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REVIEW

Hydrogen Regulates Ulcerative Colitis by Affecting the Intestinal Redox Environment

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Abstract: The redox balance in the intestine plays an important role in maintaining intestinal homeostasis, and it is closely related to the intestinal mucosal barrier, intestinal inflammation, and the gut microbiota. Current research on the treatment of ulcerative colitis has focused on immune disorders, excessive inflammation, and oxidative stress. However, an imbalance in intestinal redox reaction plays a particularly critical role. Hydrogen is produced by some anaerobic bacteria via hydrogenases in the intestine. Increasing evidence suggests that hydrogen, as an inert gas, is crucial for immunity, inflammation, and oxidative stress and plays a protective role in ulcerative colitis. Hydrogen maintains the redox state balance in the intestine in ulcerative colitis and reduces damage to intestinal epithelial cells by exerting its selective antioxidant ability. Hydrogen also regulates the intestinal flora, reduces the harmful effects of bacteria on the intestinal epithelial barrier, promotes the restoration of normal anaerobic bacteria in the intestines, and ultimately improves the integrity of the intestinal epithelial barrier. The present review focuses on the therapeutic mechanisms of hydrogen-targeting ulcerative colitis.

Plain Language Summary: The balance of oxidation-reduction is crucial for maintaining the overall health of the intestines. However, disruption of this equilibrium leads to the development of various diseases, such as ulcerative colitis. Ulcerative colitis is a chronic inflammatory bowel disease that is characterized by inflammation and ulcers in the lining of the colon and rectum. Abnormal oxidative stress in ulcerative colitis leads to the excessive activation of immune cells, heightened inflammation, and imbalance of gut microbiota, which accelerates the development of this disease. Hydrogen gas is a reducing gas that is produced by bacteria in the intestine or administered exogenously. It has an important selective antioxidant role and alleviates ulcerative colitis without interfering with normal physiological processes. The present article summarizes the direct and indirect effects of hydrogen gas on ulcerative colitis by analyzing the relevant literature, which indicates that hydrogen gas is a potential molecular drug for the treatment of ulcerative colitis.

Keywords: inflammatory bowel disease, ulcerative colitis, oxidative stress, hydrogen, molecular medicine

Introduction

Ulcerative colitis (UC) is a complex, immune-mediated chronic inflammatory disease that primarily affects the rectum and colon. It is associated with various factors such as inflammation, oxidative stress, and disorders of the microflora.[1–3] Current treatment options for UC include medications, such as 5-aminosalicylic acid, corticosteroids, and biological agents such as infliximab. However, these drugs have side effects, and some patients may not respond well to these drugs.[4,5] The overall control of this disease using traditional treatments is unsatisfactory, which supports an increasing need to identify new drug treatment targets.[3,6,7] Molecular hydrogen is a recently discovered medical gas that has shown promising results in various clinical studies. It has the unique ability to penetrate cell membranes, spread to the cytoplasm, and target specific organelles. One of its key properties is its ability to selectively reduce cytotoxic oxygen radicals, such as hydroxyl radicals (·OH) and peroxynitrite (ONOO-), without affecting physiological reactive oxygen

