Introduction

Metabolic syndrome (MS) is considered as the concomitant clustering of obesity, insulin resistance (IR), hypertriglyceridemia, dyslipidemia, and hypertension. MS has gained importance because of its association with subsequent development of cardiovascular disease and type 2 diabetes.[1]

Rosiglitazone is the most potent activator of the peroxisome proliferator-activated receptor gamma (PPARγ). The PPARγ belongs to a nuclear hormone receptor superfamily, which regulates transcription by binding to retinoid X receptor that is in turn bound to DNA in various cell types. Activation of PPARγ promotes insulin-stimulated glucose uptake and suppresses proinflammatory responses.[2]

Quercetin (3,5,7,3’,4’-pentahydroxyflavone) is one of the most common flavonoids in the human diet. It is an important dietary flavonoid found in red onions, apples, berries, citrus fruits, and tea. It has been reported to increase the genomic stability in rats and enhance the antioxidative defense system by upregulating antioxidant enzyme.[3] Moreover, quercetin intake shows decreased incidence of cardiovascular and neoplastic diseases.[4]

The aim of this study was to gain more insight into the beneficial effects of quercetin in fructose-induced IR syndrome alone or in combination with rosiglitazone to establish whether it can be useful in the prevention of MS and IR related to it.

ABSTRACT

Objectives: Quercetin exhibits a wide range of biological functions. The present study aimed to investigate the possible beneficial effects of rosiglitazone, quercetin as well as their combination on metabolic and biochemical changes associated with the fructose-induced metabolic syndrome (MS).

Materials and Methods: Four groups of rats were fed on fructose-enriched diet for 14 weeks. One group served as fructose-enriched diet control, while the remaining groups were treated with rosiglitazone (4 mg/kg/day), quercetin (50 mg/kg/day), and their combination during the last 4 weeks. A fifth group was fed on normal laboratory diet. At the end of the experiment, blood samples were withdrawn for the estimation of markers of MS.

Results: Rosiglitazone or quercetin attenuated the biochemical and metabolic changes associated with MS. The combination of rosiglitazone and quercetin nearly normalized these changes.

Conclusion: Quercetin, as well as its combination with rosiglitazone, showed beneficial protective effects against metabolic and biochemical changes associated with MS.

KEY WORDS: Fructose enriched diet, metabolic syndrome, oxidative stress, quercetin, rosiglitazone
Materials and Methods

Animals

All the experimental procedures were conducted using male Wistar Albino rats (220–30 g) provided by the National Cancer Institute, Cairo, Egypt and left to accommodate in the animal facility of the Faculty of Pharmacy, Beni Suef University, for 1 week before being subjected to experimentation. All animals were maintained under a 12-h light–dark cycle, with controlled humidity (60–80%) and constant temperature (22°C ± 1°C). Throughout the study, food and water were supplied ad libitum. All experimental procedures were controlled and approved by the Ethics Committee of Faculty of Pharmacy, Beni Suef University.

Drugs and Chemicals

Rosiglitazone, quercetin, fructose, mineral and vitamin mixtures were purchased from Sigma–Aldrich, USA. All other chemicals were of the highest grade commercially available.

Rosiglitazone and quercetin were suspended in 1% Tween 80 shortly before administration to animals. The concentrations of the drugs were adjusted so that each 100 g animal’s body received orally 1 ml of either suspension containing the required dose.

Experimental Protocol and Procedure

After an acclimatization period of 1 week, rats were randomly allocated into five groups (n = 8 rats per group). Group I served as control group. This group received regular diet and water ad libitum and did not receive any medication. Group II received fructose-enriched diet (FED) for 10 weeks and served as FED-fed control group.

Group III received FED for 10 weeks followed by rosiglitazone (4 mg/kg/day) for 4 weeks.

Group IV received FED for 10 weeks followed by quercetin (50 mg/kg/day) for 4 weeks Group V received FED for 10 weeks followed by a combination of rosiglitazone (4 mg/kg) and quercetin (50 mg/kg/day) for 4 weeks.

Blood samples were collected randomly after 4, 6, 8, and 10 weeks from the initiation of the FED. Serum levels of fasting blood glucose (FBG), triglycerides (TG), and total cholesterol were estimated to ensure the induction of IR syndrome. Insulin resistant rats were randomly allocated into four groups (8 rats each).

