

Phloroglucinol from *Vitis Vinifera*: Experimental and Computational Insights into α -Glucosidase Inhibition

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Abstract: This study explores the process of extracting, characterizing, and assessing the therapeutic potential of phloroglucinol obtained from *Vitis vinifera* seeds. In this study, we collected the plant seeds of *Vitis vinifera*, followed by a sequential evaluation of the phytochemical constituents, such as phloroglucinol. Later, we assessed the inhibition studies and then evaluated the binding affinity of phloroglucinol using AutoDock. We successfully isolated and identified phloroglucinol by utilizing a combination of analytical techniques, such as gas chromatography-mass spectrometry and high-performance liquid chromatography. The occurrence was subsequently confirmed by Nuclear Magnetic Resonance spectroscopy. The chemical had notable antioxidant and α -glucosidase inhibitory properties, as indicated by its low IC₅₀ values in the DPPH radical scavenging and α -glucosidase inhibition tests. In addition, molecular docking studies were performed to assess the interaction between phloroglucinol and crucial proteins involved in glucose metabolism. These tests uncovered favorable binding affinities, indicating feasible anti-diabetic effects.

Keywords: anti-diabetics; in-silico; phloroglucinol; phenolic compounds; phytochemicals.

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1. Introduction

Phytochemicals are bioactive substances found in plants that play a key role in their survival and metabolism [1-3]. There are several chemical properties and structures associated with these substances, including antioxidants [4], anti-inflammatory [5], anti-cancer [6], and antimicrobial properties [7-10]. The major categories of phytochemicals found in plants include phenols, terpenoids, alkaloids, saponins, glycosides, phytosterols, proteins, and peptides [10-12]. Phytochemicals are primarily composed of phenolic compounds, which are very prevalent [13]. They play an important role in plant antioxidants and contribute significantly to flavors, colors, and aromas [14]. In addition to flavonoids, phenolic acids, tannins, and lignans, phenolic compounds are also found in dietary supplements [15-17]. It is generally accepted that phytochemicals are a range of substances found in plants that have therapeutic applications [18].

The observations from Wang *et al.* found that one of the most profound phenolics in plants includes polyphenolic compounds [19]. The chemical structure of polyphenolic compounds is characterized by the presence of a few phenolic groups [20]. In recent years, substantial research has been conducted on polyphenolic substances because of their potential therapeutic effects [21]. Researchers have demonstrated that they possess anti-inflammatory

[22, 23], anticancer [18, 24-26], anti-diabetic [27-29], antioxidant [30, 31], and neuroprotective [32, 33] properties. In the research discussions from Rahman *et al.*, the bioactive chemicals responsible for the health benefits of polyphenolic compounds derived from plant-based extracts [34]. Imran *et al.* discussions presented the mechanisms by which these substances act, including their effects on cellular signaling pathways and gene expression [35].

One such interesting polyphenolic compound is phloroglucinol (PG), which is naturally occurring and belongs to the polyphenol family [36]. There are several plants that contain PG, including *Eucalyptus globulus* [37], *Quercus serrata* [38], and *Malus pumila* [39], and some bacteria [40] and fungi [41] synthesize it as well. Several studies have examined the health benefits of PG and its derivatives, including their antibacterial [42], anti-inflammatory [43], and antioxidant [44] properties. These substances have also been studied for therapeutic purposes to treat conditions such as cancer [45], diabetes [46], and cardiovascular disease [47] in recent years. Based on the studies of Ait El Had *et al.*, PG and its derivatives have anti-cancer properties since they cause cancer cells to undergo apoptosis, prevent tumor growth and spread, and reduce inflammation [48]. Studies by Dong *et al.* showed that antioxidants also have neuroprotective benefits by fending off oxidative stress and inflammation in the brain [49].

