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Cutting-edge advances in hydrogen applications for the medical and pharmaceutical industries

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ABSTRACT

The adoption of clean hydrogen is expected to transform the global energy landscape, reducing greenhouse gas emissions, bridging gaps in renewable energy integration, and driving innovation across multiple sectors. In the medical and pharmaceutical industries, hydrogen offers unique opportunities for transformative progress. This review critically examines recent advances in three domains: hydrogen fuel cells as reliable, scalable, and sustainable energy solutions for hospitals; molecular hydrogen as a therapeutic and preventive medical gas, particularly for brain disorders; and hydrogenation technologies for the efficient and sustainable pharmaceutical production. Despite encouraging advancements, widespread adoption remains limited by economic constraints, regulatory gaps, and limited clinical evidence. Addressing these barriers through technological innovation, large-scale studies, and life-cycle sustainability assessments is essential to translate hydrogen's full potential into clinical and industrial practice. Responsible adoption of green hydrogen is poised to reshape the clinical approach to global health and enhance the quality of life for people worldwide.

1. Role of hydrogen in future global energy generation and decarbonisation

The global population growth and the accelerated pace of economic activities have increased the demand for energy, which resulted in the unbridled use of fossil fuels [1,2]. The overexploitation and utilisation of fossil fuels, in turn, have significantly elevated global greenhouse gas emissions and led to a cascade of climatic and environmental crises. Such challenges have made the global transition obligatory from conventional fossil fuels to cleaner renewable energy sources. In this context, hydrogen (H_2) has garnered significant international attention as a promising superior clean energy carrier, energy vector, and auxiliary component for several industrial processes that can be obtained through renewable and non-renewable sources [3,4]. According to an ever-increasing number of studies, hydrogen is being predicted as a critical and transformative component in the global sustainable energy plan shown in Fig. 1 [5]. The International Renewable Energy Agency (IRENA) has projected that clean hydrogen can reduce global carbon emissions by about 10 %, and its production is estimated to represent 30 % of the total electricity demand by 2050 [6].

Amongst the capability of being truly carbon neutral or even negative on a life cycle basis, hydrogen has many beneficial characteristics, including high energy density, versatility, rapid recovery, large storage capacity, purity, renewability, easy transportation, and high transformation [7–9]. Nevertheless, its sustainability depends upon the cleanliness of the production pathway and the energy used during the manufacturing process, with about 96 % of the hydrogen still being produced from fossil fuels and only the remaining 4 %, known as green hydrogen, from other alternative renewable sources [10–13]. The adoption of green hydrogen in particular offers substantial environmental and socio-economic benefits poised to revolutionise the global energy landscape, reducing greenhouse gas emissions, bridging gaps in renewable energy integration, and driving innovation across multiple sectors [14–18]. To adequately realise the potential of green hydrogen and address existing challenges and barriers, strategic investments, international collaboration, and progressive policies are required [19–25].

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Several hydrogen-based projects are already attracting funding around the globe. Air Products, a worldwide leader in the hydrogen value chain, has been a first mover, committing more than $15 billion to energy transition projects and launching several large clean energy projects. The preeminent one is NEOM – green-hydrogen-based ammonia production facility that will run on renewable energy and produce up to 600 tonnes per day of carbon-free hydrogen in the form of green ammonia. Another large investment is the Louisiana Clean Energy Complex for low-carbon blue hydrogen production, aiming to capture and sequester 95 % of its carbon dioxide (CO_2) emissions which total over 5 million tonnes per year. These hydrogen production facilities and the onsite hydrogen generator are highly efficient, robust, and economical supply option that is designed to supply fuelling stations with up to 5000 nm^3/h.

Hydrogen has already been an important feedstock across various industries, such as metal reduction, oxyhydrogen flames for metal cutting and welding in metallurgy, ammonia and methanol synthesis in chemical manufacturing, hydrocarbon fuels processing and upgrading of, fuel cells, synthetic fuels, transportation, and heating. It is also used, in other industrial applications including electronics, aerospace, maritime, pharmaceutical, medical, and food sectors. Fig. 2 demonstrates hydrogen production routes and the main directions of consumption in the world.

Numerous studies have demonstrated the progress made in the field of hydrogen fuel including production methods, storage and transport facilities, economic value, and applications in oil refining and chemical production. However, the current literature on the next-generation applications of hydrogen, especially in the pharmaceutical and medical industries, is limited, restricting research dissemination, broader recognition of hydrogen's potential, and therefore hindering its widespread adoption. To address this, the review adopts a selective, evidence-driven approach to critically synthesise and explicitly investigate peer-reviewed studies that provide clear methodological detail, validated experimental or clinical data, and translational relevance to medicine or pharmaceutical practice. By consolidating current knowledge, identifying gaps, and outlining future research priorities, the review aims to provide a critical foundation for advancing hydrogen's emerging role in these industries.

