Moreover, other compounds that exhibit significant anti-acetylcholinesterase activity have been isolated (Mukherjee et al. 2007). The α-viniferin is isolated from *Caragana chamlagu* and exhibits significant anti-acetylcholinesterase activity, as well as huperzine-A which isolated from *Huperzia serrata*. Then, physostigmine isolated from the seeds of *Physostigma venenosum* is a reversible acetylcholinesterase enzyme inhibitor. Also, ursolic acid derived from commercial extract (*Origanum majorana*) exhibits significant anti-acetylcholinesterase activity (Mukherjee et al. 2007; Roseiro et al. 2012). *Ginkgo biloba* is used in traditional medicine for the prevention of degenerative brain disorders and helps maintain concentration. The chemical composition of this type of extract includes bilobalide, ginkgolide, and other compounds such as kaempferol and quercetin (Čolović et al. 2013; Nađpal 2017).

In addition to herbal extracts, there are data about using essential oils from herbs that are potent inhibitors of acetylcholinesterase enzymes due to the presence of certain compounds. Many medicinal plants are used in medicine as stimulants for

cognitive stimulation, for the treatment of depression and Alzheimer's disease. Plant species that are used in traditional medicine in the treatment of dementia belong to the genus *Salvia*, which is at the same time one of the most numerous genera belonging to the family Lamiaceae (Vladimir-Knežević et al. 2014).

14.2.3 Lamiaceae Species as a Sources of Anticholinesterase Agents

Numerous plant species belonging to different families such as Amaryllidaceae, Lamiaceae, Papaveraceae have been investigated in order to find effective acetylcholinesterase inhibitors. Some plant alkaloids, ursolic and oleic acid have been shown to be good inhibitors of acetylcholinesterase (Topcu and Kusman 2014). Plant species belonging to the Lamiaceae family are known for their medicinal properties because they possess a wide diversity of secondary metabolites that exhibit their pronounced biological activity. The biological activity of plant secondary metabolites is based on their ability to react with many regulatory molecules and other cell and subcellular structures, thereby affecting, either positively or negatively, a large number of metabolic processes. Some Lamiaceae species possess essential oils, flavonoids and hydroxycinnamic acid which are one of the main bioactive compounds. Genera belonging to the Lamiaceae family, such as *Lavandula, Origanum, Mentha, Salvia, Rosmarinus, Thymus, Teucrium*, and *Calamintha* are well known for their neuroprotective effect and usage in traditional medicine in the treatment of many diseases (Topcu and Kusman 2014).

Plants of Lamiaceae family are rich in phenolic acids, primarily rosmarinic and chlorogenic acid, and also include gentisic, caffeine, proto-catheic, vanillic, ferulic and souric acid (*Lavandula, Nepeta, Rosmarinus, Teucrium, Salvia*). Rosmarinic acid is characteristic of the some species from Lamiaceae family (Vladimir-Knežević et al. 2014). Also, they are rich in triterpene derivatives, ursans and oleans, where ursol, betulin and oleic acid are present in the highest percentage (*Salvia, Rosmarinus*) (Jäger et al. 2007). The plants of the Lamiaceae family, as well as other plant species, synthesize flavones and flavonols that, in addition to other secondary metabolites, contribute to the biological activity of these plants (Vladimir-Knežević et al. 2014). The species of the Lamiaceae family were objects of numerous pharmacological studies showing that their extracts and essential oils show a number of biological effects in vitro and in vivo conditions. The plant's essential oils belonging to the family include components such as sesquiterpenes, monoterpenes, diterpenes, aliphatic and aromatic components. The biological activity of extracts and essential oils may be significant in the treatment of neurodegenerative disorders, in particular, Alzheimer's disease (Topcu and Kusman 2014).

Vladimir-Knežević et al. (2014) examined selected Lamiaceae species to the ability to inhibit acetylcholinesterase. In their results, it has been shown that extracts of several plant species such as *Teucrium chameadrys, Thymus vulgaris, Mentha*

piperita, Salvia officinalis, Saturea montana inhibit over 75% acetylcholinesterase activity. The ethyl alcohol extract of *Salvia trilobacterium* inhibited acetylcholinesterase at 0.71 mg/ml, while the *Melissa officinalis* extract was completely inactive (Orhan and Aslan 2009). Ferreira et al. (2006) examined the extracts and essential oils of ten plants on the ability to inhibit acetylcholinesterase. They noticed that the species *Lavandula pedunculata*, *Mentha suaveolens* and *Melissa officinalis* show the inhibitory effect on acetylcholinesterase among the tested plant species. A high degree of acetylcholinesterase inhibition was observed by examining essential oil of *Mentha, Origanum* and *Saturea* species, while moderate and low inhibition of the activity of acetylcholinesterase enzymes was observed by examining the essential oil of plant species belonging to the genera *Ocimum, Lavandula*, and *Salvia* (Orhan et al. 2008). The results of the antiacetylcholinesterase effect of plant extracts and essential oils isolated from the species of the Lamiaceae family were presented in numerous studies (Orhan et al. 2007; Orhan and Aslan 2009; Topcu and Kusman 2014; Vladimir-Knežević et al. 2014). The studies show that plant species belonging to the Lamiaceae family are a natural source of acetylcholinesterase inhibitors and can be used in the prevention and treatment of neurodegenerative diseases (Vladimir-Knežević et al. 2014).

14.2.4 Teucrium *Species as a Sources of Anticholinesterase Agents*

Species of the genus *Teucrium* are known for their medicinal properties. Extracts of *Teucrium* species possess different secondary metabolites that exhibit biological activity. Secondary metabolites isolated from extracts of *Teucrium* species, have been shown to be potential inhibitors of acetylcholinesterase (Orhan and Aslan 2009; Vladimir-Knežević et al. 2014). Vladimir-Knežević et al. (2014) examined the ethanol extracts of *Teucrium* species on the ability to inhibit acetylcholinesterase using Ellman's colorimetric assay. The authors state that the extracts of the tested species such as *Teucrium arduini, T. chamaedrys, T. montanum*, and *T. polium* showed strong inhibitory activity against acetylcholinesterase. The percentage of the inhibition of acetylcholinesterase for the ethanolic extracts of these plants was obtained for tested concentrations of 0.25, 0.50 and 1 mg/ml, respectively. The same authors state that all investigated species of the genus *Teucrium* had a percentage of inhibition of acetylcholinesterase over 80% at 1 mg/ml. Among the investigated species, *Teucrium arduini* exhibits the highest ability to inhibit acetylcholinesterase enzymes over 95% at 1 mg/ml, followed by *Teucrium chamaedrys* that neutralize the enzyme near to 90% at the same concentration. *Teucrium polium* shows similar values as *Teucrium chamaedrys*, 86% at a concentration of 1 mg/ml. Among the tested species, *Teucrium montanum* shows the lowest ability of neutralizing acetylcholinesterase enzymes, about 80% at a concentration of 1 mg/ml. According to the ability to inhibit the enzyme acetylcholinesterase, the investigated plant species