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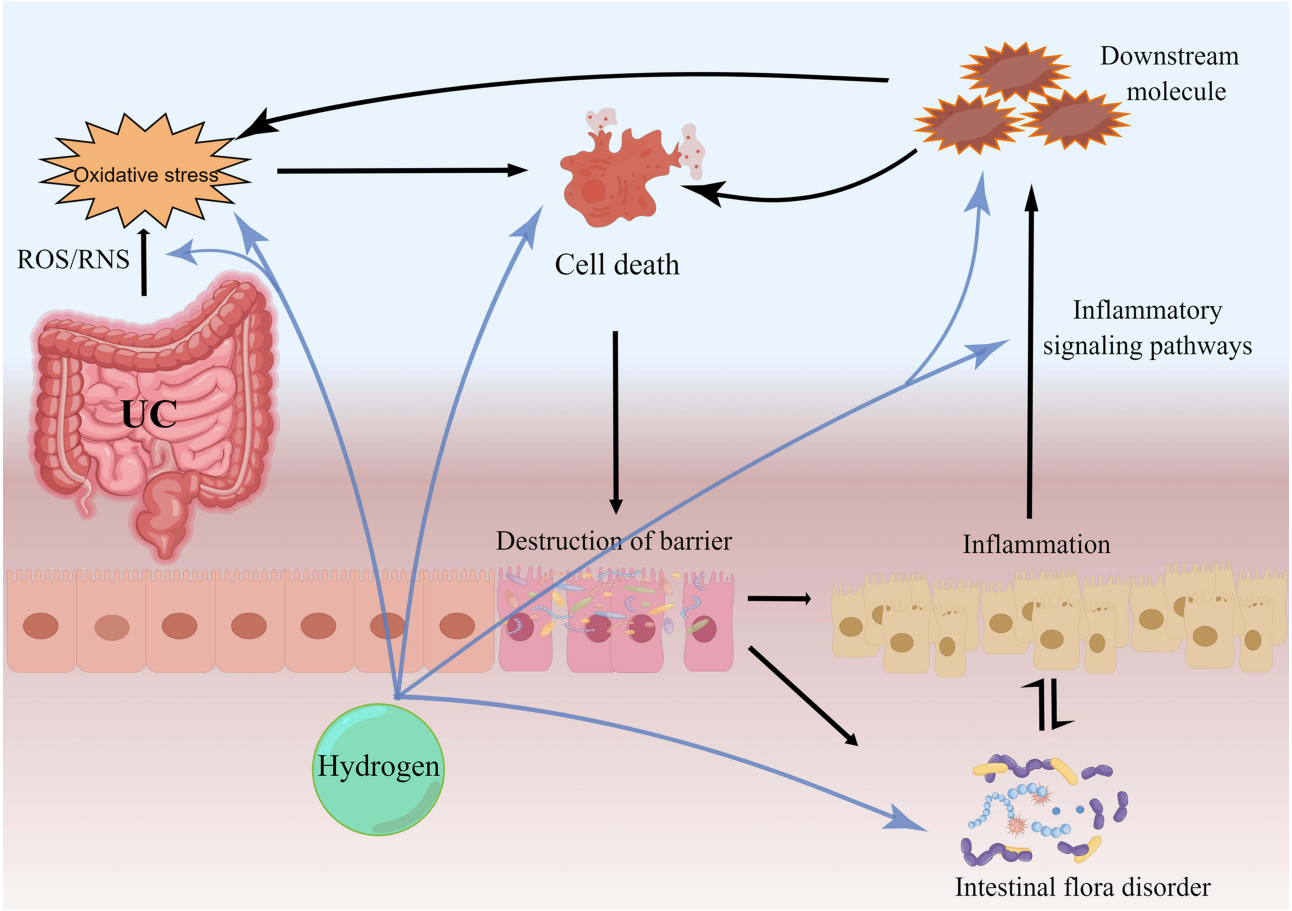
Graphical Abstract



species (ROS) or reactive nitrogen species (RNS), which are involved in normal cell signaling.[8–13] This selective targeting makes hydrogen a safe and effective therapeutic option. Clinical experiments demonstrated the safety of hydrogen gas and showed its benefits in different medical fields,[14–16] including sports medicine,[17,18] cognitive impairment,[19] stroke,[20] cancer,[21] metabolic syndrome,[22] and in patients with COVID-19.[23,24] Animal models of ulcerative colitis also showed therapeutic effects of hydrogen, including anti-inflammation, anti-oxidative stress, regulation of endoplasmic reticulum stress, and regulation of the gut microbiota.[25–30] Hydrogen gas therapy was administered to animals via the direct consumption of hydrogen-rich water or intraperitoneal injections of hydrogen-rich physiological saline and indirectly by the administration of drugs that increase hydrogen production in the intestines, such as lactulose.[12,31,32] The present review focused on the protective mechanism of hydrogen against ulcerative colitis from an antioxidant perspective. An increased understanding of hydrogen regulation oxidative stress, inflammation, and the gut microbiota will provide insights into its potential as a therapeutic option for patients with UC.

Ulcerative Colitis, Oxidative Stress, and Inflammation

Oxidative stress and inflammation are closely related to UC and are among the main mechanisms involved in its occurrence and development.[33,34] Due to various factors, such as genetics, the environment, and microorganisms, excessive activation and imbalance of immune cells lead to the excessive production of free radicals by immune cells such as neutrophils and macrophages.[35–37] Specifically, the excessive levels of activated free radicals continue to increase and lead to severe oxidative stress and disruption of redox balance, which substantial damage to proteins, lipids, and

deoxyribonucleic acid.[38–40] When free radicals attack intestinal epithelial cells (IECs) and cause damage, the death of IECs increases, the expression of intestinal tight junction proteins decreases, and the permeability of the epithelial barrier increases, which lead to the invasion of intestinal bacteria and other antigens into the intestinal mucosa. The damaged barrier absorbs an increasing number of luminal antigens, which cause dysbiosis of the microbiota and worsening of inflammation.[41–44] When inflammation and oxidative stress signaling pathways are activated by factors such as intestinal injury, bacteria, and related antigens, downstream factors accelerate the apoptosis and necrosis of IECs, which lead to further intestinal injury and dysbiosis of the microbiota.[45–47]

Hydrogen in the Regulation of the Oxidative Stress Environment in Ulcerative Colitis

