Effect of *Ananas comosus* L. juice on the efficacy of glimepiride in alloxan induced diabetic rats

Md. Gayasuddin\(^1\)*, S. Kavimani\(^2\), S. Shakil Sait\(^3\), G. Venkataiah\(^1\) and Md. Parvez.\(^1\)

\(^1\)Smt.Sarojini Ramulamma College of Pharmacy, Seshadrinagar, Mahabubnagar
\(^2\)Mother Theresa Institute of Health Sciences, Puducherry
\(^3\)Dr. Reddys laboratories Pvt. Ltd, Bachupally, Kukatpally, Hyderabad

**ABSTRACT**

Food-drug interaction is a challenging concept, since the consumption of food and other herbal drugs is not documented in patient's profile. With this aspect the present study was designed to investigate the possible effect of Pineapple juice on glimepiride (substrate for CYP2C9) an oral hypoglycemic drug in wistar albino rats. Relative to the standard group (glimepiride 1mg/kg alone treated), the reduction of blood glucose level of test group (Pineapple juice 3mL+glimepiride 1mg/kg treated) was more in both acute and sub-acute in alloxan induced diabetic rats when Pineapple juice (3 mL) was injected p.o.1 h before the p.o. administration of the glimepiride (1mg/kg). These results suggest Pineapple juice ingestion increases the efficacy of glimepiride may be by inhibiting intestinal CYP2C9 enzyme in albino wistar rats.

**Keywords:** Pineapple; Bromelain; alloxan induced diabetes.

**INTRODUCTION**

Pharmacodynamic Interactions are those in which the activity of the object drug at its site of action is altered by the precipitant (Food/herb) with or without alteration of pharmacokinetic alteration. Such interactions resulting synergism/potentiation or loss of therapeutic activity of object drugs. An example of potentiation effect of alcohol on the analgesic activity of aspirin and caffeine has additive effects on theophylline [1].

Foods may interact with medications by altering their pharmacologic actions. Diets high in vitamin K may cause antagonism of warfarin and decreased therapeutic efficacy of the anticoagulant. Alcoholic beverages may increase the central nervous system depressant effects of medications such as benzodiazepines, antihistamines, antidepressants, antipsychotic, muscle relaxants, narcotics or any drug with sedative actions [2].

It has been reported that some fruit juices affect the oral bioavailability of drugs as a results alters the pharmacodynamic (efficacy) activity. Cranberry alters the pharmacodynamics of warfarin with the potential to increase its effects significantly [3]. Pomegranate juice increase the efficacy of cytochrome P450 (P450) 3A substrates, and the mechanism of these interactions is mainly thought to be caused by the inhibition of CYP3A in the small intestine [4-7]. Previously studies reported that a component (bromelain) of Pineapple juice inhibited human CYP2C9 activity in vitro [8]. With this aspect the present study was designed to evaluation of pineapple juice of efficacy of glimepiride (CYP2C9 substrate) in wistar albino rats.

---

Scholars Research Library


**ISSN 0975-5071**
**USA CODEN: DPLEB4**

Available online at www.scholarsresearchlibrary.com
Diabetes mellitus is a common metabolic disorder characterized by hyperglycemia, glycosuria, polyurea and polydipsia induced by insulin deficiency [9] and insulin resistance [10]. Recent estimates indicate that there were 171 million people in the world with Diabetes in year 2000 and this may be projected to increase to 366 millions by 2030[10].

Pineapple is a rich source of bromelain proteolytic enzyme and having health benefit pharmacological actions including proteolytic activity [11]. Bromelain is a crude, aqueous extract from the stems and immature fruits of Pineapples (Ananas comosus Merr, mainly var. Cayenne from the family of bromeliaceae), constituting an unusually complex mixture of different thiol-endopeptidases and other not yet completely characterized components such as phosphatases, glucosidases, peroxidases, cellulases, glycoproteins and carbohydrates, among others [12].

Glimepiride is an oral hypoglycemic agent which is metabolized by CYP2C9 [13].

**MATERIALS AND METHODS**

**Drugs and Chemicals:** Glimepiride was obtained from HETERO DRUGS Pvt.Ltd (Baddi, India). Alloxan monohydrate was provided by institution.