Animals were maintained on the FED during the treatment period.

Body weight was recorded once weekly. By the end of the treatment period, animals were then fasted for 12 h and blood samples were withdrawn from the retro-orbital plexus for the estimation of the levels of FBG, insulin, total cholesterol and total TG, uric acid, urea, creatinine, glutathione (GSH), malondialdehyde (MDA), and tumor necrosis factor-alpha (TNF-α). The homeostatic model assessment for IR (HOMA-IR) was calculated from basal insulin and glucose values. Liver samples from each group were homogenized in 50 Mm potassium phosphate pH 7.5 and 1 millimolar (Mm) ethylenediaminetetraacetic acid for total nitrates and nitrates (NOx) measurements. Homogenized tissues were subjected to a sonication procedure twice with 30 s intervals at 4°C. After the sonication process, homogenized tissues were centrifuged at 4000 (revolutions per minute rpm) for 10 min at 4°C. Other liver portions from each group were preserved in 10% formalin prepared in saline and kept for histological and immunohistochemical examination.

Methods

Induction of metabolic syndrome

MS was induced by feeding rats FED according to the method described by Bezerra et al. FED was composed of fructose (660 g/kg), soya protein (200 g/kg), sheep fat (60 g/kg), cellulose (30 g/kg), L-lysine (10 g/kg), choline chloride (10 g/kg), DL-methionine (10 g/kg), mineral mixture (10 g/kg), and Vitamin mixture (10 g/kg). Diet was freshly prepared every 3–4 days and stored at 2–8°C.

Assessment of metabolic and biochemical parameters

- Fasting serum glucose (mg/dl) was determined colorimetrically using a test reagent kit (Biolabo SA, France)
- Determination of serum insulin (µIU/ml) was performed using rat insulin ELISA kit (Biovendor, Czech Republic)
- HOMA-IR score was used as an index of IR as described by Matthews et al. using the following formula:
  - HOMA-IR score = serum glucose (mmol/l) × serum insulin (µIU/ml)/22.5
- TNF-α level (pg/ml) was determined using a test reagent kit (ID labs, Canada)
- Serum total cholesterol and TG were estimated using test reagent kits (Spinreact, Spain) and expressed as mg/dl
- Uric acid, urea and creatinine levels were determined using test reagent kits (Biodiagnostics, Egypt) and expressed as mg/dl
- Blood GSH, serum MDA, and liver nitric oxide (total nitrates and nitrates, NOx) were determined according to the methods described previously.

Nitric oxide synthase immunohistochemistry

At the end of the experiment, animals were decapitated. Liver tissue was removed, cleaned and fixed in 10% neutral buffered formalin overnight and transferred to 70% ethanol. Tissues were then embedded in paraffin. Paraffin–embedded tissue blocks were sectioned at 4-mm paraffin and were mounted on poly-L-lysine slides. Sections were air-dried, deparaffinized and rehydrated. Mounted specimens were washed in 0.01 mol/L phosphate-buffered saline (PBS). After three washes with PBS, an antigen retrieval solution (0.01 M citrate buffer, pH 6.0) was given for 10 min at 100°C in a microwave oven, endogenous peroxidase was eliminated by incubation in 3% H2O2 in pH 7.4 in phosphate-buffered saline (PBS; 0.01 M) for 10 min. After washing, the specimens were treated with a blocking serum (Labvision, TR-060-UB) at room temperature for 10 min. The sections were incubated with primary rabbit polyclonal anti-inducible nitric oxide synthase (iNOS, dilution 1:100, Santa Cruz Biotechnology, Santa Cruz, CA) or primary rabbit polyclonal anti-endothelial nitric oxide synthase (eNOS, dilution 1:100, Santa Cruz Biotechnology, Santa Cruz, CA) at room temperature for 1 h. Then, the sections were washed 3 times with PBS and incubated with the biotinylated secondary antibody (DAKO, UK) and then streptavidin peroxidase (Dako UK) was given at
room temperature for 30 min. Diaminobenzidine (DAB, Sigma Chemical Company) was used as a chromogen, and the sections were counterstained with hematoxylin and were prepared for microscopic examination.

**Histopathological examinations**
Liver slides for histopathological study were prepared and stained with routine hematoxylin and eosin staining.

