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Phenolic microencapsulation of *Alhagi maurorum*: a novel approach to enhancing diabetes nutrition therapy

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Abstract
Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia, oxidative stress, and impaired glucose homeostasis. This study investigates the antidiabetic potential of microencapsulated phenolic-rich fractions from *Alhagi maurorum* (PRF-AM) as a novel nutritional therapy. Phenolic fractions were extracted and encapsulated using a combination of maltodextrin, modified starch, and whey protein concentrate via spray-drying, yielding uniform spherical microcapsules averaging 497.2 nm with 91% encapsulation efficiency. Key phenolics identified included gallic, caffeic, cinnamic, and ellagic acids, known for their antioxidant activity. In an alloxan-induced diabetic mouse model, oral administration of PRF-AM (100 mg/kg) for five weeks significantly reduced blood glucose, triglycerides, total cholesterol, and LDL cholesterol while increasing HDL levels. Histopathological evaluation confirmed no adverse effects on liver, pancreas, or spleen tissues. Mechanistically, PRF-AM enhanced antioxidant defense by upregulating catalase and suppressing iNOS expression, alongside significant increases in GLUT2 and GLUT4 mRNA levels, promoting improved glucose transport and insulin sensitivity. These findings suggest that microencapsulated phenolic compounds from *A. maurorum* offer a safe and effective adjunctive approach for diabetes management, combining metabolic regulation with antioxidant and anti-inflammatory benefits.

Keywords Antidiabetic, Microencapsulation, Phenolic compounds, Glucose transporters, *Alhagi maurorum*

Introduction

Diabetes mellitus (DM) is a global metabolic disorder characterized by chronic hyperglycemia, insulin dysfunction, and increased oxidative stress, which contribute to severe complications including cardiovascular disease, nephropathy, neuropathy, and retinopathy [1, 2]. Despite advances in pharmacotherapy, conventional antidiabetic treatments often face limitations such as adverse side effects, variable patient compliance, and suboptimal long-term efficacy [3, 4]. Consequently, there is growing interest in complementary or adjunct nutritional approaches that leverage natural bioactive compounds to support diabetes management [5].

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Among such bioactives, polyphenols, a large family of plant-derived phenolic acids, flavonoids, and related compounds have attracted considerable attention for their broad biological activities. These include antioxidant and anti-inflammatory effects, inhibition of carbohydrate-digesting enzymes, improvement of insulin secretion and sensitivity, modulation of lipid metabolism, and mitigation of oxidative damage [6, 7]. Indeed, numerous in vitro and in vivo studies have demonstrated that polyphenol-rich extracts can ameliorate hyperglycemia, dyslipidemia, and oxidative stress in diabetic models [8]. However, the therapeutic utility of polyphenols is often compromised by poor stability, low water solubility, rapid degradation under gastrointestinal conditions, and limited systemic bioavailability, which together reduce their efficacy when administered orally [6, 9, 10].

To overcome these challenges, micro- and nano-encapsulation technologies have been proposed and extensively studied. Encapsulation involves enclosing bioactive compounds within protective carriers such as polysaccharides, proteins, or lipids to shield them from adverse environmental conditions (e.g., pH, light, oxygen, heat), mask undesirable taste, improve solubility, and control their release kinetics during digestion and absorption [10–12]. Recent reviews have highlighted that encapsulation can significantly enhance the bioavailability, stability, and bioactivity of polyphenolic compounds compared to their free forms [12–14]. Moreover, micro- or nano-carriers have demonstrated promise as oral delivery systems for therapeutic agents, including peptides such as insulin, offering improved absorption, controlled release, and better patient compliance [15, 16].

Given these advances, naturally-derived polyphenol-rich plants emerge as attractive candidates for development into functional nutraceuticals or adjunct therapies in metabolic diseases such as DM. Among these, *Alhagi maurorum* is a perennial shrub widely used in traditional medicine and reported to contain a variety of bioactive phenolics, flavonoids, and other phytochemicals with antioxidant, anti-inflammatory, and metabolic regulatory potentials [17]. Previous studies have documented antihyperglycemic and antioxidant effects of crude extracts of *A. maurorum* in diabetic animal models including modulation of insulin levels and antioxidant enzyme activities but these studies remain constrained by issues of stability, poor bioavailability, and lack of controlled administration [18].

To date, no study has explored the antidiabetic effects of microencapsulated phenolic-rich fractions derived from *A. maurorum* in a diabetic animal model. In this context, microencapsulation offers the potential to overcome the intrinsic limitations of free phytochemical extracts, stabilize phenolic compounds against degradation, improve their bioaccessibility and absorption upon oral administration, and thereby enhance their therapeutic efficacy. Therefore, in the present study, we extracted the phenolic-rich fraction from *A. maurorum*, microencapsulated it via spray-drying using a carrier matrix composed of maltodextrin, modified starch, and whey protein, and characterized the resulting microcapsules (particle size, encapsulation efficiency, phenolic content). We subsequently evaluated their antidiabetic, antioxidant, and metabolic effects, including lipid and glucose profiles, hepatic enzyme markers, and gene expression of glucose transporters in an alloxan-induced diabetic mouse model. This investigation aims to provide proof-of-concept data supporting microencapsulated plant polyphenols as a novel, stable, and effective nutritional therapy for diabetes management.

Material and methods

Materials

All chemicals and reagents used in this study were obtained from Merck, Germany, unless otherwise specified. Maltodextrin (DE = 18–20; Foodchem, China) and modified starch (HI-CAP ® 100, Ingredion, Hamburg, Germany) were utilized as carrier matrices for microencapsulation. Alloxan monohydrate, daidzein, and lecithin were purchased from Sigma Aldrich, Germany. Male Balb/c mice were supplied by Razi Vaccine and Serum Research Institute, Mashhad, Iran, and were housed under standard laboratory conditions prior to experimental use.

Extraction procedure

The extraction of the phenolic-rich fraction (PRF) from *Alhagi maurorum* was performed based on our previous methodology [19]. The aerial parts of the plant were first freeze-dried. Subsequently, 100 g of dried material were extracted with 1000 mL of 80% aqueous methanol under constant agitation. The extract was filtered through Whatman No. 1 filter paper, and the solvent was removed using a rotary evaporator (Büchi, Flawil, Switzerland) at 60°C under vacuum conditions. To enrich the phenolic content, the crude extract underwent sequential liquid–liquid fractionation using solvents of increasing polarity: hexane, chloroform, ethyl acetate, n-butanol, and water, repeated three times. Each fraction was filtered and concentrated using the rotary evaporator to obtain the final PRF [19].