**Fruit Samples:** Pineapple fruits were obtained from local commercial sources and authentication was done by botanist Dr. Madhava chetty, Assistant Professor, Department of Botany in S.V. University, Tirupathi, A voucher specimen number (1165). The fruit was stored at 4°C until use. The Pineapple juice was obtained by squeezing the edible portion of the fruit, and the juice was filtered to remove the residues. Then juice was used within 1 h after preparation and filtered.

**Animals:** Wistar albino rats (150–200 g) of male were purchased from Sainath Agencies, 1-6-197/45/D, Bapujinagar, Musheerabad, (REG.No282/99/CPCSEA), Hyderabad, India and Maintained under standard environmental laboratory conditions and fed with laboratory diet and water *ad libitum*. The protocol was approved by the Institutional Animal Ethical committee (IAEC) of Smt.Sarojini Ramulamma College of Pharmacy (R.No: 51/01-CPCSEA/2012/18).

**Hypoglycemic activity**

**Induction of diabetes:** Alloxan monohydrate was first weighed individually for each animal according to its weight and then solubilized with 0.2 mL saline just prior to injection. Diabetes was induced by injecting it at a dose of 100 mg/kg b. wt. intraperitonially [14]. After 1 hr of alloxan administration, the animals were given feed *ad libitum* and 5% dextrose solution was also given in feeding bottle for a day to overcome the early hypoglycemic phase [15-18]. The animals were kept under observation, and after 48 hr, blood glucose was measured. One group served as a control which received vehicle alone. The diabetic rats (glucose level > 200 mg/dl) were separated and divided into four different groups for experimental study.

**Experimental design:**

**Acute treatment and subacute treatment:**

Four groups of animals containing five rats in each group were divided as follows. Group I: diabetic control (saline). Group II: standard (glimepiride alone only 1 mg/kg/day p.o). Group III (Test-1) and IV (Test-2) were treated orally with Pineapple juice (3mL) and Pineapple juice + glimepiride (1mg/kg) respectively. Treatment continued for seven days.

Blood samples were collected by retro-orbital plexus puncture method and blood glucose levels were estimated at 0, 1, 2, 4 and 6 h after the glimepiride administration and then after 1, 3, 5, and 7 days. Blood glucose levels were determined by GOD-POD [19, 20].
Table 1. Effect of Pineapple juice on the efficacy of glimepiride in alloxan-induced diabetic rats after single dose administration

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0 h</th>
<th>1 h</th>
<th>2 h</th>
<th>4 h</th>
<th>6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>265.40±3.89</td>
<td>269.60±3.66</td>
<td>275.30±1.76</td>
<td>280.20±3.63</td>
<td>282.20±1.12</td>
</tr>
<tr>
<td>Standard</td>
<td>271.60±6.10</td>
<td>267.40±6.10</td>
<td>260.60±6.71</td>
<td>239.20±4.98*</td>
<td>219.40±9.40***</td>
</tr>
<tr>
<td>Test - 1</td>
<td>267.00±5.68</td>
<td>272.80±5.85</td>
<td>277.00±5.56</td>
<td>281.20±5.28</td>
<td>286.20±6.50</td>
</tr>
<tr>
<td>Test - 2</td>
<td>274.60±6.45</td>
<td>268.60±6.37</td>
<td>260.00±5.83*</td>
<td>238.00±4.98*</td>
<td>215.80±5.72***</td>
</tr>
</tbody>
</table>

Values are mean±SEM; n=5. *P value < 0.04 vs. diabetic control *p<0.01, ***p<0.001, ***p<0.001

