14.º ENQO 14TH NATIONAL ORGANIC CHEMISTRY MEETING

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7.º ENQT 7TH NATIONAL MEDICINAL CHEMISTRY MEETING

Analysis of the antidiabetic potential of natural xanthones through the inhibition of α-amylase and α-glucosidase activities

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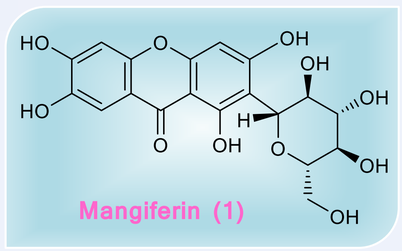
Introduction

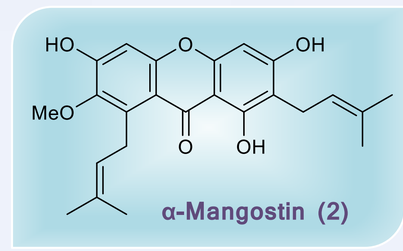
Diabetes *mellitus* (DM) is a complex endocrine disorder associated with a state of hyperglycemia caused by the deficiency in the secretion of insulin and/or in the action of this pancreatic hormone. Thus, the control of postprandial blood glucose level via the inhibition of carbohydrate-hydrolyzing enzymes, such as α-amylase and α-glucosidase, is a consistent strategy for the management of type 2 DM and its related complications.[1,2]

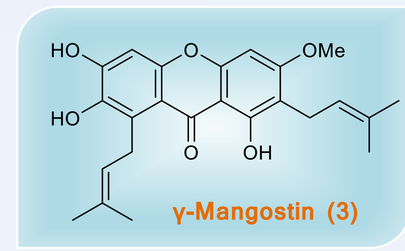
In the past two decades, diversely functionalized xanthones, an important class of oxygen-containing heterocyclic compounds, have been recognized by scientific community for their interesting antidiabetic profile, exemplified by the number of studies developed in this area.[3] Recent advances have been noticed in the inhibition of α-glucosidase activity by natural xanthones. However, the effects of this class of compounds on the activity of α-amylase enzyme is still scarce.[1-3]

Objectives

The main goal of the present study is to evaluate the inhibitory effects and type of inhibition of the natural xanthones mangiferin (**1**), α-mangostin (**2**) and γ-mangostin (**3**) against both α-amylase and α-glucosidase enzymatic activity, using a spectrophotometric screening methodology.[4,5]







α-Amylase Inhibitory Assay

The α-amylase inhibitory assay was carried out in a 96-well plate, by incubating porcine α-amylase, xanthone **1-3** and the substrate 2-chloro-4-nitrophenyl-α-D-maltotrioside (CNPG3) at 37 °C, and monitoring the α-amylase-mediated transformation of the substrate CNPG3 into 2-chloro-4-nitrophenol (CNP), spectrophotometrically at 405 nm for 30 min. The obtained results were expressed as the mean % inhibition ± SEM and, when possible, calculated the respective IC_{50} values (Table 1, Figures 1 and 2).

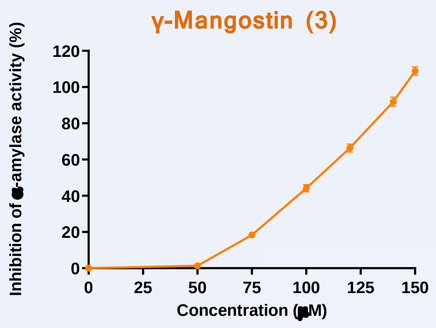


Figure 1. α-Amylase inhibition by γ-mangostin (**3**).

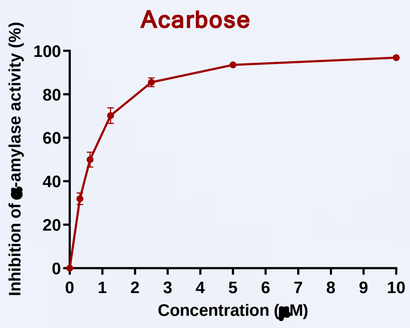
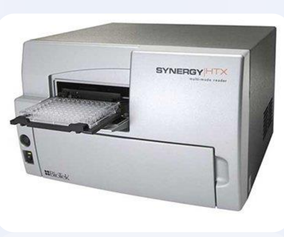


Figure 2. α-Amylase inhibition by acarbose, the positive control.



- Tested compounds dissolved in DMSO.
- Acarbose was used as positive control.
- Each assay corresponds at least to four experiments, conducted in triplicate.

α-Glucosidase Inhibitory Assay

The α-glucosidase inhibitory assay was carried out in a 96-well plate, by incubating the yeast α-glucosidase, xanthone **1-3** and the substrate *p*-nitrophenyl-α-D-glucopyranoside (pNPG) at 37 °C, and monitoring the α-glucosidase-mediated transformation of the substrate pNPG into 4-nitrophenol, spectrophotometrically at 405 nm for 30 min. The obtained results were expressed as the mean % inhibition ± SEM and, when possible, calculated the respective IC_{50} values (Table 1, Figures 3-5).

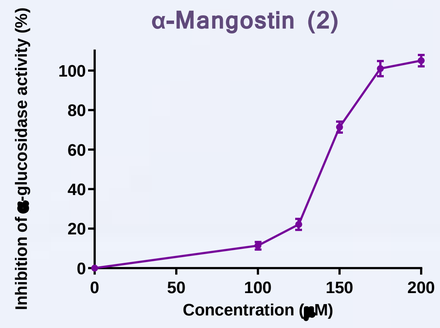


Figure 3. α-Glucosidase inhibition by α-mangostin (**2**).

