Indian Journal of Biochemistry & Biophysics
Vol. 59, February 2022, pp. 183-188

Evaluation of *trans*-cinnamaldehyde as an anti-hyperglycemic compound through inhibition of α- amylase

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Received 01 April 2019; *revised 20 February 2022*

The present study aims to evaluate the effectiveness of Cinnamon (*Cinnamomum verum*) derive bioactive compound *viz.trans*-cinnamaldehyde, cinnamyl alcohol, and cinnamic acid on inhibition of *Bacillus licheniformis* α-amylase (BLA) and pancreatic porcine α-amylase (PPA) activity. The inhibition extent of each of the compounds was determined along with their inhibition kinetics and compared with standard inhibitor-acarbose (Synthetic anti-diabetic agent). The IC_{50} values for *trans*-cinnamaldehyde with respect to BLA and PPAwere observed to 5.38 μg mL^{-1} and 3.76 μg mL^{-1}, respectively. The IC_{50} value of acarbose was estimated to be 6.2 μg mL^{-1} for both the amylases. The maximum percent enzyme inhibition of 75.8 (at 10.75 μg mL^{-1}) and 71.6 (5.38 μg mL^{-1}) were observed in case of BLA and PPA, respectively, using *trans*-cinnamaldehyde. Cinnamyl alcohol and cinnamic acid on the other hand were observed to show no specific inhibitory effect on the both the α-amylases even at high concentrations. Catalytic efficiency (V_{max}/K_m) of both the amylases was observed to decrease significantly in presence of *trans*-cinnamaldehyde compared to acarbose. Overall, *trans*-cinnamaldehyde was observed as a better inhibitor of α-amylase compared to known synthetic inhibitor-acarbose. Thus, *trans*-cinnamaldehyde could effectively be used for controlling hyperglycemia and diabetes mellitus.

Keywords: Amylase inhibitor, Hyperglycemia, Inhibition kinetics, *Trans*-cinnamaldehyde, α-amylase

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia (high blood glucose level) due to defects in both insulin secretion and/or insulin action. In recent years the number of DM cases have been increasing alarmingly and in the coming years the number of DM patients may cross 415 million[1]. The DM is now considered as one of the severe intimidation to worldwide public health[2]. Patients diagnosed with hyperglycemia are also prone to an increase rate of heart & kidney diseases, lipid metabolic disorders, liver impairment, and neuropathy[3,4]. On account of these preceding intricacies, a balanced or lowered blood glucose level is a prerequisite for the treatment of diabetes.

One of the important therapeutic approaches to treat DB is to inhibit or slow down the dietary carbohydrate metabolism by inhibiting the enzymes involved in it. In this regard, inhibiting the action of amylase and glucosidase is one of the effective ways to control the postprandial blood glucose level *via* a reduced rate of glucose uptake[5-7]. Amylase secreted from the saliva and the pancreas in humans catalyzes the breakdown of complex dietary starch into smaller oligosaccharide units[8]. The oligomers are then subsequently broken down into simple monomeric glucose units by the enzyme glucosidase secreted from the small intestine[9,10]. Thus if the action of these two enzymes is blocked/inhibited, the blood glucose level can be easily lowered[8,11].

Available commercial synthetic inhibitors such as acarbose and voglibose possess adverse side effects in the form of flatulence, digestive and liver function disorders[1]. Consequently, there is a requirement of low-cost natural inhibitors compounds having lower toxicity. Therefore, the focus has been shifted to plant-based natural anti-diabetic products, and search forsuch natural compounds is a topic of immense interest[10,12]. Considering this several enzyme inhibitor compounds from different plant sources *viz Psidium guajava* fruit, *Aframomum melegueta* fruit, *Salacia oblonga* stem extracthave been reported by Jiao *et al.*[1], Mohammed *et al.*[12], and Chelladurai & Chinnachamy[13], respectively, for controlling DM. Plants due to the presence of phenolics, tannins, and alkaloids in their tissue are considered as an effective natural antioxidants and herbals[9]. The use of plant extract or bioactive compounds obtained from them in

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stimulating pancreatic insulin secretion and *vis-à-vis* lower uptake of glucose has been reported by several authors[14]. Plant sources have been used to treat other clinical conditions as well. For *e.g.* in a recent study, the root extracts of *Scolymus hispanicus* L. were used to reduce the formation of kidney stones[15]. Another study reported the efficacy of oats beta glucan in modulating diabetes mellitus[16]. The leaves of *Kigelia africana* have been used for the synthesis of Ag nanoparticles which were found quite potent against pathogenic bacteria[17].