2. Next-generation hydrogen applications

2.1. Hydrogen fuel cells

Hydrogen fuel cells, both primary and backup use, show potential as power solutions for critical infrastructure such as hospitals. The implementation of renewable energies in hospitals is a promising method that can use hydrogen as an energy carrier to satisfy heat and electricity demand and oxygen, as a by-product, to supply the medicinal oxygen requirements. Fuel cells (Fig. 3) as solid hydrogen sources can convert chemical energy stored in hydrogen fuel into electrical energy in a sustainable, reliable, and efficient way that is in particular crucial in hospital buildings to maintain vital equipment and guarantee patient safety [26].

These backup power systems can provide reliable and continuous power to critical hospital infrastructure in biological signal monitoring devices, radiotherapy systems, medical imaging systems, operating room and ventilators; and sterilisers and oven devices, to name a few. Hydrogen fuel cells offer numerous benefits over conventional backup power solutions, such as diesel generators or lead-acid batteries. Growing evidence indicates that they can maintain continuity of operations, minimise downtime and losses, reduce the risk of system failures and the associated consequences, improve safety and sustainability, allow meeting regulatory requirements, protect assets, have a long lifespan, and offer energy independence, scalability, and quiet operation [28].

Recently, promising findings were reported by Ghimire et al. [27], who have conducted a techno-economic assessment of fuel cell-based combined heat and power systems both on-site and off-site as an alternative to diesel generators for hospital applications. The economic analysis revealed that the on-site hydrogen production (Fig. 4) for Dhulikhel Hospital in Nepal is both technically and economically feasible with a net present value of $42,717, an internal rate of return of 8.4 % and a 10-year payback period. The uncertainty and sensitivity analysis revealed that the net present value (NPV) is positive in 87.5 % of cases and the electricity tariff rate is the most significant cost factor. Overall, proposed on-site hydrogen production has been shown to be economically and environmentally advantageous due to low operating costs, low noise, no emissions, and reduced reliance on imported fossil

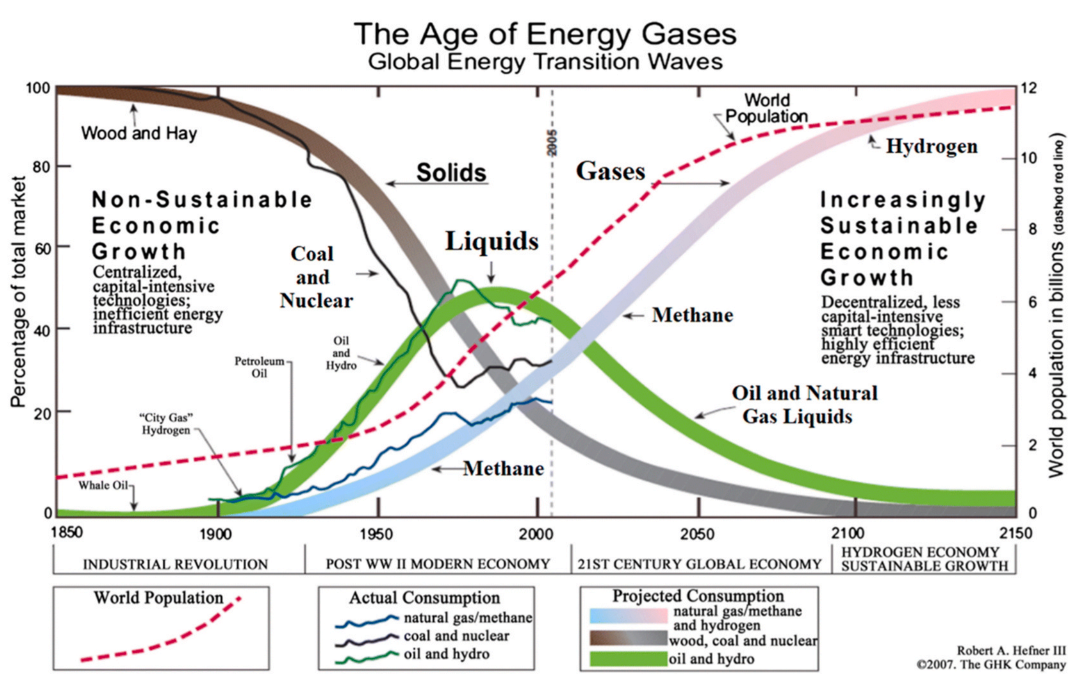

Fig. 1. The transformation of the global energy system from solid to liquid from 1850 to 2150 [5].

