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Comprehensively Revealing the Profile of *Pistacia vera* L. cv. Siirt Turpentine - Antioxidant, Antidiabetic, Anti-Alzheimer, and Antiglaucoma Effects

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Abstract: Pistacia species containing turpentine which has protective effects and used as a medicine against diabetes, and infections for a long time. To interpret the antioxidant capacities of turpentine from *Pistacia vera* L. cv. Siirt, 2,2'-azino-bis-3-ethylbenzthiazoline-6-sulphonic acid radical ($ABTS^{\bullet+}$) and 1,1-diphenyl-2-picrylhydrazyl free radical (DPPH·), Fe^{3+}-2,4,6-tris(2-pyridyl)-S-triazine (TPTZ) and Cu^{2+} reducing ability were studied and compared to reference antioxidants of BHT, BHA, α-Tocopherol, and Trolox. The IC_{50} of turpentine for $ABTS^{\bullet+}$ and DPPH· scavenging capacities were determined to be lower than reference antioxidant standards as 231.1 µg/mL and 346.6 µg/mL, consequently. The total flavonoid and phenolic contents in turpentine were measured as 12.5 mg GAE/g and 38.852 mg QE/g, respectively. For determination of antidiabetic, anti-Alzheimer, and antiglaucoma effects of turpentine, acetylcholinesterase (AChE), α-glycosidase and carbonic anhydrase II (hCA II) enzymes inhibition abilities of turpentine were performed. The IC_{50} values of turpentine extract against α-glycosidase, hCA II, and AChE enzymes were found as 2.04, 3.59 and 14.6 µg/mL, respectively. The quantity of protocatechuic acid and naringenin were determined using LC-MS/MS against 53 standards. The results clearly demonstrated polyphenolics in *P. vera* L. cv. Siirt turpentine is a natural product has potential usage in amelioration of glaucoma, AD, diabetes, and epilepsy.

Keywords: Phenolic compounds; turpentine; antioxidant; α-glycosidase; acetylcholinesterase; carbonic anhydrase.

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1. Introduction

Herbal products were used to treat some dysmetabolic illnesses like diabetes mellitus, obesity, and cardiovascular diseases. Pistacia genus plants are used in conventional medicine for improving hyperlipidemia and blood glucose management. *Pistacia vera* is one of the five most well-known pistacia species [1]. It belongs to the Anacardiaceae family and is native to Anatolia. It is extensively dispersed in the Mediterranean region, including Türkiye [2]. The turpentine tree (*Pistacia terebinthus*) is a shrub of the Pistacia genus found in Greece, Morocco and western and southeastern Türkiye [3]. Turpentine is the resin of tree. Sap harvesters harm the tree by removing the bark. Debarked trees exude oleoresin onto the wound's surface as a defensive measure in an attempt to close the opening. In addition to the eponymous terebinth tree, several other species generate such protective resins; the chemical makeup of the sap varies greatly not just with species but also with season and geographical distribution. The distillation of resin collected from live trees gives spirit of turpentine, also known as oil of turpentine (*Oleum terebinthinae*) or simply turpentine. It was previously used as medicine for internal or external administration, but it is currently used as a solvent and source of ingredients for organic synthesis [4]. Because of its antibacterial properties, pistacia resins have been employed in ancient Mediterranean medicine as herbal treatments for some illness. Oleoresins were first used as a nutritional supplement in ancient time [5]. In addition to being used to flavor bread and rice dough, the resin also serves as a mastic gum [6,7]. Secondary metabolites such as phenolics have been identified and employed to treat a few medical conditions. Growing demands and numerous studies have recently been made for the approval, development, and use secondary metabolites of herbs in medications to cure a different ailment [8,9].

In aerobic life, which is characterized by the predominance of molecular oxygen, free radicals and reactive oxygen species (ROS) are byproducts of regular cellular metabolism [10]. In addition to being pollutants in the air, neutrophils, and macrophages create ROS when there is inflammation. They are also byproducts of mitochondrial electron transport processes and formed by other methods. They are also produced during exposure to UV, X and γ-radiations [11,12]. ROS are different types of triggered oxygen and involve non-radical species like hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$) and free radicals like hydroxyl radicals ($OH^{\cdot}$), and superoxide anion radicals ($O_2^{\cdot-}$) [13]. The antioxidants in organisms maintains an equilibrium among the production of ROS and its deactivation. Under pathological conditions, an excess generation of ROS causes oxidative stress. When antioxidant defense is inadequate, ROS are created [14]. Biomolecules, like nucleic acids, lipids, carbohydrates, and proteins experience some oxidative damage as a result of ROS. Ageing, cancer, and numerous other diseases are brought on by their damage [15]. All aerobic organisms have antioxidant defense mechanisms, such as antioxidant molecules and antioxidant enzymes, to get rid of or fix the distorted molecules. As lipid peroxidation composes one of the substantial factors in the degradation of pharmaceutical products and food through manufacturing and transportation, antioxidant substances can remove ROS and free radicals and extend lifespan by delaying this activity [16]. Antioxidant substances and antioxidant enzymes are part of the immune system's defense mechanism. Proteins, nucleic acids, carbohydrates, and lipids found in alive are just a few of the biomolecules that they can fix or remove. Antioxidants slow down, stop, or prevent these biomolecules from oxidizing. They consist of polyphenols, which are powerful inhibitors of ROS or free radicals that can effectively neutralize their harmful and undesirable effects [17]. However, antioxidant supplements or meals can assist in preventing oxidative damage to the body produced by ROS and free radicals [5]. Numerous antioxidants present in plants have been discovered as ROS or free radical scavengers. Finding antioxidants that are naturally occurring to utilize in foods or medications has lately drawn a lot more attention because synthetic antioxidants, which are banned because to their negative consequences like carcinogenicity, are evolving more and more unpopular. Currently, butylated hydroxyanisole (BHA), propyl gallate, tert-butyl hydroquinone and butylated hydroxytoluene (BHT) are the putative and synthetic antioxidants that are utmost frequently utilized [18]. However, regulatory limitations have been placed on BHA and BHT due to worries regarding their carcinogenic and harmful impacts. As a result, consumer desire for natural antioxidants is increasing, as antioxidants that are safer and more natural for use in food are gaining popularity, and both of these have inspired attempts to study natural antioxidant sources [19,20].

Most plants have naturally occurred antioxidants in their fruits, flowers, seeds, roots, and leaves. High concentrations of polyphenols, ascorbic acid, carotenoids, and tocopherols are among the compounds found in many fruits and vegetables that have positive health effects. The risk of chronic illnesses like cancer and cardiovascular disease may be decreased by eating more fruits and vegetables [21]. The medicinal plant, the subject of numerous studies to recently, is an example of foremost significant natural antioxidant resources. The phenol content of medicinal plants is high. Fruits, cereals and plants are the primary sources of natural antioxidants in the diets of human [22]. Secondary metabolites found in plants, phenolic compounds, protect against oxidative stress and degenerative diseases like cataract, heart diseases, rheumatoid arthritis, diabetes, cancer, arteriosclerosis, and hypercholesterolemia in humans. Natural antioxidants can shield the body against ROS and free radicals, slow the progression of many chronic illnesses, and prevent food from becoming rancid due to lipid oxidation [23].