Hydrogen

The bacteria in the intestinal tract primarily include Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria.[48,49] Firmicutes and Bacteroidetes are abundant anaerobic bacteria that colonize the colon and produce hydrogen as the end product of complex carbohydrates degradation.[50–52] Hydrogen production is determined by the hydrogenase activity of hydrogen-producing bacteria.[53] Hydrogenase is a metal enzyme in bacteria and fungi that produces hydrogen, and the most abundant hydrogenase in Firmicutes and Bacteroidetes is [FeFe]-hydrogenase.[50] Some of the produced hydrogen is excreted directly from the gastrointestinal tract or absorbed into the bloodstream.[54,55] The remaining hydrogen can be converted to other metabolites by the gut microbiota.[56–58] There is relatively little research on the direct physiological effects of endogenous hydrogen production in the intestine on the human body. However, animal experiments have shown that reducing hydrogen production in the intestine increased tissue damage, and exogenous supplementation with hydrogen or hydrogen-producing bacteria reduced tissue damage.[59] These findings indicate that endogenous hydrogen gas may have certain biological effects in the body. H_2 is a major byproduct of gut bacteria, and microorganisms that use H_2 as a substrate have evolutionary advantages in anaerobic gut ecosystems. H_2 provides an additional substrate for the growth and energy metabolism of hydrogenotrophs, which increases their abundance and promotes hydrogen metabolism in the intestine.[58,60,61] The various bioactive compounds produced further regulate the gut microbiota. For example, propionic acid and hydrogen sulfide have many physiological functions related to intestinal and systemic immune regulation, gene expression, and cellular signal transduction.[62,63] Studies on exogenous hydrogen and the promotion of hydrogen production in the intestines indicated that hydrogen had various bioactive functions, with selective antioxidant effects being the most significant. Japanese scientists discovered that hydrogen molecules selectively bound and neutralized toxic free radicals while preserving other important ROS and RNS for normal cellular signaling.[10] Hydrogen also inhibits the intestinal redox potential, which affects various factors including the bacterial population in the body.[64] Changes in free radicals can be tracked directly to determine the effects of hydrogen.[65] Hydroxyphenyl fluorescein (HPF) and other reactive oxygen species fluorescent probes have been used to track changes in highly toxic oxidative factors. For example, HPF has been used to detect changes in highly toxic oxidative factors in mouse testes.[13] This molecule provides researchers with a tool to explore the specific anti-oxidative stress mechanisms of hydrogen in different tissues or cells, as alterations in free radicals play a critical role in redox signaling pathways.[66] However, hydrogen circulation in the body is affected by various factors, and oxidative stress in the intestines plays a critical role. Oxidative stress in the intestine damages the normal gut microbiota via the excessive production of substances, such as ROS. Disruption of the original redox balance affects the anaerobic environment in the intestine, which leads to an imbalance between pathological aerobic microbial communities and physiological anaerobic microbial communities.[29,34,67,68] When various factors, such as inflammation and oxidative stress levels in the intestine change, the dynamic balance between hydrogen-producing bacteria and hydrogenotrophic bacteria is disrupted, which leads to disruption of the hydrogen cycle.

Direct Regulation of the Oxidative Stress Environment in Ulcerative Colitis by Hydrogen

Oxidative stress is closely associated with UC, and it plays a vital role in its development and progression.[34] Various factors, such as genetics, environmental factors, and microorganisms, trigger the excessive production of free radicals by immune cells, such as neutrophils and macrophages, in patients with UC.[35–37] When free radicals attack biofilms, excessive formation of the lipid peroxide malondialdehyde (MDA) leads to structural changes and immune responses.[69,70] In mouse models of dextran sulfate sodium salt (DSS)- induced UC, the activity of the enzyme myeloperoxidase (MPO), which is an indicator of neutrophil infiltration, increased with the severity of inflammatory damage.[71,72] MPO catalyzes the production of cytotoxic oxidants, including hypochlorite, from hydrogen peroxide and chloride ions under stress conditions.[73] L-glutathione (GSH), which is a non-enzymatic antioxidant, plays a protective role by inhibiting the formation of oxidative damage.[74] Superoxide dismutase (SOD) exerts beneficial effects by converting superoxide free radicals (O-) into hydrogen peroxide (H_2O_2), which protects cells from oxidative damage.[75,76] However, chronic inflammation in UC leads to the excessive production of ROS, which results in the depletion of GSH and SOD.[27,77,78] Numerous animal models of UC showed that hydrogen-rich water effectively inhibited oxidative stress, which was evidenced by the inhibition of increased MDA and MPO levels in the intestines and the elevation of GSH and SOD levels[27,28,30,79](Table 1). Heme oxygenase-1 (HO-1) is an anti-inflammatory and antioxidant that protects cells.[80,81] Water rich in hydrogen upregulates the expression of HO-1.[27] The literature suggests that treatment with hydrogen-rich water leads to recovery of weight loss and a reduction in colon length in mice with UC, and a decrease in histological inflammation. When free radicals attack intestinal mucosal epithelial cells and cause

