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ANTIOXIDANT, IN VITRO ANTIDIABETIC, AND ANTI-INFLAMMATORY APPLICATIONS OF A CHEMICALLY MODIFIED SALVIA HISPANICA L. SEED MUCILAGE

Original Research

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ABSTRACT

Background: Hydrogel-based drug delivery systems have gained increasing attention due to their ability to improve therapeutic efficacy through controlled release and biological responsiveness. Natural polysaccharides are particularly attractive for such applications because of their biocompatibility and functional versatility. Chia seed mucilage (*Salvia hispanica* L.) is a polysaccharide-rich material with inherent gel-forming and bioactive properties, yet its potential in amide-modified, thermo-responsive hydrogel systems for multifunctional biomedical use remains underexplored.

Objective: This study aimed to synthesize an amide-modified, thermo-responsive hydrogel from chia seed mucilage and acrylamide and to evaluate its in vitro antioxidant, antidiabetic, and anti-inflammatory activities to assess its suitability as a multifunctional therapeutic and drug delivery material.

Methods: The hydrogel was synthesized via free radical polymerization using acrylamide as the monomer, ammonium persulfate as the initiator, and N,N′-methylenebisacrylamide as the cross-linker. Antioxidant activity was assessed using DPPH radical scavenging and ferric reducing antioxidant power assays. Antidiabetic potential was evaluated through α-amylase inhibition kinetics, while anti-inflammatory activity was determined using the egg albumin protein denaturation assay. All experiments were performed in vitro using concentration-dependent analyses and compared with standard reference compounds.

Results: The hydrogel demonstrated strong antioxidant activity, achieving 71.90% DPPH radical scavenging at 250 µg/mL, closely comparable to ascorbic acid (71.74%). In the FRAP assay, reducing power increased dose-dependently, reaching 73.44 µmol Fe(II)/g, near the standard value of 77.29 µmol Fe(II)/g. The hydrogel exhibited marked α-amylase inhibition, achieving 76.07% inhibition at 30 µg/mL compared with 83.46% for acarbose. Anti-inflammatory assessment revealed concentration-dependent inhibition of protein denaturation, reaching 67.20% at 250 µg/mL, compared with 72.41% for diclofenac sodium.

Conclusion: The synthesized amide-modified chia seed hydrogel exhibited significant, concentration-dependent antioxidant, antidiabetic, and anti-inflammatory activities, highlighting its potential as a biocompatible, multifunctional material for drug delivery applications and metabolic disorder management.

Keywords: α-Amylase Inhibitors, Antioxidants, Drug Delivery Systems, Hydrogels, Inflammation, Salvia hispanica, Thermoresponsive Polymers.

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INTRODUCTION

The development of advanced drug delivery systems has emerged as a central priority in contemporary pharmaceutical research, driven by the growing burden of chronic diseases that demand long-term, safe, and effective therapeutic strategies. Conventional drug delivery approaches often suffer from inherent limitations, including poor stability, uncontrolled drug release, and lack of site-specific targeting, which collectively compromise therapeutic efficacy and patient compliance (1,2). These shortcomings have intensified interest in alternative delivery platforms capable of providing controlled, sustained, and targeted drug release while maintaining biocompatibility and safety. Among the various materials explored, hydrogels have gained considerable attention due to their unique three-dimensional polymeric networks, high water-holding capacity, and structural similarity to biological tissues. Their ability to encapsulate therapeutic agents and release them in a sustained manner, along with responsiveness to environmental stimuli such as pH, temperature, and ionic strength, makes hydrogels particularly attractive for biomedical and pharmaceutical applications (3,4). These properties allow hydrogels to respond dynamically to physiological conditions, enabling improved drug bioavailability and therapeutic precision. Consequently, hydrogel-based systems are increasingly regarded as essential components of modern drug delivery technologies. Despite their promise, conventional hydrogels face notable challenges, particularly with respect to fine-tuning stimuli responsiveness and achieving predictable drug release profiles under complex biological conditions. To address these limitations, recent research has focused on the design of copolymeric hydrogels that integrate natural polysaccharides with synthetic monomers. This hybrid approach seeks to combine the inherent biocompatibility, biodegradability, and biological functionality of natural polymers with the mechanical strength, stability, and tunable responsiveness offered by synthetic counterparts (5-15). However, despite extensive exploration of various natural–synthetic combinations, chia seed mucilage (CSM) remains largely unexplored as a foundational polymer for hydrogel-based drug delivery systems.