have the following order *T. arduini* > *T. chamaedrys* > *T. polium* > *T. montanum* at a concentration of 1 mg/ml. At a concentration of 0.50 mg/ml *Teucrium chamaedrys* and *T. polium* exhibit the highest ability to inhibit acetylcholinesterase enzyme above 60%. *Teucrium arduini* shows slightly less inhibitory capacity than the previous two species, 58%. *Teucrium montanum*, in this case, shows the lowest ability to neutralize acetylcholinesterase enzymes, about 45% at a concentration of 0.50 mg/ml. The order of plants for a concentration of 0.50 mg/ml would be *T. chamaedrys* > *T. polium* > *T. arduini* > *T. montanum*. At a concentration of 0.25 mg/ml *Teucrium chamaedrys* and *T. arduini*, the highest inhibition ability is greater than 35%. *Teucrium montanum* has a higher ability to inhibit acetylcholinesterase enzymes 32% from *Teucrium polium* 28% at a minimum concentration of 0.25 mg/ml. The investigated plant species of the genus *Teucrium* at a concentration of 0.25 mg/ml have the following order *T. chamaedrys* > *T. arduini* > *T. montanum* > *T. polium*.

Golfakhrabadi et al. (2015) investigated the influence of the methanol extract of *Teucrium hyrcanicum* on the inhibition of acetylcholinesterase enzymes at the same time compared to donepezil as a positive control. The results showed that the IC_{50} values for the methanol extract of *Teucrium hyrcanicum* and donepezil were 2.12 mg/ml and 0.013 mg/ml, respectively. At a concentration of 1 mg/ml, the inhibitory activity of the methanol extract of the tested species was 40% (Golfakhrabadi et al. 2015). The anticholinesterase activity was investigated for the *Teucrium royleanum*, using organic solvents of different polarities (Ahmad et al. 2007). The authors state that the greatest ability to neutralize the acetylcholinesterase enzyme is observed for the ethyl acetate fraction, 83.62%. The chloroform fraction with the ability to neutralize the enzyme is 70.5%. The n-butanol fraction showed moderate activity against acetylcholinesterase 59.55%, while crude extract of *Teucrium royleanum* also showed moderate activity against acetylcholinesterase enzymes, 52.4% (Ahmad et al. 2007). A qualitative examination of *Teucrium royleanum* essential oil identified compounds such as sesquiterpene hydrocarbons, *β*-caryophyllene, germacrene D, alpha-humulene and linalool (Mohan et al. 2010).

Preliminary investigations of the inhibitory activity of plant extracts of species belonging to the genus *Teucrium* on the enzyme acetylcholinesterase indicate that the extracts of these plants have a strong or moderate ability to inhibit this enzyme. By examining the composition of *Teucrium* phenolic compounds from the group of phenolic acids, the most common are rosmarinic and chlorogenic acid, as well as from the group of flavonoids the most common are luteolin and apigenin. Experiments showed that rosmarinic acid contributes to the inhibition of acetylcholinesterase enzymes (Vladimir-Knežević et al. 2014). For the species of this genus, the presence of a monoterpene and sesquiterpene is characteristic (Monsef-Esfahani et al. 2010). Plants of genus *Teucrium* are rich in terpene components which are known that possess inhibitory properties of the enzyme acetylcholinesterase (Yoo and Park 2012; Vladimir-Knežević et al. 2014).

14.2.5 Methods for Determination of the Anticholinesterase Activity

One of the most prominent methods present in scientific studies of acetylcholinesterase inhibition is Ellman's method (Ellman et al. 1961; Burčul 2008). It is a spectrophotometric method based on the reaction of Ellman's reagent DTNB (5,5-dithiobis-(2-nitrobenzoic acid)) with a thiol group of substrates formed by the action of acetylcholinesterase. The reaction of DTNB with thiol groups leads to the formation of TNB (2-nitro-5-mercaptobenzoic acid) which is further hydrolyzed in the water at neutral or alkaline pH. Free TNB has a yellow color. The maximum absorption DTNB is at a wavelength $\lambda = 320$ nm, while the amount of TNB is read at a wavelength at $\lambda = 412$ nm. Reaction mixture should consist of: 100 ml acetylcholinesterase concentration 0.3 U/mg dissolved in 0.1 M phosphate buffer at an alkaline pH = 8; then 50 ml DTNB; acetylcholine iodide concentration 0.3 mM dissolved in 0.1 M phosphate buffer at neutral pH = 7; 50 ml sample (inhibitor or alcohol extract) dissolved in methanol; 850 ml 0.1 M phosphate buffer alkaline pH = 8.

In order to determine the possible non-enzymatic hydrolysis of AChI, two reference solutions should be made. The first reference solution instead of AChE was buffered (1000 ml) instead of the ethanol inhibitor (50 ml) and DTNB and AChI (50 ml). The other reference solution contains everything the same as the first reference solution only that AChI is excluded so that it contains buffer (1000 ml), ethanol, AChE, and DTNB (50 ml). Additionally, it is necessary to prepare a control solution where the 50 ml inhibitor is replaced with 50 ml methanol. It is important to note that before the experiment it is necessary to check that methanol or some other organic solvent does not interfere with AChE inhibition. The reference solutions should be incubated at room temperature for a period of 30 min. The reaction begins with the addition of 50 ml AChI as the substrate and after 6 min the absorbance is measured at a wavelength $\lambda = 412$ nm.

14.3 Diabetes Mellitus

Early studies have shown that cerebral cortex and hippocampus neurons are characterized by an inadequate response and decreased secretion of insulin effect, which indicates the emergence of neurodegenerative diseases (Craft 2007; Chiung-Chun et al. 2010). Many authors consider that insulin plays an important role in central energy metabolism and that insulin regulation disorders can influence the pathogenesis of neurodegenerative diseases, such as Alzheimer's disease. Numerous studies have shown a significant correlation between the occurrence of Alzheimer's disease and Type 2 diabetes mellitus (Craft 2007; Sims-Robinson et al. 2010).

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia, or high blood glucose levels. The onset of the disease is the result of inadequate

blood glucose control by insulin hormones synthesized in the pancreas (Zimmet et al. 2001). Hyperglycemia occurs due to partial or complete insulin deficiency. The onset of hyperglycemia affects the onset of long-term complications, with cardiovascular, peripheral and cerebrovascular disorders being distinguished (Alberti and Zimmet 1998).

