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Antihyperglycemic Activity and Toxicity of Nanocapsules containing Roasted Moringa Leaf Antioxidants

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Abstract

Moringa oleifera Lam is a plant used in the management of type 2 diabetes. The Antihyperglycemic activity of Nanoencapsules formulated using antioxidant-rich fraction of roasted *Moringa oleifera* Lam leaf extract was investigated in rat models using oral glucose tolerance test, in comparison with the non-encapsulated fraction. To ascertain the safety of these nanocapsules, acute and sub-chronic toxicity was evaluated using animal experimentation. Animals were observed for changes in behavior, weight gain, hematological and biochemical parameters. Consumption of Moringa nanocapsules (200 mg/kg body weight) by normoglycemic rats prior to glucose loading (2 g/kg body weight) improved glucose tolerance more (42%) compared to the non-encapsulated fraction (29%). The antihyperglycemic activity of nanoencapsules was 1.3 times higher than the non-encapsulated fraction. These results show that roasted Moringa leaf antioxidants have antihyperglycemic activity; and affirm the greater efficiency of nanoencapsulation in the delivery of bioactives compared to the non-encapsulated form. Consumption of nanocapsules loaded with antioxidant-rich fraction of roasted Moringa leaf extract showed no signs of toxicity, suggesting that they are relatively safe. These results have important implication in the formulation of Moringa based nutraceuticals for the management of type II diabetes.

Keywords: Roasted Moringa Leaf antioxidants; Moringa nanocapsules; Antihyperglycemic activity; Toxicity

Introduction

Moringa oleifera Lam. is a plant used in the management of type 2 diabetes and belongs to the Moringaceae family. Water and ethanol extracts of its leaves have been shown to possess hypoglycemic, antihyperglycemic and antidiabetic activity in normoglycemic and in diabetic rats. Consumption of *Moringa oleifera* leaf power [1-3], aqueous leaf extract [4-6] and ethanolic leaf extract [7,8] reduces fasting blood glucose, post prandial glucose and increases insulin production in human and animal experiments. Antihyperglycemic activity of Moringa leaves is attributed to its phytochemical components notably flavonoids, glucosinolates, phenolic acids, terpenes and alkaloids [3,7,9]. In related studies, it has been shown that treatment with phenolic antioxidants improves glucose tolerance and controls glycemic status in animal [7,10,11] and human [12,13] models. Furthermore, encapsulation of phenolic antioxidants was found to effectively enhance their therapeutic efficacy for glycemic control [14]. Nanocapsules provide a vehicle for controlled or sustained release of bioactives and a larger contact surface area for adherence, that may improve intestinal uptake and bioavailability [15,16]. Inferring from the above, it could be assumed that nanocapsules made from a concentrate of Moringa leaf antioxidants could improve their delivery and efficiency in biological systems and subsequently their antihyperglycemic activity. Previously, roasting treatment was found to best enhance antioxidant activity in Moringa leaves compared to blanching, fermentation and drying [17]. Consequently, roasting and extraction conditions of antioxidants from Moronga leaves were optimized [18]. Extracts obtained at these optimal conditions were purified using solvent-solvent partitioning in solvents of increasing polarity and the antioxidant activity was concentrated in the ethyl acetate and butanol fractions. These two fractions were pooled together, freeze dried and nanoencapsulated using alginate (ALG) and chitosan (CTS) as polymers (submitted). ALG-CTS (3:1) nanocapsules had high Encapsulation Efficiency (87.6%) and Loading Capacity (13%). Up to 60 to 70% of bioactives from these nanocapsules were released in simulated gastric and intestinal fluids respectively after 400 min indicating good stability in these media (submitted). In this study, we investigate the antihyperglycemic

activity of nanocapsules containing the antioxidant rich fraction from roasted *Moringa oleifera* leaves (Moringa nanocapsules) in the control of hyperglycemia in rat models in comparison with the non-encapsulated extract (Moringa extract). Acute and sub-chronic toxicity of Moringa nanocapsules was equally evaluated in rat models to ascertain their safety.

Material and Methods

Antihyperglycemic activity of nanocapsules containing Roasted *Moringa oleifera* leaf antoxidants (Moringa Nanocapsules)

Experimental animals

Male Wistar rats obtained from the animal house of the Institute of Himalayan Bioresource Technology (IHBT, India) were used. They were kept in a 12-h light–dark cycle and at a temperature of 20-28 °C. The animals were allowed access to food and water ad libitum. The experiment received ethical clearance No IAEC/IHBT-P9/MAR2017 from the Institutional Animal Ethics Committee.

