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Immune-Boosting Plants Used in Turkish Folk Medicine and their Potential against COVID-19

Sargin SA[1]* and Dogan Y[2]

[1]Faculty of Education, Alanya Alaaddin Keybubat University, Turkey
[2]Buca Faculty of Education, Dokuz Eylul University, Turkey

***Corresponding author:** Seyid Ahmet Sargin, Faculty of Education, Alanya Alaaddin Keybubat University, Alanya, Antalya, Turkey, Email: sasargin@gmail.com, yunus.dogan@deu.edu.tr

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Abstract

Having suffered from a global epidemic of Covid19 mutants and variants, the entire world has turned its attention and hope to natural treatments that can keep the immune system active and strong. Recent research on some herbal preparations promises high hopes that they may be potential candidates for developing effective and safe immune-boosting drugs. Considering that Turkey has the richest flora of Europe and the Middle East and has an invaluable ethnomedical background, it offers a treasure-worthy potential for serious researchers. 128 plant taxa belonging to 41 families were determined from 99 works carried out in different regions of Turkey. Of these, only 60 (46.9%) were found to be responded to in experimental studies worldwide on immune system enhancement and other similar activities. Quercetin (10.3%), β-glucan, and catechin (5.1%) emerged as the most common active substances among 39 identified active substances. *Urtica dioica* (39.4%), *Rosa canina* (34.3%), and *Punica granatum* (17.2%) were recorded as the most used plants in Turkey. In addition, *Phoenix dactylifera* has appeared as the taxon with having more active compounds in the literature. This study presents the first national inventory of immune-boosting plants that are regularly used in traditional Turkish medicine, not only against Covid-19 but for the prevention and treatment of epidemic diseases in general. We present 68 (53.1%) plants whose effective immune-stimulating and strengthening properties have been confirmed in experimental studies in the world literature as ready-made material to the relevant pharmacological sectors.

Keywords: Covid-19; Immune-Boosting; Immunostimulant; Medicinal plant; Pandemic; Turkey

Introduction

The Covid-19 outbreak, which emerged in Wuhan, China in late 2019, is still the first contagious epidemic the world has encountered after the Spanish Flu in terms of scope and size. The virus, which causes Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) with its enveloped and single-stranded RNA content, rapidly expanded into a global dimension, with rising serious mortality rates after it turned into a regional epidemic [1]. The first verified Covid-19 case in Turkey was detected on March 11. As of 10 May 2021, 5,016,141 confirmed cases and 42,746 deaths have been reported to the World health organization [2]. In order to combat this rapidly emerging threat, prevention and treatment protocols were established and some social restrictions were imposed in a very short time [3].

The immune system is a complex system that forms the defence mechanism against diseases in a living thing, recognizes and destroys pathogens and tumour cells, and protects the body from foreign and harmful substances [4]. Two types of immunities - innate and adaptive, play a powerful role with increased susceptibility against infections. The likelihood of being diseased depends on the effectiveness of the immune response. Therefore, low immunity results in reduced ability to fight the pathogen and become more susceptible to disease. Most of the deaths associated with coronavirus are due to the suppressed immune system of the human body that is unable to fight against it, rather than the damage caused by the virus [5]. When the immune response is low, weak, or damaged, infections such as coronavirus attack people, especially young and older people. It also becomes an open invitation for other diseases such as diabetes, heart disease, or cancer [6,7]. Since there is not yet a registered drug or vaccine 100% effective against COVID-19 and all its mutants or variants, the immune system is actually still the best defence we have. As long as the immune system is functioning normally, infections such as Covid-19 may go undetected [8]. It has been found that patients suffering from infectious and non-infectious diseases of the lungs are at greater risk from this viral infection due to their low immune system [9,10]. Therefore, strengthening immunity (natural body system) can make a major contribution as a prophylactic measure against multiple pathogenic conditions as well as maintaining optimum health [10,11].

The most common symptoms are fever, headache, cough, difficulty breathing and diarrhea. In some cases or in different variants of the virus, these symptoms may also remain silent. Or, on the contrary, it might be presented as severe pneumonia causing shortness of breath, kidney failure or even death. After the virus enters the respiratory mucosa cells of another host through droplets that are released by coughing and sneezing (or close-range speech), it releases its genetic code to initiate viral replication, then uses the following three mechanisms to circumvent the immune response: The virus implements various mechanisms to circumvent the immune response. In the first step, it inhibits the rapid expression of interferon type 1 (IFN-1), known as the "initial alarm", which modulates immune cells to the "antiviral state" in the case of the system encountering the virus. Second, it blocks IFN-1's existing signals in the system through inhibition of the phosphorylation of STAT-1 (Signal converter and transcription activator 1). Its third mechanism is the dysfunctioning of the immune system through excessive and prolonged production of IFN-1 by plasmacytoid dendritic cells (pDCs). The process causes an overproduction of activated neutrophils and macrophages, resulting in lung immunopathology (e.g. acute respiratory distress syndrome) [12]. This, in turn, activates a rapid reaction of innate immunity and results in the release of cytokines in large amounts, which play a key role in determining the extent of the infection. They damage beneficial cells and organs in the body, including defence cells, thus causing destruction and leading to death [4]. In the severe cases, a severe immune response is observed with deep lung exudates production, which limits ventilation and can subsequently trigger an uncontrolled inflammatory response, acute respiratory distress syndrome (ARDS) and septic shock, following bilateral pneumonia [13]. These two complications are the primary reasons of hospitalization in intensive care and mortality for COVID-19 in patients with a history of smoking and comorbidities [14]. Chronic obstructive pulmonary disease, including chronic inflammation of the upper respiratory tract (URI), hypertension, diabetes, malignant tumour, coronary heart disease, cerebrovascular disease, and chronic kidney disorders are among the most common of these clinical stories [4,8].

Due to their ability to easily mutate their genetic material and gain resistance, developing a broad-spectrum antiviral drug/vaccine that is completely safe and has a potential of 100% effectiveness and it reaching the market level is really difficult and quite a time consuming [15]. Moreover, synthetically developed antiviral drugs sometimes have harmful or even fatal side effects that can cause significant health problems [16]. Indeed, a newly developed popular vaccine that received market approval a few months ago created clots as a side effect and caused deaths in vaccinated people. Within a week, its use was suspended by about 18 countries worldwide [17]. Therefore, their ability to minimize these side effects and having effective antiviral potential, herbs and plant-based herbal remedies seem promising in minimizing these side effects [16,18].

A healthy and proper diet can strengthen the immune system and prevent the development of diseases and immune depression. For example, antioxidants can prevent or repair damage caused by harmful agents such as viruses and free radicals. The most powerful antioxidant in the human body is glutathione (GSH). If its level in the body increases, there is a simultaneous decrease in cytokine factors such as interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), which cause to worsen the disease (proinflammatory), thereby helping the patient recover [4]. Especially medicinal plants, due to their rich content in minerals and vitamins, regularly contribute to the healthy development of the general intestinal microbiome, which constitutes 85% of the immune system, and to keep the immune system active in the fight against infections. Highlights of immune-enhancing herbs are garlic, black cumin and liquorice [6,7]. They produce many important phytochemicals through their secondary metabolism and act as a defence against stress caused by environmental triggers and pathogens. In fact WHO's an announcement that 80% of the world's population

trusts them for treatment highlights this fact [19,20].

Herbal preparations/medicines are always defined as a therapeutic regimen that, rather than consisting of a single compound that interacts with a single target, is a concerted pharmacological intervention of several compounds that interact with multiple targets [21]. The results showed that not only do they modulate pathways related to strengthening the immune system, but also modulate multiple pathways that contribute to the progression of multiple disease pathogenesis that would add beneficial effect on specific issues such as hypertension and diabetes patients [10]. After the first SARS-CoV epidemic, it has been shown in many studies that plant extracts and phytochemicals produced from plants affect the virus with different mechanisms. These consist of direct antiviral activity, immune stimulator, inflammation modulator and symptom management. Direct antiviral activity includes inhibition of early replication through viral entry inhibition and late replication inhibition [20].

The most likely mechanism for immune enhancers is to trigger humoral and cellular immune responses [22]. For example, it has been found that aqueous and methanol extracts of basil leaves and seed oil increase the immune response by increasing T-helper and natural killer cells, lymphocyte count, phagocytic activity, neutrophil count, antibody titer, and the like [23,24]. Similar positive effects of a wide variety of flavonoids found naturally in plants, such as quercetin, naringin, hesperetin, and catechin, against severe acute respiratory syndrome coronavirus (SARS-CoV) have been reported [25]. Researchers such as Terali, et al. [26] and Bibi, et al. [27] also elucidated the inhibitory action pathway against the ACE2 enzyme receptor, which enables COVID-19 to enter host cells. Hence, Utomo, et al. [28] reported that curcumin isolated from turmeric (*Curcuma longa*) inhibits SARS-CoV-2 protease, spike glycoprotein-RBD and PD-ACE2 receptors, based on their molecular insertion studies. As a result of their in-silico studies, Jakhmola Mani, et al. [29] stated that active ingredients such as a-hederin, thymohydroquinone and thymoquinone, obtained from the extract of *Nigella sativa* seeds, efficiently bind and block ACE2 and reduce hypoxia and inflammation caused by oxidative stress, strengthening immunity and can greatly assist in the fight against Covid-19. Also, ACE2 inhibitors have been identified in various species such as *Allium sativum, Cerasus avium, Berberis integerrima, Alcea digitata, Rubia tinctorum, Peganum harmala* etc. [30]. It has also been disclosed that herbal blockers which can inhibit the "pathogenic" kinase (PAK1), which plays a major role in the infection of many viruses, can support the immune system and serve as potential therapeutic agents against COVID-19 [31]. Also, curcumin rhizome [32] and tea-shaped extract of *Schinus molle* (pink peppercorn) fruits [33] contribute to the blocking of PAK1, strengthening the immune system against COVID-19 and other viral infections, and its essential anti-inflammatory formulations has been reported. On the other hand, Shaghaghi [34] showed in molecular dynamic simulations with terpinoid compounds, including thymoquinone extracted from *Nigella sativa*, that thymoquinone can reduce the likelihood of infection of SARS-CoV-2 [35]. Therefore, it is envisaged that medicinal plants may be effective in the prevention and treatment of COVID-19, either through direct use or their isolated compounds. However, many more advanced studies are needed for optimum effective dosage formulation and usage descriptions.

The followings can be given as examples of similar studies conducted in Turkey: In an in-silico study conducted by Adem, et al. [36], phytochemicals such as rutin, apiin, hesperidin, diosmin, and diacetylcurcumin were identified as potent COVID19-main-protease (Mpro) inhibitors. Yilmaz, et al. [37] reported that black mulberry (*Morus nigra*) syrup increased serum lysozyme, myeloperoxidase, superoxide dismutase and catalase activities and expression levels of immune-related genes, increasing innate immune parameters and antioxidant-related gene expression responses. In another study, Bilen, et, al. [38] revealed that the aqueous methanolic extract of lemon balm (*Melissa officinalis*) has antioxidant and cell-mediated-immune system-stimulating effects by increasing lysozyme, pepsin and trypsin activities. Thus, they highlighted that these herbal use recipes can play a vital role in reducing the symptoms of COVID19 infection and preventing the further spread of such pandemics.

