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Full Length Research Paper

Antioxidant effects of Zamzam water in normal rats and those under induced-oxidative stress

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Alkaline water have been claimed to boost antioxidant mechanisms. Thus, this study aimed to investigate if Zamzam water that is similarly alkaline, can promote antioxidant mechanisms in normal rats and those stressed with the high dose of gentamicin. In one experiment, the effects of Zamzam water were compared to those of ordinary bottled water in normal rats. In the second experiment, the effects of Zamzam water were compared to those of ordinary bottled water in rats injected intra-peritoneally with either saline or gentamicin at a dose of 80 mg/kg body weight. No significant differences in serum levels of a group of trace elements including arsenic were observed between the groups of rats given the two types of water. Serum antioxidant enzymes (catalase and dismutase) were similar between the different groups of rats both in normal or those stressed by gentamicin injection. In the two groups injected with gentamicin, total antioxidant capacity was significantly higher in the group given Zamzam water. In conclusion, giving Zamzam water to normal rats for three weeks does not show any sign of toxicity and seems to be associated with increased total antioxidant in rats stressed with gentamicin overdose. Further studies are needed to evaluate these findings.

Key words: Zamzam water, oxidative stress, gentamicin, antioxidant capacity, antioxidant enzymes.

INTRODUCTION

Oxidative stress, an imbalance between oxidant and antioxidant mechanisms in animal bodies, has been implicated in many diseases and their complications (Pitocco et al., 2010, Wei et al., 2009; Reuter et al., 2010). This imbalance may result either form excessive exposure to pro-oxidants or from compromised anti-oxidant mechanisms. The later may result from deficiency of essential elements or from incapacitation of disease, while the former might emanate from exposure to exo-genous toxins or the pathologic stress of disease (Pitocco et al., 2010, Narayana, 2008). Thus, oxidative stress may occur in normal animals when antioxidant mechanisms are not working properly as in dietary deficiencies of vitamin E, vitamin C or the essential elements like selenium, zinc, and manganese among others. The later elements are essential components of the antioxidant the antioxidant enzymes glutathione peroxidase, superoxide dismutase and catalase (Rotruck et al., 1973, Beem et al., 1977, Horn et al., 2010). Another important cause of oxidative stress is the exaggerated endogenous production of free radicals by disease processes as in diabetes mellitus and cancer (Pitocco et al., 2010).

Exposure to exogenous toxins is still another mode for inducing oxidative stress as in the toxicity of some drugs like gentamicin (Narayana, 2008) or industrial chemicals like carbon tetrachloride (Cuciureanu et al., 2009). Ap-parently then, oxidative stress can be combated by strategies that promote and foster the antioxidant defense mechanisms.

Water has been shown to strengthen the antioxidant capacity of animal bodies (Nassini et al., 2010). Most of the work in this respect focused on alkaline water, which has been reported to reduce oxidative stress in patients with chronic renal disease (Huang et al., 2003) and slow the aging process for which oxidative stress has been proposed as the main contributor (Hofer et al., 2008). This water has also been shown to improve the glycemic

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Table 1. Ranges of some elements, salts and pH of Zamzam water.

Parameter	Range
Calcium Carbonate (ppm)	300 - 340
Magnesium (ppm)	19 - 24
Chromium (ppb)	0.7 - 0.75
Manganese (ppb)	0.07 - 0.10
Cobalt (ppb)	0.3 - 0.4
Copper (ppb)	0.5 - 1.0
Zinc (ppb)	1 - 2
Arsenic (ppb)	19 - 26
Selenium (ppb)	3 - 4
Strontium (ppb)	700 - 800
Cadmium (ppb)	0.2 - 1.0
Lead (ppb)	0.05 - 0.1
Nitrate (ppb)	70 - 90
pH	7.75 - 8.0

control in diabetic rats by unknown mechanisms (Jin et al., 2006). Although the beneficial effects of alkaline water are assumed to be due to its alkaline nature, its composition in terms of minerals and trace elements may also play a role.

