Chapter 6

Conclusion
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From the overall results it is evident that methanolic extracts of *P. granatum* exhibited hypoglycaemic activity in normal rats as well as STZ-induced diabetic rats. It also improved the parameters in high fat fed diabetic rats. From the report findings also, it is clear that, *P. granatum* extracts showed hypoglycaemic activity in normal as well as alloxan induced diabetes (Jaffri *et al.*, 2000) and it has agonist activity on PPAR-γ receptor (Huang *et al.*, 2005), it improved the circulating lipids in Zucker diabetic fatty rats (Huang *et al.*, 2005a). It is also reported to be a potent α-glucosidase inhibitor (Li *et al.*, 2005). The α-glucosidase inhibition action could have contributed to the antihyperglycaemic activity of *P. granatum* during the 21 day study in STZ-induced diabetic rats, as the blood glucose levels were taken in non fasting conditions. But its hypoglycaemic action in normal fasted rats and in glucose loaded rats indicates that it appears to contain active constituents which might act independent of insulin signalling cascade. The increase in liver hexokinase activity and decrease in PEPCK activity could be the major contributing factor of the antidiabetic activity of *P. granatum* in normal and STZ-induced diabetic rats. Agonist activity on PPAR-γ receptor can be contributed to its antidiabetic action in high fat diet fed rats. Huang *et al.*, (2005) identified the active component responsible for the PPAR-γ receptor agonistic action of *P. granatum* as gallic acid.

Further molecular level studies required to unravel the mystery behind the antidiabetic action of Unani herbal drug *P. granatum*.

It has to be studied for its effect on,
- GLUT 4 levels and gene expression in skeletal muscles
- GLUT 2 levels and expression in pancreatic β-cells (glucosensing)
- TNFα, IL-1, IL-2, IL-4 and IL-6 levels and their gene expression
- Leptin and Adiponectin levels and expression
- pre-receptor and post-receptor events
- enzymes such as hormone sensitive lipase
- skeletal muscle glucose uptake, glycogenolysis
and further advanced cellular level studies should be carried out to pinpoint the exact mechanism of action of *P. granatum* flowers.

From the results, it is evident that methanolic extract of *N. nucifera* possessed hypoglycaemic activity in normal rats as well as STZ-induced diabetic rats. But however, it is not effective in improving the insulin resistance and other associated parameters in high fat diet fed rats. In STZ-nicotinamide diabetic rats it did not show any significant increase in serum insulin levels when compared with the standard insulinotropic drug glibenclamide, ruling out the possible insulinotropic action as the mechanism of action of *N. nucifera* extract.

The effect of extract on glucose metabolism and on gluconeogenesis can be attributed to its antidiabetic effect in normal as well as STZ-diabetic rats. It is evident that *N. nucifera* extracts did not require presence of insulin for their antidiabetic activity. And also they are unable to increase the glucose metabolism and to inhibit the gluconeogenesis in insulin resistant rats, evident from liver hexokinase and PEPCK activities in high fat diet rats. If the *N. nucifera* extract altered the enzyme activities by a mechanism other than the insulinomimetic pathway, it would have been effective in high fat diet fed rats, which have insulin resistance at cellular level (Kanoh *et al*., 2003).

This leads to a conclusion that, *N. nucifera* possibly has insulinomimetic activity, at insulin receptor level, thereby producing insulin like effects. Its ineffectiveness in high fat diet fed rats can also be explained from the fact that, high fat feeding produces widespread *in vivo* insulin resistance (Storlien *et al*., 1986). Thus stimulation of insulin receptors directly or stimulation of the post receptor events by *N. nucifera* might have become futile.

But further molecular level studies are necessary to come up with concrete evidence on the mechanism of action of *N. nucifera* flowers extract. It has to be studied for its effects on:

- insulin receptor; insulin receptor substrates
- further insulin signalling cascade (PKC, PKB/Akt,)
- Protein Tyrosine Phosphatase (PTP 1B)
In conclusion, this work generated a clear evidence of antidiabetic action of *P. granatum* and *N. nucifera* flowers and gave a direction on possible future course of research that should be taken up with these Unani herbal drugs. The findings from this study gave an idea about the mechanism of antidiabetic action of these herbal drugs. Further advanced studies could confirm the mechanisms of action.