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Analytical profiling of vescalagin: Antioxidant Capacity and multi-enzyme inhibition spectrum

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ABSTRACT

Vescalagin have been isolated from Camu-camu (*Myrciaria dubia*). Vescalagin compound was a found to be the main C-glycosidic ellagitannin with a bridging open ring D-glucose. A variety of techniques were used to assess vescalagin's antioxidant capacity, including its capacity to reduce potassium ferric cyanide, scavenge N,N-dimethyl-p-phenylenediamine dihydrochloride radicals ($DMPD^{\bullet+}$), scavenge 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulphonate) radicals ($ABTS^{\bullet+}$), scavenge 1,1-diphenyl-2-picrylhydrazyl radicals ($DPPH^{\cdot}$), and reduce cupric ions (Cu^{2+}). Likewise, butylated hydroxyanisole (BHA), Trolox, α-tocopherol, and butylated hydroxytoluene (BHT) were employed as reference antioxidants for assessment. For DPPH radical scavenging, vescalagin had an IC_{50} value of 9.65 μg/mL (r^2: 0.9225), while the IC_{50} values for BHA, BHT, α-Tocopherol, and Trolox were 10.10, 25.95, 11.31, and 7.05 μg/mL properly. The resarch revealed that vescalagin reacted better than BHA, α-tocopherol, and BHT with regard to $DPPH^{\cdot}$ scavenging, but nearly similiar to Trolox. Vescalagin was also shown to be a polyphenolic secondary metabolite that inhibited a number of metabolic enzymes, particularly α-glycosidase, carbonic anhydrases I and II (CA I and II), butyrylcholinesterase (BChE), and acetylcholinesterase (AChE). The Ki values of vescalagin showed 5.87, 3.89, 11.75, 16.23, and 16.08 nM towards AChE, BChE, hCA I, hCA II, and α-glycosidase, respectively. These enzymes are linked to several ilness such as diabetes, Alzheimer disease (AD), epilepsy and glaucoma. The obtained findings clearly indicate that vescalagin can be used as a reference polyphenolic antioxidant or enzyme inhibitor in analytical and screening assays.

1. Introduction

Vescalagin is a hexahydroxydiphenol found in unripe wax apple fruit (Fig. 1). It is a member of the ellagitannin family, which has a distinct set of highly hydrosoluble C-glycosidic variations [1]. The hydrolysable tannins in old wines, Castalagin and Vescalagin, which migrate from the wood for the drinks, make up 40–60 % of the tannins found in oak wood. Additionally, they can be found in some teas, *Myrciaria dubia*, and chestnuts [2]. Vescalagin, an ellagitannin, is found in the fruit of the pink wax apple (*Syzygium samarangense*). Biologically active polyphenols called ellagannins have anti-inflammatory and antioxidant properties. According to reports, Vescalagin possesses anticancer, cardiovascular disease prevention, insulin-resistance alleviation, and dyslipidemia mediating properties [3]. Vescalagin, a substance that belongs to the ellagitannin family, has demonstrated antibacterial action against *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Staphylococcus epidermidis* [4]. Particularly, the hydrolysable tannins Castalagin and Vescalagin are commonly present in oak bark and wood [5]. Many plants have been found to contain Vescalagin/Castalagin molecules, which are two isomers of C-glycosidic ellagitannins that vary solely in their stereochemistry at location C6 of the glucose core [6]. Castalagin is the result of the isomerization at C-1 that occurred when an aqueous solution of Vescalagin was heated [7].

The two types of tannin molecules are hydrolysable and condensed. The former is exhibited by flavonoid polymers, whilst the latter is made up of a sugar moiety that is joined to gallic and ellagic acid units by an

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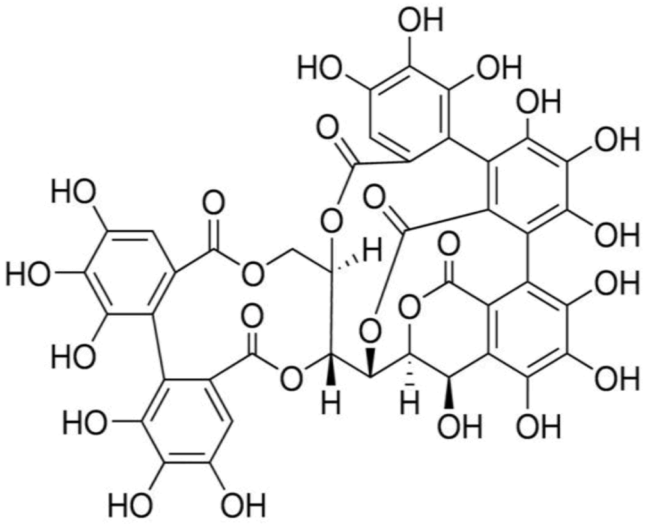

Fig. 1. The molecule structure of Vescalagin.

ester bond to create gallotanins and ellagitannins. Vescalagin and Castalagin are the primary members of this family; they are positional isomers that differ solely in the location of the OH-group at the C1 of the glycosidic chain [8]. Acids, bases, and enzymes easily break down gallotannins and ellagitannins, the main components of hydrolyzable tannins, to provide gallic and ellagic acids, respectively [9]. Gallotannins are phenolic substances that exist naturally and are members of the hydrolysable tannin class. They come in a range of shapes and sizes and are found across the kingdom of plants. Condensation of one or more gallic acids to a polyol core, such as D-glucose, is a characteristic structural feature of gallotanins [10].

Excessive reactive oxygen species (ROS) and reactive nitrogen species (RNS) can cause oxidative and nitrosative stress and damage the neuronal membrane. The metabolic reaction known as "nitrification stress" is brought on by RNS formed from nitric oxide (NO) and ROS. This reaction causes the aromatic rings of residues of amino acids to be hydroxylated, which can cause apoptosis or other harmful consequences in cells [11]. A rise in ROS in living things, which are known to have an equilibrium between oxidants and antioxidants, causes oxidative stress. The use of antioxidants from outside sources is essential since variables like stress, air pollution, diabetes, and chronic illnesses damage the antioxidant defense system. Consuming dietary items with antioxidant qualities is therefore crucial to lowering oxidative damage [12]. ROS have been shown to cause numerous pathophysiological conditions, such as diabetes, inflammatory diseases, oxidative stress, malignancies, cardiovascular problems, and arthritis [13]. Although ROS and RNS have a limited lifespan, unchecked redox reactions constantly produce new ROS, and RNS are thought to have a role in common illnesses, like, diabetes, cancer, age-related macular degenerations, and neurodegenerative diseases including Alzheimer and Parkinson's diseases [14]. Antioxidants, however, may delay or decrease oxidative damage, preventing and/or treating diseases brought on by oxidative stress. Enzymatic antioxidants and non-enzymatic antioxidants are two well-known categories into which antioxidants can be classified [15]. The oxidative pathways that lead to degenerative disorders are suppressed by antioxidants such as flavonoids, phenolic acids, tannins, and phenolic diterpenes because they scavenge free radicals like lipid peroxyl, hydroperoxide, and peroxide radicals [16]. Strong defenses against free radical attacks, which are the primary cause of serious health issues, can be found in antioxidant compounds. Therefore, finding novel sources of antioxidants is essential to curing the degenerative diseases listed above. Certain chemicals, like butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT), were chemically manufactured and utilized in the chemical industry; nevertheless, their possible hepatotoxicity and carcinogenic effects on humans have raised public concerns about their use [17]. Phenolic ingredients are a wide range of compounds that arise naturally and are present in many plant structural components. The body's immune system is protected from the damaging effects of free radicals by their exceptionally strong antioxidant properties. Thus, consuming them prevents the antioxidative balance from being upset, which in turn reduces the risk of developing numerous illnesses, such as cancer, heart disease, diabetes, and neurological disorders [18]. Multiple in vitro and in vivo studies have suggested that plant extracts, fruits, and their secondary metabolites may help avoid diabetes and neurological problems [19]. Therefore, plant-based polyphenolic antioxidant molecules should be used instead of synthetic antioxidants that are made chemically.