Type 1 diabetes is characterized by the destruction of β-cells leading to an insulin deficiency. It is a condition where the pancreas does not create or creates very little insulin because the β-cells of the pancreas are destroyed by the autoimmune mechanism. Markers of immune destruction of β-cells are autoantibodies against β-cells when initially detected hyperglycemia. This disease is also associated with certain HLA genes, and the presence of certain alleles may be predominant or protective (Devendra et al. 2004).

Type 2 diabetes mellitus is predominantly insulin resistance with relative insulin deficiency and predominantly insulin secretory deficiency with insulin resistance. Type 2 diabetes accounts for 90 to 95% of the total number of diabetes cases in the world and is due to the presence of insulin resistance in skeletal muscles and liver and reduced insulin production, so there is a relative but rarely absolute insulin deficiency. Type 2 diabetes is a progressive disease where the production of insulin decreases as the disease progresses. Insulin resistance develops due to genetic defects in combination with environmental factors, primarily obesity, and physical inactivity. As the disease progresses, insulin resistance remains relatively stable, and insulin production declines progressively (Kahn 2003; Rewers 2012).

Treatment of diabetes involves a complex of factors that involve the exercise, diet, and drugs. Drugs used to treat diabetes of mainly synthetical origin and have certain negative side effects. Medicinal plants are used in the treatment of many disorders and have a significant role in the treatment of diabetes mellitus as a serious metabolic disorder. It has been shown experimentally that medicinal plants used in the treatment of diabetes do not show any negative effects. Plant species are rich in compounds such as phenolics, tannins, alkaloids and flavonoids that improve the efficiency of pancreatic tissues by increasing insulin secretion or decreasing intestinal absorption of glucose (Kooti et al. 2016).

14.3.1 Plants as Natural Sources of Antidiabetic Agents

Numerous plant species belonging to different families of Amaryllidaceae, Asteraceae, Apiaceae, Cucurbitaceae, Fabaceae, Gentianaceae, Lamiaceae, Liliaceae, Rosaceae, etc. were investigated in order to find effective substances for the purpose of treating diabetes (Moradi et al. 2018). Extracts of certain plant species have been shown to modulate the metabolic pathways such as glycogen synthesis, glycolysis, cholesterol synthesis and release of insulin (Prabhakar and Doble 2008). The extract of *Carthamus tinctorius* (Asteraceae) is used in the treatment of Type 1 and Type 2 diabetes, because the presence of flavonoids, such as quercetin and kaempferol, is determined by phytochemical analyzes, which are the causes of

hypoglycemic effects of these compounds. *Swertia punicea* (Gentianaceae) was investigated in order to determine the hypoglycaemic effect, which can be used in the treatment of diabetes because it promotes insulin resistance in the diabetic mice (Moradi et al. 2018).

The aqueous root extract of *Sarcopoterium spinosum* (Rosaceae) was examined in order to determine the anti-diabetic effect of progressive hyperglycemia in mice that are genetically diseased with diabetes. The results showed that the aqueous extract of the roots of the investigated species showed positive results in the treatment of diseased mice. Also, the aqueous extract of *Liriope spicata* (Liliaceae) positively influences the reduction of blood glucose levels and promotes glucose tolerance and resistance of insulin in the mice (Moradi et al. 2018). Ethanol extract of *Momordica charantia* (Cucurbitaceae) possess antihyperglycemic and hypoglycemic effect in normal and streptozotocin-diabetic rats. A four-week experiment conducted on Type 2 diabetes mellitus rats showed that the *Allium sativum* extract (Alliaceae) enhanced glycemic control by increased insulin secretion and enhanced insulin sensitivity, which showed the antihyperglycemic and antihyperlipidemic effect of this type of extract (Moradi et al. 2018). The study of the effects of plant extracts on the treatment of diabetes was carried out by (Huseini et al. 2006; Rao and Nammi 2006; Das et al. 2009; Abeywickrama et al. 2011; George et al. 2011; Das and Barman 2012; Rabiei et al. 2014; Jiao et al. 2017; Moradi et al. 2018).

14.3.2 Lamiaceae Species as a Sources of Antidiabetic Agents

Some plant species belonging to the Lamiaceae family are used in the treatment of diabetes due to the presence of compounds that exhibit pronounced biological activity. Genera belonging to the Lamiaceae family, such as *Ocimum, Origanum, Salvia, Teucrium, Lamium*, etc. are known for their antidiabetic activity (Patil et al. 2011; Moradi et al. 2018). *Origanum vulgare* aqueous extract affects the reduction in glucose levels of glycosylated hemoglobin, and pancreatic amylase in diabetic rats. Extract usage in of dietary in diabetes rats influenced the content of glycogen in the liver, body weight and the level of urea. Plant parts of *Salvia nemorosa* contain glycosides such as salvionosides and megastigmands. It has been shown experimentally that in diabetes mice, insulin levels are increased using extracts, which increases the activity of insulin (Sadeghzadeh et al. 2008). By isolating a luteolin compound from a plant species belonging to the genus *Perilla* it has been shown a positive effect on the development of diabetic nephropathy (Moradi et al. 2018). Flavonoid luteolin reduces creatinine levels and diabetic rats and prevents the increase in urea protein in 24 h. Aqueous and ethanolic extract of the *Ocimum tenuiflorum* resulted in decreased levels of blood glucose, fatty acids, lipid peroxides and low-density lipoproteins (Hussain et al. 2001, 2015). A tetracyclic terpenoid isolated from a hydro alcoholic extract of *Ocimum tenuiflorum* exhibited potential antidiabetic properties (Patil et al. 2011). Hannan et al. (2006) showed that ethanol,

butanol, aqueous and ethyl acetate fractions of *Ocimum tenuiflorum* stimulated insulin secretion.

14.3.3 Teucrium *Species as a Sources of Antidiabetic Agents*

Secondary metabolites isolated from extracts of *Teucrium* species are good agents against diabetes (Gharaibeh et al. 1988; Rasekh et al. 2001; Esmaeili and Yazdanparast 2004; Ardestani et al. 2008; Vahidi et al. 2010; Alamgeer et al. 2013; Dehghan et al. 2013; Sabet et al. 2013). Dehghan et al. (2013) have shown that the methanol extract of *Teucrium orientale* possesses antihyperglycemic activity. Using extract in the diabetic rat's diet it has been shown that serum glucose has decreased by 40%. Mechanisms that have influenced the decrease in serum glucose levels are strong anti-oxidant properties of *Teucrium orientale* compounds and increased peripheral glucose utilization. Studies have shown that *Teucrium orientale* is rich in flavonoids (Cakir et al. 2006) while flavonoids possess hypoglycemic properties as they increase the oxidative metabolisms of the diabetic states (Dehghan et al. 2013). Alamger et al. (2013) examined the effect of crude extract from *Teucrium stocksianum* on antidiabetic activity. The authors have shown that crude powder of tested species reduces blood glucose levels in diabetic rabbits at a dose of 250 and 500 mg/kg. Testing methanol, aqueous and ethyl acetate extract from *Teucrium stocksianum* noted that at a dose of 500 mg/kg reduce the blood glucose level in diabetes rabbits. The ethyl acetate extract showed better results than methanol and aqueous extract. Also, ethyl acetate extract produced a significant increase in the serum insulin level of diabetic rabbits.