Among different plant sources, Cinnamon (*Cinnamomum verum)*, a member of the Lauraceae family is one of the common spices and condiment plant possessing numerous pharmacological activities including antimicrobial, antipyretic, and anti-inflammatory[18,19]. Active ingredients in cinnamon have been reported to decrease plasma glucose levels in diabetic rats by several authors[20-23]. However, the use of pure bioactive compounds or phytochemicals derived from cinnamon in controlling DB through inhibition of amylase and glucosidase is not much explored. To the best of our knowledge, there is the only a report of Okutan *et al.*[4] in which cinnamaldehyde obtained from the cinnamon extract was identified as potent α-amylase inhibitor. In the present study, the effect of cinnamon-derived bioactive compounds *viz. trans*-cinnamaldehyde, cinnamyl alcohol, and cinnamic acid on α-amylase activity were evaluated along with synthetic inhibitor-acarbose. The inhibition kinetics of each of the compounds were determined and compared in order to figure out the most potent inhibitor of α-amylase.

Materials and Methods

Materials

α-amylase from two sources *Bacillus licheniformis* and porcine pancreatic were purchased from Sigma Aldrich (USA). Acarbose (commercially available synthetic inhibitor of amylase and glucosidase) and *trans*-cinnamaldehyde, cinnamyl alcohol & cinnamic acid (Cinnamon- derived bioactive compounds) were procured from SISCO Research Laboratories (Mumbai, India) and Sigma Aldrich (USA), respectively. All other chemicals used were of analytical grade.

Amylase assay

Amylase activity was estimated according to the method of Kumar and Khare[24], using starch as a substrate. One unit of amylase activity was defined as the amount of enzyme releasing 1 µmol of maltose equivalent per minute from soluble starch under assay conditions.

α-amylase inhibitory activity

For estimating the inhibitory effect of various cinnamon derived compounds (*trans*-cinnamaldehyde, cinnamyl alcohol, and cinnamic acid) on α-amylase activity, various concentrations of test compounds were individually added to enzyme solution to make a final reaction volume of 500 µL. The reaction was initiated by adding 500 µL of 1% (*w/v*) starch solution followed by incubation of the reaction mixture at 37°C for 15 min. The reducing sugar formed due to amylotic activity was estimated using DNS reagent as described above. Acarbose-a synthetic standard amylase inhibitor was used as a positive control. Based on the extent of enzyme inhibition, the IC_{50} (half maximal inhibitory concentration) value of each of the active bioactive compounds was recorded.

Kinetics of α-amylase inhibition

K_m and V_{max} values of amylase in the absence and presence of each inhibitor (test compounds) was estimated by measuring enzyme activities under various concentrations (0.2 to 1% *w/v*) of starch as substrate. The kinetic parameters were calculated using Lineweaver-Burk plot. Unless otherwise mentioned, *Bacillus licheniformis* α-amylase was 10^5 times diluted before use, hence its exact activity is 10^5 (denoted as *) multiple of observed activity.

Results and Discussion

α-amylase is one of the important enzymes responsible for the regulation of blood glucose level[6]. Inhibiting the activity of this enzyme is one of the ways to control glucose level and therefore this could be used as one of the strategies in the management of DM. In this context, the search of inhibitors from natural sources will be beneficial as they are known to have no adverse effects. Cinnamon is one of the widely used medicinal plant having insulin- secreting and insulin-sensitizing properties[20]. Cinnamon extract was observed to mimics the effect of insulin and has also been reported to improve the insulin receptor function[25]. It was also observed that intake of cinnamon along with rice pudding reduced postprandial blood glucose and delayed gastric emptying[20,26]. Considering the above notion, in this study anti-diabetic efficacy of compounds derived from cinnamon *viz. trans*-cinnamaldehyde, cinnamyl alcohol, and cinnamic acid were individually evaluated based on their inhibition studies on α-amylase activity.

The work was started with estimating half-maximal inhibitory concentration (IC_{50}) value of each of the cinnamon derive compounds on the activity of

Bacillus licheniformis α- amylases (BLA) and porcine pancreatic α- amylase (PPA). IC_{50} is a measure of the potency of a compound in inhibiting a specific biological or biochemical function and is used to determine the extent of inhibition by the desired compound.