Table 1 The Mechanism of Hydrogen Molecule on UC in Current Research

Mechanism of Hydrogen or Hydrogen-Producing Substances on UC	Study Design	Animal Model Used	Main Results	References
Direct anti-oxidant and anti-inflammatory effect	Mice were divided into five groups: control group; DSS group; DSS + sulfasalazine group; DSS + H_2 group; DSS + sulfasalazine + H_2 group.	DSS-induced colitis mice	Inhibited MDA activity and increased SOD activity.	[28]
	Mice were divided into three groups: DSS group; DSS + H_2 group; H_2 group.	DSS-induced colitis mice	Reduced the levels of TNF-α and IL-1β.	[25]
	Mice were divided into seven groups: DSS + H_2 group; DSS group; DSS + oral lactulose group (0.1, 0.15, 0.2 mL/10 g, respectively); DSS + lactulose (0.2 mL/10 g) + oral antibiotics group.	DSS-induced colitis mice	Inhibited MDA and MPO activity and reduced the levels of TNF-α and IL-1β.	[79]
	Mice were divided into three groups: control group; DSS group; DSS + H_2 group.	DSS-induced colitis mice	Inhibited MDA activity and increased GSH and SOD activity, and reduced the levels of TNF-α and IL-6.	[30]
	Mice were divided into four groups: control group; DSS group; DSS+ H_2 group; DSS + H_2 + ZnPP group.	DSS-induced colitis mice	Inhibited MDA and MPO activity, increased GSH and SOD activity, reduced the levels of TNF-α, IL-6, and IL-1β and reduced the key proteins of ERS, including P-EIF2α, ATF4, XBP1s, and CHOP.	[27]

(*Continued*)

Table 1 (Continued).

Mechanism of Hydrogen or Hydrogen-Producing Substances on UC	Study Design	Animal Model Used	Main Results	References
	Mice were divided into four groups: control group(received no treatment); vehicle group; DSS group; DSS + H_2 group.	DSS-induced colitis mice	Inhibited the TLR-4/MyD88/NF-κB signaling pathway and reduced the levels of TNF-α and IL-6.	[29]
Effect of indirect regulation of gut microbiota	Mice were divided into four groups: control group(received no treatment); vehicle group; DSS group; DSS + H_2 group.	DSS-induced colitis mice	Maintained colon cell hypoxia and the anaerobic environment by increasing the abundance of beneficial gut bacteria such as butyrate-producing microorganisms, and inhibited the growth of pathogenic enterobacteria.	[29]
	Mice were divided into three groups: control group; DSS group; DSS + H_2 group.	DSS-induced colitis mice	Inhibited the growth of pathogenic enterobacteria.	[30]

damage, the expression of intestinal tight junction proteins decreases and the intestinal mucosal epithelial barrier is disrupted.[43,82] This damage disrupts the integrity of the intestinal mucosal epithelial barrier, and allows more luminal antigens to be absorbed, which leads to increased intestinal damage and inflammation.[42,83,84] The damage to the intestinal epithelial barrier and imbalance in the bacterial ecosystem in UC lead to abnormal activation of Toll-like receptor 4 (TLR4), which ultimately results in the abnormal activation and translocation of nuclear factor kappa B (NF-κB).[85,86] This abnormal activation triggers an immune response that is characterized by the release of inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α).[46] These factors accelerate the apoptosis and necrosis of IECs, which further exacerbates inflammation in UC.[87,88] Rat and mouse models of UC showed that hydrogen had significant inhibitory effects on inflammatory factors such as IL-1β, TNF-α, and IL-6.[25,27,29,30,79] Hydrogen-rich water significantly downregulated the protein expression of TLR-4 and myeloid differentiation factor 88 (MyD88), which inhibited phosphorylation of the inhibitory subunit of NF-κB α (IκBα). This finding suggested that exogenous hydrogen improved the inflammatory environment in the intestine by reducing inflammatory factor levels via the TLR-4/MyD88/NF-κB signaling pathway.[29] When intestinal cells are exposed to stressors, such as inflammatory mediators and oxidative stress substances, excessive endoplasmic reticulum stress (ERS) occurs, which leads to the accelerated apoptosis of epithelial cells. This apoptosis damages the intestinal mucosal barrier and increases intestinal epithelial permeability.[89] Excessive ERS is present in the intestinal epithelial cells of UC patients and animal models, and it is closely associated with disease progression.[90–92] Hydrogen-rich water significantly reduced the expression of key ERS proteins in the DSS model, including the phosphorylated α subunit of eukaryotic initiation factor 2 (P-EIF2 α), activating transcription factor 4 (ATF4), spliced X-box binding protein 1 (XBP1s), and C/EBP homologous protein (CHOP).[27] These findings suggested that hydrogen played a crucial role in alleviating UC by reducing ERS and inhibiting excessive apoptosis (Figure 1). The excessive activation of free radicals in UC leads to severe oxidative stress, which results in an imbalance between antioxidants and prooxidants, leads to loss of protection and damage to cells.[39,40,93] When the damage to IECs increases, disruption of the intestinal epithelial barrier leads to the invasion of harmful bacteria and other antigens into the intestinal mucosa. The damaged barrier absorbs an increasing number of luminal antigens, which causes dysbiosis of the microbiota and worsening of inflammation.[41–44] When inflammation and oxidative stress signaling pathways are activated by factors, such as intestinal injury, bacteria, and related antigens, downstream factors accelerate the apoptosis and necrosis of IECs, which lead to further intestinal injury and dysbiosis of the microbiota.[45–47] The selective reducing effect of hydrogen on toxic free radicals effectively reduces the occurrence of excessive oxidative stress by enhancing antioxidant levels, lowering pro-oxidant levels, and reducing endoplasmic reticulum stress to protect cells,[27,28,30,79] which protect the intestinal epithelial barrier. Hydrogen also exerts

