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Physicochemical Properties and in Vitro Anti-Obesity Potential of Anethum graveolens (Dill) Seed Cake

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ABSTRACT

The present study investigates the in vitro anti-obesity potential of Anethum graveolens L. (Family Apiaceae) dill seed cake (DSC). DSC contained dietary fibers, proteins, lignans, and phenolic compounds. Food rich in dietary fiber is vital in lowering dyslipidemia, complications of metabolic disorders, and obesity. DSC was obtained after oil extraction of the dill seed. Physicochemical characterization and lignan profiling were performed by HPLC. An in vitro study assessed the degree of hydrolysis, α-amylase, α-glucosidases, and pancreatic lipase inhibitory activity. The DSC has high dietary fiber, moderate protein, and less than ten percent moisture, ash, and fat content with low foreign matter. HPLC chromatogram of DSC showed the presence of lignin-like carvone, perillyl alcohol, perillaldehyde, and cineole. The IC_{50} value for α-amylase, α-glucosidase, and pancreatic lipase inhibitory activity was 60.18 ± 2.21, 456.42 ± 5.32, and 54.13 ± 2.25 µg/ml, respectively. DSC can help with obesity and its accompanying metabolic issues by reducing glucose and fat metabolism and absorption in the intestines. The study's findings suggest that dill seeds are employable in a nutraceutical supplement to help with obesity management.

Keywords: *Anethum graveolens, Dill seed cake, Lignans, Dietary fiber, Obesity*

INTRODUCTION

Obesity is one of the severe concerns worldwide resulting from imbalanced energy intake, which is associated with serious diseases related to cardiac disorder and hormonal imbalance [1]. In the wellness industry, complementary medicine has recently become very popular. Dietary measures and traditional herbs from the indigenous systems of medicine are been extensively used in India to combat obesity. Studies substantiate the protective potential of dietary antioxidants against oxidative damage in the body associated with obesity. Dill (*Anethum graveolens*) is a common edible herb in the Umbelliferae family. In the Mediterranean basin, it grows naturally and is also commonly found in India and Asia. Since ancient times, dill has had various uses in traditional Indian medicine [2]. Dill seeds contain substantial quantities of antioxidative phytoconstituents like phenolic acids and lignans. Significant amounts of soluble and insoluble fiber are present in the residue after oil extraction of dill seed and byproducts. Foods high in dietary fiber are beneficial for managing type 2 diabetes, lowering cholesterol, and reducing obesity. Seed cake is the leftover material from oil extraction that is typically fed to cattle. Dill seed cake is rich in dietary fiber and other antioxidant constituents.

Yazdanpanah reported the potential antioxidant and hypocholesterolemic effects of dill juice [3]. Dill supplementation in patients with metabolic syndrome can improve lipid profile and insulin resistance [4]. Clinical trials showed the hypolipidemic potential of dill in type 2 diabetic patients [5]. Dill seed hydroalcoholic extract and tablet containing 68% dill seed showed hypolipidemic action in hamsters by inhibiting HMG-CoA reductase

activity [6]. Oshaghi *et al*. [7] reported the presence of antioxidant constituents like phenolic and flavonoids, flavonol, alkaloids, anthocyanin, tannin, and saponin in dill tablets. Dill seed extract displayed antioxidant, hypolipidemic, and hypoglycemic effects in diabetic patients [8].

Haidari *et al*. [9] investigated dill seed powder consumption on glycemic profile, lipid parameters, antioxidant efficacy, inflammatory marker level, and gastrointestinal conditions of patients with type 2 diabetes. In the treatment group, the injection of dill powder dramatically reduced serum insulin levels, low-density lipoprotein, total cholesterol, malondialdehyde, and insulin resistance. Along with α and p-phellandrene, carvone and limonene are the two main constituents of dill seed [10]. Carvone and limonene could be effective as suppressant effects against a hypercaloric diet in obesity. Carvone acts against high-fat, diet-induced, and obesity-associated metabolic complications by altering inflammatory and lipogenesis gene expression in adipose and liver tissues [11]. A literature survey reveals that the anti-obesity properties of dill seed cake (DSC) have not been explored so far. This research endeavor seeks to explore the in vitro anti-obesity potential of DSC. Phytochemical characterization of dill seed cake was performed along with an assessment of α- amylase, α-glucosidases, and pancreatic lipase inhibitory activity to establish its applicability as a natural supplement to control obesity and weight gain.

