Curcumin ameliorates gastrointestinal dysfunction and oxidative damage in diabetic rats

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Abstract
Diabetes is known to be associated with gastrointestinal complications characterized by nausea, vomiting, early satiety, bloating, and abdominal discomfort or pain commonly occurring in the advanced stages of the disease. Curcumin is the lipid-soluble antioxidant obtained from the rhizomes of *Curcuma longa* Linn, also known as turmeric. Curcumin targets multiple chemotherapeutic and oxidative stress pathways and has demonstrated safety and tolerability in humans, supporting its potential as a therapeutic agent; however, literature lacks conclusive evidence supporting its use as a therapeutic agent for the treatment of diabetes induced gastrointestinal complications. Hence, Curcumin was given in different doses to SD rats after 4 weeks of diabetic GI complication induction. At the end of 4 weeks, significant GI dysfunction characterized by weight loss, delayed gastric emptying and intestinal transit associated with reduction in antioxidant enzyme levels and increased lipid peroxidation was observed. Upon treatment with Curcumin for further 4 weeks, reversal of GI dysfunction evidenced by restoration of body weight, GI emptying, intestinal transit, and restoration of antioxidant enzyme level and lipid peroxidation proves the beneficial role of Curcumin in diabetes induced GI complications due to its antioxidant potential.

Keywords: Diabetic complications, Gastroparesis, Gastric emptying, Intestinal transit, Oxidative stress, Antioxidant, Diabetes, Curcumin

1. Introduction
Diabetes mellitus, a common metabolic disorder resulting from defect in insulin secretion or action or both, is characterized by hyperglycemia often accompanied by glycosuria, polydypsia, and polyurea. The World Health Organization (WHO) estimates that worldwide, there are currently 220 million people living with diabetes. Diabetes is becoming an important chronic disease in India. In 2010, 45.5 million individuals had diabetes. In 2010, there were 45.2 million cases of type 2 diabetes mellitus in India. Of these, 14.7 million and 30.5 million were found in rural and urban areas, respectively. By the end of 2020, Datamonitor estimates that the total prevalent cases of type 2 diabetes will increase to 69.7 million.

During diabetes, persistent hyperglycemia and various contributing abnormalities are known to cause various complications such as diabetic retinopathy, cardiomyopathy, nephropathy, gastropathy, neuropathy, etc; one of them is increased production of free radicals especially reactive oxygen species (ROS), causing glucose auto-oxidation and protein glycosylation. Gastroparesis is a chronic complication of diabetes, also called delayed gastric emptying characterized by nausea, vomiting, early satiety, bloating, and abdominal discomfort or pain. Gastroparesis is a manifestation of diabetic autonomic neuropathy. Although often believed to be more common in patients with type 1 diabetes, it is actually also quite common in patients with type 2 diabetes.

In the diabetic condition the formation of ROS cause the oxidative stress in the body, which might be related to the development of gastric organic disorders such as gastritis, gastric ulcers, and gastric cancer, as well as functional disorders such as functional dyspepsia. Oxidative stress, which is a state of elevated levels of reactive oxygen species (ROS), causes a variety of conditions that stimulate either additional ROS production or a decline in antioxidant defenses. Several phenotypes of gastrointestinal diseases, such as peptic ulcer disease and gastroparesis, are known to be related to antioxidant property dysfunction.

The present study was undertaken to investigate the therapeutic potential of Curcumin, a dietary spice with antioxidant activity. Curcumin is a potent antioxidant and anti-inflammatory agent that has the potential to provide far-reaching health benefits. It has been shown to be helpful in rheumatoid arthritis, inflammatory bowel disease, pancreatitis, Alzheimer’s disease, heart disease, diabetic retinopathy, and cancer. Curcumin can protect against colon, intestinal, oral, and skin cancer. In addition, Curcumin prevents diabetes-induced oxidative stress, reduces blood glucose and increase plasma insulin, act as gastroprotectant against irritants, protective action against vascular...
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Research Article

dementia by exerting antioxidant activity. Curcumin is an ingredient that is naturally in the turmeric spice; a wealth of scientific data shows Curcumin (curcuminoids) has powerful anti-inflammatory, anti-tumor and antioxidant properties. In Indian system of Ayurvedic medicine, it has been recognized for thousands of years as a key balancing and detoxifying herb and is considered to be one of the very best all-round herbs for general well-being.