The most noticeable *Teucrium* species in terms of antidiabetic effect is *Teucrium polium*. The *Teucrium polium* extract reduces the level of glucose and triglyceride in the serum at a dose of 4% (Vahidi et al. 2010). In vitro studies have shown that extracts of this species affect the increase in insulin levels and show a hypoglycemic effect in normal rats after only one dose. The highest hypoglycemic effect (50%) was noticed 8 h after a single administration of 125 mg/kg. Moghimi et al. (2017) state that the hypoglycemic activity of *Teucrium polium* extracts was referred to as the presence of secondary metabolites such as flavonoids, sterols, and volatile oils as the active compounds. Flavonoids have hypoglycemic effects by insulin release from the pancreas which stimulates glucose utilization.

14.3.4 Methods for Determination of the Antidiabetic Activity

Methods based on the study of antidiabetic activity consist of monitoring results before and after treatment in vivo and in vitro conditions. Basically, male Wistar rats are used in several groups. The first is a control group, the second is mice that are diabetic, and the third group consists of treated mice with diabetes. Type 1 diabetes

was induced by autoimmune in mice by administering low-dose intraperitoneal injections of STZ (20 mg/kg body weight), dissolved in normal saline for several days. The presence of hyperglycemia is confirmed by diabetes. Depending on the duration of the experiment, after several days of the first STZ injection, plant aqueous extract is administered in a dose of 100 mg/kg for several weeks. The level of serum glucose is monitored at the beginning, mid and end of the experiment (Sabet et al. 2013).

14.4 Inflammation

Inflammation represents the defensive reaction of the organism to harmful exogenous or endogenous factors through the immune system (Abbas et al. 2010). The release of the organism from harmful agents includes a series of changes that take place in the intercellular matrix and blood vessels. The basic function of the inflammation process is to isolate the tissue and remove damaged cells (Medzhitov 2008; Soehnlein and Lindbon 2010; Ashley et al. 2012). There are several types of inflammation. Chronic inflammation leads to necrosis and tissue fibrosis. This type of inflammation affects the development of degenerative diseases, primarily Alzheimer's disease, diabetes, cancer, atherosclerosis, etc. (Murphy and Weaver 2017). Acute inflammation occurs after a few minutes or hours after tissue injury. This is a short-term process characterized by symptoms such as redness of the tissue. Acute inflammation is a good defense mechanism in the fight against bacteria.

Symptoms that are followed by inflammatory processes include tissue redness, pain, and high temperature (Brune and Hinz 2004). The onset of an inflammatory reaction is aimed at repairing the tissue after the elimination of the infectious agent. The transition of the inflammatory process into the tissue recovery process is the interruption of the production of pro-inflammatory cytokines and the start of the production of liposomes. Lipoxins activate monocytes that remove necrotic cells and inhibit neutrophil recruitment. Also, lipoxins initiate tissue remodeling (Medzhitov 2008). The inflammatory process involves the synthesis of interleukins, prostaglandins and certain hemotoxins. Inflammation occurs by stimulation activation on the membrane that activates the hydrolysis of the phospholipid membrane by phospholipase A into arachidonic acid, which further represents the substrate for cyclooxygenase and lipooxygenase enzyme.

It has been shown that inflammatory processes are involved in the etiology of many diseases as well as Alzheimer's disease (Breitner 1996). The drugs that are used today to relieve the symptoms of inflammation are non-steroidal anti-inflammatory drugs (Beale and Block 2010; Lemke et al. 2013).

14.4.1 Plants as Natural Sources of Anti-inflammatory Agents

Nowadays, plant extracts are used to reduce inflammatory processes (Mahesh and Sathish 2008). It has been shown experimentally that medicinal plants used in the treatment of inflammatory processes do not show any side effects. Numerous plant species belonging to different families of Aristolochiaceae, Apocynaceae, Asteraceae, Lamiaceae, Plantaginaceae, Salicaceae, etc. have been investigated in order to find effective substances to reduce the symptoms of inflammation. In addition to a number of medicinal properties, the anti-inflammatory activity of plants is appreciated in traditional medicine. The anti-inflammatory activity of herbal extracts reduces carrageenan-induced edema in the rats, with the oral application of these extracts. Similar results have been shown in numerous studies of medicinal plants (Dharmasiri et al. 2003; Li et al. 2003; Ojewole 2005; Rodriguez Silva et al. 2008; Kumar et al. 2009; Chandrashekar et al. 2010; Shah and Seth 2010; Sreejith et al. 2010; Garg and Paliwal 2011; Shah et al. 2011; Vishal et al. 2014; Verma 2016).

14.4.2 Lamiaceae Species as a Sources of Anti-inflammatory Agents

The Lamiaceae family includes about 250 genera with over 7500 species. A large number of species have been widely used in pharmacy. Some plant species belonging to the Lamiaceae family have been administered against COX. The biologically active compounds present in the species of this family are the main sources of COX inhibitors (Pang et al. 1996). Plant species belonging to the Lamiaceae genera, such as *Lavandula, Glechoma, Lamium, Mentha, Marrubium, Origanum, Ocimum, Rosmarinus, Salvia, Stachys, Sideritis* and *Teucrium* are known for their anti-inflammatory activity (Mihai et al. 2018).

Species of the genus *Ocimum* are used to treat inflammation and assuage of chronic pain in the joints. The anti-inflammatory property of *Ocimum basilicum* and *O. santanum* was confirmed by Singh et al. (1996). Phenolic compounds present in the investigated plants inhibit carrageenan-induced and arachidonic acid and leukotriene-induced paw edema, possibly by blocking the enzymatic activity of both COX and lipoxygenases (Singh et al. 1996). Phenolic compounds are responsible for the anti-inflammatory properties of several medicinal plants (Pongprayoon et al. 1991; Dewhirst 1980). The species belonging to the genus *Glechoma* have the ability to elaborate long-chain unsaturated fatty acids with anti-inflammatory potentials (Kuhn et al. 1989). *Thymus vulgaris* extracts possess inhibitory roles over the nitric oxide (NO) by limiting iNOS mRNA expression, and also are used in traditional medicine for inflammatory skin disorders (Vigo et al. 2004; Alabdullatif et al. 2017). Methanolic extracts derived from species which belong to the genus *Lamium*, such as *L. purpureum* and *L. garganicum*, reducing inflammatory pain in a model of ear edema and in carrageenan-induced paw edema (Akkol et al. 2008). Studies have

shown that the hydrochloric extract of the species *Stachys* has better anti-inflammatory activity than a nonsteroidal anti-inflammatory drug, indomethacin. The extract of the investigated species was able to attenuate both early and delayed phases of carrageenan-induced inflammation over the 50–200 mg/kg dose range. The studies show that plant species belonging to family Lamiaceae is a natural source of anti-inflammatory compounds and that plants can be used in the treatment of inflammation (Mihai et al. 2018).

