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Review

Effects of Alkaline-Reduced Water on Gastrointestinal Diseases

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Abstract: Living a healthy lifestyle is the most important need in the world today. However, oxidative stress (OS) is caused by several stress-inducing factors such as smoking, alcohol consumption, chronic diseases, and inflammatory responses, oxygen-free radicals are produced in excess and can damage major organs in the body. This phenomenon has been implicated in the pathogenesis of several gastrointestinal (GI) diseases, including gastritis, constipation, and inflammatory bowel diseases, which include Crohn's disease, ulcerative colitis, functional dyspepsia, acid reflux, diverticular disease, and irritable bowel syndrome. In this review article, we provide a brief overview of the role of OS in the pathogenesis of GI disorders. Additionally, we discuss the therapeutic role of alkaline-reduced water (ARW) on GI diseases and existing studies on ARW related to GI diseases. Furthermore, we believe that findings from this review article will enhance the knowledge of the readers on the role of ARW on OS and inflammation-based GI diseases.

Keywords: alkaline-reduced water; gastrointestinal diseases; inflammation; oxidative stress

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1. Introduction

Gastrointestinal (GI) diseases are the third leading cause of death globally [1]. Over the past few decades, the prevalence of GI diseases has increased and is characterized by structural and physiological abnormalities in the GI system. These abnormalities include alterations in intestinal gut microbiota, the modification of mucosal and immune functions, hypersensitivity of the visceral layer, and the development of mortality disorders [2,3]. Among the numerous GI disorders, constipation and inflammatory bowel diseases (IBD), which include Crohn's disease (CD), Ulcerative colitis (UC), functional dyspepsia, acid reflux, diverticular disease, and irritable bowel syndrome (IBS) are the most common and serious known diseases [4]. While the exact known cause of GI diseases remains idiopathic, genetic and pharmacological factors and unhealthy lifestyle choices, such as irregular eating, lack of physical activity, smoking, and low consumption of fiber, play a vital role in the development and perpetuation of GI disorders [5–7]. Moreover, all of these aforementioned GI diseases commonly manifest as pain in the abdominal region, diarrhea, constipation, abdominal distention, acidity in the stomach, GI bleeding, malabsorption, and intestinal obstruction [8]. Evidence suggests that oxidative stress (OS) plays an important role in the pathophysiology of GI diseases. The overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS), such as superoxide (O_2^-), nitric oxide (NO), hydroxyl radical (^-OH), hydroperoxyl radical (O_2H), hydrogen peroxide (H_2O_2), and

singlet oxygen, leads to chronic intestinal inflammation and causes oxidative damage in the GI tract [9,10]. Numerous studies have shown that inflammation is generally the main contributing factor of GI disorders starting with reflux esophagitis, gastritis, and inflammation-associated bowel diseases, such as UC and CD [11].

Numerous pharmacological agents have been used to improve symptoms of GI diseases, including antacids, antispasmodics, laxatives, and prokinetic agents. However, these conventional therapies have not accomplished complete symptomatic improvement [12]. Therefore, these days, people are more attracted to several alternative therapeutic treatment methods, including modifications in lifestyle, healthy eating choices, and the use of natural products and functional water rich in mineral supplements. Furthermore, the use of functional water rich in various electrolyte compositions, such as alkaline reduced water (ARW), has been investigated in the treatment of GI diseases [13,14]. ARW has been widely studied in several countries such as Japan, China, and Korea, and is also termed "alkaline electrolyzed water," "alkali-ionic water," "electrolyzed reduced water," and "alkaline ionized water (AIW)," among other names, based on the physiochemical properties. Normally, ARW is generated through the process of electrolysis of water and exhibits properties like an alkaline pH, micro-clustered water molecules, rich dissolved hydrogen molecule content, active hydrogen, extremely negative oxidation-reduction potential (ORP), and ROS-scavenging properties [15–17]. One Japanese study stated that the Japanese Ministry of Health and Welfare claimed that ARW showed effective results against GI diseases, such as chronic diarrhea, indigestion, abnormal gastrointestinal fermentation, and hyperacidity [16]. Another study showed that ARW significantly improved abdominal symptoms normally complained about, especially in patients with chronic diarrhea [18]. Until now, several studies related to the effects of ARW on many diseases, including GI diseases, have already been published. Hence, in this review, we summarize the relationship of ROS with GI diseases and the existing research outcomes and advances made in the protective and therapeutic uses of ARW in clinical and animal-related experiments.