As it was proved by the researchers that oxidative stress is one of the causes for diabetes and its complications, this study was undertaken to investigate the beneficial effects of Curcumin in the treatment of diabetic gastropathy using rat as an animal model. The purpose of this study was to focus attention on the importance of early intervention in the development of diabetic gastropathy in order to prevent the debilitating symptoms, enhance glucoregulation associated with it and to improve quality of life.

2. Materials

2.1 Animals
Healthy male Sprague-Dawley rats (250-300gm) were used for the pharmacological screening. The animals were housed in polypropylene cages with wire mesh top and husk bedding and maintained under standard environmental conditions (25 ± 2°C, relative humidity 60 ± 5%, light-dark cycle of 12 hours each) and fed with standard pellet diet (Trimurtti feeds, Nagpur) and water ad libitum, were used for the entire animal study. The experiments were performed during day (08:00-16:00 hours). Rats were housed and treated according to the rules and regulations of CPCSEA and IAEC. The protocols for all the animal studies were approved by the Institutional Animal Ethical Committee (IAEC).

Groups and Treatment:
The animals were randomly divided into mainly two groups as described below.

I. Non-diabetic:
   a) Normal [n=8]
   b) Normal+ D1 [20mg/kg] [n=8]
   c) Normal+ D2 [40mg/kg] [n=8]

II. Diabetic:
   a) Alloxan [n=8]
   b) Alloxan + D1 [20mg/kg] [n=8]
   c) Alloxan + D2 [40mg/kg] [n=8]

D1= Curcumin treated at low dose,
D2= Curcumin treated at high dose.

Rats were grouped as non-diabetic and diabetic. Alloxan (120 mg/kg, ip) was used to induce hyperglycemia in rats of the diabetic group and was maintained during the time of the study by the reinforcement of 100 mg/kg alloxan (ip) at day 12 and 21 after the first administration. Curcumin in 0.5-1% CMC as a vehicle was given orally in two doses i.e. lower dose, 20mg/kg BW and higher dose, 40mg/kg BW daily for 4 weeks after induction of diabetic gastropathy.

2.2 Drugs and Chemicals:
Crystalline Curcumin, alloxan, Phenylmethane sulfonylfluoride (PMSF), thiobarbituric acid were purchased from Lobachemie, India. 5'-5'-dithiobis-2-nitrobenzoic acid (DTNB) was purchased from Sigma-Aldrich, USA. Total protein assay kit and Glucose GOD-POD kit were purchased from Ambica Diagnostics, India. All other chemicals were of analytical grade.

3. Methods

3.1 Induction of Diabetes using alloxan rat model

3.1.1 Assessment of Diabetes
Rats were made diabetic by intraperitoneal injection of alloxan (hydrate) at a dose of 120 mg/kg. Alloxan was first weighed individually for each animal according to the body weight and solubilized with 0.5 ml of normal saline. It was then injected to 18 hr. fasted diabetic group rats to induce hyperglycemia and was maintained during the time of the study by the reinforcement of 100 mg/kg alloxan (ip) at day 12 and 21 after the first administration23,24.

3.1.2 Collection of Blood samples
All rats fasted for 18 h prior to the determination of blood glucose levels on day 3, 15 and 57. During this time interval, 1.0 ml of blood was withdrawn from the retro orbital plexus under light ether anesthesia and centrifuged at 3000 rpm to separate plasma and cells. The plasma was used to estimate glucose levels.

