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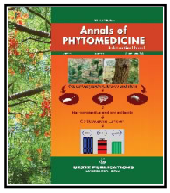

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In vitro α-glucosidase inhibitory activity of nanoencapsulated *Cuminum cyminum* L. (Angiosperms: Apiaceae) and it's interaction with acarbose

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Abstract

Diabetes is a group of metabolic disorder, characterized by increase in the level of glucose, resulting from defects in insulin secretion, its action or sometimes both. The effects associated are prolonged organ damage, dysfunction of especially the eyes, kidneys, nerves, heart, and blood vessels or at times even multiple organ failure. Oral medications may be prescribed, but they are associated with many side effects. Condiments, herbs, various spices and other plant products are considered to be safer in the treatment of diabetes. A commonly used spice is cumin, which is used in the present study to modulate the *in vitro* α-glucosidase inhibitory activity of hydroacetone extract of spice and its antidiabetic potential. The spice was also studied for its enzyme inhibitory activity post nanoencapsulation and for herb-drug (acarbose) interaction.

The IC_{50} value of *Cumin. Cyminum* L. extract for α-glucosidase inhibitory activity, was found to be 122.83 µg/ml while that of nanoencapsulated extract was 90.965 µg/ml, indicating that nanoencapsulation enhances enzyme inhibitory activity. Herb-drug interaction of nanoencapsulated *C.cyminum* extract along with acarbose, was also explored. A gradual increase in % α-glucosidase inhibitory activity from 27.36 ± 1.45% at T_0 to 93.67 ± 0.21% at T_{360} was observed indicating a 2.4% increase over a period of 6 h, suggestive of sustained release and prolonged enzyme activity.

The results, thus depict that *Cuminum cyminum* L. can be a potent candidate for managing blood glucose levels in the diabetic patients by delaying the α-glucosidase activity.

1. Introduction

Diabetes occurs due to disregulation of carbohydrate metabolism, thereby leading to an increase in glucose level, affecting cell function. Diabetes leads to one of the highest healthcare costs and high rate of morbidity and mortality across the globe. The comorbidities commonly observed include high risk of cardiovascular and cerebrovascular disorders, dysfunction of vision as well as kidneys, with the former two contributing maximally to fatal conditions (Dal Canto *et al*., 2019).

Pharmacological surveys state that more than 800 plants are used in Ayurveda for their hypoglycemic effects (Draan *et al*., 2015). Many spices possess medicinal properties and are used across globe as non-conventional therapy (Mehrotra, 2021). Among all the spices and plants that are used for their antidiabetic effect, one such spice is Cumin (Modak *et al.,* 2007). Cumin is used in many home remedies and also in certain ayurvedic preparations. Cumin is widely used in ayurvedic medicine as a stimulant, carminative, and astringent and for the treatment of dyspepsia, diarrhea and jaundice.

In the ayurvedic system of medicines, cumin seeds have immense medicinal value, particularly for digestive disorders (Fatima *et al*., 2018). Cumin is rich in iron and other minerals, which strengthen immunity and protects against infections. It is also known to relieve symptoms of the common cold and flu (Parekh and Sumitra, 2011). It has multiple health benefits as a digestive, for treatment of piles, asthma, bronchitis, jaundice dyspepsia and diarrhea. Due to its medicinal properties, it is used as an antimicrobial, antispasmodic, carminative, diuretic, emmanogogic, fungicide, and a stomachic (Sneha *et al*., 2021). The most predominant phytoconstituent in cumin seeds is cuminaldehyde, providing antioxidant qualities, and α-glucosidase inhibitory activities, and thus an effective hypoglycemic agent (Padayachee *et al*., 2012).

Preety *et al.* (2020) showed that cumin oil encapsulated in silver was evaluated for its antidiabetic activity using α-amylase inhibitory assay in a dose dependent manner for control of post prandial hyperglycemia. It lowers blood sugar and cholesterol and has a good effect on the advanced glycation end products that cause damage, especially in diabetics.Thus, inhibition of this enzyme can be a potent strategy to maintain the blood sugar levels. Doha *et al.* (2018) studied the antidiabetic potential of ethanolic extract of cumin seeds, which indicated that cumin seeds can be used as an

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alternative for the treatment of diabetes. The results also suggested that cumin seed extract improves the plasma lipid profile, a risk factor for CVD and heart failure in diabetic patients.