MATERIALS AND METHODS

Chemicals

Commercial α-amylase, sodium dodecyl sulfate, N-acetylcysteine, O-phthalaldehyde, and Folin-Ciocalteu phenol reagent were sourced from Hi-Media, India. P-nitrophenylα-D-glucopyranoside, sodium phosphate buffer, pancreatic lipase, α-glucosidase, acarbose, and orlistat were purchased from NS Scientific, India. Sodium dodecyl sulfate, borate buffer, and bovine serum albumin were purchased from Thermo Fisher Scientific, India. O-phthalaldehyde (OPA) was procured from Merck, India. All the chemicals and reagents consumed in the study were HPLC and analytical grade.

Collection of dill seed

Fresh dill (*A. graveolens*) seeds were bought from the local market in Bhopal, Madhya Pradesh. Taxonomist Dr. S. Naaz at the Saifia College, Bhopal, India, authenticated the seeds, and the specimen was preserved in the departmental Herbarium (147/Bot. Saifia/Sci. /College/Bpl).

Preparation of dill seed cake

Mature dill seeds were dried in the shade, size reduced by grinding, and kept in a cool, dry environment until further use. Extraction of oil was done using a multi-oil seeds press. Dill seeds (500 gm) were kept in the hopper of the oil press machine (Eco Smart ES, Surat, India), oil was removed, and the seed cake left after oil extraction was collected. The shade-dried DSC was pulverized further for size reduction.

Phytochemical evaluation

Dried coarse DSC (25 gm) was extracted separately with 200 ml petroleum ether, chloroform, ethyl acetate, and ethanol (90%) using a soxhlet extractor for 12 hrs. The extracted materials were then filtered and vacuum-evaporated to a concentrate (Jyoti Scientific, India). After being weighed, the final residue was stored in the refrigerator for further qualitative analysis. Phytochemicals such as alkaloids, flavonoids, phenolics, carbohydrates, saponins, steroids, tannins, and proteins were detected following the methods reported by Khandelwal [12].

Physicochemical evaluation

Ash, dry matter, and moisture content: DSC (2 gm) was placed in a tarred silica crucible, weighed, and incinerated below 450 °C until it was carbon-free, then weighed again after cooling. The percentage of ash generated was calculated based on the initial DSC weight. Following that water soluble and acid insoluble ash content was estimated. To determine acid-insoluble ash, use 10% hydrochloric acid as a solvent instead of deionized water [13]. The weighed quantity of DSC was dried in the oven at 105 °C until get to a constant weight. Weight loss about the initial weight of DSC was applied to calculate the moisture content [14].

Foreign matter: The DSC sample was weighed (100 gm) and spread thinly. The foreign case was detected and weighed by inspection with the unaided eye and using a lens (6x) [12].

Fat content: Fat content was estimated following the method of AOAC subjecting to 8 hrs soxhlet extraction with n-hexane at 70 °C. Forty gm of DSC was extracted with 350 ml of n-hexane to estimate the oil content [15].
Total protein content: Total protein content was estimated using the Lowry technique compared with bovine serum albumin (BSA) as equivalent to plotting a calibration curve. The absorbance of the sample and BSA was measured spectrophotometrically at 660 nm [16].

Preparation of purified DSC extract
Hexane (500 ml) was used to extract the DSC (20 gm) three times at room temperature. To remove soluble carbohydrates and proteins, the defatted residue was washed three times with distilled water (500 ml) and dried below 70 °C. The resultant dried residue (20 gm) was extracted with methanol (400 ml) in a soxhlet extractor for 16 hours. The filtered methanol extract was dried under a vacuum and weighed. The residue was refrigerated until analysis, dissolving in 100 ml of methanol to get phenolic and lignans extract [17].