The alkaline nature of water is associated with the richness of aquifers with certain elements like magnesium on one hand and on the other hand the alkaline nature leaches certain elements from the soil or rocks through which aquifers stream. Despite the low levels of elements or trace elements in water, their contribution is still likely at least for some of them (WHO, 2005). Thus, if harmful contaminants of water are taken care of, water, in addition to its hydration property, may have other important effects. This study was an attempt to explore if drinking of Zamzam water, which is similarly alkaline, can boost the antioxidant mechanisms in normal rats or those stressed by gentamicin.

MATERIALS AND METHODS

Zamzam water samples were obtained directly from the well. The samples were neither treated with any chemical nor with procedures. Two experiments were conducted on a total of 60 Wistar rats, each weighing between 340 to 400 g. In both experiments, animals were housed individually in cages and had free access to ordinary rat chow diet and ordinary bottled water during the acclimatization week.

Experiment 1: Effect of Zamzam water in normal rats

Following the acclimatization week, 20 rats were assigned randomly to one of two groups, 10 rats each, and continued with free access to the ordinary rat diet. In Group 1, the control group continued the free access to the ordinary bottled water, while for Group 2, the experimental group was shifted to free access to the Zamzam water for the rest of the experiment duration of three weeks. The rats were weighed on weekly basis and their water consumption was calculated.

Experiment 2: Effect of Zamzam water in gentamicin-stressed rats

Following the acclimatization week, 40 rats were randomly assigned to one of two groups (20 rats each) and continued with free access to the ordinary rat diet. For Group 1, the control group continued the free access to the ordinary bottled water, while for Group 2, the experimental group was shifted to free access to the Zamzam water for the rest of the experiment duration of nine days. The rats were weighed on daily basis. On day 1, each of the two groups was subdivided into two subgroups of 10 rats each. In each group, one subgroup was injected with normal saline while the other was injected daily with gentamicin intra-peritoneally for 8 days. The dose of gentamicin was 80 mg/kg body weight, which is known to cause toxicity in rats (Banday et al., 2008). An equivalent volume of normal saline was injected to rats in the control group.

Termination of experiments and collection of blood

The experiments were terminated on day 21 for experiment 1 and on day 9 for experiment 2. In the morning of the termination day, rats were anaesthetized with 0.5 ml of a 2:3 ketamine-zylocaine mixture. The abdomen was opened, the aorta exposed and 5 to 10 ml of blood were collected in plain tubes and left to clot. Serum was separated by centrifugation at 2500 rpm.

Serum was then analyzed for total antioxidant capacity, catalase, superoxide dismutase, glutathione and thiobarbituric acid reactive substances (TBARS). In the case of the experiment 1, serum was also analyzed for the level of ten selected trace elements to see whether or not Zamzam water impact the levels of these elements in the body.

Laboratory analysis

Catalase, superoxide dismutase, glutathione and TBARS were analyzed by Cayman kits (Cayman Chemical Co Inc, Ellsworth Rd, Ann Arbor, USA). All the analyses were based on methods previously described (Johansson and Borg, 1988; Wheeler et al., 1990; Liu 1996; Baker et al., 1990; Armstrong and Browne, 1994). Constituents of Zamzam water used were measured by ionic chromatography (ionic chromatograph, Metrohm, USA). The trace elements levels in serum were measured by inductively coupled plasma mass spectrometry.

Statistical analysis

The Statistical Package for Social Sciences (SPSS 14) was used for statistical analysis. Paired t-test was used to analyze change in weight at week 1, 2 and 3 from baseline body weight in the first experiment. Differences between groups were explored by unpaired t-test when two groups were involved (Experiment 1) or analysis of variance when more than two groups are involved (Experiment 2).

RESULTS

The volume of water consumed was similar in all groups. Table 1 shows the ranges for elements, salts and pH for the samples of Zamzam water utilized in this study.

