Hypouricemic and antioxidant activities of *Allium cepa Lilliaceae* and quercetin in normal and hyperuricemic rats

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ABSTRACT

الأهداف: من اجل تقييم نقص البول في الدم وآثار مضادات الأكسدة لعنصر أليوم سيبا إل وعنصر كويرسيتين لدى الجرذان الطبيعية والجرذان التي تزيد نسبة البول في الدم لديها.

الطريقة: أجريت الدراسة التالية في قسم التغذية والكيمياء الحيوية – جامعة طهران للعلوم الطبية – إيران، خلال الفترة ما بين مايو 2007م وحتى مارس 2008م. تم تقسيم إجمالي عدد 48 ذكر جرذ من النوع ويستار بشكل عشوائي (وزن الجسم: 180-200g) إلى ثمان مجموعات متساوية بما فيها مجموعة التحكم: طبيعي + عنصر أليوم سيبا إل (5g/kg)، طبيعي + عنصر كويرسيتين (5mg/kg)، طبيعي + عنصر ألوبيرنول (5mg/kg)، زيادة نسبة البول في الدم: زيادة نسبة البول + أليوم سيبا إل (5g/kg)، زيادة نسبة البول + عنصر كويرسيتين (5mg/kg)، زيادة نسبة البول + عنصر ألوبيرنول (5mg/kg) مرة واحدة في اليوم لمدة 14 يوماً. تم تحريض زيادة نسبة البول في الدم التجريبية لدى الجرذان بواسطة حقن اوكسونات البوتاسيوم داخل البريتون بمقدار (250mg/kg).

النتائج: خفضت المعالجة بعنصر اليوم سيبا إل وعنصر كويرسيتين لمدة 14 يوماً من مستويات مصل حمض البول بشكل ملحوظ (p=0.000)، لدى الجرذان المصابة بزيادة في نسبة البول في الدم وذلك بصورة معتمدة على الوقت. ثبطت جميع المعالجات نشاط إكسانثين الكبد وأكسيداز /إكسانثين النازعة للهيدروجين بشكل ملحوظ. أدت المعالجة بعنصر أليوم سيبا إل وعنصر كويرسيتين إلى تحسن بشكل ملحوظ في العلامات الحيوية لجهد الأكسدة لدى الجرذان المصابة بزيادة نسبة البول في الدم (p=0.000). ورغم أن أثر نقص نسبة البول في الدم لعنصر ألوبيرنول أعلى من عنصر اليوم سيبا إل وعنصر كويرسيتين، قد لا يغير بشكل ملحوظ من العلامات الحيوية لجهد التأكسد.

خاتمة: قد تكون هذه النتائج مسئولة في جزء من الآثار المفيدة لعنصر أليوم سيبا إل وعنصر الفلافونويد الرئيسي لديها على زيادة نسبة البول في الدم على جهد التأكسد.

Objective: To evaluate the hypouricemic and antioxidant effects of *Allium cepa Lilliaceae (Allium cepa L.)* and quercetin in normal and hyperuricemic rats.

Methods: The following study was conducted in the Department of Nutrition and Biochemistry, Tehran University of Medical Science, Iran, between May 2007 and March 2008. A total of 48 male Wistar rats (body weights: 180-200 g) were randomly divided into 8 equal groups including normal; normal + *Allium cepa L.* (5g/kg); normal + quercetin (5mg/kg); normal + allopurinol (5mg/kg); hyperuricemic; hyperuricemic + *Allium cepa L.* (5g/kg); hyperuricemic + quercetin (5mg/kg); hyperuricemic + allopurinol (5mg/kg) once a day for 14 days. Experimentally, hyperuricemia in rats was induced by intraperitoneal injection of potassium oxonate (250mg/kg).

Results: *Allium cepa L.* and quercetin treatments for 14 days significantly reduced (p=0.000) the serum uric acid levels of hyperuricemic rats in a time-dependent manner. All treatments significantly inhibited hepatic xanthine oxidase/xanthine dehydrogenase activity. *Allium cepa L.* and quercetin treatments led also to a significant improvement in biomarkers of oxidative stress in hyperuricemic rats (p=0.000). Although the hypouricemic effect of allopurinol was much higher than that of *Allium cepa L.* and quercetin, it could not significantly change oxidative stress biomarkers.

