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Inhibitory Action Against Alpha Glucosidase by Selected Dihydroxy Flavones

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ABSTRACT

Background: Diabetes is one of the common metabolic disorder that occurs due to poor secretion of insulin. It is more common among aged people in India. The incidence of diabetes is increasing every day and this indicates the increasing need for the treatment for diabetes.

Objective: The objective of the present study is to screen the effects of selected substituted dihydroxyflavone for its *in vitro* antidiabetic effect by finding the potential to inhibit the enzymes α-Glucosidase.

Materials and Methods: The dihydroxy flavones used in the present study includes 2',3'- dihydroxy flavone and 2', 4' dihydroxy flavones. They were synthesized using standard procedures. *In vitro* α-glucosidase inhibitory activity was evaluated by Li et al., 2004. The different concentration of the flavonoid (0.1, 0.3, 1, 3,10, 30, 100, 300, 1000 (µM/ml) were used and the experiment was done for triplicate sample. The standard antidiabetic drug used in the study was Acarbose. The inhibitory activity was calculated and tabulated.

Results: The selected Dihydroxy flavones 2',3'- dihydroxy flavone and 2', 4' dihydroxy flavones showed significant invitro anti diabetic activity when compared with standard drug acarbose. The IC50 value of 2',3'- dihydroxy flavones and 2', 4' dihydroxy flavones was found to be 0.47µM/ml, 46.37 µM/ml respectively.

Key Words: Diabetes, Dihydroxy flavones, *in vitro*, Alpha glucosidase, Metabolic disorder

INTRODUCTION

Diabetes is often called the silent killer because people who have it are often unaware they are affected. It is one of the oldest and most prevalent chronic non-communicable disease. Diabetes Mellitus is characterized by hyperglycemia, impaired metabolism of lipids, carbohydrates and proteins with an increased risk of complication related to vascular diseases. The minimum defining feature to identify diabetes mellitus is the chronic and substantiated rise in circulating glucose concentration. The normal level of blood sugar in a fasting person is between 80-120mg percent. If the fasting level of blood sugar is more than 110mg percent or after meals more than 160mg percent, it is called high blood sugar (Diabetes Mellitus). In diabetic patients, sugar can be detected in the urine also. Patients with diabetes have a higher chance of development of coronary blockages. They also get several other diseases like kidney damages as well as damage to the nerves and eyes[1-3].

According to an estimation of the International Diabetes Federation, approximately 366 million people are suffering from diabetes and this may double by 2030, in India to be 40.9 million, which is expected to grow to 60.9 million by 2025[4].

This can also be characterized by a state of chronic hyperglycemia, glucosuria, polyurea, polydipsia, polyphagia sudden weight loss, ketoacidosis and ketonuria. In type 1 diabetes, the pancreas fails to produce insulin. Because insulin transports sugar into cells, when a body lacks insulin, its cells starve for energy. In type 2 diabetes, there is plenty of insulin in the body, but sugar still cannot get inside the cells. In both types of diabetes, sugar in the blood becomes very high.

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Type 2 is more prevalent than type 1, with more than 90% of the total diabetic patients suffering from it. Postprandial hyperglycemia plays an important role in the development of T2D[5].

Number of environmental factors act on genetically susceptible individuals. They includes Sedentary life style, Diet, Malnutrition, Viral Infections, Chemical agents and Stress.

Diabetes is generally accepted as a major challenging health problem all over the world and especially in the developing countries. India has the dubious distinction of being home to one in five persons with diabetes world. The World Health Organization (WHO) predicts that the number of people with diabetes is to double in the next couple of decades and that the major burnt of this will be borne by the developing countries[6].

The management of Diabetes Mellitus is considered as a global problem whose successful treatment is yet to be discovered. Insulin is widely accepted as an ideal choice for treatment of diabetes mellitus but the difficulty of repeated administration led to the search for the hypoglycemic agents.

Chronic hyperglycemia has been considered as one of the principal causes for several diabetic complications. In patients with Type II diabetes, postprandial blood glucose is elevated due to absorption of glucose from the gastrointestinal tract. The major enzyme involved in carbohydrates digestion is α-glucosidase (Figure-1), it is present in the brush borders of small intestine. It plays a vital role in preventing postprandial rise in blood glucose, this is because Inhibition of these enzyme systems helps to reduce the rate of digestion of carbohydrates and reduces the rate of glucose absorption from the gut and finally lowers the postprandial rise in blood glucose level[7-9]. Therefore, inhibition of α-glucosidase is a key in the management and treatment of Type II diabetes[10,11]. Alpha glucosidase inhibitors are used as oral anti diabetic drugs for treating type 2 diabetes mellitus[12,13].

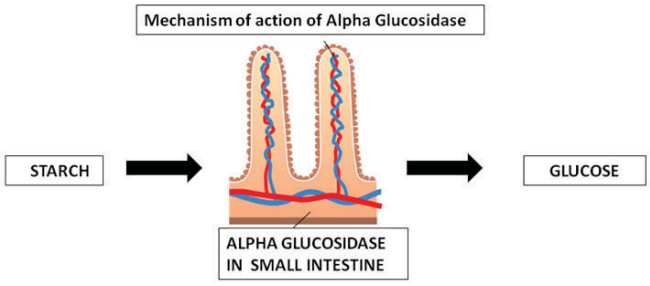

Figure 1: Mechanism of action of Alpha Glucosidase in Carbohydrate metabolism.

