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# THE ROLE OF MOLECULAR HYDROGEN IN THE MODULATION OF OXIDATIVE AND INFLAMMATORY PROCESSES IN THE HUMAN BODY: A REVIEW OF ITS THERAPEUTIC EFFECTS

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## ABSTRACT

Molecular hydrogen ($H_2$) has been extensively studied for its antioxidant and anti-inflammatory properties. This integrative review aimed to explore the mechanisms of action of $H_2$, focusing on its application in chronic and degenerative diseases, including cardiovascular, neurodegenerative, and inflammatory diseases. Through the analysis of clinical and preclinical trials published between 2010 and 2024, it was found that $H_2$ exerts a protective effect against oxidative stress by selectively neutralizing reactive oxygen species (ROS), such as hydroxyl radicals (•OH) and peroxynitrite (ONOO−). Additionally, $H_2$ regulates inflammation by reducing pro-inflammatory cytokines, such as TNF-α and IL-6, while increasing the production of anti-inflammatory cytokines like IL-10. The reviewed studies also showed that $H_2$ improves endothelial function in patients with cardiovascular diseases and has significant neuroprotective effects in models of cerebral ischemia-reperfusion. However, evidence remains limited due to small clinical trials and the lack of standardization regarding $H_2$ dosage and administration routes. It is concluded that molecular hydrogen is a promising, safe therapy with potential for application in a variety of clinical conditions, but more robust studies are needed to validate its therapeutic benefits on a large scale.

**Keywords**: Molecular hydrogen; Oxidative stress; Inflammation; Cardiovascular diseases; Neuroprotection.

# INTRODUCTION

Molecular hydrogen ($H_2$), once considered a biologically inert gas, has revealed potent antioxidant and anti-inflammatory properties in recent decades. Studies demonstrate that $H_2$ is able to rapidly cross cell membranes and act as a selective antioxidant, neutralizing reactive oxygen species (ROS) and reactive nitrogen species (RNS), particularly the hydroxyl radical (•OH) and peroxynitrite ($ONOO^-$), without interfering with the physiological functions of less reactive ROS, such as hydrogen peroxide ($H_2O_2$) [1,3]. This selectivity makes molecular hydrogen a promising approach in therapies for diseases related to oxidative stress.

Oxidative stress is a phenomenon that occurs when the production of ROS exceeds the body's antioxidant capacity, leading to cellular and tissue damage. This condition is associated with a number of chronic and degenerative diseases, including cardiovascular, neurodegenerative, and chronic inflammatory diseases [4,5]. Several experimental studies have shown that the administration of $H_2$, whether by inhalation, ingestion of hydrogenated water, or injection, results in a significant reduction in ROS levels in animal and human models, protecting cells against damage induced by oxidative stress and promoting cellular homeostasis [3,5].

Regarding the modulation of inflammation, molecular hydrogen has also demonstrated beneficial effects. Studies indicate that $H_2$ is able to regulate the expression of inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), while simultaneously promoting the elevation of anti-inflammatory cytokines, such as interleukin-10 (IL-10), which contributes to the reduction of systemic and local inflammatory processes [7,9,10]. These anti-inflammatory effects have been observed in various models of chronic inflammatory diseases, such as rheumatoid arthritis, liver diseases, and neurodegenerative conditions [8,9].

In the context of cardiovascular diseases, molecular hydrogen has also shown promise. Clinical studies demonstrate that patients with heart failure and coronary artery disease who received treatment with hydrogenated water showed a significant improvement in endothelial function and a reduction in the levels of inflammatory markers such as TNF-α and IL-6. [10,11] In addition, a decrease in lipid peroxidation was observed, suggesting protection against vascular damage related to oxidative stress.[6]

Another area where molecular hydrogen has stood out is in neuroprotection. In experimental models of cerebral ischemia-reperfusion, $H_2$ was able to reduce neuronal damage by inhibiting the overproduction of ROS and RNS, preserving the integrity of neuronal tissues and improving the functional prognosis of patients [7]. These findings suggest that $H_2$ may be a viable therapeutic strategy for the prevention of neurological damage in conditions such as stroke and neurodegenerative diseases [2,7].

## METHODOLOGY

To conduct this integrative literature review, a systematic search strategy was adopted in the following databases: PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. The search encompassed articles published between 2010 and 2024, and the following descriptors were used, in both English and Portuguese: "molecular hydrogen", "oxidative stress", "inflammation", "cardiovascular diseases", "neurodegenerative diseases", "inflammation", "hydrogen therapy", "hidrogênio molecular", "estresse oxidativo", "inflamação", and "doenças crônicas". The combination of descriptors was performed using Boolean operators AND and OR to increase the sensitivity of the search.

**Inclusion Criteria**

**Included in the review were:**

Original articles that investigated the antioxidant and anti-inflammatory effects of molecular hydrogen in experimental or clinical models.

Clinical trials and preclinical studies published between 2010 and 2024, which evaluate the action of molecular hydrogen in cardiovascular, neurodegenerative, liver and inflammatory diseases.

Studies that present quantifiable results, such as the reduction of reactive oxygen species (ROS), regulation of inflammatory cytokines and clinical parameters related to endothelial function and neuroprotection.

Studies available in English, Portuguese or Spanish.

Exclusion Criteria Studies were excluded if:

They did not directly investigate the effect of molecular hydrogen.

Studies with small samples or without adequate statistical validation.

Case reports, non-systematic reviews and opinion articles.

Articles that focused exclusively on other therapeutic gases, such as oxygen or nitrogen, without addressing molecular hydrogen.

**Study Selection**

The selection of studies was carried out in three phases. Initially, the titles and abstracts of the articles identified in the search were screened to exclude those that did not meet the inclusion criteria. In the second phase, the selected articles were analyzed in full text to verify their relevance and methodological quality. Finally, in the third phase, the final articles included in the review were analyzed in detail, with the extraction of the following data:

Type of study (clinical trials, in vitro or in vivo experiments).

- Intervention with molecular hydrogen (route of administration, dosage, duration).
- Primary outcomes related to oxidative stress, inflammation, endothelial function, neuroprotection, among others.

Main outcomes (ROS reduction, cytokine regulation, clinical improvement).

**Data Analysis**

The extracted data were organized in a table to facilitate comparison of results between studies. A qualitative analysis of the studies was performed, focusing on the mechanisms of action of molecular hydrogen, inflammatory and oxidative parameters, and the clinical results observed. The findings were grouped according to the areas of application (cardiovascular, neurodegenerative, inflammatory diseases, etc.), and the methodological quality of the studies was assessed using the Jadad scale for clinical trials and quality guidelines for preclinical studies.

Limitations of the Methodology This review has some limitations. First, the publication period of the studies was restricted to the last 13 years, which may have limited the inclusion of older studies. Second, the heterogeneity between the studies in terms of experimental models, dosages, and routes of administration of molecular hydrogen makes it difficult to generalize the results. In addition, many experimental studies were performed in animal models, which may limit the extrapolation of the results to human clinical practice.

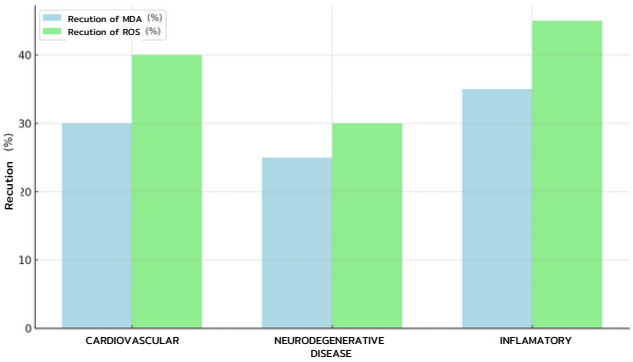
**RESULTS**

1. Antioxidant Effects of Molecular Hydrogen Molecular hydrogen ($H_2$) has demonstrated a potent antioxidant action, especially by selectively neutralizing reactive oxygen species (ROS) such as hydroxyl radical (•OH) and peroxynitrite (ONOO−), without interfering with the physiological functions of other less reactive ROS, such as hydrogen peroxide ($H_2O_2$) 【13】.

Several preclinical studies have indicated that $H_2$ administration, either by inhalation or ingestion of hydrogen water, resulted in a significant reduction in ROS levels, promoting improved cellular and tissue health. In models of oxidative stress-induced liver injury, $H_2$ treatment significantly reduced levels of malondialdehyde (MDA), a marker of lipid peroxidation, suggesting effective protection against oxidative damage.

Figure 1 below shows the percentage reduction in MDA and ROS levels in different types of diseases, highlighting the antioxidant effect of molecular hydrogen in cardiovascular, neurodegenerative and inflammatory diseases.

**Figure 1. Reduction of Oxidative Markers by Molecular Hydrogen**

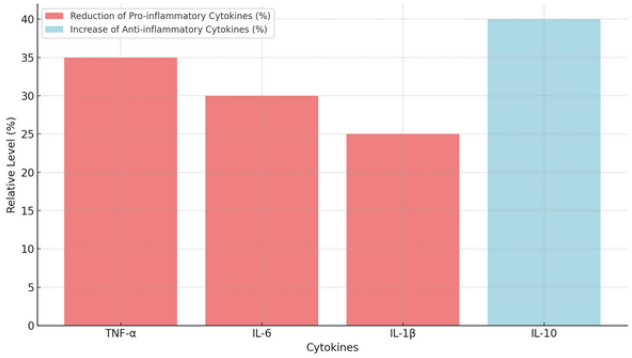



The percentage reduction of malondialdehyde (MDA) and reactive oxygen species (ROS) in cardiovascular, neurodegenerative and inflammatory diseases demonstrates the potent antioxidant effect of molecular hydrogen ($H_2$) in different clinical contexts.