2. Oxidative Stress as a Contributing Factor of GI Diseases

In the human body, the GI tract is known to be the largest surface that is exposed to the external environment and acts as a major immunologic organ that can sense two diverse environments. In the GI tract, the luminal surface is exposed to trillions of microbes, the highest amount of bacteria compared to other mucosal surfaces in the body. ROS are generated during various metabolic and physiological processes and play a double role in the biological system [19]. At lower concentrations, ROS plays an important role in physiological and cellular responses in the body, such as fighting against infectious mediators and regulating a number of cellular signaling pathways, including gene transcription, protein kinase activation, and phosphatase inhibition. In contrast, the overproduction of ROS by endogenous or exogenous sources acts as a damage mediator that breaks down cellular structures, such as lipids, proteins, nucleic acids, and membranes, contributing to the immediate development of the inflammatory process and ultimately resulting in cell death through apoptosis. This phenomenon is involved in OS [20,21]. In the GI tract, the production of ROS plays a key role in the progression of many inflammatory diseases, including GI diseases. Despite the epithelial layer in the GI tract functioning as a protective barrier, ingested substances and pathogens contribute to the inflammatory process in GI diseases by activating the epithelium, polymorphonuclear neutrophils (PMNs), and macrophages to produce inflammatory cytokines and other factors that contribute to OS. There are two main enzymatic reactions that generate ROS in the GI tract: (i) the hypoxanthine (HX)/xanthine oxidase (XO) system; and (ii) the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system [22]. XO is also known as an isoform of xanthine dehydrogenase activity. It can catalyze the monovalent and divalent electron transfer to O_2, which generates free radicals such as O_2^- and H_2O_2 In fact, the human GI system constitutes the highest amount of XO in the body, which combines with numerous phagocytic cells to generate large amounts of O_2 [23]. The intestinal mucosa has a tremendous capacity

to oxidize HX by XO. Moreover, HX plays an important role in regulating the production of H_2O_2 and O_2^- in GI diseases such as IBS [24]. On the other hand, NADPH oxidases (NOXs) play a vital role in the production of ROS and RNS in the GI tract. Besides that, NOX plays an important role in the proliferation of colonic cells. NOXs release several membrane-bound NOX isoforms and dual oxidase (DUOX) complexes in the gut area that increase the production of ROS/RNS in the form of O_2^- and H_2O_2 and contribute to the inflammatory process. Among NOX and DUOX, DUOX complexes are present in all parts of the intestine, whereas NOX is only present in the ileum, cecum, and colon epithelial region and are responsible for the generation of O_2^- and H_2O_2 [25,26]. Apart from this, the mitochondria generate intestinal ROS during the electron transport chain and NO synthase processes [26]. A recent study showed that mitochondria play an important role in influencing gut functions, as intestinal barrier protection, immune response in the intestinal mucosa, and in the maintenance of eubiotic intestinal microbiota [27,28]. However, the overproduction of ROS due to the dysfunction of mitochondrial actions results in the pathogenesis of GI diseases, such as IBD [29]. In addition, ROS production was shown to increase the inflammatory response via the nuclear factor-kappa B (NF-κB) and increase the level of transglutaminase in the intestinal epithelial cells in celiac disease [30]. Moreover, chronic inflammation and the loss of redox balance lead to the pathogenesis of numerous GI diseases, such as celiac disease, peptic ulcer, IBD, CD, and UC. In UC, immunocytes, such as T cells, move to the epithelial barrier, resulting in the release of inflammatory mediators and destroying the mucosal layer of the colon due to the disintegration of intestinal epithelial cells and the tight junction. In CD, all layers of the GI tract wall are affected due to inflammation [26]. However, these destructive effects caused by OS and free radicals can be removed by the activity balance of anti-oxidative enzymes, such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), and their substrates, including glutathione and α tocopherol, which act as free radical scavengers or oxidative inhibitors in cells in the GI tract. Previous studies showed that the levels of antioxidant enzymes, such as SOD and GPx, were decreased in the intestinal mucosa of patients with CD [31–33]. In addition, increased levels of SOD were found in the intestinal tissues of IBD and patients recovering from peptic ulcers [34,35]. Therefore, shedding light on the role of OS in various GI tract disorders is essential for the development of new therapeutic treatment approaches. ARW can be one potential candidate due to its antioxidative and anti-inflammatory mechanisms, as shown in Figure 1.

