Antioxidant properties of Zamzam water: a review for arsenic concerns and potential modulation of drug toxicity

Naif Aljuhani

ABSTRACT
Zamzam water is a well-known natural alkaline (pH: 8) drinking water originating from Zamzam well in Makkah (Saudi Arabia) that needs many research efforts being consumed worldwide. A recently published German study confirmed the purity, alkalinity, and stability of Zamzam water components. Zamzam water confers many health benefits and tissue-protective benefits that are promising based on the high mineral and electrolyte contents that correct dehydration and relieve malnutrition besides water alkalinity gastro-esophageal conditions and metabolic acidosis. Pharmacologically, Zamzam water exerts antioxidant hepatoprotective effects against toxins-induced oxidative stress (against carbon tetrachloride and other toxins). Mineral contents of Zamzam water cannot be gained from any other drinking water source except for food. Absent signs, symptoms, and clinical reports of arsenic toxicity greatly relieve British Broadcasting Corporation concerns regarding the consumption of Zamzam water. Reported arsenic concentrations in Zamzam water produce arsenic trioxide (anti-leukemia). Also, co-administration of antioxidants and arsenicals abolished arsenic-induced cellular cytotoxicity. Zamzam water’s overall antioxidant effects strongly support its therapeutic roles as potential antitoxic water, a pharmacological property that may better be utilized in clinical toxicology and treating different kinds of toxicities. We emphasize many drugs-induced free radicals through drug metabolism and discuss biochemical pathways that describe drug metabolites’ disposition in humans. In this review article, all these issues are discussed.

Keywords: Zamzam water, ROS, antioxidant, arsenic, GSH, drugs.

Introduction
Many Muslims believe that Zamzam water, “holy water,” has beneficial medicinal value for curing illness. The Saudi Authorities facilitate Zamzam water to the public throughout Masjid Al Haram in Makkah, and the Prophet’s Mosque in Madinah provided via cooler stationed and special taps. Pilgrims can easily fill water canisters during their pilgrimage for either future use or as gifts for relatives and friends. The physicochemical properties of Zamzam water have been reviewed. There are 34 elements in Zamzam water, including calcium, magnesium, sodium, and chloride in high concentrations compared to natural water. The concentrations of arsenic, lithium, and nitrates in Zamzam water are 27 μg/l, 15 μg/l, and 150 mg/l, respectively [1]. This article will shed light on similarities and differences between Zamzam water and alkaline processed water produced and consumed enormously in Japan and the potential role of Zamzam water in modulating drugs toxicity.

Gastrointestinal Concerns Regarding Arsenic in Zamzam Water
Zamzam water has many advantages over other drinking water types in many aspects. In a recent German report, Shomar [1] reported that Zamzam water did not go bad, and its characteristics did not change over 2 years. Many reported other health merits in Zamzam water that gave it superiority over many drinking water types as being antioxidant, rich in minerals, and alkaline in reaction. That may confirm water purity and its gastrointestinal benefits [2].

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Arsenic contamination of groundwater does not occur to
Zamzam well as proved by the lack of any reported arsenic
Toxicity in Mecca (Makkah, Saudi Arabia) inhabitants or
Saudi Arabian citizens. It is highlighted that the possible
health hazards regarding a relatively high arsenic content
(27 µg/l) in Zamzam water that is less than three times the
maximum permitted level (10 µg/l) [3]. 90% of arsenic
is absorbed from the gastrointestinal tract, and it carries
much gastrointestinal harm, as discussed below.

In the beginning, the BBC [3-5] reported concerns about
bottled water coming from Makkah had been found to
contain high levels of cancer-causing chemicals (arsenic).
It was thought that this type of water is not genuine. Later,
trading standards officers tested bottled Zamzam water
samples at many U.K. outlets and reported some failed
water quality tests due to high arsenic and nitrate contents.
For that reason, some shopkeepers stopped selling Zamzam
water while British health authorities posed a penalty for
selling false Zamzam water by charging unlimited fine
or 2-year imprisonment. BBC [6] concerns came to its
peak after the Association of Public Analysts decided
that “The water is poisonous, particularly because of the
high levels of arsenic, which is a carcinogen”. However,
no evidence was provided to support these concerns or its
expected gastrointestinal harms apart from the relatively
high arsenic and nitrates in Zamzam water. No studies in
humans or animals supported the BBC’s concerns to date
regarding any gastrointestinal or health hazards.

