International Journal of Biochemistry and Biotechnology ISSN: 2167-0404 Vol. 2 (3), pp. 282-288, March, 2013. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Full Length Research Paper

Pharmacokinetic and Pharmacodynamic Studies on Nanoparticulate Gymnemic Acids

R. Ravichandran

Regional Institute of Education (NCERT), Bhopal – 462 013, India

Accepted 21 February, 2013

Gymnemic acids, the main phytoconstituents of *Gymnema sylvestre* possess potential natural pharmacological activities like supression of taste sensitivity to sweetness, inhibition of intestinal glucose absorption and lowering the plasma glucose levels. Nanonisation of active drug components are shown to improve their physiological action. In this study, nanoparticulate formulations of gymnemic acids prepared were studied for its Pharmacokinetic and Pharmacodynamic behavior compared with marketed product. The nano-formulation exhibited significant anti-diabetic activity compared to marketed product.

Key words: Gymnemic acids, Nanoparticles, Pharmacokinetics, Pharmacodynamics.

INTRODUCTION

Gymnema sylvestre commonly known as 'Gudmar' in Hindi is an important Indian medicinal plant used in different systems of medicine as a remedy for the treatment of diabetes, rheumatism, cough, ulcer, jaundice, dyspepsia, constipation, eyes pain and also in snakebite (Patel et al., 2012). The major phytoconstituents of G*. sylvestra* are gymnemic acids, gudmarin and saponins. Gymnemic acid ($C_{43}H_{68}O_{14}$) is a pentacyclic triterpenoid and is the main active phytoconstituents of *G. sylvestre*, exhibiting potent anti-diabetic activity (Shivani Vaidya, 2011). Gymnemic acids show different physiological activities like they suppress taste sensitivity to sweetness, lower plasma glucose and insulin levels in the diabetic subjects and inhibit intestinal glucose absorption (Ankit Saneja et al., 2010). Recent times have witnessed increased incidence of diabetes across the globe, along with increased popularity of herbal products in the international market (John B Classen, 2012). Gymnemic acids are poorly soluble in water and thus show reduced pharmacological activity (Ankit Saneja et al., 2010). The need for new and improved approaches to increase its solubility and bioavailability remains a key focal point for many researchers (Parijat Kanetkar et al., 2007). Recently, many poorly soluble drugs have been nanonized to increase their dissolution rate, their saturation solubility and in turn to enhance their oral bioavailability (Ravichandran, 2009a,b). In this direction recently we reported the preparation and characterisation of nanosuspension of gymnemic acids (Ravichandran, 2010a) and its oral formulation (Ravichandran, 2010b). In this paper we report the pharmacokinetic and pharmacodynamic behavior of nanoparticulate gymnemic acids.

*Corresponding author. E-mail: ravincert@gmail.com

MATERIALS AND METHODS

Chemicals

Gymnemic acid was purchased from Amruta Herbals Private Limited, Indore (India). Gymnemic acids nanosuspensions were prepared by high pressure homogenization method and the results of its characterization, and solid dosage form development have been recently reported by us (Ravichandran, 2010a,b). The nanosuspention was stabilized by sodium dodecyl sulfate (Fluka Switzerland). Avicel pH 101, AcDiSol (FMC BioPolymer, USA), Explotab (JRS Pharma, Germany), talc and magnesium stearate (Magnus Pharmaceuticals, Ahmedabad) were used as tablet excipients. Insulin used was purchased from Sigma-Aldrich, USA and Alloxan from Explicit Chemicals, Pune. Milli-Q Plus double-distilled water (Millipore, USA) was used as dispersion medium. The other chemicals were of analytical reagent grade (SRL, Mumbai, India).

Experimental animals

Male Wistar rats weighing 250–300 g were fed with commercial pellet diet (Kamadenu Agencies, Bangalore, India) and water *ad libitum*. The animals were acclimatized to laboratory hygienic conditions for 10 days before starting the experiment. The animals were maintained in groups of six and were fasted for 8 h prior to the commencement of the study.

Treatment of animals

Animals were fed with glucose (4 g/kg) for hyperglycemia (Parveen Kumar, 2012) and insulin was administered

Table 1. The change in blood glucose levels with time (min) in glucose loaded hyperglycemic rats after dosing with gymnemic acids nano-formulations, market tablet and insulin.

Treatments	Blood glucose concentration (mg/dL)				
	0 h	0.5 h	1 h	2 h	3 h
Gluc. control	89.80 ± 3.02	144.40 ± 4.85	150.60 ± 4.01	124.40 ± 3.32	105.20 ± 4.77
Insulin	94.20 ± 3.59	105.20 ± 3.49*	92.20 ± 4.60*	78.40 ± 4.20*	66.20 ± 3.68*
GA-M	86.80 ± 4.41	124.20 ± 8.23	132.60 ± 9.60	108.60 ± 10.60	101.00 ± 7.70
GANS-A	95.80 ± 5.80	124.40 ± 8.80	87.20 ± 5.09*	83.20 ± 4.04*	79.20 ± 2.70*
GANS-B	95.00 ± 4.15	126.60 ± 6.80	88.40 ± 3.69*	89.60 ± 6.80*	92.40 ± 5.16
GANS-C	90.80 ± 5.18	120.40 ± 10.20	112.20 ± 10.19	106.20 ± 8.20	98.20 ± 8.90

Each value represents the mean ± S.E.M. of six observations. *P < 0.01 Vs control.

