Effects of hydrogen rich water and pure water on periodontal inflammatory factor level, oxidative stress level and oral flora: a systematic review and meta-analysis

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Background: Hydrogen rich water (HRW) was used as an auxiliary treatment for periodontitis and peri-implantitis due to its good antioxidant properties. However, the stability of artificially added active hydrogen was far less than that of pure natural active hydrogen, which greatly reduced active hydrogen molecules number in HRW. Meanwhile, the effect of HRW was relatively slow. Finally, long-term drinking of HRW may cause abnormal liver function. Hence, this study sought to summarize and analyze the effects of HRW on oral inflammation and oral flora in various studies to determine whether HRW can be used to inhibit dental plaque formation and aliviate oral inflammation.

Methods: Randomized controlled trials (RCTs) of HRW and pure water (PW) in the treatment of periodontal diseases published before March 2022 in the PubMed, Web of science, EMBASE, Cochrane, China Knowledge Resource Integrated, Wanfang, and Weipu databases were searched. Changes in the inflammatory factor levels, oxidative stress response, and oral flora were summarized and used as outcome indicators. The quality of included studies was assessed by Cochrane risk of bias assessment tool, and the standardized mean differences (SMD) and the 95% confidence intervals (CIs) were calculated using Review Manager 5.3.

Results: In total, 17 studies, comprising 304 subjects, were included in this meta-analysis. Among them, 5 studies had a high risk of bias, and the rest had a certain risk of bias, thus, the total risk of bias was medium to low. The levels of interleukin (IL)-1β (SMD =–0.73; 95% CI: –1.29 to –0.18; P=0.009), tumor necrosis factor alpha (SMD =–2.51; 95% CI: –3.56 to –1.46; P<0.00001), IL-6 (SMD =–1.31; 95% CI: –1.96 to –0.67; P<0.0001), 8-hydroxyguanosine (SMD =–1.61; 95% CI: –2.35 to –0.87; P<0.0001), and reactive oxygen metabolites (SMD =–0.49; 95% CI: –0.91 to –0.06; P=0.02) in the HRW group decreased significantly, while the glutathione peroxidase level increased (SMD =2.5; 95% CI: 1.85 to 3.15; P<0.00001). Additionally, HRW was shown to effectively inhibit oral pathogenic bacteria activity (SMD =–0.91; 95% CI: –1.16 to –0.66; P<0.00001).

Conclusions: HRW effectively inhibits the inflammatory reaction, oxidative stress level, and bacterial proliferation activity in patients with periodontal disease.

Keywords: Hydrogen rich water (HRW); inflammatory factor; oxidative stress; periodontitis; peri-implantitis

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Introduction

As the oral cavity is an important structure connecting the human body with the external environment, many microorganisms in the external environment are easy to enter the oral cavity and reproduce in it, thus forming a unique oral micro ecosystem(1). Among these microorganisms, >700 kinds of bacteria are related to the occurrence of diseases (2). If good oral hygiene is not maintained, bacteria adhere to the tooth surface through an acquired membrane, forming a plaque biofilm. The formed dental plaque secretes a variety of virulence factors that act on the teeth and periodontal tissue, which in turn can cause tooth defects and lead to periodontal inflammatory injury (3). With the widespread application of implant denture restoration in clinical settings, peri-implantitis has become an important factor affecting the prognosis of implants, and has an incidence rate of approximately 9% (4). The initiating factor of peri-implantitis is plaque biofilm, and its main pathogen is the same as that of periodontitis. Additionally, periodontitis is an important risk factor for peri-implantitis (5).

The production of reactive oxygen species (ROS), which is a normal immune reaction product that inhibits pathogens, such as bacteria *in vivo*, can effectively control the inflammatory response progress. However, the excessive production of ROS induces a serious oxidative stress reaction and further aggravates oxidative damage to periodontal and peri-implant tissues (6). Oxidative stress is also an important factor leading to inflammatory diseases. The continuous accumulation of ROS further promotes the release of related pro-inflammatory factors, such as interleukin (IL)-1β and IL-6, which leads to the continuous progression of oral diseases, such as periodontitis or peri-implantitis (7). These oral diseases cause tissue damage, tooth loss, and implant loss, which seriously affect patients' quality of life. Thus, the question of how to inhibit the formation of dental plaque, and effectively control the inflammatory response in the oral cavity are popular areas of research in stomatology.

At present, brushing and flossing are widely used to remove oral biofilm. However, the use of these mechanical methods to remove dental plaque is not ideal. Thus, mouthwash gargling has become an auxiliary method to control the formation of dental plaque. Chlorhexidine is the most commonly used mouthwash, which can effectively inhibit plaque formation and prevent the occurrence of periodontitis (8). However, Chlorhexidine also has many adverse reactions related to use, such as gum swelling, bleeding, taste change, staining, and mucosal soreness. Additionally, as usage increases, drug resistance to relevant oral bacteria develops (9,10). Such reactions have adversely affected the use of Chlorhexidine and led to the development of safer and more effective oral hygiene products.