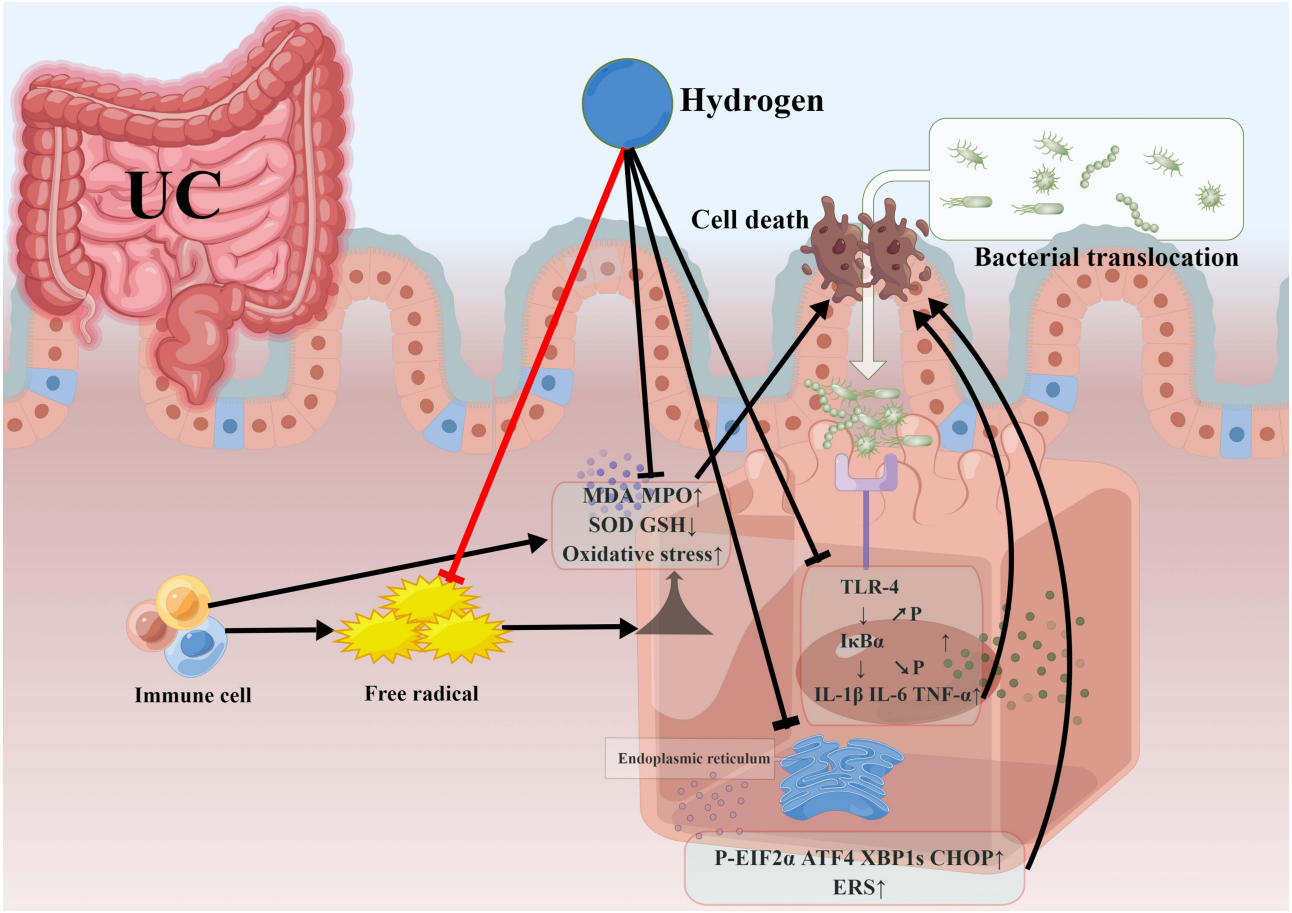


Figure 1 Hydrogen maintains an anaerobic environment in the intestine and reduces oxidative damage via selective antioxidant effects. Hydrogen functions by reducing excessive free radicals produced by immune cells, which regulates the balance of oxidative stress. It also regulates endoplasmic reticulum stress and inflammation via the TLR-4/MyD88/NF-κB signaling pathway to ultimately protect the intestinal barrier and maintain a balanced gut microbiota. By Figdraw.
Abbreviations: MDA, malondialdehyde; MPO, myeloperoxidase; GSH, glutathione; SOD, superoxide dismutase; TLR4, toll-like receptor 4; IκBα, inhibitory subunit of NF-κB α; IL-1β, interleukin-1β; IL-6, interleukin-6; TNF-α, tumor necrosis factor alpha; P-EIF2 α, phosphorylated α subunit of eukaryotic initiation factor 2; ATF4, activating transcription factor 4; XBP1s, spliced X-box binding protein 1; CHOP, C/EBP homologous protein; ERS, endoplasmic reticulum stress. This figure is original and was created using Figdraw.

a protective effect on intestinal cells by inhibiting the expression of related inflammatory pathways[29] and reducing downstream inflammatory factors.[25,27,29,30,79] These findings suggest that hydrogen exerts its selective antioxidant effects in UC by neutralizing toxic free radicals. This selective effect helps maintain the balance of redox states in the intestine, reduces damage to intestinal epithelial cells, protects the intestinal epithelial barrier, and ultimately alleviates intestinal inflammation and symptoms of ulcerative colitis.

Indirect Regulation of the Oxidative Stress Environment in Ulcerative Colitis by Hydrogen

Hydrogen-producing bacteria are relatively abundant in the gut microbiota. The most important bacteria are Firmicutes and Bacteroidetes, which reside in the colon.[50] Resistant starch and complex carbohydrates undergo anaerobic fermentation by intestinal bacteria, such as Bacteroidetes and Firmicutes, to form short-chain fatty acids (SCFAs),[94] such as acetic acid, propionic acid, and butyric acid,[95] which are quickly absorbed by surrounding epithelial cells as an important source of energy for intestinal epithelial cells.[96] Hydrogen gas is produced as a byproduct.[97] SCFAs help maintain the integrity of the mucosal barrier and regulate the inflammatory response and cell growth/differentiation, which help maintain the normal physiological function of colon epithelial cells.[98–100] Oxidative stress in UC intestines damages the normal gut microbiota via the excessive production of substances such as ROS. Disruption of the original redox balance affects the anaerobic

