Enzyme inhibitors as controllers of neurodegenerative diseases: An update of *in vitro* effects of medicinal plants

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Considering the increase of the elderly population in recent years, the growing prevalence of age-related neurodegenerative diseases (NDDs), including Alzheimer's disease (AD) and Parkinson's disease (PD), has become one of the leading healthcare problems. Currently, available therapies for AD and PD are still limited, while medicinal plants used in traditional medicine for millennia can inhibit enzymes involved in the neurodegeneration processes in AD (acetylcholinesterase, AChE, and butyrylcholinesterase, BChE) and PD (tyrosinase, TYR), hence their inhibiting effects are continuously being investigated especially in the past decade. This study was aimed to review data on medicinal plants as potential cholinesterases and TYR inhibitors reported from January 2018 until May 2021. The literature search was performed using several online bibliographical databases (Scopus, Web of Science, Science Direct, Google Scholar, PubMed, and ResearchGate) and two websites. Data analysis showed that the highest number of representatives belongs to Lamiaceae family (up to 20 %), followed by Asteraceae. Almost half of the tested samples were prepared from whole plant/aerial plant parts followed by leaves. The most frequently tested preparations were methanolic extracts (about 25 % of the samples examined). Additionally, synergistic interactions between different herbs and/or isolated compounds were considered as a promising strategy for further research. The presented data showed that medicinal plants preparations represent an unlimited source for research of new and more effective AD and PD treatments. This review will provide a useful starting point for further research on this topic.

Key words: Alzheimer's disease; Parkinson's disease; cholinesterase inhibition; tyrosinase inhibition; medicinal plants; synergistic effects

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ABBREVIATIONS

NDDs - neurodegenerative diseases; AD - Alzheimer's disease; PD - Parkinson's disease; AChE - acetylcholinesterase; BChE - butyrylcholinesterase; TYR - tyrosinase, T2D - type 2 diabetes.

1. INTRODUCTION

The term neurodegenerative diseases (NDDs) covers many insidious and incurable diseases featured by increasing prevalence, in part because the elderly population has increased in recent years (Gitler et al., 2017). NDDs represent a huge public concern and one of the largest healthcare issues, with the physical, psychological, social, and economic impacts on people suffering from NDDs, their families, caregivers and society. Accordingly, there is a great scientific interest to develop new and more effective strategies for NDDs prevention and treatment.

The main characteristics of NDDs include progressive loss of both structure and function of neuronal cells, causing changes in nervous system structure, which finally results in degeneration and/or death of neurons (Magalingam et al., 2018). NDDs are manifested by movement problems and mental dysfunction such as dementia, both of which are commonly observed symptoms in NDDs such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia and spinocerebellar ataxias (Fadaka et al., 2019; Gitler et al., 2017). Among them, AD and PD are the most common NDDs affecting a large population worldwide.

NDDs, including AD and PD, share some common characteristics such as age-related decline, multiple genetic defects distributed across the genome, deposits of abnormal proteins

in the brain, and diverse environmental risk factors (Cacabelos, 2020). Although the exact mechanisms underlying the pathogenesis of NDDs have not yet been fully understood, it has been proven that oxidative stress and neuroinflammation are the initiators of NDDs. Elevated levels of oxidative stress are responsible for the activation of several biochemical pathways that induce oxidative damage of neuronal cells, leading to their neurodegeneration and death. On the other hand, neuroinflammation arises due to a complex immune response of the brain to injury, leading to the activation of glial cells and release of inflammatory cytokines, causing serious consequences related to NDDs (Fadaka et al., 2019; Khan et al., 2020). The main risk factors included in NDDs development are summarized in Figure 1.

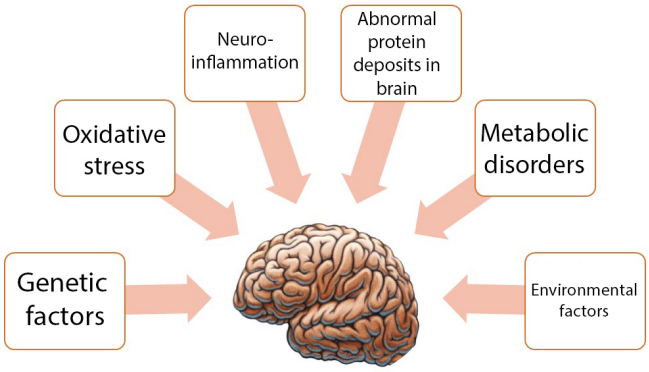

Fig. 1. Main risk factors for neurodegenerative diseases (NDDs) development

Dementia involves progressive neurodegenerative brain disorders characterized by cognitive impairment and gradual decay of mental functions, followed by progressive deterioration of physical function, leading to disability and ultimately – death. According to the newest data reported by the World Health Organization (WHO, 2021) and Alzheimer's Disease International (ADI, 2021), over 50 million people are living with dementia globally, and this number is projected to reach 82 million by 2030 and 152 by 2050. Alzheimer's Disease International (ADI, 2021) reported that already 60 % of people with dementia live in low and middle-income countries, however, it is estimated that by 2050 this number will rise to 71 %, with occurence of new case every 3 seconds in the world.

AD represents the most common form of dementia (60-80 % of dementia cases worldwide), which is manifested by a decline of memory and cognitive functions. The majority of AD cases are recognized as sporadic with increasing prevalence over the age of 65. One of the main characteristics of AD is the lack of neurotransmitter acetylcholine (ACh), which is degraded by the enzyme acetylcholinesterase (AChE). Thus, the prevention of ACh degradation by inhibiting AChE in cholinergic synapses represents a promising approach in AD management (Bui and Nguyen, 2017; Damuka et al., 2020; Dohrmann et al., 2019; Edwards III et al., 2019; Hampel et al., 2018; Kumar et al., 2015; Podcasy and Epperson, 2016). PD represents the second most common age-related, progressive NDD after AD, affecting 7-10 million people worldwide. The prevalence of the disease ranges from 41 people per 100,000 in the fourth decade of life to more than 1,900 per 100,000 in people aged 80 and older (Parkinson's News Today, 2021). The main symptom of PD, slowness of movement (bradykinesia), is due to progressive dopamine (DA) deficiency in the dopaminergic neurons of neuromelanin-containing neurons of substantia nigra. Tyrosinase (TYR) plays a significant role in neuromelanin formation, and its overproduction together with oxidative stress could be responsible for the PD-associated neurodegeneration (Jiang et al., 2018; Zucca et al., 2014). Thus, inhibition of TYR and the reduction of oxidative stress are recognized as indirect and non-conventional strategies for the treatment of PD.

Numerous studies have shown that medicinal plants represent a rich source of diverse secondary metabolites, including terpenes, phenolic acids, flavonoids, alkaloids, lignans, sterols, tannins, displaying various beneficial biological activities, such as antioxidant, anti-inflammatory, enzyme inhibiting, antimicrobial, and many others (Bui and Nguyen, 2017; Kamal et al., 2019; Khan et al., 2020; Santos et al., 2018; Zolghadri et al., 2019).

Similarly to many commercial synthetic substances, medicinal plants and their isolated metabolites inhibit efficiently the activities of AChE and TYR. As a natural source of biologically active compounds, medicinal plants possess many advantages compared to synthetic drugs: they are safer to use and easily available, have less pronounced side effects, their production supports green sustainability standards, and are economically justified. The potential of medicinal plants in AChE and TYR inhibition, recognized as one of the prospective alternative therapeutic strategies for AD and PD, will be discussed in detail hereinafter.

One of the current trends in natural products research includes testing the potential interactions of extracts and/or their components to discover potential synergistic interactions, i.e. the best-expressed activity for combination of extracts and/or their components compared to individual extracts/components. Thus, special attention in this review will be paid to synergistic interactions between plants, in the light of bioactivities that could be exploited in NDDs management.

Bearing that in mind, this study is aimed to review data on medicinal plants as potential AChE and TYR inhibitors reported from January 2018 until May 2021. The data were obtained by searching Scopus, Web of Science, Science Direct, Google Scholar, PubMed, and ResearchGate databases, and selected research articles published in this period are presented in tabular manner. This period is considered as long enough to notice research trends regarding the choice of plant species, material for extraction, isolation techniques, isolated compounds, tests employed for assessment of enzyme inhibition activity, as well as the presentation of the obtained data. Thus, this study is intended to provide a useful starting point for further research on this topic.

2. METHODOLOGY

For the present study, an extensive search of review and original research articles was conducted. In order to provide a comprehensive literature survey, several complementary online bibliographical databases such as Scopus, Web of Science, Science Direct, Google Scholar, PubMed and ResearchGate were used. Moreover, only articles published in English have been taken into consideration. The articles' search was performed by combining the following keywords: neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, medicinal plants, *in vitro* AChE inhibition, *in vitro* BChE inhibition, *in vitro* TYR inhibition, plant extracts, essential oils, synergistic effects.

Numerous search results were filtered according to relevance, and selected review articles and original research studies were used to provide background for the general part of the text describing symptoms, pathophysiology and current therapeutical strategies of both AD and PD. Among them, the papers published in the last decade were predominantly selected.

Moreover, website sources such as Alzheimer's Disease International (ADI, 2021) and Parkinson's News Today (2021) were also used to report the newest statistical data on both diseases. A preliminary search of original research articles related to the inhibition of AChE, BChE and TYR by medicinal plants was additionally filtered to cover a 40 months-period from the beginning of 2018 until May 2021, and initially about 1000 research papers were screened. The comprehensive research papers involving all of these enzymes were predominantly included, while those dealing with one of these enzymes separately were subsequently added to the selected article list. The papers dealing with more than one examined plant species were also rather selected.
Finally, of totally cited 288 references, the results of 211 research papers were analysed and presented in tabular manner in the main part of this study. Subsequently, data were additionally processed and presented graphically as pie charts drawn using MS Excel (2013). To provide a clear, systematic survey of published results, which could be useful for planning the succeeding researches, we have shown the next parameters for both AD and PD:

- Participation percentage of plant families' representatives examined for anticholinesterase and antityrosinase activity regarding the total number of taxa;
- Participation percentage of plant parts used for investigation of anticholinesterase and antityrosinase activity regarding the total number of examined samples;
- Participation percentage of plant preparations tested for anticholinesterase and antityrosinase inhibiting activity regarding the total number of examined samples.

Data on synergistic effects of medicinal plants and their compounds in the AChE and TYR inhibition were obtained by an exhaustive search of the available databases and the most relevant papers were presented, regardless of the year of publication.
Considering that this research has been limited to *in vitro* studies, the results of *in vivo* studies and clinical trials were excluded from the search. Additionally, the research articles exclusively focused on isolated compounds and synthetic inhibitors were also excluded, as well as papers which were not available in full. Moreover, conference papers and proceedings were also not taken into consideration.

3. ALZHEIMER'S DISEASE (AD)

3.1. Description, symptoms, and pathophysiology of AD

Alzheimer's disease (AD), described for the first time by Dr. Alois Alzheimer in 1907, is the most frequent form of dementia and one of the major healthcare problems in developed countries (Bui and Nguyen, 2017; Damuka et al., 2020; Edwards III et al., 2019; Folch et al., 2016; Kumar et al., 2015). Females are at greater risk of developing AD dementia, whereas males are at greater risk of developing vascular dementia (Podcasy and Epperson, 2016). AD is a slowly evolving disease manifested by progressive declines in cognition, memory, attention, and language and by the inability to learn (Hampel et al., 2018; Kumar et al., 2015; Magalingam et al., 2018). Two forms of AD should be distinguished, familial AD with genetic predisposition (occurs in up to 5% of cases), while the majority of cases are recognized as sporadic AD (Bui and Nguyen, 2017; Dohrmann et al., 2019; Edwards III et al., 2019; Folch et al., 2016; Kumar et al., 2015). Considering clinical phenotypes and genetic risks observed in AD patients, the sporadic AD cases could be segregated into two subgroups, early-onset AD under age 65 (3–5 % prevalence) and late-onset AD with typical onset after the age of 65 (95–97 % prevalence) (Folch et al., 2016; Jagust, 2018).

Besides common risk factors for AD (aging, sex, and genetics), modifiable risk factors, including medical conditions such as hypertension and other cardiovascular problems, diabetes, epilepsy, brain injuries, and depression as well as lifestyle choices (poor nutrition, sleeping disturbance, lack of physical activity, smoking, etc.) may have a significant role in the development of AD (Edwards III et al., 2019). There is an increasing evidence on the coexistence of type 2 diabetes (T2D) and AD in many patients, which could be explained by elevated levels of oxidative stress and chronic inflammation. Furthermore, it is reported that both AD and T2D patients are more susceptible to severe outcomes after SARS-CoV-2 infection because the immune response and excessive inflammation in COVID-19 may also accelerate the progression of inflammatory neurodegeneration of the AD brain (Naughton et al., 2020). As previously stated, Japanese and Mediterranean diets rich in mono- and polyunsaturated fatty acids and antioxidants have the preventive potential for the development of senile dementia and AD (Dohrmann et al., 2019; Edwards III et al., 2019).

The pathophysiology of AD is not yet completely resolved, however aging is currently recognized as a key factor that activates several neurodegenerative pathways resulting in loss of neuronal cells (Karakaya et al., 2019a; Magalingam et al., 2018). Hallmarks of AD include β-amyloid (Aβ) proteins aggregation to senile plaques, τ-protein hyperphosphorylation, neurofibrillary tangles, low level of ACh, neuroinflammation, dendritic pathology, etc. (Bui and Nguyen, 2017; Damuka et al., 2020; Edwards III et al., 2019; Folch et al., 2016; Jagust, 2018; Magalingam et al., 2018; Thakur et al., 2019). Among several existing hypotheses on the origins of AD, Aβ cascade and cholinergic hypotheses are the most widely accepted.

According to the β-amyloid cascade (or Aβ) hypothesis, developed in 1991, the extracellular β-amyloid plaques are the main cause of AD. Precisely, small clusters of accumulated Aβ proteins tend to form so-called amyloid or senile plaques in the brain. Amyloid plaques also provoke the formation of neurofibrillary tangles of τ-protein, which along with Aβ plaques provoke the destruction of neuronal cells. Additionally, the formation of Aβ plaques leads to oxidative stress in the neurons, which accelerates the development of AD (Bui and Nguyen, 2017; Folch et al., 2016; Kawamoto et al., 2019; Kumar et al., 2015; Magalingam et al., 2018; Selkoe and Hardy, 2016).

