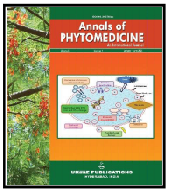
Annals of Phytomedicine 9(1): 107-112, 2020

DOI: http://dx.doi.org/10.21276/ap.2020.9.1.12

Annals of Phytomedicine: An International Journal

http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885



Original article: Open access

α-Amylase inhibitory activity of microencapsulated *Nigella sativa* L. and herb-drug interaction: An *in vitro* analysis

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Article Info

Article history
Received 13 April 2020
Revised 1 June 2020
Accepted 6 June 2020
Published online 30 June 2020

Keywords
Nigella sativa L.
α-amylase inhibitory activity
Herb-drug interaction
Antidiabetic
Microencapsulation
Acarbose

Abstract

Diabetes mellitus poses a threat to the developed and developing countries, especially India. The availability of drugs for diabetes mellitus remains largely inadequate, especially in the rural areas of India. Various antidiabetic medications available in the market result in undue side effects. Spices and herbs have long been used as a traditional medicine for diabetes as they possess several antidiabetic properties. In the present study, microencapsulated Hydroacetone extract of *Nigella sativa* L. seeds was analyzed for its α-amylase inhibitory activity and its herb-drug interaction with antidiabetic drug, Acarbose.

The IC_{50} value of *N. sativa* extract was found to be 314.4 µg/ml while that of the microencapsulated extract was 224.1 µg/ml indicating that microencapsulation enriches the α-amylase inhibitory activity. The extract released from microcapsules, led to higher α-amylase inhibitory activity in comparison to that in presence of the drug Acarbose, over 360 min. This elucidates that microencapsulated *N. sativa* is less likely to cause serious hypoglycemia or diabetic coma, since for its antidiabetic properties, the spice is consumed along with the regular therapeutic drugs.

Further, microencapsulated *N. sativa* extract shows promising potential as an antidiabetic that can be incorporated as a nutraceutical.

1. Introduction

India is one of the epicenters of the global diabetes mellitus pandemic (Ranjit *et al.*, 2016). According to a 2019, International Diabetes Federation report, 77 million Indians are affected by diabetes mellitus which is set to increase to 134 million in the next 25 years. The catastrophic increase in diabetes makes it imperative to address the issue at both the regional and national levels (Kaveeshwar and Cornwall, 2014). The etiology of diabetes mellitus varies across the different subtypes. Diabetic patients are at a high risk of cardiovascular and cerebrovascular disorders, loss of vision, and renal failure (American Diabetes Association-Diabetes care, 2014).

The enzyme α-amylase has been recognized as a therapeutic target for modulation of postprandial hyperglycemia. Inhibition of α-amylase leads to a reduction in starch hydrolysis which shows beneficial effects on glycemic control in diabetic patients. Synthetic inhibitors of α-amylase or other carbohydrate metabolizing enzymes such as Acarbose, Miglitol and Voglibose cause obesity, cardiovascular disorders, and damage to the GI tract. Therefore, it is vital to identify inhibitors from natural sources with minimal adverse effects (Camilla *et al*., 2019, Amutha and Godavari, 2015, Bhat *et al*., 2011). The search for new pharmacologically active agents obtained by screening of culinary spices or their extracts can lead to potent and specific inhibitors for key enzymes linked to diabetes (Xinyan *et al*., 2017; Narkhede, 2012).

N. sativa seeds (NS seeds) have been used as a natural remedy for diabetes and other ailments since ancient times in Asian and Middle east countries (Anwar *et al*., 2020; Sobhi *et al*., 2016). Thymoquinone is the most abundant phytoconstituent in NS seeds and contributes to it's medicinal properties. Srinivasan (2018) and Sandhya *et al*. (2020) studied the α-amylase inhibitory effect of NS seeds, *in vivo* and *in vitro*, respectively, and reported good inhibitory activity. A study by Salmani *et al*. (2014), concluded that thymoquinone, the primary active constituent of *N. sativa* is extremely sensitive to light, leading to its degradation even on short exposure.

Bansode *et al*. (2010) suggested that molecules sensitive to light, moisture or oxygen can be stabilized by microencapsulation. Cyclodextrins are cyclic carbohydrates formed by the enzymatic modification of starch. They are chemically and physically stable molecules with a relatively hydrophobic central cavity and hydrophilic outer surface (Tao and Zheng, 2014). β-cyclodextrin shields the volatile compounds in the oil from photolysis, degradation by heat and oxidation (Petrovic *et al*., 2010).

