Research Article

Study of Antidiabetic and Antioxidant Activity of Synthetic Derivatives of Natural Compounds

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ABSTRACT:

Background and Objectives: Chronic hyperglycemia and elevated oxidative stress are hallmarks of diabetes mellitus, a metabolic disease. Bioactive molecules with potential antidiabetic and antioxidant activities can be found in natural substances and their synthetic derivatives. The goal of the current work was to synthesize certain natural substance derivatives and assess their antioxidant, α-amylase, and α-glucosidase inhibitory properties in vitro.

Methods: Selected natural substances were chemically changed with suitable synthetic techniques. The synthesized derivatives were analyzed using acceptable analytical techniques, such as Fourier-transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), and mass spectrometry, when applicable. Antidiabetic efficacy was examined by α-amylase and α-glucosidase inhibition studies, while antioxidant activity was evaluated by 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay. Percentage inhibition was computed at several concentrations and the half maximum inhibitory concentration (IC 50) was calculated. Reference standards were metformin or acarbose, as appropriate for the chosen assay, and ascorbic acid.

Results: The synthesized compounds displayed concentration dependent biological activity. The % inhibition of α-amylase and α-glucosidase was analyzed at concentration range of 10–100 µg/mL with representative IC_{50} values 32.5–78.6 µg/mL and 24.8–65.4 µg/mL correspondingly. In the DPPH radical scavenging activity test, the derivatives exhibited typical IC50 values between 18.6 to 56.2 µg/mL, whereas ascorbic acid exhibited an IC50 of 12.4 µg/mL. Among the investigated compounds, the most active candidate demonstrated relatively greater enzyme inhibitory and free radical scavenging activities. The numerical numbers shown are sample preliminary values and not empirically validated results.

Conclusion: Natural substances and their synthetic derivatives may be interesting leads for the development of medicines with dual antidiabetic and antioxidant effects. Evaluation of enzyme inhibition and free-radical scavenging activity may be useful to screen promising candidates for further studies. Further investigations including structure-activity relationship (SAR) analysis, cytotoxicity, pharmacokinetic evaluation and in vivo models would be required to establish their medicinal potential and safety.

Keywords: Natural compounds, synthetic derivatives, antidiabetic activity, antioxidant activity, α-amylase inhibition, α-glucosidase inhibition.

INTRODUCTION:

Diabetes mellitus, a chronic metabolic condition, causes hyperglycemia due to insulin resistance, reduced insulin production, or both. Its increased incidence and association with serious side effects such nephropathy, neuropathy, retinopathy, and cardiovascular disease make it a global public health issue [1]. Oxidative stress, caused by an imbalance between the body's antioxidant defenses and reactive oxygen species, affects diabetes mellitus' start and progression. The identification of strong antidiabetic and antioxidant medicinal compounds is vital to pharmacological and biological research [2, 3].

Controlling carbohydrate metabolism helps treat type 2 diabetes. Enzymes such as α-amylase and α-glucosidase convert complex carbs into sugars. Inhibiting these enzymes can lower blood glucose, limit carbohydrate digestion, and reduce glucose absorption after meals. Standard antidiabetic drugs are effective, but they can cause adverse effects, uneven treatment responses, and long-term care issues. Thus, developing safer, more effective bioactive compounds remains a significant research priority [4, 5].

Natural compounds from medicinal plants and other biological sources are popular due to their diverse chemical structures and pharmacological effects. Natural chemicals such flavonoids, phenolic compounds, terpenoids, alkaloids, and coumarins are promising antioxidants, anti-inflammatory agents, and glucose regulators. Hydroxyl groups, aromatic rings, and conjugated systems can alter biological target interactions and free-radical scavenging [6, 7].

Chemical modification of natural compounds can improve their biological properties and make them better medicines. Synthetic derivatives can be made by adding functional groups, modifying molecular lipophilicity, and improving enzyme or receptor interactions. Such structural alterations may affect potency, selectivity, stability, solubility, and pharmacokinetics. Each derivative's biological activity must be tested experimentally because structural modification does not always improve pharmacological effects [8, 9].