Total dietary fiber
Quantification of insoluble and soluble dietary fibers was performed following the method of Zhao *et al*. [18]. The purified extract of DSC was gelatinized by treating it with heat-stable alpha-amylase (100 °C, pH = 6) for 15 min. Following that, the sample was enzymatically digested with protease (60 °C, pH = 7.5) for 30 min. This was followed by a 30-minute incubation with amyloglucosidase (60 °C, pH = 4.5) to separate protein and starch. Digested samples were washed (simultaneously with water, 95% ethanol, and acetone), dried, and weighed to obtain insoluble fiber. Preheated ethanol (95%) at 60 °C was mixed with filtrate, and the precipitate thus obtained was filtered. Step-by-step, 70% ethanol, 95% ethanol, and acetone were used to wash the residue. Subsequently, the residue representing soluble fiber was dried and weighed. After correction for ash and protein, total dietary fiber was calculated by adding the insoluble and soluble fiber content.

Total phenolic compound
Based on the calibration curve, the phenolic quantity as gallic acid equivalent (mg/100 mg) was determined following the Folin-Ciocalteu method. The purified extract of DSC (2 mg) was added with 2 ml ethanol (90%) and 10 ml of distilled water. Folin-Ciocalteu reagent (1 ml; 50% v/v) was added, mixed well, and kept for 5 min. After that, 2 ml of sodium carbonate (5%) was combined with the reaction mixture, vortexed for 15 seconds, and allowed to rest for 60 minutes at 40 °C. The absorbance of the color developed was spectrophotometrically measured at 725 nm (Genesys 180, Thermo Fisher Scientific Inc., USA). Plotting a standard curve for different concentrations of gallic acid in water was performed. The absorbance values were converted to the total phenolic content of the DSC sample [19].

Authentication of lignans by HPLC
Waters Alliance 2695 separations module HPLC system (Milford, USA) equipped with photodiode array detector, auto-sampler, 20 µl injection loop, and a column oven was employed. Using a reverse phase Primesep 200 C18 (250 × 4.6 mm, 5 µm) column coupled by a 3 µm particle size guard column (Phenomenex, Macclesfield, UK), the baseline resolution of lignan was achieved at 25 ± 2 ºC and evaluated using Ace software. The amount of sample and standard injected was 20 µl. Methanol and water (65:35; v/v) mobile phase was passed through a 0.45 PVDF filter and degassed before use. The flow rate was kept at 1.3 ml/min based on the isocratic system for 20 min and monitored at 220 nm. The purified extract of DSC was dissolved in 90% methanol (1 mg/ml), sonicated, and filtered. Diluted stock solution at the concentration of 10 µg/ml in methanol was passed through a 0.45 µm microfilter before injection [20].

In vitro studies
Degree of hydrolysis: The OPA reagent was prepared by combining 50 mmol OPA, 50 mmol NAC, and 20% (w/v) sodium dodecyl sulfate with borate buffer (0.1 M, pH 9.5). The assay was carried out by adding a weighed amount of purified DSC extract with OPA reagent, vortexed for 5 sec, and incubated at room temperature for 2 min. The mixture was analyzed with a spectrophotometer (Genesys 180, Thermo Fisher Scientific Inc., USA) at a wavelength of 340 nm [21].
Inhibition of alpha-amylase: An equal amount of purified extract of DSC and acarbose was added to 0.20 mmol α-amylase in phosphate buffer (pH = 6.9) and then incubated for ten minutes at 25 °C. Further starch (1%) in 0.02 M sodium phosphate buffer (pH = 6.9) was mixed and incubated at 25 °C for 10 min. Color reagent 3, 5 dinitro

salicylic acid was added and then allowed to cool to room temperature after being incubated for five minutes in a hot water bath to terminate the reaction [22]. The absorbance of the reaction mixture was determined at 540 nm, and the percentage of α-amylase inhibition was calculated using the formula:

$$A_c - [A_s - A_0]/ A_c \times 100 \quad (1)$$

Ac = Absorbance of control; As = Absorbance of the sample with enzyme; A0 = Absorbance of the sample without enzyme.