Comprehensive characterization of phenolic compounds increasingly relies on multi-assay analytical profiling, where antioxidant capacity and enzyme inhibition measurements are integrated to generate a reproducible "bioanalytical signature" under standardized conditions [20–23]. In this context, enzyme inhibition assays serve as screening and benchmarking platforms, allowing potency ranking and selectivity comparisons across chemically diverse natural products using validated reference inhibitors [24–26].

Among the most frequently implemented in vitro targets in such platforms are α-glycosidase, AChE, BChE, CA I, and CA II, owing to their robust assay formats, clear catalytic endpoints, and extensive use in comparative inhibition studies [27–31]. For carbohydrate-hydrolyzing enzymes, reference inhibitors such as miglitol, 1-deoxynojirimycin, voglibose, and acarbose are routinely employed to support calibration and cross-study comparability [32–35]. Cholinesterase assays similarly benefit from well-established reference compounds (e.g., tacrine, galantamine, rivastigmine, and donepezil) that enable standardized benchmarking of inhibitory profiles [36–38]. Likewise, CA I and CA II inhibition assays are widely used in analytical screening settings, supported by commonly applied CA inhibitors (e.g., acetazolamide, methazolamide, dorzolamide, and brinzolamide) as reference standards [39, 40]. The standard inhibitors used in this study for CA I, CA II, AChE, BChE, and α-glycosidase assays are presented in Fig. 2.

Accordingly, the present work employed these assays to provide an analytical and screening-oriented characterization of Vescalagin. Testing vescalagin across the selected enzyme panel enables definition of its multi-enzyme inhibition spectrum and facilitates comparative benchmarking against routinely used reference inhibitors under controlled conditions [41]. Together with the antioxidant measurements, this integrated profiling improves the analytical relevance of the study and supports the use of Vescalagin as a reference polyphenolic antioxidant and enzyme inhibitor in future assay development and screening applications.

In this study, enzyme inhibition assays were included primarily to support an analytical and screening-oriented profiling of vescalagin rather than to imply therapeutic efficacy. The selected enzymes (e.g., AChE, BChE, CA I, CA II and α-glycosidase) are among the most frequently used in vitro screening targets in natural product and polyphenol research, enabling standardized comparison of inhibitory potency across different compound classes. Accordingly, evaluating Vescalagin against this panel allows us to define its multi-enzyme inhibition spectrum under controlled assay conditions and to benchmark its performance against commonly used reference inhibitors. This comparative approach provides practical value for analytical assays and early-stage screening workflows, where vescalagin may serve as a reference polyphenolic antioxidant and/or enzyme inhibitor.

So, within this research, we investigated the antioxidant, antidiabetic, anti-Alzheimer, and anti-glaucoma properties of Vescalagin at different concentrations by some utilized antioxidant assays, Fe^{3+} reducing, Cu^{2+} reducing, scavenging outcomes of $ABTS^{\bullet+}$, $DMPD^{\bullet+}$, and $DPPH^{\bullet}$. This study aimed to investigate the possible inhibitory effects of Vescalagin on α-glycosidase, AChE, BChE, CA I, and CA II enzymes, which are linked to prevalent illnesses such T2DM, AD, and glaucoma.

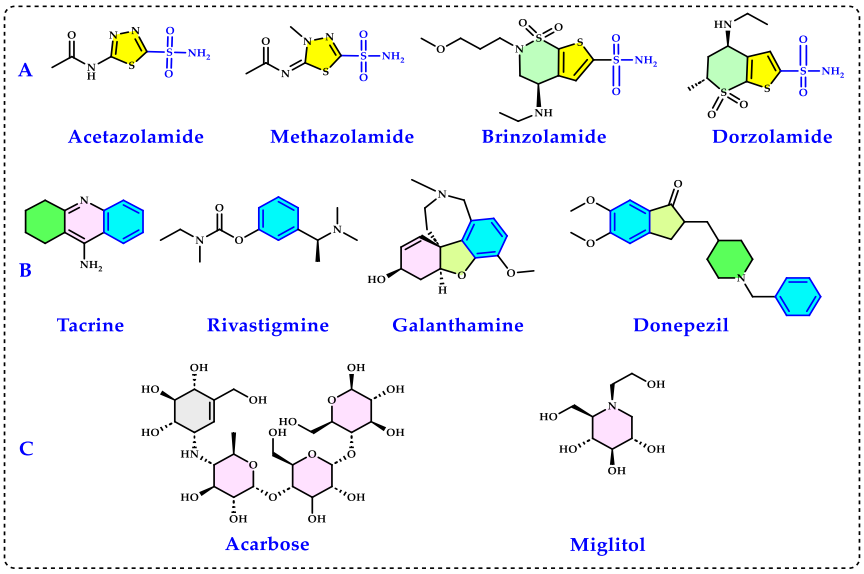

Fig. 2. Commonly utilized standard inhibitors were provided for the carbonic anhydrase isoenzymes I and II (CA I and CA II) (A), acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) (B) and α-glycosidase (α-Gly) enzymes (C).

2. Materials and methods

2.1. Chemicals

Sigma-Aldrich Chemie GmbH (Steinheim, Germany) provided commercially available compounds, such as Vescalagin (CAS No: 36,001-47–5, ≥95.0 %), tacrine CAS Nno: 206,658-92–6, ≥99 %), acetazolamide (CAS no: 59–66–5, ≥99 %), α-tocopherol CAS no: 10,191-41–0, ≥95.5 %), butylated hydroxytoluene (BHT, CAS no: 128–37–0, ≥99 %), butylated hydroxyanisole (BHA, CAS no: 25,013-16–5, ≥98.5 %), Trolox CAS no: 53,188-07–1, ≥98.0 %), 1,1-di(4-tert-octylphenyl)-2-picrylhydrazyl free radical (DPPH·, CAS no: 84,077-81–6, ≥95.0 %), 2,2-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS, CAS no 30,931-67–0, ≥98.0 %), and N,N-dimethyl-p-phenylenediamine dihydrochloride (DMPD, CAS no: 536–46–9, ≥99 %).

2.2. Reducing ability assays

In accordance with previous research [42], Vescalagin capability to reduce Fe^{3+} was achieved. According to prior work, the Fe^{3+}-reducing effect of vescalagin was completed. The absorbance readings for references and Vescalagin were recorded at 700 nm [43]. The Apak et al. [44]. approach was applied to evaluate Vescalagin ability to reduce Cu^{2+} ions. Following the appropriate analytical procedures, the absorbances at 450 nm were spectrophotometrically detected.

2.3. Radical scavenging activities

The $DPPH^{\bullet}$ scavenging capability of Vescalagin was measured utilizing the Blois technique [45]. The remaining DPPH· absorbance was measured at 517 nm [46]. Additionally, Vescalagin's $ABTS^{\bullet+}$ scavenging capacity was discovered in accordance with another work and detected at 734 nm [47]. Utilizing the previously established Fogliano approach [48], the ability of Vescalagin to eliminate $DMPD^{\bullet+}$ was assessed. The residual $DMPD^{\bullet+}$ absorbance values were measured at 505 nm.