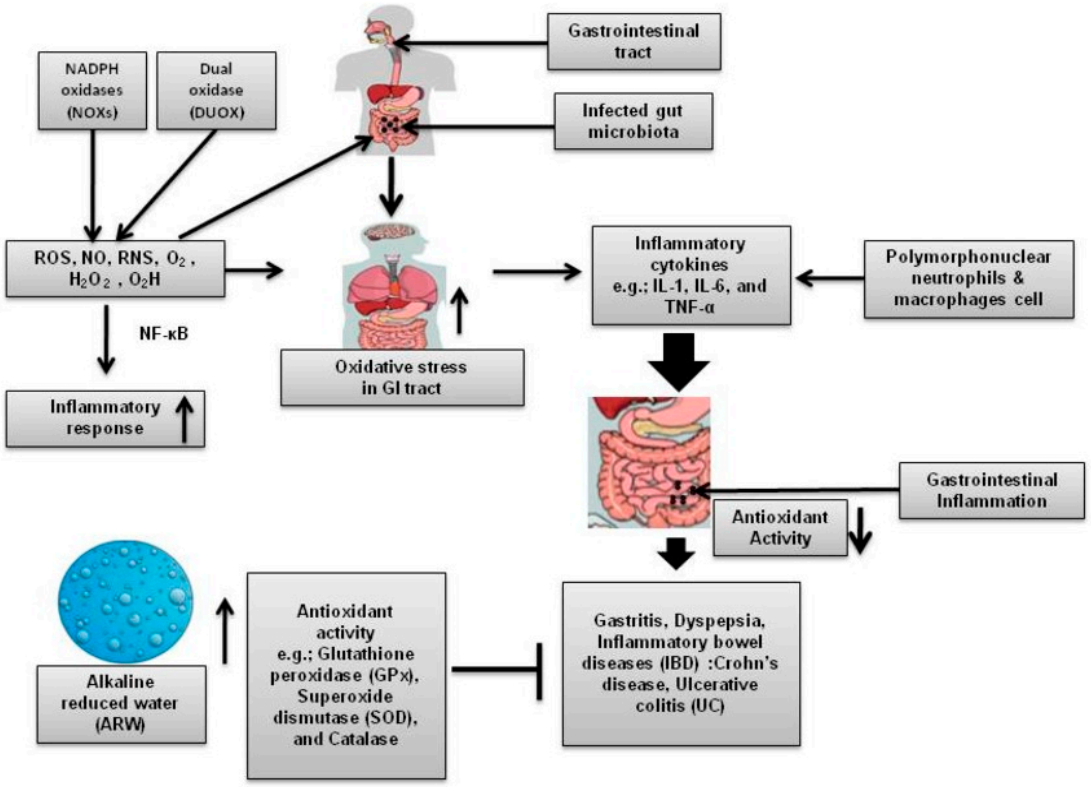

Figure 1. Role of OS in GI diseases and effect of ARW as a potential candidate in GI diseases due to its antioxidative and anti-inflammatory action. ARW: Alkaline reduced water; ROS: Reactive oxygen species; NO: Nitric oxide; RNS: Reactive nitrogen species; O_2 H: Hydroperoxyl radical; O_2, Superoxide; H_2O_2, Hydrogen peroxide; NF-κB: Nuclear factor-kappa B; TNF-α: Tumor necrosis factor alpha; IL: Interleukin; GPx: Glutathione peroxidase; SOD: Superoxide dismutase; IBD: Inflammatory bowel diseases; UC: Ulcerative colitis; NOXs: NADPH oxidases; DUOX: Dual oxidase.

3. ARW and Its Mechanism of Action

Water is the most important component in the human body as it constitutes approximately 70% of total body mass, 99% of all cellular molecules, and most components of bodily fluids, like saliva, blood, lymph, cerebrospinal fluid, and other digestive fluids. In the human body, water functions as a vital nutrient and is involved in the majority of biochemical reactions, such as the maintenance of blood pressure, detoxification, and lubrication, and is considered to be the matrix of life [36]. Recently, there have been numerous concerns regarding the quality of drinking water worldwide. In 1931, Japan first introduced the concept of functional water. Later on, in the 1960s, functional water was researched and applied to medical care as health-beneficial water for the treatment of numerous GI problems, such as diarrhea, indigestion, hyperacidity, and abnormal GI fermentation in Japan [15,16]. Among the analyzed functional waters, electrolyzed water (EW) has been widely studied in countries like Japan, Korea, and China. ARW is a type of functional water that is usually generated by a water electrolysis process and is widely known for its several health benefits in humans. This water has numerous special properties, which makes this water distinct from any form of regular purified water or tap water. It is characterized by high alkalinity (pH 8–10) depending on the generating device, lower ORP, small size of water clusters, lower level of dissolved oxygen, and being rich in hydrogen molecules (H_2) [16,37]. These functional properties of water, such as pH, ORP, and H_2 are comparatively unstable; thus, drinking it on an empty stomach is recommended to optimize the beneficial effects in the GI tract.