The Covid-19 Pandemic is perhaps the most dangerous and deadly epidemic in human history, due to its rapid infection ability from person to person and its high incidence of mortality. The worldwide spreading rate and the concern that vaccines will be insufficient increase the need for new and natural medicine resources that will stimulate and strengthen our immunity without causing complications such as coagulation and side effects. However, well-designed, further-clinical studies are needed to demonstrate the potential efficacy of local herbal diets and preparations that have the potential to increase immunity against SARS-CoV-2 infection [39]. Turkey contains ethnomedical rich history and experience with the potential worth of ore for researchers and industry who are interested in this issue because it has the richest flora of Europe and the Middle East. The country's official pharmacopoeia includes contributions from 37 countries, including the European Pharmacopoeia. The number of monographs with rich content prepared to standardize the use of commonly used herbs is increasing day by day [40].

While the previous study exhibited a national-plant list that promises a potential for anti-influenza activity in Turkey, in this study, the most comprehensive national-wide inventory of important medicinal plants that make the immune system quite active and strong is presented. In addition, the repercussions of these plants in the traditional medicine works of neighbouring and nearby countries and in the experimental studies conducted worldwide for the above-mentioned activities were examined, and the results were presented in tables and graphs. The taxa, which were not subject to any experimental research, are unique resource for drug researchers looking for new and natural resources.

Materials and Methods

Data Collection

This study was conducted in three different stages by using only English and Turkish terms and by searching electronic databases respected by scientific circles such as Web of Science, Scopus, ScienceDirect, PubMed, ProQuest, Medline, HighWire Press, Cochrane Library, Google Scholar and EBSCO. As a result of the first, an inventory list of plants used as immune system stimulants, enhancers, or boosters in Turkish folk medicine was displayed (Table 3). In order to reach for more detailed information, master's and doctoral theses conducted in all regions of the country (Figure 1) were also included in the study. To this end, approximately 1000 national works were determined between January 1999 and December 2020, and a consensus reached only over 99 (Table 1). The medicinal plants traditionally used by the people of the country for centuries were carefully distinguished from these studies according to the following criteria and demonstrated in Table 3. In the second, the equivalents of these plants in similar studies conducted in neighbouring and nearby countries were investigated. Thirdly, the implications of the experimental studies in the world literature on immune-boosting and other similar activities such as immunostimulant, immunomodulatory, immune-enhancing, and immunotherapeutic are discussed and the results are presented in Table 4.

Region	Work	Citation	Citation%	Selected Studies
Eastern Anatolia	15	53	7.5	[41-55]
Marmara	12	68	9.6	[56-67]
Mediterranean	12	66	9.3	[68-79]
Black sea	10	85	12	[80-89]
Southeastern Anatolia	10	78	11	[90-99]
Aegean	9	66	9.3	[100-108]
Central Anatolia	7	49	6.9	[109-115]
All Regions	24	246	34.4	[18,40,116-137]
Total	**99**	**711**		

Table 1: Distribution of ninety-nine works selected from ethnomedical studies conducted in Turkey by region.

Figure 1: Regional map of Turkey.

Data Selection

For the first and second part scans, the works determined to be within the scope of the study were carefully analyzed, compared and preferred according to the following criteria:

I. The work shoud have been carried out within the boundaries of Turkey.
II. It must have been presented in an ethnobotanical, ethno-medicinal or ethno-pharmacological framework.
III. The plant taxa mentioned in the work should have been given in the study together with their scientific and local names.

The third screening study, which compares the taxa determined as a result of the first screening with the experimental studies published in the world literature, was

made based on the following criteria:

I. It should be an experimental study (in vitro or in vivo)
II. The scientific name of the plant used should be included in the title of the work or in the text.
I. One of the words "immune-boosting, immunostimulant, immunomodulator, immune-enhancing or immunotherapeutic" should be included in the title.
II. The method of obtaining the compound or extracts used from the plant and the mechanism of action determined should be included in the text.
III. For each taxon, only one experimental study should be selected that meets the above criteria. However, in the title, studies with active compounds are preferred.

Data Arrangement

Accurate-scientific nomenclature with international validity of the plant taxa identified in national surveys was performed using "Turkey Plant List (Vascular Plants)" [138], "The Plant List (http://www.theplantlist.org)" and "International Plant Names Index (http://www.ipni.org)", and exhibited in Table 3 after arranging in alphabetical order.

Family names, English names, used parts, preparetions and references are included in the same table. The English names of taxa have been added to the table using the following databases or search engines: Springer Link (https://link.springer.com/article), National Gardening Association (https://garden.org/plants/search/text.php), Encyclopedia of Life (https://eol.org), and USDA PLANTS (https://plants.sc.egov.usda.gov/java). Due to showing distribution only in Turkey and its immediate vicinity and possibly have not been recognized yet in the English-speaking countries, the English names of Turkey's endemic plants and the plants belonging to the "Irano-Turanian element" could not be detected in any sources. The results of the reseach whether the plants listed in Table 3 have been the subject of experimental studies in the world literature on their immune-boosting and other similar activities are presented in Table 4. In addition to the scientific names of the taxa with a match, active compounds (if any), used parts, type of activity, type of immune response, mechanism of action and related references are also included in the same table.

Comparative Analysis

After determining the definitive list of plants that have the potential to stimulate or strengthen the immune system in Turkish folk medicine, a second screening was performed to compare similarity rates with similar studies conducted in neighboring and nearby countries, and the results are presented in Table 2. Since there are very few taxa related to the immune system in the identified works, we tried to select as many works as possible from each country. However, the negative effects of repeated taxa on the total number and percentage have been avoided. For example; if taxa related to the immune system were mentioned in only three of the studies conducted in one country, only different taxa in these three works were included in the study. If *Melissa officinalis* was repeated for the same activity in all three, its number was considered to be 1, and it was not allowed to affect the total number as 3. The table includes country, region, total number of taxa used for immunity, number of similar taxa, percentage of similarity, and references to related studies. Countries are listed in descending order of similarity percentages.

Countries	Regions	Total taxa used for immunity	Similar Taxa #	Similarity %	References
Albania	All	14	9	64.3	[139-145]
Cyprus	All	23	14	60.9	[146-148]
Bulgaria	All	16	9	56.3	[149-151]
Palestine	All	31	16	51.6	[152-155]
Bosnia & Herzegovina	All	22	11	50	[156,157]
Iran	Mashhad, Azerbaijan Province	32	16	50	[158-161]
Kosovo	Anadrini region, Albanian Alps and south Kosovo	15	7	46.7	[162,163]
Macedonia	All	15	7	46.7	[164-166]
Nakhchivan	All	26	12	46.2	[167-169]
Iraq	Northern Iraq	22	10	45.5	[170-173]

Croatia	Northeastern Istria, Knin area and Pannonian region	16	7	43.8	[174-176]
Azerbaijan	All	7	3	42.9	[177]
Armenia	All	12	5	41.7	[178]
Syria	Aleppo	12	5	41.7	[179,180]
Georgia	All	10	4	40	[181-184]
Greece	Thessaloniki (Northern)	68	27	39.7	[185,186]
Serbia	Eastern and Southeastern	63	24	38.1	[187-191]
Ukraine	Southwestern	35	13	37.1	[192-195]
Lebanon	All	11	4	36.4	[196-199]
Jordan	All	26	9	34.6	[200-204]
Romania	Transylvania, Dobruja and West Romania	36	12	33.3	[205-209]
Montenegro	Northern Montenegro	13	4	30.8	[210,211]
Israel	All	30	9	30	[212,213]
Russia	All	15	4	26.7	[214,215]

Table 2: Taxon similarity percentages in similar studies conducted in neighboring and nearby countries.

Results and Discussion

Medicinal herbs are a thousands-year-old source in a variety of traditional herbal medicine systems, from raw uses in the form of direct preparations, such as infusions, decoctions, maceration, pastes, to the extraction of key compounds. In fact, their secondary metabolism is a phytochemical treasure with promising results for all of humanity. Therefore, as trials for testing vaccines continue, traditional herbal remedies in the form of decoctions, tea, or powders require increased clinical testing and research to alleviate symptoms [20]. As in many parts of the world, people living in Turkey, especially in rural areas, have rich traditional knowledge and experience about the use of medicinal herbs in the prevention and treatment of various diseases, but also open to serious clinical evaluation studies [216].

Regional Analysis

The dispersion of 99 works with respect to the regions where they were acquired was as follows: 15 in Eastern Anatolia (15.2%), 12 in the Mediterranean and Marmara (12.1%), 10 in Southeastern Anatolia and Black Sea (10.1%), 9 in the Aegean (9.1%), 7 in Central Anatolia (7.1%), and 24 general studies across all regions (24.2%). The reason why ethnomedicinal works related to immunity come mostly from Eastern Anatolia, Mediterranean and Marmara regions may be due to the fact that separate regional studies have been carried out for each region spread over a wide area because these regions contain very different topographies.

The sectional dissolution of 711 total reports received was as follows: Black Sea: 85 (12.1%), Southeastern Anatolia: 78 (11.0%), Marmara: 68 (9.6%), Mediterranean and Aegean: 66 (9.3%), Eastern Anatolia: 53 (7.5%), Central Anatolia: 49 (6.9%), and general studies covering all regions: 246 (34.4%). The fact that the obtained taxon references come mostly from the Black Sea region may be due to the fact that these regions contain locations with very high biodiversity and endemism such as Bolu, Düzce, and Artvin [138]. In addition, the traditional high-plateau life, which is scattered far away from the city and district centers, and the abundant rainy climate in these regions, may have prompted the local people to use more varieties of plants [217].

The following can be said as the reason for the lowest percentages in Central Anatolia: First of all, the capital Ankara and Eskişehir, known as the city of universities, are located within the borders of the region. Therefore, widespread urbanization might be providing local people with easy access to healthcare services [218] and reduce the tendency to plants. Secondly, it can be shown that there are not many options as a medicinal plant even for people who are far from healthcare, due to the dominance of the plateau landform in the region, the low annual rainfall percentage [219], and the much lower level of plant biodiversity than other regions [220].