Relevant studies have shown that hydrogen (H_2) is an effective therapeutic antioxidant that can reduce the degree of oxidative damage by selectively scavenging oxygen free radicals in tissues (11,12). Its antioxidant process is mild and does not interfere with the normal redox reaction of the body. Additionally, it does not have an adverse effect on ROS that transduce signals (13). Further, a previous study has shown that H_2 can also inhibit the release of proinflammatory factors (14). The above research shows that the use of hydrogen rich water (HRW) for oral cleaning can restore the redox balance in the oral cavity and reduce the oxidative stress response.

However, in an experiment of beagle dog peri-implant inflammation model, after washing with HRW, the gingival index, improved bleeding index, and probe depth of the animal models were improved to some extent compared with those of pure water (PW) group, but not significantly. Besides, according to 16SRNA sequencing technology, HRW can inhibit the proliferation of oral pathogenic bacteria to a certain extent, but the change is not significant, which will not be conducive to inhibiting the formation of dental plaque (15). In addition, He *et al.* (16) found that long-term drinking of HRW may cause abnormal liver function and increase blood lipid levels in rat models. The reason maybe that the active hydrogen in HRW water is extremely unstable and prone to volatilization, resulting in a large reduction of active hydrogen molecules, which will greatly affect its clinical efficacy. Besides, the molecular mechanism of HRW's biological effect has not been fully clarified, and long term drinking may affect the body function. Therefore, the clinical treatment of HRW for oral diseases remains controversial. This meta-analysis sought to summarize and analyze the data of previous studies to determine the effects of HRW on the inhibiting inflammatory reaction and oxidative stress levels to provide clinical guidance for controlling dental plaque formation and treating periodontitis and peri-implantitis. We present the following article in accordance with the PRISMA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4422/rc).

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Methods

Data retrieval and collection

We searched the PubMed, Web of Science, Embase, Cochrane, China Knowledge Resource Integrated, Wanfang, and Weipu databases for relevant articles using the following key words: "Hydrogen-rich water" or "Hydrogen" and "Gingivitis" or "Periodontitis" or "Oral cavity" and "Oxidative stress" or "Inflammation" or "Bacteria." The retrieval time was limited to March 2022. The literature retrieval was conducted by 2 individuals with >3 years of retrieval experience.

Inclusion criteria

To be eligible for inclusion in this meta-analysis, articles had to meet the following inclusion criteria: (I) comprise subjects who experienced various inflammatory reactions (e.g., gingivitis, periodontitis, and peri-implantitis.) (II) concern a randomized controlled trial; (III) include a HRW group, which received HRW only, and a pure water (PW) control group, which received PW; and (IV) have study indicators that included related inflammatory factors [e.g., IL-1β, IL-6, or tumor necrosis factor alpha (TNF-α)], oxidative stress indicators [e.g., 8-hydroxyguanosine (8-OHdG), reactive oxygen metabolites (ROM), or glutathione peroxidase (GPx)], or oral flora.

Exclusion criteria

Articles were excluded from the meta-analysis if they met any of the following exclusion criteria: (I) concerned case reports, reviews, comments, or guidelines; (II) concerned pseudo-randomized controlled trials; (III) had incomplete data or the complete data could not be obtained; (IV) included none of the relevant study indicators; and/or (V) were duplicate articles.

Data extraction

For all the articles included in the study, we extracted the author, year of publication, study subjects, number of samples, and IL-1β, IL-6, TNF-α, 8-OHdG, ROM, GPx, and bacteriostasis results. If necessary, we contacted the author of the article to obtain more detailed data.

Quality evaluation of the included articles

The Cochrane risk of bias assessment tool was used to assess the quality of included articles. The assessment includes the following 6 aspects: (I) random allocation method; (II) allocation concealment; (III) blinding; (IV) data integrity; (V) selective reporting; (VI) other bias. The evaluation degree of the above six items was divided into three grades: low bias, high bias, and uncertainty bias.

Statistical analysis

Revman 5.3 was used for the meta-analysis. The continuous variables of inflammation, oxidative stress, and colony formation unit (CFU) are expressed as the standardized mean differences (SMDs) and the 95% confidence intervals (CIs), and forest plots were generated using a random-effects or fixed-effects model. For each meta-analysis, Cochrane Q test and I^2 index were used to evaluate the heterogeneity of the study, if $P>0.1$ or $I^2 \leq 50\%$ mean that no heterogeneity existed between studies, and fixed effect model was used for analysis; If $P \leq 0.1$ or $I^2>50\%$ indicated that the research heterogeneity was obvious, and subgroup analysis or sensitivity analysis would be carried out. For studies that still could not eliminate heterogeneity but have clinical consistency, random effect model would be used for analysis. Meanwhile, funnel plot distribution was used to determine whether there was publication bias in the included literature. If the combined SMD and the 95% CI in the meta-analysis did not overlap with 0, the effect of the outcome index was considered statistically significant. $P<0.05$ indicated significant difference.