3.1.3 Determination of blood glucose
The plasma glucose levels were estimated using the glucose oxidase-peroxidase (GOD-POD) method with the Glucose GOD-POD kit. Blood glucose levels were expressed as mg/dl. The rats showing a fasting glucose of more than 170 mg/dl three days after the first administration of alloxan were considered diabetic.

3.1.4 Assessment of Diabetic Gastropathy Symptoms
Diabetic gastropathy was assessed by determining food intake, body weight, gastric emptying and intestinal transit using reported methods.

3.1.5 Measurement of body weights
Individual body weights of rats were recorded at 0th, 12th, 21st and 57th day of study.
3.1.6 Measurement of food intake
Average food intakes were recorded at 0th week, 4th week, and 8th week during study.

3.2 Estimation of GI parameters
3.2.1 Gastrointestinal emptying
The gastric emptying of a non-nutrient solution was assessed by previously reported method. On day 57, the overnight fasted rats from both the groups received 1.5 ml test meal consisting of 0.05% phenol red in 1.5% aqueous methylcellulose solution by intragastric route. Animals were sacrificed after thirty minutes. Stomach was excised and placed on the formation of a red chromophore that absorbs at 532 nm. The chromophore formation from the administration of test meal was centrifuged at 16000 × g for 1 h in a cooling centrifuge at 4°C. The supernatant was mixed with 4.0 ml of 0.5 N NaOH and absorbance was read spectrophotometrically at 560 nm and considered as final absorbance, whereas the absorbance observed in the supernatant of stomach and its contents, isolated just after orogastric administration of test meal was considered as the initial absorbance. The percentage gastric emptying in rat was calculated by the formula:

\[
\text{GI emptying} = 100 - \frac{\text{Amount of Phenol red recovered after 20 min}}{\text{Amount of Phenol red recovered after 0 min}} \times 100
\]

3.2.2 Measurement of Intestinal transit time
Intestinal transit time was assessed by charcoal meal method. On day 57, the overnight fasted rats from both non-diabetic and diabetic groups received charcoal meal containing 10% activated charcoal and 5% gum acacia orally (2.0 ml/rat). After 15 minutes, the rats were sacrificed by deep ether anaesthesia. The small intestine was removed from the pyloric sphincter to the ileocecal junction. Avoiding the stretching, total length of intestine and the distance traveled by the charcoal meal was noted. The intestinal transit was calculated as percent intestinal transit using following formula-

\[
\% \text{ Intestinal Transit} = \frac{\text{Distance travelled by charcoal meal}}{\text{Total length of small intestine}} \times 100
\]

3.3 Evaluation of oxidative stress
3.3.1 Preparation of tissue homogenate
After receiving the treatments for 56 days, rats were sacrificed using deep ether anesthesia on 57th day. Stomach and intestine were removed and thoroughly washed with ice-cooled 0.1 M phosphate buffered saline (PBS) containing 0.1 mmol/L phenylmethanesulfonyl fluoride. The individual tissue was blotted dry and homogenized in 0.1 M PBS in an ice bath to prepare a 10% suspension. This suspension was then centrifuged at 16000 × g for 1 h in a cooling centrifuge at 0°C. The supernatant was employed to assess the parameters of oxidative stress after estimating the protein content.

3.3.2 Total Protein (Biuret method)
Total protein estimation was based on the most common and simple biuret reaction using Total protein Estimation Kit.

3.3.3 Lipid peroxidation (LPO) in tissue
MDA, an end product of fatty acid peroxidation, was measured in tissue homogenates as described. The method was based on the formation of a red chromophore that absorbs at 532 nm. The chromophore form from the reaction of thiobarbituric acid (TBA) with malondialdehyde (MDA) and other break-down products of peroxidized lipids, collectively called thiobarbituric acid reactive substances (TBARS). All samples were run in duplicate and peroxidation was expressed as nm MDA/mg protein.

