

An investigation of palmyrah (*Borassus flabellifer*) fruit pulp mediated inhibition of intestinal glucose uptake and its toxicity

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Palmyrah fruit pulp (PFP) is an underutilized resource of *Borassus flabellifer*. PFP contains flabelliferins which are steroidal saponins with glucose and rhamnose molecules linked to β -sitosterol at the 3-OH group. Several flaberrins are found in PFP and one such compound is F-II a steroidal tetraglycoside of β -sitosterol (MW, 1030) and is the bitter flaberrin from PFP.

Reduced weight gain by the Institute of Cancer Research (ICR) mice had been previously reported after feeding 10% palmyrah (*Borassus flabellifer*) fruit pulp (PFP) containing feed. In the above studies F-II was strongly implicated as the active principle. The objective of this study was to confirm the above, its effect on glucose uptake and determine the mechanism of action and some of the factors affecting this effect.

The study has provided evidence that confirms the weight reducing property of PFP and also demonstrated its ability to inhibit intestinal glucose uptake in mice. Studies showed that feeding of PFP had no effect on fasting blood sugar levels of mice ($p=0.64$) but had significantly reduced the liver glycogen content of test mice ($p<0.01$). A mixture of flabelliferins (dose: 10 mg/50 g mouse) extracted by the methods described previously on administration to mice after a glucose challenge resulted in a decline in serum glucose levels ($p<0.0001$), increased intestinal glucose levels ($p<10^{-10}$) and increased faecal glucose levels ($p<0.01$). On isolating F-II and other flabelliferins ($F_B, F_D/F_E$), it was found that only F-II has the ability to lower serum glucose ($p<10^{-8}$) and increase intestinal glucose ($p<10^{-6}$). This effect was shown at a dose of 1 mg F-II/50 g mouse. The findings of the mice study were supported by evidence from a study conducted with mild diabetic type-II patients. In the human study it was decided to use pinattu, a dried PFP which can be classified as fruit leather. The dose of 6 g of pinattu (30 mg F-II) was calculated on the basis of IC_{50} studies and mean human body weight. When pinattu was given to mild, type-II diabetic patients who are not under any therapeutic regimen there was a reduction of 24-48% serum glucose after a glucose challenge when compared to controls. It has also been shown that the inhibition of intestinal glucose uptake by PFP mediated has been mainly by F-II and not by the fibre it contains.

A fibre control showed that a small part of this is due to fibres (2-11% reduction in serum glucose level).

It has been known for some time that all flabelliferins are bound by a UV active binder. The present study revealed that this binder comprised a major carotenoid component identified as phytofluene and a minor component phytoene. Removal of the binder increased the efficiency with which F-II inhibited intestinal glucose uptake even when the dose was reduced to 2 mg mixed flabelliferin/50 g mouse. Upon separation of the binder, F-II alone reduced blood glucose levels and increased intestinal glucose levels ($p<0.001$) of test mice when compared with that of controls.

Inhibition of Na^+/K^+ ATP ase activity was found to be a mechanism by which F-II mediates its inhibitory action on intestinal glucose uptake (the IC_{50} values were $9 \times 10^{-5} M$ and $5 \times 10^{-5} M$ with and without UV binder respectively). Computational studies showed that the lowering of the inhibition by the binder was probably due to the distortion of the carbohydrate moiety of the F-II, which is strongly connected to the activity of the molecule. The beneficial effects of any pharmaceutical agent depend on it being non toxic. Results showed that feeding 10% PFP containing feed for one week (short term) or feeding 10% and 50% PFP containing feed for 30 days (long term) did not show any increase in the levels of key hepatic enzymes *viz*; alkaline phosphatase, alanine transaminase and aspartate transaminase in the test group when compared with that of the controls. Haematological parameters tested (haemoglobin level, packed cell volume, red cell count and white cell count) were not significantly different in the test and control groups. Creatinine levels in the test and control groups were not significantly different from each other indicating absence of renal damage. Microscopic examination of liver, kidney and intestine of test group did not show any pathological changes when compared to those in the control group.

From the overall results it may be concluded that PFP possibly has an application in treating type -II diabetics most probably those that are obese. However the dosage of PFP pinattu must be closely monitored as different PFPs contain different amounts of F-II.