Antihyperglycemic activity of Moringa Nanocapsules

Antihyperglycemic activity of Moringa nanocapsules was assessed by oral glucose tolerance test [2]. Eighteen normal rats were divided into three groups of six rats each and fasted for 16 hours. Group I received blank nanocapsules devoid of antioxidants and served as control. Groups II and III received a dose of 200 mg/kg bw respectively, of Moringa nanocapsules or non-encapsulated roasted Moringa leaf AO-rich fraction (Moringa extract) suspended in distilled water. Fasting blood glucose (FBG) was taken initially and the test solutions administered. Thirty minutes after treatment, the experimental animals received 2g/kg bw of glucose orally and their glucose tolerance was monitored up to 3 hours. Blood samples were collected from the tail vein at 0, 30, 60, 90, 120 and 180 minutes after glucose administration. A hand glucometer (AccuChek Active, Roche Diagnostics GmbH, Germany) was used to determine blood glucose level. The variation in blood glucose was plotted as a function of time. The area under the curve (AUC) was calculated using the trapezoidal rule and antihyperglycemic activity of Moringa was expressed as the ratio of AUC from test group by the AUC obtained after intake of the reference glucose (control group).

Acute and sub-chronic toxicity of Moringa Nanocapsules

Toxicity assays were carried out following the guidelines of the Organization for Economic Cooperation and Development [19].

Acute toxicity

Rats of either sex (200-250 g) were randomly divided into five groups of six animals each. Graded doses of Moringa nanocapsules (200, 400, 800, 1600 and 3200 mg/kg) were administered orally by intubation. The treated rats were observed for 24 h post-treatment for mortality, behavioral changes (restlessness, dullness and agitation) and signs of toxicity.

Sub-chronic toxicity

Rats of either sex (200-250 g) were randomly allotted to two groups of 6 animals each. The animals in the test group were orally administered Moringa nanocapsule at the equivalent dose of 200 mg/kg daily for 14 days. The control group was orally supplemented with blank nanocapsules daily for the same period. Individual rat body weight was measured every two days and the variation in animals' weight throughout the course of the experiment was evaluated. The animals were closely observed for behavioral changes such as restlessness, hyperactivity, dullness and general morphological changes. On the 15th day of experimentation, blood samples were collected from the retro-orbital vein. One part of the blood was collected in heparinized tubes for hematological analysis while another part of blood was submitted to centrifugation at 4500 g for 20 minutes at 4-6 °C to obtain serum for the analysis of biochemical parameters.

Evaluation of hematological parameters

Hematological analyses were performed on blood samples using an automated hematology analyzer (Humacount XT-1800iV, Sysmex, Germany). The recorded parameters were white blood cells (WBC), red blood cells (RBC), lymphocytes (LYM), neutrophils (NEU), monocytes (MONO), hemoglobin (HGB), hematocrit (HCT), platelets (PLT), eosinophils (EO), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), monocytes (MONO), basophiles (BASO), standard deviation in red cell distribution width (RDW-SD), coefficient of variation in red cell distribution width (RDW-CV), platelet distribution width (PDW), mean platelet volume (MPV) and platelet larger cell ratio (P-LCR).

Evaluation of biochemical parameters

Blood serum samples were used to quantify some biochemical parameters (creatinine, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase (APP), total protein, albumin and glucose), using Erba kits in an automated biochemical analyzer (Erba Mannheim 200, Germany). Detailed procedures were performed according to the kit manufacturer's instructions.

Statistical analysis

All measurements were performed in triplicate in each experiment. Results are presented as means ± SD. Statistical analysis was performed by one-way ANOVA using Stat graphics centurion XVI with $p < 0.05$ considered to be statistically significant.

Results and Discussion

Antihyperglycemic activity of Moringa nanocapsules

Figure 1 depicts the effect of a single dose oral administration of Moringa nanocapsules (eq 200 mg AO-rich fraction per kg BW)

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or non-encapsulated AO-rich fraction (200 mg/kg bw) of roasted Moringa leaf extract on oral glucose tolerance in normal rats. A rapid and intense glycemic load was observed in rats of the control group that peaked 80 minutes after glucose administration. On the contrary, the glycemic load was significantly ($p < 0.05$) inhibited in test rats which received either Moringa nanocapsules or the non-encapsulated Moringa extract 30 minutes prior to glucose loading. Comparing both treatments, the inhibition was more pronounced with nanocapsules than with the non-encapsulated fraction although glucose level in both cases peaked at 80 minutes and then decreased. These results suggest that the AO-rich fraction of roasted Moringa leaf extract have antihyperglycemic activity and enhance glucose tolerance in rats; and that nanoencapsulation reinforces this effect. The antihyperglycemic activity was evaluated by measuring the area under the curve (AUC) in the control and test groups.