Aside from their uses in food and cosmetics, PG and its derivatives are also being investigated for their possible medicinal effects [50]. Because they contain antibacterial and anti-inflammatory properties, they are perfect ingredients for food preservation and cosmetic formulations [51, 52]. PG derivative aspidinol, found in the rhizome of *Dryopteris crassirhizoma*, is one of the most extensively studied studies by Phong *et al.* [53]. Because of its strong antioxidant and anti-inflammatory properties, Moreno Cardenas *et al.* showed that aspidinol is being investigated for use in treating diabetes [54] and cardiovascular disease [55]. A different derivative of phloroglucinol, phorizin, has been found to inhibit glucose absorption in the gut and reduce insulin sensitivity [56].

Our current research is focused on the study of the isolation and characterization of PG and the study of the binding efficacy of Human α -Glucosidase using molecular docking methodology. The outcome of this research may establish the binding mechanism of the above-mentioned compounds as a possible therapeutic agent for treating type 2 diabetes (T2D).

2. Materials and Methods

2.1. Chemicals and reagents.

Chemicals with high purity (99.0%) HPLC grade organic solvents, including methanol (ME) and ethyl acetate (EA), were purchased from Merck Millipore. Commercially available compounds, including phloroglucinol (PG) and α -glucosidase, were bought from Sigma-Aldrich. Reagents and buffers such as 2,2-diphenyl picrylhydrazyl (DPPH) reagent, Tris HCL buffer, sodium hydroxide (NaOH), hydrochloric acid (HCL), potassium hydroxide (KOH) were acquired from TCI Chemicals Ltd.

2.2. Isolation and characterization of phloroglucinol.

Fruits of *Vitis vinifera* were obtained from local markets in Hyderabad, India, followed by verification of the fruits done at the Botanical Survey of India's database with Ref No. BSI/DRC/2022-23/Tech./Identification/174. The isolation methodology was based on the previously established reports [57], where in a typical process, the seeds were isolated, dried

in the shade, ground into powder, and then weighed, amounting to ~150 grams. The powder was extracted in a Soxhlet apparatus using 100% methanol (ME) at a temperature of 30°C for a duration of approximately 6 hours. After extraction, the samples were concentrated by applying reduced pressure and dried using a rotary evaporator. They were then stored at a temperature of -20°C.

The seed extract was subjected to gas chromatography-mass spectrometry (GC-MS) analysis utilizing an Agilent Technologies 7890A instrument equipped with a mass-selective detector and a polar Agilent HP-5ms capillary column. The carrier gas used was helium (He), with a flow rate of 1 mL/min. Compound identification relied on analyzing mass spectra, retention durations, and comparison with databases (Wiley Registry, 8th Edition / NIST 2005). For further separation, high-performance liquid chromatography (HPLC) was utilized. A PerkinElmer LC system equipped with a C18 column was employed. The system functioned within the pressure range of 1820–1950 psi and utilized a wavelength of 260 nm. Isocratic elution was employed, employing several solvents. The fractions of interest (FOI) were obtained and examined using a Bruker MSL 500 NMR (nuclear magnetic resonance) spectrometer in a DMSO-d₆ solution. The data was then analyzed using MestReNova-11.0.3 software, comparing the ¹H and ¹³C NMR spectra with available molecular information.

2.3. Antioxidant and α -glucosidase inhibition activity.

To evaluate the antioxidant activity of PG, we utilized the technique described by Sharma *et al.* 2009, which involves the removal of color from a methanol solution of DPPH [58]. During this experimental process, a solution containing 1 mL of 0.2 mM DPPH in methanol was combined with 1 mL of the PG at different concentrations ranging from 50 to 750 μ g/mL. The solution was placed in an incubator and maintained at a temperature of 25°C for a duration of 30 minutes. The variation in absorbance was quantified at a wavelength of 517 nm using a BIO-RAD Model 680 microplate reader.

The DPPH radical's percentage inhibition was determined by applying the following formula,

$$\%DPPH\ inhibition = \left[\frac{(AbsC - AbsE)}{AbsC} \right] \times 100 \quad (1)$$

The absorbance of the extract is denoted as *AbsE*, while the absorbance of the control is denoted as *AbsC*. The IC₅₀ value, which represents the concentration needed to block 50% of the DPPH radical, was obtained using a non-linear regression coefficient approach.