According to previous studies, ARW shows antioxidative properties upon consumption due to the presence of H_2 and negative ORP values, which protect the body from OS

caused by free radicals [17,38]. This function of ARW was first confirmed in an in vitro study conducted by Shirahata et al. in 1997. They reported that AIW has the potential to protect against oxidative damage and destroy free radicals, such as superoxide (O_2^-) and H_2O_2 [39]. Another study reported that ARW prevented the oxidative cleavage of protein and enhanced the antioxidant activities of ascorbic acid [40]. Furthermore, prior research showed that the administration of ARW on animal models with metabolic diseases decreased the abnormal blood glucose level, total cholesterol, and triglyceride levels [41,42]. A clinical study also reported the efficacy and the safety of drinking ARW for senile patients on the basis of the results that all of the blood parameters, such as white blood cell count, adiponectin, cholesterol level, potassium level, and liver enzymes associated with lipid metabolism were involved in the normal range [37]. These results conclude that ARW does not induce side effects and might yield a positive response in terms of uplifting health status. Likewise, Hung et al. reported that ARW administration on patients undergoing hemodialysis showed a protective effect against ROS and inflammation markers such as C-reactive protein and interleukin (IL)-6, and moderately restored antioxidant enzymatic activities [43]. Apart from this, the administration of ARW revealed positive effects on the metabolic acid-base balance, significantly increasing fasting arterial blood and reducing acid reflux [44–46]. Moreover, drinking ARW was helpful in relieving abdominal discomfort and GI problems [18,47]. In support of this, a double-blind placebo-controlled clinical trial conducted by Tashiro et al. reported the positive effects of AIW on abdominal symptoms, such as pyrosis, dysphoria, distension of the abdominal region, chronic diarrhea, and constipation [18]. Similarly, Shin et al. reported that drinking ARW for 8 weeks significantly improved IBS symptoms and the IBS quality-of-life score [47]. Additionally, a recent study conducted by Chaves et al. reported that ARW consumption might have clinical benefits in patients diagnosed with gastritis [48]. Table 1 shows the summary of the list of various clinical trial results related to the effects of ARW.

Table 1. Clinical studies related to the effects of ARW in different diseases and improvement of health conditions.

Author and Year	Disease/Condition	Route of Administration	Dose and Duration	Outcomes	Reference
Tashiro et al., 2000	Abdominal complaints	Oral	pH 9.5, 0.5 L/d, 30 d	Improvement in abdominal complaints	[18]
Shirahata et al., 2007	Type 2 diabetes	Oral	2 L/d, 6 d	Decreased ROS level and improvement in blood cholesterol, low-density lipoprotein, and serum creatinine	[17]
Yang et al., 2007	Senile disease	Oral	pH 9.5, 1.5 L/d, 60 d	Improvement in blood parameters	[37]
Ostojic et al., 2014	Exercise-induced acidosis	Oral	pH 9.3, 2 L/d, 14 d	Significantly increased fasting arterial blood pH	[45]
Chycki et al., 2018	Exercise-induced metabolic acidosis	Oral	pH 9.13, 2.6–3.2 L/d, 21 d	Enhances hydration, improves acid-base balance and anaerobic exercise performance	[44]
Shin et al., 2018	IBS with Diarrhea	Oral	pH 8.5–10, 2 L/d, 57 d	Improvement in abdominal pain, IBS quality-of-life score significantly increased	[47]
Chaves et al., 2020	Gastritis	Oral	pH 8.5–10, 5 months	Clinical benefit, observed higher expression of miR-135b and miR-29c	[48]

ROS: reactive oxygen species; IBS: irritable bowel syndrome.

4. Development and Characteristics of ARW

Many kinds of EW-producing devices are available in the global market, such as in Japan, China, the United States of America, Europe, South Korea, and Taiwan. Among these countries, Japan is the leading manufacturer of EW-producing devices [49]. In many countries, such as Korea and Japan, ARW-generating devices have been officially approved as home medical devices (grade two) due to their health benefits. Generally, ARW-generating devices are composed of two units: a water purification unit, such as carbon and ultraviolet filters, and an electrolysis chamber unit containing platinum-coated electrodes. The electrolysis chamber is divided into two compartments by a semi-permeable membrane (diaphragm). In the chamber, alkali water is produced in the compartment containing the cathode pole, and acidic water in the opposite compartment containing the anode pole. Various anions and cations, which are ionized during water electrolysis, move to the cathode and anode areas, respectively, by passing through the diaphragm [49]. During this process, the reduction reactions near the cathode compartment generate H^+ ions and OH^- ions. H^+ ions take up the electrons (e^-) from the negatively charged cathode to produce H_2 and active hydrogen resulting in an increase in OH^- ions in the cathode compartment. This generation of OH^- ions increases the water's pH (alkalinity), decreasing the ORP potential and increasing H_2 in the cathode compartment [50–52]. The electrochemical reaction for the production of ARW and acidic water is shown in Table 2. ARW is usually produced by electrolysis. However, another type of ARW-generating device is commercially available due to its cost-effectiveness and high portability. This method can also produce H_2-enriched water characterized by high alkalinity and a low ORP value through the principle of an electrochemical reaction between water and particular minerals such as magnesium (Mg) (Mg) +2 $H_2O \rightarrow Mg(OH)_2 + H_2$ [48].

Table 2. Electrochemical reaction for the production of ARW and acidic water.