Table 2. Effect of Pineapple juice on the efficacy of glimepiride in alloxan-induced diabetic rats after subacute treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0 day</th>
<th>1 day</th>
<th>3 day</th>
<th>5 day</th>
<th>7 day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>265.40±3.89</td>
<td>276.80±3.42</td>
<td>293.60±3.81</td>
<td>315.40±3.82</td>
<td>342.40±2.08</td>
</tr>
<tr>
<td>Standard</td>
<td>271.60±6.10</td>
<td>246.70±6.61*</td>
<td>224.30±5.82***</td>
<td>194.80±5.97***</td>
<td>171.00±4.17***</td>
</tr>
<tr>
<td>Test - 1</td>
<td>267.40±5.32</td>
<td>279.00±5.76</td>
<td>302.40±5.00</td>
<td>322.60±3.28</td>
<td>350.20±6.11</td>
</tr>
<tr>
<td>Test - 2</td>
<td>274.60±6.45</td>
<td>245.60±5.84**</td>
<td>210.40±5.99***</td>
<td>175.20±5.57***</td>
<td>144.40±5.44***</td>
</tr>
</tbody>
</table>

Values are mean±SEM; n=5. **P value <0.002 vs. diabetic control. *p<0.01, ***p<0.001, ****p<0.001

Statistical analysis:
All the values of the experimental results were expressed as means±SEM and analyzed by one way ANOVA followed by "Dunnett's Test"

RESULTS AND DISCUSSION

The effect of Pineapple juice on the fasting blood glucose levels of both acute and subacute diabetic rats are given in Table 1 and 2. The efficacy of test-2 group (Pineapple juice + glimepiride) increased when compared to standard group (glimepiride alone only) in both acute and subacute treatments. The data reveals that there is a maximum reduction of blood glucose level 41.60% in test-2 (Pineapple+glimepiride treated) group, when compared to standard (glimepiride alone only, 29%). The data shows that the blood lowering activity of test-2 (Pineapple+glimepiride treated) group was started significantly from 4th hour in acute treatment and 1 day in subacute treatment.

Recently, there have been many reports regarding food-drug interactions by the inhibition of drug metabolism mediated by the CYP3A subfamily. However, few reports are available on the inhibition of CYP2C9 activity by fruit juices or the extracts. In this study, we revealed that Pineapple juice component bromelain enhanced the hypoglycemic activity of glimepiride by inhibiting the human CYP2C9 activity in albino wistar rats.

This result suggests that Pineapple juice may affect the pharmacokinetics of substrates for CYP2C9 in humans. Pineapple is a rich source of bromelain proteolytic enzyme. The inhibitory activity of Pineapple juice and bromelain was studied in in-vitro may be caused by the proteolytic activity of the juice. Therefore, we used to determine whether the inhibition of CYP2C9 activity in-vivo and increased activity of CYP2C9 substrate.

Glimepiride, an oral hypoglycemic drug, is mainly metabolized by CYP2C9 [13]. It has been reported that the coadministration of, rifampicin on the pharmacokinetics and Pharmacodynamics of glimepiride decreased the blood concentration of glimepiride [21]. If Pineapple juice could inhibit the CYP2C9 that is expressed in the small intestine and/or the liver; it could increase the blood concentration of glimepiride and potentially induce hypoglycemia. Previously studies reported that a component (bromelain) of Pineapple juice inhibited human CYP2C9 activity in vitro. Therefore, we further investigated whether Pineapple juice could affect the efficacy in rats. The results showed that the co-administration of Pineapple juice significantly increased the glucose lowering activity of glimepiride would be caused by an increase in bioavailability by decreasing the metabolism of glimepiride.

CONCLUSION

The present study concluded that Pineapple juice increases the efficacy of glimepiride in alloxan-induced diabetic rats when pineapple juice administered before 1 hr of glimepiride administration in test-2 (pineapple juice+glimepiride) group when compared to standard (glimepiride alone treated) group, possibly by the inhibition of...
CYP2C9. The enhancing glucose-lowering effect of glimepiride may be due to inhibitory activity of the Pineapple component (bromelain) proteolytic enzyme on the activity of CYP2C9 in albino wistar rats. The pineapple and food containing bromelain may alter the pharmacodynamics of CYP2C9 substrates. Hence, CYP2C9 substrates like warfarin, amitriptyline doses may require special attention if used along with bromelain containing herbal preparations to avoid the complications.

Acknowledgements
The authors are thankful to Chairman of S.S.R.C.P, Seshadrinagar, Mahabubnagar, HETERO DRUGS Pvt.Ltd (Baddi), India, for the gift samples of glimepiride.

REFERENCES