Meanwhile, the α -glucosidase inhibitory assay was conducted using the procedure outlined by Indrianingsih *et al.* [59]. The procedure consisted of combining 50 μ L of PG with 100 μ L of 0.1 M phosphate buffer (pH 6.9) that contained 1.0 M α -glucosidase. The reaction mixture was subjected to incubation for a duration of 10 minutes at a temperature of 25°C. After incubation, 50 μ L of a 5 mM solution of p-NPG in the same buffer was introduced and left to react for an additional 5 minutes at a temperature of 25°C. The reaction was stopped by adding 50 μ L of a 0.1 M Na₂CO₃ solution. The absorbance was measured at a wavelength of 405 nm using a BIO-RAD Model 680 microplate reader, with acarbose serving as the control for comparison.

The percentage inhibition was determined by applying the formula,

$$\% \alpha - glucosidase\ inhibition = \left[\frac{(DAC - DAE)}{DAC} \right] \times 100 \quad (2)$$

DAC and *DAE* indicate alterations in absorbance of the control and extract, respectively. The IC_{50} value for inhibiting α -glucosidase was found using a standard calibration curve.

2.4. Molecular docking.

This study was initiated by acquiring the protein structures of human lysosomal acid α -glucosidase (AG) with PDB ID 5NN3, and human maltase-glucoamylase (MG), N-terminal subunit, with PDB ID 2QLY as the first step of our procedure. The formatting of these structures was optimized to ensure compatibility with AutoDock4.0 (AD) for molecular docking, as per previous reports [11, 60]. The protein structures were prepared by eliminating superfluous ligands, ions, or water molecules, introducing hydrogen atoms, and assigning partial charges. The binding location for molecular docking was precisely determined utilizing AD's internal utility and Biovia Discovery Studio. The search space for the ligand was defined using a three-dimensional grid box that included the whole binding site as well as nearby regions that are important for the interaction between the protein and the ligand. We generated and stored grid parameter files (GPF) and docking parameter files (DPF) for future docking studies.

Regarding the creation of the ligand, we acquired 3D ligand structures in formats that are suitable for use with AD, i.e., PG. The data was obtained from Drug Bank in respective formats (DPF, MOL2, etc.). We eliminated superfluous water molecules and heteroatoms from the ligand file, assigning charges and atom types through the utilization of software such as AutoDockTools (ADT) and Open Babel. The ligands were transformed into PDBQT format, which encompasses atom type and charge data, and thereafter preserved for future docking investigations [10].

AD was used to conduct molecular docking simulations, employing the generated protein and ligand files in conjunction with grid box parameters. We optimized the effectiveness and precision of the search by adjusting docking factors such as the number of runs, population size, and mutation rate. The docking data encompassed forecasted binding affinities and modes. Finally, we examined the docking outcomes by employing ADT and Biovia Discovery Studio [61, 62]. The primary objective of this investigation was to compute the binding energies, compare the most highly rated conformations with experimental data or crystal structures, and investigate the anticipated binding mechanism and interactions. This method facilitated the identification of crucial residues and interactions that contribute to the binding strength.

3. Results and Discussion

The extraction method from *V. Vinifera* seeds yielded a pale-yellow extract, which was obtained using Soxhlet extraction using methanol, as illustrated in Figure 1. The extract, weighing roughly 150 grams, underwent a concentration and drying procedure using a rotary evaporator under vacuum. The final concentrated extract was stored at a temperature of -20°C , assuring its preservation for further analytical processes.

GC-MS was performed in this work to detect and analyze bioactive substances in the extract primarily. This method identified a wide range of chemical components through distinct spectral peaks, allowing for their identification and characterization. An identifiable peak, with a retention time of around 10 minutes, was provisionally recognized as PG, a molecule

renowned for its bioactive characteristics, as shown in Figure 2a. The initial identification was made by comparing the existing databases (the list of chemicals identified is shown in Supporting Information Table S1). Later, HPLC was employed to isolate and analyze this compound further. The HPLC method specifically focused on a fraction found at a retention time of 7.30 minutes, which aligns with the established retention period of PG, as shown in Figure 2b. The spectral peak of this fraction corresponded to the reference spectrum of phloroglucinol, therefore supporting the GC-MS results and verifying the presence of PG in the extract, which is referred to in Supporting information Figure S1.