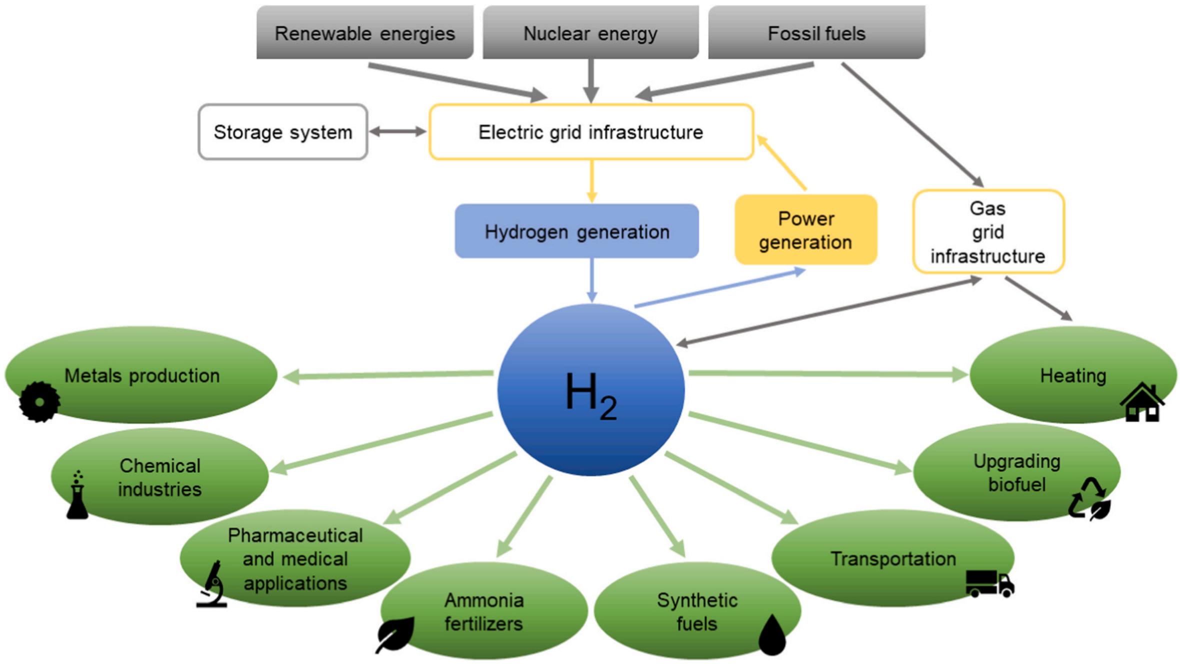

Fig. 2. Hydrogen production routes and main industrial applications.

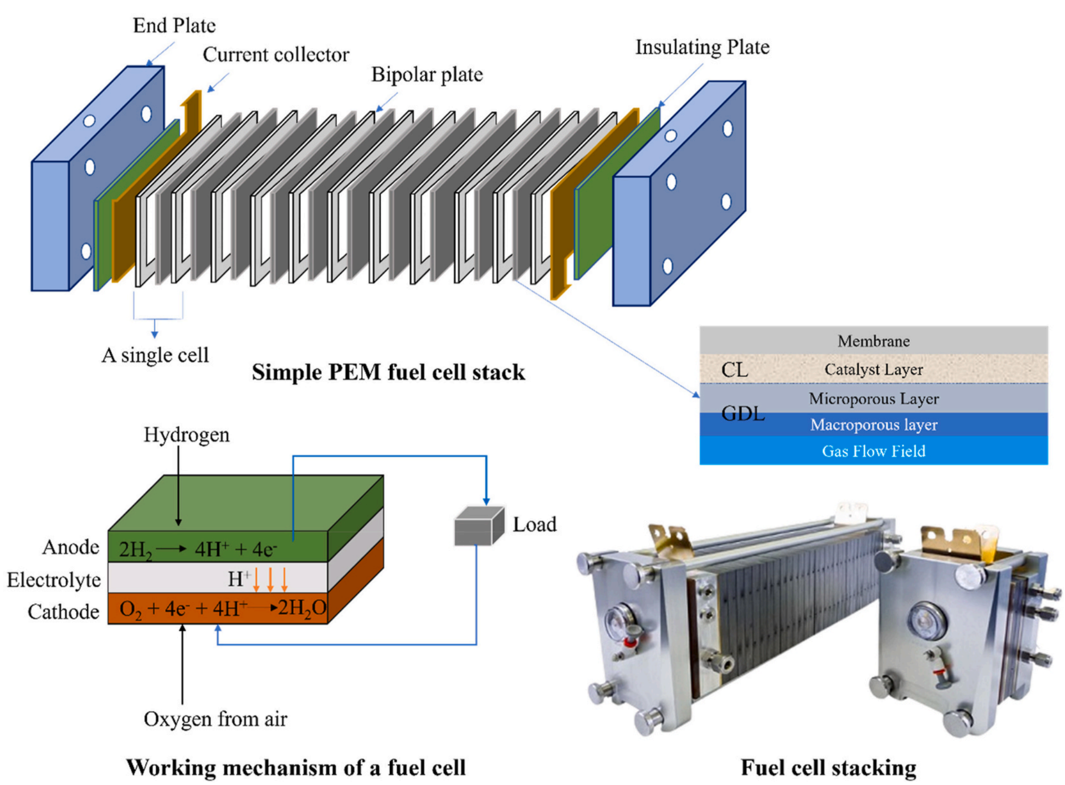

Fig. 3. Principle and structure of a fuel cell. PEM: polymer electrolyte membrane [27].

fuels.