Microencapsulation of PRF-AM

The pilot plant-scale spray dryer, designed with countercurrent airflow, was utilized for this process. Specifically, eight grams of PRF of *A. maurorum* and three grams of Tween 80 were gradually incorporated into 100 mL of distilled water, along with 32 g of wall material, which consisted of 70% maltodextrin, 20% modified starch, and

10% whey protein concentrate, achieving a core-to-wall ratio of 1:4. To ensure thorough rehydration and homogenization, the mixtures were refrigerated overnight at 4 ± 2 °C on a stirrer set to 200 rpm (IKA, Germany). The solution was subsequently homogenized at 10,000 rpm for five minutes using an Ultra Turrax homogenizer. The spray dryer operated at inlet and outlet temperatures of 130°C and 80°C, respectively, with a pressure of 0.4 kg/cm^2 and a flow rate of 8 mL/min. Finally, 100 mL of the solution was pumped, and the resulting powder was stored for further analysis [19].

Bioactive profiling and characterization of PRF-AM

The phenolic compounds in the microcapsules were analyzed using HPLC (Agilent 1200 Series), which was equipped with a UV–Vis detector and a C18 analytical column (150 mm × 4.6 mm, 5 µm). The mobile phase consisted of deionized water (Solvent A) and acetonitrile (Solvent B), with the ratio set to 15% A and 85% B over a duration of 50 min. The standards used in this analysis included gallic acid, syringic acid, vanillic acid, salicylic acid, caffeic acid, pyrogallol, catechin, cinnamic acid, ellagic acid, naringin, chrysin, and ferulic acid.

To determine the size and dispersion index of the synthesized microcapsules, a dynamic light scattering (DLS) technique was employed. The surface potential of the microcapsules was assessed using a Zeta sizer instrument. Additionally, the morphology of the PRF-AM was analyzed using a scanning electron microscope (SEM).

Entrapment efficiency

The entrapment efficiency of microcapsules was analyzed as previously described based on the below equation [20, 21]. A total of 100 mg of dried microcapsules was dispersed in 1.5 mL of 80% methanol and then centrifuged at 12,000 rpm for 5 min. The supernatant was analyzed to determine the total phenolic compounds. The pellet (residue) was then re-extracted using 1.5 mL of 80% methanol and sonicated at 60 kHz for 30 s. The extract obtained from the pellet also measured the total phenolic compounds.

$$\mathrm{EE}\,(\%) = 100 \times \frac{\text{total phenolics in the pellet} - \text{total phenolics in the supernatant}}{\text{total phenolics in the pellet}}$$

Phenolic content and antioxidant potential of PRF-AM

The total phenolic content of each fraction was quantified colorimetrically using a visible spectrophotometer (Novaspec II, Japan) at a wavelength of 765 nm, following the Folin-Ciocalteu assay protocol. The results were expressed as milligrams of gallic acid equivalent (GA eq.) per gram of dry crude extract. To evaluate the antioxidant activity of microcapsules, the DPPH (2,2-diphenyl-1-picrylhydrazyl) free radical scavenging activity assay was employed, with Vitamin C serving as the control [19].

Experimental animal trial

Forty male Balb/c mice, aged 4 weeks and weighing between 30 and 32 g, were individually housed and acclimatized for one week on a standard chow diet with unlimited access to clean water. The in vivo dosage of 100 mg/kg BW for the microencapsulated phenolic formulation was selected based on previously published studies using comparable polyphenol-rich plant extracts in diabetic rodent models. Similar dosage ranges (80–150 mg/kg BW) have been shown to exert significant antioxidant, anti-inflammatory, and antihyperglycemic effects without observable toxicity [22]. Additionally, microencapsulation increases bioavailability and stability [23], allowing effective biological activity at this concentration. Therefore, the selected 100 mg/kg dose aligns with established preclinical practices and is considered both effective and safe for evaluating therapeutic potential in alloxan-induced diabetic rats. The mice were kept in a controlled environment at 23 ± 1°C and 85% humidity, following a 12-h light/dark cycle. After fasting for 13 h, diabetes was induced by a single intraperitoneal injection of alloxan monohydrate at a dosage of 20 mg/kg. Blood glucose levels were measured 48 h post-injection, selecting mice with levels exceeding 200 mg/dL. The mice were then divided into four groups of 10 each: Groups 1 and 2 served as normal and diabetic controls receiving standard food; Group 3 was treated with PRF-AM at 100 mg/kg; and Group 4 received Metformin at 250 mg/kg per day. After five weeks of treatment, the mice were anesthetized with a combination of ketamine and xylazine for further evaluation, following ethical guidelines established by the Institute of Animal Care and Use Committee of Islamic Azad University of Mashhad.

Serological markers of liver and lipid level

Blood samples were collected through cardiac puncture and placed into standard tubes. Serum was then separated using a centrifuge at 2000 rpm for 10 min. The serum levels of total high-density lipoprotein (HDL), low-density lipoprotein (LDL), cholesterol, and triglycerides were measured using an auto-analyzer (Hitachi 902, Japan). Additionally, the serum concentrations of liver enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), were determined with an automated chemistry analyzer (Roche, Hitachi 902 analyzer, Japan).

Histopathological evaluation

To distinguish the histopathological changes in the spleen, pancreas, and liver tissues, the samples were

carefully cut, lightly washed with physiological saline, and preserved in buffered formalin (10% formalin in 0.1 M sodium phosphate buffer, pH 7). The samples were then paraffin-embedded (4 µm sections) and stained with eosin and hematoxylin. Finally, they were examined under a light microscope (Nikon, Japan) at a magnification of X100.

Gene expression method

The pancreas tissues were rapidly separated and stored in liquid nitrogen at -80°C for RNA extraction. Total RNA was isolated according to the instructions provided with the RNeasy lipid tissue mini kit (Cat. number 74804, Qiagen, Hilden, Germany). Following this, single-stranded cDNA was synthesized using the method outlined in the Quantitect® reverse transcription kit instructions (Qiagen, Hilden, Germany). The expression levels of inducible nitric oxide synthase (iNOS), catalase (CAT), and glucose transporters 2 and 4 (GLUT-2, GLUT-4) were analyzed, with the β-actin gene serving as the internal control. The specific target primers used in this study are listed in Table 1.

Statistical analysis

Data were analyzed using one-way ANOVA, following the MIXED instruction in the SAS software package version 9.1 (SAS Institute Inc., Cary, NC, USA). The normality of the data was assessed using the UNIVARIATE instruction in SAS. A p-value of less than 0.05 was considered significant.

Results and discussion

Fractionation analysis

Our fractionation procedure demonstrated that the ethyl acetate fraction of the *Alhagi maurorum* extract exhibited the highest total phenolic content, at 278.5 ± 4.72 mg GAE/g DW. The other fractions followed in decreasing order: n-butanol (153.5 ± 5.32 mg GAE/g DW), water (89.1 ± 4.18 mg GAE/g DW), chloroform (57.5 ± 5.01 mg GAE/g DW), and hexane (32.1 ± 4.84 mg GAE/g DW). Given the significantly higher yield, the ethyl acetate fraction was selected for subsequent microencapsulation and bioactivity studies.