2.4. Anticholinergic assay

According to Ellman's approach, AChE/BChE from electric eels (*Electrophorus electricus*) and equine serum were shown to be inhibited by vescalagin [49]. The absorbance measurements were taken at 412 nm.

2.5. Antidiabetic assay

Following the procedure outlined by Tao et al. [50]. the impact of Vescalagin on α-glycosidase enzyme was predicted the substrate p-nitrophenyl-D-glucopyranoside (p-NPG). At 405 nm, the samples' absorbances were measured. One α-glycosidase unit is the quantity of enzyme that can catalyze 1.0 mol of substrate per minute (at pH 7.4).

2.6. Antiglaucoma assay

Human erythrocytes serve as a source of CA isoenzymes. Fresh human erythrocytes were spun 10,000*xg* for 30 min. Solid Tris was employed to adapt the pH of the serum to 8.7 after it had been separated [51]. Purification of the hCA I and II isoenzymes was accomplished using Sepharose-4B-L-Tyrosine-Sulfanilamide affinity chromatography. During the purification step, the protein concentration was measured using the Bradford method [52]. The reference protein used was bovine serum albumin. SDS-PAGE was used in earlier studies to assess the purity of the hCA II isoform [53]. The p-nitrophenyl acetate substrate, which is changed by both isoforms into the p-nitrophenolate ion [54], was used to measure the esterase activity of the hCA isoforms at 348 nm in accordance with Verpoorte's approach [55].

2.7. IC_{50} values determination

IC_{50} is the inhibitor concentration that reduces enzyme activity (or response) by 50 %. From plots of activity (%) versus Vescalagin, the IC_{50} values were determined [56]. Measure activity at a fixed substrate level across a series of inhibitor concentrations, calculate percent inhibition relative to a no-inhibitor control, and plot inhibition versus log[inhibitor]. Fit a dose–response curve (e.g., sigmoidal) and read the concentration at 50 % inhibition. On the other hand, Lineweaver–Burk graphs are obtained by converting Michaelis–Menten data to a double-reciprocal form. The inhibition constant (K_i) is calculated from enzyme kinetics by measuring reaction rates at several substrate concentrations in the presence of different inhibitor levels. Initial velocities are plotted using Lineweaver–Burk (1/v vs 1/[S]). Measure initial reaction rates (v) at several substrate concentrations ([S]), then calculate

1/v and 1/[S]. Plot 1/v (y-axis) versus 1/[S] (x-axis) and fit a straight line to estimate K_m and V_{max}. The inhibition pattern is identified, and K_i is obtained from the change in slope or intercept versus inhibitor concentration [57].

2.8. Statistical analysis

There was a total of three runs of the studies ($n = 3$). The data was shown as mean ± SD. Following the one-way ANOVA, the Tukey post hoc test was performed; differences were analyzed and considered significant when $p < 0.05$.

3. Results

The Fe^{3+}-reducing activity reflects a compound's electron-donating ability to reduce Fe^{3+} to Fe^{2+} and is widely used as a general indicator of antioxidant potential [58]. As shown in Table 1 and Fig. 3A, vescalagin showed a high Fe^{3+}reduction capacity. This capacity was found to be extremely significant ($p < 0.01$). The reducing capacity of Vescalagin, Trolox, α-Tocopherol, BHT and BHA raised in accordance with rising in Vescalagin quantities. Fe^{3+} reducing capacity of Vescalagin and the references was found following: BHA (λ_{700}: 1.663±0.051, r^2: 0.9086) > Vescalagin (λ_{700}: 1.360±0.040, r^2: 0.9374) > Trolox (λ_{700}: 1.259 ±0.032, r^2: 0.9863) > α-Tocopherol (λ_{700}: 1.012±0.04, r^2: 0.9586) > BHT (λ_{700}: 0.634±0.049, r^2: 0.9154) at 30 μg/mL. The results showed that Vescalagin's Fe^{3+} reducing capacity is lower than that of BHA but higher than that of α-Tocopherol, BHT and Trolox reducing capacity.

The reduction capabilities of cupric ions (Cu^{2+}) and Vescalagin at the same concentration (30 μg/mL) are displayed in Table 1 and Fig. 3B A positive correlation between the different Vescalagin concentrations and the ability to decrease Cu^{2+} was demonstrated. Higher doses (10–30 μg/mL) were discovered to be necessary for Vescalagin to decrease Cu^{2+}ions. Cu^{2+} reducing ability of Vescalagin and the references at 30 μg/mL was identified according to: BHA (λ_{450}: 0.626±0.043, r^2: 0.9928) > α-Tocopherol (λ_{450}: 0.552±0.085, r^2: 0.9305) > Vescalagin (λ_{450}: 0.519±0.009, r^2: 0.9223) > BHT (λ_{450}: 0.454±0.052, r^2: 0.9937) > Trolox (λ_{450}: 0.224±0.05, r^2: 0.9897).

The radical scavenging assay is widely used to evaluate the antioxidant properties of pure or recently produced materials. The most well-known and widely applied radical scavenging method for this purpose is the DPPH radical scavenging test. In the DPPH free radical scavenging technique, the IC_{50} value for vescalagin was evaluated to be 9.65 μg/mL (r^2: 0.9225) (Table 2 and Fig. 4A). Contrarily, the IC_{50} levels were determined to be 7.059 μg/mL for Trolox (r^2: 0.9614), 10.10 μg/mL for BHA (r^2: 0.9015), 11.31 μg/mL for α-Tocopherol (r^2: 0.9642) and 25.95 μg/mL for BHT (r^2: 0.9221). The findings exhibited that vescalagin had better DPPH radical scavenging activity in comparison to BHT, α-Tocopherol and BHA standard references, and Vescalagin's scavenging ability was comparable near to scavenging levels of Trolox antioxidant activities.

DPPH and ABTS radical scavenging activities of Vescalagin were measured 7.81 ± 0.06 and 6.58 ± 0.12 mol Trolox equivalent respectively [59]. In this research, Vescalagin's IC_{50} value for the $ABTS^{\bullet+}$ radical scavenging test was determined to be 4.90 μg/mL (r^2: 0.9413) (Table 2 and Fig. 4B). In contrast, the IC_{50} levels were determined as 8.37 μg/mL for α-Tocopherol (r^2: 0.9015), 6.99 μg/mL for BHT (r^2: 0.9350), 6.16 μg/mL for Trolox (r^2: 0.9692), and 5.07 μg/mL for BHA (r^2: 0.9356). The findings showed that as a phenolic compound Vescalagin had best and efficient $ABTS^{\bullet+}$ scavenging activity in comparison to used references.

DMPD radicals were produced in vitro by oxidizing with ferric chloride. The IC_{50} value for Vescalagin was determined to be 8.73 μg/mL (r^2: 0.9275) (Table 2 and Fig. 4C). In contrast, the IC_{50} values were recorded as 4.33 μg/mL for Trolox (r^2: 0.9447), 11.99 μg/mL for BHA (r^2: 0.9580), 7.11 μg/mL for α-Tocopherol (r^2: 0.9509) and 8.72 μg/mL for BHT (r^2: 0.9375). The findings showed that vescalagin had remarkable efficient $ABTS^{\bullet+}$ scavenging activity in comparison to all synthetic antioxidants used in research.