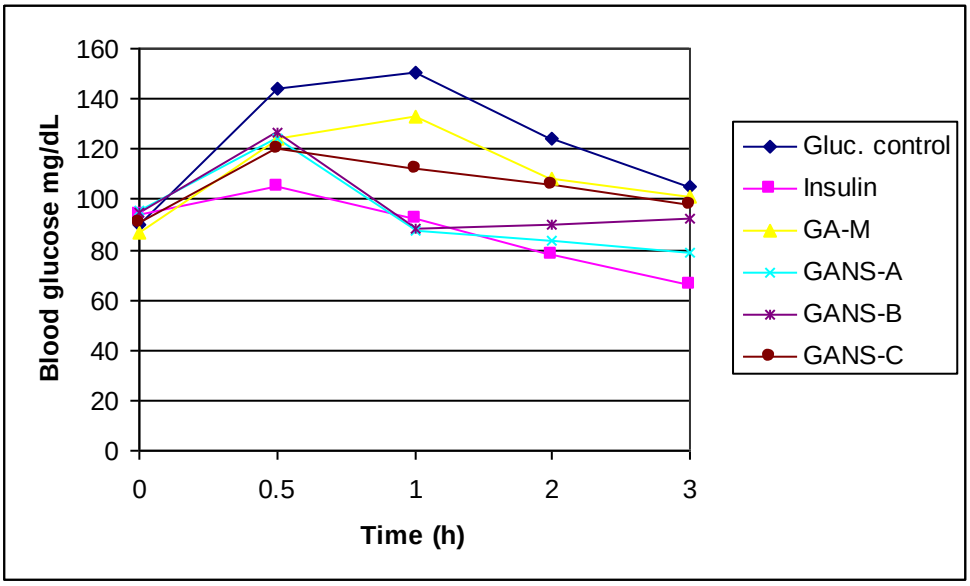

Figure 1. Effect of various formulations in glucose loaded hyperglycemic rats

subcutaneously. After 30 min, gymnemic acids tablet formulations (Ravichandran, 2010a,b) were fed. Diabetes was induced by injecting 120 mg/kg of alloxan monohydrate intraperitoneally in 0.9 % w/v NaCl to overnight-fasted rats. 10% glucose solution bottles were kept in their cages for the next 24 h to prevent hypoglycemia. Diabetic animals (>300 mg/dl) were divided into 5 groups (n = 6). On 7th day the rats were fasted for 16 h and blood parameters were determined.

Blood collection and biochemical parameters

Blood samples were analyzed for blood glucose levels by the Accutrend alpha glucometer (LOD = 0 to 33 mmol/L) and for insulin using radioimmunoassay (LOD = 3 µU/ml). The plasma lipid profile was analyzed for cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine, urea, hemoglobin and glycosylated hemoglobin by standard enzymatic methods (Yaseen, 2012) and glycosylated hemoglobin by colorimetric method (Sovia Evi, 2012).

Statistical analysis

The values are expressed as mean ± SEM. The standard deviation (SD) represents variation in the values of a variable, whereas the Standard Error of the Mean represents the spread that the mean of a sample of the values would have if we kept taking samples. So the SEM gives us an idea of the accuracy of the mean, and the SD gives us an idea of the variability of single observations. The two are related as SEM = SD/(square root of sample size). The results were analyzed for statistical significance using one-way ANOVA followed by Dunnet's test. The $p<0.05$ was considered significant.

RESULTS

Studies on glucose loaded hyperglycemic animals

Table 1 shows the anti-hyperglycemic effect in glucose-loaded hyperglycemic rats, after administration of gymnemic acids nanoparticulate formulations at a dose of 400 mg/kg. Thirty minutes after the glucose load, there was a significant rise in the blood glucose levels of control animals and a decline after one hour. The anti-hyperglycemic activity of any substance would be determined by its ability to lower the increasing blood glucose after a glucose load. The gymnemic acids

Table 2. Hypoglycemic activity of gymnemic acids nano-formulations in normal rats.

Treatments	Blood glucose concentration (mg/dL)				
	0 h	0.5 h	1 h	2 h	3 h
Normal control	84.40 ± 2.32	83.00± 1.80	81.80± 2.42	82.20± 1.70	80.20± 2.38
Insulin	82.00 ± 2.15	45.20± 3.86**	36.60± 1.43**	33.20± 1.39**	35.00± 3.16**
GA-M	83.80 ± 2.40	82.40± 2.24	81.20± 3.10	71.20± 2.28*	75.20± 2.88
GANS-A	85.20 ± 3.01	82.40± 2.80	70.00± 3.14*	68.60± 3.37**	65.80± 2.32**
GANS-B	83.20 ± 1.89	71.20± 2.80*	65.40± 3.10**	60.80± 4.02**	63.00± 3.32**
GANS-C	84.40 ± 2.10	82.20± 2.80	72.40± 2.80*	71.20± 2.28*	65.80± 2.32**