Oxidation Reaction at Anode	Reduction Reaction at Cathode
$4H_2O + 4e^- \rightarrow 4OH^- + 4H^+ + 4e^-$	$2H_2O + 2e^- \rightarrow 2OH^- + 2H^+ + 2e^-$
$4OH^- \rightarrow O_2\uparrow + 2H_2O + 4e^-$	$2H^+ + 2e^- \rightarrow H_2\uparrow$ $2H^+ + 2e^- \rightarrow 2H$ (Active hydrogen)
$2H_2O \rightarrow O_2\uparrow + 4H^+ + 4e^-$ (Overall reaction)	$2H_2O + 2e^- \rightarrow H_2\uparrow + 2OH^-$ (Overall reaction)

In order to distinguish the change of water by electrolysis, we can measure various parameters, such as pH, ORP, and total dissolved solids (TDS), using commercial electrolytic devices (Table 3).

Table 3. Characterization of ARW by using electrolyzing device.

Water	pH	ORP	TDS
Tap water	7.31	551	122
ARW	9.52	−99	127

The water used in this examination was produced by electrolyzing device (CGM MWPI-2101, CERAGEM Co. Ltd., Cheonan, Korea). TDS: total dissolved solids; ORP: oxidation-reduction potential; ARW: alkaline reduced water.

5. ARW and Its Role in the Alleviation of Different GI Diseases

It is well-known fact that ARW has antioxidant properties due to its extremely low ORP and the presence of H_2 [15,17,38]. Additionally, several studies have already proved the therapeutic effect of H_2 as a bioactive gas, which acts as a selective antioxidant in treating many OS-related GI diseases [53,54]. Due to its small molecular size, H_2 can be easily absorbed in all parts of tissues and can easily penetrate the blood–brain barrier [54,55]. Moreover, due to the antioxidant property of H_2, it also exerts its beneficial effects by reducing inflammation and regulating many signaling pathways, thereby exerting protective effects on cells [54,55]. In line with this, a study on ARW showed the inhibition degenerative reaction of DNA in a dose-dependent manner [39]. In the gut microbiota, over 100 trillion microbial cells are responsible for influencing the physiology of human, metabolism, nutrition, and immune-mediated functions. One recent rodent study pub-

lished by Xiao et al. investigated whether the administration of hydrogen-rich water (HRW) would affect radiation-induced small intestine toxicity in mice models. They found that the oral administration of HRW (H_2 0.80 mM) for 5 days consecutively led to an improvement in radiation-mediated GI toxicity, tract functions, and the integrity of the epithelial layer. Surprisingly, their study also showed a stabilized gene response (MyD88 gene) in the small intestine, as this gene plays an important role as a key modulator of the immune response to gut pathogens [56]. Another in vivo study by Higashimura et al. reports the effect of HRW on the gut environment. Furthermore, their findings revealed that 6 weeks of ARW administration (H_2 0.32 mM concentration) significantly increased a marker of intestinal fermentation (weight of cecal contents), produced significantly more short-chain fatty acid (SCFA) content, and showed a distinct microbiota composition favorable to the gut [57]. Additionally, another in vivo study by Ikeda et al. reported the positive effect of HRW on the sepsis model. Their results demonstrated that oral administration of HRW for 7 days prevented intestinal dysbiosis, hyperpermeability, and bacterial translocation in mice [58]. Similarly, another study conducted by Zheng et al. explored the effect of HRW on the intestinal microbiota response in female piglets. They found that 25 days of HRW oral administration (with H_2 0.6 mM concentration) increased the concentration of H_2 in the gut, especially in the mucosal layers of the stomach and duodenum, and decreased the incidence of diarrhea rate. Additionally, they also found increased levels of butyrate in the colon and total SCFAs in the cecum, a decreased abundance of *Escherichia coli*, and an increased abundance of *Bifidobacterium* in the ileum [59]. A succeeding study related to the effects of hydrogen-rich ARW on gut permeability and fecal microbiota conducted by Bordoni et al. with rat Parkinson models found an improvement in the intestinal barrier integrity and tight junction integrity in the ileum, increased levels of butyric acid in the feces, and improved gut microbiota as evidenced through fecal microbiota analysis [60]. Interestingly, another animal study conducted with mice models revealed that HRW administration alleviated oxaliplatin-induced hyperalgesia. Moreover, the oral administration of HRW showed a reduction in microbial diversity, the modification of the structure of gut microbiota, and the reversal of the excessive production of inflammatory cytokines and OS [61]. In addition, a recent clinical trial on HRW administration for two months consecutively among female football athletes showed positive effects on gut microbiota. Moreover, their results illustrated that regular HRW consumption of about 1.5–2 L led to a higher abundance and diversity of gut intestinal flora, which is an indicator of balanced microbes in the gut region [53,62]. Table 4 summarizes the list of various animal and clinical studies on the effects of ARW and HRW on intestinal flora.