The cholinergic hypothesis explains the pathophysiology of AD by a decrease of neurotransmitter ACh. It is proven that cognitive decline and memory loss are linked to the loss of cholinergic activity in the neocortex and hippocampus of AD patients brain (Bui and Nguyen, 2017; Damuka et al., 2020; Folch et al., 2016; Hampel et al., 2018; Kawamoto et al., 2019). AChE primarily degrades ACh in cholinergic synapses, while a closely related enzyme BChE has a role as a coregulator of cholinergic neurotransmission by hydrolyzing ACh. The inhibition of these enzymes is a key target for the management of AD since this inhibition leads to an increase in the availability of ACh in several brain regions (Bui and Nguyen, 2017; Hampel et al., 2018; Penumala et al., 2018), which is why it represents the main pharmacotherapeutic approach in the treatment of AD (Blažević et al., 2019).

According to the literature data, there are several other hypotheses aimed at explaining AD pathophysiology focusing on the hyperphosphorylated τ-protein, dendritic abnormalities, oxidative stress, mitochondrial dysfunction, metal ions, neuroinflammation, and even metabolic disorders (Fadaka et al., 2019; Folch et al., 2016; Thakur et al., 2019).

3.2. Current therapeutic strategies for AD

The potential therapeutic strategies for AD are developed according to the existing hypotheses on AD pathophysiology, and should be classified into two main groups:

a) Strategies focused on reducing Aβ aggregation and plaque formation. This strategy recognizes Aβ dyshomeostasis as the most extensively validated model in the development of potential treatments (Bui and Nguyen, 2017; Folch et al., 2016; Jagust, 2018; Selkoe and Hardy, 2016). It is reported that this group involves inhibitors of β-secretase and γ-secretase, nonsteroidal inhibitors of cyclooxygenase activity (NSAIDs), inhibitors of Aβ aggregation, modulators of β-amyloid transport and active immunotherapy (Folch et al., 2016; Kumar et al., 2015). Finally, a study claimed AD in older ages can be prevented if a subject took inhibitors of β-secretase and Aβ aggregation regularly from adolescence (Kawamoto et al., 2019).

b) Strategies focused on increasing the ACh level and improving cholinergic transmission. This group includes various therapeutic strategies directed towards elevating ACh levels, inhibiting ACh hydrolysis using AChE inhibitors, stimulating nicotinic and muscarinic receptors, and cholinomimetic substances (Bui and Nguyen, 2017; Damuka et al., 2020; Folch et al., 2016; Hampel et al., 2018).

c) Other therapeutic strategies include different approaches focusing on τ-protein pathology, dendritic pathology (N-methyl-D-aspartate (NMDA)-receptor antagonists), 5-HT6 receptors (their inhibitors were shown to promote ACh release), the linkage between AD and T2DM pathologies ("type 3 diabetes" hypothesis, suggesting antidiabetic drugs for the AD treatment), neuroprotection (antioxidants such as vitamins C and E, and polyphenols can prevent, delay or even reverse neuronal damage), etc. (Fadaka et al., 2019; Folch et al., 2016; Kamal et al., 2019; Kumar et al., 2015; Thakur et al., 2019).

Despite many research efforts, therapeutic options for AD are still limited to four drugs approved by The Food and Drug Administration (FDA): donepezil, galanthamine, and rivastigmine as a class of cholinesterase inhibitors and memantine, NMDA-receptor antagonist (Hampel et al., 2018; Kumar et al., 2015; Thakur et al., 2019). Cholinesterase inhibitors, e.g. galantamine, donepezil, and rivastigmine inhibit the activity of AChE, increase the level of ACh and enhance cholinergic transmission in the central nervous system (Bui and Nguyen, 2017). They are most effective when treatment begins in the early stages, while memantine is shown to be effective in the later stages of AD (Kumar et al., 2015). Galanthamine, acting as an allosteric modulator at nicotinic ACh receptors, is an alkaloid isolated from the snowdrop (*Galanthus* spp.) and it is also found in other members of the Amaryllidaceae family, e.g. *Narcissus* and *Leucojum* species (Kawamoto et al., 2019; Thakur et al., 2019), while donepezil and rivastigmine are synthetic drugs. It has been reported that the aforementioned AChE inhibitors have numerous harmful effects including diarrhea, abdominal pain, skin rash, hepatotoxicity (Bui and Nguyen, 2017), which leads to the conclusion that there is an urgent need to search for new, efficient and safe AChE inhibitors.

3.3. Potential of medicinal plants in AD therapy

The effects of aromatic and medicinal plants, crucial in the Mediterranean diet, in the prevention of neurocognitive disorders are well known (Dohrmann et al., 2019). On the other hand, medicinal plants have been continuously used as folk remedies for thousands of years, and the investigation of plants and their constituents provided scientific evidence on their immense potential for the treatment of various health disorders, including neurodegeneration. The advantage of herbs is that they have low toxicity compared to pharmaceutical agents, and they can be used together with drugs, providing possible synergistic effects (Singhal et al., 2012).

Although the synthetic drugs used in the treatment of AD are available, the search for new compounds originating from natural sources is of great importance. Numerous researchers around the world are investigating the cholinesterase inhibitory potential of a variety of plants, focusing on the compounds which demonstrated antioxidant, anti-amyloidogenic, anti-inflammatory and anti-apoptotic properties, so that could represent important sources of potential drug candidates against AD (D'Onofrio et al., 2017; Fadaka et al., 2019; Libro et al., 2016).

Previous reviews comprised a high number of literature data concerning the AChE and BChE inhibitors obtained from medicinal plants collected in different regions. The representatives of more than 150 plant families have been examined for AChE and BChE inhibition ability and reviewed as potential herbal drugs for AD treatment (Bui and Nguyen, 2017; Howes and E., 2011; Kumar et al., 2015; Mukherjee et al., 2007; Murray et al., 2013; Raghunath et al., 2018; Santos et al., 2018).

According to the reviewed literature, many papers present results obtained for plants collected in Turkey (Bozkurt et al., 2021; Deveci et al., 2018; 2019; Emir and Emir, 2021; Karakaya et al., 2020; 2019a; 2018; 2019b;c; Orhan et al., 2019; Ozkan et al., 2018b;a; Saleem et al., 2020c; 2019b; 2020a; 2019a; 2020b; 2021; 2019c; Sarikurkcu and Zengin, 2020; Sut et al., 2019b;a; Uysal et al., 2019a; 2018a;b;c; 2019b; 2021; Yilmaz et al., 2018; Zengin et al., 2018a; 2019a;b;c; 2018b;c;d; 2019d;e; 2018e; 2019f;g; 2018f; 2019h; 2021; 2020a;b; 2019i; 2018g; 2019j; 2018h; 2019k;l; 2018i). Turkey has unique geomorphology, topography, climate due to its position at the intersection of three phytogeographical regions (Euro-Siberian, Mediterranean and Irano-Turanian), which makes it a biodiversity hotspot with 12000 plant taxa, among which is 32 % endemic (Zengin et al., 2018b).

Covering examined 40 months-period, selected papers on the anticholinesterase activity of 289 taxa belonging to 68 families are presented in Table 1. The Figure 2 illustrates the percentage of representatives of families regarding the total number of taxa encompassed within this study. As can be seen in Table 1 and Figure 2, the largest number of examined taxa belongs to the families Lamiaceae (20 %), Asteraceae (12 %), Apiaceae (8 %), Fabaceae (5 %), Amaryllidaceae (4 %), Rosaceae (4 %), Caryophyllaceae (3 %) and Hypericaceae (3 %). Among Lamiaceae species, the most frequently examined taxa belong to *Salvia*, *Thymus*, *Stachys*, *Origanum* and *Sideritis* genera (Table 1), although the most quoted species known for their neuroprotective action were*Salvia officinalis*, *Rosmarinus officinalis* and *Melissa officinalis*. Some of the plant families comprising less than 3% are Brassicaceae, Araliaceae, Myrtaceae, Lauraceae, Rutaceae, Bogarinaceae, Plumbaginaceae, etc.

The representatives of the Lamiaceae family, often aromatic, are widely distributed and cultivated, having a long history of usage for food and medicinal purposes. In attempts of finding new natural compounds for the treatment of AD based on the cholinesterase inhibitory mechanism, numerous researchers analyzed various plants belonging to the Lamiaceae, and such trend can be also seen in the latest published papers. The important phenolic compounds found in the Lamiaceae representatives are rosmarinic and carnosic acid, which demonstrated neuroprotective effects in various studies, including the activity against diverse modes of neuronal cell death (Taram

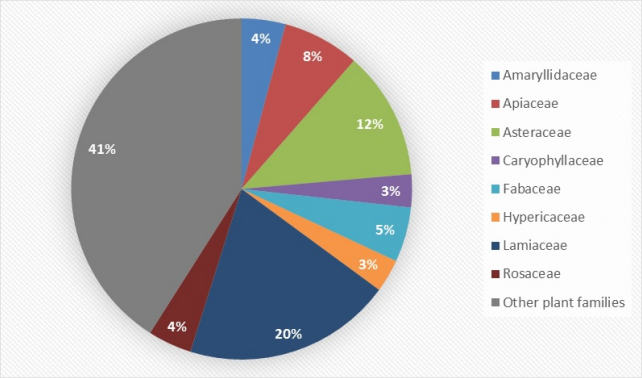

Fig. 2. Participation percentage of plant families' representatives examined for anticholinesterase activity regarding the total number of taxa

et al., 2018). Rosmarinic acid was the most abundant phenolic compound in *Thymus argaeus* and *Salvia modesta* methanolic extracts, which contributed to the AChE inhibition activity, while in the case of *T. argaeus* dichloromethane extract was the strongest inhibitor of both enzymes (Zengin et al., 2019b).

According to data presented in the Table 1, *Salvia* species have been the most extensively studied representatives of the Lamiaceae family, due to the high content of active compounds which could enhance cognitive activity and protect from neurodegenerative diseases (Lopresti, 2017). *In vitro* and *in vivo* studies revealed that several *Salvia* species extracts and oils (*S. officinalis*, *S. lavandulifolia*, *S. miltiorrhiza*, *S. fruticosa*) and their constituents are effective AChE and BChE inhibitors. Phenolic acids, such as caffeic, rosmarinic, salvianolic acids, flavonoids (luteolin, apigenin, hispidulin, kaempferol, and quercetin) and terpenoids (camphor, carnosic acid, carnosol, ursolic acid) are among frequently isolated compounds from the *Salvia* representatives. Because of its richness in different chemical constituents, *Salvia* species can influence multiple physiological pathways in the brain (Lopresti, 2017). Several *Salvia* species were studied lately for their possible antineurodegenerative effect. Three Turkish *Salvia* species showed the best cholinesterase inhibitory effects when dichloromethane was used as a solvent, with a slightly better result obtained for *S. euphratica* var. *leiocalycina* (Zengin et al., 2018e). Turkish endemic plant *S. eriophora* aqueous and methanolic leaf extracts strongly inhibited AChE and BChE (Bursal et al., 2019). Several *Salvia* species extracts were evaluated for their AChE inhibition by our research group. Libyan *S. lanigera* ethanol and water extracts showed better results than *S. fruticosa* in AChE inhibition (Duletić-Laušević et al., 2018b), while ethyl acetate extract of Cretan *S. pomifera* was the most potent AChE inhibitor compared to other tested extracts (Duletić Laušević et al., 2018c). As *S. officinalis* was previously proved due to its memory-enhancing properties, Duletić-Laušević et al. (2019a) tested AChE inhibition potential of ethanolic, aqueous and hydroethanolic extracts of *S. officinalis* collected in the three locations in Montenegro. All examined *Salvia* species samples performed anti-AChE effect, nevertheless, it was weaker than galathamine used as positive control. In the study of Uysal et al. (2021), the dichloromethane extract obtained from *S. ceratophylla* roots exhibited the strongest inhibitory effects against AChE compared to other tested extracts.

Besides extracts, essential oils of Lamiaceae species were also proved to be effective enzyme inhibitiors, especially those of the species belonging to genera *Salvia*, *Satureja*, *Thymus*, *Origanum* which are well-known to be rich in thymol, carvacrol, β-pinene and 1,8-cineole. Moreover, Savelev et al. (2004) concluded that synergy among essential oil components of several tested *Salvia* oils contributes to anticholiesterase activity of total essential oil.

Various plant parts are being analyzed for the evaluation of anticholinesterase activity – whole plant or separately roots, leaves, stems (including branches, stem bark and wood), flowers and individual flower parts, fruits and fruit parts, seeds, rhizomes, bulbs (Table 1). In aforementioned period, in the view of total number of samples examined for anticholinesterase activity, whole plant/aerial parts (46 %) are the most frequently used, followed by leaves (20 %), roots (9 %), flowers/flower parts and stems. Among the other plant parts, rhizomes and seeds are included in a part below 3 % regarding the total sample number (Figure 3).

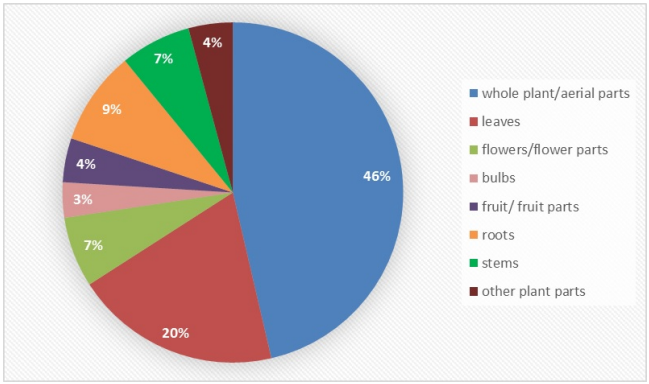

Fig. 3. Participation percentage of plant parts used for anticholinesterase activity regarding the total number of examined samples

The results of numerous studies indicated that the extracts obtained from various plant parts possessed different anticholinesterase inhibiton potential. For example, Sut et al. (2019a) demonstrated that the methanolic extract obtained from *Paeonia kesrounansis* aerial parts exhibited the highest AChE inhibition, while root extract was most effective towards BChE.