Results

Literature search

In total, 1,541 relevant articles were retrieved. After deleting duplicate articles, we screened the remaining 1,123 records according to the title and abstract, and 761 additional articles were excluded. The remaining 362 articles were further screened, and 345 records were excluded (41 case studies, 175 reviews, 58 pseudo-randomized controlled trials, and 71 studies with insufficient data). Ultimately, 17 studies, comprising 304 subjects, were included in the meta-analysis (11-14,17-29). In all the studies, the subjects in the HRW group received the HRW intervention, while those in the PW group received a placebo or PW. The retrieval process is shown in *Figure 1*, and the research characteristics are shown in *Table 1*.

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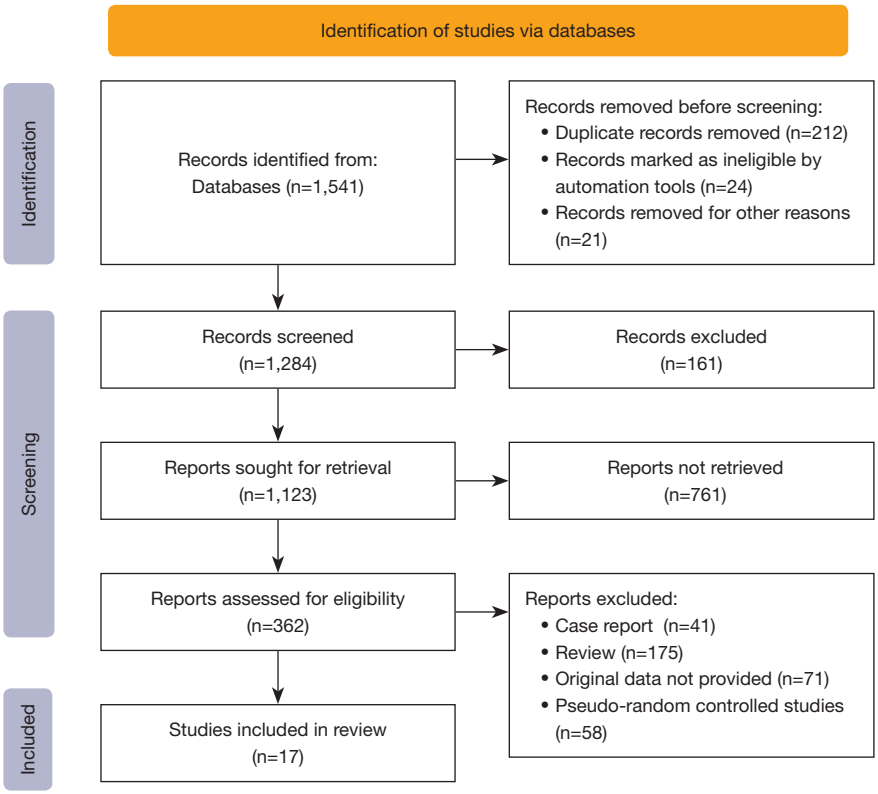

Figure 1 Flow diagram of data retrieval and collection.

Quality evaluation

The Cochrane risk of bias assessment tool was used to evaluate the quality of the articles and showed that the total risk of bias was medium to low. After the risk of bias graph and bias summary were generated for the included studies, we found that 2 studies mentioned unreasonable random assignment, 2 studies mentioned data shedding, 1 study mentioned "selective reporting", and no studies mentioned "allocation concealment" or the "blinding of outcome assessment" (see *Figure 2*).

Effects of HRW on the release of inflammatory factors

After dental plaque is formed, it stimulates the body to secrete a large number of inflammatory factors. As an important immune mediator in the inflammatory response process, changes in inflammatory factor levels have a key effect on the degree of the inflammatory response and the development of infection.

Of the included studies, 5 reported changes in IL-1β after HRW therapy. The results showed that after treatment with HRW, the IL-1β level of the HRW group decreased significantly (SMD =–0.73; 95% CI: –1.29 to –0.18; P=0.009; see *Figure 3A*). Additionally, by summarizing the TNF-α data of 7 groups in 5 studies, we found that HRW effectively reduced the TNF-α level (SMD =–2.51; 95% CI: –3.56 to –1.46; P<0.00001; see *Figure 3B*). Finally, by summarizing the IL-6 data of 6 groups in 4 studies, we observed that the IL-6 level of the HRW group decreased significantly (SMD =–1.31; 95% CI: –1.96 to –0.67; P<0.0001; see *Figure 3C*).