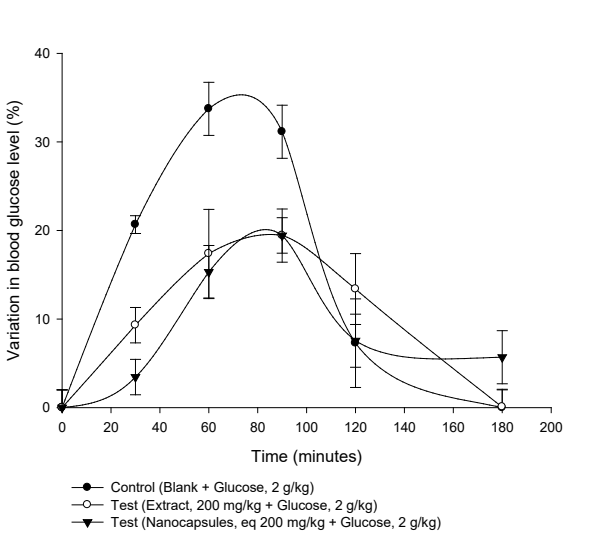

Figure 1: Antihyperglycemic effect of Moringa nanocapsules and non-encapsulated AO-rich fraction of M. oleifera L. leaf extract in normal rats.

Compared to the control group (AUC = 19) there was an important reduction in the AUC of nanocapsules treated rats (AUC = 11) as against AUC of 13.5 for the non-encapsulated powder fraction. Hence, based on the AUC, oral administration of Moringa-loaded nanocapsules resulted in a 42% improvement in glucose tolerance in rats compared to the control group as against 29% enhancement observed with the non-encapsulated fraction of roasted Moringa leaf extract. This observation highlights the greater efficacy of nanocapsules; which is 13 % or 1.4 times more effective than the non-encapsulated powder fraction. The improvement of glucose tolerance is of importance because glucose intolerance is considered as an intermediate condition in the transition between normal blood glucose levels and diabetes (especially type 2 diabetes) [20]. Several studies also reported ameliorating effects of Moringa leaf extracts on glucose tolerance in experimental animals [7,21,22]. The greater enhancement of antihyperglycemic activity observed with encapsulated AO-rich fraction is in agreement with previous report that nanoencapsulation improves efficiency of bioactives [14,23]. After oral ingestion of glucose, homeostasis of blood glucose depends mainly on insulin secretion, glucose absorption rate through intestinal epithelium and glucose uptake by peripheral tissues. Previous work by [1,20] showed that Moringa leaf extract inhibits intestinal glucose absorption in diabetic rats by inhibiting carbohydrases. This could be attributed to their phenolic content.

Ader et al. [24], suggested that quercetin glucosides namely isoquercetin and quercetin-4'-glucoside (spiraeosid) competitively inhibit sodium dependent mucosal uptake of the non-metabolisable glucose analogue methyl-α-D-glucopyranoside via SGLT-1 using rat mid-jejunum. Furthermore, Cermak et al. [25] in a similar experiment with SGLT-1-containing brush-border-membrane vesicles from porcine jejunum, showed that Q3G inhibits not only Na+-dependent but also Na+-independent uptake of glucose. Hence, the competitive inhibition of the intestinal sodium glucose transporter-1 (SGLT-1) by quercetin glucosides also found in roasted Moringa leaf extract [20] can be suggested as explanation for the observed blood glucose lowering effect. Rutin present in significant quantity in roasted Moringa leaf extract [20], have equally been shown to effectively lower plasma glucose by 64 % in diabetic rats when taken orally at doses of 100 mg/kg bw [26]. Oldoni et al. [7] equally attributed the antihyperglycemic activity of Moringa leaf extracts to the presence of glycosylated flavonoids. Other probable mechanisms supporting the glucose lowering activity of Moringa leaf extract can be linked to the insulinotropic effect of bioactive in Moringa

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which have demonstrated ability to enhance insulin secretion in vivo and in vitro [27-29]. It has been hypothesized that flavonoids in Moringa scavenge reactive oxygen species released from the mitochondria thereby protecting the beta cells and in turn keeping hyperglycemia under control [30].

Toxicological aspects of Moringa nanocapsules

International regulations relating to human health require that all new pharmaceutical and nutraceutical products are tested for their safety, and key to ensuring this is to conduct toxicity tests [31].