3.3.4 Superoxide dismutase (SOD) activity
Tissue SOD activities were determined by the method of Marklund et al. The ability of the enzyme to inhibit the autoxidation of pyrogallol in the presence of EDTA was used as a measure of SOD activity. One unit of the enzyme activity was defined as 50% inhibition of the rate of the autoxidation of pyrogallol as determined by the change in absorbance/min at 420 nm. The activity of SOD is expressed as units/mg protein. The assay was performed in duplicate in a two-fold concentration range.

3.3.5 Catalase (CAT) activity
50 μl of the tissue homogenate was added to a cuvette containing 2 ml of phosphate buffer (pH 7.0) and 1 ml of 30 mM H₂O₂. Catalase activity was measured at 240 nm for 1 min using spectrophotometer. The molar extinction coefficient of H₂O₂, 43.6 M cm⁻¹ was used to determine the catalase activity. One unit of activity is equal to one millimoles of H₂O₂ degraded per minute and is expressed as units per milligram of protein.

3.3.6 Reduced glutathione (GSH)
Reduced glutathione was measured by addition of 0.2 ml of tissue homogenate to 1.8 ml distilled water followed by 3.0 ml of precipitating mixture (1.67 g metaphosphoric acid, 0.2 g EDTA and 30 g NaCl to make 100 ml of solution). It was centrifuged at 5000 X g for 5 min and 1 ml of the filtrate was added to 1.5 ml of the phosphate solution, followed by the addition of 0.5 ml of DTNB reagent. The optical density was measured at 412 nm using spectrophotometer.
3.4 Statistical analysis

Data were analyzed using Graph Pad Prism version 5.0 for Windows (Graph Pad Software, San Diego, CA, USA). Data of blood glucose, body weight and food intake were statistically analyzed using repeated measure two way ANOVA. All other data were analyzed using unpaired, One-tailed Student’s t-tests. Unless otherwise indicated, data were presented as the mean values ± SEM. The groups of experimental rats were compared to the appropriate normal groups. Differences were considered significant when \( p < 0.05 \).

4. Results

4.1 Body weight

**Table 1: Body weight (g) of normal and diabetic rat, treated, untreated with curcumin**

<table>
<thead>
<tr>
<th>Groups</th>
<th>O day</th>
<th>12 day</th>
<th>21 day</th>
<th>57 day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-diabetic</td>
<td>266.25±13.44</td>
<td>275.0±10.20</td>
<td>272.5±16.52</td>
<td>260.0±9.12</td>
</tr>
<tr>
<td>Normal</td>
<td>267.5±13.76</td>
<td>272.5±13.50</td>
<td>270.0±12.24</td>
<td>261.25±9.65</td>
</tr>
<tr>
<td>Normal+D1</td>
<td>272.5±12.33</td>
<td>290.0±4.08</td>
<td>285.0±25.33</td>
<td>275.0±17.55</td>
</tr>
<tr>
<td>Normal+D2</td>
<td>251.25±8.26</td>
<td>217.5±13.69*</td>
<td>177.5±11.8***</td>
<td>165.0±7.36***</td>
</tr>
<tr>
<td>Diabetic Alloxan</td>
<td>272.5±16.0</td>
<td>265.0±11.90*</td>
<td>146.2±6.25</td>
<td>222.5±11.08*</td>
</tr>
<tr>
<td>Diabetic Alloxan+D1</td>
<td>266.25±13.44</td>
<td>227.5±13.76</td>
<td>185.0±15.54</td>
<td>258.7±19.18***</td>
</tr>
<tr>
<td>Diabetic Alloxan+D2</td>
<td>227.5±13.76</td>
<td>258.7±19.18***</td>
<td>185.0±15.54</td>
<td>258.7±19.18***</td>
</tr>
</tbody>
</table>

\( \text{n}=8 \)

Values are expressed as Mean ± SEM, *\( p<0.05 \), ***\( p<0.0001 \), when compared with corresponding control group.