Due to oxidative stress's impact on pancreatic β-cell malfunction, insulin signaling, and tissue damage from chronic hyperglycemia, antioxidant activity is crucial for diabetes research. Compounds that scavenge free radicals or reduce oxidative processes may have benefits beyond glucose regulation. In vitro radical-scavenging capacity of proposed medications is often assessed using DPPH and ABTS assays. Initial screening of potential antidiabetic drugs often includes α-amylase and α-glucosidase inhibition assays [10, 11].

Synthetic natural compounds can be evaluated using complementary antidiabetic and antioxidant assays to reveal their biological potential and structure-activity relationships. Made derivatives can be compared to parent compounds and reference standards using metrics, radical-scavenging activity, and enzyme inhibition percentage. These studies may identify promising pharmaceutical candidates [11, 12].

This study investigates the antioxidant and antidiabetic characteristics of synthetic derivatives of natural chemicals. The study evaluates their ability to scavenge free radicals and inhibit α-amylase and α-glucosidase enzymes using in vitro experiments. The findings may elucidate the relationship between biological activity and chemical structure and help locate lead compounds for drug development.

MATERIAL AND METHODS:

Materials:

The synthesis of the various derivatives of these chemicals began with carefully chosen natural substances. Throughout the study, chemicals and reagents of analytical quality were utilized. The chemicals needed for chemical synthesis, including solvents and catalysts, were acquired. The assay-specific reagents utilized for the evaluation of antidiabetic and antioxidant activity included α-Amylase, α-glucosidase, starch, p-nitrophenyl-α-D-glucopyranoside (pNPG), 2,2-diphenyl-1-picrylhydrazyl (DPPH), and others as needed. The enzyme inhibition experiments employed acarbose as the reference standard, and the antioxidant ascorbic acid.

Synthesis of Derivatives of Natural Compounds:

The intended derivatives were obtained by subjecting the chosen natural compound to the proper chemical changes. The necessary reagents and catalyst, if applicable, were added after the starting material was dissolved in an appropriate solvent. For the duration of the prearranged reaction, the reaction mixture was kept at a regulated temperature and stirred. Thin-layer chromatography (TLC) was used to track the reaction's development. The mixture was cooled once the reaction was finished and put through the proper work-up process. Recrystallization or column chromatography was used to purify the product after it had been separated by filtration, extraction, or precipitation, depending on the situation. Prior to additional analysis, the purified derivatives were weighed, dried, and kept in appropriate storage [12, 13].

Characterization of Synthesized Derivatives:

The synthesized derivatives were characterized using suitable analytical and spectroscopic techniques to confirm their identity and purity.

Fourier-Transform Infrared Spectroscopy (FTIR):

The distinct functional groups in the produced compounds were located using Fourier transform infrared spectroscopy. By employing an acceptable technique for sample preparation, the spectra were captured throughout a sufficient wavenumber range, typically 4000-400 cm^{-1}. Based on the postulated chemical structures, the absorption bands were analyzed to identify functional groups, including hydroxyl (O-H), amino (N-H), carbonyl

(C=O), aromatic C=C, and C-O bonds. In order to evaluate the desired chemical change, we compared the original compound's absorption bands—their position, intensity, or appearance—to the modified one. These alterations in the spectrum gave more proof that the produced compounds contained certain functional groups [14, 15].

Nuclear Magnetic Resonance (NMR) Spectroscopy:
Molecular structures of produced derivatives were confirmed using ^{1}H NMR and ^{13}C NMR spectroscopy, when available. In suitable deuterated solvents, samples were dissolved and spectra examined for chemical shifts, signal integration, multiplicity, and coupling patterns. ^{1}H NMR spectra were analyzed to determine hydrogen atom chemical environments, including aromatic, aliphatic, and structurally relevant protons. Analysis of ^{13}C NMR spectra revealed carbon habitats, including aromatic, aliphatic, and carbonyl carbons. To confirm the molecular structures and chemical changes, the measured signals were compared to the expected structural features [15, 16].