Each value represents the mean ± S.E.M. of six observations. *P < 0.05, **P < 0.01 Vs control

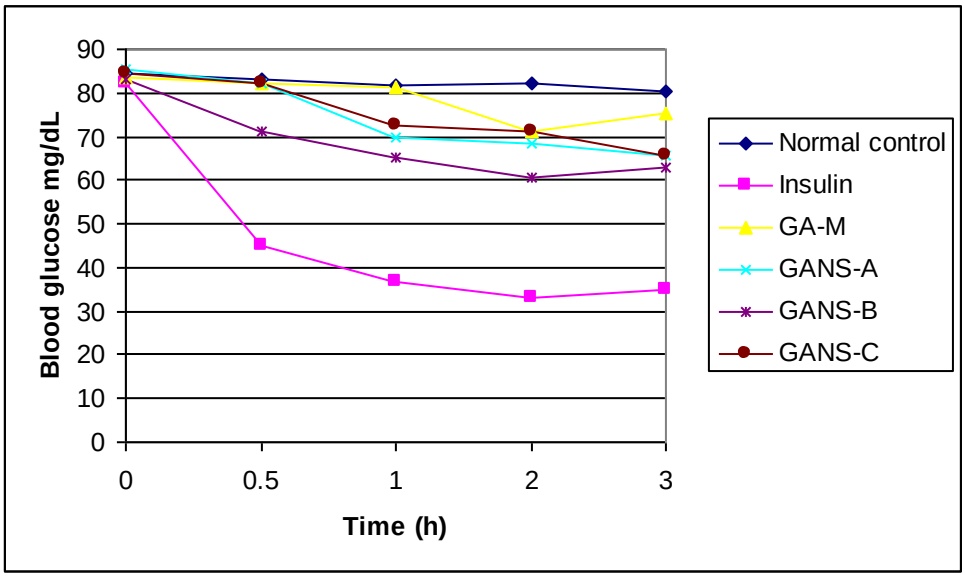

Figure. 2 Effect of various formulations on hypoglycemic effect in normal rats

Table 3. Biochemical parameters of experimental animals on 7th day post treatment.

Parameters	Normal control	Diabetic control	Insulin	GA-M	GANS-A	GANS-B	GANS-C
Blood glucose	81.4±3.2**	512.0±15.3	124.4±7.8**	282.2 ± 9.1**	192.0±10.4**	134.4 ±10.2**	150.0±12.2**
Urea	30.2±1.8**	279.0±14.0	32.8 ± 1.4**	93.4± 2.4**	77.2±5.1**	38.6 ± 2.2**	47.0±5.5**
Creatinine	0.45±0.0**	1.9±0.4	0.4 ± 0.03**	1.5 ± 0.0	0.9±0.1*	0.5 ± 0.4**	0.5 ± 0.03**
Cholesterol	34.0±1.7**	84.0 ±4.9	32.2 ± 2.5**	70.2± 3.5**	65.4±1.6**	38.2 ± 1.9**	44.8 ± 3.3**
Triglyceride	33.4±3.5**	123.0±6.6	38.2 ± 1.9**	96.2± 3.5**	88.4±3.6**	47.0 ± 2.4**	55.8 ± 3.3**
HDL	24.6±1.7**	10.2±1.1	25.8 ± 1.0**	14.2± 0.6**	14.8±2.2**	21.0 ± 2.0**	18.0 ± 0.7**
LDL	22.0±2.1**	58.8±3.2	23.6 ± 1.9**	36.6± 2.4**	30.0±2.4**	24.4 ± 2.2**	29.2 ± 3.3**
Hemoglobin	11.2±0.3**	6.9±0.4	11.0 ± 0.5**	8.80± 0.3*	9.0±0.4**	11.4 ± 0.3**	10.0 ± 0.4**
Gly. Hemoglobin	1.9±0.2**	5.7 ± 0.4	2.0 ± 0.2**	4.20± 0.3*	3.0±0.2**	2.2 ± 0.2**	2.6 ± 0.2**

Each value represents the mean ± S.E.M. of six observations. *P < 0.05, **P < 0.01 Vs diabetic control

nanoparticulate formulations studied for its bioactivity exhibits significant anti-hyperglycemic activity after 30 min at 1, 2 and 3 h after the glucose load compared to control. GANS-A exhibited significant anti-hyperglycemic activity. GA-M exhibited the effect only after one hour. The insulin treated produced hypoglycemia most effectively from 30 min onwards. Comparatively GANS-A & B was found to be more active than GANS-C (Figure. 1). The best result was shown by insulin and the least by GA-M.