Conclusion: These results may be responsible partly for the beneficial effects of *Allium cepa L.* and its major flavonoid on hyperuricemia and oxidative stress.

Hyperuricemia, which is characterized by high serum uric acid level is present in 5-30% of the general population and seems to be increasing worldwide.[1] It has been considered as an important risk factor for gout, and may be associated with development of the reactive oxygen species (ROS)-mediated diseases, such as cancer and cardiovascular diseases.[2] The control of uric acid production has been widely considered as a key factor in the prevention and treatment of hyperuricemia.[3] Liver xanthine oxidase/xanthine dehydrogenase (XO/XDH) is the key enzyme in the catabolism of purines, and catalyses the oxidation of hypoxanthine to xanthine and xanthine to uric acid. Xanthine dehydrogenase is the frequent active form under physiological conditions. Under pathological states, however, in parallel to the degradation of adenosine triphosphate into adenine and xanthine, an extensive conversion of XDH to XO takes place. The latter uses molecular oxygen as an electron acceptor and leads to the formation of superoxide anion and hydrogen peroxide in parallel with uric acid production and acts as a source of ROS.[4] Therefore, the inhibition of XO activity may decrease uric acid and ROS production and result in antihyperuricemic and antioxidant effects. Allopurinol is the only XO inhibitor under clinical application, and has served as a dominant uric acid-lowering agent in the past 4 decades.[5] However, some severe adverse effects such as hepatitis, nephropathy, allergic reactions, and 6-mercaptopurine toxicity limit the clinical use of allopurinol, and it would be highly desired to search for new XO inhibitors, particularly from natural sources, as alternatives for allopurinol.[2,6,7] Flavonoids are a group of phenolic compounds that are prominent components of many food plants, including aromatic plants such as the onion (*Allium cepa Lilliaceae*).[8] These compounds have attracted attention because of their potential beneficial effects on human health. Most of the therapeutic properties of flavonoids have been ascribed to their antioxidant and enzyme inhibitory activities. Xanthine oxidase is one of the most important enzymes that are inhibited by some flavonoids.[9] Onion (*Allium cepa Lilliaceae*) is a flavonoid-rich staple food, and is grown and consumed worldwide. It has been considered for centuries as beneficial for health, and is recommended for curing, or preventing a wide variety of diseases.[10,11] Its major flavonoids have been identified as quercetin, quercetin-4'-glucoside, and quercetin-3, 4'-diglucoside.[12,13] In addition, onion has been found to have the highest quercetin content (284-486 mg/kg) in a survey of 28 vegetables and 9 fruits.[14] Although the preventive effects of onion and its flavonoids have been clearly demonstrated in epidemiological studies, their mechanisms of action have not been yet specified.[10] In the present in vivo study, we investigated the hypouricemic and antioxidant actions of onion (*Allium cepa Lilliaceae*) and quercetin in a normal and hyperuricemic animal model induced by potassium oxonate. To explore the possibly involved mechanism of hypouricemic action, the potential inhibitory effect of onion and quercetin on rat hepatic XDH and XO were also investigated.

Methods. *Reagent.* Quercetin, potassium oxonate (PO), xanthine, nicotinamide adenine dinucleotide (NAD+), uric acid, allopurinol, tetraethoxypropane (TEP), trichloroacetic acid (TCA), 2-thiobarbituric acid (TBA), bicinchoninic acid kit, and 6-mercaptopurine were purchased from Sigma-Aldrich Chemical Co. (Steinheim, Germany). All other reagents were purchased from Merck (Darmstadt, Germany). The reagents used were of analytical grades. The onion (*Allium cepa Lilliaceae*) was purchased from a wholesale market. The following study was conducted in the Department of Nutrition and Biochemistry, Tehran University of Medical Sciences, Iran, between May 2007 and March 2008.

Test compound preparation. The outer dry skins and any inedible outer portions of onion (*Allium cepa Lilliaceae*) were removed, and the remaining edible portion was weighted and completely blended in distilled water (1:1 w/v). Quercetin was dissolved in propylene glycol. Allopurinol used as a positive control, was prepared in 0.9% saline.