Effects of HRW on the oxidative stress response

The formation of excessive ROS leads to deoxyribonucleic acid (DNA) and lipid damage, which in turn cause apoptosis and strengthen the degree of the inflammatory response. Thus, monitoring the levels of oxidative stress *in vivo* effectively reflects the effect of HRW on inhibiting the inflammatory response.

GPx is considered the first defense line of the antioxidant enzyme system in inhibiting the production of ROS. By summarizing and analyzing the data of 6 groups in

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Table 1 Basic information and the related inflammatory indexes of the included studies

Author, year	Research object	Total cases		IL-1β		TNF-α		IL-6		GPx		8-OHdG		ROM		CFU	
		HRW	PW	HRW	PW	HRW	PW	HRW	PW	HRW	PW	HRW	PW	HRW	PW	HRW	PW
Ara (11), 2018	Chronic forced swimming	7	7	5.82±0.67	3.96±0.67	5.98±0.57	9.81±1.79	9.63±2.23	12.02±2.05	0.35±0.03	0.29±0.02						
				4.93±0.3	5.07±0.75	8.65±0.45	9.06±0.67	14.45±1.34	6.79±0.59	0.36±0.02	0.27±0.04						
Asada (12), 2020	Diabetes	9	9									6.35±0.98	7.78±1.13				
												3.73±0.54	7.78±1.13				
Azuma (13), 2015	Periodontitis	7	6											28.22±29.39	55.12±53.39		
														–24.07±73.48	51.33±90.58		
Dobashi (14), 2020	Severe exercise	4	4											303.4±13.8	268.1±9.8		
														303.5±14.3	273.1±9.5		
Kasuyama (17), 2011	Periodontitis	7	7							8.12±0.87	5.88±1.25	0.097±0.036	0.32±0.072	324.68±16.34	382.48±20.79		
														378.65±32.67	479.53±41.58		
Kim (18), 2017	Oral bacteria	18	18													12.18±11.23	189.84±121.96
Lee (19), 2006	Oral bacteria	16	16													231.09±10.51	2037.82±52.52
																136.56±21.01	1313.03±42.01
																199.58±10.5	1722.69±42.02
																199.58±21.01	1817.23±84.03
Lee (20), 2013	Oral bacteria	3	3													228.01±91.21	11902.3±638.4
																137.85±47.13	4265.99±447.81
																108.48±54.23	5532.2±515.25
Nayak (21), 2021	Chronic periodontitis	20	20													59.55±47.35	81.72±55.63
																45.72±30.51	81.72±55.63
																53.55±38.71	81.72±55.63
																75.2±44.92	115.2±74.11
																70.3±37.53	115.2±74.11
																61±38.29	115.2±74.11
Saitoh (22), 2022	Gingival cells	6	6	19.19±0.58	19.77±0.07	8.64±0.38	10.27±0.67	7.26±1.81	13.12±2.09								
Si (23), 2021	Kidney injury	8	8	140.39±5.77	151.92±1.92	711.54±28.85	788.46±19.23			515.39±46.15	407.69±30.77			1.08±0.058	2.53±0.059		
Sim (24), 2020	Healthy adults	20	18									0.73±0.6	1.04±0.59	384.4±96.4	349±56.1		
Song (25), 2022	Chronic ulcerative colitis	5	4			3.88±0.92	9.55±1.27	5.66±2.25	10.95±2.3	39.74±11.6	13.91±2.31						
Tamaki (26), 2016	Oral palatal wound	6	6	82.11±8.58	198.53±36.76	28.82±3.43	52.5±5.49	8.04±0.97	15.29±2.84					260.59±7.72	372.79±28.98		
				94.36±17.16	123.78±31.86	37.06±5.15	44.95±4.46	11.67±1.28	13.14±1.37					225.39±5.77	258.36±9.64		
Tomofuji (27), 2014	Aging periodontal tissues	6	6	6.79±0.36	1.7±0.1							0.392±0.204	0.644±0.136				
												0.18±0.04	0.2±0.05				
												0.17±0.03	0.25±0.04				
												0.19±0.04	0.27±0.05				
Yoneda (28), 2017	High-fat diet	6	6									0.12±0.03	0.17±0.05				
Yuan (29), 2018	Traumatic brain injury	6	6							22.87±2.73	9.24±3.08						

Data are presented as No. and mean ± standard deviation. HRW, hydrogen rich water; PW, pure water; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor alpha; GPx, glutathione peroxidase; 8-OHdG, 8-hydroxyguanosine; ROM, reactive oxygen metabolites; CFU, colony formation unit.