Supportive findings were reported by Assuncao et al. [29], who focused on the economic and environmental analysis of the implementation of on-site decentralised co-production of oxygen and hydrogen through electrolysis for Santa Maria Hospital in Lisbon, Portugal, with an integrated hydrogen refuelling station. In the pursuit of providing the necessary oxygen hospital needs and simultaneously producing hydrogen to fuel electric vehicles such as ambulances, the proposed integrated system has shown both positive economic and environmental benefits, with the potential to enhance the self-sufficiency and sustainability of healthcare facilities. This includes lower global warming potential (GWP) impact and yearly expenses compared to the traditional diesel concept.

A hydrogen storage system has been evaluated in a hybrid renewable energy system (HRES) using solar photovoltaic (PV) panels to produce electricity and oxygen for COVID-19 patients in a hospital located in

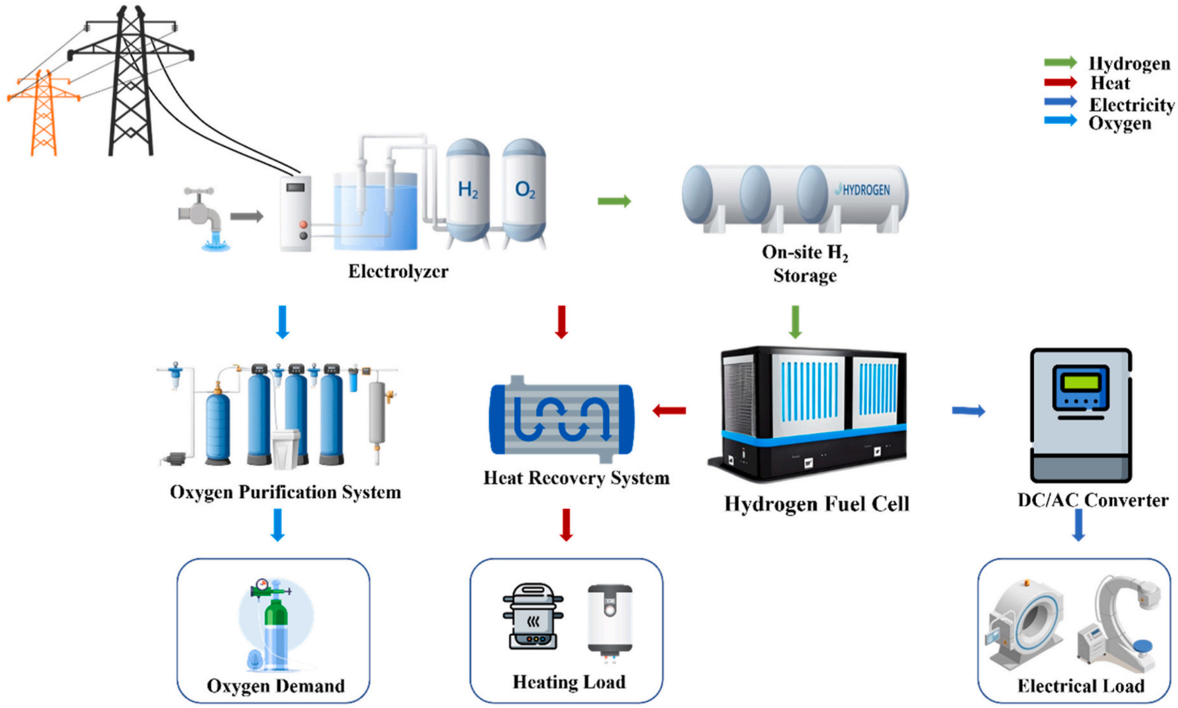

Fig. 4. Fuel cell-based combined heat and power (CHP) system with on-site hydrogen production [27].