Table 4. Summary of various animal and clinical studies on the effects of ARW and HRW on intestinal flora.

Author & Year	Model	Disease/Condition	Route of Administration	Dose and Duration	Outcomes	Ref.
Xiao et al., 2018	Mice	Radiation-induced intestinal toxicity	Oral	H_2 0.8 mM, 5 d	Improvement in radiation-mediated gastrointestinal toxicity, tract functions, and the epithelial layer of intestinal integrity	[56]
Higashimura et al., 2018	Mice	Intestinal flora	Oral	H_2 0.32 mM, 4 wks	Significantly increased a marker of intestinal fermentation (weight of cecal contents), produced significant more SCFAs contents, and showed a distinct microbiota composition favorable to gut	[57]
Ikeda et al., 2018	Mice	Sepsis model	Oral	HRW 15 mL/kg, 7 d	HRW prevent intestinal dysbiosis, hyperpermeability, and bacterial translocation	[58]

Table 4. *Cont.*

Author & Year	Model	Disease/Condition	Route of Administration	Dose and Duration	Outcomes	Ref.
Zheng et al., 2018	Piglet	Fusarium mycotoxins diet	Oral	H_2 0.6 mM, 25 d	Decreased diarrhea rate, increased acetate, butyrate, total SCFAs, increased relative abundance of specific taxa	[59]
Bordoni et al., 2019	Rat	Parkinson's disease	Oral	ARW, H_2 0.4–0.9 mM, 15 d	Increased barrier integrity, increased butyric acid, and butyrate-producing bacteria	[60]
Sha et al., 2019	Human	Female football athletes	Oral	HRW1.5–2 L/d, 60 d	Increased blood hemoglobin, malondialdehyde, SOD, total antioxidant capacity, species diversity of gut and fecal microbiota	[61]
Shim et al., 2020	Human	Healthy adults	Oral	HRW (H_2 0.753 $\pm$ 0.012 mg/L) 1.5 L/d, 4 wks	Reduced cell death and inflammatory responses by modulating transcriptional networks of TLR-NFκB signaling	[62]
Lian et al., 2021	Mice	Chemotherapy-induced neuropathic pain	Oral	H_2 0.8–1 ppm, 20 d	Reduction in the microbial diversity and modifies the structure of gut microbiota and reverse excessive production of inflammatory cytokines and OS	[63]
Tanaka et al., 2021	Human	Healthy volunteers gut microbiota and stool condition	Oral	ARW (pH 9.5, H_2 0.3 mg/L) 500 mL/d, 14 d	Increase in specific gut bacterial species *Bifidobacterium*	[64]

Ref.: reference; ARW; alkaline-reduced water, OS; oxidative stress, SOD; superoxide dismutase, SCFA; short-chain fatty acid, ppb; parts per billion.

Previous studies have shown that numerous clinical symptoms and pathological states in the GI tract, such as diarrhea, constipation, UC, gastritis, and ulcer disease might be due to the changing composition and functions of normal gut microflora [65,66]. Several methods have been used to restore the gut microflora, including the administration of residential microflora in the form of probiotics or chemicals [66]. In line with this, one study reported the importance of ORP for microbial growth. Both aerobic and anaerobic microbes require different ORPs for their growth. Anaerobes require a negative ORP between −300 to −400 mV. A prerequisite for the recovery and maintenance of obligatory anaerobic microflora in the intestinal tract is a negative ORP of the intestinal milieu. ARW possesses the ability to induce such conditions with redox potential values between 0 and −300 mV or more negative ORP values produced in electrolysis devices. Therefore, the consumption of such functional water favors the growth of residential microflora in the gut [65].

To date, only a handful of animal and clinical trials have investigated the direct effects of drinking ARW on gut microbiota and GI diseases. However, several studies related to the effects of the HRW have been investigated and summarized in this article [56–59,62,63]. Besides the effects induced by the H_2 in ARW, alkali pH also plays an important role due to its known advantages in intestinal flora. One study reported that an alkaline pH is necessary to neutralize acids in the stomach [46]. Since ARW has a high pH (8–10), it is justifiable that ARW might be useful against hyperacidity and other related accumulated acid-and toxin-induced diseases via the neutralization of these acids. Another beneficial effect of ARW consumption is its influence on blood pH levels. Thus, all this evidence shows that the consumption of ARW might help in maintaining physiologic gut homeostasis in the human body [15]. Here, we summarized a few GI diseases and the role of ARW on this disease condition. However, limited studies have been conducted in this field. Therefore,

further studies with animal and clinical models are required to verify the efficacies of ARW as a treatment for GI diseases. Figure 2 shows the role of ARW on GI diseases.