The global popularity of traditional herbal medicines for therapeutic purposes, is on the rise. Although, many benefits have been derived from the use of traditional herbal medicines, concerns are raised about herb-drug interactions (Gouws, 2018), as these nutraceuticals are supplementary to the therapeutic drugs prescribed. The array of phytochemicals present in herbs may alter the pharmacokinetics

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and pharmacodynamics of a drug, which may at times prove fatal. Singh and Kaicun (2017) and Karthickeyan *et al.* (2018), observed a decrease in blood glucose levels in patients who were administered polyherbal products and oral hyperglycemic drugs. They concluded that polyherbal products possibly interacted with the drugs leading to the drop in the blood sugar levels. The mechanism of interaction between herbs and drugs are complex (Gupta *et al*., 2017) and studies on the same are limited.

In the present study, microencapsulated hydroacetone extract of NS seeds was investigated for its α-amylase inhibitory activity, thus supplementing claim for its antidiabetic potential. Further, the herb-drug interaction was also studied along with antidiabetic drug, Acarbose. The herb-drug analysis will help elucidate modulation of α-amylase inhibitory activity, if any, due to interaction between the spice extract and the drug.

2. Materials and Methods

2.1 Preparation of plant extract

NS seeds were purchased locally and authenticated by Dr. Bindu Gopalkrishnan from the Department of Botany. The seeds were oven dried at 40 degrees C to remove any moisture content and were ground to powder. The powder obtained was sieved and stored at 4 degrees C for further use. Hydroacetone extract of the spice was prepared in acetone: water (1:1 v/v), and the percentage yield calculated as per the method suggested by Patel *et al.* (2019).

2.2 Phytochemical analysis

The medicinal properties of NS seeds can be attributed to its phytochemical composition, and the same was analyzed qualitatively by method suggested by Mehrotra *et al*. (2019).

2.3 α-amylase inhibitory activity

The α-amylase inhibitory activity of 50% hydroacetone extract was estimated by method suggested by Mehrotra *et al*. (2019), at 160, 80, 40, 20 and 10 µg/ml concentrations. Similarly, the α-amylase inhibitory activity of standard drug Acarbose was also studied at 2500, 1250, 625, 312.5 and 156.25 µg/ml. For herb-drug interaction Acarbose was used at 2500 µg/ml.

2.4.1 Microencapsulation of extract

The microencapsulation of the extract was conducted using modification of Petrovic *et al*. (2010) method. 4.5 g of β-cyclodextrin was dissolved in Ethanol:Water mixture (1:2 v/v) at a regulated temperature of 55 degrees C, on a magnetic stirrer. 10% spice extract (in DMSO) was added slowly, to avoid any precipitation. The mixture was again magnetically stirred for 4 h and allowed to cool to room temperature and refrigerated overnight. The precipitate thus obtained was collected by vacuum filtration using a Whatman filter paper, 42. It was dried at 37 degrees C in an incubator for 24 h. The dried powder was weighed and stored in an airtight container at 4 degrees C.

2.4.2 Total oil, surface oil and total encapsulated oil estimation

The total oil was calculated using the modified method of Petrovic *et al*. (2010). In a conical flask, Hexane: distilled water (1:2 v/v) and 0.5 g of encapsulated powder were mixed and stirred over a rotary shaker for 24 h. Thereafter, the organic layer was separated and collected in a pre-weighed crucible. The contents were evaporated and difference in weight accounted for the total oil present.

During microencapsulation, some extract may be adsorbed on the surface and this was calculated as the surface oil. A protocol like the one used for total oil was used, except that the incubation time was restricted to 30 min.

Total encapsulated oil in β-cyclodextrin complex was the difference between the total and surface oil.

2.4.3 Release efficiency of encapsulated extract

The release efficiency of oil encapsulated in β-cyclodextrin was analyzed by method developed by us. 0.5 g of encapsulated powder was taken in a conical flask. 10 ml of phosphate buffer was added. Starting from t=0, every 30 min 100 µl of sample was drawn till t=360 min. The sample was diluted to 2 ml using phosphate buffer and extinction estimated at 289 nm in a UV-Visible spectrophotometer, as the absorption maximum for the extract was observed at the mentioned wavelength.