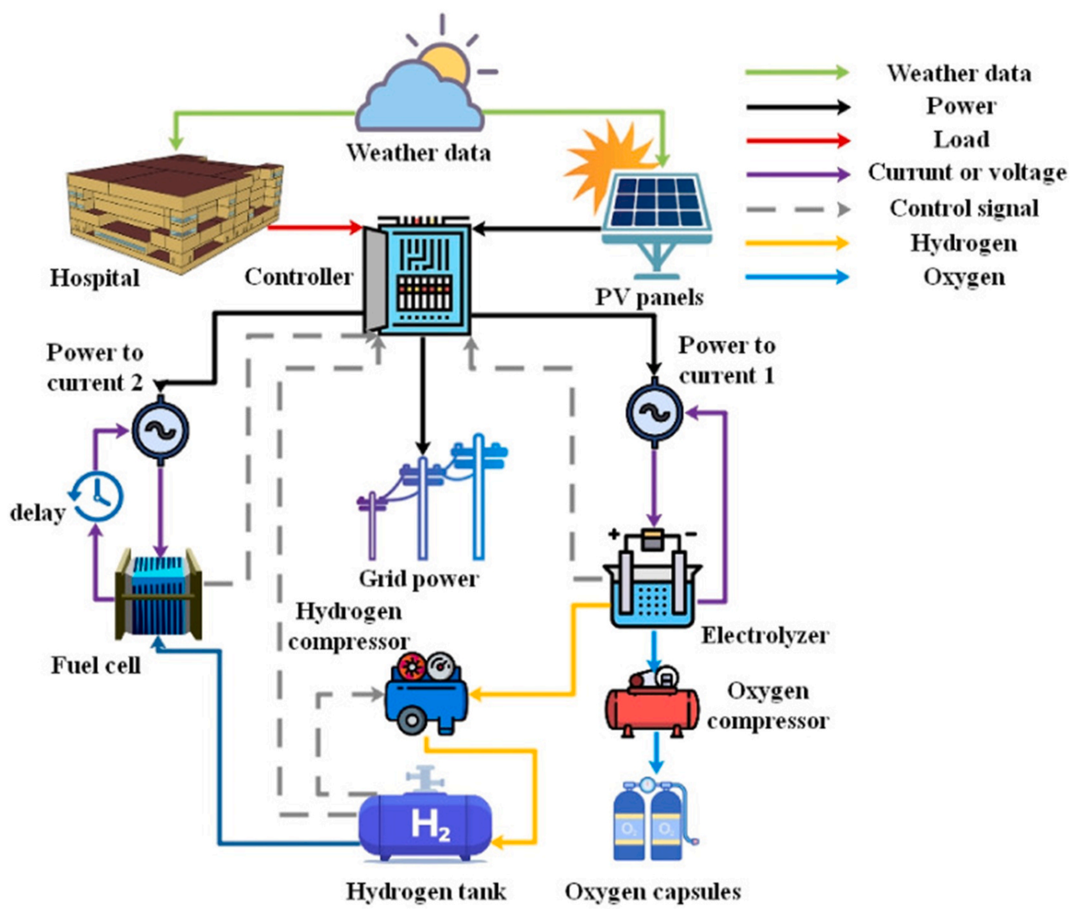

Fig. 5. The schematic of the novel renewable hybrid system [30].

Tehran, Iran (Fig. 5) [30].

After employing a neural network-genetic algorithm optimization, optimum results have been achieved covering the energy and oxygen demand through renewable resources, reducing dependency on grid power, CO_2 emissions and costs.

2.2. Molecular hydrogen as a therapeutic and preventive medical gas

At the heart of hydrogen's transformative role is its therapeutic potential in reshaping the clinical approach to global health [31–34]. It is now well documented that molecular hydrogen exhibits exceptional pharmacokinetics, allowing it to exert selective antioxidant, anti-inflammatory, anti-apoptotic, anti-allergic, cytoprotective, gene regulation, energy generation, autophagy and cell death modulation properties on mammalian cells (Fig. 6) [35–37]. Swiftly traversing the blood-brain barrier and cellular biomembranes to access subcellular organelles, molecular hydrogen is surmised to act as a hormetic substance in several molecular mechanisms, including hydroxyl radicals (•OH) and nitrite (•NO_2) reduction, regulation of endogenous antioxidant pathways, adrenal receptor agonist activity, and suppression of Wnt/β-catenin signal, to name a few [38–42].

Among other clinical justifications for hydrogen clinical use is safety and non-interference with the underlying mechanisms of most treatments [44]. Coupled with progressive innovations in targeted delivery methods ranging from inhalation devices and intravenous injections to dietary supplements and topical administration (Table 1), this provides a convenient approach to target and address a wide range of conditions in chronic, emergency, and convalescent care.

Bibliometric analysis reveals a thriving trend of research with over 1000 publications with **dozens of human studies and over 80 registered clinical trials** supporting the translational therapeutic and preventive potential of molecular hydrogen across multiple organs and disease models [68,69]. Owing to the common pathological basis of many diseases being oxidative stress, metabolic dysregulation, and inflammation, the molecular mechanism and biological effects of hydrogen can be exploited for an array of conditions including cardiovascular, respiratory, thoracic, haematological, dermatological, neurological and neurodegenerative conditions, cancer, diabetes, metabolic syndrome, rheumatoid arthritis, chronic hepatitis B, hyperlipidaemia, wounds, as well as ageing-related disorders, improving exercise performance, and sport injuries recovery. However, the research is still in its relative infancy, with the primary targets, molecular mechanisms, specific concentrations and optimal forms of administration remaining elusive and yet to be determined. Further large-scale, multicentre, randomized, double-blind trials are required to confirm efficacy and validate long-term safety.

As an illustration, the biological properties of hydrogen have attracted significant attention due to its remarkable antioxidant and