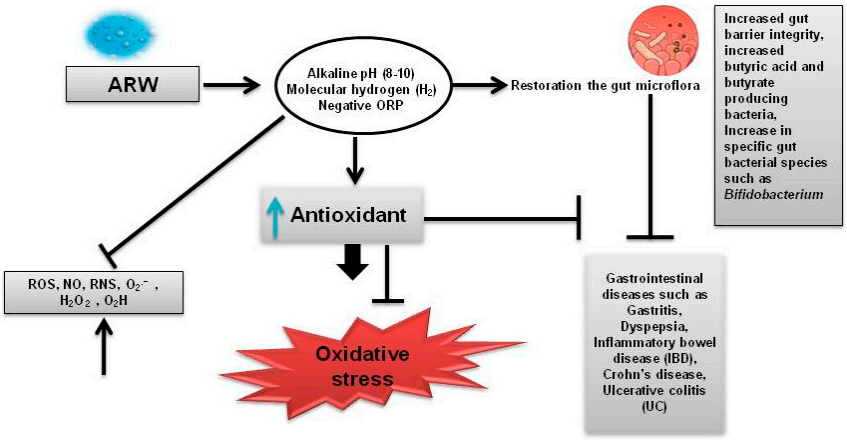

Figure 2. Role of ARW in OS-induced GI diseases. ARW, Alkaline reduced water; H_2, Molecular hydrogen; ORP, Oxidation-reduction potential, ROS, Reactive oxygen species; NO, Nitric oxide, RNS, Reactive nitrogen species; O_2 Hydroperoxyl radical; O_2^-, Superoxide; H_2O_2, Hydrogen peroxide; IBD, Inflammatory bowel diseases; UC, Ulcerative colitis.

5.1. Gastritis

Gastritis is a stomach disease that results from the inflammation of the mucosal layer of the gastric wall [67]. This condition is characterized by pain, swelling, and irritation of the mucosal membrane of the stomach and manifests further through signs and symptoms like nausea, vomiting, dull pain, abdominal discomfort, a feeling of fullness, and loss of appetite [67,68]. This disease remains a global public health issue as the underlying signs and symptoms affect individuals' socioeconomic status, health behaviors, and standard of living [69]. The exact cause of gastritis is unknown; however, one of the known causes of gastritis is *Helicobacter pylori* (*H. pylori*) infection. Studies reported that the important mechanisms through which *H. pylori* induces gastritis are the production of ROS and the peroxidation of lipids such as malondialdehyde [69–71]. Due to this, free radicals such as O_2^-, H_2O_2, and ^-OH, are continuously produced, leading to OS being even more crucially responsible for the development and progression of epithelial necrosis and mucosal ulceration in individuals with gastritis [71]. Additionally, gastritis is known as a preneoplastic condition in the early stage of gastric carcinoma, followed by gastric atrophy, ulcerations, metaplasia in the intestines, dysplasia, and ultimately malignant neoplasia [48,72]. Recently, there has been an extensive discussion on the effects of the pH of drinking water on human health and its relationship with OS and inflammation, but currently, there is only limited scientific evidence to support this relationship. Toward this end, Chaves et al. reported that the oral administration of ARW (pH 8.5–10) for five months consecutively showed an improvement in gastritis, which was evaluated through an esophagogastroduodenoscopy. In addition, the elevated expression of tumor suppressor genes miR-135b and miR-29-c was observed after five months of ARW consumption. These results demonstrate the protective effect of ARW against the inflammation of the gastric mucosa [48]. Another study also showed that ARW with a pH of 8.8 can inactivate pepsin and is helpful as a treatment for acid reflux as pepsin play a key role in causing damage to the macro and microenvironment of the cellular structure in the GI tract [46]. Therefore, it is recommended to consume ARW on an empty stomach as it might increase stomach pH and reduce gastritis. However, the effects of ARW against gastritis cannot be sufficiently concluded from these studies. Therefore, further in vivo and clinical studies are necessary to investigate the effects of ARW on gastritis.

5.2. Dyspepsia

Dyspepsia is a recurring chronic GI tract disorder that poses therapeutic challenges and decreases the quality of life of the patient. It is mainly characterized by pain in the epigastric region, bloating, early satiety, vomiting, heartburn, and nausea in the absence of underlying organic or metabolic diseases [73,74]. The exact causes of dyspepsia are still unknown. However, there are numerous proposed mechanisms for the same, such as acute inflammation secondary to infection and OS contributing to the development of dyspepsia [75]. Studies have shown that patients with functional dyspepsia are characterized by low-grade duodenal and systemic inflammation due to the release of systemic cytokines and $CD4^+\alpha4\beta7^+CCR9^+$ lymphocytes. This release of systemic cytokines, such as IL-1β, tumor necrosis factor (TNF)-α, and IL-10 and $CD4^+\alpha4\beta7^+CCR9^+$ lymphocytes, is correlated with the intensity of symptoms, such as pain, cramps, nausea, vomiting, and delayed gastric emptying [76,77]. Thus, ARW has a positive effect on immune response through a preventive process against cellular protein break down and can inhibit pro-inflammatory cytokines, such as IL-1, and TNF-α [78]. Additionally, ARW was found to be effective in relieving postprandial fullness and gastric distension severity and frequency, while showing favorable modulation of gastric motility [79]. However, further research studies are needed to elucidate the mechanism of ARW on dyspepsia to fully verify these effects.

