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· 综述 ·

富氢水对牙周炎的作用及机制的研究进展

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【摘要】 富氢水具有良好的抗菌、抗炎、抗氧化及促进伤口愈合等作用，在脑损伤、肾损伤等多种疾病的治疗中发挥积极效应。在牙周炎的治疗中，富氢水也具有一定的临床应用潜力。目前研究认为，富氢水可抑制牙周致病菌生物膜形成，抑制口腔结缔组织及骨组织破坏，对炎症及氧化应激相关的牙周炎具有潜在治疗作用。富氢水通过抑制氧化应激反应，上调抗氧化酶如谷胱甘肽过氧化物酶(glutathione peroxidase，GPX)、超氧化物歧化酶(superoxide dismutase，SOD)表达，减轻牙周炎环境下的牙周组织损伤。调节与炎症密切相关的核因子E2相关因子2(nuclear factor erythroid 2-related factor 2，Nrf2)抗氧化防御通路和丝裂原活化蛋白激酶(mitogen-activated protein kinase，MAPK)信号通路，抑制炎症细胞因子如白细胞介素(interleukin, IL)的表达，是富氢水发挥抗炎作用的主要机制。在菌斑生物膜的形成中，富氢水可以抑制细菌生长增殖，并下调糖基转移酶(glycosyltransferase，GTFs)和葡聚糖结合蛋白(glucan-binding protein，GBP)以抑制细菌黏附，预防牙周炎发生。此外，富氢水对多种细胞生长因子、α-平滑肌肌动蛋白(α-smooth muscle actin，α-SMA)和I型胶原表达也具有积极作用，可以促进伤口愈合。目前临床研究中尚未发现富氢水使用的不良反应，其生物安全性能够得到一定保证，但有关富氢水在牙周炎中的研究多为体内外临床前研究，且对于富氢水在治疗中的有效浓度和剂量的选择仍不明确，需要进一步研究证明富氢水在牙周炎中的治疗意义，并探究富氢水的最佳使用方案。本文旨在对目前富氢水在牙周炎治疗中的作用及机制进行综述。

【关键词】 分子氢； 富氢水； 牙周炎； 菌斑生物膜； 伤口愈合； 氧化性应激； 炎症； 细胞生长因子； 抗菌

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Research progress on the therapeutic roles and mechanisms of hydrogen-rich water in periodontitis

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【Abstract】 Hydrogen-rich water (HRW) shows excellent antibacterial, anti-inflammatory, antioxidant, and wound-healing properties and plays a positive role in the treatment of various diseases, such as brain injury, kidney injury, and periodontitis. Current studies found that HRW can inhibit periodontopathogenic biofilm formation, inhibit oral connective tissue and bone tissue destruction, and show anti-inflammatory and antioxidant properties in periodontitis. Additionally, HRW can alleviate periodontal tissue damage by inhibiting oxidative stress and up-regulating the expression of antioxidant enzymes, such as glutathione peroxidase and superoxide dismutase. HRW exerts anti-inflammatory effects by regulating the nuclear factor erythroid 2-related factor 2 and mitogen-activated protein kinase pathways, which are closely associated with inflammation. Additionally, HRW inhibits the expression of inflammatory cytokines, such as interleukins,

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inhibits the growth and proliferation of bacterial plaque biofilms, and down-regulates glycosyltransferases and glucan-binding proteins to prevent bacterial adhesion and subsequent development of periodontitis. Furthermore, HRW has a positive effect on the expression of various cell growth factors, α-smooth muscle actin, and type I collagen, which promotes wound healing. Current clinical studies have demonstrated the biological safety of HRW (to a certain extent) and reported no adverse reactions. However, most studies on HRW in oral diseases are preclinical *in vivo* and *in vitro* studies. Therefore, further clinical studies are required to validate the therapeutic significance and optimal therapeutic regimen of HRW in human periodontitis. This article aims to review the therapeutic role and the underlying mechanisms of HRW in periodontitis.