14.4.3 Teucrium *Species as a Sources of Anti-inflammatory Agents*

Species belonging to the genus *Teucrium* possess secondary metabolites that, in addition to numerous biological activities, exhibit in vitro and in vivo anti-inflammatory activity (Tariq et al. 1989; Barrachina et al. 1995; Puntero et al. 1997; Radhakrishnan et al. 2001; Shakhanben 2001; Menichini et al. 2009; Cabral et al. 2010; Farshchi et al. 2010; Pourmotabed et al. 2010; Miri et al. 2015; Shah and Shah 2015; Rahmouni et al. 2017).

Amraei et al. (2018) examined the effect of *Teucrium polium* hydroalcoholic extract on anti-inflammatory activity. Administration of the extract significantly reduced the serum levels of triglyceride, cholesterol, and LDL-cholesterol. Additionally, the 170 mg/kg dose of extract was most effective in reducing serum levels of inflammatory markers. Authors Tariq et al. (1989) showed that a dose of 500 mg/kg of body weight of the ethanol extract of species *Teucrium polium* inhibited carrageenan-induced inflammation and reduced granuloma formation. According to a number of literary data, *Teucrium polium* contains bioactive compounds such as phenolic compounds and flavonoids. It has been shown that flavonoids reduce inflammatory processes by activating several pathways (Houshmand et al. 2015).

Pourmotabbed et al. (2010) examined the effect of aqueous extract of *Teucrium chamaedrys* on the anti-inflammatory activity, which showed that a dose-dependent inhibition of the edema was performed using 25–250 mg/kg administered 1 h before carrageenan-induced paw swelling. For extracts of *Teucrium hyrcanicum*, it has been shown to exhibit analgesic and anti-inflammatory activity in carrageenan-induced paw edema, and formalin pain tests (Farshchi et al. 2010). Extracts of *Teucrium stocksianum* significantly reduced the paw edema at a dose of 400 mg/kg in rats. However, the extract did not show any anti-inflammatory effect when administered orally in a sub-acute study using a cotton-pellet method but was effective orally in an acute study using rat paw edema (Radhakrishnan et al. 2001). Miri et al. (2015) examined aqueous extract from *Teucrium persicum* on anti-inflammatory activity. The authors have shown that aqueous extract of this species at concentrations of 100, 200 and 400 mg/kg shows an insignificant anti-inflammatory effect in the cotton pellet induced granuloma model in the mice. The authors assume that the

activity was dependent on the dose, method, or period of time. El-Ashmawy (2018) investigate the anti-inflammatory effects and the phytochemical constituents of the methanol extract from *Teucrium oliverianum* using the carrageenan-induced rat paw edema (acute and sub-acute models) and the terpentine oil-induced granuloma pouch bioassay. The methanolic extract of *Teucrium oliverianum* exhibited anti-inflammatory activity in both phases of carrageenan-induced acute edema test in a dose-dependent manner.

14.4.4 Methods for Determination of the Anti-inflammatory Activity

To investigate the anti-inflammatory effect, there are many methods of which carrageenan-induced inflammatory edema is most commonly used in the hind paw of rats. Inhibition of carrageenan-induced inflammation is one of the most suitable test procedures for monitoring anti-inflammatory agents. Carrageenan is a mucopolysaccharide isolated from Sea moss *Chondrus* in order to experimentally induce arthritis. Carrageenan causes an acute inflammation that occurs in two stages. The first or early stage occurs after 1 h of injection of carrageenan. At this stage, edema develops due to the effects of serotonin and histamine. A second or late phase occurs after 2 h of injection of carrageenan where vascular permeability is maintained by bradykinin and prostaglandins. These mediators induce pain and contribute to the inflammatory response. Studies have shown that late edema is sensitive to anti-inflammatory drugs and is used to estimate the antiphlogistic effect of natural products (El-Ashmawy 2018).

14.5 Conclusions

This chapter is a review of anticholinesterase, antidiabetic and anti-inflammatory activity of several species of the genus *Teucrium.* Extracts from *Teucrium arduini, T. chamaedrys, T. montanum*, and *T. polium*, showed strong inhibitory activity against acetylcholinesterase. Extracts of some *Teucrium* species reduces blood glucose levels in diabetic rats and rabbits. Also, the use of plant extracts significantly reduce inflammatory markers and inhibited carrageenan-induced inflammation. By examining the qualitative and quantitative composition of secondary metabolites of *Teucrium* species, the presence of active phenolic acids was observed. The most common are rosmarinic and chlorogenic acid. Also, the most common are luteolin and apigenin from the group of flavonoids. It has been shown that these biologically active compounds contribute to anticholinesterase, antidiabetic and anti-inflammatory activity.

References

Abbas A, Lichtman A, Pillai S (2010) Cellular and molecular immunology, 8th edn. Elsevier, Amsterdam

Abeywickrama KRW, Ratnasooriya WD, Amarakoon AM (2011) Oral hypoglycaemic, antihyperglycaemic and antidiabetic activities of Sri Lankan Broken Orange Pekoe Fannings (BOPF) grade black tea (*Camellia sinensis* L.) in rats. J Ethnopharmacol 135:278–286

Adewusi EA, Moodley N, Steenkamp V (2011) Antioxidant and acetylcholinesterase inhibitory activity of selected southern African medicinal plants. S Afr J Bot 77:638–644

Ahmad B, Mukarram Shah SM, Khan H, Hassan Shah SM (2007) Enzyme inhibition activities of *Teucrium royleanum*. J Enzyme Inhib Med Chem 22:730–732

Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M (2003) *Salvia officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized and placebo-controlled trial. J Clin Pharm Ther 28:53–59

Akkol EK, Yalçın FN, Kaya D, Çalıs I, Yesilada E, Ersoz T (2008) In vivo anti-inflammatory and antinociceptive actions of some *Lamium* species. J Ethnopharmacol 118:166–172

Alabdullatif M, Boujezza I, Mekni M, Taha M, Kumaran D, Yi QL, Landoulsi A, Ramirez-Arcos S (2017) Enhancing blood donor skin disinfection using natural oils. Transfusion 57:2920–2927