**Statistical Analysis**
Data were expressed as mean ± standard error of mean. Comparison between the mean values of different groups was carried out using one-way analysis of variance, followed by Tukey–Kramer *post-hoc* test for multiple comparisons. The *P* < 0.05 were considered to indicate statistical significance between groups.

**Results**

**Effect on Body Weight**
Feeding rats with FED resulted in an increase in body weight at the end of the study. Treatment of FED rats with rosiglitazone, quercetin as well as their combination suppressed the increase of body weight at the end of the experiment. Although there was no significant difference between body weight of rosiglitazone or quercetin and their combination, the effect of the combination on body weight tended to be lower compared to that of rosiglitazone or quercetin treated rats [Table 1].

**Effect on Lipid Profile**
Levels of serum total cholesterol and TG were significantly elevated in MS rats compared to those three of the control group (*P* < 0.05). Rosiglitazone, quercetin or their combination significantly alleviated dyslipidemia by decreasing total serum cholesterol and TG levels in FED treated rats [Table 2].

**Effect on Serum Uric Acid, Urea and Creatinine Levels**
As shown in Table 2, compared with normal control rats, fructose-fed rats exhibited clustering features of MS syndrome including elevated levels of uric acid, urea, and creatinine. Treatment with rosiglitazone, quercetin, and their combination reversed the elevated serum levels of uric acid, urea, and creatinine. In addition, the combination of rosiglitazone and quercetin reversed the elevated serum levels of uric acid, urea, and creatinine.

### Table 1:

**Effect of rosiglitazone, quercetin, or their combination on body weight, serum glucose, insulin levels and insulin resistance in fructose-fed rats**

|                            | Normal control (n=8) | Fructose-fed (n=8) |
|-----------------------------|----------------------|--------------------|
|                            | Control              | Rosiglitazone (10 mg/kg) | Quercetin (50 mg/kg) | Rosiglitazone + quercetin |
| **Initial body weight (g)**| 226.11±1.22          | 224.20±1.09         | 224.93±1.20         | 225.63±1.15         | 225.73±1.03         |
| **Final body weight (g)**  | 327.92±11.58         | 382.01±5.63*        | 343.5±14.88*        | 345.6±0.33*        | 339.93±3.33*        |
| **FBG (mg/dl)**             | 70.66±2.13           | 145.87±6.06*        | 101.18±3.29*        | 86.72±2.10*        | 73.98±2.28*         |
| **Insulin (µIU/ml)**        | 12.11±0.40           | 29.21±2.84*         | 17.97±1.03*         | 16.32±0.94*        | 12.92±0.51*         |
| **HOMA-IR score**           | 2.15±0.09            | 11.36±1.14*         | 6.41±0.41*          | 3.18±0.45*         | 2.50±0.13*          |

Data were expressed as mean±SEM. Statistical analysis was carried out using one-way ANOVA followed by Tukey–Kramer multiple comparisons test. *Significantly different from the normal control group at *P*<0.05, †Significantly different from the fructose control group at *P*<0.05, ″Significantly different from rosiglitazone treated group at *P*<0.05, ″″Significantly different from quercetin treated group at *P*<0.05, ″″″Significantly different from rosiglitazone treated group at *P*<0.05, ″″″″Significantly different from quercetin treated group at *P*<0.05, ANOVA=Analysis of variance, SEM=Standard error of mean, HOMA-IR=Homeostatic model assessment for insulin resistance, FBG=Fasting blood glucose

### Table 2:

**Effect of rosiglitazone, quercetin, or their combination on serum TG, cholesterol, uric acid, urea, and creatinine in fructose-fed rats**

|                            | Normal control (n=8) | Fructose-fed (n=8) |
|-----------------------------|----------------------|--------------------|
|                            | Control              | Rosiglitazone (10 mg/kg) | Quercetin (50 mg/kg) | Rosiglitazone + quercetin |
| **TG (mg/dl)**              | 42.36±3.02           | 83.90±2.80*         | 55.80±3.40*         | 54.15±3.10*         | 41.70±2.61*         |
| **Cholesterol (mg/dl)**     | 55.61±2.44           | 90.92±2.35*         | 64.17±3.71*         | 60.52±4.20*         | 53.17±4.40          |
| **Uric acid (mg/dl)**       | 2.67±0.37            | 7.53±0.25*          | 4.64±0.34*          | 4.84±0.37*          | 3.37±0.22*          |
| **Urea (mg/dl)**            | 30.65±1.94           | 56.55±2.58*         | 41.57±2.65*         | 42.47±2.38*         | 32.65±1.64*         |
| **Creatinine (mg/dl)**      | 0.38±0.02            | 0.74±0.05*          | 0.56±0.02*          | 0.54±0.03*          | 0.38±0.02*          |