Porcine pancreas α-glycosidase inhibitory activity: The p-nitrophenyl α-D-glucopyranoside substrate-based reaction employed to estimate α-glucosidase inhibitory activity [23]. α-Glucosidase 0.006% solution (0.02 M phosphate buffer; pH = 6.9) was incubated with purified extract of DSC (0.02 M phosphate buffer) for 1 hr at 250 °C. Then, p-nitrophenyl α-D-glucopyranoside (2 M) was added and incubated for 30 min at 300 °C. The reaction terminated following the addition of Na_2CO_3 (1 M), and the p-nitro phenol thus formed was spectrophotometrically measured at 405 nm. α-glucosidase inhibitory activity was measured and compared with acarbose using the formula:

$$\% \text{ α-glucosidase inhibition} = A_c - [A_s - A_0]/ A_c \times 100 \quad (2)$$

Ac = Absorbance of control; As = Absorbance of the sample with enzyme; A0 = Absorbance of the sample without enzyme.

Porcine pancreas lipase inhibitory activity: DNPB was utilized as a substrate to quantify the inhibitory action of DSC against pancreatic lipase [24]. The pancreas lipase (0.1 mmol potassium phosphate buffer; pH = 6.0) was pre-incubated with Tween 80 (0.6%) and the purified DSC extract (0.1 mmol in potassium phosphate buffer; pH = 7.3) for one hour at 30 °C. DNPB (25 mmol) was added to begin the reaction, which was then incubated for five minutes at 30 °C. Using spectrophotometry, the amount of 2,4-dinitrophenol generated in the reaction mixture was quantified at 400 nm. The percentage inhibition of pancreatic lipase was calculated according to the formula:

$$I\% = [(A - a) - (B - b)] / (A - a) \times 100 \quad (3)$$

A = activity without an inhibitor, a = negative control without an inhibitor, B = activity with an inhibitor, and b = negative control with an inhibitor. In the case of a, the reaction was stopped as soon as the substrate was added to the assay buffer containing the enzyme; whereas in b, the inhibitor was incubated with the enzyme mixture before the substrate was added.

Statistical analysis

All data point is displayed as mean ± SEM. Tukey's multiple comparison test was employed after analysis of variance to see whether there were any differences between the groups. A P-value of 0.05 is considered statistically significant.

RESULTS AND DISCUSSION

Phytochemical evaluation

Carbohydrates, steroids, flavonoids, and phenolics were found in all four petroleum ether, chloroform, ethyl acetate, and methanol extracts of DSC. The ethyl acetate and methanol extracts contained alkaloids, tannins, and saponins, whereas the petroleum ether and chloroform extracts contained protein **(Table 1)**.

Table 1. Phytochemical evaluation of dill seed cake

Chemical class	Petroleum ether extract	Chloroform extract	Ethyl acetate extract	Ethanol extract
Alkaloids	–	–	+	+
Carbohydrate	+	+	+	+
Glycoside	–	–	–	–
Flavonoids and phenolics	+	+	+	+

Saponins	–	+	+	+
Phytosterols and Triterpenes	+	+	+	+
Tannin	–	–	+	+
Proteins	+	+	–	–
Fat and oil	+	+	+	+

Where + is Present and – is Absent.

Physicochemical evaluation

Total fat content was 4.11 mg/100 mg in DSC. The moisture and ash contents were 6.39 and 8.95% in the composition. The total fiber content of DSC was found to be 21.37%, combining both soluble and insoluble fiber. Dry matter and foreign organic matter were 84.36% and 0.75%, respectively. The phenolic compound and protein content were 38.23 and 22.21 mg/100 mg of DSC **(Table 2)**.

Table 2. Physicochemical evaluation of dill seed cake

Physicochemical parameters	Values (% w/w)
Total ash	8.95 ± 0.24
Acid insoluble ash	1.89 ± 0.03
Water soluble ash	4.86 ± 0.11
Dry matter	84.36 ± 3.23
Moisture content	6.39 ± 0.21
Foreign organic matter	0.75 ± 0.006
Total fat	4.11 ± 0.21
Total fiber	21.37 ± 2.21
Soluble fiber	4.32 ± 0.17
Insoluble fiber	17.31 ± 1.02
Total phenolic compound	38.23 ± 7.36
Total protein	22.21 ± 0.05

All the data are presented as mean ± SEM of three determinations.