Nanoencapsulation employs encapsulating pharmacologically active components with different coating materials, leading to particle size in the nanoscale range. It is a highly advantageous technique as it protects the active components from degradation with improved precision of delivery at the target sites. It also has an improved time release mechanism (Kanakdande *et al*., 2007; Krishna *et al*., 2021).

The present study was conducted using 50% hydroacetone extracts of the above mentioned spice, pre and post nanoencapsulation to evaluate *in vitro* α-glucosidase inhibitory activities. It has also been observed that the alternative therapy involving use of herbs and spices, for their antidiabetic potential, is generally not monitored by physicians and further, the regular drug regime of the individual is not compromised. The objectives of the present study were to estimate per cent inhibitory activity of α-glucosidase enzyme from *C. cyminum* in 50% hydroacetone at different concentrations of extract, *viz*., 10, 20, 40, 80 and 160 µg/ml. Further, this hydroacetone extract was nanoencapsulated and the α-glucosidase inhibitory activity released over a time period was evaluated. Additionally, the interaction with the standard drug, acarbose, was also conducted to gain insight into spice-drug interaction, if any.

2. Materials and Methods

2.1 Preparation of plant extract

The cumin seeds were locally purchased, and authentication was conducted by Department of Botany, Mithibai College (Autonomous). The seeds were oven dried at 40°C to remove moisture and ground to fine powder, which was sieved and stored in an air-tight container at 4°C for further use. The spice extract was prepared in of acetone: water (1:1 v/v) and its percentage yield calculated as per Patel *et al.*, (2019). The extract was dried and reconstituted in DMSO to achieve 160, 80, 40, 20 and 10 µg/ml concentrations.

2.2 Phytochemical analysis

The phytochemicals in medicinal herbs attribute to its medicinal properties and qualitative analysis of the same was conducted as per method suggested by Mehrotra *et al.* (2019).

2.3 α-glucosidase inhibitory activity

The α-glucosidase inhibitory activity of 50% hydroacetone extract was estimated (Mehrotra *et al*., 2019) at 160, 80, 40, 20 and 10 µg/ml concentration. Standard drug acarbose activity was studied at 2500, 1250, 625, 312.5 and 156.25 µg/ml and the highest concentration was used for studying spice-drug interaction.

2.4 Nanoencapsulation of extract

Nanoencapsulation was performed as per modification of Raj and Jayalakshmi (2015). To 50 ml of 0.01M Zinc acetate dihydrate was added 5 ml of cumin extract with continuous stirring for 2 h over a magnetic stirrer, and the pH was adjusted to 12. The contents were then centrifuged at 3000 rpm for 30 min. The precipitate was washed with distilled water and dried overnight at 50°C.

2.5 Characterization of nanocapsules

2.5.1 Total oil, surface oil and total encapsulated oil estimation

Characterization of nanoencapsulated cumin extract was conducted by method suggested by Varghese and Mehrotra, (2020). The size was observed under motic live screening microscope.

2.6 Release efficiency of encapsulated extract

Release of spice extract from nanocapsules was estimated (Varghese and Mehrotra, 2020). 0.5 g of encapsulated powder was taken in conical flask and 10 ml phosphate buffer added.Starting from time zero to 360 min, at intervals of every 30 min, 0.05 ml of sample was drawn, diluted to 2 ml using phosphate buffer and the concentration of phytochemicals calculated using spectrophotometric readings at λ = 260 nm.

2.7 Release and α-glucosidase inhibitory activity of encapsulated extract

The α-glucosidase inhibitory activity of the extract released from the nanocapsules was estimated (Varghese and Mehrotra, 2020). Encapsulated powder was added to the phosphate buffer in a conical flask and kept on a rotary shaker. 0.5 ml of samples were withdrawn every 30 min upto 360 min and was analyzed for the α-glucosidase inhibitory activity.