Results of body weight (Table 1) demonstrate significant decrease in body weight on 8th week in diabetes induced rats compared to normal (\( p<0.0001 \)). Upon treatment with Curcumin to diabetic group rats at both the doses, body weight was significantly increased as compared to alloxan alone treated group (\( p<0.0001 \)).

4.2 Blood Glucose level

**Table 2: Plasma glucose level (mg/dl) of normal and diabetic rat, treated, untreated with Curcumin**

<table>
<thead>
<tr>
<th>Groups</th>
<th>0 day</th>
<th>3 day</th>
<th>15 day</th>
<th>57 day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-diabetic</td>
<td>115.6±14.33</td>
<td>98.20±10.49</td>
<td>114.97±12.06</td>
<td>110.66±10.55</td>
</tr>
<tr>
<td>Normal</td>
<td>117.02±13.7</td>
<td>103.74±10.35</td>
<td>110.91±12.61</td>
<td>107.38±10.7</td>
</tr>
<tr>
<td>Normal+D1</td>
<td>109.08±12.1</td>
<td>92.40±9.72</td>
<td>104.75±13.41</td>
<td>122.03±18.08</td>
</tr>
<tr>
<td>Diabetic Alloxan</td>
<td>106.4±5.56</td>
<td>328.2±24.84***</td>
<td>288.49±44.65***</td>
<td>286.16±69.05***</td>
</tr>
<tr>
<td>Diabetic Alloxan+D1</td>
<td>94.47±10.56</td>
<td>270.2±44.08</td>
<td>252.59±27.09</td>
<td>145.45±8.02***</td>
</tr>
<tr>
<td>Diabetic Alloxan+D2</td>
<td>100.56±11.1</td>
<td>295.93±50.62</td>
<td>273.1±24.92</td>
<td>139.60±7.34***</td>
</tr>
</tbody>
</table>

\( \text{n}=8 \)

Values are expressed as Mean±SEM, ***\( p<0.0001 \) when compared with corresponding control group.

Blood glucose level data (Table 2) shows significant increase in the blood glucose levels in the diabetic group at various time intervals (i.e. day 3, 15 and 57) as compared to normal (\( p<0.0001 \)). Curcumin treatment to diabetic group rats at both the doses significantly reduced blood glucose level to normal, as compared to alloxan alone treated group (\( p<0.0001 \)).

4.3 Food Intake

**Table 3: Food intake (g) of normal and diabetic rat treated, untreated with Curcumin**

<table>
<thead>
<tr>
<th>Groups</th>
<th>0 week</th>
<th>4 week</th>
<th>8 week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-diabetic</td>
<td>13.75±2.39</td>
<td>13.25±2.39</td>
<td>16.75±2.68</td>
</tr>
<tr>
<td>Normal</td>
<td>14.5±2.10</td>
<td>12.5±2.53</td>
<td>14.0±2.27</td>
</tr>
<tr>
<td>Normal+D1</td>
<td>14.7±1.93</td>
<td>14.25±2.46</td>
<td>16.25±2.25</td>
</tr>
<tr>
<td>Normal+D2</td>
<td>12.0±1.08</td>
<td>7.50±0.95</td>
<td>9.50±1.04*</td>
</tr>
<tr>
<td>Diabetic Alloxan</td>
<td>13.75±2.42</td>
<td>10.0±0.70</td>
<td>16.75±0.47*</td>
</tr>
<tr>
<td>Diabetic Alloxan+D1</td>
<td>12.0±1.68</td>
<td>8.0±1.58</td>
<td>17.75±0.62*</td>
</tr>
<tr>
<td>Diabetic Alloxan+D2</td>
<td>12.0±1.68</td>
<td>8.0±1.58</td>
<td>17.75±0.62*</td>
</tr>
</tbody>
</table>

\( \text{n}=8 \)

Values are expressed as Mean±SEM, *\( p<0.05 \) when compared with corresponding control group.