Numerous studies revealed that root extracts were more effective cholinesterases' inhibitiors compared to aerial parts. For example, the ethanolic extracts of roots of two *Achillea* species were rich in phenolic acids, while aerial parts were rich in flavonoids; *A. monocephala* aerial parts, with high content of luteolin and apigenin, showed the best activity against AChE and BChE (Yilmaz et al., 2018). Additionaly, Yener (2020) showed that ethanolic extract of *Salvia poculata* roots has stronger AChE and BChE inhibition activity in comparison with other studied plant parts, and also compared to galanthamine. In a study involving different plant parts of several *Ferulago* species, the root extracts demonstrated the strongest inhibition potential towards AChE and BChE, containing the highest content of certain phenolic compounds (Karakaya et al., 2018; 2019b). Similar findings were obtained for *Hypericum perforatum* (Tusevski et al., 2018), *Filago germanica* (Saleem et al., 2019c), *Euphorbia milii* (Saleem et al., 2019c), *Potentilla* spp. (Sut et al., 2019a; Uysal et al., 2019b), *Leiotulus dasyanthus* (Karakaya et al., 2020), etc.

Also, the bulbs and roots from different monocots are shown to be a considerable source of bioactive compounds. The bulbs from the genus *Allium* possessed a lower AChE and BChE activity than the rest of the aerial parts (Emir et al., 2020), however, alkaloid extracts of the bulbs from the genus *Phaedranassa* showed considerable activity against AChE and BChE (Moreno et al., 2020), which is attributed to the presence of galanthamine-type alkaloids. Sevim and Şener (2020) demonstrated strong BChE inhibitory activity of the dichloromethane fraction of the *Iris pseudoacorus* bulbs. This finding is impor-

tant because it was noticed that BChE activity increases along with the severity of dementia, while AChE activity declines (Lane et al., 2006), which emphasizes the importance of finding potent BChE inhibitory compounds.

Besides chia, the seeds of other plants are rarely tested for the enzyme inhibition analyses, so this review included only a few literature data (Table 1). Chia (*S. hispanica*) seeds contain healthy beneficial ingredients, displaying high potential for use in the food industry. *In vitro* and *in vivo* studies proved health beneficial effects of chia seed, and (Kobus-Cisowska et al., 2019a) examined the potential of commercially available white, gray, brown and black chia seeds from Argentina in inhibition of AChE and BChE. The ethanol extracts of colored seeds exhibited the highest inhibitory activity against AChE and BChE.

Additionally, the literature survey demonstrated that different plant preparations were used for the investigation of anticholinesterase activity, including essential oils, as well as various solvent extracts and their fractions. Solvents with different polarity are being used for extraction: methanol, ethanol, water, acetone, butanol, dichloromethane, chloroform, ethyl acetate, hexane, as well as diverse solvent mixtures (methanol/water, ethanol/water, methanol/chloroform, etc.) to make extraction process more efficient (Table 1). In this period, considering the total number of plant preparations tested for anticholinesterase activity, methanolic extracts (27 %) are the most frequently used, followed by aqueous (16 %), and ethyl acetate extracts (13 %), while essential oils were represented with 9 %. Plant preparations such as infusion, decoction, butanolic extracts, chloroform extracts, etc., which were presented with less than 3 % of examined samples, are included in "other plant preparations" (Figure 4).

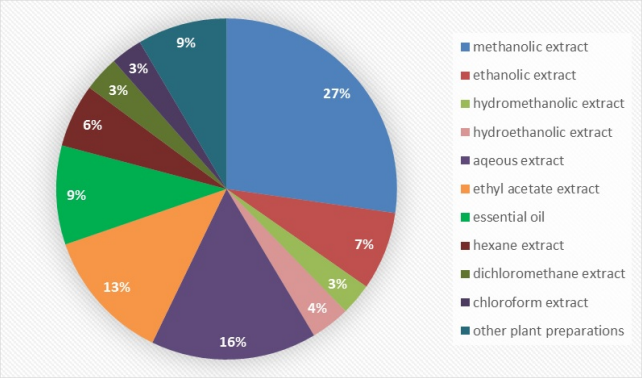

Fig. 4. Participation percentage of plant preparations tested for anticholinesterase activity regarding the total number of examined samples

Methanolic, followed by the aqueous and ethyl acetate extracts of the aerial parts of different medicinal plants are most frequently used for the investigation of phytochemistry and pharmacology including a variety of bioactivities. The methanolic extracts obtained from aerial parts of six wild edible *Silene* species from Turkey effectively inhibited AChE and BChE (Zengin et al., 2018f). In the study of Ceylan et al. (2021)) the methanolic extracts of aerial parts of 11 *Inula* species were tested, whereby *I. ucheriana* exhibited the highest anti-AChE activity, while *I. britannica* showed the strongest anti-BChE activity. The aerial parts and root methanolic extracts of six *Limonium* species showed that all examined samples possess anticholinesterase activity (Senizza et al., 2021). Methanolic extract of *Ocimum basilicum* was stronger AChE inhibitor than acetone and aqueous extracts (Duletić-Laušević et al., 2019b). Comparing AChE inhibiting potential of ethanol and aqueous extracts of sweet marjoram (*Origanum majorana*), Duletić-Laušević et al. (2018a) obtained better results for aqueous extracts which were less active than positive control galanthamine. Furthermore, the hydroalcoholic mixtures were proven as appropriate for the extraction of anti-AChE components. For example, 70 % hydroethanolic extract showed the higher AChE inhibition than individual fractions of this extract, as previously demonstrated for *Punica granatum* (Šavikin et al., 2018) and *Aronia melanocarpa* (Zdunić et al., 2020). In addition, the ethyl acetate extracts of *Potentilla recta* and *P. argentea* expressed the highest AChE and BChE inhibitory activity in comparison with methanolic and aqeous extracts (Sut et al., 2019b). Besides extraction solvent, the extraction method significantly infuenced cholinesterase inhibiting capacity of the obtained extract. For example, Zengin et al. (2019g) have found variations of AChE and BChE inhibition of *Salvia viridis* ethanolic root extracts obtained by different extraction methods, achieving the best results by supercritical fluid extraction, connected with the presence of β-sitosterol.

4. PARKINSON'S DISEASE (PD)

4.1. Description, symptoms, and pathophysiology of PD

PD is one of a host of parkinsonian disorders featured by parkinsonism, primarily by prominent bradykinesia (Dickson, 2012). Described for the first time by James Parkinson in 1817, PD is second the most frequent NDDs after AD (Corti et al., 2005; Gitler et al., 2017; Jiang et al., 2018; Maiti et al., 2017; McLean et al., 2017; Váradi, 2020). Epidemiological studies have revealed that PD affects 1-2 % of people older than 65 years, and 4-5 % of those aged over 85 years, with a higher incidence in developed countries (Corti et al., 2005; Maiti et al., 2017). It is estimated that the male population is more prone to PD comparing to their female counterpart (about 1.5 times) (Maiti et al., 2017; Srivastav et al., 2017) which is attributed to the protective effect of estrogen in women (Fadaka et al., 2019; Váradi, 2020).

The most conspicuous symptoms of PD comprise motor dysfunctions including bradykinesia, rigidity, resting tremor and postural instability, and different non-motor symptoms (Balestrino and Schapira, 2020; Corti et al., 2005; Dickson, 2012; Maiti et al., 2017; McLean et al., 2017; Pathak-Gandhi and Vaidya, 2017). Although the etiology and pathogenesis of PD are not completely explained, there is evidence that both environmental risk factors and genetic predisposition can contribute to its development. Different genetic causes, i.e. familiar PD forms have been identified in approximately 5-15 % of PD cases (Balestrino and Schapira, 2020). PD may coexist with dementia and depression in over 2 % of the cases (Cacabelos, 2020). Furthermore, it is reported that PD is associated with physical and mental comorbidity, particularly hypertension, constipation, coronary heart disease, painful conditions, depression, anxiety, and dementia (McLean et al., 2017). There is an increasing number of reports of neurological symptoms in COVID-19 patients, suggesting the potential for neurotropism of SARS-CoV-2 (Beauchamp et al., 2020).

Pathophysiologically, PD is characterized by dopamine (DA) deficiency resulting by loss of the dark-pigmented dopaminergic nigrostriatal neurons of the substantia nigra pars compacta (SNc) (Balestrino and Schapira, 2020; Corti et al., 2005; Hasegawa, 2010; Jiang et al., 2018; Maiti et al., 2017; Song et al., 2012; Srivastav et al., 2017; Zucca et al., 2014) and degeneration of non-dopaminergic systems such as noradrenergic, serotonergic and cholinergic systems (Maiti et al., 2017; Song et al., 2012). Neuromelanin-containing neurons of SNc are particularly susceptible to degeneration and their depigmentation is a hallmark of advanced disease (Hasegawa, 2010; Zucca et al., 2014).

It is already known that mitochondrial dysfunction and altered oxidative stress along with aging are crucial cellular stress factors playing the most important role in PD pathogenesis (Iarkov et al., 2020; Srivastav et al., 2017; Váradi, 2020). The proposed mechanisms underlying the pathogenesis and progression of neurodegeneration in SNc include iron-catalyzed oxidative stress, toxic oxygen-free radicals during enzymatic dopamine catabolism, mitochondrial dysfunctions, trophic support, dyshomeostasis of kinase activity and intracellular calcium, neuroinflammation and disturbances of protein metabolism (Hasegawa, 2010; Maiti et al., 2017; Song et al., 2012). The neuronal damage in PD is ascribed to abnormal intracellular aggregation and accumulation of presynaptic nerve terminal protein α-synuclein leading to Lewy bodies (LBs) formation (Balestrino and Schapira, 2020; Corti et al., 2005; Iarkov et al., 2020; Maiti et al., 2017; Pathak-Gandhi and Vaidya, 2017; Srivastav et al., 2017; Váradi, 2020).

Tyrosinase (TYR) is a key enzyme in the biosynthesis of melanin and plant polyphenols. In mammals, TYR is specifically expressed in melanocytes distributed in the skin, hair, and retina epithelium (Chang, 2009; Hasegawa, 2010; Pillaiyar et al., 2017). In the central nervous system of mammals, DA-derived pigment neuromelanin is found in nigral dopaminergic cells, which suggests that TYR might play a significant role in neuromelanin formation and could be responsible for the neurodegeneration associated with PD (Hasegawa, 2010; Pillaiyar et al., 2017; Zucca et al., 2014). TYR catalyzes both the hydroxylation of tyrosine to L-DOPA and the subsequent oxidation of L-DOPA to dopaquinone in order to form melanin. In addition, under certain circumstances, TYR may oxidize DA leading to melanin, through DA quinines formation. Furthermore, DA quinones can interact with α-synuclein and form a toxic intermediate in nigral cells (Hasegawa, 2010; Pillaiyar et al., 2017). DA-derived reactive species may interact with some key molecules in neuronal cells, leading to neuronal cell death and the concomitant neuropathological changes (Hasegawa, 2010). Neuromelanin showed a dual nature; intra neuronal neuromelanin protects the cells from toxic effects of redox-active metals, toxins, and excess of cytosolic catecholamines, while neuromelanin released by dying neurons can contribute to the activation of neuroglia triggering the neuroinflammation associated with PD (Zucca et al., 2014).

4.2. Current therapeutic strategies for PD

Enormous research done in this field has shown that some natural and synthetic products exhibit potential in the management of PD. Patients suffer from several motor (bradykinesia, rigidity, and resting tremor) and non-motor complications (constipation, cognitive decline, depression, fear, anxiety, weight changes, fatigue, and loss of energy, autonomic dysfunction/hypotension, dementia, hallucinations, sleep disorders, depression, psychosis, sexual problems, etc.) (Balestrino and Schapira, 2020; Corti et al., 2005; Jiang et al., 2018; Maiti et al., 2017; McLean et al., 2017; Pathak-Gandhi and Vaidya, 2017). Currently, the available treatments for PD are symptomatic and according to the mode of action drugs are divided into two categories:

1. dopaminergic drugs and
2. non-dopaminergic drugs.

Dopaminergic drugs. The main conventional strategies of PD treatment includes administration of dopaminergic drugs which actions are directed towards restoring the level of dopamine (DA), either by increasing of supply of levodopa (L-3,4-dihydroxyphenylalanine/L-DOPA) or by inhibition of DA breakdown catalyzed by monoamine oxidase B (MAO-B) to preserve DA level (Balestrino and Schapira, 2020; Maiti et al., 2017; Pathak-Gandhi and Vaidya, 2017; Srivastav et al., 2017; Váradi, 2020).

Dopamine is not able to pass through the blood-brain barrier, unlike its precursor L-DOPA. Administration of L-DOPA is very effective in reducing the "resting-tremors" and other primary symptoms in PD patients, but long-term benefits are not likely because L-DOPA is unable to preserve or replace degenerated DA-neurons and to stop further progression of PD. Long-term L-DOPA treatment is linked to motor complications called dyskinesias and other peripheral side effects including nausea, vomiting, low blood pressure, etc. Combined administration of L-DOPA with a peripheral DOPA decarboxylase inhibitor carbidopa prolongs the therapeutic effect of L-DOPA and helps in facilitating its side effects (Balestrino and Schapira, 2020; Iarkov et al., 2020; Maiti et al., 2017; Srivastav et al., 2017; Váradi, 2020). Another strategy for PD therapy is focused on MAO-B inhibitors used to maintain DA levels in the PD brain. The activity of the MAO-B enzyme is increased on account of DA metabolism which elevates oxidative stress and mitochondrial dysfunctions, so therapeutic approaches that optimize ROS and ameliorate mitochondrial function by inhibition of this enzyme are being considered as one of the current neuroprotective strategies (Balestrino and Schapira, 2020; Maiti et al., 2017; Srivastav et al., 2017). Although selegiline, rasagiline and safinamide show many side effects, they are currently the most commonly used MAO-B inhibitors (Jiang et al., 2018; Maiti et al., 2017). Unlike rasagiline and selegiline, safinamide is a reversible MAO-B inhibitor used in the middle and late stages of PD, showing many additional properties, including the anti-dyskinetic effect demonstrated in animal models (Balestrino and Schapira, 2020).