Data were expressed as mean±SEM. Statistical analysis was carried out using one-way ANOVA followed by Tukey–Kramer multiple comparisons test. *Significantly different from the normal control group at *P*<0.05, †Significantly different from the fructose control group at *P*<0.05, ″Significantly different from rosiglitazone treated group at *P*<0.05, ″″Significantly different from quercetin treated group at *P*<0.05, ″″″Significantly different from rosiglitazone treated group at *P*<0.05, ″″″″Significantly different from quercetin treated group at *P*<0.05, ANOVA=Analysis of variance, SEM=Standard error of mean, TG=Triglycerides
quercetin showed a marked decrease in serum uric acid, urea, and creatinine levels as compared to rosiglitazone and quercetin-treated groups.

**Effect on Oxidative Stress Biomarkers**

Both rosiglitazone, quercetin as well as their combination significantly raised blood GSH level and significantly reduced serum MDA level as compared to FED control rats \( (P < 0.05) \) [Table 3].

**Effect of Liver Nitric Oxide (Nitrates and Nitrites) and Serum Tumor Necrosis Factor-alpha Level**

Liver NOx concentration was markedly increased in FED rats \((81.52 \pm 2.59 \mu mol/g tissue)\) compared to normal rats. Treatment with rosiglitazone, quercetin, and their combination significantly decreased liver NOx \((54.74 \pm 1.86 \mu mol/g tissue, 55.02 \pm 2.4 \mu mol/g tissue, and 46.1 \pm 1.42 \mu mol/g tissue, respectively)\). It is to be noted that the combination of rosiglitazone and quercetin restored the elevated liver NOx concentration. The elevation in serum TNF-\(\alpha\) level in FED rats was attenuated by rosiglitazone and quercetin treatment.

Moreover, Treatment of FED rats with the combination of rosiglitazone and quercetin reversed the elevated serum TNF-\(\alpha\) levels [Table 3].

**Inducible Nitric Oxide Synthase and endothelial Nitric Oxide Synthase Immunohistochemical Reactions**

iNOS activity was significantly increased in the liver of FED rats [Figure 1a and b]. Treatment of FED rats with rosiglitazone or quercetin prevented the increase of iNOS activity [Figure 1c and d]. The combination of rosiglitazone and quercetin nearly restored iNOS and eNOS activity in the liver [Figures 1e and 2e]. eNOS activity was significantly decreased in the liver as compared to normal control group [Figure 2a and b] and significantly increased eNOS activity as compared to FED control rats [Figure 2c and d].

**Histopathological Examination of Rat Liver**

As demonstrated in Figure 3, liver histopathological studies of hepatocyte morphological changes provided evidence to support the observed biochemical effects of FED treated groups. Liver section of normal control rats showed normal

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**Table 3:**

| Normal control (n=8) | Fructose-fed (n=8) |
|----------------------|-------------------|
|                       | Control | Rosiglitazone (10 mg/kg) | Quercetin (50 mg/kg) | Rosiglitazone + quercetin |
|----------------------|---------|--------------------------|----------------------|--------------------------|
| GSH (mg %)           | 62.01±4.15 | 36.85±4.38*              | 54.23±4.17*          | 53.42±2.75*              | 58.37±3.34*              |
| MDA (nmol/ml)        | 1.60±0.11  | 5.25±0.27*               | 2.12±0.16*           | 2.23±0.17*               | 1.87±0.23*               |
| TNF-\(\alpha\) (pg/ml) | 37.05±1.50 | 144.50±4.90*             | 48.26±1.50*          | 46.08±1.38*              | 38.70±1.22*              |
| Liver NOx (\(\mu mol/g tissue\))   | 45.94±2.04 | 89.16±1.92*              | 54.80±1.90*          | 55.02±2.32*              | 46.10±1.42*              |