Food intake data revealed (Table 3) significant reduction in food consumption in diabetic rat after 4 weeks as compared to normal rat (\( p<0.05 \)). Curcumin treatment to diabetic group rats at both the doses significantly increased food intake (\( p<0.05 \)).
Diabetes is a metabolic disorder characterized by hyperglycemia. Persistent hyperglycemia for long period is known to cause various complications of diabetes; one of them is gastrointestinal complication characterized by delayed gastric emptying and intestinal transit. In this study, animal model of diabetic GI complication was developed by giving alloxan. As alloxan is producing reversible hyperglycemia, multiple doses of alloxan were given on day 12 and 21 in order to maintain persistent hyperglycemia through out the study period. When alloxan was given the glucose level increased and body weight loss was observed due to poor food intake which is one of the symptoms of GI complication. It is known that persistent hyperglycemia is responsible to produce oxidative stress via generation of free radicals and decreases antioxidant enzyme level producing damage to various tissues. In our study, when diabetes was induced by injecting alloxan and persistent hyperglycemia was maintained by reinforcement of multiple alloxan doses, GI complications were developed which were evidenced by decreased body weight and food intake. At the end of 8th week, GI function parameters such as gastric emptying and intestinal transit were determined. A significant reduction in gastric emptying and intestinal transit was observed in diabetic vehicle treated rats as compared to normal non-diabetic rats. Upon determination of oxidative stress parameters, lipid peroxidation was increased and antioxidant enzyme levels were decreased significantly in diabetic rat at the end of 4th week of diabetes induction (P<0.0001). Curcumin treatment for 4 weeks restored gastric emptying and intestinal transit in diabetic group rats.

4.5 Oxidative stress parameters

**Table 5: Oxidative stress parameters in normal and diabetic rat treated, untreated with Curcumin**

<table>
<thead>
<tr>
<th>Groups</th>
<th>LPO (MDA nM/g protein)</th>
<th>SOD (Units/mg protein)</th>
<th>CAT (Units/mg protein)</th>
<th>GSH (Units nM/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-diabetic</td>
<td>Normal</td>
<td>163.6±9.6</td>
<td>183.9±4.02</td>
<td>251.6±15.07</td>
</tr>
<tr>
<td></td>
<td>Normal+D1</td>
<td>176.1±9.25</td>
<td>190.5±17.32</td>
<td>243.3±17.74</td>
</tr>
<tr>
<td></td>
<td>Normal+D2</td>
<td>174.0±10.74</td>
<td>200.5±1.02</td>
<td>235.0±11.75</td>
</tr>
<tr>
<td>Diabetic</td>
<td>Alloxan</td>
<td>106.1±9.6*</td>
<td>117.9±4.39*</td>
<td>151.3±16.67**</td>
</tr>
<tr>
<td></td>
<td>Alloxan+D1</td>
<td>165.5±11.97*</td>
<td>165.1±10.6*</td>
<td>213.8±9.18*</td>
</tr>
<tr>
<td></td>
<td>Alloxan+D2</td>
<td>185.4±21.79**</td>
<td>180.1±10.61**</td>
<td>263.8±19.44***</td>
</tr>
</tbody>
</table>

n=8

Values are expressed as Mean±SEM,

*** p<0.0001 when compared with corresponding control group

**p<0.001 when compared with corresponding control group

*p<0.05 when compared with corresponding control group

Results (Table 5) of this study show that administration of alloxan for a period of 4 weeks induces oxidative stress in diabetic rat. Oxidative stress was indicated by the levels of oxidative stress markers, including lipid peroxidation, reduced glutathione, superoxide dismutase and catalase in the tissue. The antioxidant components, such as SOD, CAT and GSH, were significantly lower in the gastopathic rats. Curcumin treatment for 4 weeks in gastopathic rats, reduced lipid peroxidation and increased antioxidant enzyme levels to near normal (P<0.05).