The scientific fact was reported in many studies confirming
that Zamzam water exerts antioxidant effects [7,8]. Being
antioxidant is enough to protect against oxidant harmful
effects induced arsenic, nitrates, other toxins, drugs, and free
radicals on gastrointestinal, urinary, and other body tissues.
Antioxidant substances include vitamin C, vitamin E, beta-
carotene, selenium, and glutathione (GSH) (an amino acid),
in addition to antioxidant enzymes. Those substances are
reducing agents, i.e., can neutralize oxidants that cause
oxidative tissue damage. Antioxidants supply electrons to
neutralize free radicals and block the free radicals’ interaction with body tissue [9].
Interestingly, it was reported that in case water itself exhibits
antioxidant power in addition to the low molecular weight
of water, antioxidant water may be better than antioxidant
vitamins as water is fast-acting and able to reach all tissues
of the body in a short time [10].

There are various studies showed the Zamzam water contents.
However, there has been some controversy over Zamzam
water contamination by trace elements, such as arsenic and
nitrate. Namely, arsenic, it is a virtually ubiquitous compound
found in the earth’s crust-rock and soil [11]. The agricultural
and industrial activities may involve trace elements
contamination, including arsenic and lead [12]. The trace
elements are present with higher concentrations in waters
sold in glass bottles than plastic bottles. The discrepancy
in drinking water’s chemical composition may refer to the
geological and local mineral water regulations [13].

Gastrointestinal sequelae of arsenic are related mainly to
the liver. It has been investigated the effect of drinking
groundwater contaminated with arsenic on the liver.
Using experimental animals, the 3.2 mg/l of arsenic
showed time-dependent toxicity, namely non-cirrhotic
fibrosis of the liver. The chronic exposure of arsenic
feeding could also increase liver enzymes (glutamate
pyruvate transaminase and glutamate oxaloacetate
transaminase) and lipid peroxidation, significantly
reducing enzymatic and non-enzymatic antioxidants’
activities, including GSH, glutathione peroxidase,
glutathione reductase (GR), and catalase, culminating in
hepatomegaly [14]. Those findings could suggest free
radicals and, subsequently, oxidative stress in the arsenic
toxicity. Arsenic toxicity affects the skin, also. It has
been reported that there is a dose-response relationship
between arsenic concentrations and the prevalence of
skin lesions, including hyperpigmentation and keratosis.
Arsenic-induced hyperpigmentation usually occurs
with drinking water containing arsenic less than 100
µg/l, implicating that malnutrition could enhance the
susceptibility to arsenic toxicity [15].

Arsenic and Nitrate Levels in Zamzam Water

Zamzam drinking water is well-studied water. The safety
of drinking water is defined as “water that does not
represent any significant risk to health over a lifetime of
consumption” [16]. It has been found that the total organic
carbon could present in low concentrations in Zamzam
water as compared to alkaline water. It was reported that
the concentrations of arsenic in Zamzam water were
higher than WHO standards, suggesting that long term
research on toxicology should be done. For a medium
period, the safety of feeding Zamzam water containing
(27 µg/l) was reported using animal models. Interestingly,
the stability of Zamzam water composition and alkalinity
has been investigated, in which no changes were observed
in its mineral compositions and alkaline pH after 2 years,
indicating that its composition is strongly stable. Taken
together that the stability of Zamzam water and the nature
alkalinity without the presence of bacterial toxins may
alleviate BBC concern regarding nitrate contamination.
Although the safety and non-toxic nature of Zamzam
water, the dose-time response for skin lesions and cancer
is needed to reveal the association of drinking water at
concentrations below (50 µg/l) of arsenic with increased
risks of cancers, such as bladder cancer [17-19].

Arsenic Metabolism and Toxicity in Living Cells
Utilize the Gastrointestinal Tract

Chemicals such as carbon tetrachloride [20], lead [21],
and arsenic [22] could lead to a decrease in total GSH,
resulting in cytotoxicity through free radicals and
oxidative stress formation [23]. In particular, GSH,
a reductant agent in arsenic reaction, can convert the
pentavalent arsenic to trivalent arsenic [24,25]. The
metabolism of arsenic and GSH is depicted in Figure 1. Biologically, it has been detected that trivalent arsenicals
are quickly complexed with GSH and producing glutathione disulfide (GSSG), hence are inextricably

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linked in cells. The GSH complex with arsenicals (arsenite, methylarsenous acid, and dimethylarsenous acid) could inhibit GR, leading to alter the intracellular GSH: GSSG ratio. It has been proposed that the oxidation of arsenite to arsenate may result in forming reactive oxygen species (ROS) including hydrogen peroxide (H₂O₂); the latter product with the presence of trace metals culminates in the production of hydroxyl radical (•OH), a potent oxidizing radical [26]. Taken together, the generation of free radicals and alteration of GR’s activity could reveal the action of arsenicals as toxicants and carcinogens. Interestingly, total antioxidant capacity was enhanced by feeding Zamzam water in rats stressed with gentamicin overdose. Although the alkalinity and mineral composition of Zamzam water (e.g., selenium) could potentially strengthen its antioxidant capacity, a larger sample size and more extended ingestion period should be carried out to confirm its antioxidant effect.