2.4.4 Release inhibition of encapsulated extract and herb drug interaction

The α-amylase inhibitory activity of the extract released from the microcapsules was estimated by an extension of the above protocol. In a conical flask, encapsulated powder was added to phosphate buffer and kept on a rotary shaker. 0.5 ml samples were withdrawn every 30 min up to 360 min and analyzed for the α-amylase inhibitory activity.

Further, to estimate the herb drug interaction, another 0.5 ml sample was withdrawn at above mentioned times and 100 µl of Acarbose solution (2500 µg/ml concentration) was added and α-amylase inhibitory activity calculated.

2.5 Statistical analysis

The data is represented as mean ± standard error of the mean (SEM). Further, statistical analysis was performed using the student's t-test and $p<0.05$ was statistically significant. The IC_{50} values for α-amylase inhibitory activity was calculated using software, ED_{50} plus.

3. Results

Phytoconstituents play a vital role in the pharmaceutical properties of the plant. In the current study, hydroacetone extract of NS seed was screened for the phytoconstituents and the results are depicted in Table 1.

Table 1: Phytochemical analysis of *N. sativa* seed extract

Phytochemicals & biomolecules present	Phytochemicals & biomolecules absent
Carbohydrates	Monosaccharides
Free reducing sugars	Combined reducing sugars
Tannins	Starch
Sterols	Proteins
Terpenoids	Phenols
Quinones	Saponins
Alkaloids	
Flavonoids	

Thus, the hydroacetone extract of NS seeds revealed the presence of carbohydrates, tannins, sterols, terpenoids, quinones, flavonoids and alkaloids.

The percentage yield of the extract was found to be 4.89 ± 0.05%.

3.2 α-amylase inhibitory assay

Since ancient times, spices have been used not only to enhance the flavor of food but also as traditional medicine for various ailments. There are several documented evidences for the use of spices as potential antidiabetic. The present study aims to evaluate the α-amylase inhibitory activity of *N. sativa*. The α-amylase inhibitory activity (%) of *N. sativa* extract, increased with an increase in the concentration. (Table 2, Figure 1) and values were found to be 16.69, 19.57, 27.53, 31.67 and 32.31% at concentrations 10, 20, 40, 80 and 160 µg/ml, respectively. The effect of drug Acarbose on the α-amylase inhibitory activity (%) was also studied, and it was observed that between 10-40 µg/ml the inhibitory activity increased significantly and thereafter, a decrease in activity was observed. Acarbose by itself depicted α-amylase inhibitory activity of 25% at 2500 µg/ml. The IC_{50} is the concentration possessing half maximal inhibitory activity and was calculated as 314.4 µg/ml for the NS seed extract.

Table 2: α-amylase inhibitory activity (%) of *N. sativa* and in presence of Acarbose

Concentrations (µg/ml)	α-amylase inhibitory activity (%)	α-amylase inhibitory activity (%) in presence of Acarbose
10	16.69 ± 2.42	31.10 ± 1.89*
20	19.57 ± 3.35	55.50 ± 2.45*
40	27.53 ± 3.73	53.85 ± 3.11*
80	31.67 ± 3.90	28.03 ± 2.89
160	32.31 ± 6.20	27.71 ± 3.33

The values depicted are Mean ± SEM where n=5.
Mean values superscripted by * are statistically significant at $p<0.05$.

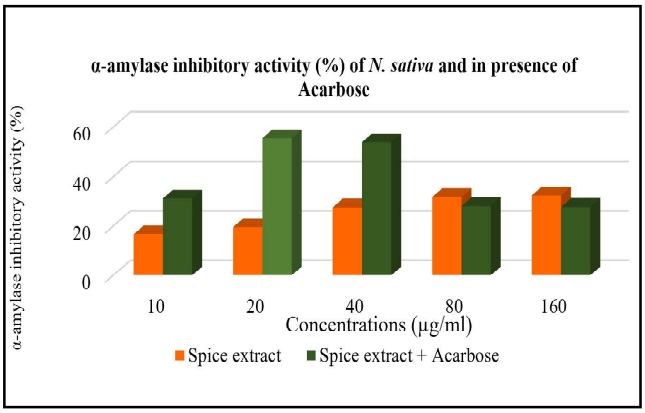

Figure 1: α-amylase inhibitory activity (%) of *N. sativa* and in presence of Acarbose.