2.8 Spice-drug interaction

The spice-drug interaction was estimated by method suggested by Varghese and Mehrotra (2020). 0.5 ml sample was withdrawn at 30 min intervals up to 5 h and 100 µl of acarbose solution (2500 µg/ml concentration) was added and α-glucosidase inhibitory activity calculated.

2.9 Statistical analysis

The results are represented as mean ± standard error of the mean (SEM). The student's t-test was conducted for statistical analysis and $p<0.05$ was considered statistically significant. The IC_{50} values for α-glucosidase inhibitory activity was calculated using ED_{50} plus software.

3. Results

3.1 Phytochemical analysis

The dried hydroacetone extract of *C.cyminum* was reconstituted with DMSO and diluted with distilled water to test for phytoconstituents. The phytochemical screening of *C. cyminum* extract showed the presence of carbohydrates, free reducing sugar, monosaccharides, soluble starch, tannins, terpenoids, flavonoids and alkaloids (Table 1).

Table 1: Phytochemicals in hydroacetone extract of *C.cyminum*

Phytochemicals present	Phytochemicals absent
Carbohydrates, free reducing sugar, monosaccharides, soluble starch, tannins, terpenoids, flavonoids, alkaloids	Combined reducing sugar, proteins, sterols, phenol, cholesterol, saponins

3.2 α-glucosidase inhibitory activity of the spice extract

C.cyminum hydroacetone extract exhibited strong inhibition of yeast α-glucosidase enzyme. Enzyme α-glucosidase breaks complex carbohydrates into monomers in small intestines and its inhibition can diminish the postprandial blood glucose excursion observed in diabetic subjects.

In the present study, per cent α-glucosidase inhibitory activity was studied at 10, 20, 40, 80 and 160 µg/ml, and was observed to be 16.75%, 28.65%, 37.65%, 45.88% and 54.45%, respectively. This suggests a 2.25 times increase of activity on increasing the concentration 16 times. The IC_{50} value was 122.83 µg/ml (Table 2 and Figure 1).

Table 2: Percent α-glucosidase inhibitory activity of *C. cyminum*

Concentration (µg/ml)	% α-glucosidase inhibitory activity
10	16.75 ± 0.49
20	28.65 ± 0.81
40	37.65 ± 0.65
80	45.88 ± 0.90
160	54.45 ± 0.83

Values are Mean ± SEM, where n = 5.

3.3 Antidiabetic potential of drug acarbose

Acarbose exhibits strong inhibition on yeast α-glucosidase enzyme, the percentage inhibition of α-glucosidase activity of the drug was observed to be 18.22%, 24.25%, 36.45%, 48.63% and 59.21%, at 156.25, 312.5, 625, 1250 and 2500 µg/ml, respectively. The IC_{50} value for acarbose is 1720.9 µg/ml (Table 3).

Table 3: Percent α-glucosidase inhibitory activity of acarbose

Concentration (µg/ml)	% α-glucosidase inhibitory activity
156.25	18.22 ± 0.42
312.5	24.25 ± 0.59
625	36.45 ± 0.90
1250	48.63 ± 0.93
2500	59.21 ± 0.64

Values are Mean ± SEM, where n = 5.

3.4 Interaction of spice with drug acarbose

The spice and drug together were allowed to act on the yeast α-glucosidase enzyme using maltose as a substrate in order to check the combined inhibitory effect of the two. The concentration range of the spice extract studied was 10-160 µg/ml, while that of the drug was constant at 2500 µg/ml. It was observed that the increase with every doubling of the concentration was 0.33, 0.5. 0.33, 0.22 times starting from 10 to 160 µg/ml, respectively (Table 4 and Figure 1). The IC_{50} value was found to be 24.41 g/ml.