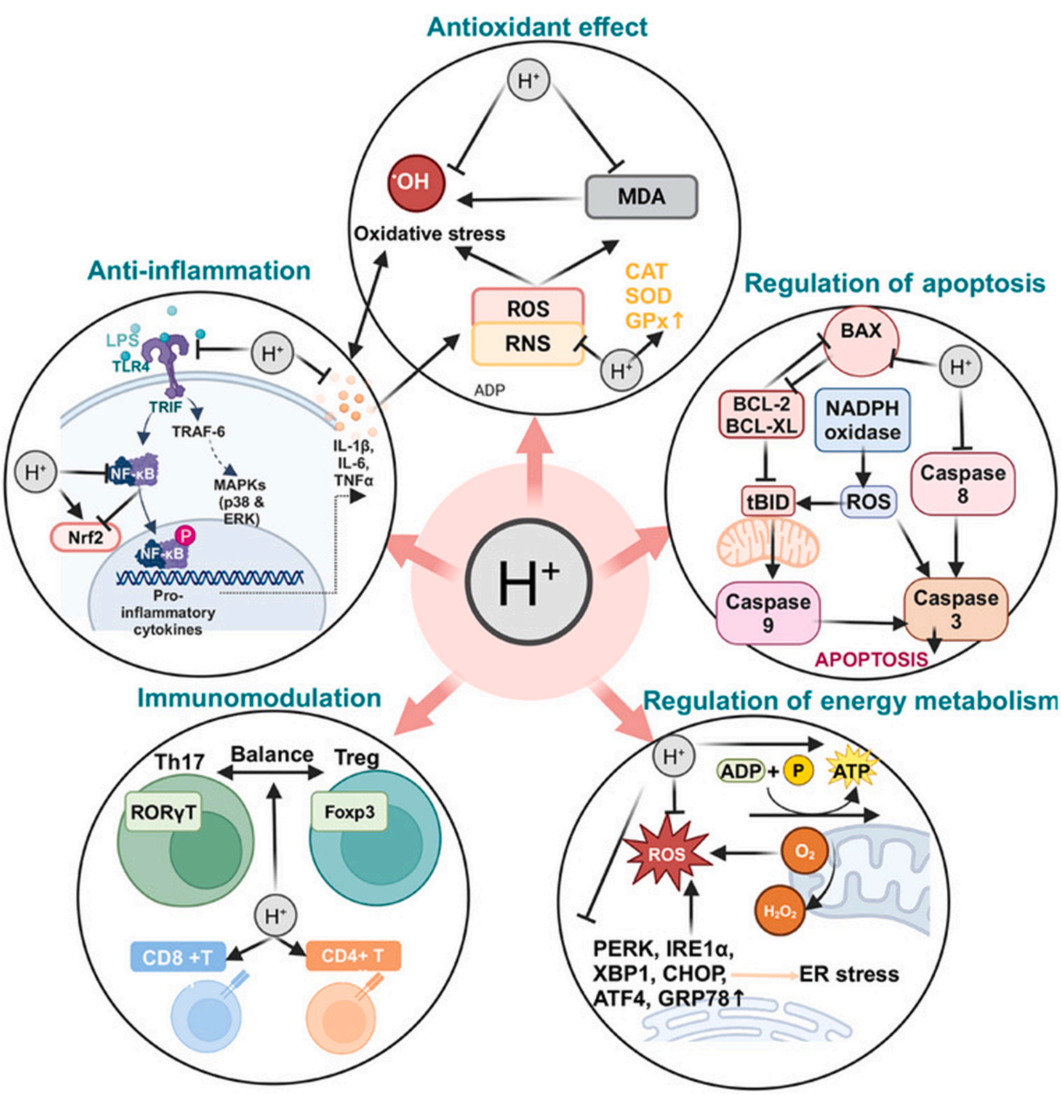

Fig. 6. Biological effects and mechanisms of action of molecular hydrogen [43].

Table 1
Method of administration of molecular hydrogen and its therapeutic targets.

Method of administration	Details	Therapeutic targets (from animal/human trials)
Ingestion	Dietary supplements (prebiotic substrates for H_2-producing bacteria or H_2-inducing calcium-rich powder) and H_2-rich water (HRW)	Gastrointestinal and inflammatory conditions, metabolic syndrome, post-exercise recovery in training athletes, prophylaxis against chronic conditions, such as cardiovascular disease and type 2 diabetes [42,45–49]
Inhalation	H_2 and oxyhydrogen (HHO)	Respiratory and cardiovascular conditions, such as severe symptoms of coronavirus infectious disease, long-term inflammatory-related lung conditions such as asthma, chronic obstructive pulmonary disorder (COPD), emphysema, cystic fibrosis, and pulmonary adenoma; and benefits for training athletes [38,50–60]
Infusion	H_2-rich saline (HRS) administered intravenously or intraperitoneally	Post-operative care, ischaemia-reperfusion, liver disease, organ grafting, and rheumatoid arthritis [61–63]
Topical administration	Bathing in a H_2-rich solution, absorbable gel, and patches	Wounds, inflammatory-related skin conditions (psoriasis and parapsoriasis *en plaques*), and traumatic injuries [64–66]
Nanotechnology	Nanodevices (magnesium/hyaluronic acid) and nanoparticles (palladium hydride (PdH) for H_2 delivery	Inflammatory-related conditions such as rheumatoid arthritis, neurodegenerative diseases, and cancer [39,67]

anti-inflammatory effects in brain disorders, including ischaemic stroke, Parkinson's disease, multiple sclerosis, Alzheimer's disease, neonatal hypoxic-ischaemic encephalopathy, traumatic brain injury, depression, and anxiety (Fig. 7) [70]. Specifically, hydrogen acts as an electron donor to selectively scavenge the excessive •OH, enhance the activity of antioxidant enzymes, and activate the KEAP1/NRF2/ARE pathways, and therefore reduce oxidative stress as one of the essential pathological processes in most brain diseases. In terms of anti-inflammatory effects, molecular hydrogen attenuates the release of proinflammatory cytokines, reactive astrogliosis, and overactivation of microglia.