【Key words】 molecular hydrogen; hydrogen-rich water; periodontitis; dental plaque biofilm; wound healing; oxidative stress; inflammation; cell growth factors; anti-bacteria

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H_2是一种良好的选择性抗氧化剂，具有良好的抗炎、抗氧化、抗凋亡等作用[1]。吸入H_2、静脉注射H_2的等渗溶液或刺激肠道细菌产H_2等方式可增加人体H_2的摄入，但饮用富氢水是更方便可行的摄入方案[2]。大量动物和临床研究表明，富氢水对缺血再灌注损伤[3]、肠道炎症[4-5]、输尿管梗阻[6]、阿尔兹海默症[7]和神经性疼痛[8-9]等疾病的治疗具有积极作用。近年来，富氢水在口腔疾病治疗中的作用及机制逐渐成为研究热点。饮用富氢水能够抑制口腔菌斑生物膜的形成，预防牙周病和龋病[10]，也能够发挥抗氧化作用抑制牙槽骨吸收，促进口腔创伤愈合[11-12]，在口腔疾病的预防与治疗中具有良好的辅助作用。本文综述了以牙周炎为主的口腔疾病中富氢水的作用及研究进展，并对其潜在作用机制进行了阐述，旨在为富氢水在口腔疾病治疗中的运用提供参考。

1 富氢水的制备与优势

目前，常用的富氢水制备方法主要有3种。一种是在高压下将H_2注入水或盐水中，促进H_2溶解。另一种方法是通过电解产生H_2并溶解于水或盐水中。第三种方法主要涉及金属与酸（如硫酸和盐酸）的反应，使水或盐水中富含H_2[13]。在室温大气压下，H_2在水中的溶解度为1.6 mg/L，较低的溶解度难以保证有效的生物利用度，但通过提高摄入频率可以克服其半衰期较短的问题[1]。然而，富氢水作为药品使用的浓度和剂量仍需进一步研究证实。

与传统的口腔疾病治疗相关的抗氧化剂相比，富氢水具有许多突出的优势：首先，H_2具有强大的穿透性。由于H_2的分子量较低，H_2可以非常容易的进入细胞内任何部位，如细胞核和线粒体等，可以针对性地清除线粒体中产生的活性氧（reactive oxygen species，ROS），发挥更好的效能[14]。其次，H_2的抗氧化效应具有选择性，能够选择性降低ROS中细胞毒性最强的羟自由基，从而有效地保护细胞，同时不与其他具有生理功能的良性ROS发生反应[14-15]。此外，富氢水较其他口腔制剂更具安全性。H_2被认为是一种生理性惰性气体，体内肠道细菌能不断产生H_2，有助于保护肠道黏膜，并且能够在血液中正常循环[16]。长期使用较大剂量的维生素E、维生素C、辅酶Q、β-胡萝卜素等抗氧化剂可能对人体有害[17-20]，但富氢水尚未在有效剂量下表现出毒性，其生物安全性可以得到保证[11]。另一方面，部分传统的漱口水，如洗必泰（chlorhexidine，CHX）在预防和控制牙菌斑的形成，抑制牙周炎的发展的同时，可能导致口干、味觉改变、腮腺肿胀、口腔黏膜脱屑或疼痛、牙齿和舌头染色等不良反应，并且部分口腔细菌会对CHX产生耐药性[21]。而富氢水表现出更小的副作用，能够更好地辅助口腔疾病预防及治疗。富氢水通过饮用即可发挥一定的治疗效应，制备方式相对简单，相比于直接使用H_2进行辅助治疗，具有便携、操作简单等优势，更加适于日常生活的口腔保健工作。

2 富氢水对牙周炎的治疗作用

2.1 抑制菌斑生物膜的形成

菌斑生物膜是牙周炎发生的始动因子，菌斑生物膜所致的宿主免疫炎症反应在牙周炎的发生发展

中起着至关重要的作用[22]，因此，抑制菌斑生物膜的形成及炎症的发生对牙周炎的治疗具有重要意义[23]。

富氢水已被证实对牙周致病菌具有良好的抗菌作用。Nayak等[24]将20例30~50岁的慢性牙周炎患者牙菌斑样本暴露于富氢水中不同时间，发现在暴露时长2.5 min时菌落形成单位少，抗菌活性较好。Lee等[25]也通过体内外研究评估了富氢水对牙周致病菌的抗菌作用。研究发现，与自来水相比，富氢水能够显著抑制培养基和牙刷上伴放线放线杆菌、具核梭杆菌、中间普氏菌及牙龈卟啉单胞菌生长。此外，富氢水对多种有氧或无氧口腔细菌均具有抗菌活性，细菌数量可减少约97%[25]，这提示将富氢水用于口腔及牙刷杀菌可能有助于预防和治疗牙周炎。