When decarboxylase inhibitors are present, L-DOPA metabolism is performed by catechol-O-methyltransferase (COMT). The currently available COMT inhibitors entacapone, tolcapone, and opicapone are used in PD therapy to prolong the effects of L-DOPA, but these drugs produce serious side effects, particularly tolcapone (Balestrino and Schapira, 2020; Jiang et al., 2018; Maiti et al., 2017).

Additionally, the administration of DA agonists is used for the direct stimulation of dopamine receptors during early-stage PD. The most common DA agonists ropinirole, pramipexole, ropinirole and apomorphine (especially effective for acute "off" episodes) are used to treat PD patients during early-stage PD, but these drugs show several potential side effects similar to L-DOPA (Balestrino and Schapira, 2020; Jiang et al., 2018; Maiti et al., 2017).

Non-dopaminergic drugs. Non-dopaminergic drugs include anticholinergic compounds, norepinephrine, serotonergic receptor- and muscarinic-receptor-related compounds, and antiviral drugs. Anticholinergic drugs (e.g. trihexyphenidyl, benztropine, orphenadrine, biperiden) can help in reducing tremors and muscle stiffness in PD but induce deficits in cognitive function (Balestrino and Schapira, 2020; Maiti et al., 2017). On the contrary, treatment with AChE inhibitors (e.g. rivastigmine, donepezil and galantamine) improves cognitive function but increases tremor (Balestrino and Schapira, 2020). NMDA (N-methyl-D-aspartate) glutamate receptor antagonists with anticholinergic activity such as amantadine activate dopamine synthesis and reduce motor symptoms, but have caused many side effects (Balestrino and Schapira, 2020; Jiang et al., 2018; Maiti et al., 2017).

Besides, there are surgical procedures, stem cell transplantation, gene therapy, as well as complementary, supportive and rehabilitation therapies that can prevent or delay the progression of this complex disease (Maiti et al., 2017). The potential therapeutic targets remain challenging keeping in mind the multifactorial heterogeneous risk factors associated with PD

Table 1. An update on *in vitro* anticholinesterase and antityrosinase activities of medicinal plants.

Plant family /species	Tested enzymes	Plant part used	Plant preparation	Reference
Amaranthaceae				
Aerva javanica	AChE, BChE, TYR	whole plant	methanolic extract	Saleem et al. (2021)
Atriplex gmelinii *Chenopodium glaucum* *Salicornia europaea* *Salsola komarovii* *Suaeda glauca* *Suaeda japonica* *Suaeda maritima*	TYR	whole plant	hydroethanolic extract	Jiratchayamaethasakul et al. (2020)
Amaryllidaceae				
Allium cepa	AChE	bulbs	methanolic extract	Kaur and Shri (2018)
Allium nigrum	AChE, BChE, TYR	aerial parts, bulbs	methanolic extract	Emir et al. (2020)
Allium stylosum	AChE, BChE, TYR	bulbs, leaves, flowers	methanolic extract	Emir and Emir (2021)
Allium subhirsutum	AChE, BChE, TYR	aerial parts, bulbs	methanolic extract	Emir et al. (2020)
Allium tuncelianum	AChE, BChE	bulbs	essential oil, aqueous extract, methanolic extract and its fractions	Karakaya et al. (2019a)
Crinum spp.	AChE	leaves	methanolic and aqueous extracts	Ghane et al. (2018)
Galanthus gracilis	AChE, BChE	aerial parts, bulbs	alkaloid extracts	Bozkurt et al. (2021)
Galanthus krasnoviii *Phaedranassa cuencana* *Phaedranassa dubia* *Phaedranassa glauciflora* *Phaedranassa tunguragueae*	AChE, BChE	bulbs	alkaloid extract	Moreno et al. (2020)
Anacardiaceae				
Pistachio vera	AChE, BChE, TYR	fruits parts	methanolic and aqueous extracts	Gezici (2019b)
Rhus tripartite	AChE	aerial parts	hydroacetone and hydromethanolic extracts	Tlili et al. (2019a)
Spondias mombim	AChE, BChE	leaves	ethyl acetate extract	Ojo et al. (2019)
Annonaceae				
Pseuduvaria macrophylla	AChE, BChE	leaves	essential oil	Salleh et al. (2021)

Apiaceae				
Actinolema macrolema	AChE, BChE, TYR	aerial parts	methanolic extract	Zengin et al. (2019h)
Ammodaucus leucotrichus	AChE, BChE	aerial parts	essential oil	Sadaoui et al. (2018)
Azorella glabra	AChE, BChE	aerial parts	hydroethanolic extract and its fractions	Faraone et al. (2019)
Bunium brachyactis *Bunium microcarpum* *Bunium pinnatifolium* *Bunium sayai*	AChE, BChE, TYR	aerial parts	methanolic extract	Zengin et al. (2019j)
Coriandrum sativum	TYR	fruits	hydromethanolic extract	Chiocchio et al. (2018)
Crithmum maritimum	AChE, BChE	leaves	ethanolic extract	Mekinić et al. (2018)
Falcria vulgaris	AChE, BChE, TYR	aerial parts	methanolic extract	Zengin et al. (2019h)
Ferula arrigonii	AChE, BChE, TYR	leaves, roots	hydromethanolic extract	Chiocchio et al. (2018)
Ferulago cassia	AChE, BChE	roots, aerial parts, flowers, fruits	methanolic, hexane, dichloromethane, ethyl acetate and butanolic extracts	Karakaya et al. (2019b)
Ferula elaeochytris	AChE, BChE, TYR	aerial parts	hexane, acetone, methanolic and aqueous extracts	Deveci et al. (2018)
Ferulago isaurica *Ferulago syriaca*	AChE, BChE	aerial parts, roots	methanolic, hexane, dichloromethane, ethyl acetate and butanolic extracts	Karakaya et al. (2018)
Glehnia littoralis	TYR	whole plant	hydroethanolic extract	Jiratchayamaethasakul et al. (2020)
Heracleum sphondylium	AChE, BChE, TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Uysal et al. (2019a)
Petroselinum crispum	AChE, BChE, TYR	aerial parts	essential oil	Jugreet et al. (2021)
Peucedanum japonicum	TYR	whole plant	hydroethanolic extract	Jiratchayamaethasakul et al. (2020)
Pimpinella anisum	AChE	seeds	aqueous extract	Farzaneh et al. (2018)
Smyrniopsis aucheri *Smyrniopsis munzurdagensis* *Smyrnium cordiifolium*	AChE, BChE, TYR	aerial parts	methanolic extract	Zengin et al. (2019h)
Trachyspermum ammi	AChE, BChE	fruits	hydroethanolic extract	Farjadmand et al. (2018)
Araliaceae				
Hydrocotyle umbellata *Panax ginseng* *Panax japonicas*	AChE	aerial parts roots rhizome	hydroethanolic extract	Hamdy et al. (2018)
Panax notoginseng *Panax quinquefolius*	AChE, BChE	roots	essential oil	Kawamoto et al. (2019)
Asparagaceae				
Asparagus oligoclonos	TYR	whole plant	hydroethanolic extract	Jiratchayamaethasakul et al. (2020)
Muscari comosum	AChE	bulbs	hydroethanolic extract	Larocca et al. (2018)

Asphodelaceae				
Aloe pruinosa	AChE	leaves	methanolic extract	Gebashe et al. (2019)
Asphodeline cilicica	AChE, BChE, TYR	leaves, stem, seeds, roots	acetone, methanolic and aqueous extracts	Zengin et al. (2019a)
Asphodelus aestivus *Asphodelus albus*	AChE, BChE, TYR	roots	infusion, dicholoromethane, ethyl acetate and methanolic extracts	Lazarova et al. (2020)
Asteraceae				
Achillea coarctata	AChE, BChE, TYR	roots, aerial parts	ethanolic and methanolic/chlorophorm extracts	Yilmaz et al. (2018)
Achillea filipendulina	AChE, BChE, TYR	flowers, leaves	ethanolic extract, essential oil	Asghari et al. (2020)
Achillea monocephala	AChE, BChE, TYR	roots, aerial parts	ethanolic and methanolic/chlorophorm extracts	Yilmaz et al. (2018)
Anthemis tinctoria var. *pallida* *Anthemis cretica* subsp. *tenuiloba*	AChE, BChE	aerial parts	ethyl acetate, methanolic and aqueous extracts	Orlando et al. (2019)
Artemisia absinthium	AChE, BChE	leaves	essential oil	Mhiri et al. (2018)
Artemisia campestris *Artemisia herba-alba*	AChE, BChE, TYR	aerial parts	essential oil	Cheraif et al. (2020)
Artemisia princeps *Artemisia scoparia*	TYR	whole plant	hydroethanolic extract, essential oil	Jiratchayamaethasakul et al. (2020)
Bidens tripartita	AChE, BChE	aerial parts	ethyl acetate, methanolic and aqueous extracts	Uysal et al. (2018c)
Bubonium imbricatum	AChE, BChE, TYR	aerial parts	hydromethanolic extracts, infusion	Aghraz et al. (2018)
Calendula officinalis *Centaurea calcitrapa*	TYR	flower parts aerial parts	hydromethanolic extract	Chiocchio et al. (2018)
Centaurea drabifolia subsp. *drabifolia*	AChE, BChE, TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Zengin et al. (2018i)
Centaurea horrida	TYR	aerial parts	hydromethanolic extract	Chiocchio et al. (2018)
Centaurea lycopifolia	AChE, BChE, TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Zengin et al. (2018i)
Centaurea napifolia	TYR	aerial parts	hydromethanolic extract	Chiocchio et al. (2018)
Centaurea saligna	AChE, BChE, TYR	leaves	ethyl acetate, methanolic and aqueous extracts	Zengin et al. (2018b)
Cladanthus arabicus	AChE, BChE, TYR	aerial parts	hydromethanolic extracts, infusion	Aghraz et al. (2018)
Cynara cardunculus	TYR	aerial parts	hydromethanolic extract	Chiocchio et al. (2018)
Doronicum macrolepis	AChE, BChE	stem, roots, flowers	ethanolic, methanolic and ethyl acetate extracts	Özcan (2020)
Filago germanica	AChE, BChE	roots, aerial parts	methanolic and dichloromethane extracts	Saleem et al. (2019a)
Gundelia rosea	AChE, BChE, TYR	seeds	ethanolic extract, infusion and decoction	Dalar et al. (2019)
Helichrysum chionophilum	AChE, BChE	flowers, stem	ethanolic, methanolic and ethyl acetate extracts	Acet et al. (2020)
Helichrysum plicatum	AChE, BChE	flowers, stem	ethanolic, methanolic and ethyl acetate extracts	Acet et al. (2020)
	AChE, TYR	flowers	hydroethanolic extract	Jovanović et al. (2020)
Inula anatolica *Inula aucheriana* *Inula britannica* *Inula discoidea* *Inula inuloides* *Inula mariae* *Inula oculus-christi* *Inula peacockiana* *Inula sechmenii* *Inula thapsoides* *Inula viscidula*	AChE, BChE, TYR	aerial parts	methanolic extract	Ceylan et al. (2021)

Asteraceae (continued)				
Pulicaria undulata	AChE, BChE, TYR	leafy stems	essential oil	Mohammed et al. (2020)
Scorzonera hieraciifolia	AChE, BChE, TYR	aerial parts, roots	infusion, dichloromethane, ethyl acetate, hexane and methanolic extracts	Dall'Acqua et al. (2020)
Sennecio biafrae	AChE, BChE	leaves	acetone extract	Ajiboye et al. (2018)
Silybium marianum	AChE, BChE	seeds	hexane, acetone and ethanolic extracts	Ulaç et al. (2019)
Sonchus brachyotus	TYR	whole plant	hydroethanolic extract	Jiratchayamaethasakul et al. (2020)
Tanacetum poteriifolium	AChE, BChE, TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Zengin et al. (2019k)
Taraxacum officinale	TYR	leaves, stem	ethanolic and hydroethanolic extracts	Xie et al. (2018)
Tithonia diversifolia	AChE, BChE	leaves	acetone extract	Ojo et al. (2018)
Berberidaceae				
Berberis calliobotrys	AChE, BChE, TYR	stem	methanolic, ethanolic, butanolic and aqueous extracts	Khan et al. (2019b)
Betulaceae				
Betula pendula	TYR	leaves	hydromethanolic extract	Chiocchio et al. (2018)
Bombaceae				
Bombax ceiba	AChE, BChE	flowers	ethanolic and hexane extracts	Sinha et al. (2019)
Boraginaceae				
Argusia sibirica	TYR	whole plant	hydroethanolic extract	Jiratchayamaethasakul et al. (2020)
Arnebia densiflora	AChE, BChE, TYR	aerial parts	methanolic extract	Zengin et al. (2018c)
Echium amoenum	AChE, BChE, TYR	flower parts	methanolic and hydromethanolic extracts, decoction, infusion	Asghari et al. (2019)
Onosma ambigens	TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Sarikurkcu et al. (2020)
Onosma isauricum	TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Zengin et al. (2019i)
Onosma sericea *Onosma stenoloba*	AChE, BChE, TYR	aerial parts	methanolic extract	Stanković et al. (2020)
Onosma tauricum var. *tauricum*	AChE, BChE, TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Kirkan et al. (2018)
Pulmonaria officinalis	AChE, BChE, TYR	aerial parts	hydroethanolic and aqueous extracts	Neagu et al. (2018)
Symphytum officinale	TYR	leaves	hydroethanolic extract	Vujanović et al. (2019)
Brassicaceae				
Barbarea auriculata var. *paludosa* *Barbarea integrifolia* *Barbarea plantaginea*	AChE, BChE, TYR	aerial parts	methanolic, ethyl acetate, aqueous and chloroform extracts	Badem et al. (2020)
Bunias erucago	AChE, BChE, TYR	flowers, leaves, stem, roots	hydromethanolic extract	Blažević et al. (2019)
Cakile maritima	AChE, BChE, TYR	aerial parts, fruits	ethanolic, acetone and aqueous extracts	Placines et al. (2020)
Fibigia clypeata	AChE, BChE, TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Zengin et al. (2020a)
Iberis sempervirens	AChE, BChE, TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Mahomoodally et al. (2018)
Scabiosa columbaria	TYR	leaves	methanolic extract	Otang-Mbeng and Sagbo (2020)
Tchihatchewia isatidea	AChE, BChE, TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Zengin et al. (2018a)