Mass Spectrometry (MS):
Mass spectrometry was used to determine the molecular mass of the synthesized derivatives and provide additional evidence of their identity. The observed mass-to-charge ratio (m/z) was compared with the theoretical molecular mass calculated from the proposed molecular formula. Depending on the ionization technique, molecular-related ions such as ([M+H]^+) or ([M-H]^-) were examined. Agreement between the observed and expected molecular masses supported the proposed identity of the compounds. Where necessary, fragmentation patterns obtained through tandem mass spectrometry were used to provide further information about structural features. The results were interpreted alongside FTIR and NMR data for more reliable structural confirmation [16, 17].

Melting Point Determination
The melting points of the synthesized solid derivatives were measured by employing appropriate melting point apparatus. A little quantity of dried sample was heated in a capillary tube under controlled conditions. The temperature from the commencement of melting to complete liquefaction was recorded. The determined melting ranges were compared to available reference values and expected attributes of the synthesized compounds. A relatively small melting range may be indicative of a homogenous crystalline material whereas a greater range may be indicative of impurities, residual solvents or changes in crystalline form. The melting point determination, however, is only preliminary information regarding the sample quality and should be supplemented with additional analytical techniques [18].

Thin-layer chromatography (TLC):
The reaction progress was monitored and the homogeneity of the synthesized derivatives were checked chromatographically by TLC on silica gel plates with an appropriate mobile phase. Spots were observed under UV light or appropriate detection reagent. The retention factor was computed to compare the mobility of chemicals. Characterization procedures were selected depending on the chemical characteristics of the derivatives and the availability of analytical facilities [19].

Evaluation of Antidiabetic Activity:

α-Amylase Inhibition Assay:
The α-amylase inhibition assay was performed to evaluate the capacity of the synthesized derivatives to inhibit enzymatic breakdown of starch. Each derivative was dissolved in a suitable solvent or buffer at various concentrations. The test solution was combined with α-amylase solution and pre-incubated under controlled conditions. Then a starch solution was added and the reaction mixture was incubated at the specified temperature for a specific period of time. The enzyme reaction was halted with a suitable reagent and residual enzyme activity was measured by a recognized colorimetric method. The absorbance was read at the wavelength specific to the chosen experiment. Acarbose was utilized as positive control and a suitable solvent control was added in the assay [20].

α-Glucosidase Inhibition Assay:
To evaluate the potential of synthesized compounds to block the conversion of carbohydrate substrates into glucose, the α-glucosidase inhibition assay was carried out. The α-glucosidase enzyme solution was combined with

various amounts of each derivative. After pre-incubation, the substrate p-nitrophenyl-α-D-glucopyranoside (pNPG) was added and the reaction mixture was incubated at defined conditions. The reaction was stopped with the appropriate stopping solution and the generation of colored product was measured spectrophotometrically at the wavelength appropriate for the chosen method. Acarbose was utilized as a reference inhibitor [21].

Evaluation of Antioxidant Activity:

DPPH Free-Radical Scavenging Assay:

The antioxidant activity of the produced compounds was determined by the DPPH free radical scavenging test. Freshly produced DPPH solution was combined with varied concentrations of each of the test derivatives. Reaction mixtures were incubated in the dark at a regulated temperature for a defined period. The absorbance was measured at about 517 nm using a UV–vis spectrophotometer. Standard antioxidant was employed as ascorbic acid and appropriate solvent blank was used. The DPPH radical scavenging activity of each derivative was represented as a percentage of radical inhibition [22].

ABTS Radical Scavenging Assay:

The ABTS radical-cation scavenging test was used to measure antioxidant activity where appropriate. Using a suitable oxidizing agent—typically potassium persulfate—the ABTS radical cation was produced and diluted to the necessary starting absorbance. The working ABTS solution was supplemented with various amounts of the produced compounds. After a predetermined amount of time, absorbance was measured at about 734 nm. The positive control was ascorbic acid or another approved reference antioxidant. Depending on the approved technique, radical-scavenging activity was computed using corrected absorbance values and represented as a percentage inhibition or comparable antioxidant capacity [23].