One of the utmost important current global health challenges is thought to be Alzheimer's disease (AD) [24]. For AD, numerous treatments have been developed. Inhibiting AChE and BChE is one of the foremost pertinent techniques [25]. It is well known that compounds with biological activity and antioxidant properties can help prevent the lipid peroxidation damage that has been linked to a number of illnesses, as well as carcinogenesis, atherosclerosis, AD, and other age-related illnesses [26]. In order to treat the symptoms of AD, various AChE inhibitors are used. Tacrine, donepezil, rivastigmine, and galantamine are a few examples of cholinesterase inhibitors that have recently been utilized in the clinical curing of AD. Due to adverse outcomes like hepatotoxicity and, gastrointestinal failure the use of these drugs is also restricted [27]. Memory loss and other progressive cognitive problems are the earliest indications of AD. It is also thought to be linked to the depletion of the acetylcholine (ACh), oxidative stress and inflammation. Ingestion of the antioxidant-rich vegetables and fruits may thereby slow the course of AD and neurodegeneration [28]. Suppression of the essential enzymes linked to these diseases is thought to be a potent treatment and a cure for these disorders. To solve this issue, the researchers started incentives aimed at discovering a natural product substitute that has fewer or no deleterious effects. On the other hand, the synthetic drugs have too much adverse effects. Bioactive molecules were frequently used in clinical trials as AChE inhibitors (AChEIs), particularly for the remedy of AD. Phenolic substances were also found to be the AChEIs and to be the first medications for treating AD [29].

Diabetes is categorized as either insulin affiliate, type-1 diabetes mellitus (T1DM) or insulin independent type-2 diabetes mellitus, (T2DM), depending on the amount of biological efficiency of the excreted insulin and the amount of insulin secreted by the pancreatic β-cells [30]. The serious flaw in T2DM is that insulin cells get resistant, disrupting the insulin signaling cascade and damages absorption of glucose in target tissues like muscles and lipids [31]. T2DM accounts for 90-95% of all cases of diabetes mellitus, making it the utmost prevalent endocrine diseases in the world. Lipid metabolism, abnormal glucose levels, insulin activity resistance and insufficient insulin secretion from pancreatic β-cells are all factors in the classification and pathogenesis of T2DM [32]. The blood glucose level in diabetic patients stays high while the cells start to starve because the body has trouble transporting blood sugar to the cells. The hydrolysis and release of glucose from polysaccharides during the digestion of dietary carbohydrates also results in postprandial glucose levels [33]. Inhibiting carbohydrate-hydrolyzing enzymes like α-amylase and α-glycosidase is one of the currently available methods for T2DM treatment. Postprandial plasma glucose values can be decreased and postprandial hyperglycemia can be depressed as a result of delaying the absorption of glucose units [34]. α-Glycosidase is released from intestinal cells and hydrolyzes either oligosaccharides or polysaccharides into fructose and glucose components of monosaccharide. In order to control T2DM and hyperglycemia for human health α-glycosidase inhibitors (α-GIs) are crucial [35].

Carbonic anhydrases (CAs), metalloenzymes, which constitute Zn^{2+}, catalyze the hydration of carbon dioxide (CO_2) reversibly to proton and bicarbonate (HCO_3^-) [36]. CAs perform a wide range of metabolically and biochemical tasks, as well as ureagenesis, gluconeogenesis and, lipogenesis. Infection, convulsions, glaucoma, and cancer can all be treated therapeutically by CA inhibition [37]. In particular, CAs sustain liquid balance throughout the body such as in the kidneys, eyes, and stomach. CA inhibitors (CAIs) can reduce or treat glaucoma caused by intraocular pressure (IOP) [38]. Inhibition studies are going to perform on AChE enzyme to determine the anti-AD effects of turpentine. The CA

II inhibition was examined for determination of its relationship to glaucoma [39]. Antidiabetic potential effect turpentine on α-glycosidase is being investigated in similar studies, and the inhibition parameters (IC_{50} values) for turpentine are being calculated. Additionally, Cu^{2+} and FRAP reduction, DPPH and ABTS scavenging tests are carried out, and the total phenolic and flavonoid quantities for turpentine are recorded to comprehend antioxidant potential of the turpentine of *Pistacia vera* L. cv. Siirt. In order to identify the chemical components that underlie the plant species, a phenolic compound analysis was conducted using the LC-MS/MS method. The other important purpose of research is to show how the turpentine inhibit the AChE, CA II, and α-glycosidase enzymes, which are associated with widespread and common health problems. It is proposed that the information from the current study is going to support the need for additional research aimed at the creation of novel diets and food supplements.

The goal of current research was to assess the phenolic content, and antioxidant characteristics of turpentine to establish the correlation among the phenolic compound ingredients and antioxidant activities. Another goal of this study was to investigate antidiabetic, anti-Alzheimer, and antiglaucoma of turpentine by AChE, α-glycosidase and hCA II enzymes inhibition.

2. Materials and Methods

2.1. Chemicals

p-Nitrophenyl-D-glucopyranoside, acetylcholine iodide, acetylcholinesterase, α-glycosidase, ABTS (2,2-azino-bis 3-ethylbenzthiazoline-6-sulfonic acid), DPPH (1,1-diphenyl-2-picryl-hydrazyl), BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), Trolox, α-tocopherol, neocuproine (2,9-dimethyl-1,10-phenanthroline), trichloroacetic acid (TCA), (Ferrozine) 3-(2-pyridyl)-5,6-bis(4-phenyl-sulfonic acid)-1,2,4-triazine and, standard phenolic compounds for LC-MS/MS were bought from Sigma (Sigma-Aldrich GmbH, Steinheim, Germany). The other materials were supplied appropriately from Sigma-Aldrich or Merck.

2.2. Plant Materials

The turpentine of *Pistacia vera* L. cv Siirt was obtained from Tillo district of Siirt province. Altitude: 1020 m (3346 ft). Ethanol extract of turpentine was fused in ethanol for the antioxidant abilities but in DMSO for the tests on enzyme inhibition because of the ethanol's potential inhibiting effects.

2.3. Preparation of Turpentine

As previously mentioned, the extraction procedure was followed [2]. For the ethanol extract of the sample, 25 g of dried turpentine was crushed before being combined with 100 mL of ethanol and swirled for an hour using a magnetic stirrer. Filtrates were gathered after the extract had been filtered. A rotary evaporator (RE 100 Bibby, Stone Staffordshire, England) set to 50°C was utilized to get rid of the ethanol. All preparations were stored at 20°C before being employed in the experiments [40].

2.4. Total Phenolic Contents

The phenolic ingredients analysis of turpentine was performed with Singleton and Rossi's methodology [41] by adopting minor modifications in method [42]. Transfer the desired 0.5 mL of each sample to the Folin-Ciocalteu reagent (1.0 mL) [43]. The mixture is later properly combined and neutralized by carbonate (0.5 mL, 1%). Subsequently incubating in a dark place at 25°C for two hours, the absorbance at 760 nm is obtained in comparison to a blank sample composed of distilled water. Gallic acid calibration curve was created, and the linear regression equation of this curve was used to calculate the contents of phenolics. The results of the phenolic ingredient analysis are given as milligrams of gallic acid equivalents (GAE) per gram of turpentine [44].

2.5. The Total Flavonoid Contents

The most prevalent class of polyphenolics in the typical human diet are flavonoids, which are also widely distributed in plants. A colorimetric test employing the method published by Koksal et al [45] was used to determine the number of flavonoids overall in turpentine. 1.5 mL of 95% methanol and 0.5 µg/mL of the turpentine sample was combined. The samples were then vortexed after 1.5 mL of 10% $Al(NO_3)_3$, 0.5 mL of CH_3COOK (1.0 M), and 2.3 mL of distilled water were added. Then, the samples have been vortexed, and left at room temperature for 40 minutes while being kept in the dark. The absorbance readings are captured at 415 nm. Distilled water was utilized as a blank and control. The linear regression calibration curve was generated for quercetin was used to determine the flavonoid concentration. The findings of the quercetin equivalents (QE) test are given as mg per gram of turpentine [46].