Acute toxicity

There was neither mortality nor signs of any toxicity recorded in animals receiving nanocapsules doses as higher as 3200 mg/kg bw. This observation attests to the relatively low toxicity of Moringa-loaded nanocapsules because mortality is the main criterion in assessing the acute toxicity of a drug or nutraceutical [31]. Previous work by Laleye et al [5], reported that doses of up to 2000 mg/kg were non-toxic to rats in acute oral toxicity test.

Sub-chronic toxicity

Sub-chronic toxicity was evaluated in normal rats to check any adverse effects that could occur in organs in relation with the consumption of the formulated nanocapsules. Figure 2 depicts the variation in body weight of normal rats fed nanoencapsulated AO-rich fraction of roasted Moringa leaf extract. The body weight increased in both the control group fed the blank nanocapsules and the test group receiving Moringa nanoencapsules. Between the 2nd and the 8th day of experimentation, body weight gain was significantly ($p < 0.05$) lower in rats receiving the Moringa nanocapsules compared to the control group; probably due to loss of appetite and or reduction in food intake. However, the body weight of rats in the test group was rapidly normalized with important body weight gain observed from the sixth day of nanocapsules administration (Figure 2). After 14 days of nanocapsules administration, body weight gain in treated group was higher than in control; indicating that treated rats got rapidly adapted to nanocapsules administration, and that Moringa could enhance weight gain. Changes in body weight are indication of adverse effects of drugs and chemicals in the body.

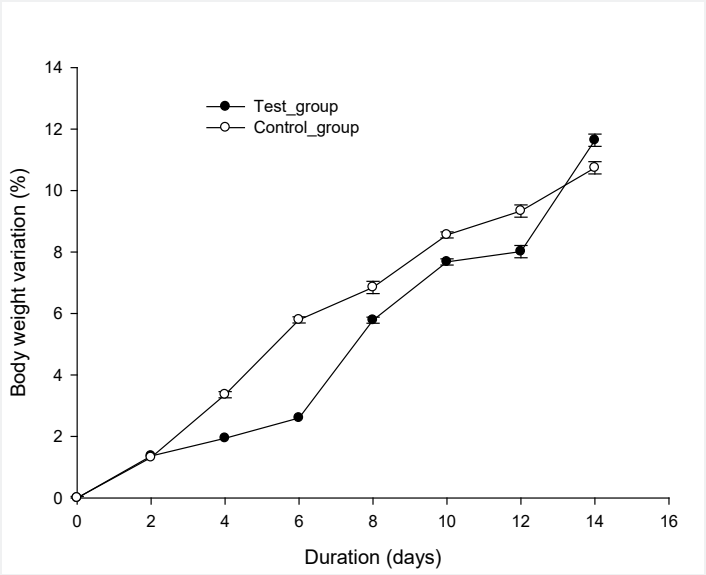

Figure 2: Variation in the body weight of normal rats fed with nano encapsulated AO-rich fraction of Moringa roasted leaf extract.

The effect of a drug on body weight is considered significant when modifications greater than 10% from the initial body weight occur [32]. Previous studies had reported no toxic effect in rats fed 2000 mg/kg bw *Moringa oleifera* leaves for 2 weeks [5,8]. It has been suggested that the hematological system has a higher predictive value for toxicity in living organisms and analysis of blood parameters is highly relevant to risk evaluation. Tables 1 & 2 present respectively hematological and biochemical parameters in normal rats, and rats supplemented with Moringa nanoencapsules. There were no significant changes ($p>0.05$) in hematological (Table 1) and biochemical (Table 2) parameters of normal rats receiving Moringa nanocapsules compared to the control group throughout the course of the sub-chronic toxicity evaluation. This observation suggests that nanoencapsules formulated using AO-rich fraction of roasted Moringa leaf extract have no adverse effect on the blood system of rats.

Laleye et al [5], had equally reported no changes in hematologic and biochemical parameters of rats fed aqueous extracts of Moringa leaves at a dose of 2000 mg/kg for 14 days, attesting to the safety of Moringa leaves. Unchanged levels of creatinine, transaminases (ALAT and ASAT) and glucose in test compared

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to control group (Table 2) suggests that the nanoencapsulated AO-rich fraction of roasted Moringa leaf extract has no adverse effects respectively on rat kidneys, liver and pancreas function. Creatinine is a waste product from creatine metabolism in muscle that is normally eliminated by kidneys, hence, its accumulation in the blood is evidence of kidney impairment. Transaminases (ALAT and ASAT) are biomarkers of liver activity and changes in their blood level is related to liver dysfunction [33]. Therefore, on the basis of these observations on hematological and biochemical parameters of normal rats, it can be affirmed that consumption of nanocapsules containing the AO-rich fraction of roasted Moringa leaf extract has no adverse effects on renal, hepatic, hematopoietic and pancreatic functions in normal animals.