These results align with broader evidence that solvent polarity strongly influences the efficiency and selectivity of phenolic compound extraction. Phenolic compounds, due to their hydroxyl groups and moderate polarity, are more effectively solubilized in moderately polar organic solvents such as ethyl acetate or mixtures thereof [28]. In a similar recent study, ethyl acetate was shown to extract a wide range of phenolic acids and flavonoids with good yield from botanical materials, outperforming non-polar solvents [29]. These findings support our choice of ethyl acetate for fraction enrichment.

Moreover, the gradually decreasing phenolic content from n-butanol to water, chloroform, and hexane fractions suggests that many of the bioactive phenolics in *A. maurorum* are semi-polar to moderately polar, and less likely to partition into non-polar solvents. This observation is consistent with prior reports indicating that non-polar solvents preferentially extract lipophilic compounds (e.g., terpenoids, sterols), while phenolic acids and flavonoids remain in more polar or mid-polarity fractions [30].

Selecting the ethyl acetate fraction for further work thus enhances the probability of capturing the maximum relevant phenolic content, which is crucial for downstream antioxidant, metabolic, and therapeutic evaluations. Importantly, this fractionation strategy provides a more concentrated source of phenolic compounds than crude extracts, potentially improving consistency, reproducibility, and biological potency of the microencapsulated formulation.

Furthermore, although more "universal" solvents like methanol or aqueous methanol are often used to maximize extraction yield, they also co-extract many other non-phenolic constituents (e.g., sugars, proteins, chlorophylls) that may interfere with bioactivity assays or stability [31–33]. By contrast, ethyl acetate fractionation improves selectivity for phenolics, minimizes co-extracted impurities, and thus supports a cleaner extract for encapsulation and biological testing.

Table 1 Sequences of the primers used in this research

Gene	Forward (5′ → 3′)	Reverse (5′ → 3′)	References
CAT	ACATGGTCTGGGACTTCTGG	CAAGTTTTTGATGCCCTGGT	[24]
iNOS	CACCTTGGAGTTCACCCAGT	ACCACTCGTACTTGGGATGC	[25]
GLU2	ATGTCAGAAGACAAGATCACCGG	CCTACTGGACGGATTTTGGCTC	[26]
GLU4	AAGATGGCCACGGAGA	GTGGGTTGTGGCAGTGAGTC	[26]
β-actin	CCTGAACCCTAAGGCCAACC	CAGCTGTGGTGGTGAAGCTG	[27]

HPLC analysis and Physicochemical characteristics

The HPLC analysis of the microencapsulated phenolic fraction from *Alhagi maurorum* (PRF-AM) revealed the presence of several bioactive phenolic compounds with significant therapeutic potential. Specifically, the microcapsules contained 211.4 µg/g DW of gallic acid, 407.3 µg/g DW of caffeic acid, 255.1 µg/g DW of cinnamic acid, and 323 µg/g DW of ellagic acid. These compounds are widely recognized for their potent antioxidant, anti-inflammatory, and antidiabetic activities, and their presence in microcapsules provides a concentrated source for in vivo applications [34, 35].

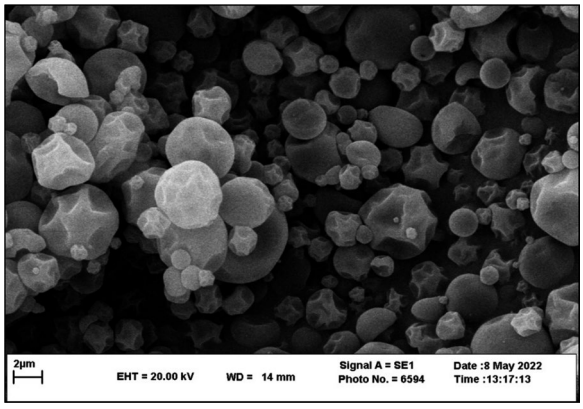


Fig. 1 Scanning electron micrographs of PRF-AM microcapsules

Table 2 Physical characteristics of synthesized microcapsules

Particle size (nm)	Polydispersity index (PDI)	Encapsulation efficiency (%)
497.3 ± 18.4	0.236	91 ± 4.83

Phenolic acids such as gallic and caffeic acids exert antioxidant effects by scavenging free radicals, chelating metal ions, and modulating endogenous antioxidant enzyme systems, thereby mitigating oxidative stress associated with diabetes and other metabolic disorders [36, 37]. Similarly, cinnamic and ellagic acids have demonstrated significant protective effects against hyperglycemia-induced oxidative damage and inflammation in multiple preclinical studies, further supporting their therapeutic relevance [38, 39].

Microencapsulation represents a strategic approach to enhance the stability, bioavailability, and controlled release of these phenolic compounds. This technology has gained substantial attention for delivering bioactive molecules with improved pharmacokinetic profiles and reduced gastrointestinal degradation [40, 41]. Various microencapsulation systems, including microspheres, microemulsions, and microparticles, enable tailored drug delivery based on particle size, wall material, and core-to-wall ratio [42, 43].

In this study, the synthesized PRF-AM microcapsules exhibited a hydrodynamic diameter of 497.3 nm, indicative of a nanoscale particle size favorable for enhanced absorption and bioactivity (Fig. 1). The encapsulation efficiency (EE) was measured at 91%, demonstrating that the majority of phenolic compounds were successfully retained within the carrier matrix. A polydispersity index (PDI) of 0.236 confirmed the uniformity and monodispersity of the microcapsules, which is critical for reproducibility, stability, and predictable release kinetics (Table 2).

Morphological evaluation via scanning electron microscopy (SEM) revealed predominantly spherical microcapsules with smooth surfaces (Fig. 1), consistent with previous reports on polysaccharide- and protein-based microencapsulation systems [44, 45]. Spherical morphology and uniform particle distribution are advantageous for minimizing aggregation, enhancing solubility, and ensuring consistent therapeutic delivery in vivo.

Antioxidant potential of microcapsules

Antioxidant therapy has emerged as a promising strategy to mitigate oxidative stress in both human and animal models. Oxidative stress arises from an imbalance between reactive oxygen species (ROS) production and the body's endogenous antioxidant defense mechanisms, contributing to the pathogenesis of chronic diseases such as diabetes, cardiovascular disorders, and neurodegenerative conditions [46, 47]. Bioactive phenolic compounds are particularly effective in this regard due to their ability to donate electrons, scavenge free radicals, chelate metal ions, and inhibit lipid peroxidation, thereby disrupting the chain reactions initiated by ROS [48].

In this study, the synthesized microcapsules of the phenolic-rich fraction of *Alhagi maurorum* (PRF-AM) demonstrated considerable antioxidant activity in the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay. The IC_{50} value for PRF-AM microcapsules was 80.3 ± 1.43 µg/mL, indicating substantial free radical inhibition. Although this IC50 value was higher than that of the standard antioxidant vitamin C (26.3 ± 2.76 µg/mL), the microcapsules still exhibited potent radical-scavenging potential.