Buxaceae				
Buxus papillosa	AChE, BChE	aerial parts, stem bark	methanolic, dichloromethane and hexane extracts	Saleem et al. (2019b)
Campanulaceae				
Edraianthus pumilio	AChE, BChE	aerial parts	essential oil and aqueous extract	Politeo et al. (2019)
Cannabaceae				
Humulus lupulus	AChE, BChE	flowers	hydroalcoholic and aqueous extracts	Kobus-Cisowska et al. (2019b)
	AChE	flowers, leaves	methanolic extract	Keskin et al. (2019)
Capparaceae				
Capparis spinosa	AChE, BChE	aerial parts	hydroethanolic extract, decoction	Mollica et al. (2019)
Caprifoliaceae				
Nardostachys jatamansi	AChE, BChE, TYR	rhizome	methanolic, acetone, chloroform, acetonitrile and aqueous extracts	Bose et al. (2019)
Caricaceae				
Carica papaya	BChE	leaves	hexane and ethanolic extracts	Khaw et al. (2020a)
Caryophyllaceae				
Dianthus calocephalus	AChE, BChE, TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Uysal et al. (2018a)
Silene alba *Silene conoidea* *Silene dichotoma* *Silene italica*	AChE, BChE, TYR	aerial parts	methanolic extract	Zengin et al. (2018f)
Silene salsuginea	TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Zengin et al. (2018h)
Silene supina	AChE, BChE, TYR	aerial parts	methanolic extract	Zengin et al. (2018f)
Silene viridiflora	AChE, BChE, TYR	flowers, leaves, stem	methanolic extract	Mamadalieva et al. (2019)
Silene vulgaris	AChE, BChE, TYR	aerial parts	methanolic extract	Zengin et al. (2018f)
Spergularia marina	TYR	whole plant	hydroethanolic extract	Jiratchayamaethasakul et al. (2020)
Clusiaceae				
Garcinia atroviridis	AChE, BChE	stem bark	hexane, dichloromethane, chloroform, ethyl acetate, methanolic and aqueous extracts	Tan et al. (2019)
Garcinia mangostana	AChE, BChE	stem bark	methanolic and aqueous extracts	Khaw et al. (2020b)
Convolvulaceae				
Calistegia soldanela	TYR	whole plant	hydroethanolic extract	Jiratchayamaethasakul et al. (2020)
Cascuta reflexa	AChE, BChE	whole plant	hexane, ethyl acetate, methanolic and aqueous extracts	Akhtar et al. (2019)
Cucurbitaceae				
Cucurbita maxima	AChE, BChE	seeds	ethanolic and hexane extracts	Sinha et al. (2019)

Cupressaceae				
Juniperus phoenicea *Juniperus oxycedrus*	AChE, BChE, TYR	aerial parts	essential oil	Cheraif et al. (2020)
Ericaceae				
Arbutus unedo	TYR	fruits, leaves	hydromethanolic extract	Chiocchio et al. (2018)
Erica manipuliflora	AChE, BChE	aerial parts, flowers, leaves	essential oil, hexane, ethyl acetate, methanolic and butanolic extracts	Kuş et al. (2019)
Euphorbiaceae				
Euphorbia convolvuloides *Euphorbia heterophylla* *Euphorbia hirta*	AChE, BChE, TYR	aerial parts	essential oil	Sinan et al. (2021)
Euphorbia milii	AChE, BChE, TYR	aerial parts, roots	methanolic and dichloromethane extracts	Saleem et al. (2019c)
Euphorbia paganorum	TYR	leaves, branches	hydromethanolic extract	Chiocchio et al. (2018)
Fabaceae				
Astragalus macrocephalus subsp. *finitimus*	TYR	aerial parts, leaves, stem, roots, flowers	methanolic extract	Sarikurkcu and Zengin (2020)
Astragalus membranaceus	AChE, BChE	roots	hydroethanolic extracts	Santoro et al. (2020)
Astragalus neurocarpus	AChE, BChE, TYR	aerial parts, roots	ethanolic and aqueous extract	Sekeroglu and Gezici (2019)
Astragalus ponticus	AChE, BChE, TYR	aerial parts, leaves, stems, roots, flowers	methanolic extract	Arumugam et al. (2019)
Caesalpinia bonduc	AChE, BChE	seeds	ethanolic and hexane extracts	Sinha et al. (2019)
Caesalpinia bonduc *Caesalpinia decapeleta* var. *japonica*	AChE, BChE, TYR	leaves, stem bark	dichloromethane, ethyl acetate, methanolic and aqueous extracts	Zengin et al. (2021)
Caesalpinia crista	AChE, BChE	leaves	hexane, petroleum ether, methanolic and aqueous extracts	Chethana et al. (2018)
Caragana ambigua	AChE, BChE, TYR	aerial parts	methanolic, ethyl acetate, hexane and aqueous extracts	Khan et al. (2019a)
Cassia sieberiana	TYR	root bark	hydromethanolic extract	Chiocchio et al. (2018)
Coronilla orientalis *Coronilla varia*	AChE, BChE, TYR	whole plant	essential oil, chloroform, ethyl acetate, methanolic and aqueous extracts	Renda et al. (2019)
Crotalaria retusa	AChE, BChE, TYR	leaves	infusion, ethyl acetate and methanolic extracts	Sut et al. (2020)
Genista corsica	TYR	aerial parts	hydromethanolic extract	Chiocchio et al. (2018)
Glicine max	TYR	seeds	hydroethanolic extract	Kuswanto et al. (2020)
Lotus aegaeus	TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Mahomoodally et al. (2018)
Medicago sativa	TYR AChE, BChE	aerial parts leaves, stem, flowers	hydromethanolic extract ethanolic extract	Chiocchio et al. (2018) Eruygur et al. (2018)
Mucuna pruriens *Pueraria tuberosa*	TYR	seeds roots	hydromethanolic extract	Chiocchio et al. (2018)
Retama raetam	BChE	aerial parts	petroleum ether, ethyl acetate and methanolic extracts	Edziri et al. (2018)
Senna cana *Senna pendula*	AChE	leaves, branches leaves, branches, flowers	hexane and ethanolic extracts	Monteiro et al. (2018)
Senna podocarpa	AChE, BChE, TYR	leaves	aqueous extract and its butanolic fraction	Ajiboye et al. (2019)
Spartium junceum	TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Zengin et al. (2019i)
Fagaceae				
Quercus coccifera	AChE, BChE	fruit parts	ethanolic and aqueous extracts	Gezici and Sekeroglu (2019)

Gentianaceae				
Anthocleista vogelii	AChE, BChE	leaves	hydromethanolic extract and its fractions	Ajayi et al. (2019)
Centaurium umbellatum	AChE, TYR	aerial parts	hydroethanolic extract	Neagu et al. (2018)
Gentiana lutea	TYR	roots	hydromethanolic extract	Chiocchio et al. (2018)
Hypericaceae				
Hypericum empetrifolium	AChE, BChE, TYR	aerial parts, roots	essential oil and ethanolic extracts	Boga et al. (2021)
Hypericum hircinum	TYR	aerial parts	hydromethanolic extract	Chiocchio et al. (2018)
Hypericum lanuginosum	AChE, BChE, TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Mahomoodally et al. (2019b)
Hypericum lydium	AChE, BChE, TYR	aerial parts	methanolic and aqueous extracts	Eruygur et al. (2019)
Hypericum malatyanum *Hypericum neurocalycinum*	AChE	aerial parts	methanolic extract	Ozkan et al. (2018a)
Hypericum perforatum	AChE, BChE TYR	roots, stems, flowers aerial parts	methanolic extract hydromethanolic extract	Tusevski et al. (2018) Chiocchio et al. (2018)
Hypericum pseudolaeve	AChE	aerial parts	methanolic extract	Ozkan et al. (2018b)
Hypericum scruglii	TYR	aerial parts	hydromethanolic extract	Chiocchio et al. (2018)
Hypericum spectabile *Hypericum thymbrifolium*	AChE	aerial parts	methanolic extract	Ozkan et al. (2018b)
Illecebraceae				
Herniaria fontanesii	AChE	aerial parts	hydroacetonic and hydromethanolic extracts	Tlili et al. (2019a)
Iridaceae				
Iris pseudoacorus	BChE	bulbs	methanolic extract and its fractions	Sevim and Şener (2020)
Crocus chrysanthus	AChE, BChE, TYR	flowers	ethyl acetate, methanolic and aqueous extracts	Zengin et al. (2019c)
Crocus pallasii	TYR	flowers, corms	methanolic extract	Zengin et al. (2020b)
Gynandriris sisyrinchium	AChE, BChE, TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Zengin et al. (2018g)
Juncaginaceae				
Triglochin maritimum	TYR	whole plant	hydroethanolic extract	Jiratchayamaethasakul et al. (2020)
Juglandaceae				
Juglans regia	AChE, BChE	leaves	aqueous extract	Karakaya et al. (2019c)

Lamiaceae				
Ajuga bombycina *Ajuga chamaepitys* subsp. *chia* var. *chia*	AChE, BChE, TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Llorent-Martínez et al. (2019)
Ajuga orientalis	AChE, BChE, TYR	aerial parts	methanolic extract	Zengin et al. (2018c)
Ballota macrodonta	AChE, BChE, TYR	aerial parts	methanolic and aqueous extracts	Uysal et al. (2018a)
Calamintha incana	AChE, BChE, TYR	aerial parts	essential oil	Popović-Djordjević et al. (2019)
Clinopodium brownei	AChE, BChE	aerial parts	essential oil	Matailo et al. (2019)
Clerodendrum splendens	TYR	leaves	methanolic extract	Rowida et al. (2019)
Cyclotrichium origanifolium	AChE, BChE	aerial parts	decoction, infusion	Özer (2019)
Clinopodium serpyllifolium	AChE, BChE	aerial parts	essential oil, methanolic and aqueous extracts	Ali-Shtayeh et al. (2018)
Dracocephalum kotschyi *Dracocephalum multicaule* *Dracocephalum polychaetum*	AChE, BChE, TYR	aerial parts	hexane, chloroform, ethyl acetate, methanolic and aqueous extracts	Khodaei et al. (2019)
Glechoma sardoa	TYR	aerial parts	hydromethanolic extract	Chiocchio et al. (2018)
Lamium purpureum var. *purpureum*	AChE, BChE	aerial parts	hydroethanolic extract	Ekin et al. (2019)
Lavandula officinalis	AChE, BChE, TYR	aerial parts	essential oil	Cheraif et al. (2020)
Lavandula stoechas	TYR	aerial parts	hydromethanolic extract	Chiocchio et al. (2018)
Marrubium alysson	BChE	aerial parts	petroleum ether, ethyl acetate and methanolic extracts	Edziri et al. (2018)
Marrubium vulgare	TYR AChE, BChE	aerial parts aerial parts	hydromethanolic extract hydroacetone and hydromethanolic extracts	Chiocchio et al. (2018) Tlili et al. (2019a)
Mentha longifolia	AChE	leaves	essential oil, ethanolic, hexane and ethyl acetate extracts	Zouari-Bouassida et al. (2018)
Mentha piperita	AChE AChE, BChE, TYR	aerial parts leaves leaves	essential oil essential oil, methylene chloride and hexane extracts	Kennedy et al. (2018) Mhiri et al. (2018) Pavlić et al. (2021)
Mentha pulegium	AChE, BChE, TYR AChE, BChE	aerial parts aerial parts	essential oil methanolic and aqueous extracts	Cheraif et al. (2020) Politeo et al. (2018)
Mentha spicata	AChE AChE, BChE	aerial parts aerial parts	essential oil essential oil	Kennedy et al. (2018) Ali-Shtayeh et al. (2019)
Micromeria myrtifolia	TYR	leaves, buds, flowers	essential oil	Sarikurkcu et al. (2019)
Ocimum americanum	AChE, BChE, TYR	flowers, leaves	ethyl acetate, methanolic and aqueous extracts	Zengin et al. (2019d)
Ocimum basilicum	AChE AChE, BChE, TYR AChE, TYR	leaves leafy stems leaves	methanolic extract essential oil acetonic, methanolic and aqueous extracts	Kaur and Shri (2018) Mohammed et al. (2020) Duletić-Laušević et al. (2019b)
Origanum majorana	AChE, TYR	aerial parts	ethanolic and aqueous extracts	Duletić-Laušević et al. (2018a)
Origanum onites	AChE, BChE	aerial parts	hydroethanolic extract	Ekin et al. (2019)
Origanum sipyleum	AChE, BChE, TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Zengin et al. (2019e)
Origanum vulgare	TYR	aerial parts	essential oil and ethanolic extract	Moghrovyan et al. (2019)
Phlomis curdica	AChE, BChE	aerial parts	essential oil	Karadağ et al. (2020)
Plectranthus amboinicus	AChE, BChE, TYR	leaves	essential oil	Jugreet et al. (2021)