Data were expressed as means±SEM. Statistical analysis was carried out using one-way ANOVA followed by Tukey-Kramer multiple comparisons test. *Significantly different from the normal control group at \(P<0.05\), ‡Significantly different from the fructose control group at \(P<0.05\), §Significantly different from rosiglitazone treated group at \(P<0.05\), †Significantly different from quercetin treated group at \(P<0.05\). ANOVA=Analysis of variance, SEM=Standard error of mean, NOx=Nitrates and nitrites, TNF-\(\alpha\)=Tumor necrosis factor-alpha, MDA=Malondialdehyde, GSH=Glutathione
architecture [Figure 3a]. FED-control rats showed marked necrosed coagulative hepatocytes, apoptosis and proliferated fibrous tissue together with the macrophages [Figure 3b] in addition to congestion and hepatic steatosis, fatty infiltration that appears as signet rings in small globules that may coalless together forming large empty spaces [Figure 3c]. Treatment with rosiglitazone showed portal cirrhosis and congestion together with bile duct proliferation [Figure 3d]. Treatment of insulin-resistant rats with quercetin showed marked improvement in hepatic structure, bile duct and kupffer cells proliferation and lesser necrosis [Figure 3e]. The combination of both agents showed an almost normal hepatic structure, congestion and dilatation of the sinusoids and mitotic activation of aggregated lymphocytes [Figure 3f] as well as bile duct hyperplasia [Figure 3g].

Discussion

Data of the present investigation revealed that maintaining rats on FED for 14 weeks was associated with increased weight, hyperglycemia, hyperinsulinemia, IR, dyslipidemia, disrupted renal function, inflammation, and oxidative stress. This obtained model fructose-fed mimics a predominantly environmentally acquired MS model.[11] The reported increase in weight in FED rats could be partially attributed to an increase in adiposity and due to hyperinsulinemia, hypoglycemia, and IR.

Rosiglitazone showed a significant weight reduction ($P < 0.05$), reduced hyperglycemia and IR in FED rats. The reduced in body weight could be attributed to the reduction of hyperinsulinemia and improvement of IR and leptin sensitivity.[12]

In accordance with previous reports several variables including body weight, hyperglycemia, hyperinsulinemia and IR were improved after treatment of FED rats with quercetin.[13]

The beneficial effects of quercetin could be explained by the reduction in the intestinal glucose absorption mediated by glucose transporter 2 (rGLUT2)[14] and the increase in rGLUT4 transporters in skeletal muscle.[15]

The findings of this study demonstrated that MS syndrome in rats was associated with an elevation in serum uric acid, urea, and creatinine level. This reflects impairment in glomerular filtration rate and kidney dysfunction. The increased uric acid in MS rats could be attributed to increased hepatic production of uric acid[16] and/or reduction in glomerular filtration rate.[17] Moreover, accumulating evidence suggest that hyperinsulinemia enhanced urate reabsorption and reduced urate excretion in the kidney leading to elevated serum uric acid level.[18] Treatment of FED rats with rosiglitazone or quercetin lowered serum uric acid, urea and creatinine. Amelioration of IR by rosiglitazone was shown to decrease serum uric acid level[19] and possibly improve kidney functions. The favorable effect of quercetin could be due to many factors acting together including reduction of hyperinsulinemia, IR, modulation the expression level of renal specific transporters including short isoform of rGLUT9, renal-specific transporter, organic anion transporters 1 and electrogenic urate transporter and enhancement of renal excretion of uratefructose-fed rats.[20]

Disrupted lipid metabolism is considered as another feature of MS. The present findings showed that rat fed with fructose exhibited dyslipidemia as marked by increased total TG and cholesterol. This could be attributed to overproduction of lipids...
Rosiglitazone was shown to improve TG and cholesterol by increasing fat oxidation in the liver as well as redistribution of circulating fats in the tissue.\[22\]

In this study, quercetin decreased serum cholesterol and TG. Previous results showed that quercetin reduced lipid peroxidation and restored the lipid profiles to normal.\[23\]

MDA and GSH are oxidative stress markers that indicate oxidative damage and lipid peroxidation. Our results showed that the high levels of MDA and the reduced levels of GSH in FED rats. These results are consistent with other findings that showed that oxidative stress may be important characteristics of diet-induced MS in animal models.\[24\] Treating MS rats with rosiglitazone reduced MDA level and elevated GSH level. The antioxidant effect of rosiglitazone strictly depends on its ability to activate AMP-activated protein kinase that in turn, prevents the activity of NADPH-oxidase.\[25\] Likewise quercetin reduced MDA and increased GSH levels.