Effects of H_2-rich water on Parkinson's disease were examined by Yoritaka et al. [71] in a randomised controlled clinical study. The authors demonstrated that the procedure is safe and well tolerated, and a significant improvement in total Unified Parkinson's Disease Rating Scale (UPDRS) scores can be achieved. Recently, Ichikawa et al. [72] presented a study on four Parkinson's disease patients in which hydrogen inhalation allowed for the improvement of the symptoms, such as body bending and hand tremor. Theoretically, the therapeutic effect can be attributed to the ability of hydrogen molecules to easily pass the blood-brain barrier and convert the hydroxyl radicals in the brain into water molecules, inhibiting a chain reaction of dopamine oxidation.

Preliminary supportive findings were reported in 11 patients with Alzheimer's disease following H_2 gas inhalation and oral Li_2CO_3 for 4–7 months that showed significantly improved Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) [73]. H_2 gas inhalation was also safe and effective in patients with acute cerebral infarction, with significant effects found on the relative signal intensity of magnetic resonance imaging (MRI), National Institute of Health Stroke Scale (NIHSS) scores for clinically quantifying stroke severity, and physical therapy evaluation [74]. Acute cerebral infarction can also be intravenously treated with a combination of edaravone and H_2-rich saline to improve MRI indices against the natural course [75]. H_2-rich water demonstrated a potential for suppressing mild cognitive impairment (MCI) in apolipoprotein E4 (APOE4) carriers and a protective effect in newborns with hypoxic-ischaemia encephalopathy (HIE) by significantly decreasing the levels of serum neuron-specific enolase (NSE), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α) [76,77].

2.3. Pharmaceutical manufacturing

Hydrogen plays a central role in the pharmaceutical manufacturing of active pharmaceutical ingredients (APIs), vitamins, and their intermediates through the process of hydrogenation, offering benefits such as tailored physical properties, enhanced biological activity, increased shelf life, and process efficiency. Hydrogenation is a chemical transformation with the addition of hydrogen across multiple bonds with the use of a heterogeneous or homogeneous catalyst, which can be carried out in a variety of ways, either in the liquid or gas phase, using asymmetric or symmetric methods, and in batch-wise or continuous modes [78–81]. Reaction types include hydrogenations of C=C double bonds, selective semi-hydrogenations of C≡C triple bonds, hydrogenations of C = X/C ≡ X multiple bonds, and stereoselective hydrogenations. In the pharmaceutical industry, the synthesis of APIs and vitamins is being actively researched, with the most prominent examples being L-dopa, naproxen, ibuprofen, paracetamol, erythromycin, cefprozil, cefixime, vitamin K, E, and (+)-biotin, to name a few [82,83]. Undoubtedly, hydrogenation of carbon-carbon double bonds is the most common type in the industry. For instance, it is currently being involved in the production of vitamin E by the synthesis of its intermediates isophytol and trimethylhydroquinone (TMHQ). TMHQ is one of the key building blocks for the chemical production of synthetic vitamin E, which is converted into (all-*rac*)-α-tocopherol by condensation with (all-*rac*)-isophytol and sequentially to (all-*rac*)-α-tocopherol and finally vitamin E [84]. Contemporary continuous hydrogenation technologies coupled with the wide variety of catalysts available allow excellent yields under nearly full conversion to be achieved. Further research is underway to develop concepts for enhanced and optimised efficiency of transformations, continuous processing and recycling, and high chemo- and stereoselectivities, thus avoiding laborious separation protocols and achieving robust and sustainable production methods.

3. Conclusion

In the vast spectrum of its revolutionary facets, hydrogen has established itself as a critical component in the medical and pharmaceutical industries, making it possible to achieve numerous breakthrough inventions in emerging fields of medicine, clinical sciences, biotechnology, and pharmaceutical research. Given the ever-increasing body of literature that substantiates the robust data on hydrogen's transforming role in the aforesaid industries, this paper is necessarily selective, covering novel solutions and scientific or technological advances such as hydrogen fuel cells, molecular hydrogen as a therapeutic and preventive medical gas, and pharmaceutical manufacturing.

In hospital settings, hydrogen fuel cells have proven to maintain continuity of operations, improve safety and sustainability, enhance reliability, and offer energy independence, scalability, and quiet operation. Growing evidence indicates that the molecular mechanism and biological effects of hydrogen can be exploited for an array of clinical conditions but specifically in brain disorders due to remarkable antioxidant and anti-inflammatory effects. Finally, contemporary hydrogenation technologies play a central role in the pharmaceutical manufacturing of vitamins, APIs, and their intermediates, offering benefits such as tailored physical properties, enhanced biological activity, increased shelf life, process efficiency, sustainability, and cost savings.