5. Discussion

Diabetes is a metabolic disorder characterized by hyperglycemia. Persistent hyperglycemia for long period is known to cause various complications of diabetes; one of them is gastrointestinal complication characterized by delayed gastric emptying and intestinal transit. In this study, animal model of diabetic GI complication was developed by giving alloxan. As alloxan is producing reversible hyperglycemia, multiple doses of alloxan were given on day 12 and 21 in order to maintain persistent hyperglycemia through out the study period. When alloxan was given the glucose level increased and body weight loss was observed due to poor food intake which is one of the symptoms of GI complication. It is known that persistent hyperglycemia is responsible to produce oxidative stress via generation of free radicals and decreases antioxidant enzyme level producing damage to various tissues. In our study, when diabetes was induced by injecting alloxan and persistent hyperglycemia was maintained by reinforcement of multiple alloxan doses, GI complications were developed which were evidenced by decreased body weight and food intake. At the end of 8th week, GI function parameters such as gastric emptying and intestinal transit were determined. A significant reduction in gastric emptying and intestinal transit was observed in diabetic vehicle treated rats as compared to normal non-diabetic rats. Upon determination of oxidative stress parameters, lipid peroxidation was increased and anti-oxidant enzyme levels were decreased significantly in diabetic animals. It has been proved that hyperglycemia causes free radical generation which produces oxidative stress and consequent degeneration of tissues which is evidenced in our study.

The possible underlying mechanism of gastropathy induced by diabetic condition has been reported to be related to the oxidative stress caused by the production of hydroxyl radicals during autoxidation and the inhibition of (ICC) resulting in excessive oxidative stress and leading to tissue damage. Previous studies demonstrated that diabetic condition could produce the gastropathic complication in animals, and oxidative stress has been shown to play an important role in gastroinestinal function parameters such as gastric emptying and intestinal transit was significantly decreased in diabetic rat at the end of 4th week of diabetes induction (P<0.0001). Curcumin treatment for 4 weeks restored gastric emptying and intestinal transit in diabetic group rats.
Curcumin is a well known antioxidant. It is useful in treatment of various diseases and also used as an immune enhancer. It can cross blood brain barrier. Thus, it can act centrally as well as peripherally. Curcumin treatment was initiated at the end of 4th week when GI complications were developed and continued for further 4 weeks. At the end of 8th week when GI and oxidative stress parameters were determined a significant amelioration was observed at both the doses. This might be due to its antioxidant activity. Thus, results of our study strongly suggest that, daily treatment of curcumin inhibit and correct the gastrointestinal complications of diabetes due to its antioxidant potential.

Research data indicated that in diabetic patient the gastric cells are subject to oxidative stress. Excessive production of glucose derived free radicals in diabetes causes damage to cellular proteins, lipids and eventually cell death and damages the gastric mucosa by inducing oxidative stress. Specifically, ROS such as superoxide (O$_2^-$) and hydrogen peroxide (H$_2$O$_2$) induce inflammatory responses and tissue damage by fragmenting cellular DNA. In the gut, ROS can also be generated by non-steroidal anti-inflammatory drugs (NSAIDs), cold stress, ethanol, and H. pylori infection. NADPH oxidase found in phagocytic cells, vascular smooth muscle cells, endothelial cells, fibroblasts, and adipocytes convert oxygen into superoxide anions. Recently reported that NADPH oxidase activity is elevated in ischemia/reperfusion and is involved in the resultant gastric mucosal damage. Gastric motility disorders can occur in many clinical settings with a wide variety in the severity of symptoms with or without gastric mucosal injuries. Gastric motility disorders are attributable to either damage within the smooth muscle itself or dysfunctions within the neuromuscular components including the enteric nerves and interstitial cells of Cajal (ICC), which regulate smooth muscle function. It was investigated that the gastric dysfunctions in diabetes could be attributed to enteric neuronal damage and could be one of the probable mechanisms involved. In the present study we demonstrated that diabetes involves oxidative stress which might be causing changes in chemical coding of enteric neurons that can lead to the gastrointestinal motility disorders.