The cholinergic enzymes of AChE and BChE were also successfully inhibited by Vescalagin with K_i values of 5.87±0.75 and 3.89±0.33 nM, respectively (Table 3, Figs. 5B and C). As seen in Fig. 5, Vescalagin inhibited AChE and BChE as competitive and non-competitive inhibitions. Selectivity index (K_i for AChE/BChE) for both cholinergic enzymes was determined as 1.51. In this case, Vescalagin affinity for both cholinergic enzymes are near to each other. Additionally, Tacrine showed K_i values of 2.43±0.92 nM for AChE (Fig. 5C) and 5.99±1.79 nM for BChE (Fig. 5D). Tacrine was used as standard inhibitor for both cholinergic enzymes [60].

Vescalagin had a K_i of 16.08±4.96 nM towards α-glycosidase enzyme (Table 3 and Fig. 5E). As seen in Fig. 5, Vescalagin inhibited α-glycosidase as non-competitive inhibition. The findings clearly demonstrate that when compared to acarbose (IC_{50}: 22,000 nM), a typical α-glycosidase inhibitor and T2DM antidiabetic medication [61]. Vescalagin demonstrated efficient α-glycosidase inhibition.

Phenolic compounds bind to the zinc ions (Zn^{2+}) in the active-side cavity through functional groups within the scaffold, which prevents the CA isozymes from functioning. Regarding the study that profiled intracellular and predominant hCA I and hCA II isoenzymes, Vescalagin showed effective K_i value of 11.75±1.65 nM and 16.23±2.84 nM, respectively regarding AZA inhibitors value (Table 3 and Fig. 5A and 5B). Vescalagin inhibited CA I and CA II isoenzymes as non-competitive inhibitions (Fig. 5). In contrast, AZA, a therapeutic CA isoenzymes inhibitor showed a K_i value of 12.58±0.50 nM against hCA I and 4.41 ±0.35 nM towards hCA II isoforms. Nearly all cells contain physiologically dominant and cytosolic hCA I and hCA II, which are linked to several illnesses, including oedema, epilepsy, and glaucoma [62].

Table 1
Fe^{3+} and Cu^{2+} reduction abilities of Vescalagin and standards at 30 μg/mL concentration.

Antioxidants	Fe^{3+} reducing ability		Cu^{2+} reducing ability	
	λ_{700}	r^2	λ_{450}	r^2
BHA	1.663±0.051	0.9086	0.626±0.043	0.9928
BHT	0.634±0.049	0.9154	0.454±0.052	0.9937
α-Tocopherol	1.012±0.004	0.9586	0.552±0.085	0.9305
Trolox	1.259±0.032	0.9863	0.224±0.005	0.9897
Vescalagin	1.360±0.040	0.9374	0.519±0.009	0.9223

4. Discussion

The phenolic compounds have a broad range of pharmaceutical characteristics, including antioxidants, anti-inflammatory, antibacterial, anti-AD, and anti-diabetic, actions. The biological actions of those substances are presumed to be strongly correlated with each other [60]. Phenolic molecules with a wide variety of polarity can be found in plants. Because of their high hydroxyl group content, these compounds could be scavenging. The key subclasses of polyphenols include phenolic acids, tannins, and flavonoids, which are separated based on certain structural distinctions. These have several biological effects, including antibacterial action, and are strong antioxidants [63]. Plants produce phenols more frequently than any other type of secondary metabolite. Given that these compounds are potent metal chelators and radical scavengers, there has been much interest in them as potential herbal antioxidants. The antioxidant activity of phenol is attributed in large part to its redox characteristics, which include both hydrogen donors and singlet oxygen quenchers. Phenolic chemicals are found in all plants and constitute an essential component of the diet. Their biological qualities and antioxidant qualities sparked a lot of interest in them [64]. Native Americans made use of extracts from witch hazel to treat fever, colds, and discomfort. Today, they are found in skin care products, dermatological treatments for atopic eczema, sunburn, and skin

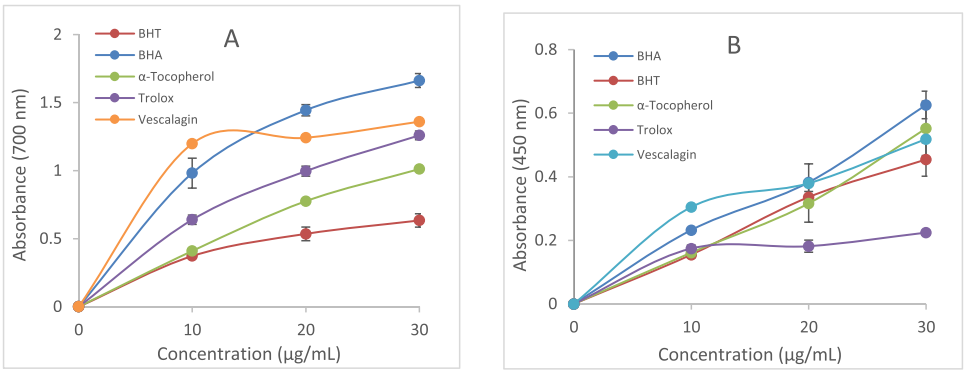

Fig. 3. (A) Fe^{3+} reducing abilities of Vescalagin and standards, (B) Cu^{2+} reducing ability of Vescalagin and standards.

Table 2
IC_{50} (μg/mL) values for $DPPH^{\bullet}$, $ABTS^{\bullet+}$ and $DMPD^{\bullet+}$ scavenging activities of vescalagin and standard antioxidants.

Antioxidants	$DPPH^{\bullet}$ scavenging		$ABTS^{\bullet+}$ scavenging		$DMPD^{\bullet+}$ scavenging	
	IC_{50}	r^2	IC_{50}	r^2	IC_{50}	r^2
BHA	10.10 ±0.007	0.9015	5.07 ±0.001	0.9356	11.99 ±0.029	0.9580
BHT	25.95 ±0.014	0.9221	6.99 ±0.001	0.9350	8.72 ±0.018	0.9375
α-Tocopherol	11.31 ±0.004	0.9642	8.37 ±0.001	0.9015	7.11 ±0.035	0.9509
Trolox	7.05 ±0.007	0.9614	6.16 ±0.029	0.9692	4.33 ±0.011	0.9447
Vescalagin	9.65 ±0.004	0.9225	4.90 ±0.035	0.9413	8.73 ±0.017	0.9275

irritation, and ultimately functions that reduce inflammation, assisting in wound healing [65]. Contrary to all studied bacterial strains, but especially methicillin-resistant ones like MRSA and MRSE, vescalagin and Castalagin shown bactericidal action. They also demonstrated the capacity to destroy preexisting biofilms and prevent the creation of new ones [66].

Antioxidants have multiple functions, including hydrogen abstraction, peroxides dissolution, reactive oxygen species elimination, and metal ion chelation. The electron-absorption capability is likewise a function of reducing power, which is the most important attribute of an antioxidant [67]. The antioxidant potential of natural substances is investigated using a variety of easy and affordable in vitro antioxidant techniques. Antioxidant chemicals are frequently examined utilizing methods such potassium ferric cyanide and cupric ions (Cu^{2+}) reduction activities, as well as $DMPD^{\bullet+}$, $ABTS^{\bullet+}$, and $DPPH^{\bullet}$ scavenging activity. A ferric hexacyanoferrate molecule ($Fe_4[Fe(CN)_6]$) with an absorption of 700 nm was produced in one of the studies carried out in this manner by adding Fe^{3+} to the reduced product by adding vescalagin. $Fe[(CN)_6]^{3+}$ is reduced to $Fe[(CN)_6]^{2+}$ when reducing molecules are present [58]. Gallotannins have the capability to attach to metal ions, such as iron and copper, rendering them unavailable to microbes [59]. The literature on this topic revealed that for usnic acid, the Fe^{3+} reducing absorbance has been shown to be 0.278 (r^2: 0.9567) for usnic acid [68], 0.432 (r^2: 0.9981) for uric acid [69], 0.739 (r^2: 0.9478) for coumestrol [70], 0.967 (r^2: 0.9938) for magnofluorine [35], 1.012 (r^2: 0.9523) for spiraeoside [71], 1.030 (r^2: 0.9990) for hamamelitannin [58], 1.249 (r^2: 0.9848) for baicalin hydrate [72], 2.428 (r^2: 0.9474) for tannic acid [73], 2.509 (r^2: 0.9906) for caffeic acid phenethyl ester [74], and 2.769 for caffeic acid (r^2: 0.9945) [75] at the same concentration.