2.6. LC-MS/MS Analysis

2.6.1. Sample Preparation

Each 100 mg of turpentine sample is diffused in a volumetric flask contain 5 mL of ethanol-water (50:50 v/v) and 1 mL of this preparation is conveyed into another volumetric flask with a volume of 5 mL. Then, 100 µL of turpentine is adjoined and the volume adjusted with (50:50 v/v) ethanol-water. A 1.5 mL aliquot from the last mixture is conveyed into a flask with a cover, and 10 µL of the specimen is inserted into the LC-MS/MS. All through the essay, the specimens in the autosampler are put up at 15°C [47-49].

2.6.2. Test Solution for Mass Spectrometer (LC–MS/MS) and Chromatography Conditions

The analytical strategy utilized in this analysis was carried out in line with the most recent findings. A previously developed and validated LC-MS/MS method was utilized to quantify the certain bioactive phytochemical composition of turpentine ethanol extract. This study's analytical strategy was created by Yilmaz [50] and customized for turpentine. The details of the validation data regarding the LC-MS/MS analytical method were given as Table S1 in the supporting information file.

2.7. Reducing Ability

2.7.1. Cupric Ions (Cu^{2+}) Reducing Ability-CUPRAC Assay

Appropriate to the methodology of Apak et al. [51] with less modification as described in detail, the Cu^{2+} reducing efficacy of the turpentine is measured. To achieve this, the identical volumes of the turpentine (10-30 µg/mL) in a glass tube was added to the same concentrations of the neocuproine (7.5 mM), $CuCl_2$ solution (10 mM), and acetate buffer solution (0.25 mL, 1.0 M). With distilled water and vigorous mixing, the combination volumes are calibrated to a total of 2 mL. The glass tubes are then sealed and kept at 25ºC until they are utilized in experiments. Finally, spectrophotometric measurements of their absorbances at 450 nm are taken after 30 minutes. As a control sample, acetate buffer solution is employed. A greater absorbance of the reaction mixtures points to a greater capability for Cu^{2+} conversion.

2.7.2. Fe^{3+}-TPTZ Reducing Ability-FRAP Assay

The reduction of Fe^{3+}-TPTZ in acidic medium is the basis for the FRAP reducing power [52]. The reduction form Fe^{2+}-TPTZ is spectrophotometrically detected at 593 nm. In buffer (2.5 mL, pH 3.6, 0.3 M) content, the FRAP reagent solution contained $FeCl_3$ (20 mM, 2.25 mL) and TPTZ (10 mM, 2.25 mL). After 0.2 mL of the specimen and 1.8 mL of FRAP reagent have been combined, the absorbance is recorded at 593 nm. The phosphate buffer is used to form a blank specimen [53].

2.8. Radical Scavenging Activities

2.8.1. DPPH• Scavenging Activity

The existence of pure substances with hydrogen atoms or electron-donating characteristics can be detected by bleaching a purple DPPH mixture in methanol. In this spectrophotometric experiment, the reagent is stable DPPH· [54]. DPPH radical removing activity of turpentine was realized according to the Blois method [55] as formerly applied by our group [56] was slightly modified and utilized to calculate the DPPH's free radical scavenging capability in the presence of turpentine extract. DPPH is then checked for brightening at a certain wavelength. The DPPH mixture was made ready the day prior to the measurement [57]. The mixture in the beaker was covered with an aluminum foil and stored in a dark place at 4°C for 16 hours while being shaken. A short time after making a 0.1 mM DPPH solution that was dissolved in ethanol, 0.5 mL of this mixture was added to 2 mL of turpentine in ethanol at various concentrations (10-30 g/mL). After being vortexed, the samples were incubated at 30°C in the darkness for 30 minutes. In comparison to blank samples, absorbance was recorded at 517 nm. A reduction in absorbance points out the presence of active DPPH free radicals [58]. DPPH absorbs at a lower wavelength than the radical form, which absorbs at 517 nm, when it is reduced by another type of radical or antioxidant. The absorbance at 517 nm reduces proportionally to an increase in the non-radical forms of DPPH when a hydrogen atom or electron is shifted to the odd electron. DPPH is actively scavenging free radicals, as evidenced by absorbance declines [59].

2.8.2. $ABTS^{\bullet+}$ Scavenging Activity

ABTS, a radical that is often stable, also decolorizes when it isn't radical. The technique of Re et al. [60] was used to determine the $ABTS^{\bullet+}$ scavenging ability spectrophotometrically. The 2.45 mM $K_2S_2O_8$ was supplemented to ABTS in water to produce $ABTS^{\bullet+}$, which was then allowed to rest for six hours in the darkness and at room temperature. The ABTS began to oxidize straight away, but it took more than 6 hours for the absorbance to attain its peak and stabilize. In this method, addition of an antioxidant to a premade ABTS radical mixture, and the residual $ABTS^{\bullet+}$ is detected at 734 nm after a short period [61]. The radical cation is persistent in this state for more than two days when stored in the dark and at ambient temperature. The solution is prepared for the experiment by diluting it in phosphate buffer (pH 7.4) to produce an absorbance at 734 nm of 0.700±0.02 in a 1 mL cuvette, and then equilibrating it at 30°C, the temperature at which all trials are carried out. Then, 3 mL of turpentine sample in ethanol at various concentrations (10–30 g/mL) are integrated with 1 mL of the $ABTS^{\bullet+}$ mixture. Subsequently 30 minutes of stirring, the absorbance is detected and for each concentration of the sample the radical scavenging rate is calculated in contrast to a no scavenger containing blank. The degree of decolorization is determined by the percentage reduction in absorbance [62].

2.9. Enzyme Inhibition Studies

2.9.1. Acetylcholinesterase Inhibition Study

Turpentine inhibitory abilities on AChE enzyme was carried out with Ellman's procedure [63]. This was achieved by employing the AChE serum of electrical eels. In summary, a particular turpentine concentration (10–30 µg/mL) in buffer solution (1.0 M Tris/HCl, 100 µL, pH 8.0) was added to the (50 µL, 5.32 10^{-3} EU) enzyme mixtures. The reagents were maintained for 10 minutes at 20°C. Subsequently, 50 µL of composition including DTNB (5,5′-dithio-bis(2-nitro-benzoic acid) (0.5 mM) and acetylthiocholine iodide (AChI) were asserted. The reaction medium was then initiated, and the absorbances of the combination were determined at 412 nm spectrophotometrically.

2.9.2. α-Glycosidase Inhibition Study

The inhibiting effects of the turpentine on α-glycosidase enzyme were determined in accordance with Tao et al. [64] as approach described in particular [65]. For this reason, various amounts of

turpentine were put into phosphate buffer solution (75 µL, pH 7.4). Following that, 20 µL of α-glycosidase solution was added to this buffer and incubating for 10 min. The resultant combination was combined with a 50 µL aliquot of p-nitro-phenyl-D-glycopyranoside (p-NPG) that had been dispersed into the prepared buffer. The combination was then incubated once again at room temperature (37ºC), and the absorbances were estimated at 405 nm in contrast to a blank sample composed of phosphate buffer.