Table 2. Body weight at baseline and at the end of weeks 1, 2 and 3 in rats given free access to ordinary bottled water and Zamzam water.

Group	Baseline	Week 1	Week 2	Week 3
Bottled	360 ± 8.5	374±9.3*	378.5 ± 10.8 *	385 ± 11.6 *
Zamzam	356.5 ± 10.7	363 ±12.8	364 ± 13.3	372 ± 16.5

Values are Mean ± Standard Error. * P < 0.001 Compared to Baseline by Paired t-test.

Table 3. Serum levels (ppb) of measured trace elements in control and experimental groups of rats after three weeks of free access to ordinary bottled water and Zamzam water.

Parameter	Control group	Experimental group	P-value
Chromium	16.03 ± 2.43 0.31 ± 0.047	14.77 ± 0.38 0.28 ± 0.007	0.170
Manganese	1.452 ± 0.509 0.026 ± 0.009	1.045 ± 0.377 0.019 ± 0.007	0.153
Cobalt *	Below detection limit	0.4062 ± 0.2448 0.0067± 0.0041	Not applicable
Copper	178.8 ± 24.5 2.82 ± 0.39	188.4 ± 21.3 2.97 ± 0.36	0.500
Zinc	150.6 ± 24.6 2.30 ± 0.38	178.1 ± 39.7 2.72 ± 0.61	0.200
Arsenic	1.564 ± 0.346 0.21 ± 0.046	1.746 ± 0.354 0.23 ± 0.047	0.423
Selenium	62.88 ± 6.38 0.80 ± 0.08	60.93 ± 0.68 0.77 ± 0.008	0.550
Strontium	21.093 ± 17.202 0.24 ± 0.20	10.923 ± 0.679 0.11 ± 0.008	0.290
Cadmium	0.134 ± 0.078 0.001± 0.00006	0.122 ± 0.081 0.001± 0.00006	0.812
Lead	1.63 ± 0.862 0.008 ± 0.004	1.077 ± 0.471 0.005 ± 0.002	0.263

Experiment 1: Effect of Zamzam water in normal rats

Tables 2, 3 and 4 summarize the effects in normal rats having free access to ordinary bottled water and Zamzam water on weight gain, serum levels of trace elements and serum antioxidant parameters. Rats in both groups were active and showed no abnormal signs throughout the three weeks of treatment. Compared to baseline, rats given free access to bottled water had significant weight gain by the end of the first, second and third week, while those given Zamzam water did not attain statistically significant weight gain (Table 2). As regard the serum levels of trace elements measured, there were no significant differences between rats given bottled water and Zamzam water at the end of the three weeks treatment (Table 3). It is noteworthy that cobalt was detectable only in serum of rats given Zamzam water. For the antioxidant parameters (Table 4), no statistically significant differences were observed between the rats given the two types of water. However, serum glutathione and total antioxidant capacity were on the verge of being statistically significantly higher in rats given Zamzam

Table 4. Serum antioxidant enzyme activities, glutathione, total antioxidant capacity and thiobarbituric acid reactive substance (TBARS) of rats after three weeks of free access to ordinary bottled water and Zamzam water.

Parameter	Control group	Experimental group	P-value
Catalase activity (nmol/ml/min)	85.68 ± 34.55	95.78 ± 36.84	0.535
Superoxide dismutase (U/ml)	3.507 ± 1.498	2.960 ± 1.160	0.373
Glutathione (µM)	5.590 ± 1.545	6.9294 ± 1.348	0.053
Total antioxidant capacity (mM)	3.065 ± 1.074	4.192 ± 1.652	0.087
TBARS (µM)	43.076 ± 15.02	41.711 ± 15.230	0.842

Table 5. Absolute and relative weight of the kidneys of normal rats and those injected with gentamicin with free access either to ordinary bottled water or Zamzam water.