Table 1: Hematological parameters in normal rats supplemented with nanocapsules of AO-rich fraction of roasted Moringa leaf extract.

	Normal control	NC200
WBC (10^3/µL)	9.4±0.6[a]	9.3±1.3[a]
RBC (10^6/µL)	8.0±0.4[a]	7.5±0.9[a]
HGB (g/dL)	12.6±1.2[a]	12.5±1.7[a]
HCT (%)	38.2±1.4[a]	36.5±3.6[a]
MCV (fL)	47.8±0.5[a]	48.6±1.4[a]
MCH (pico g)	15.8±0.8[a]	16.5±0.5a
MCHC (g/dL)	33.0±2.1[a]	34.1±1.6[a]
PLT (10^3/µL)	741±77[a]	824±73[a]
RDW-SD (fL)	25.6±0.4[a]	26.0±0.6[a]
RDW-CV (%)	16.1±0.6[a]	16.0±1.2[a]
PDW (fL)	7.2±0.3[a]	7.4±0.2[a]
MPV (fL)	6.7±0.1[a]	6.8±0.4[a]
P-LCR (%)	4.9±1.0[a]	4.8±0.6[a]
PCT (%)	0.42±0.1[a]1	0.5±0.1[a]
NEUT (10^3/µL)	1.8±0.3[a]	2.4±0.3[a]
LYM (10^3/µL)	7.2±0.2[a]	6.4±1.2[a]
MONO (10^3/µL)	0.25±0.07[a]	0.25±0.07[a]
EO (10^3/µL)	0.12±0.01[a]	0.17±0.04[a]
NEUT (%)	19±3[a]	26±5[a]
LYMPH (%)	77±3[b]	69±4[a]
MONO (%)	2.6±0.6[a]	2.7±0.5[a]
EO (%)	1.3±0.1[a]	1.9±0.6[a]
BASO (%)	0.16±0.11[a]	0.08±0.04[a]

Source: NC200: Rats supplemented with nanocapsules at a dose of 200 mg eq AO-rich fraction/kg bw, WBC: white blood cells; RBC: red blood cells; HGB: hemoglobin; HCT: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; PLT: platelet; LYM: lymphocytes; NEUT: neutrophils; EO: eosinophils; MONO: monocytes; BASO: basophiles; RDW-SD: standard deviation in red cell distribution width; RDW-CV: coefficient of variation in red cell distribution width; PDW: platelet distribution width; MPV: mean platelet volume; P-LCR: platelet larger cell ratio. Values are expressed as mean ± SD, n = 6 in each group. Means followed by different letters in the same row are significantly different ($p < 0.05$).

Table 2: Biochemical parameters in normal rats supplemented with nanocapsules of AO-rich fraction of roasted Moringa leaf extract.

	ALB (g/dL)	GLU (mg/dL)	T. PRO (g/dL)	CRE (mg/dL)	ALAT (U/L)	ASAT (U/L)	ALP (U/L)
Normal control	5.3±0.1[a]	156±17[a]	7.2±0.4[a]	0.64±0.01[a]	90±4[a]	204±23[a]	598±35[a]
NC200	5.4±0.2[a]	144±15[a]	7.3±0.3[a]	0.63±0.03[a]	91±8[a]	199±21[a]	529±57[a]

Source: NC200: nanocapsules at the dose of 200 mg eq AO-rich fraction/kg bw, ALB: albumin, GLU: glucose; T. PRO: total protein, CRE: creatinine, ALAT: alanine aminotransaminase; ASAT: aspartate aminotransaminase. Values are expressed as mean ± SD, n = 6 in each group. Means followed by different letters in the same column are significantly different ($p < 0.05$).

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Conclusion

Nanoencapsules formulated using antioxidant-rich fraction of roasted Moringa leaf extract improves its antihyperglycemic activity 1.3 times over that of the non-encapsulated fraction in normal rats. Nanocapsules are more efficient in improving glucose tolerance (42%) compared to the non-encapsulated form (29%). This affirms the efficiency of nanoencapsulation in the delivery of bioactives. Consumption of nanocapsules loaded with antioxidant-rich fraction of roasted Moringa leaf extract showed no observed toxicity in rat models, suggesting that they are relatively safe. This work has important implication in the formulation of Moringa based nutraceuticals for the management of type II diabetes.

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