Lamiaceae (continued)				
Rosmarinus officinalis	TYR	aerial parts	hydromethanolic extract	Chiocchio et al. (2018)
	AChE	leaves	essential oil	Mhiri et al. (2018)
		leaves	hexane, acetone and ethanolic extracts	Ulaç et al. (2019)
	AChE, BChE	aerial parts	essential oil	Leporini et al. (2020)
Salvia blepharochlaena	AChE, BChE, TYR	aerial parts	dichloromethane, methanolic and aqueous extracts	Zengin et al. (2018e)
Salvia cassia	AChE, BChE	leaves, stem	ethanolic, dichlormetane and aqueous extracts	Halfon et al. (2019)
Salvia ceratophylla	AChE, BChE, TYR	aerial parts, roots	hexane, dichloromethane, methanolic, hydromethanolic and and aqueous extracts	Uysal et al. (2021)
Salvia eriophora	AChE, BChE	leaves	methanolic and aqueous extracts	Bursal et al. (2019)
Salvia euphratica var. *leiocalycina*	AChE, BChE, TYR	aerial parts	dichloromethane, methanolic and aqueous extracts	Zengin et al. (2018e)
Salvia fruticosa	AChE, TYR	aerial parts	ethanolic and aqueous extracts	Duletić-Laušević et al. (2018b)
Salvia hispanica	AChE, BChE, TYR	seeds	ethanolic and aqueous extracts	Kobus-Cisowska et al. (2019a)
Salvia lanigera	AChE, TYR	aerial parts	ethanolic and aqueous extracts	Duletić-Laušević et al. (2018b)
Salvia modesta	AChE, BChE, TYR	aerial parts	dichloromethane, methanolic and aqueous extracts	Zengin et al. (2019b)
Salvia officinalis	AChE, TYR	aerial parts	ethanolic, hydroethanolic and aqueous extracts	Duletić-Laušević et al. (2019a)
Salvia pocalata	AChE, BChE, TYR	roots, branches, leaves, flowers and mixed parts	petroleum ether and ethanolic extracts	Yener (2020)
Salvia pomifera	AChE, TYR	aerial parts	dichloromethane, chloroform, ethyl acetate and ethanolic extracts	Duletić Laušević et al. (2018c)
Salvia sclarea	AChE, BChE	aerial parts	hydroethanolic extract	Ekin et al. (2019)
Salvia verticillata subsp. *amasiaca*	AChE, BChE, TYR	aerial parts	dichloromethane and methanolic extracts	Zengin et al. (2018e)
Salvia virgata	AChE, BChE	aerial parts	hydroethanolic extract	Ekin et al. (2019)
Salvia viridis	AChE, BChE, TYR	roots	ethanolic extract	Zengin et al. (2019g)
Satureja thymbra	AChE, BChE, TYR	leaves, buds, flowers	essential oil	Kirkan et al. (2019)
Scutellaria orientalis *Scutellaria salviifolia*	AChE, BChE, TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Zengin et al. (2019f)
Sideritis albiflora *Sideritis leptoclada*	AChE, BChE, TYR	aerial parts	hexane, acetone and methanolic extracts	Deveci et al. (2019)
Sideritis libanotica	AChE, BChE, TYR	aerial parts	aqueous extract	Atas et al. (2019)
Sideritis stricta	AChE, BChE, TYR	aerial parts	acetone and methanolic extracts	Deveci et al. (2018)
Stachys cretica subsp. *smyrnaea*	AChE, BChE, TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Bahadori et al. (2019)
Stachys glutinosa	TYR	aerial parts	hydromethanolic extract	Chiocchio et al. (2018)
Stachys byzantina *Stachys inflata* *Stachys lavandulifolia*	AChE, BChE, TYR	aerial parts	essential oil	Bahadori et al. (2020)
Teucrium chamaedrys *Teucrium montanum*	TYR	aerial parts	hydroethanolic extract	Vujanović et al. (2019)
Thymbra spicata var. *spicata*	AChE, BChE, TYR	leaves, buds, flowers	essential oil	Kirkan et al. (2019)
Thymus argaeus	AChE, BChE, TYR	aerial parts	dichloromethane, methanolic and aqueous extracts	Zengin et al. (2019b)
Thymus herba-barona *Thymus serpyllum*	TYR	aerial parts	hydromethanolic extract	Chiocchio et al. (2018)
Thymus sipyleus	AChE, BChE	aerial parts	decoction, infusion	Özer (2019)
Thymus vulgaris	TYR	leaves	hydromethanolic extract	Chiocchio et al. (2018)
Thymus zygioides var. *lycaonius*	AChE, BChE	aerial parts	hydroethanolic extract	Ekin et al. (2019)
Vitex rotundifolia	TYR	whole plant	hydroethanolic extract	Jiratchayamaethasakul et al. (2020)

Lauraceae				
Cinnamomum camphora	AChE, BChE, TYR	seeds leaves	ethanolic extracts essential oil	Zhang et al. (2020) Jugreet et al. (2021)
Cinnamomum verum	AChE, BChE	stem bark	ethanolic and aqueous extracts	Gulcin et al. (2019)
Laurus nobilis	AChE, TYR	leaves	acetonic, methanolic and aqueous extracts	Duletić-Laušević et al. (2019b)
Ocotea percoriacea	AChE	leaves	hydroethanolic extract and its fractions	Cassiano et al. (2019)
Lythraceae				
Punica granatum	AChE, TYR TYR TYR	fruit parts	hydroethanolic extract and its fractions hydroethanolic extract aqueous extract	Šavikin et al. (2018) Laosirisathian et al. (2020) Turrini et al. (2020))
Magnoliaceae				
Magnolia officinalis	AChE, BChE	stem bark	dichloromethane, petroleum ether, chloroform, hydroethanolic and aqueous extracts	Zhang et al. (2019)
Malvaceae				
Abutilon figarianum	TYR	whole plant	methanolic and dichloromethane extracts	Saleem et al. (2020b)
Althaea officinalis	TYR	roots	hydromethanolic extract	Chiocchio et al. (2018)
Malva sylvestris	AChE, BChE	leaves and flowers	hexane, acetonic and ethanolic extracts	Ulaç et al. (2019)
Meliaceae				
Trichilia catigua	AChE, BChE	stem bark	aqueous, ethanolic, hexane and chloroform extracts	Martins et al. (2018)
Moraceae				
Artocarpus altilis Artocarpus chama *Artocarpus integer* *Artocarpus lakoocha* *Artocarpus rigidus* *Ficus benghalensis* *Ficus callosa*	TYR	branches, leaves leaves, stem, wood, bark branches, leaves wood branches, leaves branches, leaves, bark wood branches, leaves	ethanolic extract	Dej-Adisai et al. (2019)
Ficus carica	TYR AChE, BChE	fruit parts leaves	methanolic extract methanolic and aqueous extract	Meziant et al. (2021) Ergül et al. (2019)
Ficus celebensis Ficus chartacea var. torulosa *Ficus foveolata* *Ficus fistolusa* *Ficus hispida* *Ficus infectoria* *Ficus microcarpa* *Ficus racemosa* *Ficus religiosa* *Ficus superba* *Ficus vasculosa*	TYR	branches, leaves branches, leaves wood branches, leaves branches, leaves wood wood branches, leaves resin branches, leaves leaves, wood, stem bark	ethanolic extract	Dej-Adisai et al. (2019)
Morus alba	TYR	leaves	ethanolic extract	Chaiyana et al. (2020)
Morus alba var. *chiangmai* *Morus alba* var. *buriram* *Morus alba* var. *sakhonnakhon*	TYR	leaves	hexane, benzene, ethyl acetate acetone, ethanolic and aqueous extracts	Yodthong (2020)

Moraceae (continued)				
Morus nigra	TYR	leaves	hydroethanolic extract	Vujanović et al. (2019)
Streblus ilicifolius *Streblus taxoides*	TYR TYR	leaves, wood wood	ethanolic extract petroleum ether, ethyl acetate, methanolic, ethanolic and aqueous extracts	Dej-Adisai et al. (2019)
Moringaceae				
Moringa oleifera	AChE, BChE, TYR	leaves	methanolic, hydromethanolic and ethyl acetate extracts	Rocchetti et al. (2020)
Myrsinaceae				
Cyclamen cilicium	AChE, BChE, TYR	flowers, roots, leaves, tubers	methanolic extract	Zengin et al. (2020b)
Myrtaceae				
Myrcia mollis *Myrcianthes myrsinoides*	AChE, BChE	leaves	essential oil	Montalván et al. (2019)
Myrteola phylicoides	AChE, BChE	leaves	essential oil	Calva et al. (2019)
Myrtus communis	TYR AChE, BChE	fruits, leaves leaves	hydromethanolic extract essential oil	Chiocchio et al. (2018) Maggio et al. (2019)
Psidium guajava	AChE, BChE	leaves	chloroform, ethyl acetate and butanolic extracts	Bouchoukh et al. (2019)
Syzygium coriaceum	AChE, BChE, TYR	leaves	essential oil	Jugreet et al. (2021)
Syzygium samarangense	AChE, BChE, TYR	leaves	essential oil	Jugreet et al. (2021))
Nyctaginaceae				
Bougainvillea glabra	TYR	aerial parts, flowers	dichloromethane and methanolic extracts	Saleem et al. (2020a))
Oxalidaceae				
Oxalis corniculata	AChE, BChE	whole plant	ethanolic extract and its fractions	Imran et al. (2020)
Orchidaceae				
Cremastra appendiculata	AChE, BChE	tubers	ethanolic, petroleum ether, ethyl acetate, butanolic and aqueous extracts	Tu et al. (2018)
Nitariaceae				
Peganum harmala	BChE	aerial parts	petroleum ether, ethyl acetate and methanolic extracts	Edziri et al. (2018)
Paeoniaceae				
Paeonia arietina *Paeonia kesrounansis*	AChE, BChE, TYR	roots, aerial parts	ethyl acetate, methanolic and aqueous extracts	Sut et al. (2019b)
Passifloraceae				
Turnera diffusa	TYR	leaves	methanolic extract	Rowida et al. (2019)
Phyllanthaceae				
Phyllanthus emblica	TYR	leaves	methanolic extract	Rowida et al. (2019)
Pinaceae				
Pinus sylevestris	TYR	buds	hydromethanolic extract	Chiocchio et al. (2018)
Piperaceae				
Piper betle	AChE	leaves	essential oil	Karak et al. (2018)

Pittosporaceae				
Pittosporum senacia	AChE, BChE, TYR	leaves	methanolic extract	Mahomoodally et al. (2019a)
Pittosporum senacia subsp. *senacia*	AChE, BChE, TYR	fruits	essential oil	Jugreet et al. (2021)
Plantaginaceae				
Plantago ovata	AChE	aerial parts	hydroacetone and hydromethanolic extracts	Tlili et al. (2019a)
Veronica persica	AChE	aerial parts	methanolic extract	Sharifi-Rad et al. (2018)
Plumbaginaceae				
Limonium bellidifolium *Limonium globuliferum* *Limonium gmelinii* *Limonium iconicum* *Limonium lilacinum* *Limonium sinuatum*	AChE, BChE, TYR	aerial parts and root	methanolic extracts	Senizza et al. (2021)
Polygonaceae				
Calligonum comosum	TYR	leaves	methanolic extract	Rowida et al. (2019)
Rumex abyssinicus	AChE, BChE	rhizome	ethyl acetate extract	Augustin et al. (2020)
Rumex acetosa	TYR	leaves	methanolic extract	Rowida et al. (2019))
Primulaceae				
Primula vera	TYR	roots	hydromethanolic extract	Chiocchio et al. (2018)
Poaceae				
Elymus mollis *Ischaemum antephoroides* f. *coreana* *Spartina anglica*	TYR TYR TYR	whole plant	hydroethanolic extract	Jiratchayamaethasakul et al. (2020)
Ranunculaceae				
Aconitum heterophyllum	TYR	roots	hydroethanolic extract	Chiocchio et al. (2018)
Clematis cirrhosa	TYR	aerial parts	methanolic and hydromethanolic extracts	Chohra et al. (2020)
Consolida orientalis	TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Zengin et al. (2019i)
Nigella sativa	AChE, BChE	seed	oil	Sicak and Erdoğan Eliuz (2019)
Rhamnaceae				
Ziziphus lotus	TYR AChE	leaves, fruits aerial parts	infusion hydroacetone and hydromethanolic extracts	Marmouzi et al. (2019) Tlili et al. (2019a)
Rosaceae				
Agrimonia eupatoria *Alchemilla vulgaris*	TYR	aerial parts	hydromethanolic extract	Chiocchio et al. (2018)
Amelanchier parviflora var. *dentata*	AChE, BChE, TYR	aerial parts	ethyl acetate, methanolic and aqueous extracts	Zengin et al. (2018d)
Amygdalus communis	TYR	fruit parts	ethyl acetate, methanolic and aqueous extracts	Tlili et al. (2019b)

Rosaceae (continued)				
Aphanes arvensis	AChE, BChE	leaves, flowers	hexane, acetone and ethanolic extracts	Ulaç et al. (2019)
Aronia melanocarpa	AChE, TYR	leaves	hydroethanolic extract and its fractions	Zdunić et al. (2020)
Leucosidea sericea	AChE	leaves	methanolic, hexane, dichloromethane, ethyl acetate and butanolic extracts	Pendota et al. (2018)
Potentilla anatolica	AChE, BChE, TYR	roots	methanolic extract	Uysal et al. (2019b)
Potentilla argentea	AChE, BChE, TYR	roots aerial parts	methanolic extract ethyl acetate, methanolic and aqueous extracts	Uysal et al. (2019b) Sut et al. (2019a)
Potentilla recta	AChE, BChE, TYR	roots aerial parts	methanolic extract ethyl acetate, methanolic and aqueous extracts	Uysal et al. (2019b) Sut et al. (2019a))
Potentilla reptans	AChE, BChE, TYR	roots	methanolic extract	Uysal et al. (2019b)
Prunus armeniaca *Prunus domestica*	AChE, BChE	leaves	essential oil	Bonesi et al. (2018)
Rosa centifolia	TYR	flower parts	hydromethanolic extract	Chiocchio et al. (2018)
Rosa rugosa	TYR	whole plant	hydroethanolic extract	Jiratchayamaethasakul et al. (2020)
Rubus caesius	AChE, BChE, TYR	leaves	butanolic, ethyl acetate, diethyl ether, methanolic, hydromethanolic and aqueous extracts	Grochowski et al. (2019)
Rubus fraxinifolius	TYR	stem	methanolic extract	Desmiaty et al. (2020)
Sorbus aucuparia	AChE, TYR	leaves	hydroethanolic extract	Šavikin et al. (2018)
Rubiaceae				
Geophila repens	AChE, BChE	leaves	hydroalcoholic	Dash et al. (2019)
Macrosphyra longistyla	AChE, BChE	leaves	methanolic extract, hexane, ethyl acetate and aqueous fraction	Elufioye et al. (2019)
Morinda citrifolia	AChE, BChE, TYR	fruit	essential oil	Jugreet et al. (2021)
Rutaceae				
Aegle marmelos	TYR	leaves	hydromethanolic extracts	Chiocchio et al. (2018)
Citrus aurantium	AChE, BChE, TYR	fruit parts, leaves	essential oil	Jugreet et al. (2021)
Citrus hystrix *Citrus maxima*	AChE, TYR	fruit parts	hydromethanolic extracts	Abirami et al. (2018)
Citrus reticulata	AChE, TYR	fruits	acetone, methanolic and aqueous extracts	Duletić-Laušević et al. (2019b)
Citrus sinensis	AChE	fruit parts	essential oil	Boughendjioua et al. (2019)
Ruta chalepensis	AChE, BChE	aerial parts	ethanolic extract and its fractions	Gali and Bedjou (2019)
Zanthoxylum bungeanum	AChE, BChE	fruit parts	benzene, ethyl acetate, chloroform, methanolic, ethanolic and aqueous extracts	Ma et al. (2019)
Santalaceae				
Arceuthobium oxycedri	AChE, BChE	whole plant	hexane, chloroform, ethyl acetate, aqueous and butanolic extracts	Orhan et al. (2019)
Salvadoraceae				
Salvadora oleoides	BChE	aerial parts, stems, roots	dichloromethane and methanolic extracts	Saleem et al. (2020c)
Sapotaceae				
Chrysophyllum perpulchrum	AChE, BChE, TYR	stem bark, leaves	ethyl acetate and methanolic extracts, infusion	Baloglu et al. (2019)
Saxifragaceae				
Bergenia ciliata	AChE, BChE	rhizome	methanolic extract, butanolic, ethyl acetate, hexane, chloroform and aqueous extracts	Zafar et al. (2019)
Scrophulariaceae				
Scrophularia lucida	AChE, BChE, TYR	aerial parts, roots	ethyl acetate, methanolic and aqueous extracts	Zengin et al. (2019l)