Cu^{2+} reducing activity describes a compound's ability to transfer electrons and convert Cu^{2+} into Cu^{+}, providing a convenient proxy for its overall reducing antioxidant power. The findings exhibited that Cu^{2+} reducing ability of Vescalagin was higher than that of BHT and Trolox reducing capacity but Vescalagin reducing capacity was found lower than BHA and α-Tocopherol standard antioxidants reducing capacity. Additionally, as previously mentioned in the literature, for natural phenolic compounds, absorbance values for Cu^{2+} reduction had been recorded as 0.277 (r^2: 0.9836) for usnic acid [68], 0.331 (r^2: 0.9394) for hamamelitannin [58], 0.344 (r^2: 0.9517) for baicalin hydrate [72], 0.468 (r^2: 0.9729) for magnofluorine [35], 0.519 (r^2: 0.9675) for spiraeoside [71], 1.085 (r^2: 0.8403) for resveratrol [76], 0.762 (r^2: 0.9957) for eugenol [77], 0.780 (r^2: 0.9981) for coumestrol [70], 0.750 (r^2: 0.9550) for taxifolin [78] and 1.314 (r^2: 0.9682) for olivetol [79] at the same concentration.

The number and locations of hydroxyl groups, the presence of side chains or double bonds, and other structural characteristics all affect the antioxidant potential of polyphenol molecules. Higher hydroxyl group content in polyphenols is thought to confer superior antioxidant effects upon them. Because the energy threshold for hydrogen transfer is low, the placement of hydroxyl groups and the presence of side chains or double bonds, such as ethylene, can lower the O—H bond's enthalpy of dissociation [80]. The presence of -OH groups in Vescalagin's chemical construction significantly increases its antioxidant properties. The simplicity of donation of phenolic hydrogen contributes to its improved capabilities of radical scavenging and chain breaking. The quantity of hydroxyl (-OH) groups in a molecule often enhances its antioxidative defense efficacy and ability to scavenge free radicals [81]. Antioxidant activity was demonstrated by the unsubstituted-OH groups in Vescalagin.

Since free radicals have unpaired electrons, they can combine with and change proteins, lipids, and DNA. This causes oxidative stress, which is linked to several illnesses in humans [82]. Consequently, using exogenous antioxidants can help with oxidative stress management. Plants with bioactive substances like flavonoids and phenols can help reduce oxidative stress. These substances may donate hydrogen atoms to free radicals, neutralizing them, which makes them essential antioxidant components. Furthermore, they show advantageous structural characteristics for scavenging free radicals [19]. In biological, pharmacological, and dietary applications, antioxidants' capability to remove free radicals and ROS was essential since it helped shield the products and the body from injury [83]. As rapid, simple, selective, inexpensive, and repetitive tests, the chromophore $ABTS^{\bullet+}$, $DPPH^{\bullet}$, and $DMPD^{\bullet+}$ scavenging assays are utilized. For this reason, it is very common to use these radical scavenging activities to determine the antioxidant activities of pure substances like Vescalagin. The violet $DPPH^{\bullet}$, pink $DMPD^{\bullet+}$, and green blue $ABTS^{\bullet+}$ radicals have great recognition sensitivity, which makes using them easy [84]. Besides, Vescalagin, which may function as a chain-breaking radical scavenger, may interact with the unsaturated component of the lipid chain. The existence of H-donating substituents and the free electron's capacity to delocalize, both of which are required for stability, are the most advantageous structural characteristics for

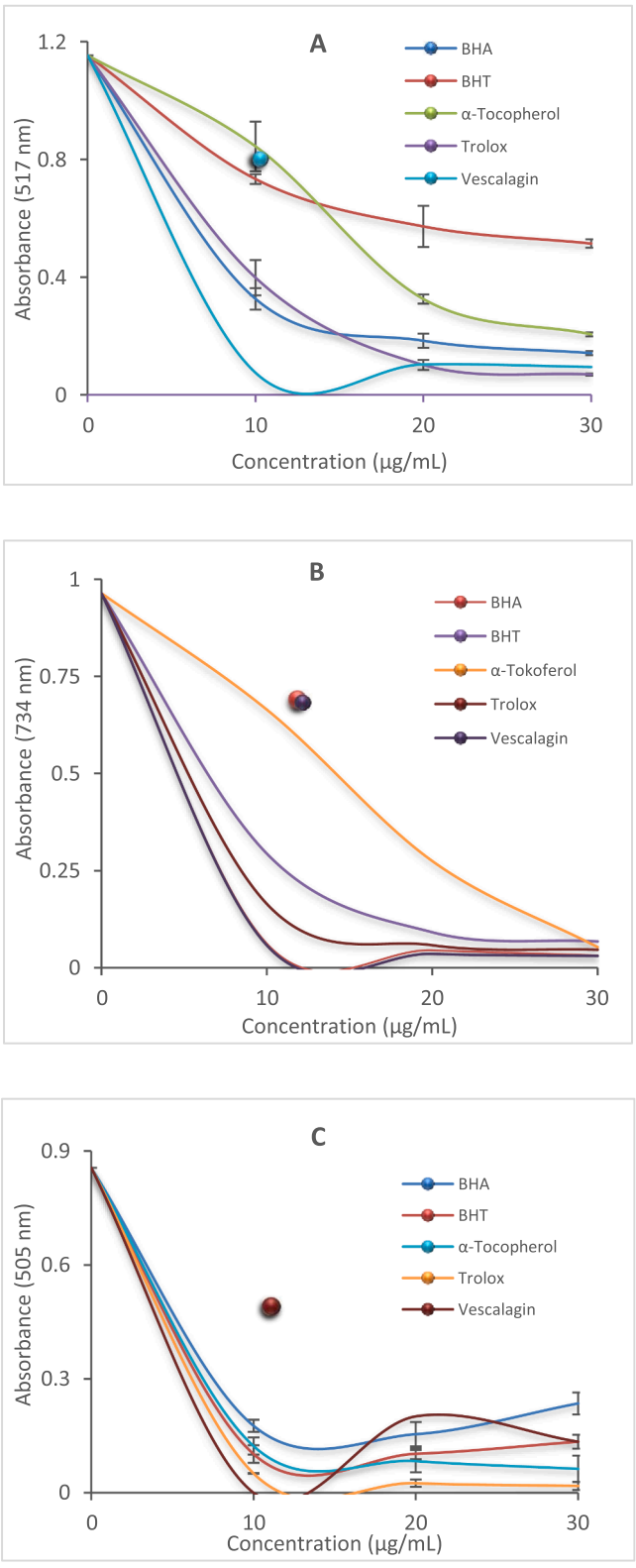

Fig. 4. Radical scavenging abilities of Vescalagin and standard antioxidants, **(A)** $DPPH^{\bullet}$ scavenging, **(B)** $ABTS^{\bullet+}$ scavenging, **(C)** $DMPD^{\bullet+}$ scavenging effects.

phenolics' antioxidant potential. The quantity and location of -OH groups inside a phenol are known to affect its ability to serve as an antioxidant and offer biological activity. These characteristics make polymeric polyphenols superior to monomeric polyphenols as antioxidants [85].