Table 4: Percent α-glucosidase inhibitory activity of *C.cyminum* in presence of acarbose

Concentration (µg/ml)	% α-glucosidase inhibitory activity
10	24.41 ± 0.52
20	37.82 ± 0.97
40	51.00 ± 0.81
80	64.91 ± 1.36
160	75.63 ± 0.51

Values are Mean ± SEM, where n = 5

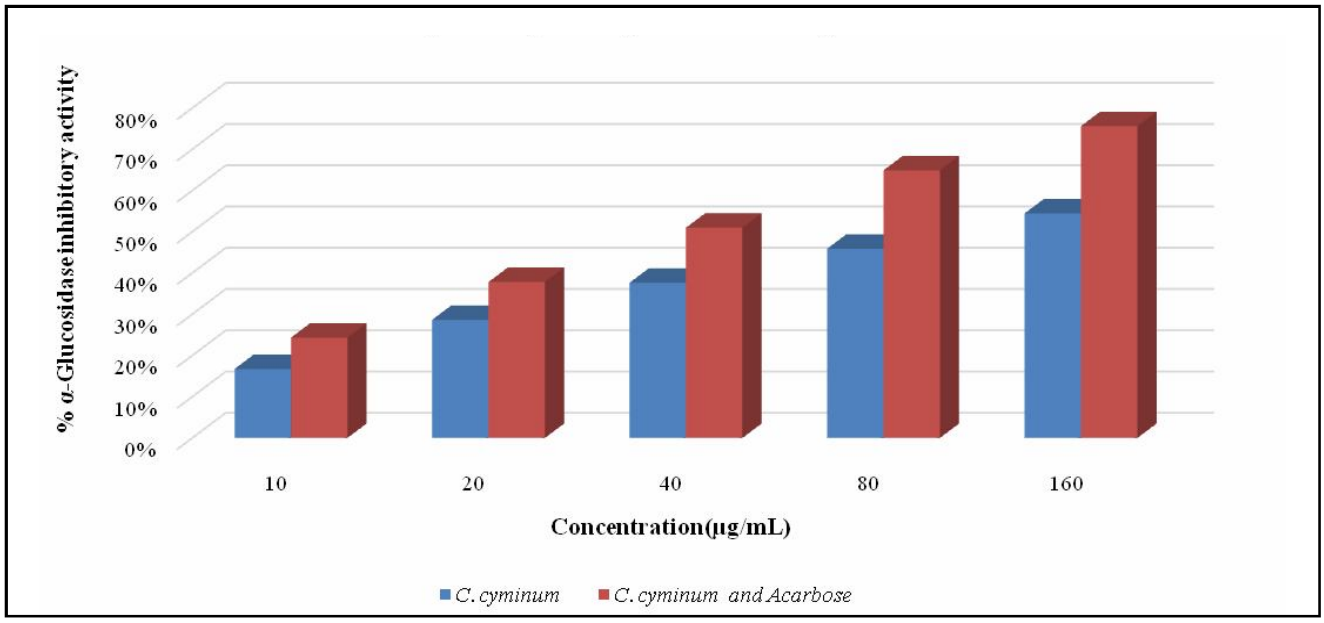

Figure1: % α-glucosidase inhibitory activity of *C. cyminum* and in presence of acarbose.

3.5 Nanoencapsulation

The hydroacetone *C.cyminum* extract was nanoencapsulated in zinc oxide. The characteristics of the nanoencapsules are depicted in Table 5. The particle size of nanoencapsulated powder was found in the range of 0.43 µm to 0.97 µm. The least count of the instrument used was 0.1µm. The shape of particles ranged from oval to spherical.

Table 5: Physical characteristics of the encapsulated powder

Characteristics	Values
Yield	4.036 g
Percentage recovery	43.39%
Total oil	248 mg/g
Surface oil	20 mg/g
Nanoencapsulated oil	228 mg/g
Color	Cream
Texture	Crystalline
Odor	Aromatic odor of cumin

3.6 % α-glucosidase inhibitory activity of nanoencapsulated spice extract and it's release

The % α- glucosidase inhibitory activity as well as the concentration of the extract, released from the nanoencapsulated powder with respect to time was estimated.

At 300 min, the released extract had 74.44% inhibitory activity. This suggests that inhibitory activity of the enzyme continues over a long time, which could be beneficial as it will delay the carbohydrate digestion preventing hyperglycemia. Beyond 300 min the release of extract attained a plateau, with a 4.83 times increase from time zero to 6 h. The IC_{50} value for nanoencapsulated spice extract is 90.9651 µg/ml (Table 6).