2.9.3. Human Carbonic Anhydrase II Inhibition Study

Sepharose-4B-L-Tyrosine sulfanilamide affinity chromatography was used to separate and purify CA II isoenzyme from human red blood cells, as previously described. After the isoenzymes had been purified, the protein levels were assessed at 595 nm as described formerly [66]. The esterase activity assay was used and absorbance measured at 348 nm using a Shimadzu spectrophotometer (UVmini-1240 UV–VIS) [67]. Acetazolamide was employed as a reference standard.

2.10. Determination of Inhibition Parameters

The IC_{50} was acquired from activity (%) versus plant concentration plots. Also, Lineweaver-Burk graphs [68] were employed for determination of K_i and inhibition types [69]. The K_i values were calculated and acquired from Lineweaver-Burk graphs [68].

2.11. Statistical Analysis

Each experiment is repeated for three times. The results are shown as mean SD. Tukey's post hoc test was used after the one-way ANOVA; differences were considered significant as $P<0.05$.

3. Results and Discussion

Phenolics are the most prevalent secondary metabolite in the plant's kingdom. As effective radical scavengers and metal chelators, these compounds have attracted a lot of recognition as potential natural antioxidants. According to reports, the redox characteristics, both singlet oxygen quenchers and hydrogen donors of phenol play significant role in the antioxidant activity of the compound. All plants contain phenolics, which are an integral and necessary component of the diet of people. They have drawn a great deal of interest for their biological activity, and include antioxidant properties [70]. On the other hand, the phenolic compounds known as flavonoids, which have been separated from a variety of plants, have antimicrobial, antioxidant, and other beneficial properties as well as the ability to block light. Since flavonoids have the capacity to both prevent the production of free radicals as well as the removal of free radicals and ROS, their antioxidant activity has drawn a lot of attention [71]. Turpentine, oleoresin, gum and mastic all describe similar substances. Contents of phenolic and flavonoid compounds in turpentine were calculated as 12.5 mg GAE/g and 38.852 mg QE/g, respectively. Total phenol and flavonoids in *Pistacia lentiscus* resin were found in a study likely to be flavonoid concentration was 30.52±1.10 mg/g quercetin equivalent, while phenol concentration was 9.92±0.27 mg/g [72]. The antioxidant capacity of methanol and acetone extracts of *Pistacia terebinthus* fruits was investigated by looking at their polyphenolic contents, its acetone and methanol extract's phenolic contents was measured 61.05±3.35, 122.78±0.02 (µg pyrocatechol equivalents/mg extract), respectively. Also, their flavonoid contents were measured 5.49±0.78, 22.60±0.96 (µg QEs/mg extract) [73]. In this study, it was shown that turpentine has higher phenolic and flavonoids than *Pistacia lentiscus* resin. These rich compounds also effect the antioxidant capabilities of the sample extract directly. turpentine has shown in this study, have comparable effective number of polyphenolics.

The LC-MS/MS technique was employed for determination the primary organic compounds in turpentine, using fifty-three phenolic compounds as standards [74]. The phenolic molecules were identified via comparison of their chromatographic characteristics, UV spectra, and MS data with reference compounds; only two compounds were detected. The components detected in ethanol extract of turpentine was protocatechuic acid (0.07 mg/g) and naringenin (0.025 mg/g). However, the other

standards of the technique were not recorded in ethanol extracts of turpentine. Research was conducted to identify the antihyperlipidemic and antioxidant abilities of protocatechuic acid in diabetic rats caused by streptozotocin. The outcomes showed that protocatechuic acid therapy has therapeutic effects by lowering oxidative stress and lipid profile. protocatechuic acid's impact was equivalent to that of glibenclamide, a well-known hypoglycemic medication [75]. Treatment with PCA at 50 mg/kg remarkably enhanced locomotor and motor activity such as rat's average speed, total time spent moving, distance traveled, body rotation, turn angle, forelimb grip, and grooming, in comparison to untreated diabetic rats. The antioxidant, anti-inflammatory, and anti-apoptotic properties of PCA are connected to its neuroprotective functions [76]. The existence of two phenolic acids, 4-hydroxybenzoic acid and protocatechuic acid, was also discovered in previous research. For the first time, the latter was identified as the major phenolic acid in *P. lentiscus* fruits. We also detected protocatechuic acid in present research in *P. vera* L. cv. Siirt. Naringenin, a flavonoid had measured in high amounts as its glycone naringin in citrus fruits [77,78], possesses antioxidant, antiatherogenic, anti-dyslipidemia, and anti-diabetic properties. It has been demonstrated that naringenin has anti-diabetic effects via inhibiting gluconeogenesis via protein kinase activated by adenosine monophosphate activation, resulting in metformin-like actions. Naringin, like metformin, has been demonstrated to have non-glycemic effects that reduce inflammation and cell proliferation [79]. Another study which was done with rats, reveals the antidiabetic, antioxidant, and antiapoptotic capabilities of naringenin, which might prevent diabetic retinopathy-related retinal damage by offering neurotrophic support, hence limiting neurodegeneration [80].

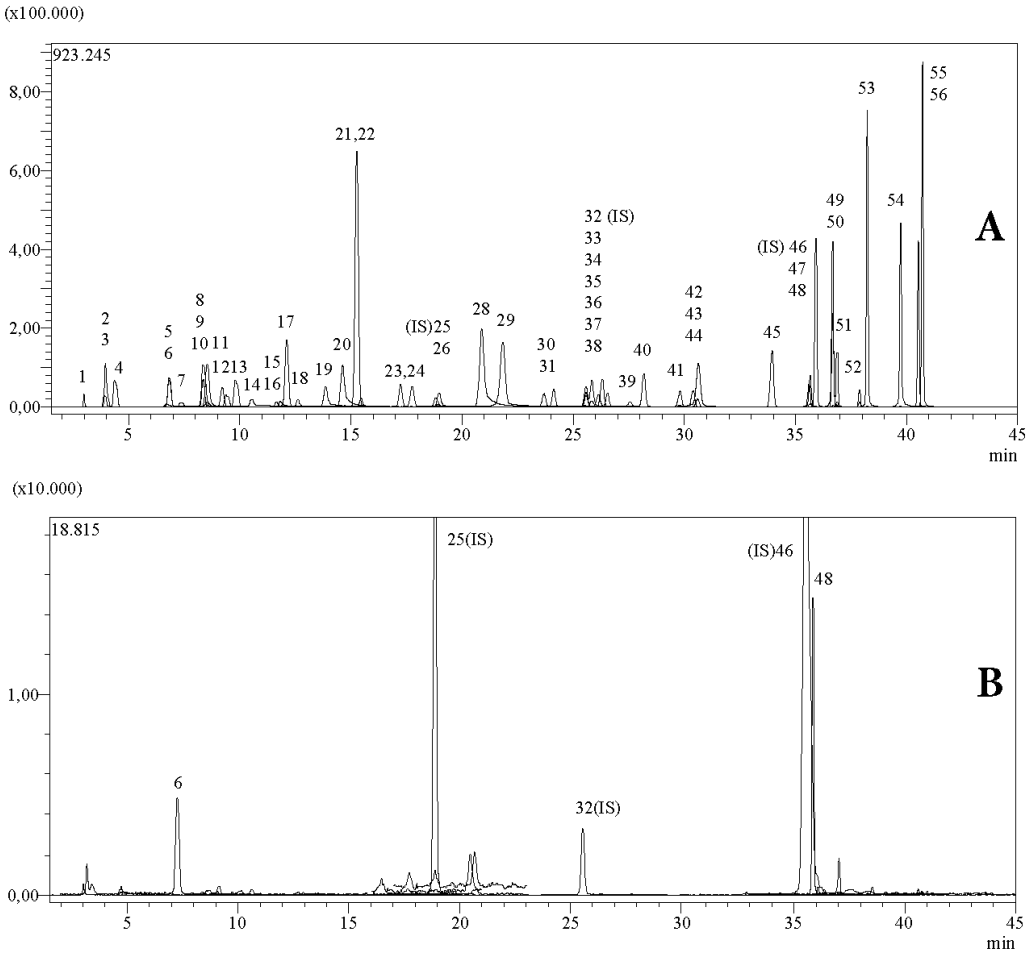

Figure 1. A) Chromatogram showing all the standard phenolic compounds that were examined using the LC-MS/MS technique. **B)** Chromatogram of Turpentine ethanol extract's compounds. 6. Protocatechuic acid, 48. Naringenin