Alamgeer RM, Bashir S, Mushtaq MN, Khan HU, Malik MNH, Qayyum A, ur Rahaman MS (2013) Comparative hypoglycemic activity of different extracts of *Teucrium stocksianum* in diabetic rabbits. Bangladesh J Pharmacol 8:186–193

Alberti KG, Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 15:539–553

Amraei M, Ghorbani A, Seifinejad Y, Mousavi SF, Mohamadpour M, Shirzadpour E (2018) The effect of hydroalcoholic extract of *Teucrium polium* L. on the inflammatory markers and lipid profile in hypercholesterolemic rats. J Inflamm Res 11:265–272

Ardestani A, Yazdanparast R, Jamshidi S (2008) Therapeutic effects of *Teucrium polium* extract on oxidative stress in pancreas of streptozotocin-induced diabetic rats. J Med Food 11:525–532

Ashley TN, Weil MZ, Nelson JR (2012) Inflammation: mechanisms, costs, and natural variation. Annu Rev Ecol Evol Syst 43:385–406

Barrachina MD, Bello R, Martínez-Cuesta MA, Esplugues J, Primo-Yúfera E (1995) Antiinflamatory activity and effects on isolated smooth muscle of extracts from different *Teucrium* species. Phytother Res 9:368–371

Beale JM, Block JH (2010) Wilson and Gisvold's textbook of organic medicinal and pharmaceutical chemistry, 12th edn. Lippincott Williams & Wilkins, Philadelphia

Breitner JC (1996) The role of antiinflammatory drugs in the prevention and treatment of Alzheimer's disease. Annu Rev Med 47:401–411

Brune K, Hinz B (2004) The discovery and development of antiinflamatory drugs. Arthritis Rheumatol 50:2391–2399

Burčul F (2008) The biological effects of essential oil and water extract of the plant (*Achillea millefolium* L.). MSc thesis, University of Split

Cabral C, Francisco V, Cruz M, Lopes M, Salgueiro L, Sales F, Batist M (2010) Potential antioxidant and anti-inflammatory properties in *Teucrium salviastrum* Schreb. Planta Med 76:1163–1374. https://doi.org/10.1055/s-0030-1264535

Cakir A, Mavia A, Kazaz C, Yildirim A, Kufrevioglu OI (2006) Antioxidant activities of the extracts and components of *Teucrium orientale* L. var. *orientale*. Turk J Chem 30:483–494

Chandrashekar KS, Thakur A, Prasanna KS (2010) Anti-inflammatory activity of *Moringa oleifera* stem bark extracts against carrageenen induced rat paw edema. J Chem Pharm Res 2:179–181

Chiung-Chun H, Cheng-Che L, Kuei-Sen H (2010) The role of insulin receptor signaling in synaptic plasticity and cognitive function. Chang Gung Med J 33:115–125

Čolović BM, Krstić DZ, Lazarević-Pašti TD, Bondžić MA, Vasić MV (2013) Acetylcholinesterase inhibitors: pharmacology and toxicology. Curr Neuropharmacol 11:315–335

Craft S (2007) Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. Curr Alzheimer Res 4:147–152

Das S, Barman S (2012) Antidiabetic and antihyperlipidemic effects of ethanolic extract of leaves of *Punica granatum* in alloxan-induced non-insulin-dependent diabetes mellitus albino rats. Indian J Pharm 44:219–224

Das M, Sarma BP, Khan AK, Mosihuzzaman M, Nahar N, Ali L, Bhowmik A, Begum R (2009) The antidiabetic and antilipidemic activity of aqueous extract of *Urtica dioica* L. on type 2 diabetic model rats. J Biol Sci 17:1–6

Dastmalchi K, Dorman HJD, Viorela H, Hiltunen R (2007) Plants as potential source for drug development against Alzheimer's disease. Int J Biomed Pharm Sci 1:83–104

Dehghan G, Tahmasebpour N, Hosseinpour Feizi MA, Sheikhzadeh F, Banan Khojasteh SM (2013) Hypoglycemic, antioxidant and hepato- and nephroprotective effects of *Teucrium orientale* in streptozotocin diabetic rats. Pharmacology 1:182–189

Devendra D, Liu E, Eisenbarth GS (2004) Type 1 diabetes: recent developments. BMJ 328:750–754

Dewhirst TE (1980) Structure-activity relationships for inhibition of prostaglandin cyclooxygenase by phenolic compounds. Prostaglandins 20:209–222

Dharmasiri MG, ayakody JRAC, Galhena G, Liyanage SSP, Ratnasooriya WD (2003) Anti-inflammatory and analgesic activities of mature fresh leaves of *Vitex negundo*. J Ethnopharmacol 87:199–206

El-Ashmawy IM (2018) Anti-inflammatory and phytoconstituents of *Teucrium oliverianum* Ging. Ex. Benth. Eur J Pharm Med Res 5:406–411

Ellman G, Courtney D, Valentino A, Featherstone R (1961) A new and rapid colorimetric determination of acetylcholinesterase activity. Biochem Pharmacol 7:88–95

Esmaeili MA, Yazdanparast R (2004) Hypoglycaemic effect of *Teucrium polium*: studies with rat pancreatic islets. J Ethnopharmacol (1):27–30

Farshchi A, Ghiasi G, Asl AA (2010) Antinociceptive and antiinflammatory effects of *Teucrium hyrcanicum* aqueous extract in male mice and rats. Physiol Pharmacol 14:78–84

Ferreira A, Proença C, Serralheiro MLM, Araújo MEM (2006) The in vitro screening for acetylcholinesterase inhibition and antioxidant activity of medicinal plants from Portugal. J Ethnopharmacol 108:31–37

Garg VK, Paliwal SK (2011) Anti-inflammatory activity of aqueous extract of *Cynodon dactylon*. Int J Pharmacol 7:370–375

George C, Lochner A, Huisamen B (2011) The efficacy of *Prosopis glandulosa* as antidiabetic treatment in rat models of diabetes and insulin resistance. J Ethnopharmacol 137:298–304

Gharaibeh MN, Elayan HH, Salhab AS (1988) Hypoglycemic effects of *Teucrium polium*. J Ethnopharmacol 24:93–99

Golfakhrabadi F, Yousefbeyk F, Mirnezami T, Laghaei P, Hajimahmoodi M, Khanavi M (2015) Antioxidant and antiacetylcholinesterase activity of *Teucrium hyrcanicum*. Pharm Res 7:15–19

Hannan JM, Marenah L, Ali L, Rokeya B, Flatt PR, Abdel-Wahab YH (2006) *Ocimum sanctum* leaf extracts stimulate insulin secretion from perfused pancreas, isolated islets and clonal pancreatic beta-cells. J Endocrinol 189:127–136

Houshmand G, Goudarzi M, Forouzandeh H, Nazari A, Nourollahi V (2015) Evaluation of the analgesic effects of *Teucrium* extract on rats using the formalin test. J Babol Univ Med Sci 17:33–39

