Synthesis of O-Alkylated Garcinol Derivatives as α-amylase and α-glucosidase Inhibitors

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Natural products and their semi-synthetic derivatives have become safer alternatives in treatment of Diabetic Mellitus. Garcinol, a polyisoprenylated benzophenone exhibits remarkable *in-vitro* anti-hyperglycemic activity with potent α-amylase and α-glucosidase enzyme inhibitory potential, which can be further enhanced through functional modifications. However, there aren't any studies on its analogues on antidiabetic properties. Hence, the present study was aimed to synthesize the structural analogs of garcinol via *O*-alkylation and evaluate their *in-vitro* anti-hyperglycemic activity. Dried and ground fruits of *Garcinia quaesita* were extracted into acetone: water (9: 1) using reciprocating shaker (24x3 hours). Garcinol was isolated from the crude extract and structure was confirmed by mass spectroscopy, NMR spectroscopy, FTIR and melting point data. Four novel derivatives of garcinol were synthesized by *O*-alkylation using RX (C_2H_5I (product 1), CCl_3Br (Product 2), $C_6H_5CH_2Br$ (product 3), $C_7H_6BrNO_2$ (product 4)) with a mild base and the products were characterized by mass spectroscopy, NMR spectroscopy and FTIR. The *in-vitro* anti-hyperglycemic activity was assessed by α-amylase and α-glucosidase enzyme inhibition assays. The product 1 (IC_{50} 28.45 ±1.17 mg L^{-1}) and product 2 (IC_{50} 34.90 ± 1.09 mg L^{-1}) showed no significance difference ($p>0.05$) while product 3 (IC_{50} 71.94 ± 6.36 mg L^{-1}) and product 4 (IC_{50} 55.27 ± 10.5 mg L^{-1}) showed significantly lower($p<0.05$) α-amylase enzyme inhibitory potential compared to garcinol (IC_{50} 37.81 ± 1.48 mg L^{-1}). The product 1 (IC_{50} 12.48 ± 0.28 mg L^{-1}) and product 4 (IC_{50} 13.92 ± 1.04 mg L^{-1}) showed no significance difference ($p>0.05$) while product 2 (IC_{50} 7.01 ± 1.61 mg L^{-1}) and product 3 (IC_{50} 47.39 ± 2.77 mg L^{-1}) showed significant difference($p<0.05$) compared to garcinol (IC_{50} 17.18 ± 1.53 mg L^{-1}) in terms of α-glucosidase enzyme inhibitory activity. These data showed that product 2 showed enhanced α-amylase and α-glucosidase enzyme inhibitory potential and it warrants further studies on *in-vivo* anti-hyperglycemic properties.

Keywords: Garcinol, *O*-Alkylation, α-amylase, α-glucosidase

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