The structure of quercetin plays an important role in its antioxidant effects. The structure of quercetin plays an important role in its antioxidant effect (the o-dihydroxy-structure in the B-ring has been observed to confer higher stability to the radical form and to participate in electronic delocalization). It was suggested that the antioxidant activities were dictated both by their structural features and by their location in the membrane. Flavonoids are known to anchor on the polar head of the main phospholipids. Hence, quercetin distributed on the surface of the lipid bilayers as well as in the aqueous phase could scavenge free radicals as a result of its hydrogen donating ability.\[26\]

The high level of circulating TNF-α was primarily considered to be an inflammatory response, which is known to be causally related to IR and MS state. In the current study, rosiglitazone, as well as quercetin, attenuated the increase in serum level of TNF-α in rats. These findings are quite consistent with that of\[27\] who showed that treating Otsuka Long-Evans Tokushima Fatty Rats with rosiglitazone reduced serum inflammatory cytokines including TNF-α. Another possible explanation for the decreases levels of TNF-α by quercetin is possibly related to decreased levels of uric acid. As reported before, hyperuricemia has shown to mediate pro-inflammatory response in the adipose tissue and has been associated with inflammation. Uric acid-induced up-regulation of monocyte chemoattractive protein expression and increased macrophage infiltration and proinflammatory responses in adipose tissue.\[28\]

NOx production in MS rats liver was dramatically increased. The source of NOx overproduction is probably reflected by increased iNOS activity and reduced eNOS activity observed in this study. These findings suggest that NOx production contributes to the pathogenesis of MS because of increased production. NO has been shown to be induced by inflammation.\[29\] Rosiglitazone and quercetin reduced NOx activity. This is in good accordance with the immunohistochemistry studies that reported attenuation of iNOS expression and increased eNOS expression. A possible explanation for quercetin effects is its ability to inhibit the expression of NF-κB-dependent cytokines, iNOS, and cyclooxygenase-2 genes.

The protective effects of rosiglitazone and quercetin were confirmed histologically through improvement of hepatic structure.

Regarding the combination of rosiglitazone and quercetin, this combination succeeded to alleviate the symptoms of MS. It restored body weight, insulin, glucose levels to normal. It also corrected lipid profile kidney functions, TNF-α, MDA and GSH levels. In addition, this combination reduced excessive NO production and this was in accordance with the reduction of

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**Figure 3:** (a) A photomicrograph of rat liver sections obtained from normal control group stained with hematoxylin and eosin. (b) A photomicrograph of rat liver sections obtained from fructose enriched diet control group stained with hematoxylin and eosin. (c) A photomicrograph of rat liver sections obtained from fructose enriched diet control group stained with hematoxylin and eosin. (d) A photomicrograph of rat liver sections obtained from rosiglitazone-treated group stained with hematoxylin and eosin. (e) A photomicrograph of rat liver sections obtained from Quercetin-treated group stained with hematoxylin and eosin. (f) A photomicrograph of rat liver sections obtained from rosiglitazone + quercetin-treated group stained with hematoxylin and eosin. (g) A photomicrograph of rat liver sections obtained from rosiglitazone + quercetin treated group stained with hematoxylin and eosin.
iNOS production in MS rats. The previously mentioned findings in this study about rosiglitazone and quercetin may elucidate the observed beneficial effects of concomitant administration of rosiglitazone and quercetin.

**Conclusion**

The findings of this study showed the beneficial effects of co-administration of rosiglitazone and quercetin in fructose – induced model of IR. Thus rosiglitazone and quercetin in combination offer further improvement to markers of MS risk including hyperglycemia, hyperinsulinemia, IR, lipid profile, increased oxidative stress, and inflammatory mediators.

**Financial Support and Sponsorship**

Nil.

**Conflicts of Interest**

There are no conflicts of interest.

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