Table 1 shows the effect of varying concentrations of cinnamaldehyde on the activity of α- amylase. The activity of both the enzymes was found to decrease with an increase in concentrations of *trans*-cinnamaldehyde. IC_{50} values for *trans*-cinnamaldehyde with respect to BLA and PPA were observed to 5.38 μg mL^{-1} and 3.76 μg mL^{-1}, respectively. The maximum relative percent enzyme inhibition of 75.8 (at 10.75 μg mL^{-1}) and 71.6 (5.38 μg mL^{-1}) were observed in the case of BLA and PPA, respectively. On the similar note, Shihabudeen *et al.*[20] used cinnamon bark extract to inhibit the yeast α-glucosidase and mammalian α-glucosidase activity and observed an IC_{50} value of 5.83 μg mL^{-1} and 670 μg mL^{-1}, respectively. Adisakwattana *et al.*[21] tested various cinnamon plant samples and obtained an IC_{50} value in the range of 1.23-1.77 mg mL^{-1} against pancreatic α-amylase.

The other two compounds, cinnamyl alcohol and cinnamic acid used in the present study were observed to show no specific inhibitory effect on both the α-amylases even at high concentrations of 0.40 mg mL^{-1}. The enzyme activities remain unaffected in the presence of these two cinnamon derived compounds. Hence they were not selected for further studies.

Since *trans*-cinnamaldehyde was observed to significantly inhibit the activity of both the amylases, hence in order to further evaluate its inhibition efficacy, its inhibition extent was compared with well-known synthetic inhibitor-acarbose. The effect of varying concentrations of acarbose on the activity of both BLA and PPA is presented in (Table 2). The IC_{50} value of acarbose was estimated to be 6.2 μg mL^{-1} for both BLA and PPA. The respective maximum inhibition percent of 65.7 and 82.6 were recorded for BLA and PPA at the highest concentration (1.25 μg mL^{-1}) of acarbose used. In view of the inhibitory nature of both the compounds, Adisakwattana *et al.*[21] used a combination of both cinnamon extract and acarbose to substantiate the inhibitory effect on intestinal α-glucosidase and pancreatic α-amylase.

Cinnamaldehydes are a class of chemicals characterized by the presence of highly reactive unsaturated carbonyl pharmacophore (Michael acceptor) in their structures, hence these are suitable to react with some enzymes and/or receptors as

Table 1 — Determination of IC_{50} value for *trans*-cinnamaldehyde against *Bacillus licheniformis* α-amylase and porcine α-amylase

Bacillus licheniformis α- amylase			Porcine α-amylase		
Enzyme Activity (10^5*U mL^{-1})	Inhibitor Cinnamaldehyde (μg mL^{-1})	Relative inhibition (%)	Enzyme Activity (U mL^{-1})	Inhibitor Cinnamaldehyde (μg mL^{-1})	Relative inhibition (%)
1.49	0	0	9.09	0	0
1.49	2.15	24.8	9.09	1.08	11.7
1.49	4.30	32.8	9.09	2.15	23.4
1.49	5.38	51.0	9.09	2.69	35.6
1.49	6.45	57.7	9.09	3.23	42.2
1.49	7.53	63.7	9.09	3.76	52.1
1.49	8.60	67.7	9.09	4.30	67.6
1.49	10.75	75.8	9.09	5.38	71.6

Table 2 — Determination of IC_{50} value for standard inhibitor acarboseagainst *Bacillus licheniformis* α-amylase and porcine α-amylase

Bacillus licheniformis α-amylase			Porcine α-amylase		
EnzymeActivity (10^5*U mL^{-1})	Inhibitor Acarbose (μg mL^{-1})	Relative inhibition (%)	Enzyme Activity (U mL^{-1})	Inhibitor Acarbose (μg mL^{-1})	Relative inhibition (%)
1.41	0	0	8.48	0	0
1.41	2.5	13.6	8.48	2.5	26.1
1.41	5.0	20.4	8.48	5.0	43.2
1.41	6.2	52.4	8.48	6.2	54.6
1.41	7.5	57.0	8.48	7.5	71.6
1.41	8.7	60.9	8.48	8.7	75.3
1.41	1.0	63.4	8.48	1.0	82.2
1.41	1.25	65.7	8.48	1.25	82.6

Table 3 — Kinetic parameters of α-amylase from *Bacillus licheniformis* and porcine pancreas in presence and absence of acarbose and *trans*-cinnamaldehyde

Kinetic parameter	*Bacillus licheniformis**		Porcine pancreatic	
	Acarbose	*Trans*-cinnamaldehyde	Acarbose	*Trans*-cinnamaldehyde
K_m(mg)	0.20	0.12	0.14	0.06
K_m (mg) for free enzyme	0.13	0.13	0.15	0.15
V_{max}(μmol min^{-1})	$3.33*10^5$	$1.11*10^5$	10.86	6.94
V_{max}(μmol min^{-1})for free enzyme	$3.33*10^5$	$1.11*10^5$	17.85	17.85
V_{max}/K_m (μmol min^{-1} mg^{-1})	$1.66*10^6$	$5.04*10^5$	72.40	113.77
V_{max}/K_m (μmol min^{-1} mg^{-1}) for free enzyme	$2.56*10^6$	$2.56*10^6$	119	119
K_i (mg mL^{-1})	12.50	3.58	17.70	33.20
Type of inhibition	Competitive	Non-competitive	Non-competitive	Uncompetitive

Free enzyme: in absence of acarbose/trans-cinnamaldehyde
**multiple of 10^5*

electrophiles, and as a result, produce several therapeutically pertinent pharmacological functions[27]. Naturally occurring molecules, *trans*-cinnamaldehyde is representatives of this group, and have attracted lots of interest for their bioactivities, especially the anti-cancer and anti-inflammatory properties[28].