Gastric emptying is most dependent to the function of vagal nerve, and it is controlled by fundus and is dependent upon the volume of the gastric content. Basal rhythm of the stomach is initiated by a pacemaker and transmitted to pylor horizontally and circularly. In fasting state the interdigestive motor activity is divided into four phases. Peak activity is observed in phase 3 and in this phase migratory motor complex of the stomach occurs making three contractions in a minute. As a result of impaired vagal function, proximal stomach relaxes less and the emptying of fluids in diabetic patients prolong. Phase 3 contractions of interdigestive migratory motor complex are generally not present in diabetic patients. As a result, this causes a loss in the function of digestion and emptying in the antral region and thus gastric retention. Results of this study revealed the therapeutic effectiveness of Curcumin in gastropathy, one of the complications of diabetes. It was found that after the progration of diabetic gastropathy for 4 weeks produced the symptoms which mimic the clinical condition as observed in gastropathic patients. Treatment with Curcumin for 4 weeks after induction of diabetic gastropathy normalized the gastrointestinal emptying and intestinal transit time.

The results of the present study demonstrate that gastropathic condition caused due to alloxan induced diabetes is associated with a significant increase of MDA levels and decrease of scavenging enzymes like SOD, catalase and reduced glutathione indicating that free radicals are effectively involved in the development of gastropathy in diabetes. Results of oxidative stress parameters obtained further prove the antioxidant potential of Curcumin. Results of this study indicate that treatment of Curcumin at both the doses had significantly reversed the gastropathic condition and restored the level of MDA and increased the level of antioxidant enzymes such as catalase, superoxide dismutase, and reduced glutathione significantly which further confirms the involvement of oxidative stress as an underlined cause for the observed diabetic gastropathy. Upon treatment with Curcumin, at the end of 8th week, blood glucose data show that hyperglycemia is reduced and restored to normal values.

The mechanisms behind this action could be a direct or indirect effect of Curcumin to scavenge free radicals and oxidize metabolites or from iron or copper chelating and inhibit lipid peroxidation properties. In addition, Curcumin exerts the protective effect in a stroke model induced by transient global ischemia. Curcumin significantly protected the neuronal cells from the oxidative stress-induced neurodegeneration in Alzheimer’s disease, decreased lipid peroxidation, improved the activity of catalase and superoxide dismutase, and also prevented glutathione depletion. It is well known fact that depletion of nerve cells in stomach due to oxidative stress, cause decreased GI emptying as well as intestinal transit, and plays an important role in gastropathy. Further the oxidative stress and decrease antioxidant enzyme level is a contributing factor for tissue damage in stomach producing gastropathic conditions. Therefore, these pieces of evidence point out the possibility that Curcumin exerts an influence in the oxidative stress condition. Our results strongly suggest that the beneficial effects of Curcumin in diabetic gastropathy might be due to its antioxidant effect by controlling the increased blood glucose level and by promoting the activities of scavenging enzymes, thus, protecting the nerve cells (ICC) and gastrointestinal tissues. Hence, this study concludes that daily treatment of Curcumin improved the diabetic gastropathy which is likely to be related with reduction in hyperglycemia and oxidative stress.

6. Conclusion and Scope

Results obtained from this study indicates that, daily use of Curcumin as a natural product supplement, may be a new choice for diabetic patients, as it bears a therapeutic potential to treat diabetes-induced gastropathy. These activities may possibly be due to presence of anti-oxidant activity which indirectly helped to decrease the blood levels of glucose.
References:


