Effect of green tea on kidney tubules of diabetic rats

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It has been documented that green tea (GT) and its catechin components improve renal failure and inhibit the growth of mesangial cells. In the present study we examined the long-term effect of GT extract on streptozotocin (STZ)-induced diabetic nephropathy and on the glycogen accumulation in the kidney tubules. Male Sprague-Dawley rats were randomly assigned to normal control groups (2, 6, 8 and 12 weeks) and five diabetic groups (n 10) of comparable age. A GT diabetic group received 16% concentration of GT for 12 weeks post-diabetes induction as their sole source of drinking water. GT treatment significantly (P<0.01) reduced the serum glucose, glycosylated protein, serum creatinine and blood urea N levels by 29.6 (SEM 3.7), 22.7 (SEM 5.2), 38.9 (SEM 10) and 41.7 (SEM 1.9) %, respectively, compared with the diabetic group of comparable age. In addition, the GT-treated group showed a significant 44 (SEM 10.8) % higher creatinine clearance (Ccr) compared with the untreated diabetic group. Likewise, GT reduced the urea N, creatinine, glucose and protein excretion rates by 30 (SEM 7.6), 35.4 (SEM 5.3), 34.0 (SEM 5.3) and 46.0 (SEM 13.0) % compared with the 12 weeks diabetic group. Administration of GT to 12 weeks diabetic rats significantly (P<0.001) prevented (99.98 (SEM 0.27) % less) the accumulation of glycogen in the kidney tubules. These results indicate that in STZ diabetes, kidney function appears to be improved with GT consumption which also prevents glycogen accumulation in the renal tubules, probably by lowering blood levels of glucose. Therefore, GT could be beneficial additional therapy in the management of diabetic nephropathy.

Green tea: Polyphenols: Diabetic nephropathy: Proximal tubules

Diabetes mellitus is characterised by hyperglycaemia, which has been strongly linked to diabetic complications such as neuropathy, retinopathy and nephropathy. Above all, diabetics are at augmented risk for end-stage renal disease consequent to diabetic nephropathy(1,2). Stringent control of the hyperglycaemia by insulin treatment has been shown to avert hypertrophy and hyperfiltration and the subsequent rise in urinary protein excretion(3). Clinical studies suggest that there is yet no completely effective treatment for diabetic nephropathy(4).

Hyperglycaemia is the principal factor responsible for structural alterations at the renal level and is directly linked to diabetic microvascular complications, particularly in the kidney(44), therefore, glycaemic control remains the main target of treatment. Prevention of nephropathy is a very important concern and many studies have been focused on traditional and herbal medicines to find novel therapeutic agents for diabetic nephropathy.

Green tea (Camellia sinensis; GT) is a rich source of polyphenols, particularly flavonoids, which have been shown to have numerous pharmacological effects. Studies using animal models show that GT catechins could be beneficial in suppressing high-fat diet-induced obesity by modulating lipid metabolism and providing some protection against lipid and glucose metabolism disorders implicated in type 2 diabetes, and could reduce the risk of CVD(5–8). Administration of GT catechins in streptozotocin (STZ) diabetic animals drastically improved kidney function as a result of its anti-thrombogenic action, which in turn controls the arachidonic acid cascade system(9). These studies also demonstrated an improvement in the glomerular filtration rate(9–11). Yokozawa et al.(12) examined variables of glomerular filtration in cisplatin (a nephropathy inducer)-treated rats and demonstrated that GT significantly decreased the blood N level, serum creatinine, serum malondialdehyde and kidney excretion of glucose and proteins and oxidative stress in the kidney(42). Another study has shown that GT reduced serum glucose and creatinine levels and serum lipid peroxidation and increased serum superoxide dismutase, suggesting that catechins influence glucose metabolism and improve kidney function by reducing oxidative stress in alloxan-treated diabetic rats(13). Moreover, GT catechins decreased plasma insulin levels but did not affect plasma glucose levels in an oral glucose tolerance test in normal rats(14). In contrast, Mustata et al. have shown that GT drinking had a marginal effect on nephropathy.

Abbreviations: Ccr, creatinine clearance; EGCG, (−)-epigallocatechin 3-O-gallate; GT, green tea; GTP, green tea polyphenols; PAS, periodic acid-Schiff; PHGG, partially hydrolysed guar gum; STZ, streptozotocin.

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parameters through improving renal mitochondrial defects; however, neither glycaemia nor urinary albumin were affected in GT-drinking diabetic animals\(^{(15)}\). These GT paradoxical effects on diabetic nephropathy animal models necessitate further studies to clarify the GT role on kidney function in the diabetic state. Accordingly, we tested the hypothesis that GT displays anti-diabetic properties on long-term follow up in the hypofiltration stage of STZ-treated diabetic animals. The effect of GT treatment on long-term (12 weeks) STZ-induced diabetic nephropathy was investigated by assessing serum and urine parameters indicative of nephropathy such as blood urea, N and serum creatinine, creatinine clearance (Ccr), urinary protein excretion and glycogen accumulation in kidney tubules.

**Materials and methods**

**Animals**

Male Sprague–Dawley rats (Kuwait Animal Laboratory Center Colony) weighing 200–230 g were cared for as outlined in the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioural Research (Institute for Laboratory Animal Research 2003). Rats were housed (four or five animals per cage) in standard plastic cages with wood chip bedding. Bedding was changed daily for all animals to maintain sanitary conditions. The animals were kept in well-ventilated rooms with adjustable light–dark cycle and temperature regulation systems. The rooms and animal cages were cleaned daily, and all animals were provided with fresh food and water on a daily basis. They were also inspected daily for any possible signs of inflammation or respiratory or gastrointestinal infection. If such signs were present, the animal was excluded from the study.

**Green tea extract preparation**

GT extract was made as described previously\(^{(16)}\). Briefly, dried GT leaves were obtained from and packed in Sri Lanka (Swan brand, pure Ceylon tea; TC/E/PR/07/82; George Payne & Co. (Ceylon) Ltd, Colombo, Sri Lanka). The same quantity of GT was used in every preparation of the tea solution. Dried GT leaves (16 g) were added to 1 litre of deionised boiled water and given only water to drink. Water and GT bottles were prepared daily, and all animals were provided with fresh food and water on a daily basis. They were also inspected daily for any possible signs of inflammation or respiratory or gastrointestinal infection. If such signs were present, the animal was excluded from the study.

**Table 1. Changes in body weight†**

(Mean values with their standard errors)

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of rats per group</th>
<th>Mean (g)</th>
<th>SEM</th>
<th>Mean (g)</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 2 weeks</td>
<td>10</td>
<td>215·9</td>
<td>5·5</td>
<td>5·9</td>
<td>2·2</td>
</tr>
<tr>
<td>Diabetic 2 weeks</td>
<td>10</td>
<td>211·9</td>
<td>8·5</td>
<td>1·9</td>
<td>3·9</td>
</tr>
<tr>
<td>Control 6 weeks</td>
<td>10</td>
<td>287·5</td>
<td>6·5</td>
<td>77·5</td>
<td>4·5</td>
</tr>
<tr>
<td>Diabetic 6 weeks</td>
<td>10</td>
<td>239·5***</td>
<td>7</td>
<td>29·5***</td>
<td>4·9</td>
</tr>
<tr>
<td>Control 8 weeks</td>
<td>10</td>
<td>358·1</td>
<td>1·7</td>
<td>149·1</td>
<td>10·1</td>
</tr>
<tr>
<td>Diabetic 8 weeks</td>
<td>9</td>
<td>296·1***</td>
<td>13·5</td>
<td>86·1***</td>
<td>8·9</td>
</tr>
<tr>
<td>Control 12 weeks</td>
<td>10</td>
<td>544·5</td>
<td>26·3</td>
<td>334·5</td>
<td>20·1</td>
</tr>
<tr>
<td>Diabetic 12 weeks</td>
<td>8</td>
<td>331·2***</td>
<td>13·4</td>
<td>121·2***</td>
<td>9·5</td>
</tr>
<tr>
<td>Diabetic 12 weeks + green tea</td>
<td>10</td>
<td>343·9***</td>
<td>17·2</td>
<td>133·9***</td>
<td>14·2</td>
</tr>
</tbody>
</table>

† Initial body weight for all animals was 210·0 (SEM 10·3) g.

**Experimental protocols and group treatments**

Experimental rats \((n = 50)\) were injected intraperitoneally with STZ (75 mg/kg) (Sigma, St Louis, MO, USA) dissolved in 0·9% saline\(^{(16)}\). STZ solutions were freshly prepared due to the limited stability of the compound\(^{(16)}\). Non-diabetic rats were studied of the same age as an onset control, to provide a starting value against which to judge any diabetes-induced damage.

Blood glucose levels were determined in all animals using an Encore Glucometer (Bayar, Elkhart, IN, USA) from blood samples obtained by tail vein bleeds. The presence of diabetes was verified at 24 h by the presence of hyperglycaemia and glucosuria (Visidex II and Diastix; Ames, Slough, Bucks, UK). After 2 weeks of uncontrolled diabetes, rats with blood glucose levels ≥ 2500 mg/l (≥ 14 mm) were randomly divided into different diabetic groups as detailed in Table 1: diabetic groups (2 weeks, 6 weeks, 8 weeks and 12 weeks) (ten rats per group) were given water to drink; 12 weeks diabetic + GT group (ten rats) were given GT to drink for 12 weeks instead of water as described previously\(^{(16)}\); control normal groups (ten rats per group) were age-matched control animals and were injected (intraperitoneally) with an equal volume of 0·9% saline (control vehicle) and given only water to drink. Water and GT bottles were made available to the animals *ad libitum*. The mean volume of GT extract intake was 122 (SEM 10·22) ml/d. At the end of the experiments, plasma glucose was estimated (GOD–Perid method; Boehringer Mannheim, Mannheim, Germany) on samples taken from the tail vein.

At the end of the experiments, blood samples were taken by cardiac puncture and used for the determination of blood urea N, serum creatinine levels and glucose (GOD–Perid method; Boehringer Mannheim). Serum glycosylated protein level was measured using the method of McFarland *et al.*\(^{(19)}\). The 24 h (before killing) urine was collected while rats were housed in metabolism cages and filtered for determination of urea N, glucose, protein and creatinine. Protein levels in freshly voided urine samples were assessed by the sulfosalicylic acid method\(^{(20)}\). Urea N and creatinine were determined...
using the commercial test kits BUN Kainos and CRE-EN Kainos (Kainos Laboratory, Tokyo, Japan) and glucose by the Momose method(21). The Ccr was calculated on the basis of urinary creatinine, serum creatinine, urine volume and body weight using the following equation as described previously(22):

\[
\text{Ccr (ml/min per kg body weight)} = \frac{(\text{urinary creatinine (mg/l)} \times \text{urinary volume (ml/d)} \times \text{serum creatinine (mg/l)} \times (1/1440 \text{ (min)})).}
\]

Specimen collection and histological staining

Respective groups (age-matched) of animals were killed after 2, 6, 8 and 12 weeks of the induction of diabetes(23). The kidneys were gently removed after opening the abdominal cavity. The fresh kidneys were gently bisected longitudinally and immediately immersed (fixed) in labelled vials containing 10% of buffered formalin and kept overnight. The segments were washed with distilled water. Then, the vials were filled with 70% alcohol (Riedel-de Haen AG, Seelze, Germany) and kept at 4°C overnight. On the next day, the specimens were dehydrated by a graded series of alcohol and then treated with xylene (Univar; Ajax Chemicals, Auburn, NSW, Australia) for 1 h. The tissues were then placed in cassettes and placed in a hot paraffin wax container at 60°C overnight. On the next day, the tissues were embedded in paraffin using paraffin embedding apparatus (Jung Histocut; Leica, Wetzlar, Germany). The paraffin blocks were then sectioned transversely (4 μm thick) using a microtome (Jung Histoecut; Leica). Sections were stained with haematoxylin and eosin stains. Some sections from diabetic animals were stained with periodic acid-Schiff (PAS) and PAS-diastase special stains in order to verify that the areas of the tubules that showed clear cytoplasm were due to the accumulation of glycogen. The PAS stain was strongly positive and the PAS-diastase was also positive for cells with clear cytoplasm.

Quantification of glycogen-filled proximal tubules

For morphometric analysis, ten sections from each block (two blocks (right and left kidneys) from each rat) were subjected to quantitative analysis. Sections from the eight to ten rats in each group were quantified. Random light microscopic fields were digitally photographed from the kidney tissues to count the clear tubules using objective lens power 40 X.

Data analysis

A one-way ANOVA was applied to assess significant differences between the mean values of the number of clear cytoplasm tubules found in controls, untreated and GT-treated diabetic rat groups. The post hoc Scheffe F and LSD tests were performed to determine individual probability values for comparisons between groups using SPSS software (SPSS, Inc., Chicago, IL, USA). The results are presented as mean values with their standard errors and the graph drawn using SPSS software. Data collected from the blood and urine samples were analysed by one-way ANOVA followed by the post hoc Scheffe F test using SPSS software to determine the significant differences between the groups. All data are presented as mean values with their standard errors. A difference among the means at P<0:05 was considered statistically significant.

Results

Changes in body weight

The average body weight of animals with diabetes was significantly lower than that of the normal control rats of comparable age (Table 1). Likewise, the body weights of the diabetic rats treated with GT were significantly (P<0.001) lower than the normal control group. There was no significant difference between the mean body weights of the untreated diabetic group compared with GT-treated groups. The average gains in body weight were similar in untreated and GT-treated animals after 12 weeks of diabetes. These weight gains were 36.2 (SEM 2.8) and 34.6 (SEM 4.93) %, respectively.

The effect of green tea on glucose and glycosylated protein levels in serum

Table 2 shows the effect of GT consumption on the levels of serum glucose and glycosylated protein. In all diabetic treated and untreated animals, the serum glucose and glycosylated protein levels were significantly (P<0.001) elevated compared with normal control rats. However, diabetic rats treated with GT showed a significant reduction in both serum glucose (P<0.01) and glycosylated protein (P<0.05) when compared with other diabetic groups. The level of serum glycosylated protein was lower in the GT-treated rats. This reduction was approximately 29.6 (SEM 3.7) %. Likewise, serum glycosylated protein levels

<table>
<thead>
<tr>
<th>Groups</th>
<th>Glucose (mg/l)</th>
<th>Glycosylated protein (nmol/mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SEM</td>
</tr>
<tr>
<td>Control 12 weeks (n 10)</td>
<td>908</td>
<td>149</td>
</tr>
<tr>
<td>Diabetic 2 weeks (n 10)</td>
<td>4958***</td>
<td>308</td>
</tr>
<tr>
<td>Diabetic 6 weeks (n 10)</td>
<td>5176***</td>
<td>333</td>
</tr>
<tr>
<td>Diabetic 8 weeks (n 9)</td>
<td>5905***</td>
<td>271</td>
</tr>
<tr>
<td>Diabetic 12 weeks (n 8)</td>
<td>5738***</td>
<td>333</td>
</tr>
<tr>
<td>Diabetic 12 weeks + GT (n 10)</td>
<td>4037***††</td>
<td>212</td>
</tr>
</tbody>
</table>

*** Mean value was significantly different from that of the control group (P<0.001). Mean value was significantly different from those of the diabetic groups: † P<0.05, † † P<0.01.
were lower in GT-treated rats. The serum glycosylated protein level was 22·7 (SEM 5.2) % lower than in the diabetic group of comparable age.

The effect of green tea on blood urea nitrogen, serum creatinine and creatinine clearance

Table 3 shows the effects of GT treatment on serum parameters under conditions of diabetes. The blood urea N level was significantly higher ($P<0.001$) in 12-week diabetic animals than control rats of the same age (148 (SEM 19) mg/l); whereas it was significantly lower ($P<0.01$) in the GT rats. This reduction was 41·7 (SEM 1.9) %. The serum creatinine level was significantly ($P<0.001$) higher in rats with diabetes in comparison with normal control rats of the same age (Table 3). Those diabetic animals given GT showed a non-significant difference in creatinine level compared with normal control rats of the same age (148 (SEM 19) mg/l) at 12 weeks. This reduction was 38·9 (SEM 0·10). In the GT rats, significantly ($P<0.001$) lower Ccr than the normal control animals. The GT-treated group showed a significant ($P<0.05$) higher Ccr than that in untreated diabetic rats. This increase was 44 (SEM 10·8) %.

The effect of green tea on glucose, protein, urea nitrogen and creatinine excreted in urine

Table 3 shows the effects of GT on the urinary function of diabetic animals. The glucose, protein, urea N and creatinine excretion rates were increased significantly ($P<0.001$) (1·70-, 3·29-, 1·95- and 1·59-fold, respectively) in 12-week diabetic compared with normal control rats. After oral administration of GT, urinary urea N excretion was significantly lower ($P<0.001$) compared with that in the 12-week diabetic group. Urea N decreased 30 (SEM 7·6) % in the 12 weeks diabetic rats compared with GT-treated animals. Likewise, creatinine, glucose and protein excretion declined 35·4 (SEM 5·3), 34·0 (SEM 4·9) and 33·5 (SEM 3·2) % in GT-treated rats. The serum glycosylated protein was 22·7 (SEM 5·2) % lower than in the diabetic group of comparable age (Table 3).

Histopathological changes

Histological examination of the normal control kidney tissues showed normal kidney histology (Fig. 1 (A)). Haematoxylin and eosin sections examined under light microscopy showed that all the kidneys of the diabetic rats had multifocal areas of tubules with clear cytoplasm (Fig. 1 ((B)–(D)). Special PAS (Fig. 1 (E)) and PAS followed by diastase staining showed that the clear cytoplasm corresponded to glycogen accumulation. The PAS stain was strongly positive in the tubules with clear cytoplasm (Fig. 1 ((B)–(D)). Special PAS (Fig. 1 (E)) and PAS followed by diastase staining showed that the clear cytoplasm corresponded to glycogen accumulation. The PAS stain was strongly positive in the tubules with clear cytoplasm (Fig. 1 (E)).

### Table 3. The effect of green tea (GT) on serum and urine kidney functional parameters

<table>
<thead>
<tr>
<th>Groups</th>
<th>Serum urea N (mg/ml)</th>
<th>Urea urea N</th>
<th>Urine creatinine (mg/d)</th>
<th>Creatinine clearance (ml/kg BW per min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 2 weeks (n 10)</td>
<td>148***</td>
<td>19</td>
<td>428***</td>
<td>270·9††††</td>
</tr>
<tr>
<td>Diabetic 2 weeks (n 10)</td>
<td>428***</td>
<td>261</td>
<td>474***</td>
<td>270·9††††</td>
</tr>
<tr>
<td>Diabetic 6 weeks (n 8)</td>
<td>463***</td>
<td>369</td>
<td>489***</td>
<td>360·7††††</td>
</tr>
<tr>
<td>Diabetic 8 weeks (n 8)</td>
<td>465***</td>
<td>410</td>
<td>510***</td>
<td>390·7††††</td>
</tr>
<tr>
<td>Diabetic 12 weeks + GT (n 10)</td>
<td>270·9††††</td>
<td>360·7††††</td>
<td>48·39††††</td>
<td>43·9††††</td>
</tr>
</tbody>
</table>