Data Analysis

The sources used in the selection of 128 plant taxa that have been found to be used traditionally for immunity enhancement consist of 67 articles, 23 theses, seven books, and two bulletins. These plant taxa are most commonly Lamiaceae (25 taxa, 19.5%), Rosaceae (18 taxa, 14.1%), Compositae (11 taxa, 8.6%), Malvaceae (7 taxa, 5.5%), Apiaceae and Brassicaceae (5 taxa, 3.9%) and other families (57 taxa, 44.5%). The reason why the Lamiaceae family is the most preferred in Turkish folk medicine can be demonstrated as the habit of preparing many conventional immune-boosting preparations such as lotion, medical bath, spice, infusion mix, and syrup due to the family that contains the highest dosage of essential oils [129] and experience of receiving good results [221] in immunostimulation and flu treatment. In addition, 44.2% of species belonging to Lamiaceae family, 65.2% of species belonging to *Origanum* genus, 52.6% of species belonging to *Thymus* genus and 28% of species belonging to *Satureja* genus are endemic in Turkey [222]. Therefore, it is not coincidental that this family comes first in presenting the richest variety of taxa to our study.

In the works carried out in different regions of Turkey, the most common genera are *Citrus* and *Salvia* (5 taxa, 3.9%) and *Mentha, Pinus, Prunus*, and *Taraxacum* (4 taxa, 3.1%). It is not surprising that the *Citrus*, *Salvia*, and *Mentha* appeared in the first place. They are grown both naturally and culturally (for healing and ornamental purposes) in park gardens, balconies, and pots in almost every part of the country. *Citrus* species are actually an exotic genus settled in the flora of Turkey. It is seen on all roadsides and gardens, especially in the southern regions [117,221]. Moreover, the *C. limon* species is sold as a "panacea!" or "Lemon for tea and soup!" in almost all local markets of the country. It is also always in high demand for direct use or in mixtures. In particular, the infusion mixture prepared from *Mentha x piperita* (pepermint) leaves and *C. limon* peel can be said to be the most widely used traditional preparation in the country to increase body resistance against winter diseases [216,223]. The other three genera, *Pinus, Prunus*, and *Taraxacum*, are also naturally distributed in a wide area in the country [117,224]. *Prunus* and *Pinus* fruits and *Taraxacum* leaves have been traditionally consumed for centuries for the purpose of healing and food to strengthen the body against diseases [77,99,225].

Among the determined plants, 61 were wild (47.7%), 55 were wild and cultural (43.0%), 11 were cultivated (8.6%), and one (*Salvia absconditiflora*) was endemic (0.9%). These parameters are shown in a column in Table 3; wild taxa as "W", cultivated "C", cultivated & wild "CW" and endemic "E". Most of the plant pieces used are fruits (39.8%), leaves (33.6%), flowers, flowering branches, petals and capitula (32.8%), aerial parts (32.0%), seeds and cones (19.5%), roots, rhizomes and bulbs (13.3%), essential oils, fixed oils, resins, and tars (12.5%), whole parts, stems, barks and shoots (10.9%), and other parts (buds, bracts, pericarps, fruit stalks, galls and pollens) (10.2%). Those parts were mostly used as infusion and infusion mix (80.5%), eating raw or after milling (35.2%), decoction, decoction mix, boiling (31.3%), jam, syrup, marmalate, molasses (21.9%), meal, roast, soup, pastry, cooked (18.0%), pickle, vinegar, tincture, maceration (14.8%), external uses such as foot bath, medicinal bath lotion and frankincense (14.1%), restorative paste, spices drop and additives (11.7%), churchkhela and mixtures (11.7%), drunk, juice, gargle (10.9%), and salad (7.8%). The taxa with the maximum number of consumption parts belong to *Juniperus oxycedrus, Pinus brutia, Rosa canina* and *Tilia tomentosa* (6 parts, 4,7%), while the taxa having with the most usage types are *Rubus sanctus* (8 types, 6.3%), *Citrus* spp. (7 types, 5.5%), *Mentha x piperita*, *Rosa x damascena*, *R. canina* and *Thymbra spicata* (6 types, 4.7%) (Table 3).

Comparative Evaluation of the Data with Studies of Nearby Countries

Of the 128 taxa we specified in our research, 81 were detected to match the studies of neighboring and nearby countries, and the similarity rate (from 81x100/128) was computed as 63.3%. 18 taxa, such as *Urtica dioica* (with 11 references and 45.8%), *Achillea millefolium* and *Allium sativum* (with 10 references and 41.7%), and *Juglans regia, Rosa canina* and *Taraxacum* spp (8 references and 33.3%) (Figure 2), have been found as the most reported plants. These herbs may have come to the fore because they have been experienced in Turkish folk medicine for centuries and are more permanent and effective in strengthening immunity. Especially, the emergence of *Urtica* spp as the most used plants as an immune booster in 11 countries (45.8%), other than Turkey, may be due to the fact that it has proven itself in the traditional medicine of many cultures rather than the fact that its distribution area is wide and easily accessible. Indeed, the similarity of 63.3% compared to the results of studies conducted in 24 neighboring and nearby countries may confirm the superior efficacy of these plants (Table 2). 47 plants such as *Urtica urens, Morus alba*, and *Tribulus terrestris*, which do not resemble at all (Figure 2), maybe due to the fact that they are not naturally widespread in these countries because of geographical or climatic differences, or even if they do, they are not traditionally preferred for immunity.

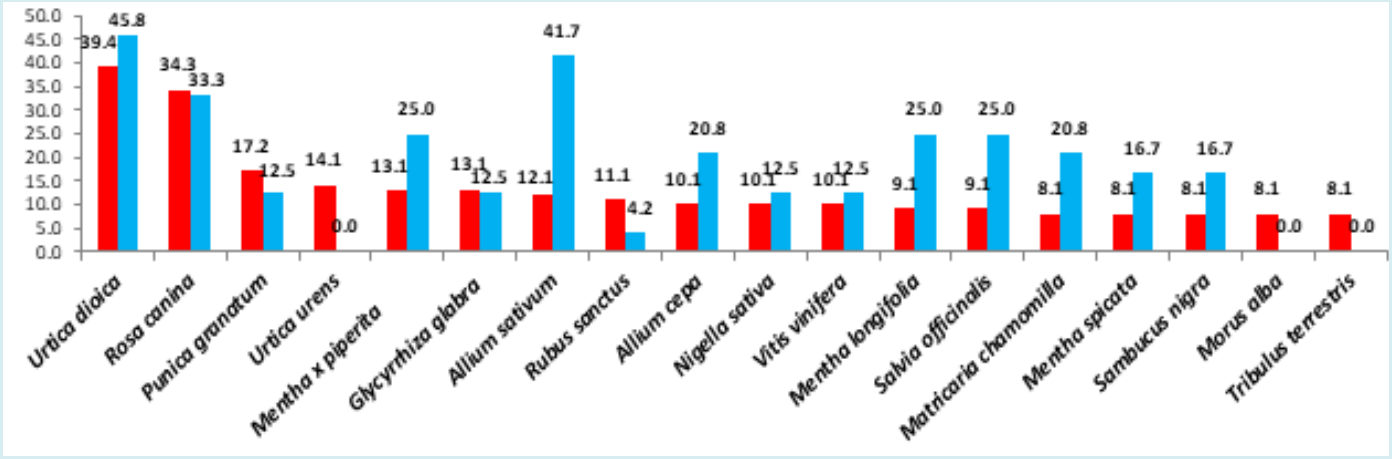

Figure 2: The most reported plants in Turkey and neighboring countries.

Nevertheless, the maximum similarity was detected with Albania (64.3%), Cyprus (60.9%), and Bulgaria (56.3%), while the minimum one was with Russia (26.7%), Israel (30.0%), and Montenegro (30.8%). In countries with high similarity, there may be similarities in climate, vegetation and land forms, as well as cultural and plant use habits from the Ottoman period. The underlying reasons for the low similarity with Russia, Israel, and Montenegro may be differences in religious rituals, social-cultural habits, flora, and topography (Table 2).

Comparative Analysis with Studies in the World Literature

As a result of the comparison screening of experimental studies conducted worldwide under the title of activities such as immunostimulant, immunomodulator, immune-enhancing, or immunotherapeutic, reflections of only 68 (53.1%) of 128 taxa were detected. 60 taxa (46.9%), which have not been investigated yet, are among the valuable data of this study and are shown in bold in Table 3. The percentage distribution of the activities mentioned in the titles of the studies is as follows: Immunomodulatory (47.1%), immunostimulant (27.9%), immunomodulatory and immunostimulant (7.4%), immune-enhancing (5.9%), immune-boosting (5.9%), immune-enhancing and immunostimulant (1.5%), immune-boosting and Immunostimulant (1.5%), and immunomodulatory and immunotherapeutic (1.5%). For only 23 taxa (18.0%) out of 68 matching taxa, the results were given with the active ingredients, while the remaining 45 taxa (35.2%) were not specified. The prominent among 39 active substances are quercetin derivatives (such as quercetin xyloside, quercetin-3-galactoside, and quercetin-3-O-rutinoside) (10.3%), β-glucan, and catechin (5.1%), respectively (Table 4).

The action mechanisms in the studies identified are listed according to the immune responses on which they were based: Cell-mediated (42.6%), humoral and cell-mediated (22.1%), innate only (11.8%), innate, humoral, and cell-mediated (11.8%), humoral only (5.9%), and innate and cell-mediated (5.9%), respectively. According to these three basic immune responses, it has been determined that the mechanisms were carried out in the following eight different groups: By increasing spleen and thymus indices/serum immune parameters/ total white and red blood cells (WBC/RBC) (20.3%), by increasing pinocytosis, phagocytic and bactericidal activity/ acting as macrophage and T helper-1 (Th-1) activators/ switching the host immune responses towards Th1 response (20.3%), by increasing interleukin cytokine levels/elevating the levels of Tumor Necrosis Factor Alpha (TNF-α) and Interferon gamma (IFNγ)/elevating the expression levels of cytokines/ activating the CD4+ T cells leading to cytokine production (18.0%), by activating the CD19+ B cells in peyer's patches/ increasing total immunoglobulin/ reducing the suppressive azathioprine effect on the cell-mediated immune response, and antibody response (13.5%), by promoting serum hemolysin formation and increasing lysozyme, myeloperoxidase, superoxide dismutase catalase, and superoxide dismutase activities (12.8%), by increasing production of nitric oxide (NO) on a level comparable with that of lipopolysaccharides/reducing the levels of serum lipids/ inhibiting the lipopolysaccharide induced interleukin-6 release (6.8%), by increasing respiratory burst activity/ reactive oxygen species (ROS) production / increasing the hematocrit level and red blood cell count/ haemoglobin content and haematocrit value (4.5%), and by increasing the cytotoxic activity of natural killer (NK) cells (3.8%), respectively (Table 4).

When the plant parts used for 68 taxa (53.1%) that were determined to match in the comparison of Turkey and the world literature were examined, a concordance of 94.1% was obtained. This result may have proved the accuracy and reliability of part selection and application methods of plants used as immunostimulants and enhancers in Turkish folk medicine.