Animals. A total of 48 male Wistar rats (body weights: 180-200 g) were obtained from the animal house of Tabriz University of Medical Sciences, Iran. They were fed with a commercial laboratory diet, and allowed food and water ad libitum for an acclimatization period of one week prior to the experiment. All animals were maintained on a 12 hour/12 hour light/dark cycle, and the temperature and humidity were kept at 18 ± 1^0C and 50%. They were handled according to the recommendation of the local and national ethic committees.

Animal model of hyperuricemia in rats. Experimentally-induced hyperuricemia in rats (due to inhibition of uricase with PO was used to study the antihyperuricemic and antioxidant effects of the test compounds.[15] Briefly, 250 mg/kg, uricase inhibitor, PO, dissolved in 0.9% saline solution was administrated intraperitoneally to each animal one hour before oral administration of the test compounds.

Experimental design. The animals were randomly divided into 8 equal groups (6 rats per group); group 1:

untreated, non-hyperuricemic animals; group 2: normal animals given 5 g/kg onion; group 3: normal animals given 5 mg/kg quercetin; group 4: normal animals given 5 mg/kg allopurinol; group 5: hyperuricemic animals; group 6: hyperuricemic animals given 5 g/kg onion; group 7: hyperuricemic animals given 5 mg/kg quercetin; group 8: hyperuricemic animals given 5 mg/kg allopurinol.

Sample preparation. The whole blood sample was taken from each rat by cutting the tail tip, one hour after the test compound administration at the pre-intervention, first, seventh, and fourteenth days of the study. Serum was obtained by centrifuging blood samples at 6000 rpm for 10 minutes. For high performance liquid chromatography (HPLC) analysis, the serum was filtered using SPARTAN 13/0.45 RC, Watman. The sera were stored at -20°C until use. At the end of the experiment, rats were anesthetized between 09:00 and 10:00 am. Their livers were removed, weighed, and then rapidly washed in cold saline (0.9%), and placed in ice-cold isotonic potassium chloride solution (1.15% KCl w/v) containing 0.1 mM EDTA. The livers were then chopped into 4-5 volumes of 50 mM phosphate buffer (pH 7.4), and homogenized by a homogenizer fitted with a Teflon pestle. The homogenate was then centrifuged at 3000 g for 10 minutes, the lipid layer was carefully removed, and the resulting supernatant fraction was further centrifuged at 15,000 g for 60 minutes at 4°C. The supernatant was stored at -80°C until use.

Uric acid determination. The serum uric acid levels were analyzed by the HPLC method using a system supplied by Waters Associates, Norwich, Cheshire, United Kingdom, which consisted of a Waters 515 pump, Waters 717 plus Autosampler, Waters 2487, Dual λ Absorbance Detector. The mobile phase was a mixture of 100 mM monopotassium phosphate (pH 3.5): methanol (97:3, v/v). Separations were performed on a C-18 column (Perfectsil Target ODS-3 (5 µM), 250x4.6 mm) with a C-18 guard column (Perfectsil Target ODS-3 (5 µM), 10x4 mm). The effluent was monitored by UV detection at 290 nm at a flow rate of 1 ml/min. Standard solutions of uric acid in the range of 0.1 to 20 mg/dl were prepared in the mobile phase. Serum uric acid concentrations were expressed as mg/dl, 6-Mercaptopurine (1 mM) was used as the internal standard.

The XO/XDH activity assay. The XO and XDH activity were measured spectrophotometrically by monitoring the production of uric acid from xanthine according to Prajda and Weber's method.[16] For XDH, the assay mixture consisted of 50 mM xanthine, 50 mM phosphate buffer (pH 7.4), 200 mM NAD+, and 100 ml of the enzyme solution. After preincubation at 37°C for 15 minutes, the reaction was initiated by the addition of the substrate solution. After 30 minutes, the reaction was terminated by adding 0.5 ml HCl (0.6 M), and the absorbance was measured at 290 nm using a Shimadzu 2550 UV/VIS spectrophotometer, which was controlled by the Shimadzu UV Probe personal software package including kinetics software. The instrument was connected to a Shimadzu cell temperature control unit. The XO activity was measured using a similar method described for XDH, with the difference being that molecular oxygen was used for NAD+ as an electron acceptor. One unit (U) of activity was defined as one nmol of uric acid formed per minute at 37°C, pH 7.4.

Protein determination. Protein concentration was determined spectrophotometrically by bicinchoninic acid kit using bovine serum albumin as the standard.