Group	Treatment	Absolute kidney weight (g)	Relative kidney wt / body wt (g/kg)
Bottled water	Saline injected	2.505 ± 0.082	6.597 ± 0.192
	Gentamicin injected	2.728 ± 0.100	7.204 ± 0.239
Zamzam water	Saline injected	2.530 ± 0.092	6.785 ± 0.234
	Gentamicin injected	2.539 ± 0.132	7.323 ± 0.276

*No significant difference between groups, P=0.358 (ANOVA).

Table 6. Serum antioxidant enzyme activities, glutathione, total antioxidant capacity and thiobarbituric acid reactive substance (TBARS) of rats after eight days of free access to ordinary bottled water and Zamzam water and injected daily with either saline or gentamicin.

Parameters	Bottled water		Zamzam	
	Saline injected	Gentamicin injected	Saline injected	Gentamicin injected
Catalase (nmol/ml/min)	45.9 ± 6.9 (7)	43.3 ± 3.7 (9)	60.12 ± 4.9 (8)	61.41 ± 13.8 (7)
Superoxide Dismutase (U/ml)	4.17 ± 0.32 (7)	3.41 ± 0.24 (9)	3.96 ± 0.23 (8)	4.19 ± 0.41 (7)
Serum glutathione (µmol)	5.38 ± 0.77 (8)	6.83 ± 1.03 (8)	7.22 ± 1.01 (8)	6.96 ± 0.32 (7)
Total antioxidant capacity (mmol)	3.01 ± 0.47 (8)	2.58 ± 0.22 (8)	3.42 ± 0.37 (8)	4.32 ± 0.54 (7)**
TBARS (µmol/l)	50.4 ± 3.5 (8)	48.5 ± 6.3 (8)	39.2 ± 4.1 (8)	49.6 ± 9.6 (7)

** Statistically significant from the other gentamicin group (ANOVA, p=0.008). Number of animals in each group is between brackets.

water compared to those given bottled water.

Experiment 2: Effect of Zamzam water in gentamicin-stressed rats

Tables 5 and 6 summarize the effects in normal rats of having free access to bottled water and Zamzam water with or without gentamicin injection on kidney weight and antioxidant parameters. Kidney weight, both absolute and relative, did not differ significantly between the four groups (Table 5). As regard the antioxidant parameter, with the exception of total antioxidant capacity, no significant differences were noted between the four groups (Table 6). The total antioxidant capacity of the group given Zamzam water and injected with gentamicin was significantly higher in serum total antioxidant capacity than the corresponding one (gentamicin group) given bottled water (Table 6).

DISCUSSION

The results of this study indicate the safety of using Zamzam water in normal rats for medium period of time. Most of the concentrations of trace elements reported here are in agreement with those reported by Shomar (2012). However, we have found greater calcium and chromium concentrations and lower manganese, copper, and nitrate than those reported by Shomar. This difference is most probably related to the timing and type of samples. The level of nitrate in the samples of Zamzam water used in this study (70 to 90 mg/L) is higher than the international guideline of 50 mg/L. However, these international guidelines have been questioned by some studies (Avery, 1999; L'hirondel and L'hirondel, 2002). The base for this international standard is the development of methemoglobinemia in bottle fed infants who consume relatively high amounts of water in relation to their body weight (as much as 250 ml/kg per

day). Such high water consumptions are unlikely to occur in adults or breast fed infants (WHO, 2011). Furthermore, as stated by the World Health Organization (WHO), there is convincing data that the risk of methemoglobinemia is first and foremost increased by concurrent gastro-intestinal infections that increase production of endogenous nitrates and enhance conversion of nitrate to nitrite, an essential step for development of methemoglobinemia. This made WHO to affirm that water with nitrate of 50 to 100 mg/L can be used for bottle fed infants if it is microbiologically safe. Zamzam water is microbiologically safe and is subjected to routine monitoring in this respect. Thus, the nitrate levels of Zamzam water may not pose any danger even for bottle-fed infants since it is microbiologically safe. On the other hand, there may be benefits of higher levels of exogenous intake of nitrate since nitrous oxide and nitrite have antibacterial actions (WHO, 2011). According to WHO, a relation between chronic exposure to nitrate in drinking water and development of cancer is unlikely and intakes of up to 3.7 mg/kg body weight have been proposed by some organizations (WHO, 2011). Thus, high nitrate levels coupled with microbiological safety might be a favorable attribute of Zamzam water and could be responsible for some of its benefits. Meanwhile, further studies along this line are recommended.