2.2　抗氧化应激作用促进组织愈合

牙周致病菌侵入后能够将血液中的白细胞趋化募集至牙周组织，其中以多形核中性粒细胞为主。中性粒细胞的过度激活会产生大量的ROS和蛋白酶，引起氧化应激并诱发炎症，从而导致牙周结缔组织的破坏和骨吸收[26]。

Bhatt等[27]进行体外实验，发现富氢水对可以显著提高慢性牙周炎患者成纤维细胞活力和迁移能力，并在富氢水处理48 h后观察到最大的抗氧化潜能，抑制了慢性牙周炎患者成纤维细胞的氧化应激。体内研究也进一步证实了富氢水对牙周炎的抗氧化应激作用，Yoneda等[12]发现饮用富氢水与饮用蒸馏水相比可减少高脂饮食喂养的大鼠体重的增长，同时能调节牙龈组织中参与氧化应激的多种分子的表达，牙槽骨骨密度也较饮用蒸馏水更高。Kasuyama等[11]通过建立大鼠实验性牙周炎模型，发现富氢水能够抑制牙周炎发生时ROS的产生，抑制破骨细胞分化和多形核白细胞的浸润。上述研究证实了饮用富氢水能够抑制牙周炎诱导的氧化应激和牙槽骨吸收，辅助牙周炎的治疗。

非手术牙周治疗是牙周炎治疗的首要阶段，能够达到控制炎症、抑制疾病进展的目的，对牙周炎治疗至关重要[28]。Azuma等[29]对牙周炎患者的所有牙周袋进行龈上/龈下清创、洁牙和根面平整等非手术牙周治疗，试验组在非手术牙周治疗期间，每天饮用富氢水约1 000 mL并持续8周，结果显示，结合富氢水治疗的患者临床附着水平（clinical attachment level，CAL）和牙周探诊深度（probing depth，PD）有显著改善，活性氧代谢物（reactive oxygen metabolites，ROM）水平降低，总抗氧化能力提高。此研究首次探究了饮用富氢水对人类牙周炎的影响，揭示了富氢水作为非手术牙周炎治疗辅助手段的潜能。

伤口愈合的过程中会发生一系列的炎症反应。中性粒细胞的募集及免疫相关分子事件的启动能够预防感染，从而加速伤口愈合。在此过程中，氧化应激是导致炎症和口腔黏膜创伤的关键因素[30]。Tamaki等[31]通过活检和血清学检测，证明了口服富氢水能够减少伤口愈合过程中的氧化应激和炎症反应，有助于伤口愈合。Xiao等[32]也通过体外划痕实验，发现富氢水能够减少过氧化氢诱导的ROS生成，保护人牙龈成纤维细胞（human gingival fibroblasts，HGFs）免受过氧化氢诱导的细胞死亡和生长抑制，促进HGFs单层创面的愈合。

3　氢分子抗炎作用的相关机制

3.1　减轻氧化应激损伤的机制

3.1.1　H_2选择性与羟自由基结合　牙周炎发生过程中，致病微生物的脂多糖（lipopolysaccharide，LPS）引发宿主免疫反应，导致大量ROS产生，呈现较高的氧化应激状态[33]。ROS以超氧阴离子自由基（$\cdot O_2$）和羟自由基（OH·）为主，其中羟自由基最为活跃，可通过促进脂质、蛋白质过氧化，损伤细胞膜结构和DNA，使细胞和组织发生炎性损伤，具有较大的破坏性[34]。而H_2可以选择性与羟自由基结合，减少细胞损伤，有益于细胞的存活[35]。周敏等[35]研究发现，给予人牙周膜细胞LPS刺激后，富氢培养基组细胞活性显著高于普通培养基组，细胞凋亡率也较普通培养基组低。证明富氢培养基可显著抑制LPS所致的细胞活性降低和细胞凋亡，减轻LPS所致的氧化应激损伤。