The extract of cumin had a λ_{max} at 260 nm, and the concentration of released extract was measured at the same wavelength, using a standard graph, wherein concentration was plotted against the extinction values (Figure 2).

Table 6: Release of % α-Glucosidase inhibitory activity from nano encapsulated *C. cyminum*

Time (min)	Concentration (µg/ml)	% α-glucosidase inhibitory activity
0	26.00 ± 0.11	12.76 ± 0.21
30	61.00 ± 0.09	20.30 ± 0.13
60	74.33 ± 0.30	31.93 ± 0.56
90	82.00 ± 0.65	36.10 ± 1.13
120	94.33 ± 0.54	42.42 ± 1.04
150	96.66 ± 0.18	45.63 ± 0.81
180	100.00 ± 0.23	55.23 ± 0.78
210	103.33 ± 0.14	63.66 ± 0.95
240	106.33 ± 0.35	68.00 ± 0.93
270	108.66 ± 0.29	74.44 ± 0.46
300	116.00 ± 0.38	74.44 ± 0.46
330	121.33 ± 0.44	74.44 ± 0.46
360	124.00 ± 0.56	74.44 ± 0.46

Values represented as Mean ± standard error, where n = 3

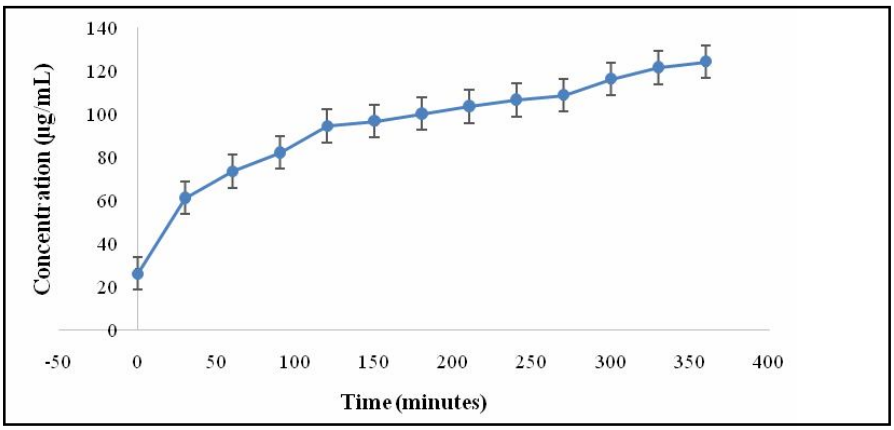

Figure 2: Concentration of released active constituents from nanoencapsulated cumin.

3.7 % α-glucosidase inhibitory activity of nanoencapsulated spice extractand spice-acarbose interaction

The release of nanoencapsulated extract in presence of acarbose was also studied to check the combined inhibitory effect of the same. At time zero, 27% inhibitory activity was observed due to presenceof surface oil on nanospheres. The inhibition of α-glucosidase was exponential at start and plateaued with passing time, with an increase of 2.42 times (Table 7 and Figure 3).