Comparative Evaluation of Active Compounds

The plants with the most active substances in terms of immune-boosting and other similar activities are *Phoenix dactylifera* (5 chemicals, 12.8%, out of 39), *Malus domestica* (4; 10.25%), *Cichorium intybus, Hypericum perforatum, Urtica dioica*, and *Rosa canina* (3; 7.7%) (Table 4). *Phoenix dactylifera* (date palm) is widespread in a vast area from North Africa to the Middle East, parts of Central and South America, and Southern Europe for both its production and consumption of its fruit for food and healing purposes [117,226]. The reason why it stands out in terms of active ingredient richness in this study may be that it is rich in fiber, mineral, and other nutritional sources, as well as its antibacterial, antifungal and immunostimulant properties, as a widely effective folk remedy in preventing various infectious diseases and increasing body resistance [227]. As in the geographical area mentioned above, consumption of dried fruit becomes widespread in Turkey, especially during the holy month of Ramadan. It is known that while fasting, the body compensates for the mineral and energy loss, thus keeping the immune system active [117,110,224]. This result is also supported by the study of Dogan Y, et al. [226]. They investigated the immunomodulatory effects of hot water extract of ripe fruits compared to prunes and fig fruits in mice and declared that the polyphenols and polysaccharides they isolated stimulated the cellular immune system in mice. Therefore, this finding may be a shred of evidence that this taxon might be more effective than others in terms of immunomodulatory activity.

As a result of this screening, quercetin and its derivatives came to the fore with their immunomodulatory and immunostimulant activities and it was determined that they were isolated from the taxa of *Capparis spinosa, Malus domestica, Urtica dioica*, and *Sambucus nigra* [228-231] (Table 4). It may not be coincidental that quercetin and its derivatives appear as the most common active compounds. Many experimental studies have revealed that these compounds are the most effective compounds used in stimulating or enhancing immunity. A few of these are given below:

Colunga-Biancatelli, et al. [232] provided evidence that the co-administration of vitamin C and quercetin shows a synergistic antiviral effect and enhances its efficacy due to its antiviral and immunomodulatory properties and the capacity of ascorbate to recycle quercetin. Wang, et al. [233] increased the immunostimulant properties, antioxidant index, and disease resistance of zebrafish with the optimal quercetin level. Singh, et al. [24] reported for the first time the in vivo immunostimulatory activity of quercetin in ovalbumin-vaccinated Balb/c mice. Their administration of quercetin showed the dominance of the Th2 immune response by increasing IgG1 antibody titers, as well as increased infiltration of CD11c + dendritic cells in the mouse peritoneum and the production of LPS-activated IL-1β and nitric oxide (NO) by peritoneal macrophages. These outcomes may validate that quercetin and its derivatives are ideal and potential aspirants for a functional nutraceutical or phytotherapy by stimulating or positively modulating immunity. In addition, β-glucan and catechin active compounds are found in many taxa traditionally used in Turkish folk medicine such as *Avena sativa, Camellia sinensis, Hordeum vulgare*, and *Malus domestica*. Some studies [119,122,124,231,234,235] pointed out that beta-glucan and catechin act through one or more of the eight groups of action mechanisms mentioned above, and that these molecules could potentially give positive results in the treatment of Covid19 in terms of immune-stimulating or accelerating activities.

Ecotic Plants

14 medicinal exotic herbs, such as *Alpinia officinarum* (lesser galangal), *Cinchona pubescens* (quina), *Echinacea angustifolia* (coneflower), *Hibiscus sabdariffa* (hibiscus), *Malpighia emarginata* (acerola cherry), and *Vaccinium macrocarpon* (cranberry) are used for stimulating, enhancing or boosting the immune system in Turkish folk medicine and sold in herbal shops and public markets. Scientific names, families, English names, used parts, preparations, native lands, and related references of these plants are introduced in Table 5.

The *Citrus* species (native to Southeast Asia) and *Phoenix dactylifera* (date palm-native to North Africa) given in Table 3 are actually exotic species that were later included in the natural flora. They showed a natural spread after they have been grown on the Mediterranean and Aegean coasts, roadsides, parks, and gardens for centuries. In the same table, *Camellia sinensis* (tea plant - native to South and Southeast Asia), *Capsicum annuum* (pepper - South and Central America), *Mfigorus alba* and *M. nigra* (mulberry - China), *Prunus cerasifera* (myrobalan plum - Japan), *Solanum lycopersicum* (tomato-South America), *Withania somnifera* (Indian ginseng) and *Ziziphus jujuba* (jujube-Southeast Asia) are other taxa that have settled in the flora since the Ottoman period [236,237].

Plant name	Family	C/W/E	English name	Part(s)	Preparation(s)	Report(s)
Achillea millefolium L.	Compositae	W	Common yarrow	Leaves, Flowers	Infusion	[73,92,116,117,123]
Achillea nobilis L.	Compositae	W	Noble yarrow	Aerial parts, Flowers	Infusion	[70,73,102,120]
Allium cepa L.	Amaryllidaceae	C	Onion	Bulbs, Leaves	Eaten raw, Boiling, Juice with some honey	[18,48,80,111,119,121,122,124,134]
Allium sativum L.	Amaryllidaceae	C	Garlic	Leaves, Bulbs, Flowers	Eaten raw, Cooked, Tincture (prepared with the bulbs, lemon and vinegar)	[18,48,80,81,111,116,119,121,122,124,134]
Althaea officinalis L.	Malvaceae	C/W	Common marsh	Buds, Flowers	Infusion	[91,116,117]
Apium graveolens L.	Apiaceae	C	Celery	Leaves, Seeds	Decoction, Mixture (eaten after milling with cloves and seeds of anise, turnip, radish and mixed with honey).	[100,117,119,121]
Asparagus acutifolius L.	Asparagaceae	C/W	Wild asparagus	Aerial parts	Infusion	[72,78,120,124]
Astragalus spp.	Leguminosae	W	Milkvetches	Aerial parts, Roots,Young shoots,	Infusion, Eaten raw after peeling, Infusion after dried and pulverized, Mixture (obtained by drying and pulverizing of the fresh shoots and mixing with honey), Tincture (prepared with lemon and vinegar)	[43,49,55,88,100,103,115,116,121]
Avena sativa L.	Poaceae	C/W	Oat, common oat	Fruits, Seeds	Pastry, Meal	[117,119,120,122]
Brassica oleracea L.	Brassicaceae	C	Cabbage, flowering cabbage, kale	Aerial parts, Leaves	Decoction, Meal, Salad	[82,115,119,128]
Brassica rapa L.	Brassicaceae	C	Turnip	Tubers, Roots, Leaves, Seeds	Juice, Boiling-Meal, Mixture (eaten after milling with cloves and seeds of anise, celery, radish and mixed with honey)	[100,119,122,128]
Calendula officinalis L.	Compositae	C/W	Pot marigold, ruddles	Flowers	Infusion	[116,120,137]
Camellia sinensis (L.) Kuntze	Theaceae	C	Green tea	Leaves	Infusion	[46,118,119,122,127]
Capparis spinosa L.	Capparaceae	W	Caper bush, flinders rose	Fruits, Buds, Roots, Barks	Infusion, Decoction	[117,118,120]
Capsicum annuum L.	Solanaceae	C	Ornamental pepper	Fruits	Eaten raw, Spice, Decoction, Meal	[71,77,81]

Castanea sativa Mill.	Fagaceae	C/W	Chestnut, sweet chestnut	Fruits, Seeds, Flowers	Decoction, Boiling, Infusion	[80,110]
Centaurea hyalolepis Boiss.	Compositae	W	Yellow star-thistle, knapweed	Flowers	Restorative paste (with honey after crashing)	[42,43,49,90]
Ceratonia siliqua L.	Leguminosae	C/W	Carob	Fruits	Eaten raw, Boiling, Molasses	[78,83,126,127]
Cichorium intybus L.	Compositae	W	Blue daisy, blue dandelion, blue sailors, blue weed	Aerial parts, Roots	Infusion, Decoction	[78,90,109,120,123]
Cistus creticus L.	Cistaceae	W	Pink rock-rose, hoary rock-rose	Leaves	Infusion	[40,69,117,124,125,127]
Cistus laurifolius L.	Cistaceae	W	Laurel-leaved rock rose	Leaves	Infusion	[40,124,125,127]
Cistus salviifolius L.	Cistaceae	W	Sage-leaved rock-rose	Leaves	Infusion	[40,117,124,125,127]
Citrus spp.	Rutaceae	C/W	Oranges, lemons, grapefruits, pomelos, limes	Pericarps, Fruits	Decoction, Jam, Eaten raw, Juice, Marmalade, Dropped in teas and soups, Gargle	[18,40,69,80,92,117-119,122]
Cota austriaca (Jacq.) Sch.Bip.	Compositae	W	Corn chamomile	Capitulums, Flowers, Aerial parts	Infusion	[45,47,50,75,90,109,118]
Crataegus monogyna Jacq.	Rosaceae	C/W	Hawtorn, may	Flowers, Fruits, Seeds	Infusion, Eaten raw, Infusion, Eaten raw, Decoction	[41,81,109,114]
Crataegus orientalis Pall. ex M.Bieb.	Rosaceae	C/W	Oriental hawtorn	Flowers, Fruits, Seeds	Infusion, Eaten raw, Infusion, Eaten raw, Decoction	[81,93,109]
Daucus carota L.	Apiaceae	C/W	Wild carrot, bird's nest	Seeds	Spice after milling	[92,119]
Drosera rotundifolia L.	Droseraceae	C/W	Round-leaved sundew, common sundew	Flowers	Infusion	[116-118]
Echinophora tenuifolia subsp. *sibthorpiana* (Guss.) Tutin	Apiaceae	C/W	Turkish çördük, tarhana	Aerial parts	Soup, Meal (after dried and pulverized)	[100,123,132]

Elaeagnus angustifolia L.	Elaeagnaceae	C/W	Silverberry	Fruits, Leaves, Flowers	Eaten raw, Infusion	[99,109,126]
Equisetum arvense L.	Equisetaceae	W	Field horsetail, common horsetail	Aerial parts	Infusion, Foot bath	[46,68,73,116]
Eriobotrya japonica (Thunb.) Lindl.	Rosaceae	C/W	Loquat	Leaves	Infusion mix (with *Cydonia* leaves and *Tilia* flowers)	[79,117,130]
Eruca vesicaria (L.) Cav.	Brassicaceae	C/W	Rocket, garden rocket	Leaves	Eaten raw, Salad	[92,101,110]
Eupatorium cannabinum L.	Compositae	W	Hemp-agrimony, holy rope	Aerial parts	Infusion	[86,116-118]
Ferula orientalis L.	Apiaceae	W	-	Whole parts	Decoction, Infusion after dried and pulverized	[42,43,49,91,132]
Ficus carica L.	Moraceae	C/W	Common fig	Fruits	Eaten raw or dried with/without nuts	[44,93,116]
Fragaria vesca L.	Rosaceae	C/W	Strawberry, wild strawberry	Fruits	Jam, Syrup	[82,100,119,121]
Glycyrrhiza glabra L.	Leguminosae	C/W	Licorice, liquorice	Leaves, Roots	Infusion after pulverizing, Syrup	[40,41,63,81,86,90-92,95,131,136,121]
Helianthus tuberosus L.	Compositae	C/W	Sunroot, sunchoke, earth apple	Tubers	Eaten raw, Salad, Soup, Meal	[74,117]
Hordeum vulgare L.	Poaceae	C/W	Barley	Fruits, Seeds	Decoction, Additive (the flour is obtained after drying and grinding is added to the meals).	[41,45,56]
Hypericum perforatum L.	Hypericaceae	C/W	St. John's Wort	Flowering branches, Aerial parts	Infusion after drying, Infusion mix (with the leaves of *Urtica* spp and *Rubus* spp).	[56,57,70,77,80,82,87]
Hyssopus officinalis L.	Lamiaceae	W	Hyssop	Flowers, Flowering branches, Leaves	Infusion	[18,120,123]
Juglans regia L.	Juglandaceae	C/W	Walnut, common walnut	Leaves, Pericarp, Fruits	Infusion, Mixture (eaten with honey and dried fig)	[70,81,117,116]
Juniperus oxycedrus L.	Cupressaceae	W	Cade, cade juniper, prickly juniper	Fruits, Seeds, Leaves, Tars, Cones, Gall	Decoction, Infusion, Distillation	[,65,68,96,101,107,109]
Lavandula stoechas L.	Lamiaceae	C/W	Spanish lavender, topped lavender	Leaves, Flowering branches	Infusion	[58,64,69,70,91,129]