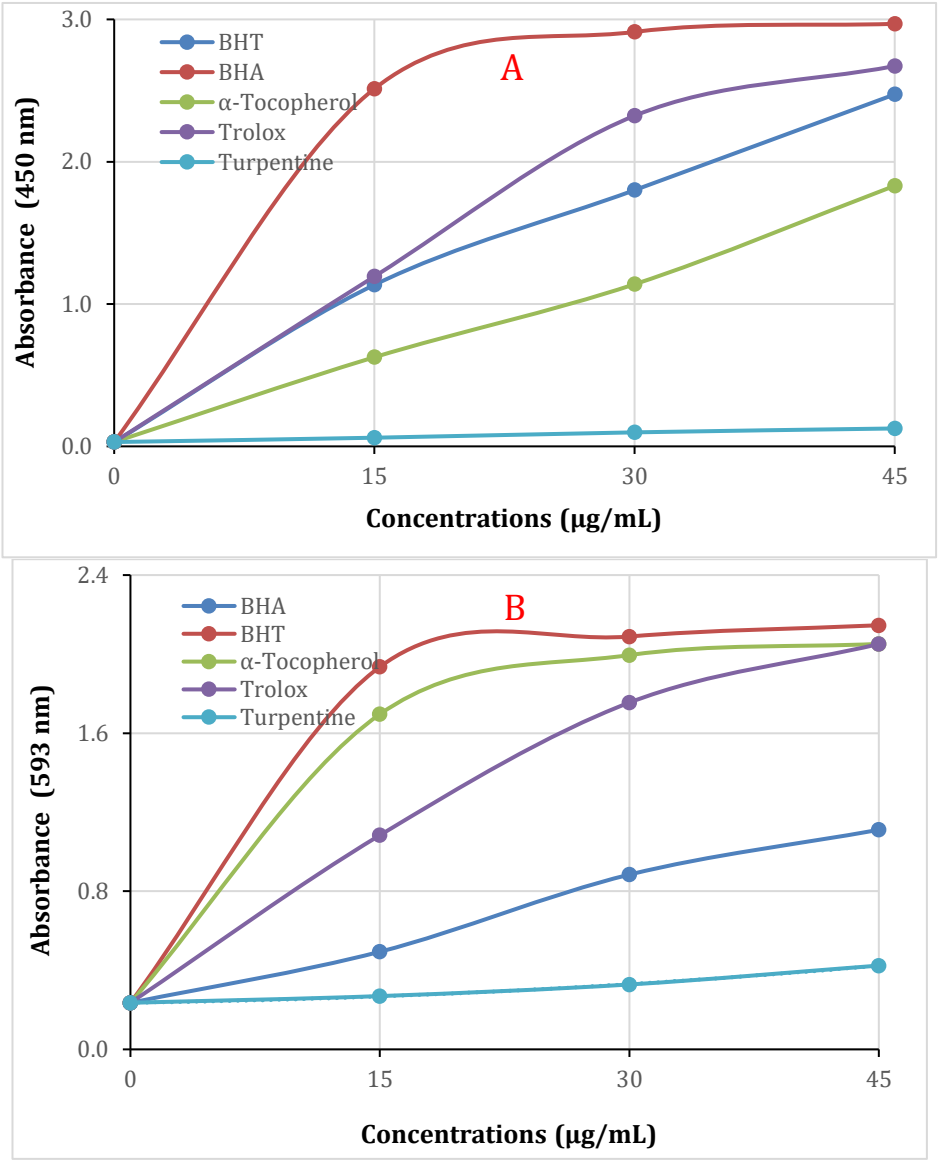

Figure 2. Cu^{2+} ions reducing ability **(A)** and Fe^{3+}-TPTZ reducing ability **(B)** of turpentine and standards.

The reduction capability of a molecule might be an essential indicator of its antioxidant action. Reactive radical species can be converted into more steady and unreactive categories by accepting electron contributions from antioxidant substances [81]. The phenolic compounds' possible reduction sources extracted from turpentine were investigated by using the reducing abilities of CUPRAC and Fe^{3+}-TPTZ. Also, ABTS and DPPH radical scavenging assays were utilized to evaluate the turpentine's radical removing properties. Natural compounds may possess reducing properties, neutralizing oxidants and ROS. The complex of Cu(II)-Neocuproine is decreased in the existence of antioxidants to the chromogenic oxidant neocuproine, which exhibits absorption at 450 nm, in the CUPRAC assay [82]. Cu^{2+} reducing capabilities of phenolic compounds in turpentine are given in Table 1 and Figure 2A. At 30 µg/mL, the important absorbance of reducing power was observed by phenolic compounds in turpentine. However, Cu^{2+} ions reducing ability of turpentine and standards were measured as follows: BHT (2.912±0.012, r^2: 0.9969) > Trolox (2.323±0.049, r^2:0.9935) > BHA (1.800±0.156, r^2: 0.9742) > α-Tocopherol (1.139±0.096, r^2: 0.9980) > Turpentine (0.098±0.003, r^2:0.9970). These results when compared to the literature, turpentine of pistachio (*Pistacia vera* L.) belonging to Gaziantep region had absorbance of 0.158 ± 0.03 at 30 µg/mL [2]. The Cu^{2+} ions reducing ability of turpentine and pistachio

gum samples were comparable. The Cuprac antioxidant method is a convenient, inexpensive, selective, fast and stable for a variety of antioxidants.

The FRAP test might be utilized to determine the total reducing ability of antioxidant substances or plants. A ferric solution is used as an oxidant in the electron transfer procedure that underpins the FRAP assay. The reducing capabilities of bioactive molecules can be ascertained using this method very effectively. In a preliminary redox-linked colorimetric reaction, the FRAP test utilizes the antioxidants in the sample as reductants. Furthermore, the FRAP test method is straightforward to standardize and easy to follow. Additionally, it has been applied to evaluate the antioxidant power of polyphenols. Depending on how powerful reducing agent are the yellow color of the assay mixture shifts to a variety of green and blue in this test. A compound's reducing capacity might be a good indicator of its potential antioxidant action [82]. The Fe^{3+}-TPTZ reducing ability was utilized to estimate the reducing capabilities of turpentine and standards. According to the outcomes given in Table 1 and Figure 2C, the reduction powers of the samples decreased in the following order: BHT (2.089±0.027, r^2: 0.9581) > α-Tocopherol (1.995±0.016, r^2: 0.9807) > Trolox (1.755±0.093, r^2: 0.9990) > BHA (0.884±0.116, r^2: 0.9899) > turpentine (0.328±0.020, r^2: 0.9996). These results were recorded with the 30 µg/mL of turpentine. According to the previous study, at 30 mg/mL of pistachio gum, the FRAP assay's findings for the Fe^{3+} to Fe^{2+} reduction capability was (0.530±0.07) [2]. The Fe^{3+}-TPTZ reducing capacity of turpentine were not too different from pistachio gum reducing capacity. The high absorbances reflect the better reducing ability of the test materials' capacity to. On the other hand, turpentine of pistachio (*Pistacia vera* L.) belonging to Gaziantep region had absorbance of 0.530 ±0.07 at 30 µg/mL [2].