HPLC analysis

HPLC chromatogram of DSC showed the presence of lignin-like carvone (Rt: 9.985), perillyl alcohol (Rt: 10.255), perillaldehyde (Rt: 11.605), and cineole. Chromatographic analysis of dill seed lignins was performed following the method of Tao and Pereira with slight modification using methanol: water (65:35) as mobile phase **(Figures 1 and 2)** [20].

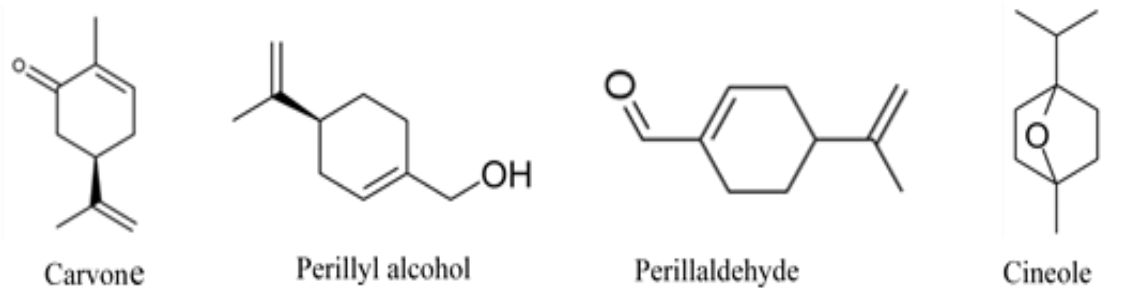

Figure 1. Chemical structure of dill seed lignan

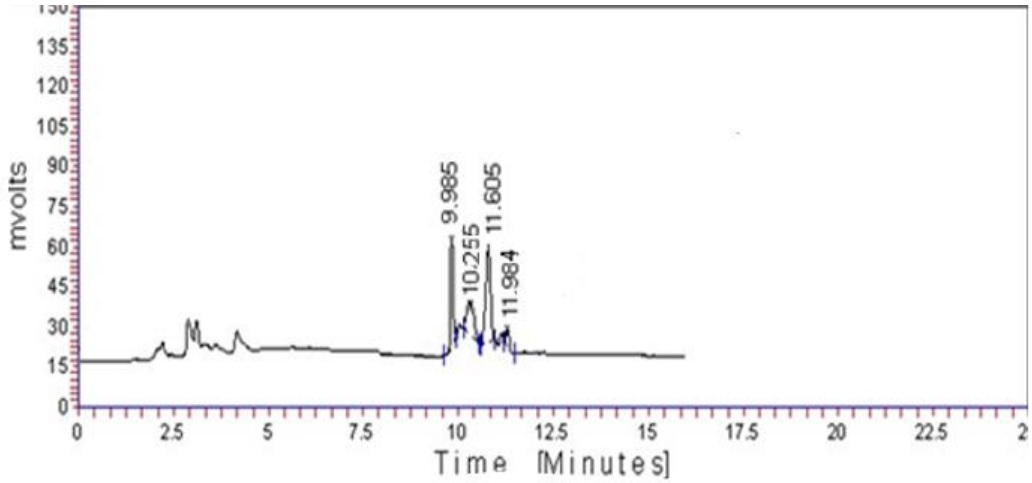

Figure 2. HPLC chromatogram of dill seed cake purified extract displaying peak of carvone (Rt: 9.985), perillyl alcohol (Rt: 10.255), perillaldehyde (Rt: 11.605) and cineole (Rt: 11.984).