Simmondsiaceae				
Simmondsia chinensis	AChE	seeds	oil	Baccouch et al. (2018)
Solanaceae				
Capsicum annuum	AChE, BChE, TYR	fruits	hydromethanolic and hexane extracts	Della Valle et al. (2020)
Hyoscyamus albus	AChE	aerial parts	hydroacetone and hydromethanolic extracts	Tlili et al. (2019a)
Sterculiaceae				
Cola caricifolia	AChE, BChE, TYR	leaves	infusion, ethyl acetate and methanolic extracts	Sut et al. (2020)
Taxaceae				
Torreya grandis	TYR	fruit parts	essential oil	Feng et al. (2019)
Theaceae				
Camellia sinensis	TYR	leaves	methanolic extract	Rowida et al. (2019)
Thymelaeaceae				
Thymelaea hirsuta	AChE	aerial parts	hydroacetone and hydromethanolic extracts	Tlili et al. (2019a)
Urticaceae				
Urtica dioica	AChE, BChE	leaves	hexane, acetonic and ethanolic extracts	Ulaç et al. (2019)
Verbenaceae				
Verbena officinalis	TYR	aerial parts	hydromethanolic extract	Chiocchio et al. (2018)
Vitaceae				
Vitis vinifera var. *zalema*	AChE, BChE	seeds, fruit, stem	ethanolic, hydroethanolic and aqueous extracts	Jara-Palacios et al. (2020)
Zingiberaceae				
Alpinia aquatica	TYR	stem, leaves, rhizome	hexane, ethyl acetate, methanolic extracts	Romes et al. (2020)
Alpinia nigra *Amomum aculeatum* *Amomum coriandriodorum* *Amomum dealbatum* *Amomum uliginosum* *Curcuma aeruginosa* *Curcuma amada* *Curcuma aromatica* *Curcuma candida* *Curcuma latifolia*	TYR	rhizome	hexane, ethyl acetate and ethanolic extracts	Rachkeeree et al. (2020)

Zingiberaceae (continued)				
Curcuma longa *Curcuma mangga* *Etlingera araneosa* *Etlingera elatior* *Etlingera linguiformis* *Kaempferia rotunda*				
Curcuma longa	AChE, BChE, TYR AChE, BChE	rhizome	essential oil methanolic and aqueous extracts	Jugreet et al. (2021) Gezici (2019a)
Zingiber officinalis	TYR	roots	hydromethanolic extract	Chiocchio et al. (2018)
Zingiber bradleyanum *Zingiber densissimum* *Zingiber larsenii* *Zingiber monglaense* *Zingiber sirindhorniae* *Zingiber smilesianum*	TYR	rhizome	hexane, ethyl acetate and ethanolic extracts	Puangpradab et al. (2020)

pathogenesis (Jiang et al., 2018; Srivastav et al., 2017).
In addition, several approaches for prevention and disease-modifying treatments are extensively investigated, including substances that reduce oxidative stress and improve mitochondrial function, calcium channel blockers, and neuroprotective agents, such as nicotine (cholinergic modulator) and caffeine (adenosine receptor antagonist) (Balestrino and Schapira, 2020; Iarkov et al., 2020; Váradi, 2020). Similar to coffee, green tea could exert its effects via caffeine-induced inactivation of the adenosine receptor, while phenolic components from its leaves such as (-)-epigallocatechin-3-gallate manifested potent antioxidant and neuroprotective effects (Iarkov et al., 2020). Furthermore, increased consumption of fruits, vegetables, legumes and cereals, with minimizing consumption of red meats, typical for the Mediterranean diet, has beneficial role on the incidence of NDDs, including PD, showing positive effects on the decrease of cardiovascular and cancer mortality, lipid metabolism, blood pressure, etc. (Dohrmann et al., 2019).

One of the indirect and non-conventional strategies for the treatment of PD includes inhibition of TYR as well as reduction of oxidative stress which plays a significant role in the neurodegeneration associated with PD. The potential of medicinal plants in TYR inhibition, recognized as one of the prospective alternatives for the treatment of PD, will be discussed in detail.

4.3. Potential of medicinal plants in PD therapy

The current therapeutics applied for this disorder bring forth a symptomatic relief, but strategies for slowing down or ceasing the disease progression are not developed.
There are many natural compounds, such as hydroquinone (HQ), arbutin, kojic acid, azelaicacid, L-ascorbic acid, ellagic acid, tranexamic acid, etc., which are confirmed as effective TYR inhibitors (Lee et al., 2016; Pillaiyar et al., 2017). Kojic acid, the most intensively studied inhibitor of TYR, is a fungal metabolite currently used as a cosmetic skin-whitening agent and as a food additive for preventing enzymatic browning. Kojic acid and arbutin are often used as the positive controls in the literature for comparing the inhibitory strength of the tested inhibitors (Chaiyana et al., 2020; Chang, 2009; Lee et al., 2016). Also, TYR inhibition is considered as one of alternative therapeutical strategies for PD, which acceletate the investigation of medicinal plants as natural source of TYR inhibitors.
Ethnobotanical investigations and subsequent screening of medicinal plants for their biological activities represent an essential step for novel drug discovery. Literature survey showed that *in vitro* TYR inhibition was intensively investigated in the last two decades, mainly on different plant extracts, while the essential oils and pure bioactive compounds isolated from essential oils and extracts were investigated to a quite lesser extent.
According to the recent literature data, in the last few years TYR inhibitory activity was the most extensively investigated in Turkish medicinal plants (Bahadori et al., 2019; Bozkurt et al., 2021; Emir and Emir, 2021; Khan et al., 2019a; Sarikurkcu and Zengin, 2020; Ulaç et al., 2019; Uysal et al., 2018a;b;c; 2021; Zengin et al., 2018a; 2019a;b;c; 2018b;c;d; 2019d;e; 2018e; 2019f;g; 2018f;g;h)). Besides, a number of traditionally used medicinal plants from South Korea (Jiratchayamaethasakul et al., 2020), Thailand (Chaiyana et al., 2020; Laosirisathian et al., 2020; Puangpradab et al., 2020; Rachkeeree et al., 2020; Yodthong, 2020), Sudan (Dirar et al., 2019; Mohammed et al., 2020), Algeria (Cheraif et al., 2020), India (Abirami et al., 2018; Chiocchio et al., 2018; Mukherjee et al., 2018; Pathak-Gandhi and Vaidya, 2017; Srivastav et al., 2017), China (Xie et al., 2018; Zhang et al., 2020)), Iran (Asghari et al., 2019; Dall'Acqua et al., 2020) also showed significant anti-TYR potential.

In the examined 40 months-period, selected papers on the anti-TYR activity of 300 taxa belonging to 53 families are displayed in Table 1. In the Figure 5, the percentage of representatives of families regarding the total number of taxa encompassed within this study is presented. The highest number of examined taxa belongs to the families Lamiaceae (18 %), Asteraceae (12 %), Moraceae (9 %), Zingiberaceae (8 %), Fabaceae, Apiaceae, Rosaceae, etc. (Table 1, Figure 5). Some of the plant families comprising less than 3% are Brassicaceae, Plumbaginaceae, Amaranthaceae, Euphorbiaceae, etc.

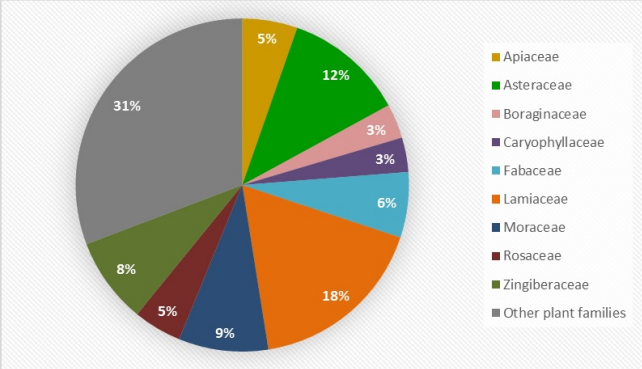

Fig. 5. Participation percentage plant families' representatives examined for anti-TYR activity regarding the total number of taxa

The diverse solvent extracts and essential oils of numerous Lamiaceae herbs were extensively evaluated for their TYR inhibition potential. Among them, the most frequently examined taxa belong to the genus *Salvia*. The genus *Salvia* comprises nearly 1000 species, many of which are proved for their bioactivities, including enzyme inhibiting effects. Methanolic, ethanolic and aqueous extracts, mainly obtained from aerial parts of different *Salvia* species, showed high anti-TYR capacity in numerous studies (Ekin et al., 2019; Halfon et al., 2019; Yener, 2020; Zengin et al., 2018b;c;e) (Table 1) Previous investigation on TYR inhibition of *Salvia* spp. showed high potential of different extracts of examined species, including Libyan *S. fruticosa*, *S. lanigera*, Cretan *S. pomifera* and *S. officinalis* from Montenegro (Duletić-Laušević et al., 2019a; Duletić Laušević et al., 2018c). It is worth-mentioning that the ethanolic and aqueous extracts of *Salvia* species from Libya (Duletić-Laušević et al., 2018b) and ethanolic extract of *S. officinalis* Duletić-Laušević et al. (2019a) showed stronger anti-TYR effects than kojic acid used as positive control. Additionaly, the dichloromethane extracts were frequently found as the most efficient TYR inhibitors compared to other extracts, as Uysal et al. (2021) demonstrated in the study of *S. ceratophylla* aerial parts and roots.
To isolate active components, whole plants and separated plant parts (roots, rhizomes, leaves, flowers, fruits, different fruits parts) have been exploited (Table 1). During the investigated period, considering the total number of samples examined for anti-TYR activity, whole plant/aerial parts (45 %) were most frequently used for plant preparations, followed by leaves (19 %), stems (9 %), roots (8 %), rhizomes (7 %), etc. Among "other plant parts", bulbs and seeds comprised only 2 % regarding the total number of samples (Figure 6).
For the investigation of TYR inhibition potential of medicinal plants, essential oils and various solvent extracts have been isolated and tested. Polar and non-polar solvents such as methanol, ethanol, water, acetone, butanol, dichloromethane, chloroform, ethyl acetate, hexane, and especially different solvent mixtures are applied for the extractions (Table 1). In the studied period, in view of total number of plant preparations tested for anti-TYR activity, methanolic extracts (24 %) are

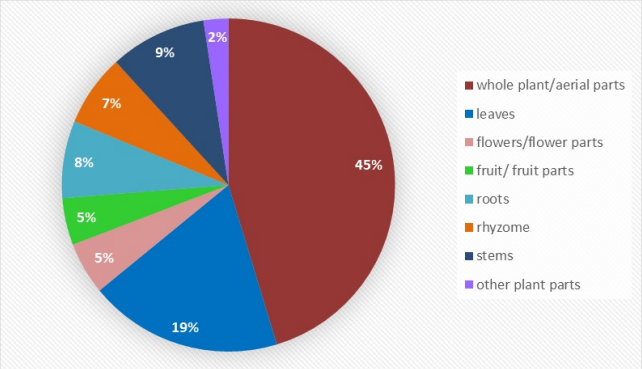

Fig. 6. Participation percentage of plant parts used for anti-TYR activity regarding the total number of examined samples

the most frequently used, followed by ethyl acetate (14 %), aqueous (13 %) and ethanolic extracts (12 %), while essential oils were represented with only 6 %. Infusion, decoction, dichloromethane, acetone extracts, etc., were present with less than 3% of examined samples, and included in "other plant preparations" (Figure 7).