2. Anti-inflammatory Effects of Molecular Hydrogen In addition to its antioxidant properties, molecular hydrogen has demonstrated remarkable anti-inflammatory action. Studies with models of inflammatory diseases, such as rheumatoid arthritis and lipopolysaccharide (LPS)-induced endotoxemia, have shown a significant reduction in the levels of pro-inflammatory cytokines, such as TNF-α, IL-6 and IL-1β, after the administration of $H_2$ 【7,9,10】. At the same time, an increase in the levels of anti-inflammatory cytokines, such as IL-10, was observed, which contributed to the control of the inflammatory process and reduction of tissue damage【9】.

Figure 2 below illustrates the effects of $H_2$ on cytokine modulation, showing the reduction of pro-inflammatory cytokines and the increase of IL-10, an anti-inflammatory cytokine.

**Figure 2. Anti-inflammatory Effects of Molecular Hydrogen**




The figure shows the reduction of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and the increase of IL-10, an anti-inflammatory cytokine, demonstrating the potential of $H_2$ to modulate inflammation in chronic conditions.

3. Clinical Applications of Molecular Hydrogen

3.1 Cardiovascular Diseases Molecular hydrogen has shown promising results in patients with cardiovascular diseases. Clinical trials in patients receiving $H_2$ supplementation, mainly through hydrogenated water, reported significant improvements in endothelial function and reduction of inflammatory markers such as TNF-α and IL-6【10,11】. In addition, there was a reduction in lipid peroxidation levels, suggesting that $H_2$ may prevent damage to the vascular endothelium and slow the progression of atherosclerosis【4】.

3.2 Neurodegenerative Diseases Studies indicate that molecular hydrogen exerts neuroprotective effects, especially in models of cerebral ischemia-reperfusion. The administration of $H_2$ has been associated with a reduction in neuronal damage, due to its ability to inhibit the production of ROS and reactive nitrogen species (RNS), preserving cellular integrity【7】.

### 3.3 Chronic Inflammatory Diseases

In models of chronic inflammatory diseases such as rheumatoid arthritis and ulcerative colitis, molecular hydrogen has been shown to modulate the inflammatory response. Studies indicate that $H_2$ significantly reduced inflammatory symptoms such as joint pain and stiffness and improved patients' quality of life 【7,9】.

4. Safety and Efficacy of Molecular Hydrogen

The studies included in this review suggest that molecular hydrogen is safe and effective as an adjunctive therapy. Clinical trials reported low toxicity and no significant adverse effects associated with $H_2$, whether through inhalation or ingestion of hydrogen water 【6,8】. Furthermore, $H_2$ was shown to be compatible with other therapies, with no significant adverse interactions【58】.

The reviewed results demonstrate that molecular hydrogen has remarkable antioxidant and anti-inflammatory effects. The reduction of ROS and pro-inflammatory cytokines, together with the increase in anti-inflammatory cytokines, reinforces the potential of $H_2$ as an effective adjuvant therapy in several pathological conditions. However, the variability between studies in terms of dosage and route of administration, as well as the limited sample sizes in many clinical trials, highlight the need for further robust studies to confirm its therapeutic benefits【9】.

The graphs presented reinforce the importance of these effects in the different clinical areas addressed, showing the ability of molecular hydrogen to modulate oxidative and inflammatory processes. Thus, $H_2$ emerges as a promising therapy, with the potential to be applied on a large scale, as long as standardized protocols and larger clinical studies are conducted in the future.

## DISCUSSION

This review highlights the promising effects of molecular hydrogen ($H_2$) in several pathological conditions, with emphasis on its antioxidant and anti-inflammatory properties. $H_2$ has been shown to be an efficient complementary therapy, particularly in diseases where oxidative stress and inflammation play crucial roles, such as cardiovascular, neurodegenerative and chronic inflammatory diseases. The mechanisms by which $H_2$ exerts its therapeutic effects are diverse. One of the main mechanisms is its ability to selectively neutralize reactive oxygen species (ROS), such as hydroxyl radical (•OH) and peroxynitrite ($ONOO^-$), without interfering with the physiological functions of other less reactive ROS, such as hydrogen peroxide ($H_2O_2$) 【1,3】. This selectivity, as observed in several studies, distinguishes $H_2$ from other antioxidants, which can impair normal cellular functions by scavenging ROS essential for cell signaling.