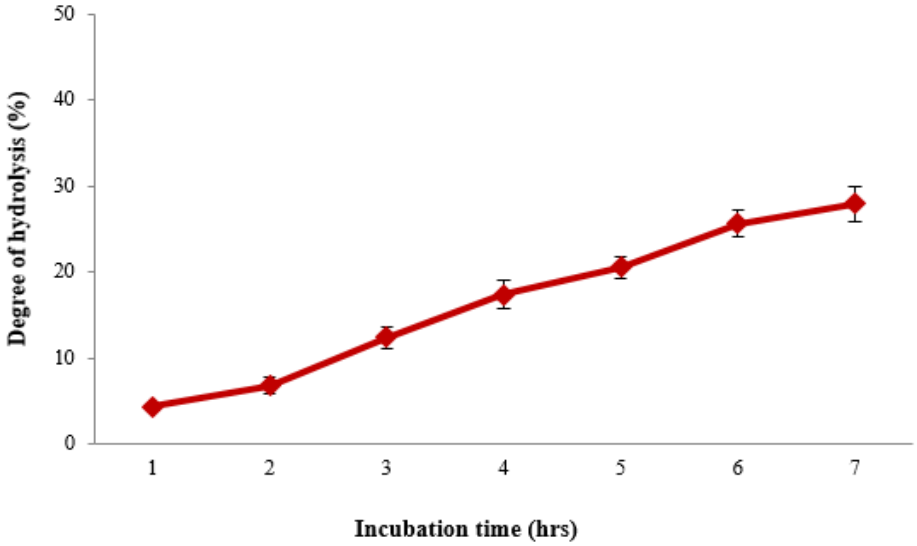

Figure 3. Percent degree of hydrolysis of dill seed cake at different time intervals.

In-vitro studies

The hydrolysis percentage of DSC ranged from 4.32-27.92%, as shown in **Figure 3**, indicating slow hydrolysis of the protein in dill seed cake material. The hydrolysis rate increased slowly in the first 2 hrs, reaching only 6.75% and then gradually increasing at a relatively constant rate ($P < 0.01$).

DSC showed a concentration-dependent inhibition of α-amylase with an IC_{50} at 60.18 ± 2.21 µg/ml. Starting from 10 µg/ml concentration, the inhibition ability increased gradually, reaching 60.33% at 100 µg/ml. DSC inhibited the α-glucosidase enzyme activity in all the tested concentrations (100 to1000 µg/ml) in a concentration-dependent manner. The IC_{50} was 456.42 ± 5.32 µg/ml, whereas, at 1000 µg/ml, it showed 56.16% inhibition of α-glycosidase. The pancreatic lipase inhibitory profile of DSC was estimated compared to orlistat, showing profound inhibition with an increase in concentration. DSC showed a maximum of 58.34% inhibition at 100 µg/ml concentration, and the IC_{50} was at 54.13 ± 2.25 µg/ml **(Figure 4)**.