Total antioxidant capacity assay. The total antioxidant capacity of serum was determined by measuring its ability to reduce ferric ions (Fe^{3+}) to ferrous form (Fe^{2+}) by the FRAP (Ferric Reducing Ability of Plasma) test. The FRAP assay measures the change in absorbance at 593 nm owing to the formation of a blue colored Fe^{2+}-tripyridyltriazine compound from Fe^{3+} by the action of electron donating antioxidants. The FRAP reagent consists of 300 µmol/ml acetate buffer (pH 3.6), 10 µmol/ml tripyridyltriazine in 40 µgmol/ml HCl and 20 µmol/ml $FeCl_3$ in the ratio of 10:1:1. Briefly, 30 µgl of serum was added to 1.0 ml freshly prepared and prewarmed (37°C) FRAP reagent in a test tube and incubated at 37°C for 10 minutes. The absorbance of the blue colored complex was read against a reagent blank (1.0 ml FRAP reagent + 30 µl distilled water) at 593 nm. Standard solutions of Fe^{2+} in the range of 10-1000 µmol/L were prepared from ferrous sulphate in water. The FRAP values were expressed as µmol Fe^{3+} reduced to Fe^{2+} per liter.[17]

Lipid peroxide determination. Lipid peroxide in the serum was measured according to the Yoshioka et al method.[18] Briefly, 0.5 ml serum was shaken with 2.5 ml of 20% TCA in a 10 ml centrifuge tube. One ml of 0.67% TBA was added to the mixture, shaken, and warmed for 60 minutes in a boiling water bath followed by rapid cooling. Then it was shaken into 4 ml of n-butanol layer in a separation tube and malondialdehyde content in the serum was determined at 532 nm by spectrophotometer against n-butanol. The standards of 0.1-20 µmol/L TEP were used. The results were expressed as µmol/L serum.

Statistical analysis. All the samples and standards were run in duplicate, and the results were expressed as means ± standard deviation (SD). The statistical comparison between the experimental groups was performed by independent-sample t-test using SPSS computer program. The probabilities of 5% or less ($p<0.05$) were considered significant.

Results. As shown in **Table 1**, oral administration of onion (*Allium cepa Lilliaceae*) and quercetin for 14 days significantly reduced (*p*=0.000) the serum uric acid levels of hyperuricemic, but not in normal rats. However, allopurinol treatment significantly reduced the levels of serum uric acid of both normal and hyperuricemic groups on day 14 (*p*=0.003 and *p*=0.000). The results also indicate that onion and quercetin exert their hypouricemic effects in a time-dependent manner in oxonate-pretreated rats. The effects of the orally administered onion (*Allium cepa Lilliaceae*) and quercetin on liver XO/XDH activity after 14 days are summarized in **Table 2**. In normal rats, the administration of onion and quercetin caused 32.4% (*p*=0.000) and 17.1% (*p*=0.05) inhibition on liver XDH activity. The inhibitory effect of onion and quercetin treatment on liver XO activity was not statistically significant in these groups. Allopurinol decreased significantly the mean activity of XDH and XO by 61.3% (*p*=0.000) and 53.2% (*p*=0.002). In hyperuricemic rats, onion and quercetin resulted in significant inhibition on both liver XDH and XO activity. The reductions in liver XDH and XO activity in these hyperuricemic animals receiving onion were 49.7% (*p*=0.000) and 39.8% (*p*=0.002). Quercetin administration resulted in 41.9% (*p*=0.000) and 34.5% (*p*=0.01) inhibition on XDH and XO activity. Treatment of the hyperuricemic animals

Table 1 - Effect of oral administration of *Allium cepa Lilliaceae* (*Allium cepa L.*) and quercetin on serum uric acid levels (a time-dependent study).