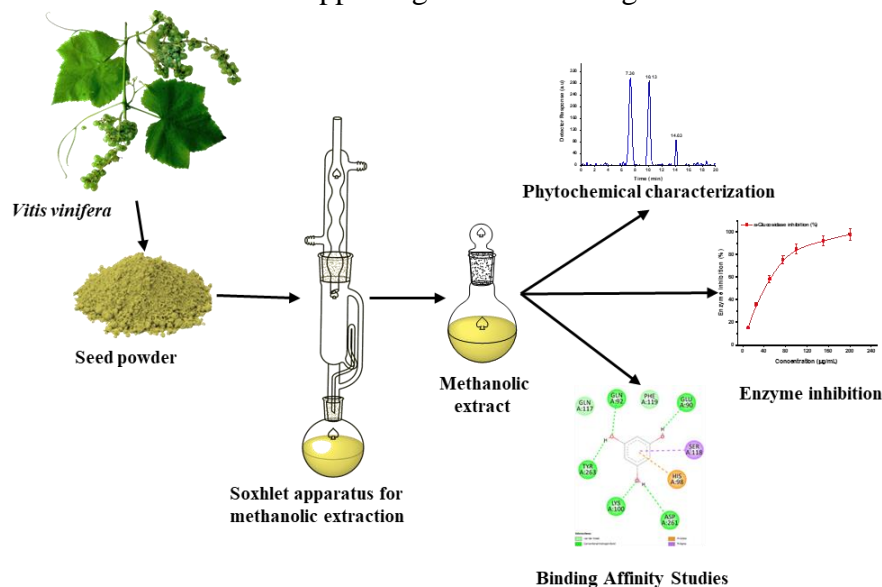


Figure 1. Schematic illustration of methanolic seed extraction of *Vitis vinifera*.

The existence of phloroglucinol was eventually confirmed using NMR spectroscopy. The identified spectrum peaks in the ^1H and ^{13}C NMR spectra agreed with the molecular structure of PG, thus verifying its existence in the extract, as shown in Figure 3. After receiving this confirmation, the fraction with a high concentration of PG was carefully harvested and preserved at freezing temperatures. The adoption of this storage method was intended to preserve the compound's integrity, ensuring its stability for further scientific investigations and potential therapeutic uses. We conducted a study to assess the antioxidant and α -glucosidase inhibitory properties of PG extracted from *V. Vinifera* seeds. Our findings demonstrate its substantial medicinal prospects. The DPPH radical scavenging assay was employed to assess the antioxidant capacity of phloroglucinol, following the approach outlined in earlier research from Sharma *et al.* [58].