Nevertheless, a review of published research to date has clearly demonstrated that the widespread adoption of many of these advances

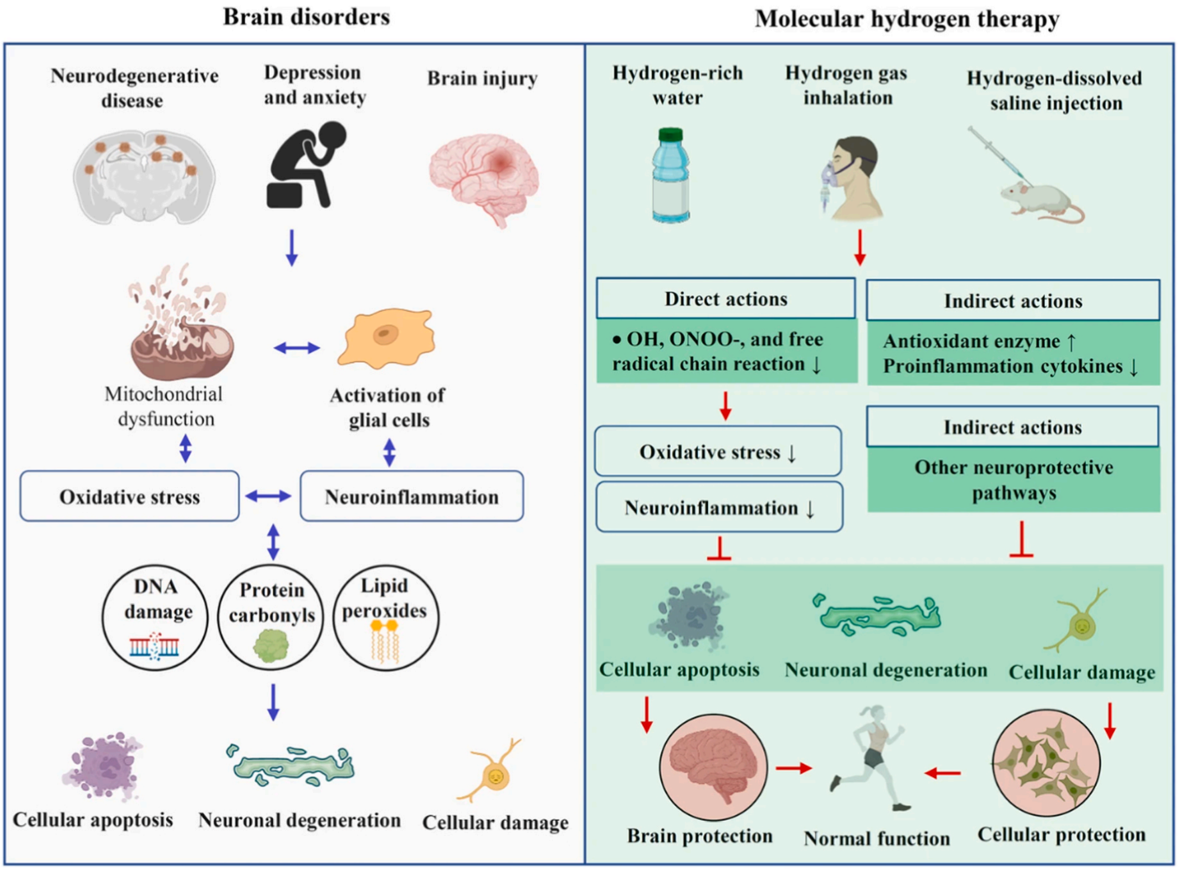

Fig. 7. Primary mechanisms of molecular hydrogen therapies in disorders [70].

has yet to gain traction and several limitations constrain their widespread implementation. Challenges remain in safe storage, flammability risks, economic feasibility, evolving regulatory frameworks, limited clinical evidence from small or pilot studies, including variability in delivery methods and incomplete understanding of the precise molecular mechanisms underlying therapeutic effects of hydrogen, and the development of efficient, cost-effective, and sustainable catalysts for hydrogenation processes, as well as process optimization. Collectively, these challenges argue for prioritized interdisciplinary research through large-scale, multicentre studies, technological innovation, and the establishment of supportive regulatory frameworks to unlock the full potential of hydrogen in these industries. Rigorous testing and validation studies are required to ensure the reliability and effectiveness in real-world applications to become part of the clinical and industry standard. Future translational and clinical studies should aim to report data on the source, purity, and carbon intensity and incorporate supply-chain and life cycle assessment analyses to enable sustainability assessment once clinical and industrial scale-up occurs. Responsible scaling should prioritise green production and medical-grade supply chains, as medical and pharmaceutical applications require high purity, secure supply, and sterilisation standards. Accordingly, upon addressing existing multitudes of specialisation-specific factors and barriers, the adoption of green hydrogen in particular is poised to revolutionise the global energy landscape, reshape the clinical approach to global health, and enhance the quality of life for people worldwide.

CRediT authorship contribution statement

Hussam Jouhara: Writing – review & editing, Visualization, Validation, Supervision, Funding acquisition, Conceptualization. **Alevtina Kodresko:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Abdulrahman Alhajeri:** Writing – review & editing, Visualization, Conceptualization. **Valentina Olabi:** Writing – review & editing, Visualization. **Heba Ghazal:** Writing – review & editing, Visualization, Supervision, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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