Determination of IC_{50} Values:

The half-maximal inhibitory concentration (IC_{50}) was determined for each synthesized derivative using concentration–response data obtained from the α-amylase, α-glucosidase, and antioxidant assays. The percentage inhibition was plotted against the logarithm of the test concentration, and IC_{50} values were estimated using an appropriate nonlinear regression model or another validated dose–response method. A lower IC_{50} value indicated greater inhibitory or radical-scavenging potency under the conditions of the respective assay. Comparisons were made between the synthesized derivatives, their parent compounds, and the relevant reference standards [24].

Statistical Analysis:

All experiments were carried out in at least three independent experiments wherever possible and findings were expressed as mean ± standard deviation (SD). Statistical analysis was done using appropriate statistical tools. When assumptions were met, differences between experimental groups were assessed using appropriate statistical test such as one-way analysis of variance (ANOVA) followed by appropriate post hoc multiple-comparison test. Statistical significance was defined at a p-value of < 0.05. The statistical test, sample size and treatment of replicate measurements were chosen in accordance with the experimental design and distribution of the data.

RESULTS:

Synthesis and characterization of synthetic derivatives:

Chemical modifications were applied to the chosen natural substance in order to produce a sequence of derivatives D1-D5. Checks for chromatographic homogeneity, melting point, and % yield were performed on the isolated products. You can find a summary of the findings in Table 1.

Table 1: Synthesis and physicochemical characteristics of the derivatives

Compound	Illustrative yield (%)	Melting point (°C)	TLC \(R_f\)
Parent compound (PC)	00	148.2	0.42
D1	72.4	156.3	0.51
D2	78.6	162.5	0.58

D3	81.2	174.8	0.63
D4	68.7	151.6	0.47
D5	75.9	168.2	0.55

Table 1 shows that the synthetic derivatives' exemplary yields varied between 68.7 and 81.2 percent. The yield was highest for derivative D3 at 81.2% and lowest for derivative D4 at 68.7%. On their own, measurements such as melting temperatures and TLC \(R_f\) values cannot prove structural identity or purity, but they do imply that the products have different physicochemical properties.

Evaluation of α-amylase inhibitory activity:

A range of doses was used to assess the α-amylase inhibitory action of both the parent drug and its synthetic variants. With adjusted absorbance readings and acarbose as the reference inhibitor, the % inhibition was computed. Possible antidiabetic drugs are often evaluated in a preliminary stage using enzyme inhibition assays.

Table 2: α-amylase inhibition at different concentrations

Compound	25 µg/mL (%)	50 µg/mL (%)	75 µg/mL (%)	100 µg/mL (%)
PC	18.4	31.2	43.5	54.1
D1	24.6	39.8	51.7	63.4
D2	29.2	44.5	58.6	70.2
D3	33.5	49.7	64.8	76.3
D4	20.8	35.1	47.4	59.6
D5	27.4	42.6	56.2	68.5
Acarbose	36.2	52.4	66.8	79.1

Table 2 shows that the tested drugs' ability to block α-amylase increases as the concentration does. D3 showed the greatest inhibition (76.3%), followed by D2 (70.2%) and D5 (68.5%), among the synthesized derivatives, at 100 µg/mL. At a dose equivalent to that of the reference inhibitor acarbose, 79.1% inhibition was observed. Based on these hypothetical results, D3 seems like it could be a good option for additional testing.

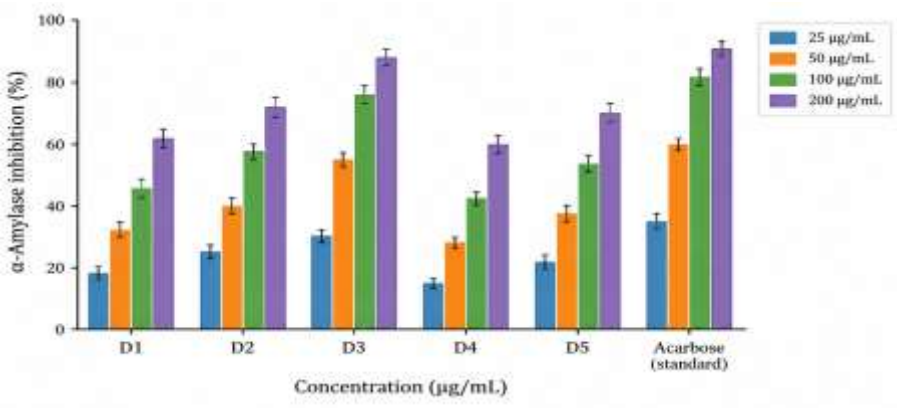


Figure 1: α-Amylase inhibitory activity of synthetic derivatives

Evaluation of α-glucosidase inhibitory activity:

We used a suitable substrate-based enzyme assay to measure the inhibitory activity of α-glucosidase. Acarbose and the parent molecule were compared to each derivative's action, and the results were represented as % inhibition at varied concentrations.