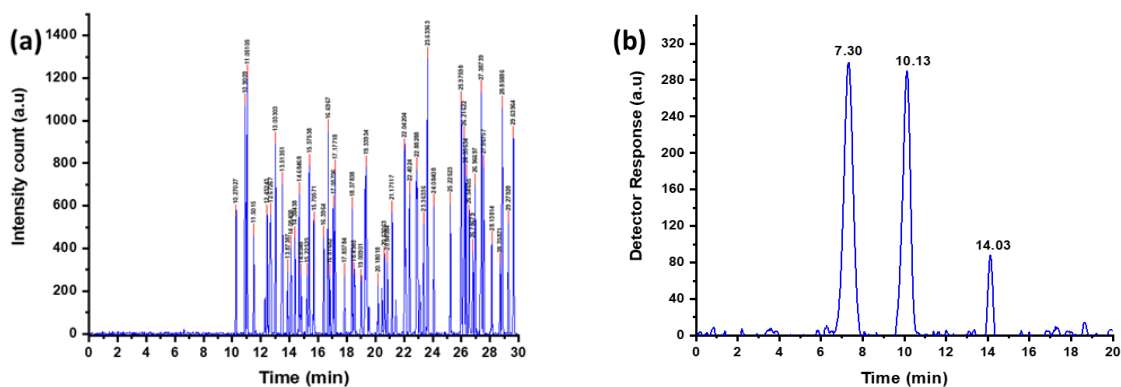


Figure 2. Characterization of the Methanolic seed extract of *Vitis vinifera* (a) Gas-liquid chromatography-mass spectral data showing the rich amount of bioactive compounds where at the peak 10.27 characterize the presence of the compound of interest followed by (b) sample fraction collection based on the high-performance liquid chromatography spectrum with peak maxima at 7.30 based on the reference.

This experiment quantified the reduction in absorbance at 517 nm, which indicates the compound's ability to counteract free radicals. PG exhibited significant antioxidant activity, indicated by its IC₅₀ value of 47.29 µg/mL. This suggests it is highly effective in neutralizing DPPH radicals and underscores its potential as a natural antioxidant agent.

In addition, the inhibitory effect of PG on α-glucosidase was evaluated using the methodology outlined by Yildirim Akatin *et al.* [63]. This assay is essential for comprehending the compound's potential in diabetes treatment, as it evaluates the inhibition of α-glucosidase, an enzyme essential to the digestion of carbohydrates. PG exhibited a noteworthy inhibitory impact on α-glucosidase, as evidenced by an IC₅₀ value of 44.79 µg/mL. The value is significantly lower compared to the values reported in prior investigations for other polyphenols, highlighting the greater effectiveness of PG in this aspect [64, 65].

The presence of potent antioxidant and α-glucosidase inhibitory properties in PG, as demonstrated by its low IC₅₀ values in both tests, suggests that it is more efficient than numerous other polyphenolic substances [66-68]. The findings confirm the therapeutic potential of PG, as demonstrated by its isolation and characterization, and reveal its potential use in treating oxidative stress and diabetes. Incorporating these outcomes with our prior discoveries regarding the isolation and delineation of PG underscores the significance of this substance in the investigation of natural products and its potential contribution to the creation of innovative therapeutic medicines.

It aimed to determine the potential anti-diabetic properties of PG by studying their interactions with two different proteins responsible for carbohydrate metabolism. In the current investigations, we used PG and two proteins, AG and MG, where we observed the binding affinities of the ligand and their conformational changes as they contacted the proteins using molecular docking studies. By using the AD program, the binding affinity was calculated between ligands and protein molecules.