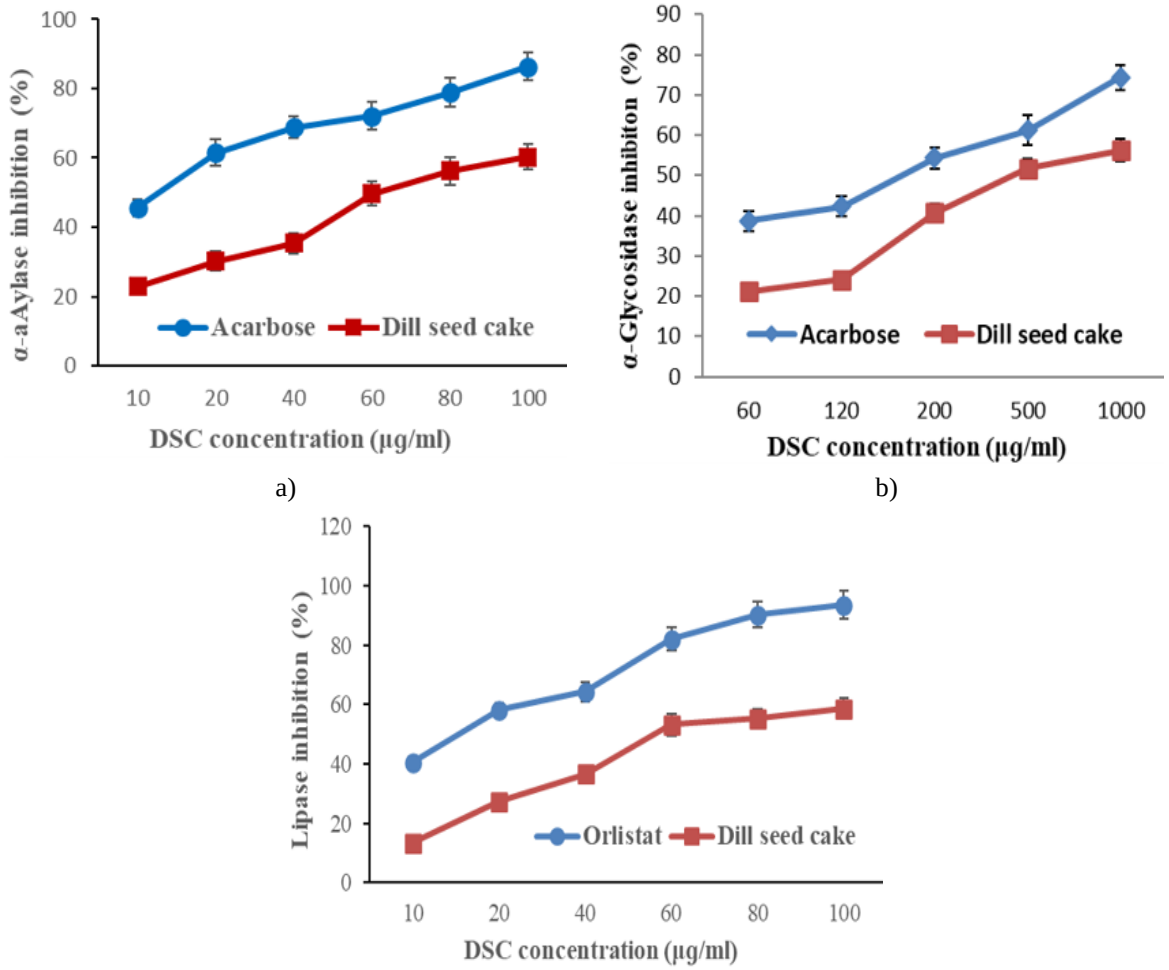

Figure 4. α-Amylase, α-glycosidase, and lipase inhibitory activity of dill seed cake at different concentration ranges.

Physicochemical properties and in vitro anti-obesity potential of dill seed cake residue left after oil extraction were assessed. The study revealed the anti-obesity potential of dill seed cake, which can be an excellent nutraceutical for developing a safe and effective anti-obesity preparation. Dietary edible seeds consumed worldwide for their nutritional value contain rich amounts of fiber, protein, lignans, and polyphenols. Market demand for edible seeds is increasing globally nowadays as trendy food supplements to counteract obesity in current changing dietary patterns. The easy availability of dill seed and the very economical cake production process after oil extraction as a dietary supplement to control obesity and its related risk factors.

Dill has potential antioxidant and hypocholesterolemic effects and has been reported to improve insulin resistance-related metabolic syndrome in type 2 diabetes mellitus [4, 5, 8]. The dill powder supplementation significantly decreased the blood glucose, insulin resistance, cholesterol level, and malondialdehyde content in patients with type 2 diabetes [9]. Dietary seeds like quinoa, chia, chandrashoor, pumpkin, and fenugreek are functional foods with potential anti-obesity properties [25]. The anti-obesity response of dill seeds could be due to the modulation of oxidative stress and inflammation besides hypoglycemic and hypolipidemic effects [26].

Hitherto, the anti-obesity effect of dill seed cake has not been explored experimentally. Dill seed cake showed the presence of carbohydrates, steroids, proteins, alkaloids, flavonoids, and phenolics. Moisture and ash content was less than ten percent in dill seed cake. The fat content of dill seed cake was considerable, with rich fiber content combining soluble and insoluble fiber. High dry matter content further correlates with the profound presence of fiber in seed cake. Dill seed cake showed moderate phenolic compound and protein content. The lignans in dill seed cake were predominantly carvone, perillyl alcohol, perillaldehyde, and cineole. The hydrolysis percentage of dill seed cake was below 30%, indicating slow hydrolysis. The time of hydrolysis affects the morphological characters of hydrolysate, signifying an inverse relation between hydrolysis time and resultant protein particle size. The enzymatic hydrolysis of seed cake by stomach proteolytic enzymes results in the production of distinct

peptide sequences. Dill seed cake has a slow and low degree of hydrolysis. With a low degree of hydrolysis, dill seed cake will yield peptide chains of high average length.