As regard arsenic, the guideline of 10 µg/L is still provisional. Some studies in areas with arsenic concentrations somewhat above 50 µg/L have not detected any arsenic-related adverse effects in the residents (WHO, 2011). Toxicity of arsenic is related not only to the absolute level of arsenic, but also the form of arsenic as well as the ability of the body to eliminate it through methylation and combat its effects through the antioxidant mechanisms available. Acute toxicity of arsenic occurs at 21 mg/L (Feinglass, 1973). The most common lesions associated with chronic arsenic toxicity occur in children after 5 years following minimum exposure and the cardiovascular effects occur in children exposed to levels higher than 0.6 mg/L (Zaldivar, 1980; Zaldivar and Ghai, 1980). Noteworthy is the fact that in this study, serum level of arsenic in rats given Zamzam water was not significantly different from that of rats given ordinary bottled water. The lack of significant weight gain in the rats given access to Zamzam water was unexpected and requires further investigations. However, similar results were reported with alkaline water (Merne et al., 2001) produced by addition of calcium carbonate and sodium hydroxide. On the contrary, when alkaline water was given to pregnant dams of rats, off-springs were heavier than those of dams given tap water (Watanabe, 2000). However, in these two later studies, tap water rather than bottled water was used as a control.

Apparently, drinking Zamzam water does not seem to enhance the antioxidant power in normal animals. This is not unexpected because in normal animals, there is a balance between oxidative stress and antioxidant mechanism (Burtona and Jauniauxb, 2011) and no derangements in the antioxidant mechanisms or features of increased peroxidation. When oxidative stress is induced either deliberately or during disease processes, antioxidant mechanisms may be overwhelmed and thus antioxidant powers may be decreased and peroxidation augmented. Under such condition, the effects of promoters of body antioxidant power can be revealed. This is one reason why experiment 2 was conducted. Unexpectedly, however, gentamicin overdose did not significantly alter levels biomarkers of oxidative stress in serum of rats given Zamzam water or ordinary bottled. Gentamicin toxicity is well known to occur even with therapeutic doses (Walker and Shah, 1987) but the mechanism of toxicity is not well known.

Induction of oxidative stress is one possible suspected mechanism for toxicity of gentamicin and has been investigated at different doses and duration of treatment (Abdel-Raheem et al., 2009; Narayana, 2008). Most studies have evaluated the biomarkers of oxidative stress in renal tissue (Sayed-Ahmed and Nagi, 2007; Naryana, 2008; Abdel-Raheem et al., 2009), but only a few have assessed these markers in serum (Sayed-Ahmed and Nagi, 2007). The study by Sayed-Ahmed and Nagi (2007) applied a protocol similar to ours in terms of dose and duration of treatment and also measured a biomarker (TBARS) of oxidative stress in serum. Unlike our study, the later study however, reported a significantly higher TBARS in serum of rats given gentamicin. The rats used in that study were also lighter than the rats used in our current study. Whether or not the difference in body weight of the rats used in the two studies could account for the different results remain to be determined. Despite the lack of clear-cut effects of Zamzam water, the trend of high serum total antioxidant capacity and the significantly high levels of this parameter in the gentamicin experiment associated with Zamzam water warrant further investigation.

In conclusion, this study found no differences between Zamzam water and ordinary bottled water regarding safety for the duration of the two experiments conducted. No signs of arsenic toxicity were also detected. Moreover, Zamzam water tends to potentiate antioxidant power in rats stressed with gentamicin.

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