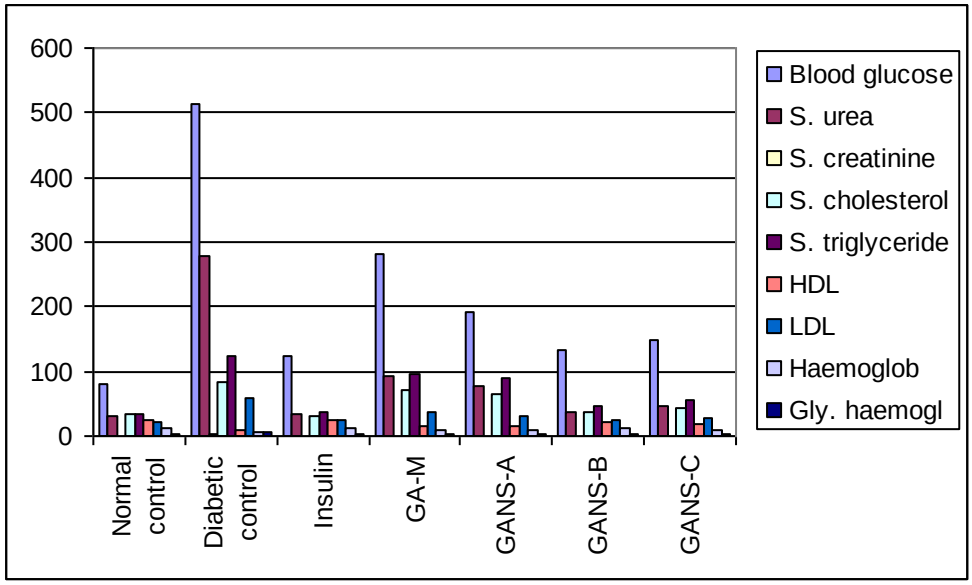

Figure 3. Biochemical parameters of rats on 7th day post treatment.

Studies on fasted normal rats

Based on the anti-hyperglycemic activity, the active gymnemic acids nanoparticulate formulations were subjected to hypoglycemic studies and the results are given in Table 2. GANS-B exhibited significant hypoglycemic activity at 30 min. GANS-C showed hypoglycemic activity little close to GANS-A. GA-M could show only little effect around 2 hours. The change observed with control was too less and a very high response was seen with insulin immediately. Comparatively, GANS-B was more active among gymnemic acids nanoparticulate formulations (Figure 2).

Studies on alloxan-induced diabetic rats

The basal blood glucose levels of all the groups were statistically not different from each other. Three days after alloxan administration, blood glucose values were 5-folds higher in all the groups and were not statistically different from each other. After 7 days, values of blood glucose decreased in all the treated groups and the diabetic rats showed a slight increase in blood glucose level. The administration of gymnemic acids nanoparticulate formulations and insulin to diabetic rats restored the level of blood glucose significantly (Table 3 and Fig. 3).

The level of total hemoglobin, glycosylated hemoglobin, urea, creatinine and lipid profiles of different experimental groups are also represented in Table 3 and shown in Fig. 3. Diabetic rats showed a significant decrease in the level of total hemoglobin and significant increase in the level of glycosylated hemoglobin. The administration of gymnemic acids nanoparticulate formulations and insulin to diabetic rats restored the changes in the level of total hemoglobin and glycosylated hemoglobin to near normal levels.

Alloxan-induced diabetic rats showed significant hypercholesterolemia as compared with control. Treatment with gymnemic acids nanoparticulate formulations and insulin showed a significant decrease in cholesterol levels at the same time increase in HDL-c. Hypercholesterolemia was associated with hypertriglyceridemia as compared with control animals. Hypertriglyceridemia was also significantly prevented by treatment with gymnemic acids nanoparticulate formulations and insulin. Diabetic control rats showed a significant increase in creatinine and urea levels as compared with control animals. Treatment with gymnemic acids nanoparticulate formulations and insulin significantly decreased these values. GA-M had little effect in alleviating diabetes and diabetes-related complications. GANS-C and A had similar activity but much better than GA-M. The activity of GANS-B was more and was comparable with that of the standard drug, insulin.

To evaluate the insulinemia activity of the gymnemic acids nanoparticulate formulations plasma insulin levels were monitored in a hyperglycemic rat model after dosing with different nanoparticulate dispersions. Table 4 compares the efficacy of the four formulations for insulinemia. The nanoparticulate formulations were effective in significantly increasing insulinemia. The effects were very much dependent on the type of formulations. There was a significant increase in insulin with GANS-A. The insulin levels of GANS-B and C were significantly higher than the insulin levels of GA-M but the insulin levels of insulin treated was the most significant.

DISCUSSION

It has been well established that nanonisation of active drug components severely alter the physiological action of the active component, and this property are to be harvested for the betterment of human health. In this study nanoparticulate formulations of gymnemic acids prepared were considered for its Pharmacokinetic and Pharmacodynamic behavior compared with commercial product. In this study in particular the nano-formulation effect on the pharmacological parameters associated with diabetics were compared with the commercial product prepared in a traditional manner. To draw out the mechanism behind their activity, the active anti-hyperglycemic formulations were subjected to hypoglycemic studies to determine the effect of these formulations in diabetes-associa-

Table 4. Pharmacokinetic parameters on the mean insulin levels (µU/ml) after dosing hyperglycemic rats with gymnemic acids nano-formulations, market tablet and insulin.