Table 2. The Cu^{2+} and Fe^{3+}-TPTZ reducing effects of 30 µg/mL turpentine and standards

Antioxidants	Cu^{2+}-Cu^{+} reducing		Fe^{3+}-TPTZ reducing	
	λ_{450}	r^2	λ_{593}	r^2
BHA	1.800 ± 0.156	0.9742	0.884 ± 0.116	0.9899
BHT	2.912 ± 0.012	0.9969	2.089 ± 0.027	0.9581
α-Tocopherol	1.139 ± 0.096	0.9980	1.995 ± 0.016	0.9807
Trolox	2.323 ± 0.049	0.9935	1.755 ± 0.093	0.9990
Turpentine	0.098 ± 0.003	0.9970	0.328 ± 0.020	0.9996

The antioxidant properties of natural compounds, foods, and herbs are frequently assessed using spectrophotometric techniques based on radical scavenging. The $ABTS^{\bullet+}$ and DPPH· scavenging techniques are also quick, easy, picky, and repeatable processes. They are therefore frequently used to describe the capacity for radical elimination. The green-blue $ABTS^{\cdot+}$ and violet DPPH· chromogens are simple to use and have great sensitivity. Antioxidant capacity is frequently evaluated using the process of converting $DPPH^{\bullet}$ to DPPH-H, is the basis of the $DPPH^{\bullet}$ test. The peak of absorption for a freshly made DPPH solution is at 517 nm, and it has a deep purple hue. When there is an antioxidant in the medium, this purple color usually goes away. Because of the antioxidant's action, the reduction in absorbance is a measurement of the free DPPH [69,71]. If turpentine is capable of scavenging DPPH·, then it may naturally possess antioxidant properties. The IC_{50} value for turpentine was calculated after its DPPH· scavenging activity was tested (Table 2, Figure 3 A). The radical scavenging abilities of turpentine were concentration-dependent. The IC_{50} values of turpentine and references including Trolox, α-tocopherol, BHT, and BHA were 346.6 µg/mL for turpentine, 21.00 µg/mL for BHT, 9.00 µg/mL for BHA, 9.63 µg/mL for Trolox, and 5.92 µg/mL for α-tocopherol (Table 2). Likely as seen in this study, turpentine has a lower antioxidant potential when compared with standard antioxidants and results of different studies given. In another study, a significant scavenging of DPPH radical due to scavenging ability of *Pistacia vera* was 23.9 µg/mL [2].

In an ABTS/$K_2S_2O_8$ system, ABTS radicals ($ABTS^{\bullet+}$) were generated. The test uses a decolorization method in which the radical is produced directly in a steady state before being exposed to potential antioxidants. In the developed assay for making $ABTS^{\bullet+}$ described here, potassium persulfate reacts with ABTS to directly performed the blue/green $ABTS^{\bullet+}$. One of the spectrophotometric techniques used to measure the total antioxidant activity of pure components, aqueous mixtures, and beverages is based on the generation of the ABTS radical cation [70]. The IC_{50}

values samples were found as 231.1 µg/mL for turpentine, 7.71 µg/mL for BHT, 7.71 µg/mL for BHA, 8.10 µg/mL for Trolox, 7.71 µg/mL for α-tocopherol (Table 2 and Figure 3B). When compared to standards, it was shown that turpentine has low $ABTS^{\bullet+}$ scavenging activity. A lower IC_{50} value, as in DPPH and ABTS free radical scavenging action.

Similar to commercial BHA, the resin appears to be equally effective at 0.05% [5]. Resin of *P. lentiscus* has very little ability to scavenge DPPH radicals, with only 37% inhibition in 1.6 mg/mL. Vitamin C, quercetin and BHA had IC_{50} values of 1.26 ± 0.11, 1.32 ± 0.07 and 13.49±1.04 µg/mL, respectively [83]. The scavenging effect of laccase obtained from *P. atlantica*'s resin at all doses was recorded dose-dependent. Laccase and BHA both had IC_{50} values of 46±0.5 and 32±0.3 µM, respectively, against $DPPH^{\bullet}$. Additionally, the IC_{50} values towards $ABTS^{\bullet+}$ for vitamin C and laccase were estimated to be 20±0.2 and 29±0.4 µM, respectively [84]. *P. atlantica* oil remarkably enhanced antioxidant shielding and hydroxyproline levels, and decreased malondialdehyde levels, according to studies on how well *P. atlantica* resin oil affected the healing of burn wounds in rats as well as its potential effects on hydroxyproline, and antioxidants in the wound area [85]. One of the natural compounds historically used for the treatment of wounds is *P. vera* oleoresin. The results of the study tend to support the traditional use of *P. vera* oleoresin in wound healing since they demonstrate their extremely high efficacy as wound healing agents [86]. By using the DPPH and ABTS tests, the essential oils of *P. lentiscus* derived from the leaves and fruits were shown to have IC_{50} values of 29.64±3.04 and 73.80±3.96 µg/mL for their antioxidant properties, respectively. Also, showed IC_{50} values of 113.72±7.91 and 38.72±6.18 µg/mL, respectively, in tests of ABTS and DPPH [87]. Turpentine of *Pinus nigra* was also reported to scavenge significant DPPH radicals in another study of ours [7]. It was found that the IC_{50} value of turpentine of pistachio (*Pistacia vera*) belonging to Gaziantep region for DPPH radical scavenging was found to be 23.9 µg/mL [2].

Table 3. The half maximum concentration (IC_{50}, µg/mL) values for $DPPH^{\bullet}$ and $ABTS^{\bullet+}$ scavenging of turpentine and standards.

Compounds	DPPH• scavenging		$ABTS^{\bullet+}$ scavenging	
	IC_{50}*	**r^2**	**IC_{50}***	**r^2**
BHA	9.00	0.9399	7.71	0.9330
BHT	21.00	0.9668	7.71	0.9330
α-Tocopherol	5.92	0.9770	7.71	0.9330
Trolox	9.63	0.9947	8.10	0.9550
Turpentine	346.6	0.9885	231.1	0.8927