It is well-documented that chronic exposure to inorganic arsenic could be associated with increased risks of internal organ cancers (e.g., gastrointestinal tract and hepatobiliary system) in both genders [27]. In Taiwan, there is a significant correlation between the ingestion of arsenic at 10 μg/kg/day and the incidence of cancers, including lung, bladder, liver, and kidney [28]. Also, cancer mortality was investigated in a large population (about 400,000 people) in Chile; the arsenic concentrations have a direct effect on increased mortality rates of cancers, namely bladder and lung cancers [29]. These findings demonstrate that prolonged arsenic exposure enhances liver cancer incidence in a dose-dependent manner [30]. Arsenic inactivates up to 200 enzymes, e.g., enzymes regulating cellular energy pathways and DNA synthesis and repair [30,31]. Acute arsenic poisoning manifests by abdominal pain, vomiting, severe diarrhea, peripheral neuropathy, and encephalopathy. Chronic arsenic poisoning may cause multisystem disease. Antioxidants are strongly recommended for treating arsenic toxicity [31].

Main Gastrointestinal Symptoms of Arsenic Intoxication

Features of arsenic poisoning (both acute and chronic) are absent in Makkah city and Saudi Arabia. Makkah city is the land of Zamzam well, the source of Zamzam water that supplies Makkah inhabitants, other cities of Saudi Arabia, and the whole world. Clinical features of acute arsenic poisoning affect many body organs. Increased arsenic concentration in urine may occur within the two first days. Gastrointestinal symptoms of arsenic intoxication include nausea, vomiting, colicky abdominal pain, profuse watery diarrhea, and excessive salivation. However, arsenic toxicity affects other tissue. Hematological abnormalities and dermatological signs as hyperkeratosis and diffuse skin rash may occur. Neuropsychiatric disturbances may follow, e.g., peripheral neuropathy, encephalopathy, seizures, and acute psychosis. Patients may die due to toxic cardiomyopathy, renal failure, respiratory failure, and pulmonary edema. Clinical features of chronic arsenic toxicity are quite variable and may include Mee’s lines in the fingernails and toenails, malignancy (especially in the urinary bladder, liver, kidney, and skin).
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Dermatological features of chronic arsenic intoxication include hyperpigmentation and keratosis of palms and soles. Cardiovascular disease, neurological, respiratory, and hematological (neutropenia) morbidities may occur [31,32].

Drug-Induced Free Radicals

An imbalance between oxidants and antioxidants is considered a significant factor in initiating several diseases such as cancer, diabetes, and inflammation. ROS are generated during these diseases, including \( \text{H}_2\text{O}_2 \) and \( \cdot\text{OH} \). The accumulation of ROS in normal cells results in macromolecules’ oxidation, including nucleic acids, proteins, and lipids [33]. Oxidative stress is produced from increased ROS with reduced antioxidant capacity, typical of many Ang II-induced signaling pathways in the vasculature [34]. The formation of oxidative stress can induce Heme Oxygenase-1, which catalyzes the degradation of heme to biliverdin, iron, and carbon monoxide. However, the overproduction of oxidative stress may inflict severe cellular damage. For instance, the myoglobin or Myeloperoxidase-peroxidase system catalyzed radical-cations production by one-electron oxidation of phenothiazine drugs [35]. Table 1 summarizes the parent drug’s chemical structure and its metabolite, causing hepatotoxicity and agranulocytosis via free radicals formation. Chloroquine, quinacrine, amodiaquine, quinine, quindine, and mefloquine are the most active pro-oxidant drugs. However, 8-hydroxyquinoline and carboline derivatives have antioxidant properties [36]. The quinoline ring can host radicals during an electron transfer process with the redox couple Fe [II] Protoporphyrin IX (PPIX), leading to generating highly reactive radicals [36]. The quinoline drugs increased free hemin levels and catalyzed the peroxidase reaction of \( \text{H}_2\text{O}_2 \) [36,37]. This peroxidative reaction culminates in the generating of oxidative stress that inactivates cysteine protease [37].