3.1.2　活化抗氧化酶　细胞内谷胱甘肽（glutathione，GSH）在抗氧化方面具有核心作用，谷胱甘肽过氧化物酶（glutathione peroxidase，GPX）、超氧化物歧化酶（superoxide dismutase，SOD）是人体重要的抗氧化酶，能够有效防御氧化应激损伤[36]，而H_2可以有效增加机体抗氧化酶SOD和谷胱甘肽过氧化物酶的水平，防止细胞内谷胱甘肽消耗，保护细胞或组织免受氧化损伤[32,37-38]。

3.1.3　调节氧化应激反应相关基因　Fancc是一种氧化应激反应基因，H_2的添加能够下调Fancc的基因表达[12]。DNA中的鸟嘌呤发生氧化损伤时会产生8-羟基脱氧鸟苷（8-hydroxy-2 deoxyguanosine，8-OHDG），可作为氧化应激的可靠指标[39]；丙二醛（malondialdehyde，MDA）与自由基造成的损伤密切

相关，是脂质过氧化的终产物[40]。H_2亦能有效降低8-OHdG与MDA的水平，减轻口腔内氧化应激损伤[35]。除牙周炎外，富氢水可以减轻口腔内由衰老、肥胖等因素引起的氧化应激[11-12,41]。通过激活抗氧化及促进愈合相关基因的表达，富氢水还能够加速大鼠口腔黏膜的伤口愈合[31]。

诱导核因子E2相关因子2（nuclear factor erythroid 2-related factor 2，Nrf2）/抗氧化防御通路的激活。Nrf2及其主要负调节因子与氧化应激密切相关，在炎症反应调节和细胞内氧化还原稳态的维持中起着重要作用[42]。Nrf2可转位到细胞核，调节NAD(P)H：醌氧化还原酶1[NAD(P)H: quinone oxidoreductase 1，NQO-1]和血红素加氧酶1（heme oxygenase-1，HO-1）等基因的表达，从而发挥抗氧化应激效应，减少细胞损伤[43]。

在慢性肠道炎症、环孢素A诱导的肾损伤的研究中，富氢水能够诱导Nrf2依赖的基因，降低氧化应激和促炎细胞因子水平，抑制炎症发展[44-45]。H_2在腭组织中也存在类似效应，Tamaki等[31]研究发现饮用富氢水的大鼠腭组织中Nrf2的mRNA表达水平显著高于对照组，HO-1、NQO-1的mRNA表达显著增加。以上结果均提示富氢水可通过激活Nrf2途径促进抗氧化基因表达。

3.2　抑制促炎介质的表达

在脑缺血再灌注损伤和脂肪肝的研究中，富氢水能够调节炎症细胞因子白细胞介素（interleukin，IL），包括IL-10、IL-2的表达，促进抗氧化酶的激活，抑制炎症反应[46-47]。Saitoh等[48]发现牙龈卟啉单胞菌LPS可诱导HGFs中IL-1α和IL-6分泌，但富氢水可显著抑制其炎症诱导效应，从而抑制牙周炎的进展；同时，在富氢水处理3 h后有80%的H_2丢失，推测H_2在该过程中较早期参与抑制IL-1α和IL-6的分泌。以上实验表明富氢水能够通过抑制促炎介质的表达，抑制牙周炎的发生发展，减轻口腔组织的炎性损伤。

3.3　激活组织愈合相关基因

在大鼠腭部损伤模型中，饮用富氢水3 d后转化生长因子β1（transforming growth factor-β1，TGF-β1）、成纤维细胞生长因子7（fibroblast growth factors，FGF7）、血管内皮生长因子（vascular endothelial growth factor，VEGF）等生长因子和α-平滑肌肌动蛋白（α-smooth muscle actin，α-SMA）等愈合相关因子的表达水平显著高于对照组；且在第3天，富氢水组的I型胶原的表达水平也显著升高，表明富氢水的摄入促进了大鼠腭组织中愈合相关基因的表达[31]。此外，HO-1是一种抗炎和抗氧化酶，与人类的伤口愈合有关[49]，而H_2可通过激活Nrf2途径使HO-1表达量升高，进一步证明了饮用富氢水对伤口愈合的促进作用[31]。在骨骼发育及骨稳态维持中，丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）通路起着至关重要的作用。ROS可激活MAPK通路，从而促进炎症性骨溶解[50]。p38 MAPK、细胞外信号调节激酶（extracellular signal-regulated kinase，ERK）和c-Jun N端激酶（c-Jun N-terminal kinase，JNK）是MAPK亚家族的主要类群[51]。Kasuyama等[11]发现使用富氢水后破骨细胞数量显著降低，JNK、p-38 MAPK和ERK表达量均下降，提示富氢水可通过抑制MAPK信号通路的表达来抑制破骨细胞的分化。