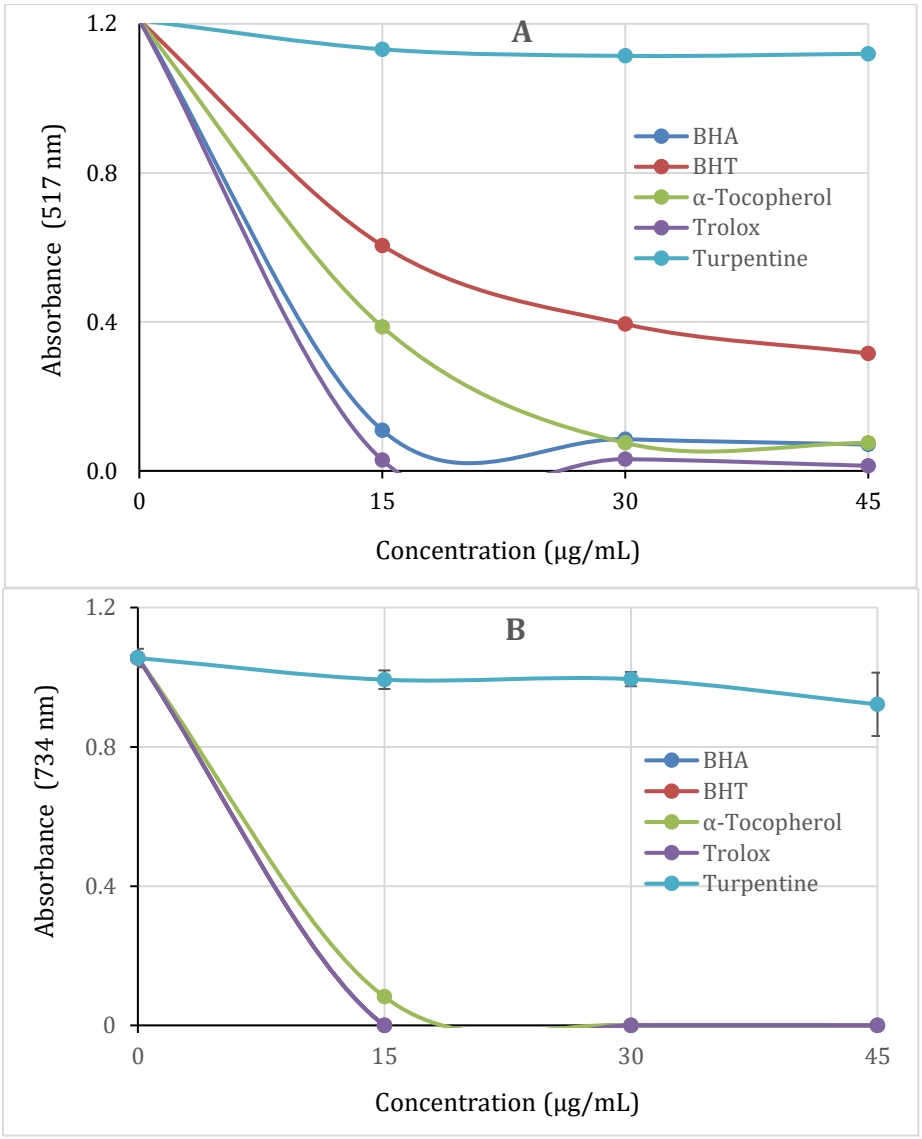

Figure 3. Radical scavenging effects of turpentine and positive controls. **A)** DPPH radical scavenging ability, **B**) ABTS radical scavenging ability.

α-Glycosidase enzyme is linked to diabetes and essential for the metabolism of carbohydrates. It is thought to be a promising drug target due to its wide range of biological functions [88,89]. There are currently being studied a number of α-glycosidase inhibitors (AGIs). Two frequently given diabetic drugs, acarbose and miglitol, competitively restrain the small intestine brush border α-glycosidase. This lessens postprandial hyperglycemia and stops the hydrolysis of carbohydrates. AGIs may be key components of the curative strategy for T2DM. Controlling of blood glucose level elevation may slow the development of secondary issues-related diabetic ailments, which are associated with postprandial hyperglycemia, a remarkable and prior complication in diabetes [88]. As seen in Table 3, turpentine has IC_{50} value 2.4 µg/mL towards α-glycosidase. According to the results, turpentine's inhibitory effect was comparable to acarbose (IC_{50}: 22.800 nM) as a typical α-glycosidase inhibitors (Figure 4).

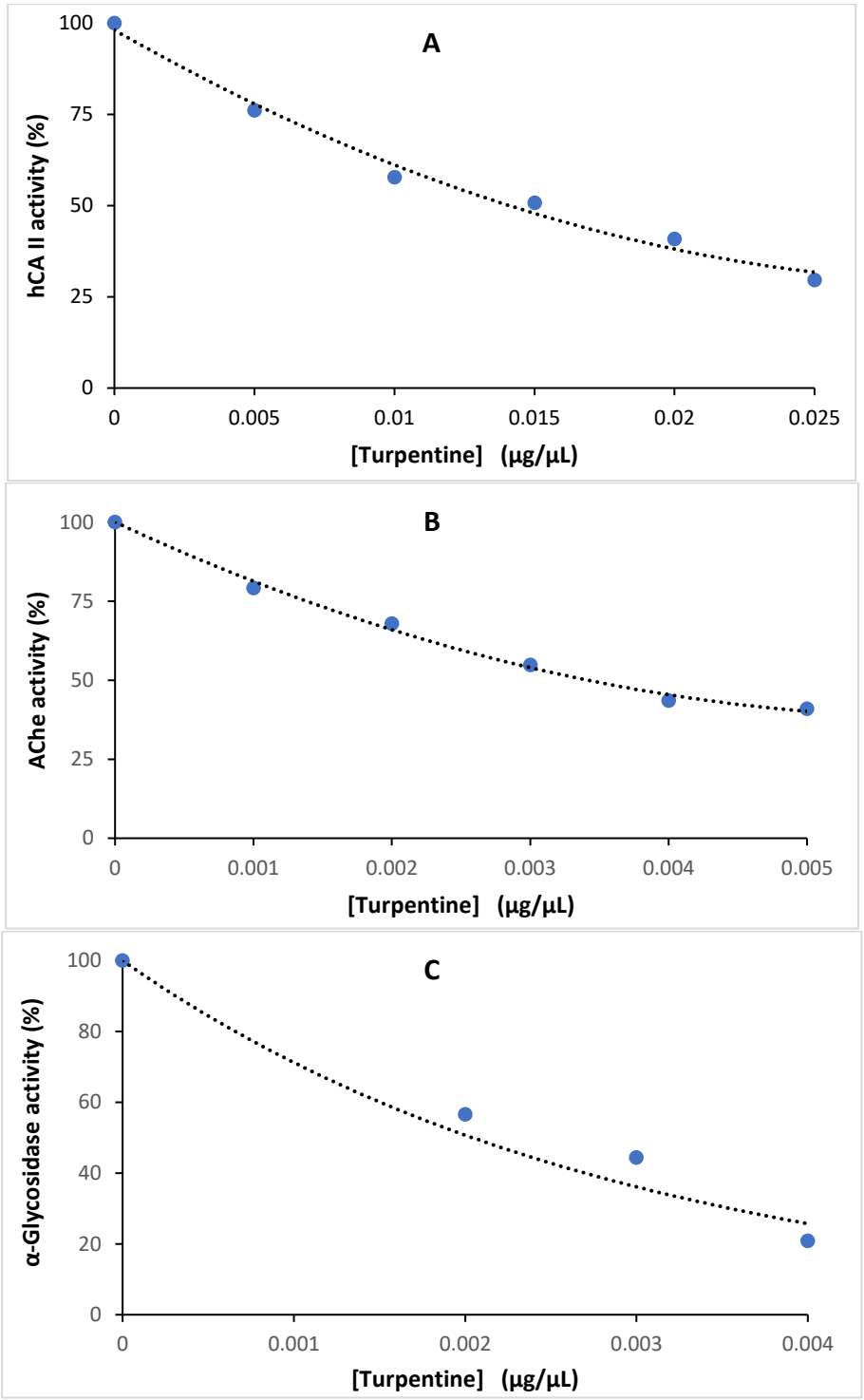

Figure 4. Half maximal inhibition concentration (IC_{50}) of turpentine against carbonic anhydrase II (**A**), acetylcholinesterase (**B**), and α-glycosidase (**C**) enzymes.