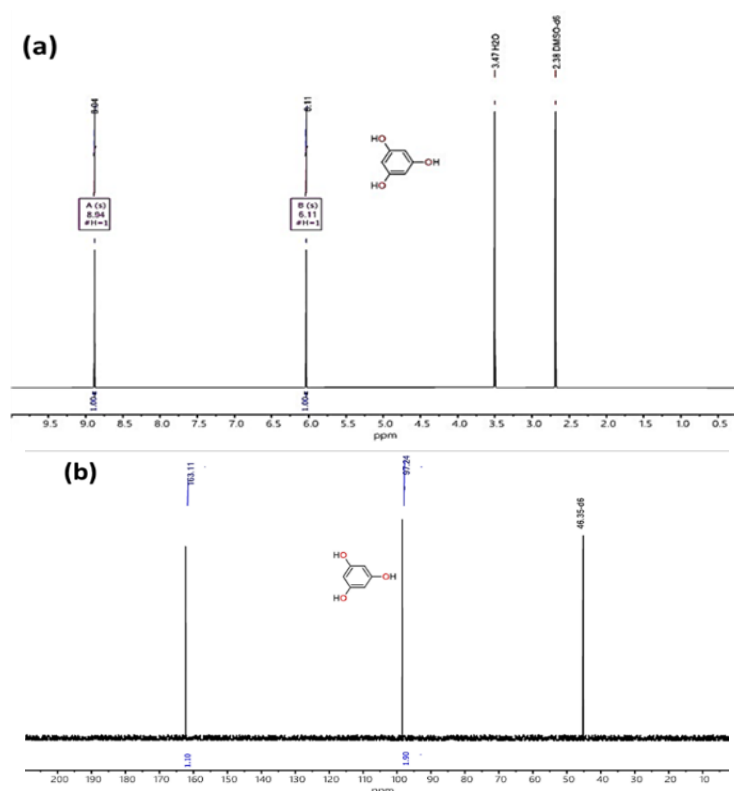


Figure 3. NMR spectra of HPLC fraction containing phloroglucinol compound isolated from seed extraction of *Vitis vinifera* (a) ¹H NMR (500 MHz, DMSO-d₆) δ 8.94 (s, ¹H), 6.11 (s, ¹H); (b) ¹³C NMR (125 MHz, DMSO-d₆) δ 163.11, 97.24.

As shown in Table 1, docking studies demonstrated the binding energy (ΔG) values, followed by the inhibition constants (K_i). The findings showed that the relative binding of the ligands bound to AG was relatively proximal for the standard drug MG (Binding energy -7.32 Kcal/Mol), as shown in Figure 5. Compared to PG, AG exhibited the inhibition constant $K_i=683.06 \mu\text{M}$, demonstrating possible inhibition of the respective protein species. By comparing the in-silico activities of PG, one can understand the impact of electron-donating and electron-withdrawing constituents. As compared to the relative hydroxyl groups in the PG, conjugation flowed on polyhydroxy groups on the phenolic skeleton and produced an extensive binding affinity. The classical reason for binding the PG to AG would be that activity clearly decreased when an electron-donating group was present. Still, as the ability to extract electrons diminished, activity increased. The reason for this is increased clomb and lipophilic contact, which increases the aromatic ring's charge density and contributes the most to binding free energy.

Our research not only adds to the existing literature on the phytochemical analysis of *V. Vinifera* but also emphasizes the particular significance of PG [71]. The congruence between our findings and previous research substantiates the validity of our methodology and the potential of PG as a bioactive chemical with substantial therapeutic implications. The above observations are consistent with the previous studies, which include the Moghadam *et al.* research report, which showed that it was discovered that 143 metabolites were present in polyphenols [69]. Measurements were conducted on 26 of these chemicals. There was a greater amount of total phenolic content, antioxidant capacity, and anti-glucosidase activity in strawberry gum. A recent report from the Nguyen *et al.* group [70] showed that in-silico analysis points to the possibility of prospective therapeutic molecules. Based on these observations of the ligand-protein interactions in this study, further asses of anti-diabetic medicines through *in-vivo* analysis would be required for the validity of the concept.

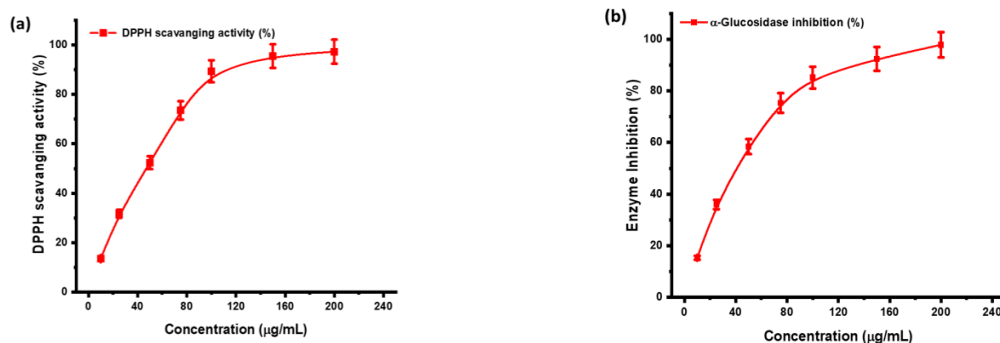


Figure 4. Biological activity of phloroglucinol compound isolated from seed extraction of *Vitis vinifera* (a) antioxidant activity was assessed with the DPPH activity; (b) inhibition of the α -Glucosidase enzyme inhibition.

Table 1. Detailed ligand protein interactions are displayed with binding energy, and inhibitions are constant for respective interactions.