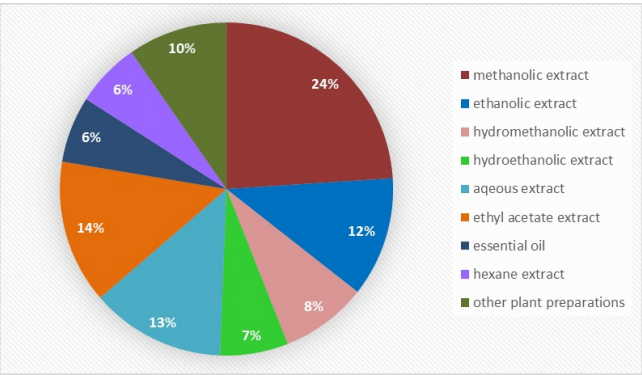

Fig. 7. Participation percentage of plant preparations tested for anti-TYR activity regarding the total number of examined samples

Different plant preparations and extraction procedures were applied to optimize the extraction process and to achieve maximal inhibition of medicinal herbs. Also, tested plant preparations are obtained using whole aerial parts and/or separated plant parts such as roots, rhizomes, leaves, flowers, etc. (Aghraz et al., 2018; Asghari et al., 2019; Chaiyana et al., 2020; Dej-Adisai et al., 2019; Turrini et al., 2020; Uysal et al., 2018a; 2021; Zengin et al., 2019e; 2020a; Zhang et al., 2020). As can be seen in the Table 1 and Figures 6-7, the methanolic extracts of whole aerial parts were the most frequently prepared for the investigation of TYR inhibition. Many aerial parts of the Apiaceae taxa displayed prominent anti-TYR effects (Deveci et al., 2018; Uysal et al., 2019a; Zengin et al., 2019f;g). Sarikurkcu and Zengin (2020) showed that all methanolic extracts from different plant parts of *Astragalus macrocephalus* subsp. *finitimus* are comparable with positive control kojic acid and the most active was the extract of the leaves. Many Asteraceae species, mostly from genus *Inula*, are shown to be potent inhibitors of TYR activity. Ceylan et al. (2021) showed that *Inula viscidula* exhibited the strongest anti-TYR activity among 11 tested methanolic extracts of aerial parts of *Inula* species. Chohra et al. (2020) recorded that two methanolic extracts of *Clematis cirrhosa* aerial parts showed noticeable anti-TYR activity compared to kojic acid.

The mixture of water and alcohols, such as ethanol and methanol, was frequently applied to improve extraction of bioactive components (about 15 % of all tested samples, Table 1 and Figure 7). Hydroethanolic extracts of *Punica granatum* (Šavikin et al., 2018) and *Aronia melanocarpa* (Zdunić et al., 2020) displayed the stronger TYR inhibition than individual fractions of this extract. Testing 100 plant extracts for anti-TYR potential, Chiocchio et al. (2018) found that hydromethanolic extracts of Mediterranean plants collected in Sardinia, such as aerial parts of *Cytinus hypocistis* and *Limonum morisianum*, as well as leaves of *Pistacia lentiscus* and *P. terrebinthus*, have prominent inhibiting effects. In the study of Jiratchayamaethasakul et al. (2020), hydroethanolic extracts of 22 South Korean species aerial parts were tested and *Spartina anglica* showed the highest anti-TYR activity. Furthermore, methanolic extracts of six halophyte *Limonium* species roots and aerial parts also showed considerable anti-TYR activity (Senizza et al., 2021).

Additionaly, it is worth mentioning that *Artocarpus* spp. and *Ficus* spp. belonging to family *Moraceae*, as well as *Curcuma* spp. and *Zingiber* spp. belonging to family Zingiberaceae, were extensively examined for anti-TYR activities (Table 1). Among 15 Sri Lankan medicinal plants, the bark ethanolic extracts of *Artocarpus altilis* and *A. nobilis* were stronger TYR inhibitors than kojic acid (Liyanaarachchi et al., 2018). Moreover, the ethanolic extracts of 48 taxa belonging to *Moraceae* family were tested by Dej-Adisai et al. (2019). This study showed that the extracts of *Artocrpus chama* stem and *Streblus taxoides* wood exhibited the highest anti-TYR activity, in both enzymatic and intracellular assays. *Morus* spp. (mulberry) belonging to the same family contain various polyphenols (Chang, 2009; Mukherjee et al., 2018; Pillaiyar et al., 2017; Zolghadri et al., 2019), including oxyresveratrol which exhibited 32-fold stronger inhibitory activity than kojic acid and 50-fold higher TYR inhibiting potential than resveratrol isolated from grapes (Chang, 2009).

Camelia sinensis is the rich source of polyphenols and catechins (green tea) with antioxidant activity, and theaflavins (black tea) which showed neuroprotective effects (Srivastav et al., 2017). It is shown that catechins reduce tyrosine hydroxylase and interfere with the α-synuclein aggregation (Jiang et al., 2018). The flavonoid rich extracts of several members of Fabaceae family were also proved as promising anti-TYR agents, including *Glycyrrhiza* spp. and *Glycine max* (Mukherjee et al., 2018). The root extracts of *Glycyrrhiza* species showed melanogenesis inhibitory activity due to the presence of isoflavonoids glabridine and glabrene (Chang, 2009), and chalcones with anti-TYR activity (Lee et al., 2016). A member of the Fabaceae family, *Mucuna pruriens*, has been used in traditional Ayurvedic medicine to manage neurodegenerative diseases like PD, because its seeds represent a natural source of levodopa (Pathak-Gandhi and Vaidya, 2017; Srivastav et al., 2017). The studies performed by Puangpradab et al. (2020) and Rachkeeree et al. (2020) have showed that plants of family Zingiberaceae, especially *Curcuma* spp. and *Zingiber* spp., represent an immerse source of compounds with anti-TYR potential, which are frequently accumulated in the rhizomes. The hexane extract of *Zingiber denisissimum* rhizome exhibited the highest anti-TYR potential among six *Zingiber* species (Puangpradab et al., 2020). Additionaly, Rachkeeree et al. (2020) revealed that among 16 Zingiberaceae plant species, using different solvents, the most prominent activity had the hexane extracts of *Curcuma* spp. rhizomes. It is previously reported that *Curcuma longa* contains curcumin and other curcuminoids which demonstrated significant TYR inhibition potential and neuroprotective effects (Jiang et al., 2018; Mukherjee et al., 2018; Song et al., 2012; Srivastav et al., 2017).

Diverse monocots also exhibited potent anti-TYR effects, as was shown for methanolic extracts obtained from diverse plant parts of Turkish *Allium* species (Emir et al., 2020; Emir

and Emir, 2021), which could be explained by high content of polyphenolics, especially catechol (Emir and Emir, 2021). Moreover, Lazarova et al. (2020) found that roots extracts of two *Asphodelus* species, particularly *A. aestivus* exhibited strong TYR inhibition.

Several studies have demonstrated that essential oils and their individual components isolated from medicinal herbs of Lamiaceae, Asteraceae, Myrtaceae, Lauraceae, Rutaceae and Cupressaceae, also possess TYR inhibition effects (Table 1). The considerable anti-TYR activity was shown by *Ocimum basilicum* and *Pulicaria undulata* essential oils (Mohammed et al., 2020). Citral and myrcene from citrus fruits essential oils and flavonoids nobiletin, hesperidin, neohesperidin and naringin from the citrus peel are proved as TYR inhibitors (Chang, 2009; Mukherjee et al., 2018). Among nine investigated species from Mauritius, essential oils of two *Syzigium* species and *Morinda citrifolia* showed the highest TYR inhibition potential (Jugreet et al., 2021; 2020). In the study including six Algerian plants, the most prominent anti-TYR effects displayed the essential oils of *Juniperus oxycedrus* and *Artemisia campestris* (Cheraif et al., 2020).

Herbal medicines can be an alternative and valuable source for anti-PD drug discovery. Some well-studied compounds such as baicalein, puerarin, resveratrol, curcumin, and ginsenosides deserve further consideration in clinical trials (Jiang et al., 2018; Lee et al., 2016; Song et al., 2012; Zolghadri et al., 2019). Furthermore, the mixtures of some TYR inhibitors such as glabridin/resveratrol, glabridin/oxyresveratrol, resveratrol/oxyresveratrol, aloesin/arbutin and several other combinations have shown the synergistic effect on TYR inhibition, which can be a useful strategy for the improvement of their inhibitory activities (Zolghadri et al., 2019).

5. SYNERGISM AMONG MEDICINAL PLANTS AS A NEW PROMISING STRATEGY IN AD AND PD TREATMENT

Synergy is a process in which some substances cooperate to reach a combined effect that is greater than the sum of their separate effects (Pezzani et al., 2019). In Traditional Chinese Medicine (TCM) different herbs can be used together as paired herbs to increase drug efficiency (Kong et al., 2019). In the last few decades, one of the promising approaches in the investigation of natural products therapeutic potential is searching for possible synergistic interactions, which are documented between/among:

- plants and/or mushrooms in their mixtures,
- components of single plant/mushroom extracts,
- isolated components of plant/mushroom extracts,
- plants/mushrooms extracts or their isolated components and commercial drugs.

According to the available literature data, different combinations of herbs, as well as individual metabolites isolated from herbs performed synergistic effects in inhibition of enzymes involved in neurodegeneration.

For example, synergistic effects in AChE inhibition were shown for 1,8-cineole- α-pinene/caryophyllene oxide in *Salvia lavandulaefolia* essential oil (Savelev et al., 2004), for combinations of essential oils obtained from *Lavandula stoechas* and *Mentha pulegium* (2:1) and for *Laurus nobilis* and *Mentha pulegium* oils (1:1) (Yakoubi et al., 2021), the mixture of *Acacia nilotica* and *Rhamnus prinoides* roots aqueous extracts (Crowch and Okello, 2009), aqueous and ethanolic extracts of *Ganoderma lucidum* and *Salvia officinalis* (Ćilerdžić et al., 2019), acetone extracts of *Hypoxis colchicifolia* and *H. hemerocallidea* corns (Ndhlala et al., 2013), berberine-coptisine-palmatine from TCM herbs *Berberis bealei*, *Coptis chinensis* and *Phellodendron chinense* (Kaufmann et al., 2016), fangchinoline-coptisine/berberine (Kong et al., 2019), palmatine and berberine (Balkrishna et al., 2019; Ma et al., 2019), curcumin-piperine (Abdul Manap et al., 2019). The several results published from January 2018 until present, showed that research on this topic was mainly focused on alkaloid-containing herbs traditionally used to treat dementia and/or due to their neuroprotective properties. Kong et al. (2019) reviewed the potential of naturally derived alkaloids as therapeutics or even nutraceuticals for managing neurodgenerative disorders. They emphasized harmine and berberine chloride, among 61 alkaloids listed, as potential modulators in the management of the progression of AD and PD, but also mentioned the limitations of application, such as dosage, penetration into the brain, low extraction yields, etc.

In the study of TCM herbs, it was reported that fangchinoline isolated from the dried root of *Stephania tetrandra* and its combinations with coptisine/berberine isolated from the dried bark of *Ph. chinense* and/or dried rhizome of *C. chinensis* synergistically inhibited AChE. As stated by Kong et al. (2019) these alkaloid-containing herbs are usually paired for dementia treatment in TCM. The results of the study encompassing fractions of five herbs used in the Ayurvedic medicine showed the highest AChE inhibition of *Tinospora cordifolia*, resulting from synergistic effects of palmatine and berberine. AChE inhibition mode of these alkaloids was non-competitive, unlike galantamine acting by competitive mode (Balkrishna et al., 2019). According to results obtained by Abdul Manap et al. (2019), the combination of curcumin and piperine in lower concentrations exhibited greater AChE inhibition than treatment with individual compounds and additionally showed significant neuroprotective effects.

In comparison to AChE, synergistic effects of combinations of herbs and/or individual components in TYR inhibition were less extensively studied up to date. To our knowledge, only a few studies are available on this topic. Liang et al. (2012) discovered a synergistic TYR inhibitor from *Smilax china* root. Namely, a mixture of oxyresveratrol and dioscin highly increased the inhibition of TYR activity as compared to single components. Sindhuja et al. (2014) found that synergistic effects of the mixture of herbal extracts of four Malaysian plants (*Tridax procumbens*, *Lantana camara*, *Euphorbia hirta* and *Thevetia peruviana*) on TYR inhibition were not observed. In the mixture containing *Phyllanthus emblica* extract, L-ascorbic acid and kojic acid, Wangkananon et al. (2018) found an optimal ratio of ingredients providing the highest level of TYR inhibition. Wang et al. (2018) studied TYR inhibiting potential of four antioxidants (glabridin, resveratrol, oxyresveratrol and phenylethylresorcinol) and found out synergistic interactions for combinations of glabridin/resveratrol, glabridin/oxyresveratrol, oxyresveratrol/resveratrol and phenylethylresorcinol/resveratrol.

Our previous research work on this topic (Ćilerdžić et al., 2019) was aimed to investigate the possible synergistic AChE and TYR inhibiting effects of combined *Ganoderma lucidum* and *Salvia officinalis* ethanol and aqueous extracts, as highly valued species in traditional medicine. In the AChE inhibition assay, the ethanolic and aqueous extracts obtained from mixture of dried *G. lucidum* and *S. officinalis* materials (70:30) as well as the mixture of their liquid extracts obtained by extraction with ethanol and water (30:70) showed the strongest synergistic effects. In the TYR inhibition assay, the ethanolic and aqueous extracts obtained from the mixture of equal dried materials showed the most prominent synergism comparing to others.

CONCLUSIONS AND PERSPECTIVES

As the literature survey for the examined period showed, majority of the tested plants exhibited *in vitro* inhibition of cholinesterases and tyrosinase, however, their effects varied in a broad range, depending on plant species, plant part used to obtain the preparation, choice of the extraction solvent, extraction technique, etc. In this review, almost 300 taxa belonging to about 70 plant families were selected. Data analysis showed that families with the highest number of tested representatives were Lamiaceae (comprising up to 20 % of the investigated taxa), followed by Asteraceae (12 % of the investigated taxa), while other families were represented with percentage below 10 %. Among them, the high number of representatives selected for the investigation of cholinesterase inhibition belongs to the families Apiaceae and Fabaceae, while tyrosinase inhibition was extensively studied for numerous Moraceae and Zingiberaceae members. Regarding the plant parts used to obtain preparations, almost half of the samples tested for enzymes inhibition was prepared from whole plant/aerial plant parts, followed by leaves (about 20 %), while other individual plant parts participated with less than 10 %. The most frequently tested preparations were methanolic extracts (about a quarter of the samples examined), followed by aqueous, ethanolic and ethyl acetate extracts. The essential oils were tested to quite lesser extent compared to the extracts, as well as infusions, decoctions and hydroethanolic extracts, although these preparations are more suitable for human consumption. Additionally, a great deal of literature data was found on the effects of synergistic interactions between different herbs, mushrooms and/or isolated compounds. The presented data showed that medicinal plants represent an immense source of diverse compounds which could be further tested as potent inhibitors of the enzymes involved in the neurodegeneration processes.

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