environment in the intestine, which leads to an imbalance in the normal anaerobic microbiota. This imbalance in UC is characterized by a decrease in the overall proportions of the beneficial bacteria Bacteroides and Firmicutes and an increase in the overall proportions of potentially harmful bacterial groups, such as Actinobacteria and Proteobacteria. These changes in the composition of hydrogen-producing bacteria in the intestines also affect the production of intestinal hydrogen gas.[29,34,38,67,68,101,102] An imbalance between beneficial and harmful gut bacteria disrupts the integrity of the gut barrier, which leads to the worsening of UC.[103,104] As a product of intestinal metabolism, hydrogen provides additional substrates for hydrogenotrophs, which increases their abundance. This increase in the abundance of hydrogenotrophs promotes hydrogen metabolism in the intestines and results in the production of additional downstream products, including methane, acetic acid, and hydrogen sulfide.[58,61,105] In addition to improving hydrogen nutrition, the consumption of hydrogen-rich water also increases hydrogen partial pressure. This increase in pressure may inhibit the redox potential within the intestinal lumen[64] and lead to the formation of an anaerobic environment, which is beneficial for the growth of anaerobic bacteria (such as Bacteroidetes and Firmicutes) and other SCFA-producing bacteria to ultimately promote intestinal fermentation.[106,107] This fermentation is conducive to the production of intestinal SCFAs, which regulate the metabolism of the gut microbiota and the host.[29,108,109] Hydrogen molecules and hydrogen-producing substances effectively alleviate ulcerative colitis by regulating microbiota disorders (Table 1). A recent study by Li Ge et al used a DSS model to investigate the specific effects of hydrogen molecules on gut microbiota homeostasis and the anaerobic environment. The experiments demonstrated that hydrogen-rich water activated the expression of epithelial peroxisome proliferator-activated receptor γ (PPAR-γ), decreased the expression of nitric oxide synthase 2 (NOS2) and inducible nitric oxide synthase (iNOS), inhibited the production of lactic acid, nitrate and the growth of pathogenic enterobacteria in the colon. Hydrogen maintains colonic cell hypoxia and an anaerobic environment in the intestines by increasing the abundance of butyrate-producing microorganisms, and the formation of an anaerobic intestinal environment inhibits the expansion of facultative anaerobic bacteria. Hydrogen-rich water may change the abundance of specific mucus-associated mucolytic bacteria to prevent the deterioration of colonic mucus, which improves intestinal barrier function and the disturbed gut microbiome.[29] This affect is because the glycoprotein rich mucus layer covering the intestinal epithelium is the first line of defense against symbiotic microorganisms and invading pathogens.[110] In experiments using a chronic UC model, hydrogen-rich water effectively hindered the growth of *Enterococcus faecalis, Clostridium perfringens*, and *Bacteroides fragile*. The relative abundance in the treatment group was similar to the normal control (NC) group, which indicated that hydrogen-rich water inhibited harmful bacteria in the intestines, provided a favorable environment for the survival of normal bacterial communities and reduced competition pressure.[30] Notably, the protective effect of hydrogen-rich water on colitis may be weakened after antibiotic treatment, which highlights the important role of the gut microbiota in mediating the beneficial effects of hydrogen molecules[29] (Figure 2). Hydrogen promotes repair of the intestinal epithelial barrier and protects intestinal cells to ultimately reduce intestinal damage and prevents the bacterial translocation caused by harmful bacteria and other antigens invading the intestinal mucosa.[29] Hydrogen selectively reduces excessive free radicals in the intestine, which reduces the damage caused by free radicals to the normal gut microbiota.[68] Hydrogen promotes hydrogen metabolism in the intestines, improves hydrogen nutrition, and reverses the disruption of the hydrogen cycle in UC.[58,61,105] The inhibition of the intestinal redox potential by hydrogen is beneficial for the growth of normal anaerobic bacteria in the intestine.[64,106,107] Recovery of the normal gut microbiota and the reduction in harmful microbiota also contribute to the restoration of the intestinal inflammation balance and redox balance.[111–113] The number and proportion of major hydrogen-producing bacteria (such as Bacteroides and Firmicutes) increases, and endogenous hydrogen production may also be restored.[29,106,107] These studies suggest that hydrogen has direct and indirect therapeutic effects on UC, and these effects may be mutually influential. Changes in the gut microbiota are closely linked to various factors, such as immunity, inflammation, oxidative stress, endoplasmic reticulum stress, and cell death.[114–120] Hydrogen acts as a "homeostasis regulator" in the intestine by restoring the hydrogen cycle and normalizing the intestinal environment and gut microbiota. This normalization process reduces damage to the intestinal epithelial barrier caused by harmful bacteria, promotes the maintenance of normal anaerobic bacteria in the intestine, and ultimately improves the integrity of the intestinal epithelial barrier. These findings also support the potential of hydrogen as a therapeutic target for ulcerative colitis.