Formulation	After 30 min	AUC	C_{max}	T_{max} (min)
Control fasting	25.9 ± 3.86	380 ± 9.2	29 ± 3.6	15
Insulin	43.7 ± 5.19	464 ± 8.5	44 ± 3.6	15
GA-M	29.3 ± 2.14	414 ± 6.2	31 ± 3.6	60
GANS-A	31.1 ± 2.48	472 ± 7.3	41 ± 3.6	30
GANS-B	34.2 ± 3.40	484 ± 8.2	38 ± 3.6	45
GANS-C	32.1 ± 2.38	481 ± 8.9	39 ± 3.6	30

Each value represents the mean ± S.E.M. of six observations.

ted complications. Comparison was also made with insulin used medically to treat some forms of diabetes mellitus. Biochemical parameters were also assessed.

Diabetes is a major health problem affecting major populations worldwide. Epidemiological studies and clinical trials strongly support the notion that hyperglycemia is the principal cause of complications. Effective blood glucose control is the key for preventing or reversing diabetic complications and improving quality of life in patients with diabetes. Thus sustained reduction in hyperglycemia will decrease the risk of developing micro vascular complications and most likely reduce the risk of macro vascular complications (Muniappan, 2004). On the basis of this statement we have selected the glucose-induced hyperglycemic model to study the anti-hyperglycemic activity of gymnemic acids nanoparticulate formulations. Any drug that is effective in diabetes will have the ability to control the rise in glucose level by different mechanisms and the ability of the gymnemic acids nanoparticulate formulations to prevent hyperglycemia could be determined by glucose-loaded hyperglycemic model.

In the glucose-loaded hyperglycemic model, the gymnemic acids nanoparticulate formulations tested for anti-hyperglycemic activity exhibited significant anti-hyperglycemic activity at a dose level of 400 mg/kg. Excessive amount of glucose in the blood induces insulin secretion. This secreted insulin will stimulate peripheral glucose consumption and controls the production of glucose through different mechanisms (Andrew, 2000). However, from the study (glucose control) it was clear that the secreted insulin requires 2 to 3 h to bring back the glucose level to normal. In the case of gymnemic acids nanoparticulate formulations and insulin-treated groups, the glucose levels have not exceeded more than the negative control group, giving an indication regarding the supportive action of the gymnemic acids nanoparticulate formulations and insulin hormone in glucose utilization. The effect of insulin, the standard used in this study, on glucose tolerance has been attributed to enhanced activity of beta cells of the pancreas resulting in secretion of larger amounts of insulin. So the mechanism behind this anti-hyperglycemic activity of nanoparticulate formulations involves an insulin-like effect, probably, through peripheral glucose consumption or enhancing the sensitivity of beta cells to glucose, resulting in increased insulin release (Muniappan, 2004). In these contexts, a number of other natural plant substances have also been reported to have hypoglycemic effects (Leila et al., 2007). The nanoparticulate formulations exhibited the tested hypoglycemic activity. The hypoglycemic effect produced by them may be due to the increased insulin release resembling the mechanism of actions of sulphonylureas (Okine, 2005; Miura, 2001). Alloxan induces hyperglycemia by selective cytotoxic effect on pancreatic beta cells. One of the intracellular phenomena for its cytotoxicity is through generation of free radicals demonstrated both *in vivo* and *in vitro* (Yadav, 2002). This investigation indicate the efficiency of the gymnemic acids nanoparticulate formulations in the maintenance of blood glucose levels in alloxan-induced diabetic rats may be possibly by the above mentioned mechanisms.

In uncontrolled or poorly controlled diabetes, there is an increased glycosylation of a number of proteins including hemoglobin. Glycosylated hemoglobin level is increased in patients with diabetes mellitus to approximately 16% and the amount of increase was found directly proportional to the fasting blood glucose level. During diabetes, the excess glucose present in blood reacts with hemoglobin. Therefore, the total hemoglobin level is decreased in alloxan diabetic rats (Pari, 2004). Administration of gymnemic acids nanoparticulate formulations for 7 days prevented a significant elevation in glycosylated hemoglobin thereby increasing the level of total hemoglobin in diabetic rats. This could be due to the result of improved glycemic control produced by gymnemic acids nanoparticulate formulations.

The levels of lipids are usually elevated in diabetes mellitus and such an elevation represents a risk factor for coronary heart disease. This abnormal high level of lipids is mainly due to the uninhibited actions of lipolytic hormones on the fat depots mainly due to the action of insulin. Under normal circumstances, insulin activates the enzyme lipoprotein lipase, which hydrolyses triglycerides. However, in diabetic state lipoprotein lipase is not activated due to insulin deficiency resulting in hypertriglyceridaemia (Pushparaj, 2007). Also insulin deficiency is associated with hypercholesterolaemia. Insulin deficiency may be responsible for dyslipidaemia, because insulin has an inhibitory action on HMG-CoA reductase, a key rate-limiting enzyme responsible for the metabolism of cholesterol-rich LDL particles. The mechanisms responsible for the development of hypertriglyceridemia and hypercholesterolemia in uncontrolled diabetes in humans are due to a number of metabolic abnormalities that occur sequentially (Murali B Upadhyaya, 2002). In present study, diabetic rats showed hypercholesterolaemia and hypertriglyceridaemia and the treatment with gymnemic acids nanoparticulate formulations significantly decreased both cholesterol and triglyceride levels. This implies that these nanoparticulate formulations can prevent or be helpful in reducing the complications of lipid profile seen in some diabetics in whom hyperglycemia and hypercholesterolaemia coexist quite often (Sharma, 2003). These findings also support the reports that the activity of gymnemic acids may be directly attributed to improvements in insulin levels upon treatment (Sharma, 2003).