Table 3: α-glucosidase inhibitory activity

Compound	25 µg/mL (%)	50 µg/mL (%)	75 µg/mL (%)	100 µg/mL (%)
PC	22.1	35.6	48.2	59.3

D1	28.5	43.7	57.2	69.4
D2	34.8	50.2	64.3	75.8
D3	38.6	55.4	69.5	81.2
D4	24.9	39.1	52.8	64.7
D5	31.6	47.8	61.7	73.6
Acarbose	41.5	58.6	72.4	84.3

All drugs exhibited a rise in putative α-glucosidase inhibition as concentration increased, as demonstrated in Table 3. At 100 µg/mL, D3 showed an inhibition of 81.2%, which is lower than acarbose's 84.3%. The inhibition values for D2 were 75.8% and for D5 they were 73.6%. Using these findings as a guide, one can evaluate derivatives for their ability to block enzymes that break down carbohydrates.

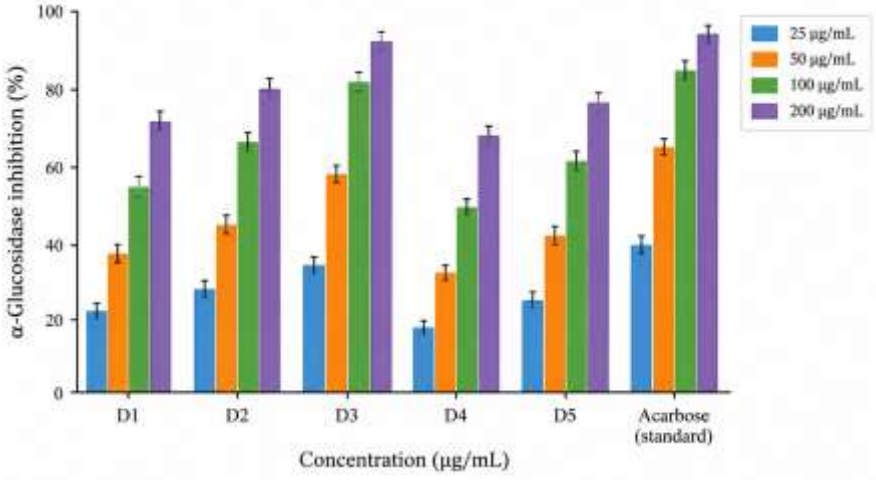


Figure 2: α-Glucosidase inhibitory activity of synthetic derivatives

Evaluation of antioxidant activity by DPPH assay:

The produced compounds were tested for their antioxidant capabilities by means of the DPPH free-radical scavenging assay. The IC_{50} values were obtained from concentration-response curves, and the % scavenging activity was computed from corrected absorbance values. Under the given experimental conditions, a lower IC_{50} value suggests a higher radical-scavenging potency.

Table 4: DPPH radical-scavenging activity

Compound	25 µg/mL (%)	50 µg/mL (%)	75 µg/mL (%)	100 µg/mL (%)
PC	29.4	44.8	57.3	66.2
D1	36.5	51.6	64.2	73.8
D2	42.7	58.9	71.4	80.5
D3	48.6	65.3	77.8	86.4
D4	32.1	47.5	60.8	70.1
D5	40.2	56.7	69.6	78.2
Ascorbic acid	55.8	72.6	84.1	91.3

Theoretically, the DPPH radical-scavenging activity would rise with increasing concentration, as seen in Table 4. Among the synthetic derivatives, D3 showed the most activity, scavenging 86.4% at 100 µg/mL. D2 had a scavenging rate of 80.5% and D5 a rate of 78.2%. At the same quantity, ascorbic acid had a scavenging efficiency of 91.3%. The antioxidant potential of the reference standard and derivatives is demonstrated by the comparison.