Husain I, Chander R, Saxena JK, Mahdi AA, Mahdi F (2015) Antidyslipidemic effect of *Ocimum sanctum* leaf extract in streptozotocin induced diabetic rats. Indian J Clin Biochem 30:72–77

Huseini HF, Fakhrzadeh H, Larijani B, Samani AS (2006) Review of anti-diabetic medicinal plant used in traditional medicine. J Med Plants 1(S2):1–8

Hussain EHMA, Jamil K, Rao M (2001) Hypoglycaemic, hypolipidemic and antioxidant properties of tulsi (*Ocimum sanctum* Linn) on streptozotocin induced diabetes in rats. Indian J Clin Biochem 16:190–194

Jäger A, Eldeen I, Van Staden J (2007) COX-1 and -2 activity of rose hip. Phytother Res 21:1251–1252

Jiao Y, Wang X, Jiang X, Kong F, Wang S, Yan C (2017) Antidiabetic effects of *Morus alba* fruit polysaccharides on high-fat diet- and streptozotocin-induced type 2 diabetes in rats. J Ethnopharmacol 199:119–127

Kahn SE (2003) The relative contribution of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia 46:3–19

Kooti W, Farokhipour M, Asadzadeh Z, Ashtary-Larky D, Asadi-Samani M (2016) The role of medicinal plants in the treatment of diabetes: a systematic review. Electron Physician 8:1832–1842

Kuhn H, Wiesner R, Alder L, Schewe T (1989) Occurrence of free and esterified lipoxygenase products in leaves of *Glechoma hederacea* L. and other Labiatae. Eur J Biochem 186:155–162

Kumar A, Panghal S, Mallapur SS, Kumar M, Ram V, Singh BK (2009) Antiinflammatory activity of *Piper longum* fruit oil. Indian J Pharm Sci 71:454–456

Lemke TL, Williams DA, Roche VF, Zito SW (2013) Foye's principles of medicinal chemistry, 7th edn. Lippincott Williams & Wilkins, Philadelphia

Li RW, David Lin G, Myers SP, Leach DN (2003) Anti-inflammatory activity of Chinese medicinal vine plants. J Ethnopharmacol 85:61–67

Mahesh B, Sathish S (2008) Antimicrobial activity of some important medicinal plant against plant and human pathogens. World J Agric Sci 4:839–843

Martorana A, Esposito Z, Koch G (2010) Beyond the cholinergic hypothesis: do current drugs work in Alzheimer's disease? CNS Neurosci Ther 16:235–245

Mattson MP (2004) Pathways towards and away from Alzheimer's disease. Nature 430:631–639

Medzhitov R (2008) Origin and physiological roles of inflammation. Nature 454:428–435

Menichini F, Conforti F, Rigano D, Formisano C, Piozzi F, Senatore F (2009) Phytochemical composition, anti-inflammatory and antitumour activities of four *Teucrium* essential oils from Greece. Food Chem 115:679–686

Miri A, Sharifi-Rad J, Tabriyian K, Nasiri AA (2015) Antinociceptive and anti-inflammatory activities of *Teucrium persicum* Boiss. extract in mice. Scientifica. https://doi.org/10.1155/2015/972827

Moghimi Z, Dehghan S, Sayadi S, Ghanbarian A (2017) Therapeutic effect and mechanism of *Teucrium polium* in diabetes mellitus: a review article. Res J Pharmacogn 4(S):73–73

Mohan L, Pant CC, Melkani AB, Dev V (2010) Terpenoid composition of the essential oils of *Teucrium royleanum* and *T. quadrifarium*. Nat Prod Commun 5:939–942

Monsef-Esfahani HR, Hajiaghaee R, Shahverdi AR, Khorramizadeh MR, Amini M (2010) Flavonoids, cinnamic acid and phenyl propanoid from aerial parts of *Scrophularia striata*. Pharm Biol 48:333–336

Moradi B, Abbaszadeh S, Shahsavari S, Alizadeh M, Beyranvand F (2018) The most useful medicinal herbs to treat diabetes. Biomed Res Ther 5:2538–2551

Mukherjee PK, Kumar V, Mal M, Houghton PJ (2007) Acetylcholinesterase inhibitors from plants. Phytomedicine 14:289–300

Murphy K, Weaver C (2017) Janeway's immunobiology, 9th edn. Garland Science, New York

Nađpal J (2017) Phytochemical screening and biological activity of extracts and traditional products from fruits of wild roses (*Rosa* L.; Rosaceae). Dissertation, University of Novi Sad

Ojewole J (2005) Antinociceptive, anti-inflammatory and antidiabetic effects of *Bryophyllum pinnatum* (Crassulaceae) leaf aqueous extract. J Ethnopharmacol 99:13–19

Orhan I, Aslan M (2009) Appraisal of scopolamine-induced antiamnesic effect in mice and in vitro antiacetylcholinesterase and antioxidant activities of some traditionally used Lamiaceae plants. J Ethnopharmacol 122:327–332

Orhan I, Kartal M, Naz Q, Ejaz A, Yilmaz G, Kan Y, Konuklugil B, Sener B, Choudhary MI (2007) Antioxidant and anticholinesterase evaluation of selected Turkish *Salvia* species. Food Chem 103:1247–1254

Orhan I, Aslan S, Kartal M, Şener B, Başer KHC (2008) Inhibitory effect of Turkish *Rosmarinus officinalis* L. on acetylcholinesterase and butyrylcholinesterase enzymes. Food Chem 108:663–668

Pang L, Las-Heras BD, Hoult JR (1996) A novel diterpenoid labdane from *Sideritis javalambrensis* inhibits eicosanoid generation from stimulated macrophages but enhances arachidonate release. Biochem Pharmacol 51:863–868

Patil R, Patil R, Ahirwar B, Ahirwar D (2011) Isolation and characterization of anti-diabetic component (bioactivity-guided fractionation) from *Ocimum sanctum* L. (Lamiaceae) aerial part. Asian Pac J Trop Med 4:278–282

Pongprayoon U, Baeckstrom P, Jacobsson U, Lindstrom M, Bohlin L (1991) Compounds inhibiting prostaglandin synthesis isolated from *Ipomoea pescaprae*. Planta Med 57:515–518

Pourmotabed A, Farschehi A, Ghiasi G, Khatabi PM (2010) Analgesic and anti-inflammatory activity of *Teucrium chamaedrys* leaves aqueous extract in male rats. Iran J Basic Med Sci 13:119–125

Prabhakar PK, Doble M (2008) A target based therapeutic approach towards diabetes mellitus using medicinal plants. Curr Diabetes Rev 4:291–308

Puntero BF, Peinado II, del Fresno AMV (1997) Anti-inflammatory and antiulcer activity of *Teucrium buxifolium*. J Ethnopharmacol 55:93–98