The diabetic hyperglycemia induced by alloxan produces elevation of plasma levels of urea and creatinine, which are considered as significant markers of renal dysfunction (Alarcon, 2005). Present results also showed significant increase in the

level of plasma urea and creatinine in the diabetic groups compared to control level. These results indicated that diabetes might lead to renal dysfunction. While, after treatment of alloxan-diabetic rats with gymnemic acids nanoparticulate formulations, the level of urea and creatinine were significantly decreased compared to the mean value of diabetic group. This further confirms the utility of these nanoparticulate formulations in diabetes-associated complications (El-Demerdash et al., 2005).

Animals dosed with gymnemic acids nanoparticulate formulations elicited a comparable response in insulin production. Table 4, shows the pharmacokinetic data for different formulations. The nanoparticle preparation appears to be better with many advantages. For animals dosed with the nano preparation, there was a noticeable increase in Insulin levels. In comparison, animals dosed with a solution of insulin experienced a steady rise in Insulin levels. At the termination of the study, animals dosed with the gymnemic acids market formulations had significantly low Insulin levels in comparison to the rest of the preparations. However, as summarized in Table 4, the pharmacokinetic data of nano formulations were not highly variable among themselves. Additional studies are needed to address this issue and to establish the actual bioavailability of the nanoparticulate formulations following oral dosing. The nanoparticles of gymnemic acids, described in this study are biologically active as demonstrated in Fig. 1 to 3. Though more extensive testing will be needed to determine if this approach offers any advantages over other delivery platforms, the data presented are intriguing. The nanoparticles of gymnemic acids, in comparison to a marketed tablets, have a relatively prolonged hypoglycemic effect and, surprisingly, are as effective as insulin. Many doctors consider 110 - 120 mg/dL (6.1 - 6.7 mmol/L) as the upper range for a normal fasting blood sugar level, I am convinced that a healthy fasting blood sugar level should be in the range of 70 - 90 mg/dL (3.9 - 5 mmol/L) with fasting insulin ideal level less than 10 µU/ml (normal insulin range is 6–27 µU/ml).

Diabetes is the bitter sweet problem of India. In a shocking revelation, the 20th annual World Diabetes Congress 1999 of the International Diabetic Federation has said that India leads the world in the looming epidemic of diabetes. The country currently has the highest number of 50.8 million people suffering from diabetes, followed by China with 43.2 million and the US with 26.8 million. By 2010 almost seven percent of India's adult population will have the disease. The increase in economic status has been linked with the disease. No wonder sedentary lifestyle, intake of polished and processed foods and trans oils and stress have been attributed as the causes behind this silent killer. Diabetes, with its attendant acute and long term complications, and the myriad of disorders associated with it, is a major health hazard. In keeping with the scenario of most developing countries, India has long passed the stage of a diabetes epidemic. The problem has now reached, in scientific language, "pandemic" proportions. To put it simply, it has crossed the dividing line in which it is a problem associated with individuals, no matter how large this number may be, and is now a very large public health problem, growing astronomically year after year. India has a distinct need for a comprehensive diabetes care program.

G. sylvestre, a traditional ayurvedic herb has been used successfully in Indian ayurveda medicine for more than 2,000 years as a well known dietary supplement known to balance elevated blood sugar levels. The active ingredients in G. sylvestre, gymnemic acid and gurmarin, have molecular structures similar to that to glucose and possess a number of health benefits. Gurmarin has the ability to fill taste bud receptors and reduce the sweet taste of sugary foods, thus greatly reducing the craving for sweets. Gymnemic acid helps increase the production of insulin by stimulating the production of new insulin-producing cells, called beta-cells, in the pancreas. Gymnemic acid also facilitates insulin release from the beta-cells into the blood stream by increasing beta-cell membrane permeability. Gymnemic acid also inhibits the absorption of sugar molecules in the intestines during digestion, thus reducing increases in blood sugar levels. Finally, consumption of G. sylvestre also has been shown to significantly lower cholesterol in animal models. *G. sylvestre* is an exclusive ingredient in Reglucol™ formula. Gymnema increases the activity of the enzymes, responsible for the sugar metabolism; controls blood sugar levels. Gymnema extract contains gymnemic acid that has the ability to decrease sugar transfer from intestines to the bloodstream, and gurmarin that decreases taste bud functions. Gymnema decreases sugar cravings, helps to suppress the appetite, and as a result, promotes weight control. Reglucol™ 400mg has been standardized to contain 100 mg (25%) of gymnemic acids.