Chia seed mucilage, derived from the seeds of *Salvia hispanica* L., is a naturally occurring polysaccharide known for its excellent gel-forming ability, biocompatibility, and physiological safety. Its primary structural component, arabinoxylan, exhibits pH-sensitive behavior and forms stable gels under varying environmental conditions, making it a promising candidate for responsive drug delivery matrices (8,9). When copolymerized with acrylamide, a synthetic monomer widely recognized for its high swelling capacity and pH-responsive characteristics, the resulting copolymeric network demonstrates enhanced physicochemical stability, swelling behavior, and environmental sensitivity. Such integration is anticipated to yield a pH-sensitive superabsorbent hydrogel with significant potential for controlled and targeted drug release, as well as broader biomedical and environmental applications (16-26). In addition to their structural and delivery-related advantages, multifunctional hydrogels capable of exerting intrinsic biological activities represent a valuable advancement in therapeutic design. The incorporation of bioactive polymeric components may confer antioxidant, antidiabetic, and anti-inflammatory properties, thereby extending the utility of hydrogels beyond passive drug carriers. Preliminary evidence suggests that amide-functionalized, thermo-responsive hydrogels derived from natural polysaccharides may exhibit synergistic biological effects, including free radical scavenging, enzyme inhibition, and protein stabilization, which are relevant to the management of oxidative stress, metabolic disorders, and inflammatory conditions (27-29). Against this background, the present study addresses the lack of reported work on chia seed mucilage–based copolymeric hydrogels for pharmaceutical applications. The research hypothesizes that a copolymeric hydrogel synthesized from chia seed mucilage and acrylamide can serve as a stable, stimuli-responsive, and biologically active platform for drug delivery. Accordingly, the objective of this study is to synthesize and characterize a CSM-co-AM hydrogel and to systematically evaluate its physicochemical properties and in vitro biological activities, including antioxidant, antidiabetic, and anti-inflammatory potential, in order to assess its suitability as a multifunctional drug delivery system for the management of oxidative stress and metabolic diseases.

METHODS

Chemicals and Reagents

All chemicals and reagents used in this experimental study were of analytical grade and were procured from Sigma-Aldrich (USA) unless stated otherwise. These included 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,4,6-tripyridyl-s-triazine (TPTZ), ferric chloride hexahydrate ($FeCl_3 \cdot 6H_2O$), ascorbic acid, porcine pancreatic α-amylase, soluble starch, sodium phosphate buffer, acetic acid, and hydrochloric acid. Methanol (HPLC grade) and other solvents were used as required. Egg albumin for the protein denaturation assay was freshly obtained from chicken eggs. All solutions were prepared using distilled water, and reagents were freshly prepared where applicable to ensure experimental reliability.

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Preparation of Amide-Modified Thermo-Responsive Chia Seed Hydrogel

Chia seeds (*Salvia hispanica* L.) were immersed in distilled water at a seed-to-water ratio of 1:20 (w/v) and allowed to hydrate at ambient temperature for 12 h. The swollen mucilage layer was separated by filtration through muslin cloth, followed by centrifugation at 5000 rpm for 15 min to remove residual seed debris. The purified chia seed mucilage was subsequently copolymerized with acrylamide using N,N′-methylenebisacrylamide as a cross-linker and ammonium persulfate as a free-radical initiator. The polymerization reaction was carried out at 60 °C under a nitrogen atmosphere for four hours to minimize oxygen-induced radical quenching. The resulting amide-modified, thermo-responsive hydrogel was thoroughly washed with distilled water to eliminate unreacted monomers and initiators, then freeze-dried and stored in airtight containers for subsequent biological evaluation.