The values depicted are Mean ± SEM where n=5.

3.3 Microencapsulation of *N. sativa*

The spice extracts were microencapsulated and analyzed for its physical characteristics like particle size, total encapsulated oil, surface oil and total oil content (Table 3, Figure 2). The size of microcapsules was estimated by photographic microscope using Motic Live Imaging System. The smallest particle was found to be of size 5.58 µm while the largest particle had a size of 13.02 µm.

Table 3: Physical characteristics of microencapsulated spice

Yield	60.36 %
Total oil	74 mg/g
Surface oil	8 mg/g
Microencapsulated oil	66 mg/g
Percent microencapsulated oil	89.18 %

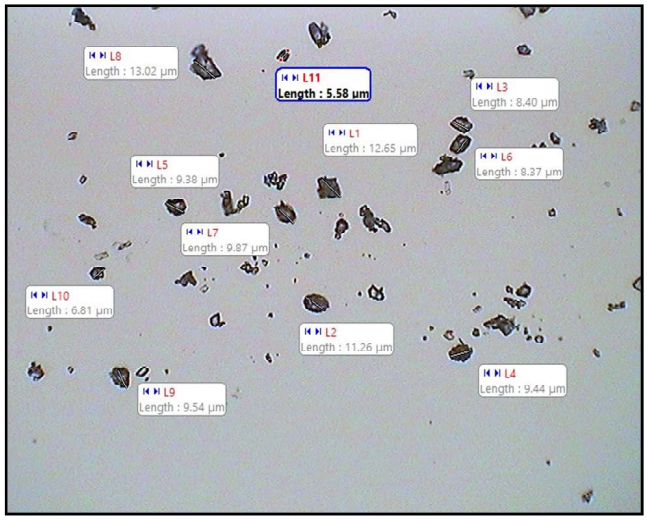

Figure 2: Size of microencapsulated spice.

3.4 Standardization for *N. sativa* extract

The extinction of the extract is directly proportional to the concentration of extract at 289 nm and the same was plotted to get the standard curve for the extract to help elucidate the concentration during release studies.

3.5 Release efficiency of encapsulated extract

The release of extract from microencapsulated powder with respect to time (0-360 min) was evaluated at 289 nm and results are depicted (Table 4, Figure 3). Some amount of release was seen at T_0 which could be contributed to surface oil, thereafter, the release increased exponentially and slowed down, thereafter.

Table 4: Release of extract from microencapsulated extract

Time (min)	Concentration of released extract (µg/ml)
0	6 ± 0.01
30	19 ± 0.01
60	24 ± 0.01
90	29 ± 0.03
120	33 ± 0.01
150	35 ± 0.01
180	37 ± 0.03
210	39 ± 0.01
240	41 ± 0.01
270	43 ± 0.01
300	45 ± 0.01
330	48 ± 0.01
360	52 ± 0.01

The values depicted are Mean ± SEM where n=3.

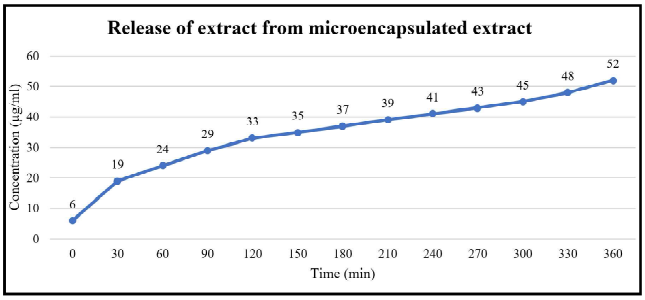

Figure 3: Release of extract from microencapsulated extract.

The values depicted are Mean ± SEM where n=3.

3.6 α-amylase inhibitory activity of microencapsulated extract of *N. sativa*

The α-amylase inhibitory activity of released extract from microencapsulated *N. sativa* was estimated in presence and absence of standard Acarbose to evaluate herb drug interaction and is depicted (Table 5, Figure 4). The IC_{50} values are depicted in Table 6.