Gymnema helps to promote weight control by its ability to reduce the cravings for sweets

and control blood sugar levels (Prakash et al., 1986; Ninomiya and Imoto, 1995). A peptide isolated from Gymnema, gurmarin, has also been shown to block the sweet taste of glucose and sucrose in animal models (Ninomiya and Imoto, 1995). Gurmarin temporarily binds to the sweet and bitter receptors on the tongue, thereby blocking the taste sensation and reducing sweet cravings (Ninomiya and Imoto, 1995). Preuss *et al.* (1998) showed a significant lowering of cholesterol with *G. sylvestre* ingestion in hypertensive rats fed a high sucrose diet, whereas the placebo group showed a significant increase in cholesterol levels. *Gymnema* is regarded as very safe and has been administered (400 mg/day) to patients with insulin dependent diabetic mellitus (IDDM) for 10-12 months with no adverse side effects (Shanmugasundaram, 1990).

Recent times have witnessed increased sale of herbal products in the international market. According to World Health Organization, present demand for medicinal plants annually, is about US$14 billion. Traditional Chinese Medicine (TCM) has made tremendous advances in terms of modern scientific research, and according to latest studies it contributes 80 % of the annual turnover of the total herbal drug industry. Medicinal plant-related trade in India is estimated to be around Rs. 550 crores per year. While the value of global trade in medicinal plants has been put at over $ 60 billion per year, of which Indians total turnover of Rs. 2300 crores (US$551 million) of Ayurvedic and herbal products. Exports of Ayurvedic medicines have reached a value of 100 million dollars a year. About 60% of this is crude herbs, about 30% is finished product shipped abroad for direct sales to consumers, and the remaining 10% is partially prepared products to be finished in the foreign countries. With the standardization wave sweeping the herbal drug industry, several companies in India are selling standardized products.

The use of plants, parts of plants and isolated phytochemicals for the prevention and treatment of various ailments has been in practice from immemorial time. According to WHO, about 80% of the World's population in 2001 used herbal medicine for the health need (Saul, 2001). Medicinal plants that are effective in controlling plasma glucose level with minimal side effects are commonly used in developing countries as alternative therapy

for the treatment of diabetes mellitus (Agarwal and Khan, 2001; Still, 2002). *G. sylvestre* has an important place among such antidiabetic medicinal plants. The scientific research on gymnemic acid revealed its biological potential for the treatment of different types of disease including diabetes. The information presented in this paper regarding the pharmacological activity of the gymnemic acid may provide the evidence for its importance in the different system of medicines.

It is generally recognized that the incidence of diabetes is rising and reportedly growing at epidemic proportions (Owens et al., 2001). The need for new and improved approaches to treat this disease remains a key focal point for many research and development programs (Saul, 2001). Though many approaches for treating the disease have arisen throughout the years and new therapeutic targets are being identified (Agarwal and Khan, 2001), herbal therapy remains the main stay of managing diabetes. To improve patient compliance over insulin and for better disease management (Still, 2002) herbal drugs can be used along with new approaches of delivery with nano-technologies for better effects (Ravichandran, 2009a,b).

CONCLUSION

Gymnemic acid nanoparticulate formulations tested for anti-diabetic activity have shown appreciable results in decreasing the glucose level and other complications associated with diabetes. The results are much better compared to gymnemic acid tablets available in market. The results are also comparable with insulin. This research supports the inclusion of this gymnemic acid nanoparticulate formulations in traditional anti-diabetic preparations and the formulations made using nanotechnology could serve the purpose better than the existing formulations. The results obtained in this study clearly shows that the pharmacological activity of the nanonised gymnemic acids are much better compared with commercial products and will certainly provide the evidence for its importance in the different systems of medicines. In depth clinical research needs to be carried out to make this a potential reality.

REFERENCES

Agarwal V, Khan MA (2001). Current status of the oral delivery of insulin. Pharmaceutical Tech., 76–88.

Alarcon AFJ, Calzada BF, Hernandez GE, Ruiz AC (2005). Acute and chronic hypoglycaemic effect of Ibervillea sonorae root extracts-II. J Ethnopharmacol. 97: 447-452.

Andrew JK (2000). Diabetes, New York: Churchill living stone, 1-9.

Ankit Saneja, Chetan Sharma, Aneja KR, Rakesh Pahwa (2010). Gymnema Sylvestre (Gurmar): A Review, Der Pharmacia Lettre, 2(1): 275-284

El-Demerdash FM, Yousef MI, Abou El-Naga NI (2005). Biochemical study on the hypoglycemic effects of onion and garlic in alloxan-induced diabetic rats. Food Chem Toxicol. 43: 57–63.

John B Classen (2012). Review of Evidence that Epidemics of Type 1 Diabetes and Type 2 Diabetes/ Metabolic Syndrome are Polar Opposite Responses to Iatrogenic Inflammation. Current Diabetes Reviews. 8(6): 413-418

Leila Z, Eliandra DS, Luisa HC, Anildo CJ (2007). Effect of crude extract and fractions from Vitex megapotamica leaves on hyperglycemia in alloxan-diabetic rats. J Ethnopharmacol. 109: 151-155.