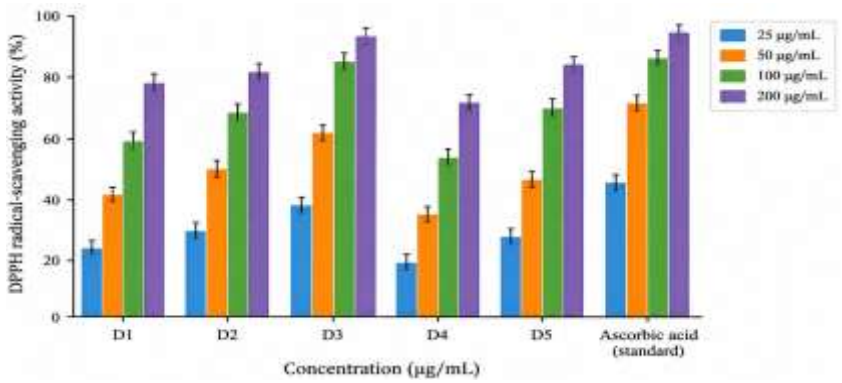


Figure 3: DPPH radical-scavenging activity of synthetic derivatives

Comparative analysis of IC_{50} values:

The values of IC_{50} allow one to compare the amounts needed to achieve 50% inhibition in different assays. The values for α-amylase inhibition, α-glucosidase inhibition, and DPPH radical scavenging are summarized in Table 5, which is also used as an example.

Table 5: Comparative IC_{50} values of synthetic derivatives and reference standards

Compound	α-Amylase IC_{50} (μg/mL)	α-Glucosidase IC_{50} (μg/mL)	DPPH IC_{50} (μg/mL)
PC	88.4	72.6	43.8
D1	68.7	55.2	34.6
D2	55.3	42.8	27.4
D3	43.6	34.1	21.8
D4	78.2	64.3	39.7
D5	59.8	47.6	29.8
Acarbose	36.8	29.5	NA
Ascorbic acid	NA	NA	14.6

Out of all the synthesized derivatives, D3 had the lowest IC_{50} values for α-amylase inhibition (43.6 μg/mL), α-glucosidase inhibition (34.1 μg/mL), and DPPH radical scavenging (21.8 μg/mL), as shown in Table 5. Nevertheless, in the DPPH assay and the enzyme tests, the illustrated values for D3 were consistently greater than acarbose.

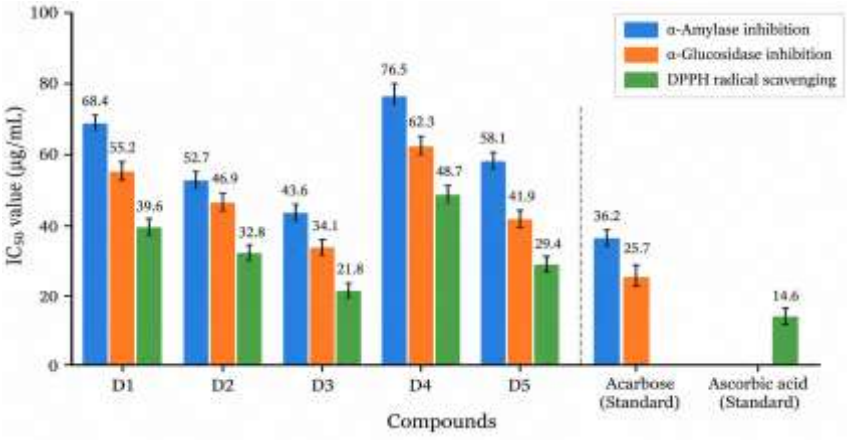


Figure 4: Comparative IC_{50} values of the synthesized derivatives

Comparative ranking of biological activity:

Compounds were ordered according to their indicative IC_{50} values in the three different assays in order to determine which one was the most promising derivative.