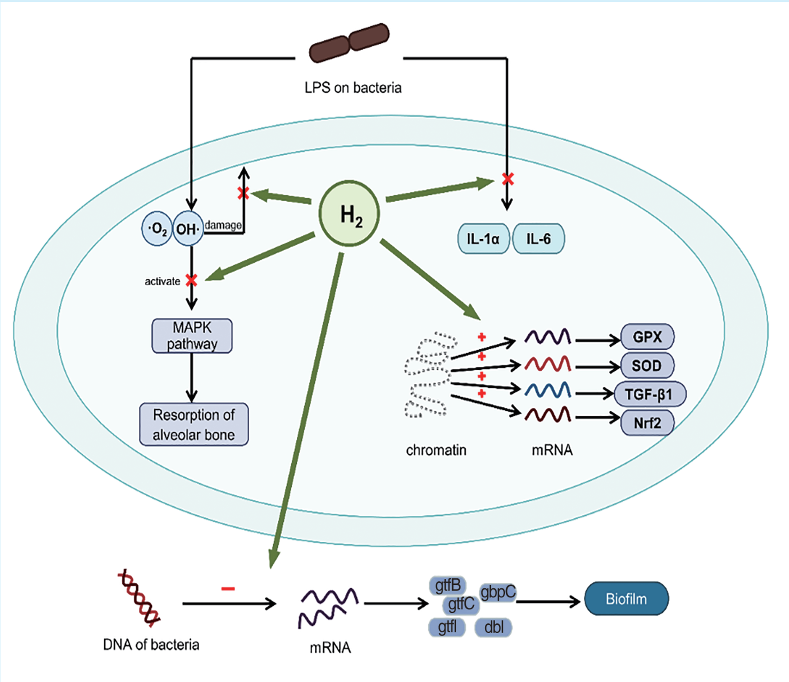
3.4　抗菌机制

菌斑生物膜的形成是变异链球菌（*Streptococcus mutans*，*S. mutans*）致龋的关键之一。*S. mutans*可形成糖基转移酶（glycosyltransferase，GTFs）以合成细胞外多糖，从而聚集并附着于牙面。葡聚糖结合蛋白（glucan-binding protein，GBP）与不溶性葡聚糖结合，是细菌生物膜形成中的关键步骤[52]。

Kim等[10]评估了富氢水对不溶性葡聚糖合成相关基因表达和葡聚糖结合的影响。细菌在富氢水中暴露60 s后，糖基转移酶（gtfB、gtfC和gtfI）和葡聚糖结合蛋白（gbpC、dblB）的mRNA表达水平均下降，*S. mutans*生物膜形成显著减少；而远缘链球菌（*Streptococcus sobrinus*，*S. sobrinus*）对富氢水更敏感，仅暴露15 s生物膜的形成便显著下降。此研究表明富氢水可以抑制细菌黏附相关基因GTFs和GBP的表达，从而抑制细菌生物膜的形成。Liu等[53]通过生物膜结晶紫染色，也证实了富氢水对细菌生物膜形成的抑制作用。

富氢水也可通过抑制细菌增殖来达到抑菌作用。用富氢水处理的培养物、牙刷和唾液中，各种牙周致病菌的生长显著减少[25]。使用富氢水进行口腔冲洗时，唾液链球菌的集落形成单位值显著降低[10]，也证明富氢水能够抑制细菌生长繁殖，从而有效地减少口腔*S. mutans*数量，有助于牙周病及龋病的预防。Liu等[53]研究发现，将致龋细菌（*S. mutans*和*S. sobrinus*）暴露于富氢水中1 min后，可有效抑制细菌生长、减少菌落形成单位数量。为富氢水作为漱口水用于口腔细菌性疾病的预防提供了新的依据。