When an antioxidant that donates hydrogen is present, the 2,2-diphenyl-1-picryl-hydrazyl-hydrate ($DPPH^{\bullet}$) radical is reduced, and at the conclusion of the process, the non-radical DPPH—H form is produced [86–88]. The antioxidant activity of sumac was thought to be attributed to its hydrolysable tannins [89,90]. Vescalagin had more activity than castalagin, while stachyurin and casuarinin showed a comparable correlation. Therefore, the shape of the hydroxyl group at C-1 of the open ring D-glucose may affect these tannins' antioxidant properties [78]. Data from the outer bark of *Quercus suber*, suggests that Vescalagin and Castalagin (the main components of fractionated sample of mixture of water and ethanol) oversee enhancing DPPH scavenging activity, meaning they effectively stabilize free radicals via an electron transfer process [91]. The IC_{50} values of DPPH radical scavenging activity of Vescalagin were found 20.9 ± 0.2 μg/mL in a study. According to tests using DPPH and Tris-(2,4,6-trichloro-3,5-dinitrophenyl)-methyl stable radicals, the most effective scavengers were also the most cytotoxic/antiproliferative agents [1]. Other phenolic antioxidants whose DPPH radical scavenging capacities have been evaluated by Durmaz et al. can be compared to Vescalagin in terms of their free radical scavenging capabilities. According to report, IC_{50} value was determined to be 49.50 μg/mL for usnic acid [68], 3.30 μg/mL for CAPE [74], 16.06 μg/mL for eugenol [77], 19.97 μg/mL for hamamelitannin [58], 6.96 μg/mL for resveratrol [76], 77.00 μg/mL for taxifolin [78], 10.58 μg/mL for magnofluorine [35], 17.77 μg/mL for olivetol [79], 13.40 μg/mL for baicalin hydrate [72], 20.8 μg/mL for silymarin [92], 25.95 μg/mL for coumestrol [70], 28.51 μg/mL for spiraeoside [71], 30.6 μg/mL for L-Adrenaline [93] and 34.9 μg/mL for curcumin, the first phenolic chemicals from a plant source to be separated [94]. Vescalagin has the capacity to scavenge DPPH radicals, according to the study's results. After generating DPPH—H by absorbing an electron or a hydrogen atom from the Vescalagin, radicals vanish when the vescalagin and DPPH come into contact. There is currently no published mechanism for how the Vescalagin molecule scavenges DPPH. The strongest evidence points to the stability of the resonance structure, which indicates that it stabilizes the radicals produced on the phenolic groups in the vescalagin. Furthermore, if a vescalagin molecule scavenges two DPPH in this manner, it can undergo a diketonic structure that transforms it from the specified radical forms to the neutral form. According to studies, the hydroxyl groups in aromatic rings have a substantial effect on their ability to scavenge free radicals [80]. These findings showed that vescalagin has a much more effective DPPH free radical scavenging capacity compared with the results of phenolic aromatic compounds in the literature.

Vescalagin has a greater ability than other synthetic antioxidants utilized in studies to scavenge $ABTS^{\bullet+}$, according to the findings. The $DPPH^{\bullet}$ and $ABTS^{\bullet+}$ procedures are also often used to evaluate the ability of concentrated chemicals, drinks, extracts, and slurry to scavenge radicals [82]. The $ABTS^{\bullet+}$scavenging method was used to evaluate organic compounds' capacity to directly react with the ABTS radical and reduce color [95]. The many hydroxyl groups that are affixed to the aromatic ring may be the reason why vescalagin shown strong free radical scavenger activity against DPPH, ABTS, and electron transfer [96]. In comparison with other natural chemicals, IC_{50} value was determined as 10.41 g/mL for usnic acid [68], 7.48 μg/mL (r^2: 0.9952) for spiraeoside [71], 9.80 μg/mL for CAPE [74], 6.96 μg/mL for resveratrol [76], 7.84 μg/mL for eugenol [77], 0.83 μg/mL for taxifolin [78], 1.94 μg/mL for olivetol [79], 8.62 μg/mL for silymarin [92], 6.93 μg/mL for L-Adrenaline [93], 12.24 μg/mL for coumestrol [70], 19.52 μg/mL for hamamelitannin [58], 18.07 μg/mL for curcumin [94], 38.37 μg/mL for baicalin hydrate [72], and 27.61 μg/mL for magnofluorine [35].

DMPD radicals are easily and efficiently scavenged by antioxidant molecules in the test samples. Higher IC_{50} values are found in Vescalagin's $DMPD^{\bullet+}$ elimination activities and other studies published in the literature. For instance, the IC_{50} values were determined as 33.00 μg/mL for usnic acid [68], 26.70 μg/mL for CAPE [74], 12.81 μg/mL for

Table 3
The enzyme inhibition values of Vescalagin towards carbonic anhydrase I and II isoenzymes (CA I and CA II), acetylcholinesterase (AChE), butyrylcholinesterase (BChE) and α-glycosidase (α-Gly) enzymes.

Compounds	IC_{50} (nM)										K_i (nM)				
	hCA I	r^2	hCA II	r^2	AChE	r^2	BChE	r^2	α-Gly	r^2	hCA I	hCA II	AChE	α-Gly	BChE
Vescalagin	14.63	0.9370	13.42	0.9342	5.18	0.9674	3.37	0.9729	13.15	0.9312	11.75 ±1.65	16.23 ±2.84	5.87 ±0.75	16.08 ±4.96	3.89 ±0.33
AZA*	16.58	0.9887	8.37	0.9825							12.58 ±0.50	4.41 ±0.35			
TAC**					5.97	0.9706	8.37	0.9846					2.43 ±0.92		5.99 ±1.79

*Acetazolamide (AZA) was used as a standard inhibitor for both hCA I and II isoenzymes.
** Tacrine (TAC) was used as a standard inhibitor for AChE and BChE enzymes [50].

coumestrol [70], 10.04 μg/mL for eugenol [77], 8.15 μg/mL for spiraeoside [71], 9.5 μg/mL for resveratrol [76], 173.25 μg/mL for taxifolin [78], 19.25 μg/mL for olivetol [79], 19.97 μg/mL for baicalin hydrate [72], 15.6 μg/mL for hamamelitannin [58], 15.6 μg/mL for L-Adrenaline [93], 15.16 μg/mL for magnofluorine [35], and 34.5 μg/mL for curcumin [94].

Lipid peroxidation, as well as free radical-induced lipid peroxidation, has caused tissue damage due to the depletion of enzymes and antioxidant molecules caused by the increase in free radicals in diabetes. Antioxidants have been demonstrated to reduce oxidative stress, which exacerbates diabetes [97]. Natural products have a lot of potential as novel medical treatments because of their wide range of chemical composition, whether they are pure substances or standardized extracts. The most economical and plentiful source for creating new drugs is plants. More powerful drug candidate molecules with few to no adverse effects are available in modern plant-based medications and medicinal plants, raising concerns regarding the treatment of diabetes [98].