5.3. Inflammatory Bowel Disease

IBD is a chronic intestinal inflammatory disorder that consists of symptoms like diarrhea, abdominal pain, bloody stools, and vomiting, and primarily includes two types of intestinal disorders: CD and UC [80]. The exact known etiology of IBD remains idiopathic, but accumulating evidence suggests that oxidative damage from free radicals and inflammatory response to intestinal microbes can cause the development of IBD [81,82]. Studies have revealed that cytokines, such as IL-6, IL-12, IL-23, IL-27, and IL-35 play a pivotal role in the inflammatory process for the progression of IBD [81,83,84]. Additionally, increased NF-kB p65 protein was found in the colon biopsies of IBD patients. This increased expression of NF-kB leads to severe intestinal inflammation and the secretion of inflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-12, and IL-23, and is ultimately directly responsible for the damage sustained by the mucosal layer in those with IBD. Cytokines like TNF-α also play a role in the up-regulation of the production of NF-kB, which further leads to repeated inflammation [85]. In addition, one study found that the pSTAT3 level in the histological examination of patients with IBD patients correlates with the degree of gut tissue inflammation [86]. D'Inca et al. reported that in patients with UC and dysplasia, 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels in the mucosal layer were found to be significantly increased. This 8-OHdG modification is the common DNA adduct produced by OS [78,87]. Additionally, OS-induced DNA damage has been identified in several genes, among which a high frequency of p53 mutation occurs in those with IBD [88]. Numerous studies on ARW have reported that due to low dissolved oxygen and high dissolved H_2, ARW exhibits a ROS scavenging activity and protective effect against oxidative damage [47,89]. Of these, one clinical study reported that the negative ORP of ARW has protective effects against pathogenic bacteria in patients with irritable bowels, along with the proliferation of protective microbiota in the gut [47]. Another study reported that the consumption of ARW led to a significant improvement of abdominal symptoms and abnormal bowel movements [18]. It is well-known that H_2 exhibits a protective effect against OS-induced diseases by inhibiting inflammatory cells and regulating pro-inflammatory cytokines and signal transduction molecular pathways such as NF-kB p65, a signal transducer and activator of transcription 3 (STAT3) and mitogen-activated protein kinase (MAPK) pathways [90,91]. To our knowledge, there is no published clinical study to date detailing the effects of ARW on UC and CD. Therefore, more animal and clinical studies are necessary to illustrate the role of a high amount of dissolved H_2 in ARW and its mechanism of action in such GI conditions.

6. Concluding Remarks

In summary, it is becoming increasingly clear that OS is an essential factor that contributes towards the pathogenesis and symptoms associated with GI diseases, which greatly inconvenience affected individuals worldwide. Emerging scientific studies support ARW as well-known functional drinking water with significant therapeutic value, including the scavenging of free radicals and reduction of inflammation. It is a useful adjunct for treating OS-induced diseases, including GI diseases, due to its minimal adverse effects and its high efficacy. These characteristics make ARW a very promising new therapeutic option for uplifting health and for the treatment of GI problems. However, this claim has still a very limited scope due to only a small number of clinical studies having been published concerning this area to date. Therefore, further well-designed clinical trials are necessary to investigate the mechanism of ARW action on numerous GI diseases to fully justify the claim.

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Abbreviations

AIW	Alkaline ionized water
ARW	Alkaline reduced water
CD	Crohn's disease
DUOX	Dual oxidase
EW	Electrolyzed water
GI	Gastrointestinal
GPx	Glutathione peroxidase
H_2	Hydrogen-rich molecules
H. pylori	Helicobacter pylori
HRW	Hydrogen-rich water
H_2O_2	Hydrogen peroxide
HX	Hypoxanthine
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IL	Interleukin
KFDA	Korea food and drug administration
MAPK	Mitogen-activated protein kinase
NADPH	Nicotinamide adenine dinucleotide phosphate
NF-kB	Nuclear factor-kappa B
NO	Nitric oxide
NOXs	NADPH oxidases
O_2^-	Superoxide
O_2H	Hydroperoxyl radical
OH	Hydroxyl radical

ORP	Oxidation potential reduction
OS	Oxidative stress
PMNs	Polymorphonuclear neutrophils
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
SCFAs	Short-chain fatty acid
SOD	Superoxide dismutase
STAT3	Signal transducer and activator of transcription 3
TDS	Total dissolved solids
UC	Ulcerative colitis
XO	Xanthine oxidase

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