The antioxidant effects of $H_2$ have been well documented in both preclinical studies and clinical trials. In experimental models, $H_2$ administration resulted in a significant reduction in oxidative markers such as malondialdehyde (MDA), reflecting lower lipid peroxidation and less cellular damage【4,5】. These effects are particularly important in the context of cardiovascular diseases, where oxidative stress is a determining factor in the progression of pathologies such as atherosclerosis and heart failure. In clinical studies, hydrogenated water supplementation has been shown to improve endothelial function, in addition to reducing levels of inflammatory markers such as TNF-α and IL-6, evidencing that $H_2$ may be an effective strategy to prevent or delay the progression of vascular diseases【10,11】.

In addition to its antioxidant properties, $H_2$ has demonstrated significant immune modulation capabilities. Several peer-reviewed studies indicate that $H_2$ regulates the expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, while promoting the increase in anti-inflammatory cytokines such as IL-10. This balance between inflammatory and anti-inflammatory cytokines suggests that molecular hydrogen may not only reduce inflammation but also prevent further damage caused by chronic inflammation, as observed in systemic and local inflammatory conditions. In chronic inflammatory diseases such as rheumatoid arthritis, studies indicate that $H_2$ is able to significantly reduce inflammatory symptoms and improve patients' quality of life, offering a less toxic therapeutic alternative compared to traditional anti-inflammatory drugs.

The benefits of $H_2$ have also been observed in the treatment of neurodegenerative diseases. In studies using cerebral ischemia-reperfusion models, $H_2$ has been shown to be effective in reducing neuronal damage, possibly due to its action in reducing reactive oxygen and nitrogen species (RNS), which are strongly associated with cellular damage in neurological diseases [7]. These findings, when combined with clinical data demonstrating an improvement in neurological outcomes in patients receiving $H_2$ after ischemic events, suggest that $H_2$ may be an important therapeutic tool for neurodegenerative diseases such as stroke [2,6].

However, despite the promising results, it is important to recognize some limitations of the reviewed studies. First, many of the clinical trials were conducted with relatively small sample sizes, which limits the extrapolation of the findings to larger populations. In addition, there is considerable heterogeneity among the studies regarding the dosage and route of administration of molecular hydrogen, which makes it difficult to create standardized protocols for clinical use【9,10】. Although the safety of $H_2$

Furthermore, $H_2$ stands out as a promising therapy for reducing oxidative stress and inflammation, with potential application in a variety of clinical conditions. However, additional studies are needed to validate these findings in larger clinical trials and to establish standardized therapeutic protocols. As more evidence is accumulated, $H_2$ may become established as a widely used therapeutic tool in the treatment of chronic and degenerative diseases.

## CONCLUSION

The results of this integrative review suggest that molecular hydrogen ($H_2$) has significant therapeutic potential due to its antioxidant and anti-inflammatory properties. $H_2$ has been shown to be effective in selectively neutralizing reactive oxygen (ROS) and nitrogen (RNS) species, playing a central role in cellular protection against oxidative stress. Furthermore, its ability to modulate the inflammatory response by reducing pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, and promoting the elevation of anti-inflammatory cytokines such as IL-10, indicates that molecular hydrogen may act as a valuable adjuvant in the treatment of chronic inflammatory diseases.

The reviewed evidence also demonstrates that $H_2$ may be an effective intervention in a wide range of pathological conditions, including cardiovascular, neurodegenerative and inflammatory diseases. In patients with cardiovascular diseases, $H_2$ improved endothelial function and reduced levels of inflammatory markers, while in models of cerebral ischemia-reperfusion, it showed promising neuroprotective effects. In chronic inflammatory diseases, such as rheumatoid arthritis, $H_2$ helped mitigate inflammatory symptoms and improve patients' quality of life.

Despite the promising results, the clinical applicability of molecular hydrogen still faces challenges. The variability between studies in terms of dosage, route of administration and duration of treatment makes it difficult to standardize therapeutic protocols. Furthermore, many studies were performed in animal models or with small clinical samples, which limits the extrapolation of results to large-scale clinical practice. Therefore, additional studies are needed to confirm the therapeutic benefits of $H_2$ in larger and more robust clinical trials.

In summary, molecular hydrogen emerges as a safe and promising therapeutic strategy for several chronic and degenerative diseases, with the potential to be used both preventively and in the management of established diseases. Future research should focus on standardizing administration protocols and evaluating its long-term effects in different patient populations, in order to consolidate $H_2$ as a viable and widely applicable therapy in clinical practice.

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