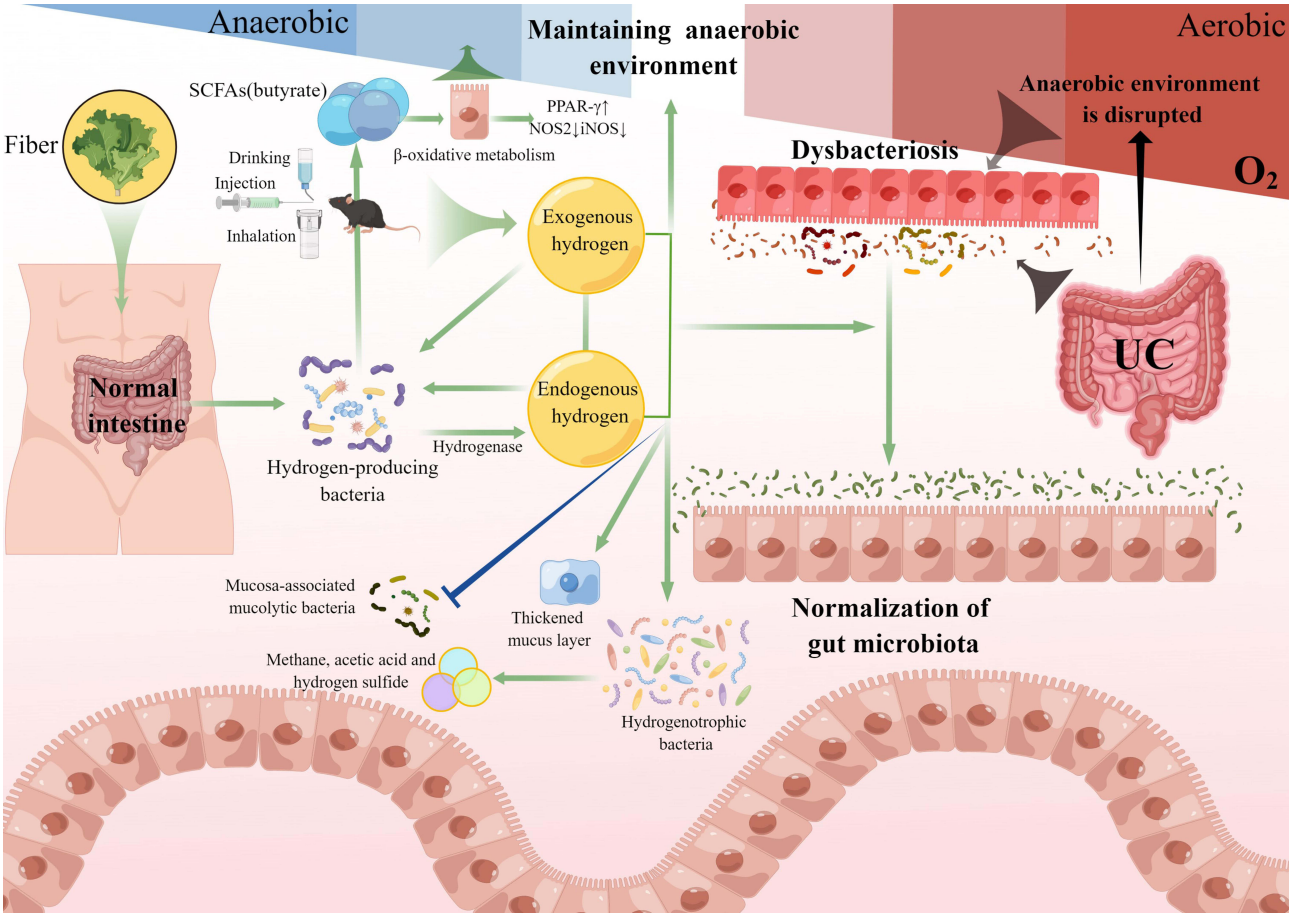


Figure 2 Hydrogen maintains the balance of the gut microbiota and plays a homeostatic regulatory role in ulcerative colitis. The hydrogen produced endogenously and exogenously supplemented hydrogen are mutually influential and improve hydrogen nutrition, which benefits growth of the normal gut microbiota by improving intestinal oxidative stress. It promotes the production of short-chain fatty acids in the intestines, which further maintains a normal anaerobic environment in the gut. By Figdraw.
Abbreviations: UC, ulcerative colitis; SCFAs, short-chain fatty acids; PPAR-γ, peroxisome proliferator-activated receptor γ; NOS2, nitric oxide synthase 2; iNOS, inducible nitric oxide synthase; O_2, oxygen. This figure is original and was created using Figdraw.

Limitations

There are many limitations in the research on the treatment of UC with hydrogen. First, the study of the mechanism of action of hydrogen in the treatment of UC is limited to superficial changes in relevant indicators. More research is needed to explore how hydrogen specifically exerts its antioxidant effects, how it acts on host cells such as immune cells and epithelial cells, how it interacts with the gut microbiota, and the detailed signal transduction pathways involved. Second, there is a lack of animal and cellular experiments on the effects of hydrogen and hydrogen-producing substances on UC. There is also a lack of large-sample, multicenter clinical randomized controlled studies and evidence. Further research is needed to elucidate the underlying mechanisms of hydrogen action, with a particular emphasis on its anti-oxidative effects because it may play a crucial role in the treatment of ulcerative colitis.

Conclusions