The polyphenol Vescalagin has anti-inflammatory and antioxidant properties. An experiment results revealed that Vescalagin elevates glutathione contents; upregulates the nuclear factor erythroid 2-related factor 2 protein expression, and antioxidant enzymes; downregulates c-Jun N-terminal kinase and p38 mitogen- activated protein kinases pathways; and thereby protects pancreatic β-cells and improves insulin secretion in methylglyoxal administered rats [3]. In chemical and biological media, the optimized freeze-dried water extract of *Myrciaria dubia* seed coats demonstrated around 13 g/100 g of ellagitannins (Vescalagin and Castalagin) and showed antioxidant properties. The optimized extract also inhibited the growth of both Gram-positive and Gram-negative bacteria and the enzymatic activity of angiotensin-converting enzymes, α-amylase, and α-glycosidase [99]. In contrast, lyophilized jabuticaba (*Myrciaria jaboticaba*) seed extract significantly increased the inhibition of α-amylase, and α-glycosidase in yogurts in a dose-dependent manner, while the control yogurt showed very low inhibition (< 20 %) of these enzymes. The primary causative agents may be phenolic chemicals, including phenolic acids, flavonoids, and condensed tannins like Castalagin and Vescalagin [100]. The results demonstrate that vescalagin lowers blood glucose with a concomitant reduction in C-peptide and plasma insulin levels. Consequently, in rats fed a high-fructose diet, Vescalagin, which reduces hypertriglyceridemia and hyperglycemia illnesses. According to the results of the α-glycosidase inhibition, Vescalagin had an effective K_i value of 16.08±4.96 nM, which was like the 22.000 nM K_i value of the starch-blocking drug Acarbose. It is commonly known that one of the most crucial ways to avoid clinical problems affecting the heart, kidneys, eyes, neurological system, and other bodily systems in T2DM is to manage blood glucose levels by blocking the α-glycosidase enzyme. Numerous diseases, including strokes, heart disease, renal failure, erectile dysfunction, blindness, visual impairment, lower limb amputations, and poor wound healing, are mostly caused by diabetes [101]. A substantial and common factor in the development, progression, and outcomes of diabetes mellitus is elevated oxidative stress.

Cholinesterase inhibitors (ChEIs), including donepezil, galantamin, rivastigmine, and memantine, are currently approved medications for AD. These medications, however, can only temporarily reduce symptoms; they cannot stop or reverse the progression of AD. Because of its significant adverse effects and low conformance, its clinical usefulness is restricted [102]. As a result, herbal medicines might be a major source of innovative medications. It is feasible that the active polyphenolic Vescalagin might have extensive pharmaceutical impacts on AD. This study determined Vescalagin's IC_{50} values on cholinergic enzymes. Moreover, the AChE and BChE enzymes showed Ki inhibition values of 5.87±0.75 and 3.89±0.33 nM, respectively, due to vescalagin. Table 3 indicates that tacrine had a lower K_i value on BChE enzymes than Vescalagin. Additionally, when the K_i levels for AChE and inhibition were examined in the earlier literature, numerous natural substances were noted as 0.239 nM for usnic acid [68], 0.518 nM for CAPE [74], 3.4 nM for spiraeoside [71], 5.13 nM for olivetol [79], 7.40 nM for hamamelitannin [58], 10.01 nM for baicalin hydrate [72], 10.25 nM for magnofluorine [35], 16.70 nM for taxifolin [78], and 21.43 nM for coumestrol [70]. The experimental observations show that ROS and free radical accumulation is inhibited effectively by these chemical compounds.

Hyperglycemia and insufficient endogenous insulin synthesis or activity are hallmarks of T2DM. This metabolic disease is associated with elevated blood sugar levels. To control the hydrolysis of carbohydrates, investigation in the last few years has focused on blocking α-glycosidase [50]. Vescalagin exhibited potent α-glycosidase inhibition (Table 3; Fig. 5E) using p-NPG as the substrate (405 nm). The inhibition was markedly stronger than the reference inhibitor acarbose. Together, these data indicate that vescalagin is a high-affinity α-glycosidase inhibitor under standardized in vitro conditions and supports its use as a benchmark compound in analytical inhibition profiling.

Since they exhibit a wide range of biological actions, phenol and polyphenols have been classified as CAIs. Several physiologically relevant isoforms have been shown to be strongly inhibited by a variety of such drugs. Phenolic compounds might be interesting lead molecules for finding novel CA isoenzyme inhibitors [79]. Phenolic compounds lose protons (H^+) from their hydroxyl groups, changing their pH from slightly acidic to very water-soluble phenolate anions. Furthermore, it has been demonstrated that phenols' inhibitory effects on CA isoenzymes are beneficial [103]. In this study, vescalagin inhibition effects on CA I and CA II enzymes were studied and showed that results were too efficient compared with acetolazamide standard. Vescalagin showed non-competative inhibition towards to all enzymes in this research, Fig. 5. Although vescalagin hasn't been investigated in relation to hCA I, hCA II, AChE and BChE enzymes inhibition previously, further studies are required. A comprehensive and important study of Vescalagin in terms of antioxidant tests and inhibition of metabolic enzymes has been performed by our group for the first time. Enzyme studies with Vescalagin are very limited and insufficient. The results of this study may serve as a prototype for other studies. The development and utilisation of the results obtained from this study will contribute to the field of pharmacology and medicine.