4. Discussion

α-amylase is a key enzyme that leads to elevated postprandial hyperglycemia (PPHG) (Sudha *et al*., 2010) and inhibition of the same can effectively decrease PPHG in diabetic patients (Karthic *et al*., 2008). The inhibitors currently in clinical use such as Acarbose and Miglitol lead to multiple adverse reactions. Therefore, the search for safer and effective inhibitors is an important area of investigation with traditional plants offering a great potential for use as antidiabetic (Klein *et al*., 2007). Amongst many spices, *N. sativa* is an annual herb, cited to possess antidiabetic potential (Aftab *et al.,* 2013).

The present study was conducted using NS seeds extract in 50% hydroacetone. The phytochemicals extracted were tannins, sterols, terpenoids, quinones, flavonoids and alkaloids. In a similar study by Amutha *et al*. (2015) using n-butanol and ethyl acetate, they could also extract saponins. In current study, the α-amylase inhibitory activity increased by 93.7% between the lowest (10 µg/ml) and the highest concentration (160 µg/ml) studied. In the study by Amutha *et al*. (2015), the maximum α-amylase inhibitory activity was observed at 5mg/ml to be 29.2%. Better inhibition was obtained in the current study with the hydroacetone extract and at a concentration 31.25 times lower. A recent study by Sandhya *et al*. (2020) has reported good inhibitory activity of amylase using an ethanol extract and they obtained 50% inhibitory activity at 100µg/ml, suggestive of better extraction of phytochemicals in ethanol. It was interesting to note that the standard error of mean increased with increasing concentration of the extract and could be attributed to the active constituent thymoquinone, being extremely light sensitive (Salmani *et al*., 2014) and even a short exposure to light leading to degradation of thymoquinone, thus altering the inhibitory activity.

Microencapsulation is a novel drug delivery system for sustained release. *N. sativa* extract was encapsulated in β-cyclodextrin with 89.2% encapsulation of extract and 60.4% recovery. The particle size ranged between of 5.58µm to 13.02µm.

The microencapsulated extract was checked for release of extract using a UV visible spectrophotometer, over 360min. Some amount of extract was present on the surface of microcapsules to the tune of 6µg/ml, which appeared at time zero. Over 360min, the amount of extract released increased by 2.5 times.

Table 5: α-amylase inhibitory activity of microencapsulated extract and effect of Acarbose

Time (min)	Concentration (µg/ml)	α-amylase inhibitory activity by released extract	α-amylase inhibitory activity of released extract + Acarbose
0	6	25.84 ± 1.80	28.17 ± 0.85
30	19	32.65 ± 1.17	33.53 ± 0.87
60	24	38.09 ± 0.99	34.21 ± 0.79
90	29	39.45 ± 1.02	34.89 ± 0.19
120	33	41.49 ± 1.79	36.9 ± 1.19
150	35	46.25 ± 1.79	40.25 ± 0.74
180	37	48.97 ± 2.04	40.13 ± 2.45*
210	39	48.97 ± 2.04	32.65 ± 2.04*
240	41	50.33 ± 1.80	31.97 ± 1.79*
270	43	52.37 ± 2.72	31.29 ± 1.35*
300	45	54.42 ± 1.79	28.17 ± 0.85*
330	48	57.82 ± 1.35	26.80 ± 1.42*
360	52	63.26 ± 1.38	26.80 ± 1.42*

The values depicted are Mean ± SEM where n=3.
Mean values superscripted by * are statistically significant at $p<0.05$.

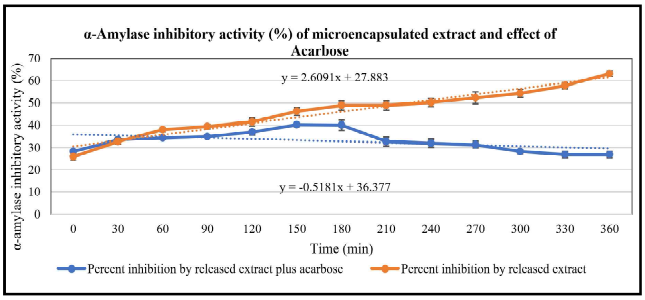

Figure 4: α-amylase inhibitory activity (%) of microencapsulated extract and effect of Acarbose.

The values depicted are Mean ± SEM where n=3.