Antioxidant Activity Assays

The antioxidant potential of the prepared hydrogel was evaluated using complementary free-radical scavenging and reducing power assays in order to capture different mechanisms of antioxidant action. All assays were performed in triplicate, and results were expressed as mean values to improve reproducibility.

DPPH Radical Scavenging Activity

The free-radical scavenging activity of the hydrogel extract was assessed using the DPPH assay following previously reported protocols with minor modifications (30,31). A 0.1 mM DPPH solution was prepared in methanol. Equal volumes (1 mL) of DPPH solution and hydrogel extract at concentrations ranging from 50 to 250 µg/mL were mixed and incubated in the dark at room temperature for 30 min. Absorbance was measured at 517 nm using a UV-visible spectrophotometer. Methanol served as the blank, while DPPH solution without extract was used as the control. Percentage radical scavenging activity was calculated using Eq. 1. Ascorbic acid was used as the reference antioxidant standard.

$$\% \text{ RSA} = \left(\frac{Abs\ of\ control\ 517 - Abs\ of\ sample\ 517)}{Abs\ of\ control\ 517}\right) \times 100 \quad (Eq.1)$$

Ferric Reducing Antioxidant Power (FRAP) Assay

The ferric reducing antioxidant power of the hydrogel was determined according to the FRAP method with slight modifications from established protocols (32,33). The assay is based on the reduction of Fe^{3+} to Fe^{2+} under acidic conditions, resulting in the formation of a blue Fe^{2+}-TPTZ complex. The FRAP reagent was freshly prepared by mixing 300 mM acetate buffer (pH 3.6), 10 mM TPTZ dissolved in 40 mM HCl, and 20 mM $FeCl_3 \cdot 6H_2O$ in a 10:1:1 (v/v/v) ratio. Different volumes of hydrogel extract (50–250 µL) were added to 1.8 mL of FRAP reagent and incubated at room temperature for 30 min. Absorbance was recorded at 593 nm. A standard calibration curve was constructed using $FeSO_4$, and results were expressed as µmol Fe(II)/g dry hydrogel extract using Eq. 2.

$$\text{X} = \left(\frac{y)}{0.0026}\right)\ R2 = 0.98 \quad (Eq\ 2)$$

In Vitro Antidiabetic Assay: Enzyme Kinetics Study of α-Amylase Inhibition

The inhibitory effect of the amide-modified chia seed hydrogel on α-amylase activity was evaluated using an enzyme kinetics approach as described previously with slight modifications (34). The reaction mixture contained porcine pancreatic α-amylase (1 U/mL) and varying concentrations of hydrogel extract (50–250 µg/mL) prepared in phosphate buffer (20 mM, pH 6.9) containing NaCl (6.7 mM). The mixture was pre-incubated at 37 °C for 10 min. The enzymatic reaction was initiated by adding soluble starch at concentrations ranging from 0.5 to 5.0 mg/mL, followed by incubation at 37 °C for 30 min. The reaction was terminated by the addition of dinitrosalicylic acid (DNSA) reagent, and the mixtures were boiled for 5 min. After cooling, absorbance was measured at 540 nm to quantify the reducing sugars released. A control reaction without hydrogel extract was used to represent 100% enzyme activity, while acarbose served as the standard α-amylase inhibitor. Percentage inhibition was calculated using Eq. 3.

$$\% \text{ inhibition} = \left(\frac{K - S)}{K}\right) \times 100 \quad (Eq.3)$$

Protein Denaturation Inhibition Assay (Egg Albumin Model)

The in vitro anti-inflammatory potential of the hydrogel was assessed using the egg albumin denaturation assay following a reported method with minor modifications (35). Fresh egg albumin was diluted 1:5 with phosphate-buffered saline (PBS, pH 6.4). One milliliter

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of the diluted albumin solution was mixed with 1 mL of hydrogel extract at different concentrations and incubated at 37 °C for 15 min. The mixtures were subsequently heated at 70 °C for 5 min to induce protein denaturation. After cooling, turbidity was measured at 660 nm using a UV-visible spectrophotometer. A control sample without extract was used, and diclofenac sodium served as the standard anti-inflammatory drug. The percentage inhibition of protein denaturation was calculated using Eq. 4.

$$Inhibition\ of\ protein\ denaturation\ (\%) = \left(1 - \frac{\text{Absorbance of sample}}{\text{Absorbance control}}\right) \times 100 \qquad \text{(Eq. 4)}$$

All experiments were conducted in accordance with good laboratory practice. As the study was entirely in vitro and did not involve human participants or experimental animals, formal institutional review board approval and informed consent were not required; however, the study adhered to ethical guidelines for responsible laboratory research.

RESULTS

DPPH Radical Scavenging Activity

The antioxidant potential of the amide-modified thermo-responsive chia seed hydrogel was evaluated using the DPPH radical scavenging assay. A clear concentration-dependent increase in free radical scavenging activity was observed across the tested concentration range of 50–250 µg/mL. The percentage radical scavenging activity increased from 38.67% at 50 µg/mL to 45.38% and 56.06% at 100 and 150 µg/mL, respectively. A pronounced enhancement was noted at higher concentrations, with values rising to 67.42% at 200 µg/mL and reaching a maximum of 71.90% at 250 µg/mL. The scavenging activity of the hydrogel at the highest concentration was comparable to that of the reference antioxidant ascorbic acid, which demonstrated a stable scavenging activity of 71.74% at a fixed concentration of 500 µg/mL. These findings demonstrate strong dose responsiveness and confirm the ability of the hydrogel to effectively neutralize free radicals at higher concentrations.

Ferric Reducing Antioxidant Power (FRAP) Assay

The ferric reducing antioxidant power assay further confirmed the antioxidant capacity of the synthesized hydrogel by assessing its electron-donating ability. The reducing power increased progressively with increasing hydrogel concentration. At 50 µg/mL, the FRAP value was 32.92 µmol Fe(II)/g, which increased to 45.77 and 56.59 µmol Fe(II)/g at 100 and 150 µg/mL, respectively. Further increases were observed at higher concentrations, reaching 67.74 µmol Fe(II)/g at 200 µg/mL and a maximum of 73.44 µmol Fe(II)/g at 250 µg/mL. In comparison, ascorbic acid exhibited a consistently high FRAP value of 77.29 µmol Fe(II)/g at a fixed concentration of 500 µg/mL. The close proximity of the hydrogel's reducing capacity to that of the standard antioxidant at the highest tested concentration indicates the presence of redox-active functional groups capable of efficient electron donation.

In Vitro Antidiabetic Activity: α-Amylase Inhibition

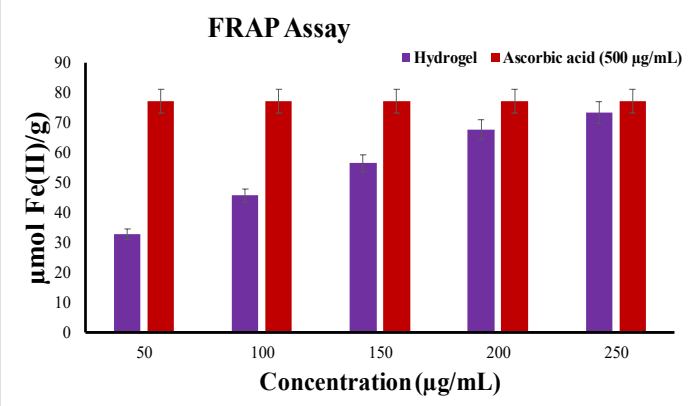
The antidiabetic potential of the amide-modified chia seed hydrogel was assessed by evaluating its inhibitory effect on α-amylase activity. The hydrogel demonstrated a concentration-dependent inhibition of the enzyme, indicating effective interference with starch hydrolysis. At 10 µg/mL, α-amylase inhibition by the hydrogel was 52.13%, increasing to 61.97% at 20 µg/mL. The highest tested concentration of 30 µg/mL resulted in substantial inhibition of 76.07%. The reference drug acarbose exhibited higher inhibition at corresponding concentrations, with values of 57.69%, 71.79%, and 83.46%, respectively. Despite slightly lower potency compared to acarbose, the hydrogel displayed a parallel inhibitory trend, suggesting a comparable inhibition profile and consistent dose responsiveness.

Anti-Inflammatory Activity: Protein Denaturation Assay

The anti-inflammatory activity of the hydrogel was evaluated through its ability to inhibit heat-induced protein denaturation using the egg albumin model. The hydrogel exhibited a progressive, concentration-dependent protective effect against protein denaturation. Inhibition values increased from 32.00% at 50 µg/mL to 39.50%, 51.00%, and 59.60% at 100, 150, and 200 µg/mL, respectively, reaching a maximum of 67.20% at 250 µg/mL. Diclofenac sodium, used as a standard anti-inflammatory agent at a fixed concentration of 500 µg/mL, showed a protein denaturation inhibition of 72.41%. The relatively small difference between the hydrogel and the standard drug at higher concentrations highlights the strong protein-stabilizing capacity of the hydrogel.

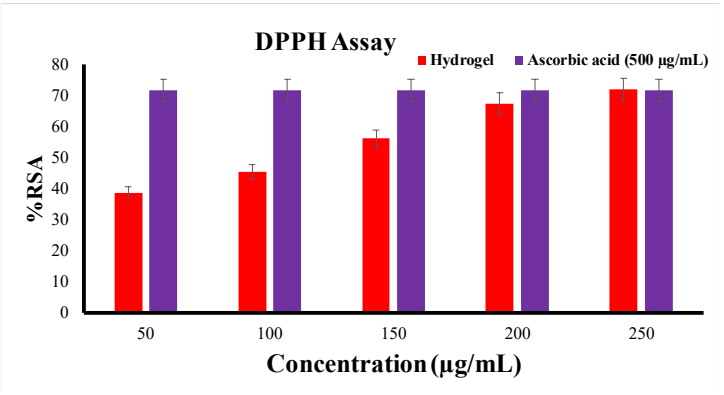
Table 1: Concentration-Dependent Inhibition of Protein Denaturation by Amide-Modified Chia Seed Hydrogel Compared with Diclofenac Sodium

Concentration (µg mL⁻¹)	Hydrogel (% Inhibition)	Diclofenac sodium (500 µg mL⁻¹) (% Inhibition)
50	32.00	72.41
100	39.50	
150	51.00	
200	59.60	
250	67.20	



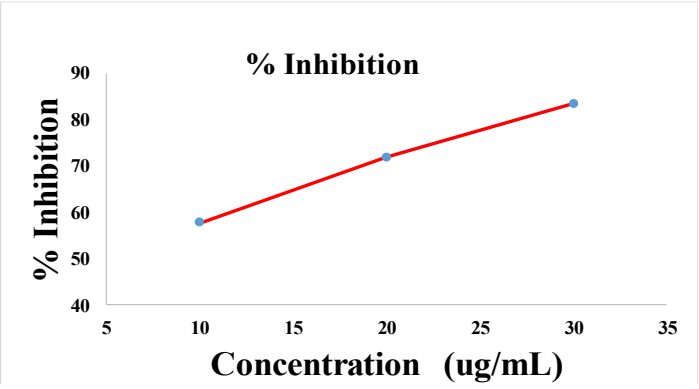
Ferric Reducing Antioxidant Power (FRAP) of Amide-Modified Chia Seed Hydrogel Compared with Ascorbic Acid (500 µg/Ml)

Figure 1 Ferri Reducing Antioxidant Power (FRAP) of Amide-Modified Chia seed Hydrogel Compared with Ascorbic Acid (500 ug/Ml)



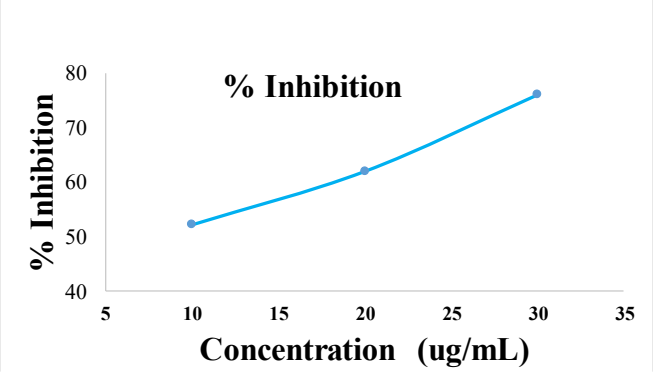
DPPH Radical Scavenging Activity of Hydrogel Extract Compared with Ascorbic Acid

Figure 2 DPPH radical scavenging Activity of hydrogel Extract Compared with Ascorbic Acid



Comparative % Inhibition of A-Amylase Activity Acarbose at Different Concentrations

Figure 2 Comparative % Inhibition of A-Amylase Activity Acarbose at Different Concentration



Comparative % Inhibition of A-Amylase Activity by Hydrogel Extract at Different Concentrations

Figure 1 Comparative % Inhibition of A-Amylase Activity by Hydrogel Extract at Different Concentration

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DISCUSSION

The present study demonstrated that the amide-modified thermo-responsive chia seed mucilage hydrogel exhibited significant antioxidant, antidiabetic, and anti-inflammatory activities in vitro, supporting its potential as a multifunctional biomaterial for pharmaceutical and therapeutic applications. The findings align with the growing body of evidence suggesting that polysaccharide-based hydrogels, when strategically modified with synthetic monomers, can provide both structural advantages and intrinsic bioactivity suitable for advanced drug delivery systems (27-29). The antioxidant activity observed through DPPH and FRAP assays showed a clear concentration-dependent trend, with the hydrogel approaching the activity of ascorbic acid at higher concentrations. This dual confirmation through radical scavenging and reducing power assays strengthens the validity of the antioxidant findings. Similar dose-responsive antioxidant behavior has been reported for other plant-derived polysaccharide hydrogels, where phenolic residues and hydroxyl-rich backbones contribute to hydrogen atom donation and electron transfer mechanisms (31,32). In the case of chia seed mucilage, arabinoxylan-based polysaccharides are known to retain bound phenolic compounds, which may explain the observed antioxidant efficacy. The amide modification and network formation likely enhanced the exposure and stabilization of redox-active functional groups, improving interaction with free radicals and ferric ions. These findings are consistent with recent reports highlighting that chemical functionalization of natural polymers can significantly amplify antioxidant performance without compromising biocompatibility (33). The α-amylase inhibition results further indicated that the hydrogel possessed notable antidiabetic potential. Although the inhibitory effect was modestly lower than that of acarbose, the hydrogel displayed a parallel, concentration-dependent inhibition profile, suggesting a comparable mode of enzyme interaction. Natural polysaccharides have previously been shown to reduce α-amylase activity through steric hindrance, hydrogen bonding, and modulation of enzyme conformation rather than direct active-site blockade, which may result in a more controlled postprandial glucose response (34).

From a clinical perspective, such moderate inhibition may be advantageous, as excessive α-amylase suppression by synthetic drugs is often associated with gastrointestinal side effects. The present findings therefore support the potential role of this hydrogel as a complementary or adjunct system in metabolic disorder management, particularly when integrated into functional foods or controlled drug delivery platforms (35). The protein denaturation assay provided evidence of the hydrogel's anti-inflammatory capability, as demonstrated by its ability to stabilize albumin against heat-induced denaturation. Protein denaturation is a recognized pathway in inflammatory processes, and inhibition of this phenomenon is widely used as a proxy indicator of anti-inflammatory potential in early-stage screening studies. The hydrogel achieved inhibition values close to diclofenac sodium at higher concentrations, which is notable for a biomaterial-based system. This activity is likely attributable to the presence of polar functional groups and amide linkages that facilitate stabilizing interactions with protein structures. Comparable observations have been reported in recent studies involving polysaccharide and hydrogel systems enriched with bioactive functional groups, reinforcing the biological relevance of such materials (34). A major strength of this study lies in its integrated evaluation of multiple biological activities within a single hydrogel system, addressing antioxidant stress, carbohydrate metabolism, and inflammatory pathways simultaneously. This multifunctionality is particularly relevant for chronic metabolic diseases, where oxidative stress, inflammation, and hyperglycemia coexist and interact. Additionally, the use of well-established in vitro assays and comparison with standard reference drugs enhanced the reliability and interpretability of the findings.

However, several limitations must be acknowledged. The study was confined to in vitro evaluations, and the absence of in vivo validation limits direct extrapolation to physiological conditions. Furthermore, drug loading, release kinetics, swelling behavior under physiological pH, and long-term stability were not assessed, despite being central to the hydrogel's intended role as a drug delivery system. The lack of statistical significance testing and mechanistic enzyme kinetics analysis also restricts deeper interpretation of the biological interactions observed. These gaps highlight the need for more comprehensive physicochemical and pharmacological characterization. Future research should focus on evaluating drug encapsulation efficiency, controlled release behavior under simulated gastrointestinal conditions, and biocompatibility through cytotoxicity and in vivo models. Investigating the molecular interactions between the hydrogel and α-amylase using kinetic modeling and spectroscopy could further clarify the inhibition mechanism (35). Additionally, expanding the study to include other inflammatory and oxidative stress biomarkers would strengthen the translational relevance of the material. In conclusion, the findings suggest that the amide-modified chia seed mucilage hydrogel represents a promising, biologically active platform with potential applications in drug delivery and metabolic disease management. While the results are encouraging, careful progression toward in vivo validation and functional optimization is essential before clinical or industrial translation can be realistically considered.

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CONCLUSION

This study established the successful development of an amide-modified, thermo-responsive hydrogel derived from chia seed mucilage and acrylamide, fulfilling the objective of creating a biocompatible and biologically active material with relevance to pharmaceutical applications. The synthesized hydrogel exhibited a robust multifunctional profile, demonstrating effective antioxidant behavior, meaningful inhibition of carbohydrate-digesting enzymes, and notable protection against protein denaturation, collectively indicating antioxidant, antidiabetic, and anti-inflammatory potential. The integration of a natural polysaccharide with amide functionalization enhanced both structural integrity and bioactivity, highlighting the value of hybrid hydrogel systems as advanced therapeutic platforms. From a practical standpoint, these findings support the hydrogel's promise as a candidate for controlled drug delivery, functional food formulations, and natural therapeutic strategies aimed at managing oxidative stress and metabolic disorders. Further investigations focusing on in vivo performance, controlled release behavior, and scalable formulation will be essential to advance this material toward clinical and industrial translation.

AUTHOR CONTRIBUTIONS

Author	Contribution
Shehar Bano	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Farzana Shahin*	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Maryam Fatima	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Attia Khalid	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Hansa Gul	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published

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