Treatment	Uric acid (mg/dl)			
	Pre-intervention day	First day	Seventh day	Fourteenth day
Normal rats				
Vehicle	1.84 ± 0.53	1.65 ± 0.26**	1.62 ± 0.23**	1.68 ± 0.29**
Allium cepa L. (5 g/kg)	1.71 ± 0.34	1.61 ± 0.28**	1.50 ± 0.47**	1.48 ± 0.28**
Quercetin (5 mg/kg)	1.69 ± 0.23	1.65 ± 0.20**	1.61 ± 0.27**	1.59 ± 0.26**
Allopurinol (5 mg/kg)	1.66 ± 0.46	1.52 ± 0.34**	1.37 ± 0.18**	0.89 ± 0.41[†],**
Hyperuricemic rats				
Vehicle	1.47 ± 0.54	3.49 ± 0.56[‡]	3.54 ± 0.58[‡]	3.61 ± 0.44[‡]
Allium cepa L. (5 g/kg)	1.85 ± 0.47	3.40 ± 0.56[‡]	2.62 ± 0.31[‡,§]	1.88 ± 0.33**
Quercetin (5 mg/kg)	1.59 ± 0.44	3.20 ± 0.44[‡]	2.83 ± 0.26[‡]	2.10 ± 0.30[*],**
Allopurinol (5 mg/kg)	1.53 ± 0.49	2.49 ± 0.23[‡,§]	1.92 ± 0.43[§]	1.22 ± 0.32[*],**

All values are expressed as mean ± SD (n=6). Independent-sample t-test was used for statistical significance assessment.
[*]*p*<0.05, [†]*p*<0.01, [‡]*p*<0.001 versus normal control group, [§]*p*<0.01, ** *p*<0.001 versus hyperuricemic control group.

Table 2 - Effect of oral administration of *Allium cepa Lilliaceae* and quercetin on liver XO and XDH activity after 14 days.

Treatment	Activity (U/mg protein)		Inhibition %	
	XO	XDH	XO	XDH
Normal rats				
Vehicle	2.50 ± 0.63	3.80 ± 0.38	-	-
Onion (5 g/kg)	1.82 ± 0.40[§]	2.57 ± 0.42[‡,**]	27.2	32.4
Quercetin (5 mg/kg)	2.32 ± 0.31	3.15 ± 0.46[*]	7.2	17.1
Allopurinol (5 mg/kg)	1.17 ± 0.28[†,††]	1.47 ± 0.40[‡,††]	53.2	61.3
Hyperuricemic rats				
Vehicle	2.49 ± 0.52	3.82 ± 0.62	-	-
Onion (5 g/kg)	1.50 ± 0.28[†,**]	1.92 ± 0.31[‡,††]	39.75	49.7
Quercetin (5 mg/kg)	1.63 ± 0.39[†,**]	2.22 ± 0.38[‡,††]	34.5	41.9
Allopurinol (5 mg/kg)	1.05 ± 0.18[***,††]	1.27 ± 0.33[‡,††]	57.8	66.75

All values are expressed as mean ± SD (n=6). Independent-sample t-test was used for statistical significance assessment. [*]*p*<0.05,
[†]*p*<0.01, [‡]*p*<0.001 versus normal control group, [§]*p*<0.05, **p*<0.01, [††]*p*<0.001 versus hyperuricemic control group,
XO - xanthine oxidase, XDH - xanthine dehydrogenase

with allopurinol significantly inhibited ($p<0.000$) both XDH (66.75%) and XO (57.8%) activity. As demonstrated in **Figure 1**, we observed a significant increase ($p<0.05$) in total antioxidant capacity (FRAP value) following treatment of the normal rats with onion for 14 days ($p=0.002$). As also shown in **Figure 1**, in hyperuricemic control rats, the total antioxidant capacity was significantly lower than that of normal rats. The oral administration of onion ($p=0.004$) and quercetin ($p=0.003$) to hyperuricemic rats induced a significant increase in total antioxidant capacity. The effects of the orally administered onion and quercetin on MDA concentration are shown in **Figure 2**. In hyperuricemic control rats, serum MDA, as a biomarker of lipid peroxidation, was statistically higher than that of normal rats ($p=0.000$). The oral administration of onion ($p=0.036$) and quercetin ($p=0.05$) for 14 days led also to a significant reduction in MDA concentration in the hyperuricemic rats.
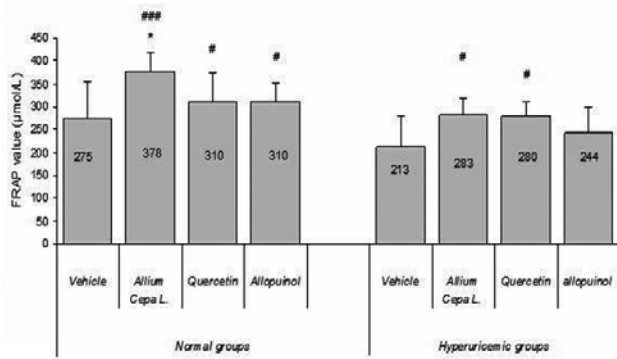