Table 6: IC_{50} for α-amylase by various constituents

Constituent	IC_{50} Values
Nigella sativa seed extract	314.44 µg/ml
Acarbose	6465.24 µg/ml
Microencapsulated extract	224.09 µg/ml
Microencapsulated extract + Acarbose	-818.84 µg/ml

The release of extract was also studied for α-amylase inhibitory activity. With increasing time (upto 360 min) the release of extract lead to 4.3 times increment in the α-amylase inhibitory activity. It was intresting to note that the standard error reduced from 6.20 to 1.28 which was in agreement with Bansode *et al*. (2010) wherein microencapsulation significantly decreased the light degradration of thymoquinone, the active phyochemical of *N. sativa*. Further, a comparision of IC_{50} values shows better inhibitory activity of microencapsulated extract, being 224.1 µg/ml as compared to the spice extract with IC_{50} as 314.4 µg/ml, a reduction by 28.7%.

The use of traditional spices and herbs as a remedy has been debated over years. Most of the times these spices/herbs are administered along with prescribed therapeutic drugs. This enhances the risk of herb-drug interactions often transforming into serious clinical consequences (Zeping *et al*., 2012). Thus, this study was conceptualized to study the spice-drug interaction on α-amylase inhibitory activity of *N. sativa*. Acarbose, the standard drug for studying α-amylase inhibitory activity was used. It was observed that in presence of Acarbose, at 10, 20 and 40 µg/ml of spice extract, the enzyme inhibitory activity was significantly increased by 0.86, 1.84 and 0.96 times, respectively at similar concentration of the spice alone, while thereafter, at 80 and 160µg/ml, a decrease was observed by 0.12 and 0.14 times. This suggests that at lower concentration the interaction of spice and drug significantly enhances the enzyme inhibitory activity while at higher concentrations the effect reduces.

Similarly, the spice-drug interaction was also calculated post-microencapsulation of extract and the observations were very interesting. The α-amylase inhibitory activity was lower in presence of Acarbose, suggestive of an interaction between the phytochemicals in spices and the drug. The slope of the curves was 2.62 and -0.52, respectively in absence and presence of the drug, depicting a significant change in enzyme inhibitory activity in presence of the drug. An earlier study by Mehrotra *et al*. (2019), on spice-drug interactions had suggested increase in α-amylase inhibitory activity and α-glucosidase inhibitory activities using *C. zeylanicum*, *C. cyminum*, *L. nobilis*, *P. nigrum* and *E. cardamomum*, in presence of Acarbose and Lorsartan. In the current study with N. *sativa*, the drug Acarbose depicted a reduction in the overall inhibitory activity of amylase. It thus suggests that the combination of spice and drug decreases the risk of serious hypoglycemia when this nutraceutical is used in combination with therapeutic drug, as Acarbose.

5. Conclusion

The present study indicates that the α-amylase inhibitory activity of microencapsulated NS seeds extract has great potential to reduce postprandial hyperglycemia and thus can be effectively used as an antidiabetic. The increase in the inhibition attributes to the fact that the active constituent, thymoquinone, is degraded by light and microencapsulation shields thymoquinone from degradation and consequently increases the inhibition of α-amylase. Moreover, herb drug interaction between the microencapsulated extract and Acarbose exhibited a decrease in the inhibition of α-amylase indicating that administration of the extract and Acarbose, may not possibly cause serious undesirable adverse effects as hypoglycemia or diabetic coma.

This study suggests that NS seeds have an immense potential as an antidiabetic. As the medical system faces a great challenge to manage diabetes without major side effects, use of plant-based medicines can prove as a boon. Although a lot remains to be researched and studied on the possible interaction between herbs and modern medicine, the study presents a positive outlook on getting the best out of both worlds.

Acknowledgements

Financial and infrastructural support to the Department of Biochemistry from Shri Vile Parle Kelavani Mandal (SVKM) and Mithibai College (Autonomous) is gratefully acknowledged. We acknowledge the efforts of Dr. Bindu Gopalakrishnan (Department of Botany) for authenticating the plant samples.

Conflict of interest

The authors declare that there are no conflicts of interest in the course of conducting the research. Both the authors had final decision regarding the manuscript and decision to submit the findings for publication.

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Citation: Lijo N Varghese and Nupur Mehrotra (2020). α-Amylase inhibitory activity of microencapsulated *Nigella sativa* L. and herb-drug interaction: An *in vitro* analysis. Ann. Phytomed., 9(1):107-112. http://dx.doi.org/10.21276/ap.2020.9.1.12