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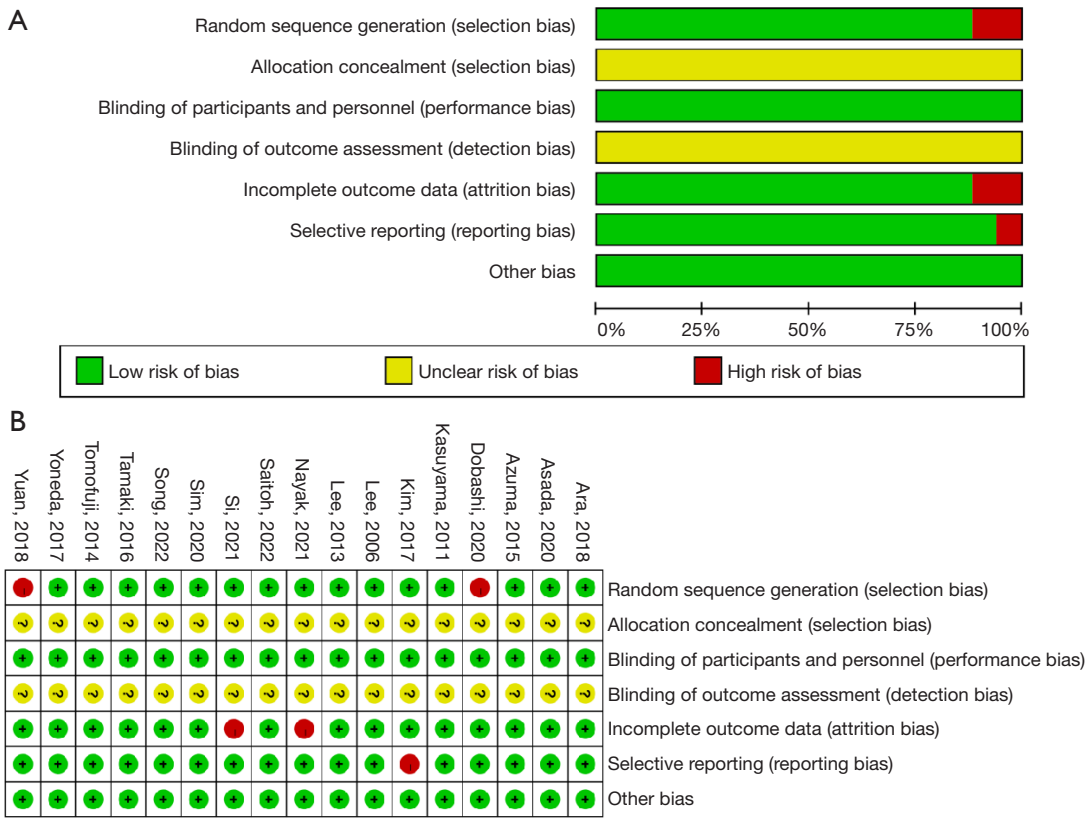

Figure 2 The risk of bias graph (A) and bias summary (B) of the included studies.

5 studies, we found that the GPx level of the HW group was higher than that of the PW group, and better inhibited the formation of ROS (SMD =2.5; 95% CI: 1.85 to 3.15; P<0.00001; see *Figure 4A*). Additionally, as the main product of endogenous DNA damage, 8-OHdG is widely used as a marker of the oxidative stress response. The data of 9 groups in 5 studies showed changes in 8-OHdG levels after HRW treatment. It was found that the level of 8-OHdG of the HW group decreased significantly (SMD =–1.61; 95% CI: –2.35 to –0.87; P<0.0001; see *Figure 4B*). Additionally, ROM effectively reflects the total oxidant capacity *in vivo*, including the level of ROS. Data from 9 groups in 5 studies reported ROM indicators, and we observed that HRW effectively reduced the ROM levels (SMD =–0.49; 95% CI: –0.91 to –0.06; P=0.02; see *Figure 4C*). Thus, HRW treatment effectively inhibits the degree of oxidative stress response *in vivo*.

Effects of HRW on CFU

First, we summarized and analyzed the pathogenic bacteria of periodontitis and peri-implantitis, and found that they share a variety of the same pathogenic bacteria, of which *Porphyromonas*, *Actinomyces*, *Streptococcaceae*, and *Treponema* were the most common (5,30-36) (see *Figure 5A*). *Staphylococcus aureus* (*S. mutans*) and *Porphyromonas gingivalis* (*P. gingivalis*) are commonly used to study the bacteriostasis of HRW, and their CFUs effectively reflect the antibacterial effect of HRW. Through a comprehensive analysis of the CFU data from 14 groups in 4 studies, we found that HRW effectively inhibits the formation of bacterial colonies in the oral cavity (SMD =–0.91; 95% CI: –1.16 to –0.66; P<0.00001; see *Figure 5B*).

Publication bias analysis of included literature

When the number of studies included in the meta-analysis is less than 10, publication bias will generally be found in the funnel plot. In the evaluation of the effectiveness of HRW in improving oral inflammation, because less than 10 articles were included in each outcome index, funnel plot mapping and publication bias analysis were not conducted.