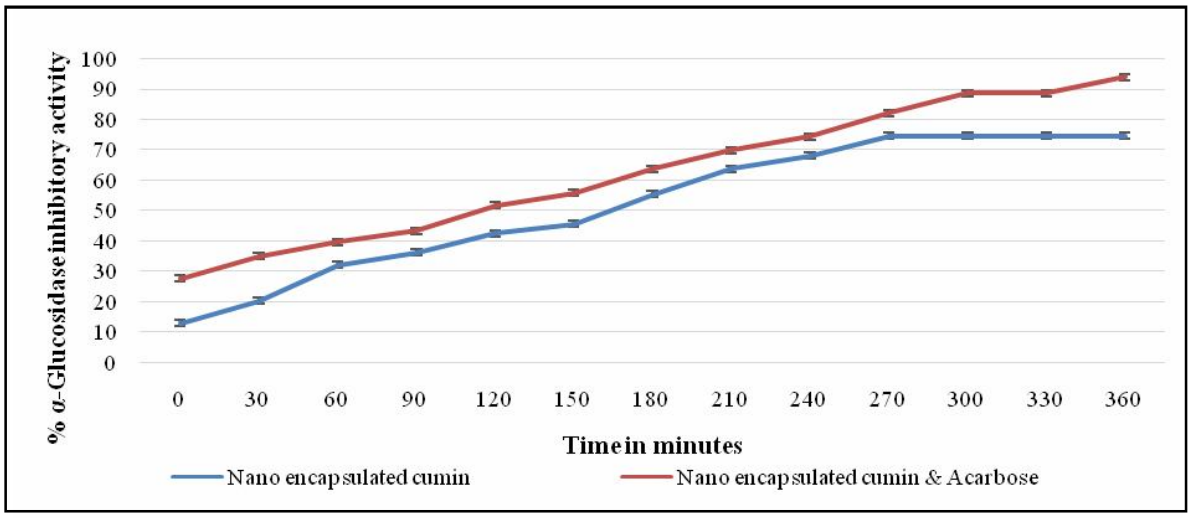

Figure 3: % α-glucosidase inhibitory activity of nanoencapsulated spice extract and spice-acarbose interaction.

Table 7: α-alucosidase inhibitory activity of microencapsulated extract and effect of acarbose

Time (min)	% α-glucosidase inhibitory activityof nanoencapsulated cumin	% α-glucosidase inhibitory activity nanoencapsulated cumin and acarbose
0	12.76 ± 0.21	27.41 ± 1.45*
30	20.30 ± 0.13	34.92 ± 0.65*
60	31.93 ± 0.56	39.41 ± 0.61
90	36.10 ± 1.13	43.10 ± 0.50
120	42.42 ± 1.04	51.51 ± 0.72
150	45.63 ± 0.81	55.63 ± 1.08
180	55.23 ± 0.78	63.62 ± 0.55
210	63.66 ± 0.95	69.63 ± 0.44
240	68.00 ± 0.93	74.25 ± 1.09
270	74.44 ± 0.46	81.81 ± 0.27*
300	74.44 ± 0.46	88.52 ± 0.48*
330	74.44 ± 0.46	88.52 ± 0.48*
360	74.44 ± 0.46	93.71 ± 0.21*

Values represented with Mean ± SEM, where n = 5.
Mean values superscripted by * are statistically significant at $p<0.05$.

4. Discussion

Diabetes mellitus is associated with dysfunction of carbohydrate metabolism, due to defects in insulin secretion, its action or sometimes both. International Diabetes Federations (IDF) suggests that India has more diabetics than any other country. The average estimated diabetics is 62 million with an increase of over 10 million

from 2011. By the year 2030, more than 100 million Indians are likely to suffer from this disorder as per Atre (2019).

Multiple modalities as dietary modifications or/and drug therapy has been suggested to alter the carbohydrate metabolic pathways for diabetes treatment. In recent times, the shift is towards use of medicinal aromatic plants, wherein the adverse reactions are minimized. This study was aimed at comparing *in vitro* α-glucosidase activity of hydroacetone extract of *C. cyminum* and its antidiabetic potential post encapsulation as nanoparticles.

Ani *et al.* (2006), like the present study, used acetone as against the most commonly used solvent- methanol, as the latter has carcinogenic effects. Cumin that is found in every household as a basic spice has been reportedly to possess antiglycative effects, both *in vitro* and *in vivo*. Zhang *et al.* (2015), reported the isolation and structural elucidation of 21 compounds from cumin extract in methanol possessing antiglycative properties against bovine serum albumin assay. Thus, it was suggested that the combined effect of different compounds of cumin would impart multiple enzyme inhibitory properties. Pawar and Borkar (2020) suggested that cumin has alpha glucosidase inhibitory activity.