Table 1. Examples of drugs-induced free radicals and their metabolites that could cause hepatotoxicity, and agranulocytosis.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Drug structure</th>
<th>Drug’s metabolite structure</th>
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<tbody>
<tr>
<td>Acetaminophen</td>
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<tr>
<td>Amodiaquine</td>
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<tr>
<td>Diclofenac</td>
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<tr>
<td>Indomethacin</td>
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<td><img src="image" alt="Indomethacin" /></td>
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<tr>
<td>Nefazodone (R¹)</td>
<td><img src="image" alt="Nefazodone" /></td>
<td><img src="image" alt="Nefazodone" /></td>
</tr>
<tr>
<td>Trazodone (R²)</td>
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<tr>
<td>Tacrine</td>
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<tr>
<td>Primaquine</td>
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<table>
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<tr>
<th>Drug name</th>
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<tr>
<td>Naproxen</td>
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<tr>
<td>Nevirapine</td>
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<td><img src="image" alt="Nevirapine_metabolite" /></td>
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<tr>
<td>Nimesulide</td>
<td><img src="image" alt="Nimesulide" /></td>
<td><img src="image" alt="Nimesulide_metabolite" /></td>
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<tr>
<td>Tolcapone</td>
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<td><img src="image" alt="Tolcapone_metabolite" /></td>
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<tr>
<td>Trimethoprim</td>
<td><img src="image" alt="Trimethoprim" /></td>
<td><img src="image" alt="Trimethoprim_metabolite" /></td>
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<tr>
<td>Vesnarinone</td>
<td><img src="image" alt="Vesnarinone" /></td>
<td><img src="image" alt="Vesnarinone_metabolite" /></td>
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<tr>
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<tr>
<td>Propranolol</td>
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<tr>
<td>Quetiapine</td>
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Thus, a peroxidase-catalyzed system with the presence of pro-oxidant drugs could generate various radicals, such as carbon, or nitrogen-centered radicals, and thiyl radicals (•S), and subsequently modulate the activity of antioxidant enzymes, for example.

Doxorubicin’s (Dox) cardiotoxicity exerts its effect by producing free radicals accompanied by inhibiting oxidative stress defense systems [38]. Dox-induced free radical formation through impairment of mitochondria, the primary source of free radicals. Superoxide anion radical is one of the ROS that is dismutation to H2O2 by superoxide dismutase enzymes. Catalase and glutathione peroxidase enzymes neutralize the (H2O2); however, its accumulation could culminate in forming radical hydroxyl anion (•OH) through Fenton and Haber-Weiss Net reactions. The reported chemical evidence suggests that dietary antioxidants help disease prevention through reacting antioxidant compounds with free radicals in one-electron reaction and prevent oxidative damage [38].

Establishing the Link Between Oxidative Stress and Zamzam Water Pathways

Toxin effects harm body cells and tissues mainly through oxidative stress mechanisms via producing free radicals (reactive oxygen and or nitrogen species). Oxidative stress is currently defined as “an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control or molecular damage” [39]. Antioxidants scavenge those harmful effects and act as tissue-protective agents. Antioxidants include enzymes, e.g., glutathione peroxidase, catalase, peroxidase, and superoxide dismutase. Zamzam water is rich in ion cofactors (e.g., selenium, magnesium, manganese, strontium, and others) that potentially enhance antioxidant enzymes’ activity. Moreover, the alkaline nature of Zamzam water (pH: 8) is a rare criterion that enhances its antioxidant effects and makes it comparable in its therapeutic benefits to the processed electrolyzed reduced alkaline water is produced in specific electrolyzer sets in Japan. Zamzam water enhances the antioxidant power by raising serum reduced GSH, which confers many therapeutic effects.

Figure 2 shows the reaction of OH, which is generated from the oxidation of drugs, with guanosine [Deoxyguanosine Triphosphate (dGTP), a DNA base] results in 8-hydroxy-dGTP (or can be rearranged to 8′-oxo-dGTP); this is an oxidative DNA modification. The OH can also attack the ribose sugar to result in base propenals. A covalent adduct via a two-electron electrophilic attack can result in an unstable covalent DNA modification, which results in the removal of this base from the DNA helix. A stable covalent adduct can also be formed. These modifications to DNA, if not repaired, may result in the initiation of cancer. The reaction with vital proteins (prevented by GSH), on the other hand, is more likely to result in organ toxicity rather than cancer, although there may be an interplay between protein oxidation and cancer signaling [40]. Nevertheless, enhancing antioxidant capacity via raising GSH could ameliorate drug toxicity and accelerate arsenic metabolism that facilitates its
subsequent excretion and, consequently, clears the body from its harm.

**Conclusions**

Paracelsus stated greater than 500 years ago, “The dose makes the poison.” The reported safe and antioxidant properties of Zamzam water, in addition to its reported antitoxic effects, suggesting that it could potentially modulate the drug’s toxicity. Chemical structure, the presence of functional groups, drug metabolite reactivity, macromolecule targets, and oxidative stress will ultimately determine the fate of a drug in a biological system. Future studies should be carried out to determine Zamzam water’s relation contribution in modulating the metabolism (i.e., cytochrome P-450) and subsequently toxicity of both pharmaceutical and nutraceutical-induced free radicals.

**List of Abbreviations**

- *OH Hydroxyl radical
- GR Glutathione reductase
- GSH Glutathione
- GSSG Glutathione disulfide
- H₂O₂ Hydrogen peroxide
- ROS Reactive oxygen species

**Conflict of interest**

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