Receptor	Binding affinity (ΔG) kcal/mol	Inhibition constant (K_i) M	Proximal amino acids
α -glucosidase	-7.32	83.06 μM	GLU 866; SER 864; HIS 717; ASP 860; HIS 717
Maltase-glucoamylase	-6.69	62.66 μM	GLN 92; GLU 90; TYR 263; LYS 100; ASP 261

4. Conclusions

The comprehensive examination of PG derived from *V. Vinifera* seeds has shown its significant bioactive characteristics, specifically in relation to its antioxidant and α -glucosidase

inhibitory effects. The study successfully utilized GC-MS, HPLC, and NMR spectroscopy techniques to demonstrate the presence and purity of PG. The low IC₅₀ values observed in the DPPH scavenging and α -glucosidase inhibition experiments highlight the potential of this substance as a natural medicinal agent. Moreover, molecular docking studies have yielded valuable information regarding the interaction between PG and crucial metabolic enzymes, indicating its potential efficacy in diabetes management. These findings are consistent with and expand upon previous research on the therapeutic uses of grape seed extracts and their components. This study emphasizes the significance of natural substances in the process of finding new drugs and highlights the potential of phloroglucinol as a promising option for further research in the treatment of metabolic disorders.

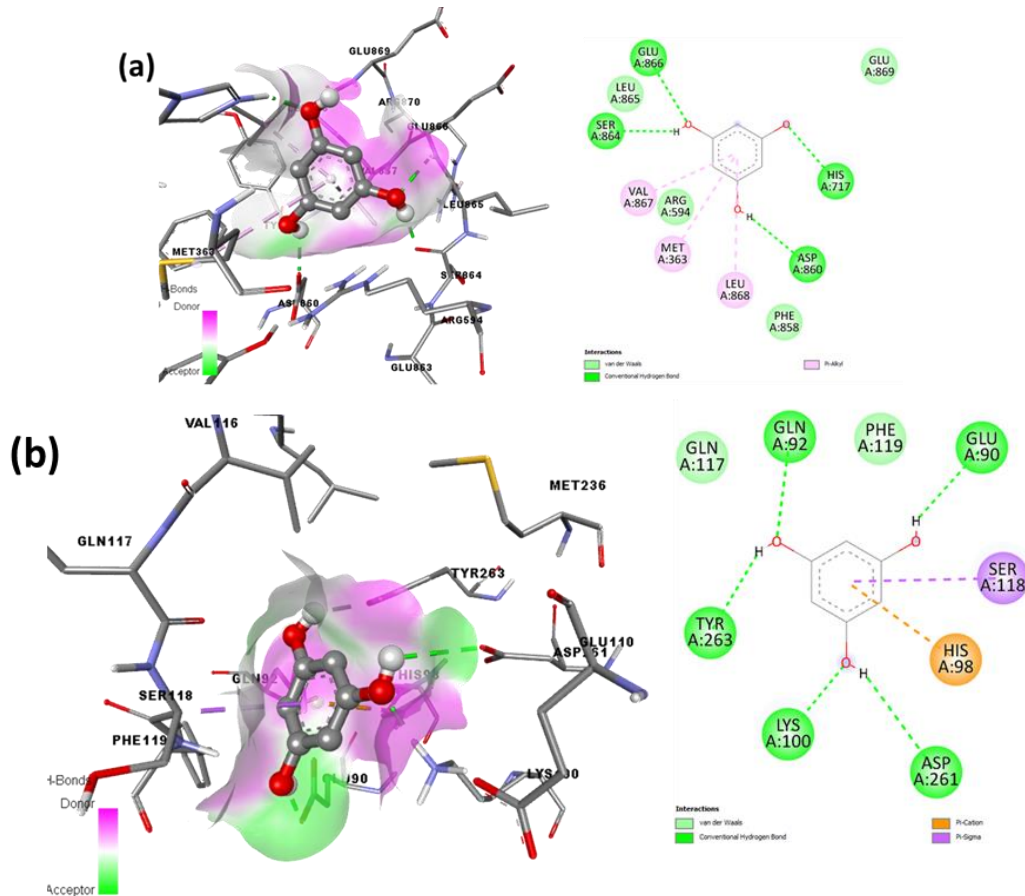


Figure 5. Ligand-protein interaction represented in 3D and 2D conformations with phloroglucinol (a) α -glucosidase; (b) Maltase-glucoamylase.