Determination of kinetic parameters

The degree of BLA and PPA inhibition was further corroborated by determining the catalytic efficiency of both the enzymes in the presence as well absence of *trans*-cinnamaldehyde and acarbose. Table 3 shows the kinetic parameters of both BLA and PPA in the presence as well as the absence of acarbose and *trans*-cinnamaldehyde. In absence of inhibitors, K_m, V_{max}, and V_{max}/K_m values of BLA was found to be 0.13 mg, 3.33*105 μmol min^{-1}, and 2.56*106 μmol min^{-1}, respectively, (*denotes×10^5). PPA on the other hand, showed 0.15 mg, 17.85 μmol min^{-1}, and 119 μmol min^{-1}, as its respective K_m, V_{max}, and V_{max}/K_m values. In presence of *trans*-cinnamaldehyde, K_m value was observed to be almost the same for BLA, whereas, V_{max} and V_{max}/K_m values were reduced to 1.11*105 μmol min^{-1} and 5.04*105 μmol min^{-1}, respectively. This shows that *trans*-cinnamaldehyde presents the non-competitive type of inhibition on BLA. Shihabudeen *et al.*[20] during their study on inhibition of α-glucosidase using cinnamon bark extract recorded competitive reversible inhibition.

In the case of PPA, *trans*-cinnamaldehyde showed the uncompetitive type of enzyme inhibition. Both K_m (0.06 mg) and V_{max} (6.94 μmol min^{-1}) were reduced in the presence of *trans*-cinnamaldehyde compared to K_m of 0.15 mg and V_{max} of 17.85 μmol min^{-1} in absence of *trans*-cinnamaldehyde.

As far as acarbose is concerned, it inhibited the BLA in competitive mode. K_m value was found to increase by a value of 0.07 in presence of acarbose whereas, no change in V_{max} was observed. The K_i (inhibition constant) was determined to be 12.50 μg mL^{-1}, showing it as a potential inhibitor. Acarbose action on PPA is non-competitive. No prominent change in K_m was detected compared to K_m in absence of it. V_{max}, decreased to 10.86 μmol min^{-1} from17.85 μmol min^{-1}. The K_i (inhibition constant) was calculated out to be 17.70 μg mL^{-1}. Thus, the binding of the inhibitor (Acarbose) to the enzyme reduces its activity but does not affect the binding of substrate

Overall, it could be concluded that *trans*-cinnamaldehyde is a good inhibitor compared to acarbose for the inhibition of the clinically relevant enzyme (α-amylase). Catalytic efficiency (V_{max}/K_m) of the enzyme was found to decrease much more in the case of *trans*-cinnamaldehyde compared to acarbose. A lesser amount of cinnamaldehyde is required to inhibit the α-amylase compared to acarbose, even the IC_{50} value of *trans*-cinnamaldehyde was much lower (3.76 μg mL^{-1}) in comparison to that of acarbose (6.20 μg mL^{-1}). Hence *trans*-cinnamaldehyde was observed as a better inhibitor compared to known synthetic inhibitor-acarbose. Thus, *trans*-cinnamaldehyde could effectively be used for the management of DB.

Conclusion

Trans-cinnamaldehyde was observed to be an excellent inhibitor compared to acarbose for inhibition of α-amylase both in terms of catalytic efficiency and IC_{50} value. The catalytic efficiency of the enzyme was found to decrease drastically in comparison to synthetic α-amylase inhibitors

(acarbose). This shows that *trans*-cinnamaldehyde act as a potential inhibitor of *B. licheniformis* and pancreatic porcine α-amylases. Therefore, *trans*-cinnamaldehyde obtained from the cinnamon plant could effectively be used for controlling the blood sugar level and *vis-a-vis* management of hyperglycemia or diabetes mellitus.

Acknowledgement

The authors gratefully appreciate IIT Delhi and the Department of Chemistry for providing the infrastructure and facilities for carrying out the research.

Conflict of interest

All authors declare no conflict of interest.

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