Lepidium sativum L.	Brassicaceae	C/W	Garden cress	Aerial parts, Seeds	Infusion, Restorative paste (prepared with honey)	[94,101,110,112,117]
Linum usitatissimum L.	Linaceae	C/W	Flax	Seeds, Fixed oils	Eaten raw, Drunk	[80,81,116,119]
Malus domestica Borkh.	Rosaceae	C	Apple	Fruits	Eaten raw, Juice, Decoction (with pear peels after dried)	[41,100,121]
Malus sylvestris (L.) Mill.	Rosaceae	C/W	European crab apple	Fruits	Eaten raw, Juice, Decoction (with pear peels after dried)	[41,45,113,121]
Malva neglecta Wallr.	Malvaceae	W	Cheeseplant, dwarf mallow	Aerial parts	Infusion, Decoction	[41,44,45,104,109]
Malva nicaeensis All.	Malvaceae	W	Bull mallow, French mallow	Leaves	Decoction with the aerial parts of *Urtica dioica.*	[58,60,93,111]
Malva sylvestris (L.) Mill.	Malvaceae	W	Large-flowered mallow, high mallow	Leaves, Aerial parts	Infusion, Meal (prepared with rice, radish, onion and butter). Another Meal is prepared with the leaves, *Papaver rhoes* petals and *Urtica dioica* and *Spinacia oleraceae* leaves.	[56,58,60,67,80,100,123]
Matricaria chamomilla L.	Compositae	W	Chamomile, German chamomile	Aerial parts, Flowering branches, Flowers	Infusion	[89,102,107,116,118,119,121,123]
Melissa officinalis L.	Lamiaceae	C/W	Lemon balm	Aerial parts	Infusion after drying, Infusion mix (with Sage leaves, Elder fruits, black pepper and ginger)	[59,62,72,121,123-125,133]
Mentha longifolia (L.) L.	Lamiaceae	W	Horse mint	Aerial parts	Eaten raw, Infusion	[18,41,51,57,83,90,103,109,123]
Mentha pulegium L.	Lamiaceae	W	Pennyroyal, pennyrile, squaw mint	Leaves	Infusion after drying, Infusion mix (with the leaves of *Petroselinum crispum* and *Origanum vulgar*e)	[18,57,80,83]
Mentha spicata L.	Lamiaceae	W	Spearmint	Aerial parts, Leaves	Infusion, Spice (after powdering)	[18,57,59,69,80,83,101]
Mentha x piperita L.	Lamiaceae	C/W	Peppermint	Leaves, Aerial parts	Eaten raw, Salad, Spice, Syrup, Infusion mix-1 (with lemon juice), Infusion mix-2 (with the leaves of *Petroselinum crispum* and Origanum vulgare)	[18,57,61,71,82,83,87,90,109,116,118,121,123,129]
Mespilus germanica L.	Rosaceae	C/W	Medlar, medlar tree	Leaves, Fruits	Infusion, Eaten raw	[71,80,82]

Morus alba L.	Moraceae	C/W	White mulberry	Fruits, Leaves	Syrup, Molasses, Churchkhela, Infusion	[41,45,56,93,94,109,120,124]
Morus nigra L.	Moraceae	C/W	Black mulberry, blackberry	Fruits, Leaves	Molasses, Syrup, Infusion	[58,82,124]
Myrtus communis L.	Myrtaceae	C/W	Common myrtle or true myrtle	Fruits, Leaves	Eaten raw, Infusion	[46,69,92]
Nasturtium officinale R.Br.	Brassicaceae	W	Watercress, yellowcress	Leaves, Flowers	Infusion, Salad, Meal	[68,76,90,93]
Nigella arvensis L.	Ranunculaceae	C/W	Wild fennel, field fennel flower	Flowers, Seeds	Infusion after dried, Restorative paste (with honey after crushed), Spices	[59,90,98,101,103]
Nigella damascena L.	Ranunculaceae	C/W	Love-in-a-mist, ragged lady	Seeds, Essential oils	Infusion, Eaten raw	[74,118,120]
Nigella sativa L.	Ranunculaceae	C/W	Black cumin	Seeds, Essential oils	Eating raw, Infusion after crashing, Spices	[80,83,91,97,101,103,116,117,121, 126]
Olea europaea L.	Oleaceae	C/W	Olive	Leaves, Fruits, Fixed oils	Infusion, Cataplasm with one tablespoon molasses, tarhana and flour, Drunk one tablespoon or added to salads	[40,80,91,119,125]
Origanum onites L.	Lamiaceae	W	Pot marjoram, Cretan oregano	Aerial parts with flowers, Flowering branches	Foot bath, Infusion-1 (with Sage leaves), Infusion-2 (with anise and minth leaves)	[40,70,101,116,129]
Origanum vulgare L.	Lamiaceae	W	Ornamental oregano	Aerial parts with/ without flowers, Flowering branches	Foot bath, Infusion-1 (with Sage leaves), Infusion-2 (with anise and minth leaves)	[40,101,123,129]
Papaver rhoeas L.	Papaveraceae	W	Flanders poppy	Flowers, Petals	Infusion with/without *Urtica dioica* leaves, Meal (prepared with the leaves of *Spinacia oleracea* and *Malva* spp or *Urtica dioica*).	[56,60,62,63,66,93]
Petroselinum crispum (Mill.) Fuss	Apiaceae	C/W	Parsley	Leaves, Aerial parts	Eaten raw, Juice (with lemon), Salad, Infusion with/without the leaves of *Mentha spp* and Origanum spp.	[41,69,91,94,109,110,121]
Phoenix dactylifera L.	Arecaceae	C/W	Date, date palm	Fruits	Eaten raw	[110,117,118,126]
Pinus brutia Ten.	Pinaceae	C/W	Calabrian pine, Turkish pine	Barks, Shoots, Pollens, Cones, Fruits, Essential oils	Decoction, Eaten with honey. Pickle, prepared with the seeds, cones, lemons, garlic and water. Medicinal bath, Frankincense	[18,84,100,116,118]

Pinus nigra J.F.Arnold	Pinaceae	W	Black pine	Resins, Tars, Essential oils	Decoction, Medicinal bath, Frankincense	[18,84,116,110,118]
Pinus pinea L.	Pinaceae	C/W	Stone pine, umbrella pine, parasol pine	Fruits, Pollens, Essential oils	Eaten with molasses, honey, dried figs or grapes	[18,84,91,118]
Pinus sylvestris L.	Pinaceae	W	Redwood, Scots fir	Buds, Resins, Cones, Essential oils	Decoction, Medicinal bath, Frankincense	[18,84,116,118]
Portulaca oleracea L.	Polygonaceae	W	Common purslane, fatweed	Aerial parts	Eating raw, Boiling, Roasting	[44,76,80,90,91]
Prunus avium (L.) L.	Rosaceae	C/W	Sweet cherry	Fruits stalks	Infusion, Restorative paste (prepared with a cherry stalk and rye after drying and pulverizing and sweetening with honey or molasses)	[46,56,84,100,102,130]
Prunus cerasifera Ehrh.	Rosaceae	C/W	Cherry plum	Fruits	Eaten raw, Infusion, Decoction	[94,103,130]
Prunus domestica L.	Rosaceae	C/W	Plum, European plum	Fruits	Eaten raw, compote	[91,110]
Prunus spinosa L.	Rosaceae	W	Sloe, blackthorn	Fruits	Eaten raw, Decoction	[56,57,62,68]
Punica granatum L.	Lythraceae	C/W	Pomegranate	Fruits, Flowers, Seeds, Pericarps	Eaten raw, Juice, Infusion, Decoction	[41,44,52,54,56,69,80,81,83,88,93,94 ,99,100,107,108,117]
Pyrus communis L.	Rosaceae	C/W	European pear, common pear	Fruits	Eaten raw, Decoction with the dried peel of apple after dried)	[45,59,96]
Rhus coriaria L.	Anacardiaceae	C/W	Tanner's sumach, Sicilian sumac	Leaves, Fruits	Infusion, Spice	[70,74,121,127]
Rosa × damascena Herrm.	Rosaceae	C/W	Rose, damask rose	Flowers	Infusion, Jam, Syrup, Juice, Pastry, Vinegar	[81,117,120]
Rosa canina L.	Rosaceae	C/W	Dog rose, briar rose, common briar	Fruits, Leaves, Flowers, Petals, Roots, Stems	Eaten raw, Infusion after drying and pulverizing, Infusion mix (with lemon balm, elderflower, plantaginis leaf and a little honey or stevia) Decoction, Jam, Marmalate	[41-43,49,57,58,60,62, 66,68,80-82,84,86,90,91, 94,95,97,101,102,105,106,109-111,113,114,116,120-122,135]
Rosa hemisphaerica Herrm.	Rosaceae	W	Sulphur rose	Fruits	Eaten raw, Decoction	[81,109,111]