Increasing evidence shows that oxidative stress caused by ulcerative colitis may lead to destruction of the intestinal barrier and disorder of intestinal flora, which may be due to attack by free radicals, changes in intestinal reduction potential, and destruction of the intestinal anaerobic environment. Hydrogen, as a product of intestinal anaerobic bacteria, selectively reduces highly active free radicals to restore the redox balance of the intestinal environment, which ultimately protects the intestinal epithelial barrier and normalizes the intestinal microbiota. These findings emphasize the importance of hydrogen in regulating the pathogenesis of UC. Studying the specific mechanism of

action of hydrogen in ulcerative colitis will provide profound insights into the development of UC prediction, diagnosis, and treatment tools.

Abbreviations

UC, ulcerative colitis; OH, hydroxyl radicals; ONOO-, peroxynitrite; ROS, reactive oxygen species; RNS, reactive nitrogen species; IECs, intestinal epithelial cells; SCFAs, short-chain fatty acids; HPF, hydroxyphenyl fluorescein; MDA, malondialdehyde; DSS, dextran sulfate sodium salt; MPO, myeloperoxidase; GSH, L-glutathione; SOD, superoxide dismutase; H_2O_2, hydrogen peroxide; HO-1, heme oxygenase-1; TLR4, toll-like receptor 4; NF-κB, nuclear factor kappa B; IL-1β, interleukin-1β; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; MyD88, myeloid differentiation factor 88; ERS, endoplasmic reticulum stress; P-EIF2 α, phosphorylated α subunit of eukaryotic initiation factor 2; ATF4, activating transcription factor 4; XBP1s, spliced X-box binding protein 1; CHOP, C/EBP homologous protein; PPAR-γ, peroxisome proliferator-activated receptor γ; NOS2, nitric oxide synthase 2; iNOS, inducible nitric oxide synthase; NC, normal control.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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