Figure 1 - Effect of oral administration of *Allium Cepa Lilliaceae* and quercetin on serum total antioxidant capacity (FRAP value) after 14 days (mean±SD, n=6). *$p<0.05$ versus normal control group, #$p<0.05$, ###$p<0.001$ versus hyperuricemic control group.
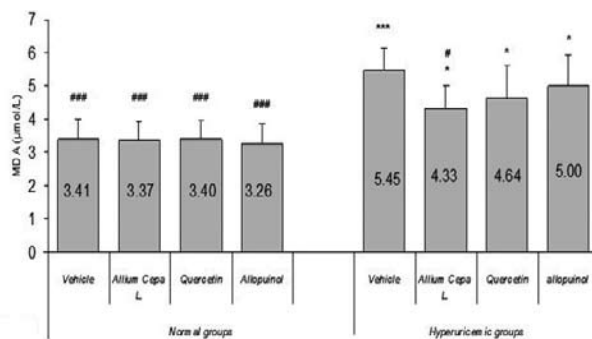

Figure 2 - Effect of oral administration of *Allium Cepa Lilliaceae* and quercetin on MDA concentration after 14 days (mean±SD, n=6). *$p<0.05$, ***$p<0.001$ versus normal control group, #$p<0.05$, ###$p<0.001$ versus hyperuricemic control group.

Discussion. The results indicate that the oral administration of onion (*Allium cepa Lilliaceae*) and quercetin exert notable hypouricemic effects in hyperuricemic, but not in normal rats. Kong et al[19] has also shown that the water extract of Ermiao wan (a Chinese herbal medicine used in the treatment of acute gout) and allopurinol have less inhibitory effects on serum uric acid levels in normal mice compared with those animals pretreated with PO. The hypouricemic effect of allopurinol, as a main uric acid-lowering agent, was more potent than that of onion and quercetin in both normal and hyperuricemic groups. As it is demonstrated in **Table 1**, although allopurinol could reduce serum uric acid levels even lower than that of normal values in either normal and hyperuricemic rats after 14 days; onion and quercetin treatments did not cause any significant reduction in serum uric acid levels in normal rats after 14 days. Moreover, in hyperuricemic rats treated with onion and quercetin, although, the hypouricemic effects of them were statistically significant on day 14 ($p=0.000$), their effect was yet weaker than that of allopurinol, and the mean uric acid concentration of these groups did not reach normal levels. These results in normal rats indicated that onion (*Allium cepa Lilliaceae*) and its major flavonoid (quercetin) might bring fewer side effects than allopurinol in the treatment of hyperuricemia. On the other hand, this property of onion, and its major flavonoid could be considered as an advantage for them. Although the elevated levels of uric acid in the circulation could give rise to gout and possibly other pathological conditions,[20] the antioxidant action of uric acid, particularly its ability to inhibit DNA damage, is also well documented.[21] Thus, excessive lowering of the uric acid level in the circulation beyond that of the normal range might even be counter productive.[7] Taking into account that onion as a food can be used safely long-term; this feature of onion makes it a possible alternative for allopurinol, or at least in combination therapy to minimize the side-effects of allopurinol.

Our study also showed that onion has a higher potential than quercetin to attenuate, and/or to reverse hyperuricemia. In onion, quercetin glycosides are predominant and it is well known that the bioavailability of flavonoids in onion is higher than that of quercetin aglycon.[14] Therefore, the higher efficiency of onion compared to quercetin to lower uric acid levels could be attributed to its higher intestinal absorption. The results also indicate that onion and quercetin exert their hypouricemic effects in a time-dependent manner in oxonate-pretreated rats. In onion treated-hyperuricemic rats, uric acid reduction was not statistically significant on the first day, but after 7 ($p=0.005$) and 14 days ($p=0.000$) of intervention,

a significant reduction was observed in the uric acid levels of hyperuricemic rats reaching to a level similar to the normal control animals. In quercetin treated-hyperuricemic rats, only after 14 days of intervention, serum uric acid levels reduced significantly (p=0.000) compared to hyperuricemic control rats. Unlike onion and quercetin, the hypouricemic effect of allopurinol was statistically significant (p=0.007) even after one day of the drug administration, indicating the quicker onset of allopurinol action compared to onion or quercetin.