总之，富氢水可选择性与羟自由基结合，减轻氧化应激损伤，激活相关抗氧化信号通路、抑制促炎介质表达、促进生长因子表达，抑制细菌生物膜形成等作用，起到抗炎的作用（图1）。



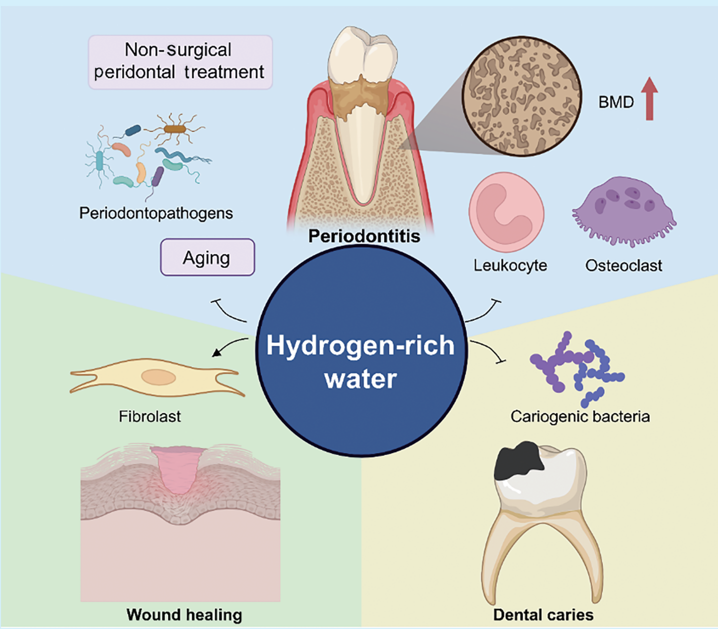
Molecular hydrogen can inhibit LPS-induced IL-1α and IL-6 production, reduce ROS-induced cell membrane damage, block MAPK pathway activation, and reduce alveolar bone resorption. Additionally, molecular hydrogen can activate the expression of GPX, SOD, TGF-β1, and Nrf2 to reduce oxidative stress and promote tissue healing. Moreover, molecular hydrogen can effectively inhibit the formation of plaque biofilms by inhibiting the expression of bacterial adhesion-related genes, such as GTFs and GBPs. GBPs: glucan-binding proteins. GPX: glutathione peroxidase. GTF: glycosyltransferases. IL: interleukin. LPS: lipopolysaccharide. MAPK: mitogen-activated protein kinase. Nrf2: nuclear factor erythroid 2-related factor 2. ROS: reactive oxygen species. SOD: superoxide dismutase. TGF-β1: transforming growth factor-β1

Figure 1　Mechanisms underlying the anti-inflammatory effects of molecular hydrogen

图 1　氢分子抗炎作用的相关机制

4　小　结

在口腔疾病治疗方面，富氢水已表现出较大的临床应用潜力，能够通过减少菌斑生物膜的形成减少细菌数目、抑制氧化应激的同时调节相关信号转导通路抑制炎性介质的产生，发挥抗菌、保护牙周支持组织、促进创伤愈合等作用，在牙周病、龋病、衰老性牙周组织氧化损伤等口腔疾病的预防及治疗中具有积极意义（图 2）。但目前对富氢水的具体作用机制认识仍不够完善，对于富氢水作用的临床检验仍不够充分。此外，以富氢水作为治疗方式时的给药方式和使用剂量，其浓度的稳定性和有效性之间的关系仍需要更多的研究。



HRW is beneficial for the treatment of periodontitis and caries and can promote wound healing, inhibit periodontopathogen proliferation, reduce alveolar bone loss by inhibiting osteoclast differentiation and leukocyte infiltration, improve the efficacy of non-surgical periodontal treatment, and reduce age-related periodontal tissue inflammation. Additionally, HRW can prevent the occurrence of caries by reducing the number of oral cariogenic bacteria and protecting human gingival fibroblasts during wound healing. BMD: bone mineral density. HRW: hydrogen-rich water

Figure 2　Therapeutic effects of hydrogen-rich water in oral diseases

图 2　富氢水对口腔疾病的治疗作用

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