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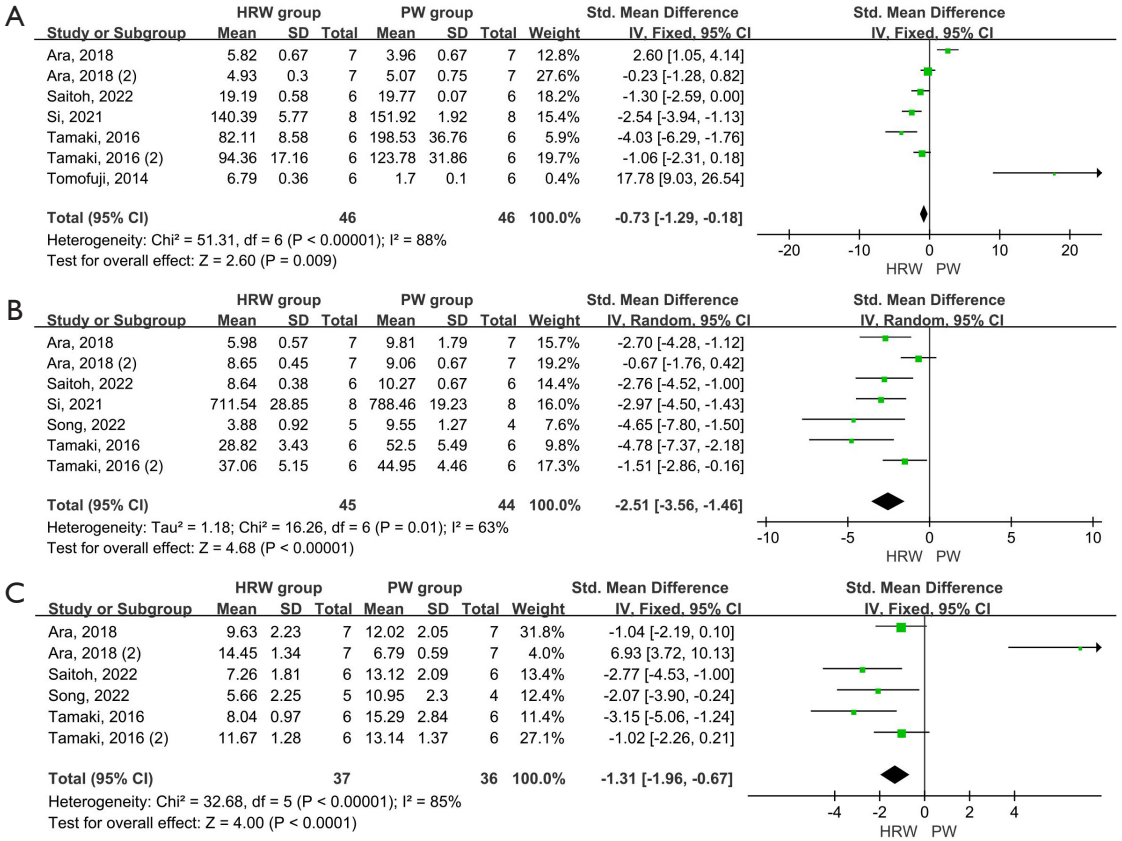

Figure 3 Meta-analysis of the inflammatory factors after HRW treatment. (A) Forest plot of IL-1β; (B) Forest plot of TNF-α; (C) Forest plot of IL-6. HRW, hydrogen rich water; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; PW, pure water.

Discussion

As people's quality of life has improved, they have begun to pay more and more attention to their oral health, including tooth whitening, controlling gum bleeding, and maintaining fresh breath. Periodontitis is the 2nd most common disease in the oral cavity (34). Additionally, dental implant is more and more commonly used because of its good appearance and functional restoration effect. Periodontitis and peri-implantitis are both infectious oral diseases, and their initiating factor is plaque biofilm. At present, guided-biofilm therapy emphasizes that good plaque control is key to the successful treatment of periodontitis and peri-implantitis (30). Plaque biofilm on the surface of the tooth and periodontal tissue continuously secretes virulence factors, which can stimulate periodontal tissue and cells to produce various inflammatory mediators. Subsequently, the persistent inflammatory reaction will result in irreversible tissue damage, and eventually cause the loss of teeth and failure of implant repair (21,27).

Periodontitis is also related to the occurrence of metabolic syndrome, atherosclerosis, Parkinson's syndrome, and other systemic diseases. Thus, plaque control and the reduction of inflammatory injury of periodontal tissue and peri-implant supporting tissue are of great significance in the prevention of periodontitis, the improvement of the long-term dental implanting success rate, and the maintenance of oral and general health.

At present, many studies have examined whether HRW can be used to inhibit the inflammatory response, but such studies have used many different research indicators, and their conclusions have differed. Thus, we summarized and analyzed the intervention effects of HRW on the inflammatory response, oxidative stress response, and CFUs in various studies to analyze the bacteriostatic effects of HRW on oral pathogenic bacteria.