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Conflicts of Interest

The authors declare no conflict of interest

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Supplementary materials

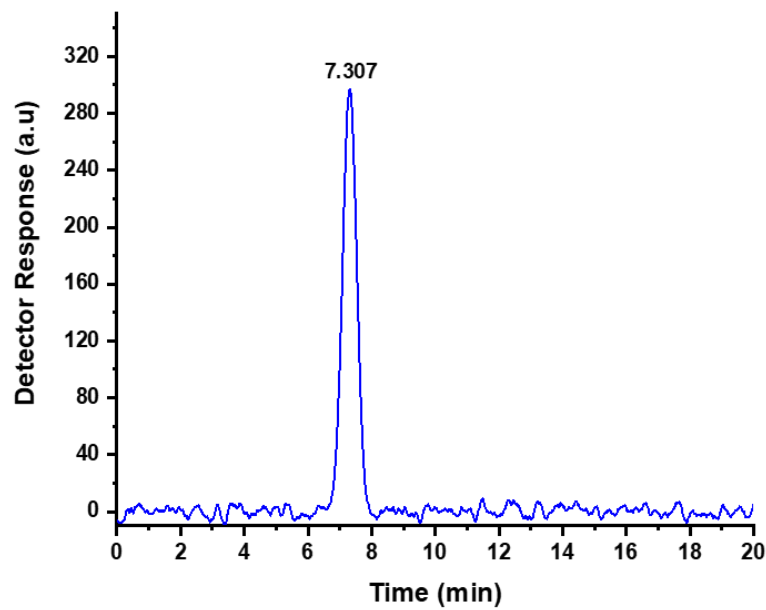


Figure S1. Characterization of the commercial phloroglucinol using the High-Performance Liquid Chromatography spectrum with peak maxima at 7.307 minutes used as reference in this experimentation.

Table S1. GC-MS spectrum retention time-based plant bioactive compounds identification.

Peak No	Retention Time	Compound
1	10.27	Phloroglucinol
2	10.90	a-D-Glucopyranoside , methyl 3,6- anhydro
3	11.50	H-pyrazole.1 - carbothioamide , 3,5-dimethyl
4	12.43	2-Furanmethanol
5	12.67	Desulphosinigrin
6	13.06	-Gala-I-ido-octonic lactone
7	13.51	D-Glucopyranoside . O-a-1)glucopyranosyl- (1. fwdanv.3)-β
8	13.87	6-0xa-bicyclo[3.1.0]hexan-3-one 2(H)-Pyrazinone 4H-pyran-4-one. 2,3-dihydro-3.5-dihydroxy-6-methyl- 3,4-
9	14.08	
10	14.38	difluoroanisole propane, I-isocyanato.
11	14.68	2 — tetrazaboroline 5- ethyl- 1.4- dimethyl- thymine Thymine.
12	15.22	L.arabinitol Xylitol
13	15.37	10,13-Octadecadienoic acid. methyl ester
14	15.70	5-hydroxymethylfurfural 4- mercaptophenol
15	16.39	9, 12-Octadecadienoic acid (Z.Z)-, methyl este
16	17.05	8.11 -Octadecadienoic acid, methyl ester
17	17.17	procyanidin dimer
18	19.00	Furfural
19	21.17	1,8-Dioxa-5 thiaoctane,8-(9- borabicyclo(3.3. linon-9-yl)-3-(9-
20	22.04	procyanidin dimer gallate
21	22.40	9.10- Secoch01esta5.7.10(19)- triene-324.25- triol.(3B.5Z.7E)-
22	22.88	10, 13-Octadecadienoic acid, methyl ester
23	23.63	3-Cyclohexene-1 - methanol.u.u.4- trimethyl- ,propanoate