Miura T, Itoh C, Iwamoto N, Aato M, Kawai M, Park SR, Suziki I (2001). Hypoglycemic activity of the fruit of the Momordica charantia in Type 2 diabetic mice. J Nutr Sci Vitaminol (Tokyo). 47: 340-344.

Muniappan L, Leelavinothan P, Sandhya S, Ramesh B (2004). Insulin-secretagogue activity and cytoprotective role of the traditional anti-diabetic plant Scoparia dulcis (Sweet Broomweed). Life Sci. 75: 2003-2014.

Murali B Upadhyaya UM, Goyal RK (2002). Effect of chronic treatment with Enicostemma littorale in non-insulin dependent diabetic (NIDDM) rats. J Ethnopharmacol. 81: 199-204.

Ninomiya Y, Imoto T (1995). Gurmarin inhibition of sweet taste responses in mice. Am J Physiol. 268: R1019–25.

Okine LKN, Nyarko AK, Osei-Kwabena N, Oppong IV (2005). The antidiabetic activity of the herbal preparation ADD-199 in mice: a comparative study with two oral hypoglycaemic drugs. J Ethnopharmacol. 97: 31-38.

Owens DR, Zinman B, Bolli GB (2001). Insulins today and beyond. Lancet. 358: 739–746.

Pari L, Amarnath SM (2004). Antidiabetic activity of Boerhaavia diffusa L.: effect on hepatic key enzymes in experimental diabetes. J Ethnopharmacol. 91: 109-113.

Parijat Kanetkar, Rekha Singhal, Madhusudan Kamat (2007). Gymnema sylvestre: A Memoir. J Clin Biochem Nutr. 41(2): 77–81.

Parveen Kumar, Shailesh Baraiya, Gaidhani SN, Gupta MD, Manish M Wanjari 2012. Antidiabetic activity of stem bark of Bauhinia variegata in alloxan-induced hyperglycemic rats. J Pharmacol Pharmacother. 3(1): 64–66.

Patel K, Gadewar M, Tripathi R, Patel DK (2012). Pharmacological and analytical aspects of gymnemic acid: a concise report. Asian Pac J Trop Dis. 2(5): 414-416

Prakash AO, Mathur S, Mathur R (1986). Effect of feeding Gymnema sylvestre leaves on blood glucose in beryllium nitrate treated rats. J Ethnopharmacol. 18: 143–6.

Preuss HG, Jarrell ST, Scheckenbach R, Lieberman S, Anderson RA (1998). Comparative effects of chromium, vanadium and Gymnema sylvestre on sugar-induced blood pressure elevations in SHR. J Am Coll Nutr. 17: 116–23.

Pushparaj PN, Low HK, Manikandan J, Tan BKH (2007). Anti-diabetic effects of Cichorium intybus in streptozotocin-induced diabetic rats. J Ethnopharmacol. 111: 430-434.

Ravichandran R (2009a). Nanotechnology-based drug delivery systems, NanoBiotechnology. 5(1): 17-33. doi:10.1007/s12030-009-9028-2

Ravichandran R (2009b). Nanoparticles in Drug Delivery: Potential Green Nanobiomedicine Applications, International Journal of Green Nanotechnology: Biomedicine. B108 –B130. doi:10.1080/19430850903430427

Ravichandran R 2010a. Physico-chemical evaluation of gymnemic acids nanocrystals, Int. J. Nanoparticals. 3(3): 280-296.

Ravichandran R (2010b). Formulation of nanosuspensions of gymnemic acids for oral administration. Int. J. Nanoparticals. 3(4): 309-325.

Saul A (2001). Search for a better method of insulin delivery. Drug Topics. 145: 2S–3S

Shanmugasundaram ERB, Rajeswari G, Baskaran K, Kumar BRR, Shanmugasundaram KR, Ahmath BK (1990). Use of Gymnema sylvestre leaf extract in the control of blood in insulin-dependent diabetes mellitus. J Ethnopharmacol. 30: 281–94.

Sharma S, Nasir A, Prabhu KM, Murthy PS, Dev G (2003).

Hypoglycaemic and hypolipidemic effect of ethanolic extract of seeds of Eugenia jambolana in alloxan-induced diabetic rabbits. J Ethnopharmacol. 85: 201-206.
Shivani Vaidya (2011). Review on gymnema: an herbal medicine for diabetes management. Pharmacia. 1(2): 1-6
Sovia Evi, Goddess Lucy N Saso, Joseph Iskendiarso Sigit (2012). Inhibition Activity of Garlic Extract and S-methyl cysteine on Albumin Glycation reactions are In Vitro. Maranatha Medical Journal. 10(2): 98-102.
Still JG (2002). Development of oral insulin: progress and current status. Diabetes-Metabolism Res. Rev. 18: S29–S37.
Yadav S, Vats V, Dhunnoo Y, Grover JK (2002). Hypoglycemic and antihyperglycemic activity of Murraya koenigii leaves in diabetic rats. J Ethnopharmacol. 82: 111-116.
Yaseen F, Jaleel A, Aftab J, Zuberi A, Alam E (2012). Circulating levels of resistin, IL-6 and lipid profile in elderly patients with ischemic heart disease with and without diabetes. Biomark Med. 6(1): 97-102.