Inflammatory factors have a key effect on the development of periodontitis. The pathogenic bacteria

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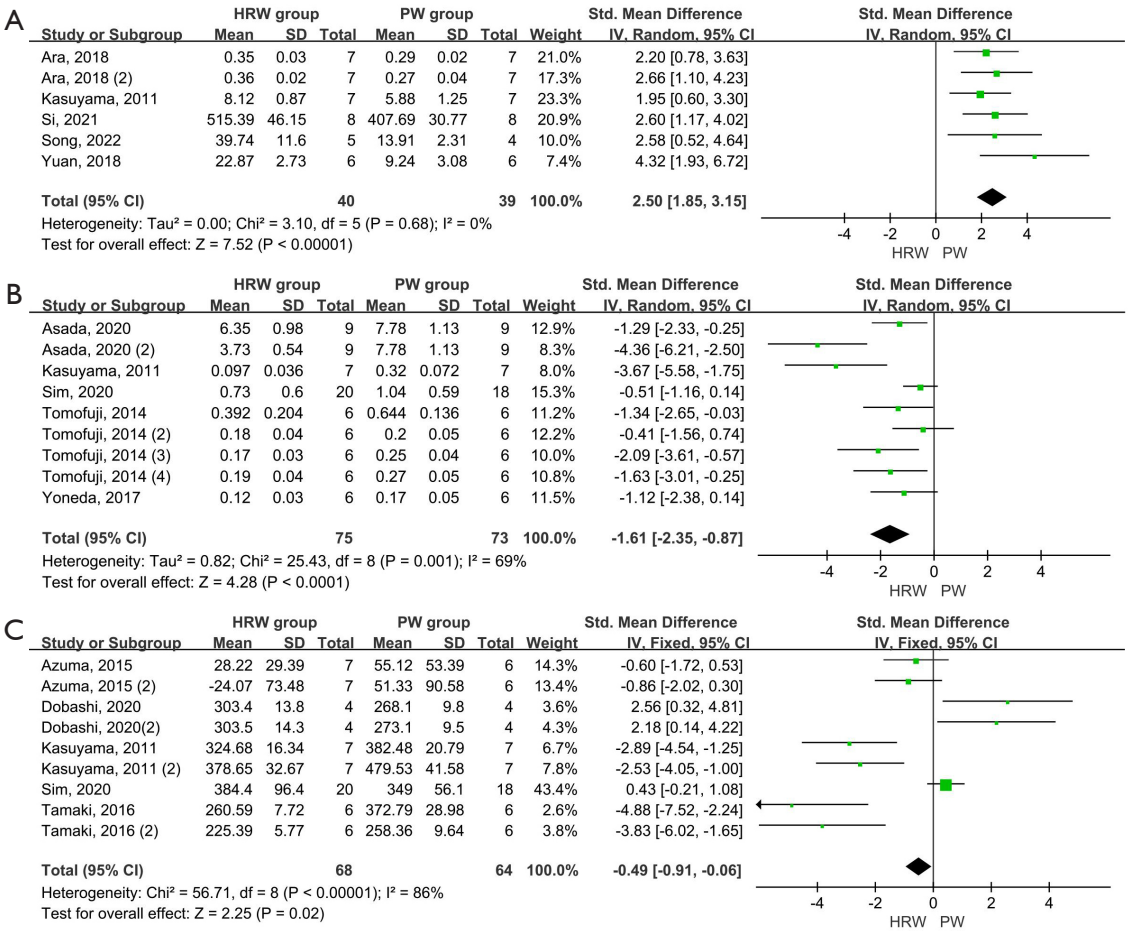

Figure 4 Meta-analysis of the oxidative stress response after HRW treatment. (A) Forest plot of GPx; (B) Forest plot of 8-OHdG; (C) Forest plot of ROM. HRW, hydrogen rich water; GPx, glutathione peroxidase; 8-OHdG, 8-hydroxyguanosine; ROM, reactive oxygen metabolites; PW, pure water.

attached to plaque biofilm not only produces a large number of toxic factors that directly destroy periodontal tissue, but also mediates the host immune and inflammatory response to promote the release of inflammatory factors, which in turn aggravate the destruction of periodontal tissue. For example, TNF-α can activate periodontal osteoclasts and collagenase to promote alveolar bone absorption and destruction (37). Meanwhile, IL-1β and IL-6 can further promote the inflammatory response and effectively reflect the severity of periodontitis (2,38).

After a comprehensive analysis of the levels of inflammatory factors in various studies, we found that only two groups of data suggested that the IL-1β level of the HRW group was higher than that of the PW group. Additionally, only 1 group of data showed that the IL-6 level of the HRW group was higher than that of the PW group, and the remaining data all showed that HRW greatly reduced the release of inflammatory factors and the degree of inflammatory reaction.