Flavonoids are the largest group of naturally occurring poly phenolic compounds present almost in all parts of flowering plants. Flavones have reported to have interesting pharmacological action such as anti-oxidant, anti-inflammatory, antihepatotoxic, anti-microbial, anticarcinogenic The combination of multiple pharmacological properties in a single nucleus is quite interesting.

In a previous study done by the authors, it has been proven that the selected dihydroxyflavones 2',3'- dihydroxy flavone and 2', 4' dihydroxy flavones have potent antinociceptive[14] and anti-inflammatory action [15]. In the present study an attempt was done to screen the effects of selected substituted dihydroxyflavone for its *in vitro* antidiabetic effect by finding the potential to inhibit the enzymes α-Glucosidase.

MATERIAL AND METHODS

α-glucosidase and 3, 5, di-nitro salicylic acid (DNS) were purchased from Sigma-Aldrich, Bangalore. P-nitro-phenyl-α-D-glucopyranoside (p-NPG), sodium carbonate (Na_2CO_3), sodium dihydrogen phosphate, di-sodium hydrogen phosphate were purchased from Hi-Media, Mumbai.

The dihydroxy flavones used in the present study includes 2',3'- dihydroxy flavone and 2', 4' dihydroxy flavones, they were synthesized using standard procedures at Research Organics, Chennai, India. The authenticities of these compounds were done with melting points and UV method.

In vitro α-glucosidase inhibitory activity was evaluated by Li et al., 2004. α-Glucosidase inhibitory assay is based on the breakdown of maltose to glucose. 200 µl of α -glucosidase solution was pre-incubated with the test and control samples for 5 min. The reaction was started by adding 200 µl of sucrose and it was terminated after 30 min incubation at 37^{0}C by heating at 90–100^{0}C. The liberated glucose was determined. The enzyme activity is directly proportional to the liberated glucose and the liberated glucose is measured by GOD-POD method at 546nm using semi auto analyzer. The different concentration of the flavonoid (0.1, 0.3, 1, 3,10, 30, 100, 300, 1000 (µM/ml) were used and the experiment was done for triplicate sample. The standard antidiabetic drug used in the study was Acarbose. The inhibitory activity of the compounds was calculated as follows

% Inhibition= [(control-test)/control)] X 100

STATISTICAL ANALYSIS

All the measurements were done in triplicate and results are expressed in terms of mean ± standard deviation and IC_{50} values were calculated using Graph Pad Prism version 5.01.

RESULTS AND DISCUSSIONS

One of the therapeutic approaches for preventing diabetes mellitus is to decrease the absorption of glucose through inhibition of α-glucosidase, which is a carbohydrates di-

gesting enzymes, located in the brush borders of the small intestine. Determining the *In vitro* α-glucosidase inhibitory activity was found to be one of the important tool used to examine the antidiabetic effect of any compound. The Percentage α-glucosidase inhibition was calculated for 2',3'-dihydroxy flavone and 2', 4' dihydroxy flavone at various concentration 1, 0.3, 1, 3,10, 30, 100, 300, 1000 (µM/ml)and presented in Table 1. Standard drug used here is acarbose. The Inhibitory concentration IC_{50} was calculate using graph pad prism software. The selected Dihydroxy flavones 2',3'- dihydroxy flavone and 2', 4' dihydroxy flavone showed significant *In vitro* α-glucosidase inhibitory activity when compared with standard drug acarbose. The IC50 value of 2',3'- dihydroxy flavones and 2', 4' dihydroxy flavones was found to be 0.47µM/ml, 46.37 µM/ml respectively.

Table 1: *In vitro* α-glucosidase inhibitory activity of 2',3'- dihydroxy flavone, 2', 4' dihydroxy flavone and the standard drug (acarbose)

S. no	Concentration (µM/ml)	%Inhibition of α - glucosidase		
		2',3'- dihydroxy flavone	2',4'- dihydroxy flavone	Acarbose
1	0.1	33.81±0.33	12.74±0.11	11.34 ±0.35
2	0.3	41.51±0.67	16.04±0.22	18.87±0.57
3	1	51.26±0.67	25.47±0.67	35.29±0.61
4	3	56.29±0.22	35.38±0.56	38.86±0.08
5	10	67.61±0.00	44.18±0.56	45.41±0.34
6	30	71.23±1.00	49.06±0.22	48.70±0.79
7	100	79.87±0.22	59.28±0.78	54.87±0.06
8	300	86.48±0.89	67.61±0.22	70.67±0.06
9	1000	89.31±1.11	88.36±0.67	97.29±0.12
	IC_{50}	0.47µM/ml	46.37 µM/ml	23.84µM/ml

All values are expressed as mean ± SD, n=3

The present study showed that 2',3'- dihydroxy flavone and 2', 4' dihydroxy flavones moderately inhibit α-glucosidase activity. Out of the two compounds 2', 3' dihydroxy flavones have excellent *invitro* antidiabetic effect in α-Glucosidase inhibitory model, hence it can be used as oral antidiabetic drug. Further preclinical evaluation studies are needed to confirm its action on postprandial hypoglycemic effect.

CONCLUSION

The study reveal that 2', 3' dihydroxy flavones have excellent *in vitro* antidiabetic effect in α-Glucosidase inhibitory assay model.

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Conflict of interest: Nil

Authors' Contribution: First author involved in the experimentation and analysis of work. The second author contributed in writing part of the study.

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