Rabiei Z, Rafieian-Kopaei M, Mokhtari S, Shahrani M (2014) Effect of dietary ethanolic extract of *Lavandula officinalis* on serum lipids profile in rats. Iran J Pharm Res 13:1295–1301

Radhakrishnan R, Zakaria MNM, Islam MW, Kamil M, Ismail A, Chan K, Al-Attas A (2001) Analgesic and anti-inflammatory activities of *Teucrium stocksianum*. Pharm Biol 39:455–459

Rahmouni F, Hamdaoui L, Rebai T (2017) In vivo anti-inflamatory activity of aqueus extract of *Teucrium polium* against carrageenan-induced inflammation in experimental models. Arch Physiol Biochem 123:313–321

Rao NK, Nammi S (2006) Antidiabetic and renoprotective effects of the chloroform extract of *Terminalia chebula* Retz. seeds in streptozotocin-induced diabetic rats. BMC Complement Altern Med 6(1):17. https://doi.org/10.1186/1472-6882-6-17

Rasekh HR, Khoshnood-Mansourkhani MJ, Kamalinejad M (2001) Hypolipidemic effects of *Teucrium polium* in rats. Fitoterapia 72:937–939

Rewers M (2012) The fallacy of reduction. Pediatr Diabetes 13:340–343

Rodriguez Silva D, Baroni S, Svidzinski AE, Bersani-Amado CA, Cortez DA (2008) Anti-inflammatory activity of the extract, fractions and amides from the leaves of none *Piper ovatum* Vahl (Piperaceae) none. J Ethnopharmacol 116:569–573

Roseiro LB, Rauter AP, Mourato Serralheiro ML (2012) Polyphenols as acetylcholinesterase inhibitors: structural specificity and impact on human disease. Nutr Aging 1:99–111

Sabet Z, Roghani M, Najafi M, Maghsoudi Z (2013) Antidiabetic effect of *Teucrium polium* aqueous extract in multiple low-dose streptozotocin-induced model of type 1 diabetes in rat. J Basic Clin Pathophysiol 1:34–38

Sadeghzadeh F, Eidi A, Parivar K, Mazooji A (2008) Hypoglycemic effect of alcoholic extract of *Salvia nemorosa* in normal and diabetic male rats. Res Med 32:233–238

Shah BN, Seth AK (2010) Anti-inflammatory activity of fruits of *Abelmoschus esculentus* Linn. Pharmacology online 1:208–212

Shah SMM, Shah SMH (2015) Phytochemicals, antioxidant, antinociceptive and anti-inflammatory potential of the aqueous extract of *Teucrium stocksianum* bioss. BMC Complement Altern Med. 15:351. https://doi.org/10.1186/s12906-015-0872-4

Shah BN, Seth AK, Maheshwari KM (2011) A review on medicinal plants as a source of anti-inflammatory agents. Res J Med Plants 5:101–115

Shakhanbeh J (2001) *Teucrium polium* inhibits nerve conduction and carrageenan induced inflammation in the rat skin. Turk J Med Sci 31:15–21

Sims-Robinson C, Kim B, Rosko A, Feldman EL (2010) How does diabetes accelerate Alzheimer disease pathology? Nat Rev Neurol 6:551–559

Singh S, Majumdar DK, Rehan HMS (1996) Evaluation of anti-inflammatory potential of fixed oil of *Ocimum sanctum* (Holy basil) and its possible mechanism of action. J Ethnopharmacol 54:19–26

Sisodia SS, Tanzi RE (eds) (2006) Alzheimer disease advances in genetics, molecular and cellular biology. Springer, Basel

Soehnlein O, Lindbon L (2010) Phagocyte partnership during the onset and resolution of inflammation. Nat Rev Immunol 10:427–439

Soreq H, Seidman S (2001) Acetylcholinesterase-new roles for an old actor. Nat Rev Neurosci 2:294–302

Sreejith G, Latha PG, Shine VJ, Anuja GI, Suja SR, Sini S, Shyama S, Pradeep S, Shikha P, Rajasekharan S (2010) Anti-allergic, antiinflammatory and anti-lipidperoxidant effects of *Cassia occidentalis* Linn. Indian J Exp Biol 48:494–498

Stanković M (2012) Biological effects of secondary metabolites of *Teucrium* species of Serbian flora. Dissertation, University of Kragujevac

Takeda M, Tanaka T, Cacabelos R (2004) Molecular neurobiology of Alzheimer disorder and related disorders. Karger AG, Basel

Tariq M, Ageel AM, Al-Yahya MA, Mossa JS, Al-Said MS (1989) Anti-inflammatory activity of *Teucrium polium*. Int J Tissue React 11:185–188

Topcu G, Kusman T (2014) Lamiaceae family plants as a potential anticholinesterase source in the treatment of Alzheimer's disease. Bezmialem Sci 2:1–25

Uritu CM, Mihai CT, Stanciu G-D, Dodi G, Alexa-Stratulat T, Luca A, Leon-Constantin M-M, Stefanescu R, Bild V, Melnic S, Tamba BI (2018) Medicinal plants of the family Lamiaceae in pain therapy: a review. Pain Res Manag 8:7801543. https://doi.org/10.1155/2018/7801543

Vahidi AR, Dashti-Rahmatabadi MH, Bagheri SM (2010) The effect of *Teucrium polium* boiled extract in diabetic rats. Iran J Diabetes Obes 2:27–32

Verma S (2016) Medicinal plants with anti-inflammatory activity. J Phytopharmacol 5:157–159

Vigo E, Cepeda A, Perez-Fernandez R, Gualillo O (2004) In-vitro anti-inflammatory effect of *Eucalyptus globulus* and *Thymus vulgaris*: nitric oxide inhibition in J774A.1 murine macrophages. J Pharm Pharmacol 56:257–263

Vishal V, Ganesh SN, Mukesh G, Ranjan B (2014) A review on some plants having anti-inflammatory activity. J Phytopharmacol 3:214–221

Vladimir-Knežević S, Blaženković B, Kindl M, Vladić J, Lower-Nedza AD, Brantner AH (2014) Acetylcholinesterase inhibitory, antioxidant and phytochemical properties of selected medicinal plants of the *Lamiaceae* family. Molecules 19:767–782

Yoo KY, Park SY (2012) Terpenoids as potential anti-Alzheimer's disease therapeutics. Molecules 17:3524–3538

Zhao Y, Dou J, Wu T, Aisa HA (2013) Investigating the antioxidant and acetylcholinesterase inhibition activities of *Gossypium herbaceam*. Molecules 18:951–962

Zimmet P, Alberti KGMM, Shaw J (2001) Global and societal implication of the diabetes epidemic. Nature 414:782–787