Obesity is associated with disarranged energy utilization causing an imbalance in carbohydrate and lipid metabolism and fat-burning process. Blood sugar level and body weight management depend on digestion and carbohydrate absorption. α-Amylase produces linear maltose and branched isomaltose oligosaccharides after starch digestion, which is further hydrolyzed to absorbable monosaccharide by α-glucosidases [27]. An essential aspect of weight control is reducing and slowing dietary carbohydrate digestion. The inhibition of α-amylase and α-glucosidases can significantly delay postprandial hyperglycemia by delaying the absorption of dietary carbohydrates [28]. Dill seed cake showed moderate inhibition of both α-amylase and α-glucosidases enzymes. In the lipid metabolic pathway, pancreatic lipase is an essential enzyme for metabolizing dietary fats to triglycerides. Triglycerides are hydrolyzed into monoglycerides, free fatty acids, and other small molecules by pancreatic lipase. These free fatty acids are absorbed back into the intestine and utilized for the resynthesis of triglycerides, leading to high blood lipid levels. Obesity can be effectively prevented by inhibiting pancreatic lipase activity as an anti-obesity drug orlistat function [29, 30]. Dill seed cake showed profound inhibition of pancreatic lipase dose-dependently. Profound suppression of pancreatic lipase and α-amylase and α-glucosidases indicates that dill seed cake has anti-obesity properties.

Adipose tissue is essential in providing energy to tissues and functions as an energy reserve. Following the consumption of energy-dense food, the excess lipids, commonly known as body fat, are stored in adipose tissues, causing obesity. The high soluble and insoluble fiber and protein content in dill seed cake may be effective in weight loss and fat burn depending on the fiber sources, functionality, supplementation, or consumption dosage [18]. Dill seed contains a rich amount of dietary fiber, protein, and phenolics with moderate fat. A low carbohydrate, low glycemic index diet containing high fiber and protein and moderate lean fat consumption positively affects weight maintenance [31]. Given this, the abundance of lignans and dietary fibers can potentially reduce cholesterol blood levels in vivo. Lignans have anti-obesity properties and can lower the chances of developing obesity-related chronic illnesses [32, 33]. Dill is rich in carvone and is reported to exert an antihyperglycemic effect by ameliorating abnormalities in glycoprotein components in plasma, liver, and kidney [34].

Dietary fibers, particularly soluble fibers, significantly increase insulin sensitivity and glycemic management in type 2 diabetic patients [35]. Dill seed cake contains valuable dietary fibers in high amounts left after oil extraction that can increase leptin release, inhibiting appetite [36]. Dill seed exerted hypolipidemic action in hamsters by inhibiting HMG-CoA reductase activity [6]. The array of phytochemicals present in dill seed may assist in controlling body fat and weight, stimulating metabolic pathways responsible for signaling adipolysis and lipolysis. The anti-obesity effect of dill seed cake in vitro on different intestinal enzyme inhibition abilities is reported for the first time. Studies are in progress for evaluating the in vivo anti-obesity profile of dill seed cake against different hypercaloric diets. Dill seed cake can be a helpful nutraceutical product for tackling obesity and promoting fat loss in obese individuals. The results indicate that dill seed cake could be utilized as an anti-obesity nutraceutical for developing a safe and effective anti-obesity supplementation. By-products of dill seed cakes may be investigated as commercially viable value-added food products with enhanced biological and functional characteristics.

CONCLUSION

Dill seeds are an important source of fiber, protein, and phenolic compounds. The presence of lignan and protein may prove its potential in nutraceutical supplements. Dill seed cake inhibits α-amylase, α-glycosidase, and pancreas lipase, which is beneficial to decreasing dietary carbohydrate and lipid digestion. The findings of the study substantiate the use of dill seed cake as a food supplement for obesity and metabolic complications.

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