Essential oil of *Pistacia atlantica* exhibited inhibitory action against α-glycosidase with IC_{50} value of 41.5±2.5 mg/mL comparison to acarbose (IC_{50}: 0.5±0.2 mg/mL) [89]. In diabetic rats, glibenclamide and raw *P. lentiscus* gum treatments were tested for their effects. Because it lowers glucose levels in serum of diabetic rats and increases glucose tolerance, the crude *P. lentiscus* gum has antihyperglycemic activity [90]. Both masticadienonic acid and isomasticadienonic acid preferentially restrained 11β-hydroxysteroid dehydrogenase I over to the 11β-hydroxysteroid dehydrogenase, at low

micromolar concentrations. These results imply that *Pistacia lentiscus* var. chia oleoresinous gum, widely known as mastic gum, exerts its anti-diabetic effects in part by inhibiting 11-hydroxysteroid dehydrogenase [91]. According to the research, flour of *P. atlantica* fruit, used as a supplementary therapy, lowers blood glucose and lipid levels in T2DM patients with hyperlipidemia [92]. The mechanism of ameliorating effects of extracts of Pistacia species in animal and human diabetes was demonstrated in our laboratory study by an *in vitro* α-glycosidase inhibition study.

The utmost common and important reason for dementia in older people is AD, as well as the most common neurodegenerative illness. A reduction of AChE levels in the brain is the most major biochemical alteration linked with AD [60]. There is evidence that when acetyltransferase and choline (Ch) levels decrease, acetylcholine (ACh) declines as a neurotransmitter. As a result, studies on the treatment of the condition as a symptomatic intervention have focused on cholinesterase (ChE) inhibitors [93-95]. AD treatment involves the use of AChE inhibitors including donepezil, tacrine and rivastigmine. However, those medicines have a number of adverse reactions. As a result, novel strong antioxidants and AChE agents are urgently needed. It was also discovered that phenolic compounds and, to a lesser extent, aliphatic molecules had the strongest AChE inhibitory effects [96]. Although AChE inhibitors are used for treatment of AD, they only provide temporary relief. ChE inhibitors have usually been abundant in medicinal plants [97,98]. The AChE inhibition level of turpentine is higher when compared to tacrine, a prevalent positive. Table 3 recapitulates the IC_{50} values of turpentine for enzyme inhibition. The IC_{50} value for turpentine against AChE enzyme inhibition found as 3.59 µg/mL compared with Tacrine (Table 3). IC_{50} value of Tacrine was 5.97 µg/mL, it served as the experimental control in the inhibition experiment for AChE enzyme.

The *P. atlantica* leaves' methanol and ethylacetate extracts were evaluated for their antioxidant capacities and AChE inhibition. According to these findings, the plant exhibits a potent antioxidant activity and a weak *in vitro* AChE inhibitory action. Before this study, no reports about AChE inhibition of Pistacia species. In this investigation, IC_{50} values were given for the methanol (60.33±0.08 µg/mL) and ethyl acetate (31.51±0.29 µg/mL) extracts [99]. The phenolic content of *P. terebinthus* leaves methanol extract was found to be the highest. Likewise, methanol extract had α-glycosidase and AChE enzyme inhibitory abilities and the strongest antioxidant activities. AChE inhibition using turpentine gave better results than the reference inhibitor. In this study, it was shown in Table 3 that turpentine effectively inhibited the AChE enzyme.

The widely prevalent cytosolic isoform CA II, which has a role in a number of disorders including epilepsy, oedema, glaucoma, hypertension, osteoporosis and altitude sickness is physiologically dominant [100-102]. Reduced HCO_3^- production and aqueous humor secretion as a result of CA II suppression decrease ocular pressure. The multifactorial optical illness known as glaucoma is defined by the degeneration of the optical nerve, which is primarily linked to elevated IOP, which can lead to blindness. Novel therapeutic considerations are necessary since hCA II inhibitors such as dorzolamide acetazolamide, and brinzolamide are successful at decreasing IOP following topical therapy [103]. Furthermore, besides glaucoma CA II is frequently associated with a variety of diseases, such as renal tubular acidosis and osteoporosis. The CA inhibitory effects of the turpentine were examined, and the outcomes are shown in Table 3. IC_{50} values of turpentine were found as 14.6 µg/mL towards CA II isoenzyme, and efficient in comparison with its reference standard of acetazolamide (AZA) (IC_{50} was 8.37 µg/mL), which employed as a reference standard for the CA II isoform inhibition [104]. With this study, a contribution to the literature has been made about the CA II isoenzyme inhibition by turpentine. The results of the study show that turpentine can be useful in the treatment of glaucoma when the appropriate use is adjusted.

Table 4. IC_{50} values (μg/mL) of turpentine against human carbonic anhydrase II isoenzyme (hCA II), acetylcholinesterase (AChE), and α-glycosidase enzymes

Compounds	hCA II		AChE		α-Glycosidase	
	IC_{50}*	r^2	IC_{50}*	r^2	IC_{50}*	r^2
Turpentine	14.6	0.9880	3.59	0.9950	2.04	0.9922
Acetazolamide*	8.37	0.9825	-	-	-	-
Tacrine**	-	-	5.97	0.9706	-	-
Acarbose***	-	-	-	-	22800	-

*It was used as reference for CA II isoenzyme
**It was used as reference for AChE enzyme
***It was used as reference for α-glycosidase enzyme

4. Conclusions

This study was carried out antioxidant, antidiabetic, anti-Alzheimer, and antiglaucoma effects of *Pistacia vera* L. cv. Siirt turpentine. These effects were compared to stands including BHA, BHT, α-tocopherol and trolox (for antioxidant activity), acarbose (for antidiabetic effect), tacrine (for anti-Alzheimer's disease ability) and acetazolamide (for antiglaucoma activity). Total phenolic and flavonoid contents of *Pistacia vera* L. cv. Siirt turpentine were calculated as gallic acid and quercetin equivalents. Also, the quantity of phenolic profile was determined using LC-MS/MS chromatography technique. Antioxidant activity *Pistacia vera* L. cv. Siirt turpentine was evaluated using DPPH and ABTS radical scavenging, cupric ions and FRAP reducing capacities. It is also the first and comprehensive enzyme inhibition ability *Pistacia vera* L. cv. Siirt turpentine were tested against α-glycosidase, AChE and CA II enzymes. The products of *Pistacia vera* plant are widely used as food, pastry, dessert and daily nut. However, the content of turpentine, which leaks from the trunks of these trees for different reasons and provides antibacterial protection to the plant itself, also has important phenolic and flavonoid compounds. Although their antioxidant and reducing capacities are weak when compared to synthetic antioxidants. When the dose is increased, since it is a natural product, the safety range can be achieved and no adverse effects are observed. In recent years, due to the limitation of the use of synthetic antioxidants, it has been examined in the context of alternative search studies. In vitro, cell cultures and animal experiments also show that when different extraction methods are applied, the phenolic and flavonoid compounds in their contents can be released and used in medicine. These extracted compounds can be used alone as well as functional together. We determined that turpentine has significant antioxidant, antidiabetic, anti-AD and antiglaucoma effects. The main components in turpentine, as discovered by the LC-MS/MS technic were found as protocatechuic acid and naringenin. Furthermore, turpentine has phenolic and flavonoid contents and could effectively inhibit the AChE, α-glycosidase, and hCA II enzymes. So, turpentine of *Pistacia vera* L. cv. Siirt is a natural remedy that may be used to treat T2DM, AD, glaucoma and metabolic diseases, as well as in the pharmaceutical and food industries, with antioxidant activity, reducing ability and radical scavenging properties. The use of turpentine for pharmacological purposes in individuals with the diseases we have stated, can be sustained by clinical pharmacology studies.

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