Oxidative stress promotes the occurrence of the inflammatory response and is a key factor in leading to periodontal disease development. Through the comprehensive analysis of 25 groups of research data, we found that HRW effectively improves the GPx level and reduces the 8-OHdG level. Thus, HRW effectively improves the antioxidant level *in vivo* to reduce DNA damage.

In terms of the ROM indicators, 3 groups of data showed that the ROM level of the HRW group was higher than that of the PW group, and all the other data showed that HRW effectively reduces the ROM level, which may be caused by H_2 selectively removing hydroxyl radicals without affecting other ROS.

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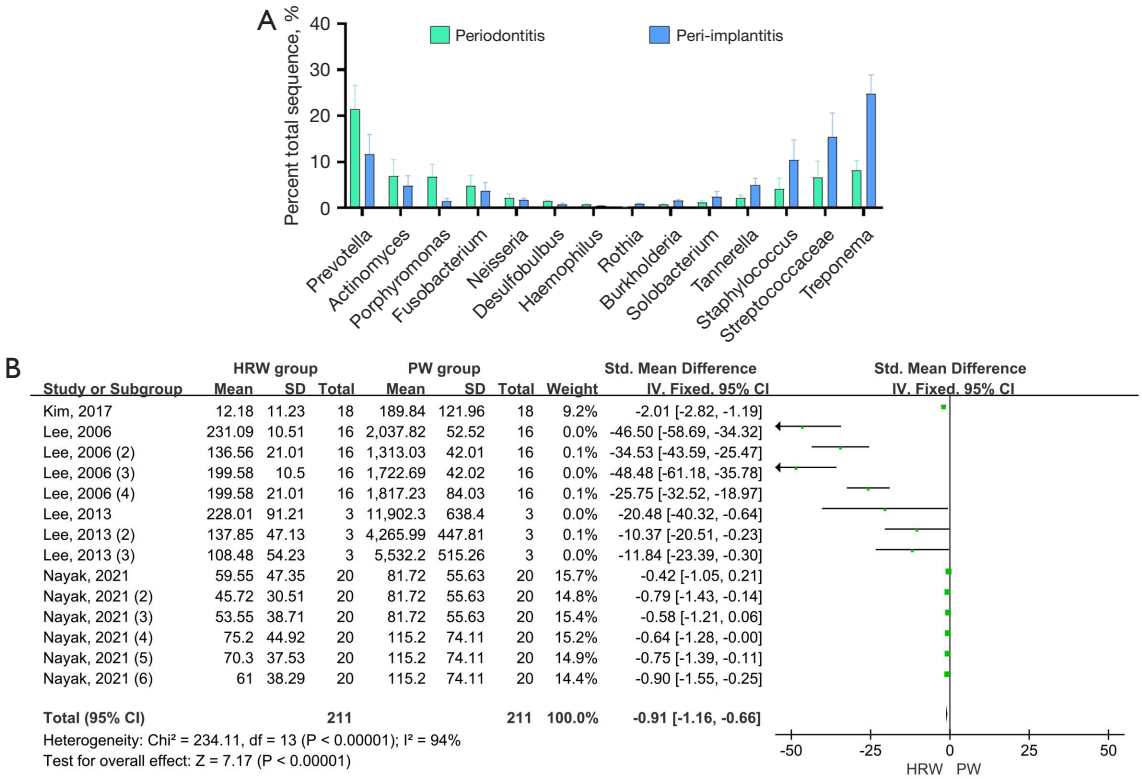

Figure 5 Comparison of pathogenic bacteria between periodontitis and peri-implantitis (A) and meta-analysis of CFU after HRW treatment (B). CFU, colony formation unit; HRW, hydrogen rich water; PW, pure water.

In addition, after a comprehensive analysis of 14 groups of data on the correlation between HRW and CFU, we found that HRW effectively inhibits the proliferation of a variety of oral pathogens, including *S. mutans*, *P. gingivalis*, and *Actinobacillus actinomycetemcomitans* (18-21), which effectively reduces the virulence of pathogens thus reduce inflammatory injury. And the reduction of the amount of bacteria can reduce the level of oxidative stress and inflammatory reaction in the body, further reducing inflammatory damage. Therefore, HRW can effectively control the formation of dental plaque, reduce the release of inflammatory factors in the mouth, and reduce the degree of oxidative stress.

However, the sample sizes of the included studies were small, and there were certain differences in the measurement methods and sample sources of various research indicators, which may have been the sources of the heterogeneity in this meta-analysis. In a follow-up study, we intend to collect more data and conduct a subgroup analysis of the sample sources and inflammation types to provide a more detailed summary.

Conclusions

In conclusion, HRW effectively inhibits the inflammatory reaction, oxidative stress level, and bacterial proliferation activity, which can be used to inhibit the formation of oral plaque biofilm, prevent and control inflammatory injury, and preserve periodontal and peri-implant supporting tissues to better maintain oral health. At the same time, prevention and effective treatment of periodontal disease is of great significance to the overall health.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4422/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4422/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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