The inhibitory effect of onion (*Allium cepa Lilliaceae*) and its major flavonoid (quercetin) on liver XO/XDH activity was also confirmed in this study. Xanthine oxidase/xanthine dehydrogenase is the key enzyme in the catabolism of purines and has a critical role in the endogenous production of uric acid.[4] Several in vitro studies confirmed the XO/XDH inhibitory activity of some flavonoids. These compounds are structurally similar to XO/XDH substrate and so can inhibit the enzyme activity.[22] Therefore, the hypouricemic property of onion and quercetin could be explained at least partly by the inhibitory effects of them on XO/XDH activity. The extent of reduction in XDH/XO activity elicited by allopurinol was much higher than that observed with the onion and quercetin administration in both normal and hyperuricemic groups. Others have reported similar results. According to these studies, the involvement of other possible mechanisms such as enhanced uric acid clearance or actions on other purine metabolizing enzymes cannot be ruled out.[7,19,23,24] This could be further supported by the existence of some hypouricemic compounds including natural products that are devoid of XDH/XO inhibitory activity.[7,24]

In addition, in this investigation hyperuricemia was associated with oxidative stress; as uric acid levels were positively correlated with MDA concentration (r=0.65, p=0.000). We presumed that such results might be due to intraperitoneal injection of PO. This compound is a selectively competitive uricase inhibitor that blocks the effect of hepatic uricase and produces hyperuricemia in rodents.[15,25] Though serum uric acid is considered to be an antioxidant within its normal physiological conditions, increased production of uric acid in pathological states has been associated with increased production of oxygen free radicals, due to the conversion of XDH to XO that plays a pivotal role in progression of oxidative stress condition.[4] It is well known that XO is a source of ROS and this fact may explain the link between hyperuricemia and oxidative stress-induced diseases.[2,4,6] Moreover, serum uric acid elevation may promote oxygenation of LDL-C and facilitate lipid peroxidation.[26] From the above discussion, we can assume that serum uric acid through lipid peroxidation, might be working towards the etiopathogenesis of oxidative stress diseases and its

serum level may be a deciding factor for progression of the disease. We found a significant inhibition of oxidative stress by increasing total antioxidant capacity and decreasing MDA concentration following treatment of hyperuricemic rats with onion and quercetin. Plants belonging to the *Allium* family have been found to have antioxidant properties in several in vitro studies.[27-29] The antioxidant activity of *Allium* plants such as onion has been mainly attributed to sulphur and phenolic-containing compounds particularly their flavonoids.[30,31] These phytochemicals improve total antioxidant capacity, suppress destructive oxygen free radicals, and prevents oxidative stress damage.[8] Our study also showed that onion (*Allium cepa Lilliaceae*) has a higher potential than quercetin to inhibit oxidative stress. As it was mentioned before, this finding could be attributed to the high bioavailability of quercetin glycosides compared to quercetin aglycon.[14]

In this study, allopurinol could not significantly inhibit oxidative stress in hyperuricemic rats. However, the inhibition of XO by allopurinol was previously reported to decrease the level of ROS production, and reduce the hepatic injury. This inconsistency between results may be due to the higher dose of allopurinol (50 mg/kg) used in Lee et al's study.[32]

In conclusion, onion (*Allium cepa Lilliaceae*) and quercetin can reduce uric acid levels in hyperuricemic rats with no effects on the level of this biological metabolite in normal animals. Such hypouricemic effects may be attributed, at least partly, to the inhibitory action of XO/XDH. Moreover, onion (*Allium cepa Lilliaceae*) and quercetin prevented oxidative stress by enhancing total antioxidant capacity and decreasing lipid peroxidation. As onion is a common component of the usual diet throughout the world, these properties of this natural food make it a possible alternative for allopurinol, or at least in combination therapy to minimize the side-effects of allopurinol, particularly in long-term application. Further investigations to explore the effect of other components of onion and define their clinical efficacy would be highly desirable.

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