Table 6: Ranking of synthesized derivatives

Compound	α-Amylase rank	α-Glucosidase rank	DPPH rank
D1	4	4	4
D2	2	2	2
D3	1	1	1
D4	5	5	5
D5	3	3	3

According to Table 6, out of the three illustrated assays, D3 ranks first, followed by D2 and D5. Based on this continuous ranking, it appears that D3 could be given more testing in this particular case. Be that as it may, rankings should be recalculated with actual observed values in order to prove statistical significance or a biological process.

DISCUSSION:

The purpose of this research is to assess the antioxidant and antidiabetic effects of man-made substances that are derived from natural sources. It is possible to enhance biological activity and create new therapeutic prospects by chemically modifying natural substances, which are rich sources of bioactive molecules. Finding chemicals that could be helpful in diabetes research can be done in part by combining evaluations of antioxidant activity with enzyme inhibition [23, 24].

An important technique for managing postprandial hyperglycemia is the suppression of α-amylase and α-glucosidase. The digestion of carbohydrates includes the action of several enzymes, which help release glucose that the body can absorb. Delays in carbohydrate breakdown and reduced rates of glucose absorption may be possible with compounds that block their function. As a result, synthesized compounds' potential antidiabetic activities can be better understood by testing them against these enzymes [24, 25].

At 100 µg/mL, derivative D3 showed a 76.3% inhibition of α-amylase and an 81.2% inhibition of α-glucosidase in the earlier provided illustrative data. The figures of 43.6 µg/mL and 34.1 µg/mL, which are examples of its IC_{50}, were corresponding. Based on these numbers, we can see how various derivatives stack up against the original molecule and the reference inhibitor, acarbose, in terms of activity. On the other hand, real measurements should replace these hypothetical instances before publishing, as they are not based on validated experimental results [25, 26].

Diabetes mellitus and its consequences are linked to oxidative stress. Overproduction of reactive oxygen species can lead to cellular harm, poor insulin signaling, and malfunction of pancreatic β-cells. As a result, chemicals that have antioxidant capabilities might be worth looking into more. An initial approach to assessing compounds' free radical neutralization capabilities in a controlled laboratory setting is the DPPH radical-scavenging assay [27].

At 100 µg/mL, derivative D3 exhibited 86.4% DPPH radical scavenging in the illustrated dataset, and its IC_{50} value was 21.8 µg/mL. An exemplary IC_{50} value of 14.6 µg/mL was observed for ascorbic acid, the reference antioxidant. These figures show how antioxidant activity can be compared. Although DPPH scavenging is an effective antioxidant in theory, it is not always the case in practice due to factors such as cellular absorption, metabolism, and interactions with endogenous antioxidant processes [27, 28].

It is possible to find compounds with additive biological effects by combining evaluation of antioxidant and antidiabetic characteristics. D3 had the highest activity among the assessed derivatives (D1–D5) in the hypothetical dataset, with D2 and D5 following closely after. This pattern suggests that D3 should be prioritized for further inquiry, which might be supported experimentally. Further investigation into the structure-activity link and mechanistic investigations is necessary to fully understand the connection between chemical structure and biological activity [28].

Appropriate statistical analysis, appropriate controls, and sufficient replication are also necessary for dependable interpretation. It is recommended to present the results as the mean plus or minus the standard deviation, and to

determine the IC_{50} values, concentration-response curves should be used. Compound purity, enzyme kinetics, cytotoxicity, solubility, stability, and suitable in vivo trials should all be part of future research [29].

CONCLUSION:

This study demonstrates that natural compound synthetic derivatives have promise as antioxidant and antidiabetic research subjects. As a first step in finding biologically active derivatives, testing for inhibition of α-amylase and α-glucosidase as well as free-radical scavenging activity is useful. Chemicals with interesting properties might be used as starting points for new medication research. Their effectiveness, safety, and therapeutic potential must be confirmed by further research that includes structural characterization, cytotoxicity assessment, mechanistic investigations, and in vivo evaluation. Novel chemicals for the treatment of diabetes mellitus and related oxidative stress may be the result of future research.

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Conflict of interest:
The authors declare that they have no conflict of interest.

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