For the current study, the extract was reconstituted in DMSO which is inert in nature and does not interfere with the extracted phytoconstituents of cumin. The reconstituted extract in DMSO was diluted with distilled water and used (Hayward *et al.*, 2019). Qualitative phytochemical analysis of hydroacetone extract confirmed the presence of various phytochemical like carbohydrates, free reducing sugar, monosaccharides, soluble starch, tannins, terpenoids, flavonoids and alkaloids (Tadera *et al.*, 2006). Reports have suggested that tannins, terpenoids, flavonoids and alkaloids are potent enzyme inhibitors (Jimenez *et al.*, 2021). The extract was then subjected to α-glucosidase inhibitory activity assay, in the range of 10-160 mg/ml. 2.25 times increase was observed between the lowest and the highest concentration studied. IC_{50} values for the α-glucosidase inhibitory activity of *C. cyminum* was found to be 122.83 µg/ml. It has been observed by many researchers that enzyme inhibitory activities depends on extraction procedure, solvent used, and substrate used (Papoutsis *et al.*, 2021; Gallo *et al.*, 2010). In association with acarbose, increase in % α-glucosidase inhibitory activity between the lowest and the highest concentration was 2.1 times. It was observed that the enzyme inhibition at the lowest concentration was 0.46 times higher while at the 160 µg/ml, it was 0.39 times higher, in presence of acarbose. The IC_{50} value was found to be 24.41g/ml, which is 5 times lower than the cumin extract alone.Thus, a synergistic effect is seen in enzyme inhibitory activity, suggestive that study of spice drug interaction is important.

To enhance the antidiabetic property of cumin, the extract was nano encapsulated in zinc. This was confirmed by change in physical properties of encapsulated powder after extraction of total oil, wherein the cream color of encapsulated powder transformed to white, with the odor of cumin disappearing, as well as change in extinction at 260 nm. During the process of encapsulation, amount of surface oil was 8.1% of total yield of encapsulated oil. The particle size analysis of encapsulated powder depicted nanoparticles in range of 0.43 µm to 0.97 µm bearing oval or spherical shape. This variation in shape can be attributed to many phytoconstituents being extracted in hydroacetone and the crude extract being used for nanoencapsulation.

The nanoencapsulated cumin powder was dispersed in phosphate buffer (pH7) and the %inhibition of α-glucosidase activity, with respect to time, was observed. The % inhibitory activity increased linearly till 4 h and tended towards a plateau, thereafter. With time, a 4.9% increase in released cumin phytoconstituents was observed till 4 h post which the inhibitory activity was found to be maintained at a constant of 74.44%. The saturation indicated that an equilibrium of phytochemicals was attained between the nanoparticles and the phosphate buffer, and hence the rate of diffusion of active phytoconstituents reached an equilibrium. This suggests that the encapsulated cumin extract has sustained release with potential to inhibit α-glucosidase activity, thereby delaying release of glucose into blood, and thus can be used in preventing hyperglycemia. Acarbose in combination with nanoencapsulated extract lead to an increase of enzyme inhibitory activity by 2.42%.

Mehrotra *et al.* (2019), have reported an increase in the activity of α-amylase and α-glucosidase inhibitory activities in presence of acarbose and lorsartan and spices as *C. zeylanicum*, *C. cyminum*, *L. nobilis*, *P. nigrum* and *E. cardamomum*. Such interactions like the one observed in the current study, can lead to hypoglycemic conditions which can be fatal. On the other hand, herb-drug interaction between *N. sativa*, and drug acarbose (Mehrotra *et al.*, 2020) showed a reduction in the α-amylase inhibitory activity. Thus, spice-drug interactions do occur and need to be ascertained for best therapeutic effects.

5. Conclusion

Natural products can be used as alternatives to synthetic oral hypoglycemia drugs with less or even no prominent side effects. In the current study, *C.cyminum* possess good potential as a supplement to regulate the blood glucose levels in diabetics. The enzyme has a potent α-glucosidase inhibitory activity, which is mediated by the secondary metabolites of the plant. A detail study on characterizing all phytochemicals in the cumin extract can be considered.

Nanoparticles, due to their enhanced surface area, have proven to significantly contribute to development of sustained release drug delivery systems. The same was observed in the present study as the breakdown of carbohydrates in presence of nanoencapsulated spice extract was delayed significantly.

The possibility of common drugs increasing the enzyme inhibitory activity has been demonstrated through this work and detailed studies in this arena will help in deriving maximum benefit and therapeutic potential of medicinal and aromatic plants.

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Conflict of interest

The authors declare that no conflict of interest exists in the course of conducting this research. Both authors contributed to the manuscript and decided on submitting the findings for publication.

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