Rosmarinus officinalis L.	Lamiaceae	C/W	Rosemary	Leaves, Fruits, Young shoots	Infusion, Syrup, jam, Eaten raw	[69,81,91,101,108,118,122]
Rubus caesius L.	Rosaceae	C/W	Dewberry	Fruits, Leaves, Roots	Syrup, Jam, Eaten raw, Infusion after drying and pulverizing, Infusion mix (with the leaves of Urtica spp and the aerial parts of Hypericum perforatum).	[83,94,114,117,119]
Rubus canescens DC.	Rosaceae	W	Woolly blackberry	Leaves, Fruits, Young shoots	Infusion, Syrup, Jam, Marmalate, Eaten raw	[62,66,68,82,116,119]
Rubus sanctus Schreb.	Rosaceae	W	Holy bramble	Fruits, Roots, Flowers, Leaves	Syrup, Jam, Eaten raw, Decoction, Infusion, Jam, Infusion after drying, Infusion mix (with the leaves of Urtica spp and the aerial parts of Hypericum perforatum).	[56,58,60,61,68,82,90,116,119,130]
Salvia absconditiflora Greuter & Burdet	Lamiaceae	E	-	Aerial parts	Infusion	[90,100,102,109,125]
Salvia officinalis L.	Lamiaceae	C/W	Culinary sage, golden sage, garden sage	Aerial parts	Infusion after drying, Infusion mix-1 (with/without the flowers or fruits of Sambucus nigra, the leaves of Melissa officinalis, black pepper and ginger). Infusion mix-2 (with flowers of Tilia and Teucrium, Urtica and Thymus leaves with honey).	[71,81,92,110,116,119,121,122,125]
Salvia palaestina Benth.	Lamiaceae	W	Palestinian sage	Aerial parts	Infusion	[76,90,125]
Salvia tomentosa Mill.	Lamiaceae	W	Balsamic sage	Aerial parts	Infusion after drying, Infusion mix (with flowers of *Tilia argentea* and *Teucrium polium*or *Urtica dioica* and *Thymus longicaulis* leaves with honey)	[75,100-102,125]
Salvia verticillata subsp. *amasiaca* (Freyn & Bornm.) Bornm.	Lamiaceae	W	Lilac sage, whorled clary	Aerial parts	Infusion	[42,45,80]
Sambucus ebulus L.	Adoxaceae	W	European dwarf elder	Fruits, Roots, Seeds	Eaten raw, Decoction, Infusion after drying and pulverizing, Infusion mix (with Sage, Melissa leaves, black pepper and ginger)	[53,99,117,125]

Sambucus nigra L.	Adoxaceae	W	Elderberry, European elder	Leaves, Flowers, Fruits, Barks	Infusion after drying and pulverizing, Infusion mix-1 (with lemon balm, plantaginis leaf, rosehip fruit powder and a little honey or stevia. Infusion mix-2 (with Sage, Melissa leaves, black pepper and ginger)	[65,68,91,116,122,124,125,131]
Satureja cuneifolia Ten.	Lamiaceae	W	Apulian savory	Aerial parts	A glass of its infusion is drunk twice a day	[59,100,102]
Satureja hortensis L.	Lamiaceae	W	Summer savory	Aerial parts, Flowering branches, Essential oil	Infusion, Spice, Lotion	[41-43,45,47,49,51,55]
Satureja thymbra L.	Lamiaceae	W	Thyme-leaved savory	Aerial parts, Flowering branches, Essential oil	Infusion, Spice, Lotion	[70,79,102]
Sesamum indicum L.	Pedaliaceae	C/W	Sesame	Seeds	Mixture (crushed and mixed with boiled grape juice), Eaten raw	[59,91,117]
Silybum marianum (L.) Gaertn.	Compositae	W	Milk thistle, Marian thistle	Seeds, Stems, Fruits	Eaten raw after peeling, Infusion	[90,102,117,131]
Solanum lycopersicum L.	Solanaceae	C	Tomato	Fruits	Eaten raw or after boiling, Soup, Salad	[80,100,119,121,128]
Spinacia oleracea L.	Amaranthaceae	C	Spinach	Leaves	Boiling, Salad, Pastry material. Mixture-meal (prepared with *Papaver rhoes* petals and *Malva* spp or *Urtica dioica* leaves).	[93,100,111,119]
Taraxacum spp.	Compositae	W	Dandelions	Flowers, Roots	Infusion, Meal, Mixture-meal (with Allium cepa, Alium sativum,Solanum lycopersicum and Capsicum annuum), Decoction, Tincture (prepared with lemon and vinegar)	[56,82,83,90,118]
Thymbra capitata (L.) Cav.	Lamiaceae	W	Spanish oregano, cone-head thyme	Aerial parts, Flowering branches, Essential oil	Infusion, Lotion, Spice	[40,102,116,127]
Thymbra spicata L.	Lamiaceae	W	Thyme spiked	Aerial parts, Flowering branches, Essential oil	Infusion, Lotion, Spice, Foot bath, Bath with/without Matricaria	[40,69,90,92,102,116,127]

Thymbra sintenisii Bornm. & Azn.	Lamiaceae	W	-	Aerial parts, Flowers	Infusion, Lotion, Spice	[40,90,116,127]
Thymus fallax Fisch. & C.A.Mey.	Lamiaceae	W	-	Aerial parts, Flowering branches, Whole parts	Infusion, Foot bath, Bath with/without Matricaria	[18,40,41,82]
Thymus longicaulis C.Presl	Lamiaceae	W	Creeping thyme	Flowering branches, Aerial parts	Infusion	[18,40,82,113]
Thymus praecox Opiz	Lamiaceae	W	-	Aerial parts, Flowering branches, Whole parts	Infusion, Foot bath, Bath with/without Matricaria	[18,40,75,82,113]
Tilia cordata Mill.	Malvaceae	W	Bast, small-leaved linden	Leaves, Fruits, Flowers, Bracts	Decoction mix (with cinnamon and cloves)	[57,81,109,110,116,128]
Tilia platyphyllos Scop.	Malvaceae	W	Broad-leaved lime	Flowers, Bracts	Decoction with cinnamon and cloves, Infusion after drying, Infusion mix (with *Salvia tomentosa* leaves), Cold maseration	[81,104,106,116,128]
Tilia tomentosa Moench	Malvaceae	C/W	European white lime, silver lime, silver linden	Leaves, Flowers, Fruits, Barks, Bracts, Roots	Cold maceration, Infusion after drying, Infusion mix (with *Salvia tomentosa* leaves)	[61,81,83,84,105,120,128]
Tribulus terrestris L.	Zygophyllaceae	W	Caltrop, devil's-thorn	Fruits	Infusion after dried	[65,70,72,74,90,101,109,117]
Urtica dioica L.	Urticaceae	W	Stinging nettle, perennial nettle, tall nettle, common nettle	Aerial parts (without flowering), Leeaves, Roots, Seeds	Infusion after drying, Infusion mix (with/without the petals of Papaver rhoeas or the leaves of Rubus spp and the aerial parts of Hypericum perforatum), The roots are eaten raw after preparing a Mixture (after milling with mustard seeds and mixing with honey). Mixture-meal (with the leaves, Papaver rhoes petals and Malva spp and Spinacia oleraceae leaves). Seeds are eaten with honey.	[18,41,45,47,50,56,57, 60,63,64,68,71-74,80,86,87,89,90, 93,94,96,98,101,104,106,109,111, 112,114,116,118,120,122,123,133,135,137]
Urtica pilulifera L.	Urticaceae	W	Roman nettle	Aerial parts, Leeaves, Seeds	Salad, Pastry, Infusion, Restorative paste (prepared with ginger, cinnamon, turmeric and *Nigella sativa* seeds after milling and mixing with honey)	[68,72,73,102,112,116,118,122]

Urtica urens L.	Urticaceae	W	Small nettle	Aerial parts	Infusion after dried	[57,58,63,64,73,80,90,104,109,112,116,122,123]
Vaccinium arctostaphylos L.	Ericaceae	W	Caucasian Whortleberry	Fruits, Leaves	Eaten raw, Infusion	[85,116-118]
Vaccinium myrtillus L.	Ericaceae	W	Bilberry, wimberry, whortleberry	Fruits, Leaves	Eaten raw/dried, Jam Infusion	[68,80,85,116,117,119,122]
Viburnum opulus L.	Adoxaceae	W	Guelder-rose	Fruits	Eaten raw, Juice	[63,80,83,112]
Viscum album L.	Santalaceae	W	European mistletoe, common mistletoe	Fruits, Leaves, Stems, Aerial parts	Infusion, Decoction, Tincture (prepared with lemon and vinegar)	[53,54,71,99,105,116-118]
Vitis labrusca L.	Vitaceae	C/W	Fox grape, concord grabe	Fruits, Seeds	Eaten raw, Eaten with honey after dried and pulverized	[85,106,116,126]
Vitis vinifera L.	Vitaceae	C	Grapevine	Fruits, Seeds	Eaten raw or dried, Cataplasm (with tarhana flour), Molasses, Churchkhela	[59,68,80,90,98,100,106,116,119,126]
Withania somnifera (L.) Dunal	Solanaceae	W	Ashwagandha, Indian ginseng	Roots	Infusion after dried and pulverized	[85,116,136]
Ziziphora clinopodioides Lam.	Lamiaceae	W	Blue mint bush	Flowering branches, Aerial parts	Infusion, Spices	[42,43,100,102]
Ziziphus jujuba Mill.	Rhamnaceae	C/W	Jujube, red date	Fruits	Eaten raw or after dried, Decoction mix (prepared with pear, ginger and lemon),Tincture (prepared with lemon and vinegar)	[71,97,120]

Table 3: The list of plant taxa used for the immune-boosting and related activities in Turkish folk medicine.
C: Cultured plants, W: Wild plans, E: Endemic plants, CW: Cultured and wild plants.
Boldly highlighted taxa (which are 60 in total and their immune-boosting and other similar activity effects have not been investigated experimentally yet).

Plant species	Active compounds effective on immune response(s) (and used parts)	Type of activity	Type of immune response	Mechanism of action	References
Achillea millefolium L.	Not specified (aerial parts)	Immune-boosting	Humoral	By reducing the levels of serum lipids and boosting the immune response. Thus, it is proposed that can be used as an antibiotic alternative.	[238]
Allium cepa L.	Agglutinin (bulbs)	Immunomodulatory	The cell-mediated	By increasing production of nitric oxide, production of pro-inflammatory cytokines, enhancing proliferation of murine thymocytes and elevating the expression levels of cytokines.	[239]
Allium sativum L.	Not specified (Bulbs)	Immune-boosting	The cell-mediated	By increasing CD4 (cluster of differentiation 4) T lymphocytes and total WBC (white blood cells) synergistically with *Allium cepa*.	[240]
Apium graveolens L.	Not specified (leaves)	Immunostimulant	The cell-mediated	By increasing total white and red blood counts, haemoglobin content and haematocrit value.	[241]
Avena sativa L.	β-glucan (seeds)	Immunomodulatory	The cell-mediated	By increasing cytokine levels.	[235]
Brassica oleracea L.	Not specified (Aerial parts)	Immune-boosting, Immunostimulant	Humoral and The cell-mediated	By showing significant improvement in phagocytic and bactericidal activity.	[242]
Brassica rapa L.	Not specified (roots)	Immunostimulant	The cell-mediated	By stimulating their endocytic/pinocytosis activity and releasing nitric oxide, tumor necrosis factor alpha (TNF-α) and interleukin-6 cytokines.	[243]
Calendula officinalis L.	Not specified (flowers)	Immunostimulant	The cell-mediated	By increasing production of nitric oxide on a level comparable with that of lipopolysaccharides.	[244]