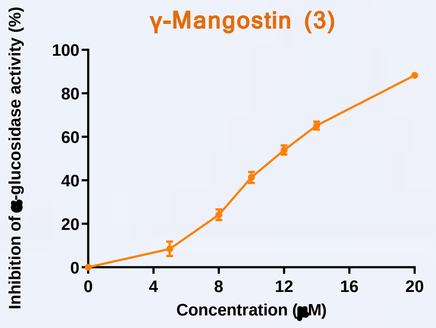


Figure 4. α-Glucosidase inhibition by γ-mangostin (**3**).

α-Amylase Type of Inhibition

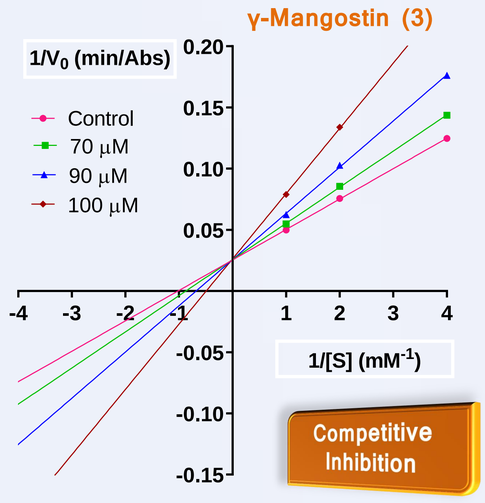


Figure 6. Lineweaver-Burk plot of α-amylase inhibition by γ-mangostin (**3**).

Table 1. Inhibitory effects of xanthones **1-3** on the porcine α-amylase and yeast α-glucosidase activities.

	IC_{50} (μM) or Inhibition (%)	
Compounds	**α-amylase**	**α-glucosidase**
1	< 20%[200 μM*]	< 20%[200 μM*]
2	< 20%[90 μM*]	137 ± 2
3	103 ± 2	11.4 ± 0.3
Positive control		
Acarbose	0.62 ± 0.07	515 ± 19

*The value represents the percentage of inhibition for the highest tested concentration (in superscript).

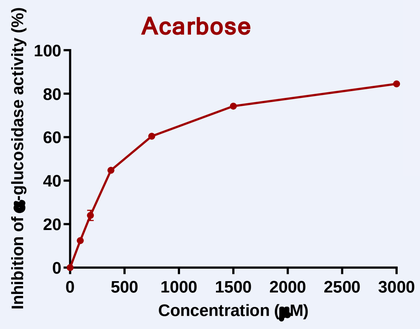


Figure 5. α-Glucosidase inhibition by acarbose, the positive control.

The study of the inhibition type for the two enzymes was carried out through nonlinear regression Michaelis-Menton enzymatic kinetics and the corresponding Lineweaver-Burk plots (Figures 6-8).

α-Glucosidase Type of Inhibition

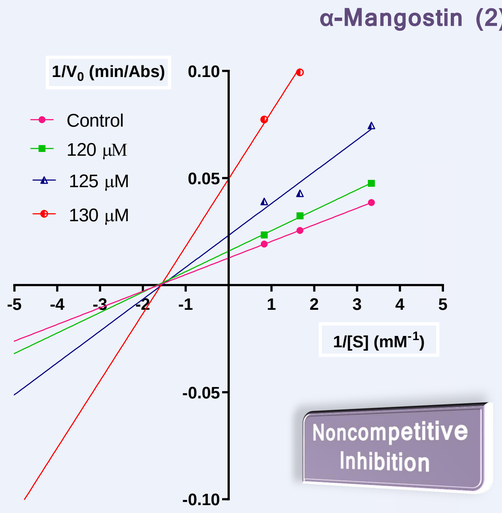


Figure 7. Lineweaver-Burk plot of α-glucosidase inhibition by α-mangostin (**2**).

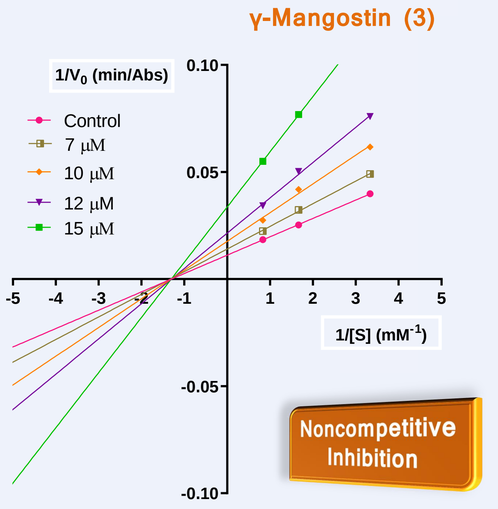


Figure 8. Lineweaver-Burk plot of α-glucosidase inhibition by γ-mangostin (**3**).

Conclusions

- Xanthones **1-3** exhibited a stronger inhibition against α-glucosidase when compared to α-amylase activity.
- Mangiferin (**1**) was not active against both enzymes.
- α-Mangostin (**2**) was only able to inhibit the action of α-glucosidase, while γ-mangostin (**3**) inhibited both enzymes, being more active against α-glucosidase activity.
- For the type of inhibition mechanism, the results indicate a competitive type of inhibition for γ-mangostin (**3**) against α-amylase activity while the action of α-mangostin (**2**) and γ-mangostin (**3**) against α-glucosidase activity is through a noncompetitive inhibition mechanism.
- **The present work can open a promising area of research based on the design of novel xanthone derivatives for targeting key enzymes involved in glucose metabolism and therefore in the management of type 2 DM.**

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Acknowledgements

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