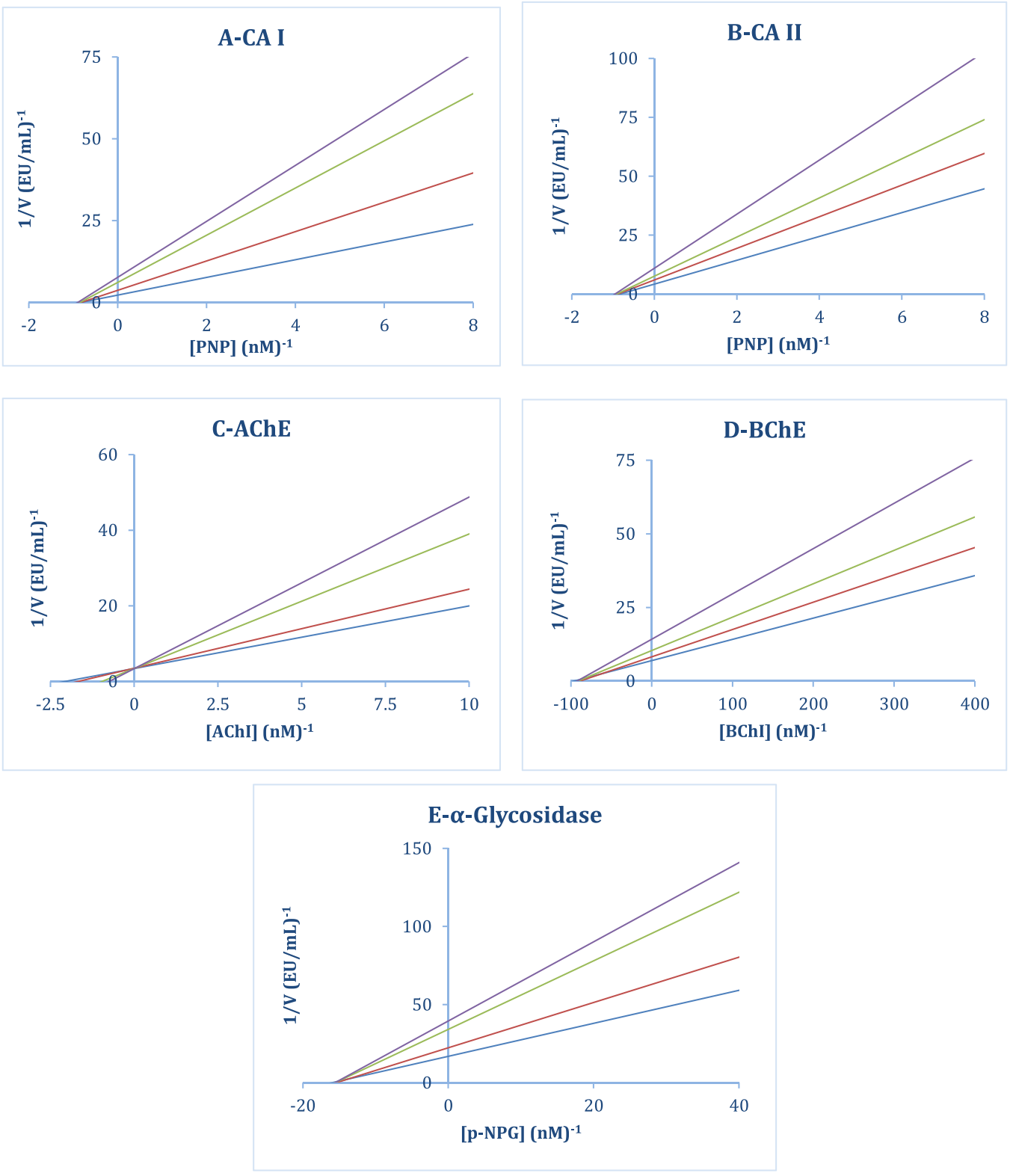

Fig. 5. Lineweaver-Burk graphs of Vescalagin against carbonic anhydrase I (CA I) (**A**), carbonic anhydrase II (CA II) (**B**), acetylcholinesterase (AChE) (**C**), butyrylcholinesterase (BChE) (**D**), and α-glycosidase (**E**) enzymes. Vescalagin was used in the several concentrations range (5–20 nM for CA I, 2–16 nM for CA II, 2–8 nM for AChE, 1.0–4.5 nM for BChE and 6–16 nM for α-glycosidase to calculate the IC_{50} value against the indicated enzymes. Lineweaver–Burk plots were then constructed using one inhibitor concentration close to the IC_{50} value, along with two additional concentrations—one below and one above this level. All experiments were performed in triplicate ($n = 3$), and data are presented as mean ± SD.

5. Conclusions

The C-glycosidic ellagitannin Vescalagin is among the plant polyphenol, and a natural product belonging to the tannin family with potent antioxidant activity and many activities beneficial for health. This study shows that the vescalagin molecule inhibits substantial metabolic enzymes by showing antioxidant activity at a molecular level. The regulation of hormonal and metabolic cycles in the healthy life cycle of the organism is the result of the expression of genetic information by changes in the activity of proteins and enzymes. When the activities of enzymes involved in the control steps are inhibited, reduced or controlled, many common, degenerative, aging-accelerating, chronic, life-reducing and fatal diseases can be prevented, stopped or alleviated. For these reasons, vescalagin molecule with phenolic content may reveal antioxidant, anti-Alzheimer, antidiabetic, antiglaucoma and antiepileptic effects with the hydroxyl groups it contains and the molecules it interacts with.

This study is the most comprehensive molecular-based study ever conducted and is a detailed scientific and quantitative description of vescalagin, which was previously mentioned in the literature with generally qualitative studies. In this study, it was experimentally recorded that vescalagin is a molecule with the activity of eliminating free radicals and ROS by various analysis methods compared to synthetic antioxidants.

This study shows that Vescalagin, a safe phenolic antioxidant of plant origin, can be used to delay or prevent oxidation in the food industry and pharmaceutical studies. For example, the IC_{50} value of DPPH radical scavenging activity of Vescalagin is 9.65 μg/mL (r^2: 0.9225). On the other hand, BHA, BHT, Trolox and α-Tocopherol exhibited IC_{50} values of 10.10, 25.95, 7.05 and 11.31 μg/mL for DPPH radical scavenging ability, respectively. This may prolong the shelf life of drugs and foodstuffs and preserve their nutritional content. The results of the study showed that vescalagin effectively inhibits BChE, AChE, α-glycosidase, CAs I and II. In the study, Vescalagin showed K_i values of 5.87 ± 0.75, 3.89 ± 0.33, 11.75 ± 1.65, 16.23 ± 2.84 and 16.08 ± 4.96 nM against AChE, BChE, CA I, CA II and α-glycosidase. These enzymes, whose inhibition has been studied, are associated with some common chronic diseases, including AD, glaucoma and T2DM. In future studies, the effect of Vescalagin on target disease pathways can be determined by controlled studies in cell cultures and experimental animals.

We have strengthened the manuscript to emphasize its analytical value: a multi-assay profiling framework that integrates complementary antioxidant tests with a standardized enzyme panel (CA I, CAII, AChE, BChE and α-glycosidase). By benchmarking Vescalagin against routinely used reference inhibitors under controlled conditions, we provide a reproducible bioanalytical signature that supports comparative potency ranking and use of Vescalagin as a reference compound in future screening and assay-development studies

The novelty of the present study lies in its analytical, multi-assay profiling design and comparative benchmarking strategy rather than in claiming broad biological efficacy. Specifically, Vescalagin was characterized using a standardized antioxidant profiling panel comprising complementary electron-transfer and radical-scavenging assays (e.g., Fe^{3+}/Cu^{2+} reducing power and DPPH·, $ABTS^{\cdot+}$, and $DMPD^{\cdot+}$ scavenging), with direct comparison to widely used reference antioxidants including BHA, BHT, α-tocopherol, and Trolox. In parallel, we established a comparative multi-enzyme inhibition spectrum for Vescalagin across a defined enzyme set (CA I, CA II, AChE, BChE, and α-glycosidase), supported by kinetic evaluation (Lineweaver–Burk) and K_i determination, and benchmarked against commonly employed standard inhibitors. This integrated analytical approach provides a reproducible profile of Vescalagin under controlled conditions and supports its potential use as a reference polyphenolic antioxidant and enzyme inhibitor in analytical and screening assays.

This study is limited to in vitro assays conducted under single, standardized conditions. Apparent inhibition parameters may vary with substrate concentration and enzyme source or preparation (AChE, BChE, CA I, CA II, α-glycosidase). Antioxidant tests reflect chemical reactivity, not biological activity. Cell-based and in vivo validation is needed across laboratories and instruments. As an analytical profiling study, our inhibition data should be interpreted with assay-specific considerations. K_i and inhibition mode can be substrate-dependent; therefore, using p-NPG for α-glycosidase and the selected substrate ranges in kinetic plots may influence the apparent potency. Enzyme source and isoform variability can also affect cross-study comparisons: AChE was obtained from *Electrophorus electricus* and BChE from equine serum, and different preparations may exhibit different specific activities. Thus, substrate, source and conditions must be considered. Moreover, buffer composition, pH, temperature, and incubation time, as well as solvent content (e.g., DMSO), can measurably shift overall IC_{50}/K_i estimates in vitro assays

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

Sample availability

Samples of the compounds are not available from the authors.

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CRediT authorship contribution statement

İlhami Gulcin: Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Conceptualization. **Lokman Durmaz:** Methodology, Investigation. **Hasan Karagecili:** Methodology, Investigation. **Eda Mehtap Ozden:** Methodology, Investigation. **Adem Erturk:** Methodology, Investigation. **Zeynebe Bingol:** Methodology, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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