Camellia sinensis (L.) Kuntze	Strictinin, Catechin (leaves)	Immunostimulant, Immunomodulatory	The cell-mediated	By using the phagocytic activity of macrophage-like cells as an indicator of immune function activation.	[245]
Capparis spinosa L.	Quercetin and Kaempferol glycosides (buds)	Immunomodulatory	The cell-mediated	By inhibiting the extracellular virus release upregulating their production of IL-12, IFN-γ and TNF-α. It should thus be employed for treatment of in immunocompromised hosts.	[229]
Capsicum annuum L.	Not specified (fruits)	Immunomodulatory	Humoral and The cell-mediated	By oral administration with capsicum extract might activate the CD4+ T cells leading to cytokine production as well as CD19+ B cells in Peyer's patches.	[246]
Castanea sativa Mill.	Not specified (fruits)	Immunostimulant	The cell-mediated	Through the skin mucus and serum immune parameters were significantly increased in fish fed with CSP compared to control.	[247]
Cichorium intybus L.	Oxycoumarins, Hydroxycinnamic acids, and Flavonoids (aerial parts)	Immunomodulatory	Humoral and The cell-mediated	By reducing the suppressive azathioprine effect on the cell-mediated immune response, antibody response, and phagocytosis with macrophages.	[248]
Citrus spp.	Auraptene (fruits)	Immunomodulatory	Humoral and The cell-mediated	By activating splenocytes and lymphocytes from mesenteric lymph nodes and increasing IL-4, Interferon gamma (IFNγ) and TNF-α production.	[249]
Crataegus monogyna Jacq.	Not specified (leaves)	Immunomodulatory	Humoral and The cell-mediated	By increasing the total number, percentage, and absolute count of T and B splenocytes.	[250]

Elaeagnus angustifolia L.	Not specified (Fruits)	Immunostimulant	Innate, Humoral and The cell-mediated	By increasing the spleen and thymus index of mice, increasing the phagocytosis of mononuclear phagocyte system, and stimulating hemolysin formation.	[251]
Equisetum arvense L.	Not specified (aerial parts)	Immune-enhancing	Innate, Humoral and The cell-mediated	By enhancement of cytokine (IL-2, INF-γ) production in Th1 cells.	[252]
Fragaria vesca L.	Gamma-aminobutyric acid (fruits)	Immunomodulatory	Innate, Humoral and The cell-mediated	By increasing IL-10 and IFN-γ in mice.	[253]
Glycyrrhiza glabra L.	Not specified (roots)	Immunomodulatory	Humoral and The cell-mediated	By increasing leukocytes, phagocytic activities, and antibody secreting cells of mouse spleen in combination with Zinc.	[254]
Helianthus tuberosus L.	Inulin (Tubers)	Immunostimulant, Immunomodulatory	Humoral and The cell-mediated	By increasing total immunoglobulin and lysozyme activity.	[255]
Hordeum vulgare L.	β-glucan (seeds)	Immunomodulatory	The cell-mediated	By increasing cytokine levels.	[235]
Hypericum perforatum L.	Germacrene D, β-Caryophyllene, α-Humulene (essential oils from leaves and flowers)	Immunomodulatory	Innate	By inhibiting neutrophil Ca2+ mobilization, chemotaxis, and reactive oxygen species (ROS) production	[256]
Juglans regia L.	Not specified (fruits)	Immunomodulatory	Innate, Humoral and The cell-mediated	By promoting macrophage phagocytosis and natural killer activity, elevating the percentages of CD3+ and CD4, up-regulating the production of antibody IgM, IgA, IgG and SIgA, and regulating Cytokines, Th1 produced.	[257]
Malus domestica Borkh.	Catechin, Procyandin B, Quercetin-3-galactoside and Quercetin xyloside (fruit peels)	Immunostimulant	Innate and The cell-mediated	By increasing lysozyme enzyme and phagocytic activity of macrophages.	[231]

Malva sylvestris (L.) Mill.	Not specified (leaves)	Immunomodulatory	The cell-mediated	By acting as macrophage and T helper-1 (Th-1) activators.	[258]
Matricaria chamomilla L.	Not specified (flowering branches)	Immunomodulatory	The cell-mediated	Through activizating immunoregulation cells of peripheral blood and increasing sensitivity of effector cells to helper signals.	[259]
Melissa officinalis L.	Not specified (aerial parts)	Immunostimulant	The cell-mediated	By increasing lipase and lysozyme activity, and elevating pepsin and trypsin.	[38]
Mentha pulegium L.	Not specified (aerial parts)	Immune-enhancing, Immunostimulant	Innate	By increasing phagocytosis, lysozyme, respiratory burst and total white and red blood cells (WBC/RBC).	[260]
Mentha x piperita L.	Not specified (aerial parts)	Immunostimulant	Humoral and The cell-mediated	By increasing erythrocytes, leucocytes, haematocrit, haemoglobin, phagocytic activity, lysozyme, anti-protease and anti-bactericidal activities, as well as evelating serum protein and globulin levels.	[261]
Mespilus germanica L.	Not specified (leaves)	Immunostimulant	Humoral	By increasing the immunoglobulin levels and interleukin 8 levels as well as elevating the level of lysozyme activity.	[262]
Morus alba L.	2-Formyl-5-(hydroxymethyl)-1H-pyrrole-1-butanoic acid and 2-Formyl-5-(methoxymethyl)-1H-pyrrole-1-butanoic acid (fruits)	Immunostimulant	The cell-mediated	By the enhancement of nitric oxide, TNF-α and IL-12 production, and the stimulation of phagocytic activity.	[263]

Morus nigra L.	Not specified (fruits)	Immunomodulatory	Innate	By increasing the activities of serum lysozyme, myeloperoxidase, superoxide dismutase and catalase, and increased the expression levels of immune-related genes (interleukin 1, beta, tumor necrosis factor, immunoglobulin M, interferon gamma and heat shock protein 70) in the spleen and antioxidant-related genes.	[37]
Myrtus communis L.	Not specified (leaves)	Immunostimulant	Innate	By increasing the number of erythrocyte (RBC), leukocyte (WBC) and haematocrit, and lysozyme activity.	[264]
Nasturtium officinale R.Br.	Not specified (leaves)	Immunomodulatory, Immunostimulant	Humoral and The cell-mediated	By enhancing hemoglobin (Hb), mean corpuscular hemoglobin concentration (MCHC), lysozyme and complement activities, as well as total protein and globulin levels.	[265]
Nigella damascena L.	Damascenine and β-Elemene (seed-essential oils)	Immunomodulatory	The cell-mediated	By inhitibiting release of interleukin 1 beta (IL-1β) and interleukin 8 (IL-8), decreasing matrix metallopeptidase 9 (MMP-9) production.	[266]
Nigella sativa L.	Thymoquinine (seed-essential oils)	Immunomodulatory, immunotherapeutic	Innate and The cell-mediated	By possessing reproducible anti-oxidant effects through enhancing the oxidant scavenger system and augmenting the T cell- and natural killer cell-mediated immune responses.	[267]
Olea europaea L.	Oleuropein (leaves)	Immunomodulatory	The cell-mediated	By inducing and maintaining high proliferation in lymphocytes.	[268]

Origanum vulgare L.	Not specified (aerial parts)	Immunostimulant	Innate and The cell-mediated	By increasing serum total protein, albumin and globulin, respiratory burst activity, phagocytic activity and serum lysozyme activity.	[269]
Petroselinum crispum (Mill.) Fuss	Not specified (aerial part-essential oils)	Immunomodulatory	The cell-mediated	Through its inhibitory effect on PHA-stimulated splenocytes which occurred due to the production of cytokines such as IFN-γ and IL-2, which are vital for T-cell proliferation and the signalling pathways.	[270]
Phoenix dactylifera L.	Chlorogenic acid, Caffeic acid, Pelargonin, Ferulic acid, Trypsin (fruits)	Immunomodulatory	Humoral and The cell-mediated	By stimulating FN-γ mRNA expression significantly in mouse Peyer's patch cell cultures, and increasing the number of IFN-γ+CD4+ CD49b+ and IL-12+CD11b+ cells.	[226]
Pinus sylvestris L.	Not specified (cones)	Immune-enhancing	Humoral	By affecting the expansion of T cells (both CD4 and CD8) during the proliferative phase.	[271]
Portulaca oleracea L.	Not specified (aerial parts)	Immunostimulant, Immunomodulatory	Innate, Humoral and The cell-mediated	By enhancing splenocyte proliferation and upregulated inflammatory cytokines (IL-2, IL-12, TNF-α, and IFN-γ) and natural killer (NK) cell activity in vitro.	[272]
Prunus avium (L.) L.	Not specified (fruits)	Immunomodulatory	The cell-mediated	By inducing the NO release from RAW264.7 cells and the expression of several immune-related molecular (TNFα, IL6, IL10, GCSF, iNOS, COX-2).	[273]
Punica granatum L.	Not specified (pericarps)	Immunomodulatory	Humoral and The cell-mediated	By increasing antibody density to typhoid-H antigen and enhancing the inhibition of leukocyte migration.	[274]
Pyrus communis L.	Not specified (fruits)	Immunostimulant	The cell-mediated	By increasing phagocytic activities.	[275]

Rhus coriaria L.	Not specified (fruits)	Immune-enhancing	Innate, Humoral and The cell-mediated	By increasing the number of leukocyte (WBC) and erythrocyte (RBC), lymphocyte, monocyte, and neutrophil value as well as serum lysozyme and TNF-α and IL-1b.	[276]
Rosa × damascena Herrm.	Not specified (petals)	Immunomodulatory	Humoral and The cell-mediated	Through Peyer's patch cells and enhanced production of IL-6 from murine macrophages.	[277]
Rosa canina L.	Oleanolic acid, Betulinic acid and Ursolic acid (fruits)	Immunomodulatory	Humoral and The cell-mediated	By inhibiting the lipopolysaccharide induced interleukin-6 release.	[278]
Rosmarinus officinalis L.	Not specified (leaves)	Immunomodulatory	Humoral	By increasing IgM (Immunoglobulin M) response at all antibody titers and proliferation of spleen cells.	[279]
Salvia officinalis L.	3-O-methyl-galactose (aerial parts)	Immunomodulatory	The cell-mediated	By inducing the proliferation of rat thymocytes.	[280]
Sambucus ebulus L.	Not specified (leaves)	Immunostimulant	The cell-mediated	By increasing the levels of IFN-γ, IL-4, nitric oxide and switching the host immune responses towards Th1 response.	[281]
Sambucus nigra L.	Cyanidin 3-glucoside and quercetin (fruits)	Immunomodulatory	The cell-mediated	By blocking viral glycoproteins as well as indirect effects by increased expression of IL-6, IL-8, and TNF.	[230]
Satureja hortensis L.	Not specified (essential oils)	Immunomodulatory	Innate	Through a significant enhancement in serum lysozyme for innate immune response of angelfish.	[282]