Mean value was significantly different from that of the control group: * $P<0.05$, ** $P<0.01$, *** $P<0.001$. Mean value was significantly different from those of the diabetic groups: † $P<0.05$, †† $P<0.01$, ††† $P<0.001$, †††† $P<0.001$. Mean value was marginally significantly different from those of the diabetic groups ($P<0.10$).
Fig. 1. Representative light microscopic photographs of proximal tubules showing the effect of green tea (GT) extract treatment on diabetic nephropathy. (A) Control normal kidney section showing normal proximal tubule epithelium with eosinophilic and granular cytoplasm (haematoxylin and eosin (H&E); x 100). (B), (C) and (D) Kidney sections from 2-, 6- and 12-week diabetic nephropathy rats showing a gradual increase in the number of glycogen-filled proximal tubules (—). The 12-week diabetic section shows the highest level of glycogen accumulation in the proximal tubules (H&E; B and C: x 100; D: x 200). (E) Tissue section from 12-week diabetic kidney stained by special periodic acid-Schiff stain for the glycoprotein showing strong positive staining (—) in the lining of epithelium of the proximal tubules (x 40). (F) GT extract treatment of diabetic animals for 12 weeks significantly decreased the number of glycogen-filled proximal tubules to zero level which was seen in the control normal animals of comparable age (H&E; x 100).
that hyperglycaemia is directly associated with diabetic result of changes in glomerular haemodynamic instigated by in the kidney. This decrease in GFR is believed to be a characteristic in the development of diabetic nephropathy, which in creatinine and reduced Ccr levels, is the most common characteristic of diabetic nephropathy. Furthermore, the combination of GTP and PHGG reduced kidney weight, levels of blood urea N and serum creatinine and increased Ccr in diabetic animals. Hyperglycaemia, as assessed by blood glucose and glycosylated protein levels, was reduced by administration of GTP plus PHGG. In line with the present study, several studies have also shown that the control of postprandial hyperglycaemia by GT can help reduce the risk of type 2 diabetes and provide evidence that GT promotes glucose metabolism in healthy humans, and produces an anti-hyperglycaemic effect in diabetic mice. Indeed, Wu et al. have shown that GT supplementation for 12 weeks improves insulin resistance and increases GLUT IV content in a fructose-fed rat model, resembling human type 2 diabetes mellitus. In contrast, Mustata et al. have recently shown that GT had marginal effects on nephropathy parameters but suppressed renal mitochondrial NADH-linked, ADP-dependent and dinitrophenol-dependent respiration and complex III activity in the STZ diabetic Lewis rat. In addition, GT did not induce any significant decrease in glomerular collagen IV, glomerular staining for reductase and tubular Fe staining. The failure to develop dramatic alterations in renal parameters may be related to the moderate hyperglycaemia and urinary albumin of these rats. These contradictory reports could result from differences in: (1) diabetic models, (2) animal strains, (3) STZ dosages resulting in mild to severe hyperglycaemia and proteinuria, and (4) insulin treatment used by different investigators.

Proteinuria is quantitatively related to the degree of nephropathy in patients with diabetes. The increased urine protein excretion results from lesions in the glomerular filtration barrier. The present study shows that in comparison with normal rats, animals with diabetic nephropathy show increased urinary excretion of protein and that administration of GT reduced the degree of proteinuria which is in agreement with previously reported results that showed GTP, PHGG and GTP plus PHGG and EGCG treatment significantly reduced the extent of proteinuria. Likewise, the present study reveals that GT consumption significantly decreased the serum glycosylated protein levels in diabetic animals. These data also suggest that GT minimises the development of glomerular and tubulointerstitial injuries. In addition, diabetic animals used in the present study confirmed the presence of glomerular hypertrophy and diffuse and exudative lesions (data not
shown) reported by Yamabe et al. (30) which also correlate with proteinuria. In addition, the decrease in total protein as a result of their excessive excretion via urine, and also an increase in lipids, whose abnormal metabolism has been proven to play a role in the pathogenesis of diabetic nephropathy and to enhance lipid peroxidation, were all improved by administration of the EGCG (30).

As a result, we contemplate that EGCG (30), GT (22) or GT consumption (in the present study) has a positive effect on blood glucose and lipid metabolic abnormalities. Recent studies have shown that the nephrotoxicity of drugs extract polyphenols and its constituents affect cell viability. Nephrotoxicity is often manifested as proximal tubule disorders, which result in the release of enzymes held in the proximal tubules. Moreover, GT reduced the urinary activity of renal tubular epithelial-cell enzymes, which are an index of renal tubular injury (42).

In conclusion, the present study demonstrated that GT extract provides a beneficial effect on long-term diabetic nephropathy via suppressing hyperglycaemia and preventing glycogen accumulation in the proximal tubules. The therapeutic property of GT seems propitious in improving kidney nephropathy by significantly improving serum and urine parameters. These findings support the importance of controlling blood glucose levels and maybe slowing or even reversing some of the early pathologies of diabetic nephropathy. However, further studies should be done in order to understand the exact cellular and molecular mechanisms which mediate such effects of GT action on proximal tubules and how GT reduces the accumulation of glycogen in the proximal tubules as well as its potential therapeutic implications against renal damage associated with diabetic nephropathy.

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References


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