The slightly lower activity compared to pure vitamin C may be attributed to the complex matrix of bioactive compounds within the microcapsules, which provides sustained release and enhanced stability, rather than immediate radical scavenging. Microencapsulation protects phenolic compounds from environmental degradation (e.g., pH changes, light, and heat), thereby preserving their antioxidant activity over time (Dandamudi et al., 2023; Zhang et al., 2024). Moreover, the combination of multiple phenolics within PRF-AM likely produces synergistic antioxidant effects, as previously reported in multi-component plant extracts [49, 50].

These results are consistent with recent studies demonstrating that microencapsulation of polyphenol-rich plant extracts significantly enhances their stability and biological activity while maintaining effective radical-scavenging properties [23, 50]. Therefore, PRF-AM microcapsules represent a viable natural antioxidant system capable of reducing oxidative stress and potentially alleviating oxidative damage in diabetic and other oxidative stress-related conditions.

Table 3 The average daily weight gain and average daily feed intake in mice receiving different treatments

Average	T1	T2	T3	T4	SEM
Average daily weight gain (mg/day)	43.6 ± 3.94[a]	35.2 ± 2.63[c]	39.4 ± 3.76[b]	31.2 ± 4.61[d]	1.28
Average daily feed intake (g/day)	3.0 ± 0.21[a]	2.6 ± 0.31[c]	2.8 ± 0.46[b]	3.1 ± 0.18[a]	0.09

T1: control

T2: Diabetic mice

T3: Diabetic mice + 100 mg /kg BW

T4: Diabetic mice + 250 mg Metformin/kg BW

Different letters in the same row indicated significant differences ($p < 0.05$)

The analyses were performed in triplicates

Weight and dietary intake alteration

Table 3 presents the average daily weight gain (ADWG, mg/day) and average daily feed intake (ADFI, g/day) in mice subjected to different treatments. The results indicate that treatment with phenolic microencapsulation (PRF-AM) significantly enhanced ADWG in diabetic mice compared to both untreated diabetic controls and those receiving standard Metformin therapy. Specifically, diabetic mice treated with PRF-AM exhibited an ADWG of 39.4 ± 3.76 mg/day, which was significantly higher than untreated diabetic mice (35.2 ± 2.63 mg/day) and comparable to or exceeding Metformin-treated mice (31.2 ± 4.61 mg/day). Similarly, ADFI improved in the PRF-AM group (2.8 ± 0.46 g/day) relative to untreated diabetic mice (2.6 ± 0.31 g/day), suggesting enhanced feed consumption and potential improvements in nutrient utilization.

These findings are consistent with the reported metabolic and bioactive effects of plant-derived phenolic compounds, which include antioxidant, anti-inflammatory, and hypoglycemic activities [22, 51]. The observed increase in weight gain among PRF-AM-treated mice may be attributed to improved glucose homeostasis, reduced oxidative stress, and enhanced energy metabolism, which collectively facilitate better growth performance in diabetic models. Importantly, the superior performance of PRF-AM relative to Metformin highlights the potential of microencapsulated phenolics as a nutritional adjunct or alternative therapeutic strategy in diabetes management, particularly in contexts where natural bioactives are preferred for their lower side-effect profiles [6, 52].

The improvement in feed intake further underscores the positive physiological impact of phenolic microencapsulation. Enhanced feed intake may result from several mechanisms, including increased palatability, modulation of gastrointestinal health, and improved nutrient absorption [6]. Given that diabetes often leads to appetite dysregulation and nutrient malabsorption, nutritional interventions that improve feed consumption can have substantial implications for maintaining optimal body weight and metabolic homeostasis [52, 53]. Furthermore, the synergistic effects of multiple phenolic compounds in PRF-AM may contribute to improved energy metabolism and gastrointestinal integrity, supporting both growth and feed utilization in diabetic mice.

Biochemical analysis of serum

As shown in Table 4, alloxan-induced diabetic mice (T2) exhibited significant alterations in biochemical parameters, including elevated blood glucose, total cholesterol, LDL, and triglyceride levels, alongside a reduction in HDL concentrations, when compared to the control group (T1). These changes are consistent with the well-documented hyperglycemia, dyslipidemia, and hepatic stress associated with diabetes mellitus. The increased serum levels of hepatic enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), in diabetic mice further indicate hepatic dysfunction, which is a common complication arising from chronic oxidative stress and insulin resistance [54, 55].

Table 4 The mice's blood parameters receiving different treatments

Treatment	Glu (mg/dl)	TG (mg/dl)	Chol (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	ALT (U/L)	AST (U/L)	ALP (U/L)
T1	196c	117b	95b	44a	32b	120b	47bc	379d
T2	260a	121a	129a	39b	36a	130a	49a	604a
T3	209b	116b	98b	44a	29c	119b	45c	432c
T4	198c	118b	92b	46a	35a	131a	50a	544b
SEM	3.1	2.9	3.2	1.8	1.4	2.73	1.68	8.96

T1: control

T2: Diabetic mice

T3: Diabetic mice + 100 mg /kg BW

T4: Diabetic mice + 250 mg Metformin/kg BW

Different letters in the same row indicate significant differences ($p < 0.05$)

The analyses were performed in triplicate

Treatment with microencapsulated phenolic compounds (PRF-AM, T3) significantly ameliorated these metabolic disturbances. Glucose levels were reduced from 260 mg/dL in untreated diabetic mice to 209 mg/dL, while cholesterol and LDL levels decreased to 98 mg/dL and 29 mg/dL, respectively, reflecting an improvement in lipid metabolism. The HDL levels remained stable, suggesting a protective effect on beneficial lipoproteins. Importantly, the PRF-AM treatment normalized hepatic enzyme activity ALT (119 U/L), AST (45 U/L), and ALP (432 U/L) indicating a hepatoprotective effect. These observations suggest that phenolic compounds exert both antihyperglycemic and hepatoprotective effects, likely mediated through antioxidant activity, modulation of lipid metabolism, and enhancement of insulin sensitivity [54, 56].

The mechanism underlying these beneficial effects is closely linked to the microencapsulation process, which enhances the bioavailability and stability of phenolic compounds. Microencapsulation protects phenolics from premature degradation in the gastrointestinal tract, facilitates controlled release, and improves targeted absorption, resulting in more consistent therapeutic outcomes [23, 57]. The reduction in liver enzymes observed in PRF-AM-treated mice is indicative of diminished oxidative stress and improved hepatic cellular integrity, supporting prior findings that dietary polyphenols can attenuate liver injury in diabetic models [54, 56].

Comparatively, Metformin-treated mice (T4) demonstrated reductions in glucose and lipid parameters but exhibited slightly higher hepatic enzyme levels than the PRF-AM group, suggesting that phenolic microencapsulation may provide complementary or superior hepatoprotective effects relative to conventional pharmacotherapy in preclinical models. The combined antihyperglycemic, hypolipidemic, and hepatoprotective actions of PRF-AM underscore its potential as a multifunctional therapeutic agent for managing diabetes and its associated complications [56].

Microscopic analysis

The histopathological analysis, as illustrated in Fig. 2, demonstrates the morphological integrity of the spleen, liver, and pancreas in alloxan-induced diabetic mice following treatment with phenolic microencapsulated *Alhagi maurorum* (PRF-AM). Across all treated groups, the absence of significant histological alterations indicates that the microencapsulated phenolic compounds did not induce cellular or tissue damage, confirming their favorable safety profile. Preservation of normal histological architecture in these organs is particularly critical for therapeutic evaluation, as hepatotoxicity, pancreatic injury, and splenic alterations are commonly reported adverse effects associated with conventional antidiabetic pharmacotherapies [58].

In the liver, PRF-AM treatment maintained normal hepatocyte morphology, intact sinusoidal structures, and an absence of inflammatory infiltration or steatosis. This finding aligns with studies reporting the hepatoprotective effects of polyphenol-rich plant extracts, which mitigate oxidative stress-induced hepatic damage in diabetic models [59, 60].

The pancreas exhibited preserved islet architecture and acinar cells, suggesting protection against β-cell damage induced by alloxan. Such preservation may facilitate improved insulin secretion and glucose homeostasis, supporting the antihyperglycemic effects observed in biochemical assays [60]. Similarly, the spleen showed

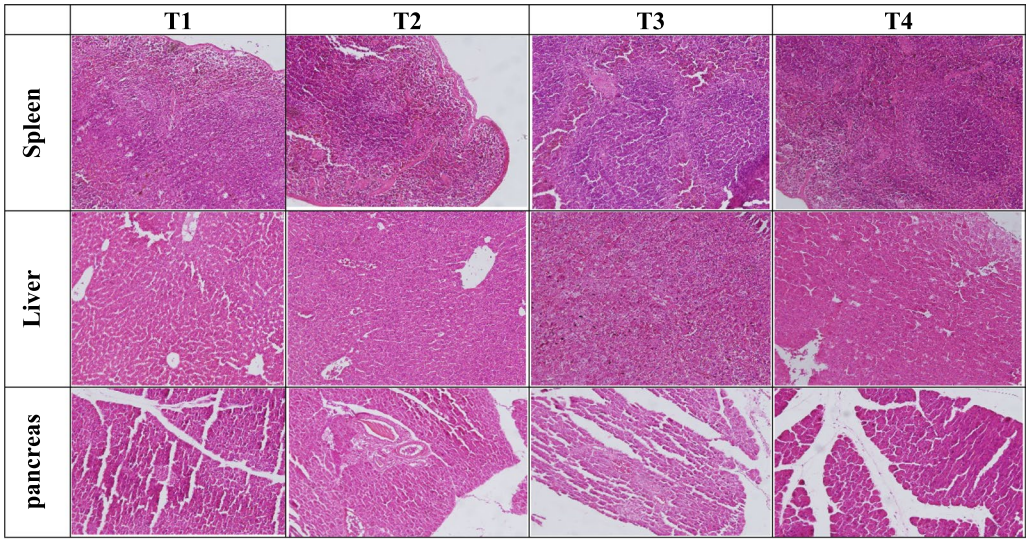


Fig. 2 The histopathological changes in the mice liver and pancreas received different treatments (T1: Control; T2: Diabetic mice; T3: Diabetic mice + 100 mg MC/kg BW; T4: Diabetic mice + 250 mg Metformin/kg BW). Images are shown at 100 × magnification

Table 5 The changes in the expression of inflammatory and glucose transporter-related genes in mice pancreatic and muscle tissues

Gene expression (Fold changes)					S.E.M
Genes	**T1**	**T2**	**T3**	**T4**	
Gene expression changes in pancreas tissue					
CAT	1a	-4.7d	-2.2c	-3.1b	0.38
iNOS	1a	-5.2d	-1.9c	-3.7b	0.56
Gene expression changes in muscle tissue					
GLUT-2	1b	-3.1d	-1.9c	+1.1a	0.30
GLUT-4	1b	-3.8d	-1.2c	+2.7a	0.26

-: Downregulated as compared to the control group

+: Up-regulated as compared to the control group

T1: control

T2: Diabetic mice

T3: Diabetic mice + 100 mg /kg BW

T4: Diabetic mice + 250 mg Metformin/kg BW

Different letters in the same row indicated significant differences ($p < 0.05$)

The analyses were performed in triplicates

normal white and red pulp morphology without evidence of congestion or cellular necrosis. This maintenance of splenic integrity highlights that PRF-AM does not adversely impact immune organ architecture, which is essential considering that diabetes often compromises immune function.

Gene expression pattern

The regulation of glucose homeostasis involves complex insulin signaling pathways, which are critically dependent on the transport of glucose into target cells via glucose transporter (GLUT) proteins and subsequent intracellular glucose metabolism [61, 62]. Within pancreatic β-cells, glucose is phosphorylated to glucose-6-phosphate (G6P) by glucokinase, serving as a key glucose sensor that triggers insulin secretion. Impairments in glucose transport, especially involving GLUT4 in skeletal muscle and adipose tissue, play a pivotal role in the development of insulin resistance, contributing to hyperglycemia in both type 1 and type 2 diabetes [62].

Table 5 summarizes the effects of phenolic microencapsulated *Alhagi maurorum* (PRF-AM) and metformin on the expression of genes associated with glucose transport (GLUT2 and GLUT4) and oxidative stress/inflammatory pathways (catalase [CAT] and inducible nitric oxide synthase [iNOS]) in pancreatic and muscle tissues. Diabetic mice (T2) exhibited significant downregulation of CAT and iNOS in pancreatic tissue, reflecting heightened oxidative stress and inflammatory signaling, which are known to impair insulin secretion and β-cell function [63]. Treatment with PRF-AM (T3) partially restored CAT and iNOS expression, indicating antioxidant and anti-inflammatory effects that likely contributed to the improvement in β-cell function and insulin secretion.

In skeletal muscle, GLUT2 and GLUT4 expression were significantly suppressed in diabetic mice, corresponding with reduced peripheral glucose uptake and insulin resistance. PRF-AM treatment markedly increased the expression of these transporters, comparable to or slightly lower than the effect observed with metformin (T4). Upregulation of GLUT2 facilitates efficient glucose sensing and bidirectional transport in hepatocytes and pancreatic β-cells, optimizing glucose homeostasis [64, 65]. Similarly, enhanced GLUT4 expression promotes insulin-stimulated glucose uptake in adipose and skeletal muscle tissues, improving systemic glucose utilization and insulin sensitivity [65]. Mechanistically, polyphenolic compounds are reported to activate AMPK and PI3K/Akt signaling pathways, which stimulate GLUT4 translocation to the plasma membrane and regulate lipid metabolism [66].

The observed modulation of oxidative stress markers (CAT, iNOS) further reinforces the role of phenolic compounds as anti-inflammatory and antioxidant agents, mitigating cellular damage in diabetic conditions [63]. This dual action, enhancing GLUT-mediated glucose uptake while reducing oxidative stress, provides a mechanistic explanation for the improved serum glucose and lipid profiles in PRF-AM-treated mice. These findings are consistent with prior studies demonstrating that microencapsulated polyphenols enhance bioavailability and targeted delivery, maximizing their pharmacological effects while minimizing degradation in the gastrointestinal tract [67].

It is important to note that the alloxan-induced diabetes model primarily mimics insulin-deficient, type 1 diabetes. Consequently, extrapolation of these results to type 2 diabetes, which is characterized by insulin resistance, should be performed with caution. Future studies using insulin-resistant models, such as high-fat diet/streptozotocin combination or genetic models, are required to validate the efficacy of PRF-AM in type 2 diabetic conditions. Additionally, while the selected dose of 100 mg/kg BW was effective in this study, dose–response and long-term safety assessments are necessary for optimization and potential clinical translation.

Overall, the upregulation of GLUT2 and GLUT4, along with modulation of oxidative stress and inflammatory markers, underscores the potential of microencapsulated *Alhagi maurorum* phenolics as adjunct therapies in diabetes management. These natural compounds could complement conventional antidiabetic agents, such as metformin, by enhancing glucose uptake, improving insulin sensitivity, and protecting pancreatic β-cells from oxidative damage.

This study demonstrates that microencapsulated phenolic-rich fractions from *Alhagi maurorum* (PRF-AM) represent a promising strategy for adjunctive

diabetes nutrition therapy. The successful microencapsulation process achieved high encapsulation efficiency and nanoscale particle size, ensuring enhanced stability, bioavailability, and controlled release of key bioactive phenolics. In an alloxan-induced diabetic mouse model, oral administration of PRF-AM effectively improved glycemic control, normalized lipid profiles, and supported healthy weight gain without inducing hepatic, pancreatic, or splenic toxicity. Mechanistically, PRF-AM enhanced antioxidant defenses by upregulating catalase, modulated inflammatory signalling via iNOS suppression, and promoted glucose homeostasis through increased expression of GLUT2 and GLUT4 transporters. Collectively, these findings highlight the multifaceted metabolic, antioxidant, and anti-inflammatory effects of PRF-AM, positioning it as a safe and effective natural adjunct to conventional antidiabetic therapies. Future studies, including long-term and clinical investigations, are warranted to validate these benefits and translate PRF-AM into functional food or nutraceutical applications for diabetes management.

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Author contributions
ASK, MA, MSM, SFK, FM, SZM, NSH: Study design, experimental work, formal analysis, and writing original draft; EK and EO: project administration, supervision, review, and editing of the original draft; All authors read and approved the final manuscript. All authors contributed equally to this work.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
All animal handling methods were accomplished as per the Islamic Azad University of Mashhad, Iran regulations with their prior approval for using the animals. All methods and procedures were carried out following the relevant guidelines and regulations. All methods are reported under ARRIVE guidelines. This research does not contain any studies with human participants performed by any of the authors. All animal experiments were conducted according to the ethical principles approved by the Islamic Azad University of Mashhad.

Competing interests
The authors declare that they have no competing interests.

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References

1. Singh H, Singh R, Singh A, Singh H, Singh G, Kaur S, Singh B (2024) Role of oxidative stress in diabetes-induced complications and their management with antioxidants. Arch Physiol Biochem 130(6):616–641
2. Goycheva P, Petkova-Parlapanska K, Georgieva E, Karamalakova Y, Nikolova G (2023) Biomarkers of oxidative stress in diabetes mellitus with diabetic nephropathy complications. Int J Mol Sci 24(17):13541
3. Evans M, Engberg S, Faurby M, Fernandes JDDR, Hudson P, Polonsky W (2022) Adherence to and persistence with antidiabetic medications and associations with clinical and economic outcomes in people with type 2 diabetes mellitus: a systematic literature review. Diabetes Obes Metab 24(3):377–390
4. Rodriguez P, San Martin VT, Pantalone KM (2024) Therapeutic inertia in the management of type 2 diabetes: a narrative review. Diabetes Ther 15(3):567–583
5. Zafar A, Alruwaili NK, Panda DS, Imam SS, Alharbi KS, Afzal M, Shalaby K, Kazmi I, Alshehri S (2021) Potential of natural bioactive compounds in management of diabetes: review of preclinical and clinical evidence. Curr Pharmacol Rep 7(3):107–122
6. Dias M, Romaní-Pérez M, Romaní A, De La Cruz A, Pastrana L, Fuciños P, Amado IR (2022) Recent technological advances in phenolic compounds recovery and applications: source of nutraceuticals for the management of diabetes. Appl Sci 12(18):9271
7. Martiniakova M, Sarocka A, Penzes N, Biro R, Kovacova V, Mondockova V, Sevcikova A, Ciernikova S, Omelka R (2025) Protective role of dietary polyphenols in the management and treatment of type 2 diabetes mellitus. Nutrients 17(2):275
8. Jia Y, Zhang Q, Zhang Y, Wang H, Niu Q, Zhu R, Li J, Fan W, Zhang YJ (2024) Effects of polyphenol-rich foods on lipids and oxidative stress status in patients with hyperlipidemia: a systematic review of randomized controlled trials. J Multidiscip Healthc. https://doi.org/10.2147/JMDH.S471372
9. Mahmutović L, Sezer A, Bilajac E, Hromić-Jahjefendić A, Uversky VN, Glamočlija UJ (2024) Polyphenol stability and bioavailability in cell culture medium: challenges, limitations and future directions. Int J Biol Macromol 279:135232
10. Adefegha SA, Ogundare PO, Oboh G, Esatbeyoglu T, Papenbrock J (2025) An overview on the mechanisms of encapsulation of polyphenols used to help fight diabetes mellitus. Discov Food 5(1):185
11. Ozkan G, Ceyhan T, Çatalkaya G, Rajan L, Ullah H, Daglia M, Capanoglu E (2024) Encapsulated phenolic compounds: clinical efficacy of a novel delivery method. Phytochem Rev 23(3):781–819
12. Wang X, Li H, Bao Y, Wang Y, Chen C (2024) Overcoming the application limitations of Ph-driven encapsulation of bioactive compounds: strategies and perspectives. Curr Opin Food Sci 59:101212
13. Gómez-Gaete C, Avendaño-Godoy J, Escobar-Avello D, Campos-Requena VH, Rogel-Castillo C, Estevinho LM, Martorell M, Sharifi-Rad J, Calina D (2024) Processing, and nutrition, 'revolutionizing fruit juice: exploring encapsulation techniques for bioactive compounds and their impact on nutrition, flavour and shelf life. Food Prod Process Nutr 6(1):8
14. Tian XY, Bai JW, Fang Q, Wang M, Wu X, Aheto JH (2025) Polyphenols in modern nutrition: green extraction technologies, encapsulation, and promissory applications. Food Bioprocess Technol 18:6035–6065
15. Chowdhury S, Kar K, Mazumder RJ (2024) Exploration of different strategies of nanoencapsulation of bioactive compounds and their ensuing approaches. Futur J Pharm Sci 10(1):72
16. Kamble MG, Singh A, Singh SV, Kamble MG, Sagar NA, Rani N (2025) Nanotechnology for encapsulation of bioactive components: a review. Discov Food 5(1):1–18
17. Chakou FZ, Boual Z, Ould El Hadj MD, Badreddine A, El Alaoui-Talibi Z, El Modafar C, Fendri I, Abdelkafi S, Dubessay P, Gardarin C (2021) Ethnobotanical utilization of *Alhagi maurorum* Medik. in traditional recipes of Algerian Sahara Illizi Wilaya. Euro-Mediterr J Environ Integr 6(3):71
18. Chakou FZ, Boual Z, Hadj MDOE, Belkhalfa H, Bachari K, El Alaoui-Talibi Z, El Modafar C, Hadjkacem F, Fendri I, Abdelkafi S (2021) Pharmacological investigations in traditional utilization of *Alhagi maurorum* Medik. in Saharan Algeria: in vitro study of anti-inflammatory and antihyperglycemic activities of water-soluble polysaccharides extracted from the seeds. Plants 10(12):2658
19. Kamelan Kafi M, Bolvari NE, Mohammad Pour S, Moghadam SK, Shafaei N, Karimi E, Oskoueian E (2022) Encapsulated phenolic compounds from *Ferula gummosa* leaf: a potential phytobiotic against *Campylobacter jejuni* infection. J Food Process Preserv 46(8):e16802
20. Oskoueian E, Abdullah N, Zulkifli I, Ebrahimi M, Karimi E, Goh YM, Oskoueian A, Shakeri M (2015) Cytoprotective effect of palm kernel cake phenolics against aflatoxin B1-induced cell damage and its underlying mechanism of action. BMC Complement Altern Med 15(1):1
21. Yi X, Zheng Q, Ding B, Pan M, Chiou Y, Li L, Li Z (2019) Liposome-whey protein interactions and its relation to emulsifying properties. LWT 99:505–512

22. Tatipamula VB, Kukavica B (2021) Phenolic compounds as antidiabetic, anti-inflammatory, and anticancer agents and improvement of their bioavailability by liposomes. Cell Biochem Funct 39(8):926–944
23. Neuenfeldt NH, de Moraes DP, de Deus C, Barcia MT, de Menezes CR (2022) Blueberry phenolic composition and improved stability by microencapsulation. Food Bioprocess Technol 15(4):750–767
24. Beyrami M, Karimi E, Oskoueian E (2020) Synthesized chrysin-loaded nanoliposomes improves cadmium-induced toxicity in mice. Environ Sci Pollut Res Int 27(32):40643–40651
25. Kou X, Qi S, Dai W, Luo L, Yin Z (2011) Arctigenin inhibits lipopolysaccharide-induced inos expression in Raw264. 7 cells through suppressing Jak-Stat signal pathway. Int Immunopharmacol 11(8):1095–1102
26. Samadder A, Chakraborty D, De A, Bhattacharyya SS, Bhadra K, Khuda-Bukhsh AR (2011) Possible signaling cascades involved in attenuation of Alloxan-induced oxidative stress and hyperglycemia in mice by ethanolic extract of *Syzygium Jambolanum*: drug-DNA interaction with calf thymus DNA as target. Eur J Pharm Sci 44(3):207–217
27. Shafaei N, Barkhordar SMA, Rahmani F, Nabi S, Idliki RB, Alimirzaei M, Karimi E, Oskoueian E (2020) Protective effects of *Anethum graveolens* seed's oil nanoemulsion against cadmium-induced oxidative stress in mice. Biol Trace Elem Res. https://doi.org/10.1007/s12011-020-02093-z
28. Xia BH, Yu ZL, Lu YA, Liu SJ, Li YM, Xie MX, Lin LM (2024) Green and efficient extraction of phenolic components from plants with supramolecular solvents: experimental and theoretical studies. Molecules 29(9):2067
29. Birinci C, Kara Y, Gıdık B, Kolaylı S, Can Z (2025) Optimization of phenolic compound extraction from bee products via solvent systems and PCA integration. Food Anal Methods 18(9):2040–2050
30. Nouioura G, El Fadili M, El Barnossi A, Loukili EH, Laaroussi H, Bouhrim M, Giesy JP, Aboul-Soud MA, Al-Sheikh YA, Lyoussi B (2024) Comprehensive analysis of different solvent extracts of *Ferula communis* L. fruit reveals phenolic compounds and their biological properties via in vitro and in silico assays. Sci Rep 14(1):8325
31. Hurkul MM, Cetinkaya A, Kaya SI, Yayla S, Ozkan SA (2025) Investigation of health effects of major phenolic compounds in foods: extraction processes, analytical approaches and applications. Crit Rev Anal Chem 55(6):1005–1039
32. Shi L, Zhao W, Yang Z, Subbiah V, Suleria HAR (2022) Extraction and characterization of phenolic compounds and their potential antioxidant activities. Environ Sci Pollut Res 29(54):81112–81129
33. Alara OR, Abdurahman NH, Ukaegbu CI (2021) Extraction of phenolic compounds: a review. Curr Res Nutr Food Sci 4:200–214
34. Alavi M, Rai M (2025) Micro-and nanocarriers for improving therapeutic effects of phenolic compounds: an up-to-date perspective. Nano Micro Biosyst 4(1):15–26
35. Firdaus J, Singh S, Sindhu, RK (2025) Basics of nano-bioactive compounds and their therapeutic potential. Bioact Based Nanotherapeutics 1–25
36. Molski M (2023) Theoretical study on the radical scavenging activity of Gallic acid. Heliyon. https://doi.org/10.1016/j.heliyon.2023.e12806
37. Qi X, Liu H, Ren Y, Zhu Y, Wang Q, Zhang Y, Wu Y, Yuan L, Yan H, Liu M (2023) Effects of combined binding of chlorogenic acid/caffeic acid and gallic acid to trypsin on their synergistic antioxidant activity, enzyme activity and stability. Food Chem X 18:100664
38. Yazdi M, Nafari A, Azadpour M, Alaee M, Moradi FH, Choghakhori R, Hormozi M, Ahmadvand H (2023) Protective effects of cinnamic acid against hyperglycemia induced oxidative stress and inflammation in Hepg2 cells. Rep Biochem Mol Biol 12(1):1
39. Shahidi S, Komaki A, Raoufi S, Salehi I, Zarei M, Mahdian M (2021) The anti-nociceptive effect of ellagic acid in streptozotocin-induced hyperglycemic rats by oxidative stress involvement. Basic Clin Neurosci 12(6):861
40. Ştefănescu BE, Nemes SA, Teleky BE, Călinoiu LF, Mitrea L, Martău GA, Szabo K, Mihai M, Vodnar DC, Crişan G (2022) Microencapsulation and bioaccessibility of phenolic compounds of *Vaccinium* leaf extracts. Antioxid (Basel) 11(4):674
41. Tang Y, Liu W, Zhang J, Juan B, Zhu Y, Zhu L, Zhao Y, Daglia M, Xiao X, He Y (2025) Advances in intestinal-targeted release of phenolic compounds. Nutrients 17(16):2598
42. Sousa VI, Parente JF, Marques JF, Forte MA, Tavares C (2022) Microencapsulation of essential oils: a review. Polym (Basel) 14(9):1730
43. Huang K, Yuan Y, Baojun X (2023) , 'a critical review on the microencapsulation of bioactive compounds and their application. Food Rev Int 39(5):2594–2634
44. Dong Z, Yu S, Zhai K, Bao N, Rashed MM, Wu X (2023) Fabrication and characterization of complex coacervation: the integration of sesame protein isolate-polysaccharides. Foods 12(19):3696
45. Akbarmehr A, Peighambardoust SH, Soltanzadeh M, Jafari SM, Sarabandi K (2023) Microencapsulation of Yerba Mate extract: the efficacy of polysaccharide/protein hydrocolloids on physical, microstructural, functional, and antioxidant properties. Int J Biol Macromol 234:123678
46. Jomova K, Raptova R, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, Valko M (2023) Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging. Arch Toxicol 97(10):2499–2574
47. Reddy VP (2023) Oxidative stress in health and disease. Biomedicines 11(11):2925
48. Rahman MM, Rahaman MS, Islam MR, Rahman F, Mithi FM, Alqahtani T, Almikhlafi MA, Alghamdi SQ, Alruwaili AS, Hossain MS, Ahmed M, Das R, Emran TB, Uddin MS (2021) Role of phenolic compounds in human disease: current knowledge and future prospects. Molecules 27(1):233
49. Moro KIB, Bender ABB, da Silva LP, Penna NG (2021) Green extraction methods and microencapsulation technologies of phenolic compounds from grape pomace: a review. Food Bioprocess Technol 14(8):1407–1431
50. Cruz-Molina AVDL, Ayala Zavala JF, Bernal Mercado AT, Cruz Valenzuela MR, González-Aguilar GA, Lizardi-Mendoza J, Brown-Bojorquez F, Silva-Espinoza BA (2021) Maltodextrin encapsulation improves thermal and pH stability of green tea extract catechins. J Food Process Preserv 45(9):e15729
51. Pieczykolan A, Pietrzak W, Gawlik-Dziki U, Nowak R (2021) Antioxidant, anti-inflammatory, and anti-diabetic activity of phenolic acids fractions obtained from *Aerva lanata* (L.) Juss. Molecules 26(12):3486
52. Kaushalya K, Rupasinghe HVP (2024) Health benefits of microencapsulated dietary polyphenols: a review. Food Rev Int 40(7):2079–2102
53. Ren X, Yuan P, Niu J, Liu Y, Li Y, Huang L, Jiang S, Jiao N, Yuan X, Li J, Yang W (2023) Effects of dietary supplementation with microencapsulated Galla Chinensis tannins on growth performance, antioxidant capacity, and lipid metabolism of young broiler chickens. Front Vet Sci 10:1259142
54. Krawczyk M, Burzynska-Pedziwiatr I, Wozniak LA, Bukowiecka-Matusiak M (2023) Impact of polyphenols on inflammatory and oxidative stress factors in diabetes mellitus: nutritional antioxidants and their application in improving antidiabetic therapy. Biomolecules 13(9):1402
55. Ziolkowska S, Binienda A, Jabłkowski M, Szemraj J, Czarny P (2021) The interplay between insulin resistance, inflammation, oxidative stress, base excision repair and metabolic syndrome in nonalcoholic fatty liver disease. Int J Mol Sci 22(20):11128
56. Jin Q, Liu T, Qiao Y, Liu D, Yang L, Mao H, Ma F, Wang Y, Peng L, Zhan Y (2023) Oxidative stress and inflammation in diabetic nephropathy: role of polyphenols. Front Immunol 14:1185317
57. Abdel-Aty AM, Barakat AZ, Bassuiny RI, Mohamed SA (2024) Chia gum-gelatin-based encapsulation of chia sprouts phenolic compounds enhanced storage stability, bioavailability, antioxidant, antidiabetic, and antibacterial properties. Sci Rep 14(1):22023
58. Tartau CG, Boboc IKS, Mititelu-Tartau L, Bogdan M, Buca BR, Pavel LL, Amalinei C (2025) Exploring the protective effects of traditional antidiabetic medications and novel antihyperglycemic agents in diabetic rodent models. Pharma (Basel) 18(5):670
59. Xu K, Lu G, Feng Q, Chen S, Wang Y (2023) Hepatoprotective effect of protocatechuic acid against type 2 diabetes-induced liver injury. Pharm Biol 61(1):737–745
60. Othman MS, Khaled AM, Al-Bagawi AH, Fareid MA, Ghany RA, Habotta OA, Abdel Moneim AE (2021) Hepatorenal protective efficacy of flavonoids from *Ocimum basilicum* extract in diabetic albino rats: a focus on hypoglycemic, antioxidant, anti-inflammatory and anti-apoptotic activities. Biomed Pharmacother 144:112287
61. Le TKC, Dao XD, Nguyen DV, Luu DH, Bui TMH, Le TH, Nguyen HT, Le TN, Hosaka T, Nguyen TTT (2023) Insulin signaling and its application. Front Endocrinol (Lausanne) 14:1226655
62. Herman R, Kravos NA, Jensterle M, Janež A, Dolžan V (2022) Metformin and insulin resistance: a review of the underlying mechanisms behind changes in Glut4-mediated glucose transport. Int J Mol Sci 23(3):1264
63. Gusti AM, Qusti SY, Alshammari EM, Toraih EA, Fawzy MS (2021) Antioxidants-related superoxide dismutase (Sod), catalase (Cat), glutathione peroxidase (Gpx), glutathione-S-transferase (Gst), and nitric oxide synthase (Nos) gene variants analysis in an obese population: a preliminary case-control study. Antioxid (Basel) 10(4):595
64. Shen Z, Hou Y, Zhao G, Tan L, Chen J, Dong Z, Ni C, Pei L (2024) Physiological functions of glucose transporter-2: from cell physiology to links with diabetes mellitus. Heliyon. https://doi.org/10.1016/j.heliyon.2024.e25459
65. Sun B, Chen H, Xue J, Li P, Fu X (2023) The role of Glut2 in glucose metabolism in multiple organs and tissues. Mol Biol Rep 50(8):6963–6974

66. Feng SY, Wu SJ, Chang YC, Ng LT, Chang SJ (2022) Stimulation of Glut4 glucose uptake by anthocyanin-rich extract from black rice (*Oryza sativa* L.) via Pi3k/Akt and Ampk/P38 Mapk signaling in C2c12 cells. Metabolites 12(9):856
67. Zhang Z, Li X, Sang S, McClements DJ, Chen L, Long J, Jiao A, Jin Z, Qiu C (2022) Polyphenols as plant-based nutraceuticals: health effects, encapsulation, nano-delivery, and application. Foods 11(15):2189

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