Sesamum indicum L.	Not specified (seeds)	Immunomodulatory	Innate, Humoral and The cell-mediated	By increasing splenocyte proliferation, balancing the secretion of Th1 and Th2 cytokines, inhibiting the secretion of key pro-inflammatory mediators (IL-6, TNFα, and nitric oxide), and increasing the cytotoxic activity of natural killer (NK) cells.	[283]
Silybum marianum (L.) Gaertn.	Silymarin (seeds)	Immunomodulatory	Innate and The cell-mediated	Through the enhancing haematological and immunological parameters including lysozyme and complement activities, total protein and globulin levels.	[284]
Solanum lycopersicum L.	Not specified (fruits)	Immune-enhancing	Humoral and The cell-mediated	By increasing phagocytosis, chemotaxis, and levels of immunoglobulins (TIg, IgG, IgM and IgA).	[285]
Spinacia oleracea L.	Not specified (leaves)	Immunostimulant, Immune-enhancing	Innate	Through a substantial improvement of serum protein profile, lysozyme activity, Hematocrit percent, and serum Superoxide Dismutase enzyme (SOD).	[286]
Taraxacum spp.	Taraxasterol (not specified)	Immunomodulatory	The cell-mediated	By increasing hepatic glutathione (GSH) and superoxide dismutase (SOD) production, inhibiting the release of pro-inflammatory cytokines tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1β, interferon-γ (IFN-γ) and IL-4.	[287]
Thymbra spicata L.	Not specified (aerial parts)	Immunomodulatory	The cell-mediated	By increasing the decreased level of the IL-6 cytokine in response to TNF-α.	[288]

Tilia tomentosa Moench	Not specified (flowers)	Immunostimulant	Innate	By increasing lysozyme activity and respiratory burst activity.	[289]
Tribulus terrestris L.	Saponins (fruits)	Immunomodulatory	The cell-mediated	By increasing phagocytic activity.	[290]
Urtica dioica L.	Quercetin-3-O-rutinoside, Kaempherol-3-O-rutinoside and Isorhamnetin-3-O-glucoside (leaves and roots)	Immunostimulant	The cell-mediated	By chemotactic effects in 4, 8, 16 µg doses and showing high intracellular killing activity.	[228]
Viscum album L.	Not specified (aerial parts)	Immune-boosting	The cell-mediated	By increasing phagocytic activity and candidacidal activity of neutrophils and stimulating the levels of CD4+CD25+ and CD8+CD25+ T cells.	[291]
Vitis labrusca L.	Arabino-3,6-galactan (Pericarp)	Immunostimulant	Innate and The cell-mediated	Through enhanced the stimulatory responses of macrophage stimulating activity ex vivo.	[292]
Vitis vinifera L.	Not specified (seeds)	Immunostimulant	Innate	By increasing nitroblue tetrazolium (NBT) activity, myeloperoxidase (MPO) activity, phagocytic activity and lysozyme activity.	[293]
Withania somnifera (L.) Dunal	Not specified (roots)	Immunostimulant	The cell-mediated	By increasing nitric oxide (NO) production by macrophages.	[294]
Ziziphora clinopodioides Lam.	Not specified (aerial partss)	Immune-boosting	The cell-mediated	By improving the immune system and blood biochemical parameters of laying hens with *Melissa officinalis* and *Tanacetum balsamita*.	[295]
Ziziphus jujuba Mill.	Not specified (fruits)	Immunomodulatory, Immunostimulant	Innate, Humoral and The cell-mediated	By increasing spleen and thymus indices, promoting serum hemolysin formation, and enhancing the phagocytic activity of macrophages.	[296]

Table 4: Worldwide immune-boosting and other similar activity research results of the taxa detected in the study.

Sc. Names	Families	English names	Parts	Preparations	Native lands	References
Alpinia officinarum Hance	Zingiberaceae	Lesser galangal	Rhizomes	Spice, Decoction or infusion (after pulverizing)	Southeast Asia	[88,91,128,131]
Cinchona pubescens Vahl	Rubiaceae	Red cinchona, quina	Barks	Decoction or infusion (after pulverizing), Syrup or liqueur prepared after pulverizing	Central and South America	[18,81,116-118,131]
Cinnamomum verum J.Presl	Lauraceae	Cinnamon, true cinnamon tree	Barks	Decoction with the puverized bark, linden leaves and cloves. Restorative paste (prepared with the dried and pulverized bark, black peper fruits, ginger rhizomes, nettle seeds, turmeric rhizomes and *Nigella sativa* seeds after milling and mixing with honey)	South and Southeast Asia	[57,68,,73,81,104,105,109,110,116,118,128]
Curcuma longa L.	Zingiberaceae	Turmeric	Rhizomes	Restorative paste (prepared with the dried and pulverized rhizomes, ginger, cinnamon, and the seeds of nettle and *Nigella sativa* after milling and mixing with honey)	Indian subcontinent and Southeast Asia	[18,40,68,72,73,112,118,121,122,124,127,131]
Echinacea angustifolia DC.	Compositae	Narrow-leaf coneflower	Roots, Rhizomes, Flowers	Decoction or infusion (after pulverizing)	North America	[81,116,118,121,122,124,127]
Hibiscus sabdariffa L.	Malvaceae	Roselle, carcade, hibiscus	Leaves	Infusion	West and East Africa and South-East Asia including Northeastern India.	[91,92,97,116,117,122]
Malpighia emarginata DC.	Malpighiaceae	Acerola cherry	Fruits	Decoction or infusion (after pulverizing)	Central and South America	[91,118,122]
Panax ginseng C.A.Mey.	Araliaceae	Asian ginseng	Roots	Decoction or infusion (after pulverizing), Paste (with honey)	Russian Far East (Outer Manchuria), Northeast China, and the Korean Peninsula	[18,65,81,83,88,91,112,118,122,128,137]

Piper nigrum L.	Piperaceae	Black pepper	Unripe Fruits	Infusion mix (with the dried and pulverized fruits and ginger rhizomes, melissa leaves, sage leaves and elder fruits), Restorative paste1 (all of them above are eaten by mixing with honey), Restorative paste2 (prepared with the dried and pulverized fruits and ginger rhizomes, cinnamon, turmeric, nettle seeds and *Nigella sativa* seeds after milling and mixing with honey)	India	[59,62,72,117,121,123-125,127,133]
Rheum officinale Baill.	Polygonaceae	Chinese rhubarb	Roots, Rhizomes	Infusion after pulverizing, Syrup, Paste (with honey)	China	[18,116-118]
Syzygium aromaticum (L.) Merr. & L.M.Perry	Myrtaceae	Cloves	Flower buds, Essential oil	Pastille, Infusion, Frankincense, Decoction mix (with cinnamon and linden leaves), Mixture (eaten after milling with seeds of celery and anise, turnip, radish and mixed with honey)	Maluku Islands	[100,117,119,121]
Terminalia citrina Roxb. ex Fleming	Combretaceae	-	Fruits, Seeds	Paste (prepared with honey after dried and pulverized)	East India	[65,91,117]
Vaccinium macrocarpon Aiton	Ericaceae	Cranberry	Fruits	Eaten after dried, Juice, Decoction	North America	[91,118,122]
Zingiber officinale Roscoe	Zingiberaceae	Ginger	Rhizomes	Infusion mix (with the dried and pulverized rhizomes, melissa leaves, sage leaves, elder fruits and black pepper), Restorative paste1 (all of them above are eaten by mixing with honey), Restorative paste2 (prepared with the dried and pulverized rhizomes, cinnamon, turmeric, nettle seeds and *Nigella sativa* seeds after milling and mixing with honey)	South Asia	[59,62,72,117,121,123-125,127,131,133]

Table 5: Exotic plants traditionally used for immune-boosting and other similar activities in Turkey.

Conclusion

Suffering from a global epidemic of Covid19 mutants and variants, the whole world has turned its attention and hope to natural treatments that can keep the immune system active and strong. Recent studies of some medicinal plant preparations hold great prospects that they may be potential candidates to develop effective and safe immune-boosting drugs against this relentless pandemic. Initiatives in this regard will primarily be hope for millions of people with weakened immune systems due to old age and pre-existing medical problems, waiting for treatment in quarantine at home or in intensive care in hospital. In particular, recent research on phytochemicals like quercetin, beta-glucan, and catechin makes us feel a little more optimistic about the future.

Thanks to a strong immune system, a person with good body health can easily get rid of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections without any complications. It is known that the side effects of existing synthetic drugs and the necessity of taking a certain dose while in the state of infection make vital organs, such as the kidney and liver, even riskier [297,298]. In fact, new cases are added every day to the reports that dozens of people who had newly developed vaccines lost their lives due to unpredictable coagulation. Countries that were lining up to be able to supply the relevant vaccines a while ago, announced that they, therefore, ban the use of these vaccines one after another [299]. At this point, medicinal plants might almost be the rescuers of humanity, for they have been providing us with the successful results observed in immune system boosting and similar activities for centuries, provided that they are regularly used according to the prescriptions specified in their pharmacopoeias. However, there is also a misperception that herbal medicines are completely safe and have no side effects. In addition, complications that may occur in case of use with existing drugs are another issue that should be taken into consideration. For this reason, we strongly recommend that people and establishments that keep and sell fresh or dried medicinal herbs in public markets and shops are inspected more strictly by local governments and that they are sold to the public in accordance with international norms. In these matters, the directives, instructions, and practices of the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) can be taken as a model and the existing system can be revised. We firmly advocate the urgent need to inform the public in more details by recording the herbal mixtures and prescriptions of traditional empirical practices with proven reliability and effectiveness after the necessary clinical tests, revealing their ingredients and active compounds through experimental studies, and updating their knowledge in their pharmacopoeias. We sincerely believe that more efficient results will be obtained in public enlightenment activities if the participation of non-governmental organizations, scientific circles and official authorities/institutions in full co-operation with civilians, which can be organized in real or virtual environments, on plants that can be used safely in the face of Covid-19 and similar pandemics or epidemics [300].

Considering that Turkey has the richest flora of Europe and the Middle East and its invaluable ethnomedical history, it presents a treasure-worthy potential for those who want to do serious research on this subject. In fact, this study presents a nationally useful inventory of immune-enhancing plants that are regularly used in traditional Turkish medicine, not only against Covid-19 but for the prevention and treatment of epidemic diseases in general. We present 68 (53.1%) plants whose effective immunostimulating and strengthening properties have been confirmed in experimental studies in the world literature as ready-made material to the relevant pharmacological sectors. In addition to the 60 (46.9%) taxa that have not been searched yet, which are shown in bold in Table 3, the first 18 plants (Figure 2), which received more citations than others about immunity enhancement in our research and were also prominent in neighbouring country studies, we strongly recommend that these should urgently be subjected to clinical trials firstly. In this way, we will feel peaceful and happy if we can be instrumental in the survival of humanity from the current and future epidemics and pandemics with minimal damage, alleviation of patients' agonies, and the development of a healthier and happier generation.

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