



Review:

Hydrogen agronomy: research progress and prospects^{*#}

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Abstract: Agriculture is the foundation of social development. Under the pressure of population growth, natural disasters, environmental pollution, climate change, and food safety, the interdisciplinary “new agriculture” is becoming an important trend of modern agriculture. In fact, new agriculture is not only the foundation of great health and new energy sources, but is also the cornerstone of national food security, energy security, and biosafety. Hydrogen agronomy focuses mainly on the mechanism of hydrogen gas (H₂) biology effects in agriculture, and provides a theoretical foundation for the practice of hydrogen agriculture, a component of the new agriculture. Previous research on the biological effects of H₂ focused chiefly on medicine. The mechanism of selective antioxidant is the main theoretical basis of hydrogen medicine. Subsequent experiments have demonstrated that H₂ can regulate the growth and development of plant crops, edible fungus, and livestock, and enhance the tolerance of these agriculturally important organisms against abiotic and biotic stresses. Even more importantly, H₂ can regulate the growth and development of crops by changing the soil microbial community composition and structure. Use of H₂ can also improve the nutritional value and postharvest quality of agricultural products. Researchers have also shown that the biological functions of molecular hydrogen are mediated by modulating reactive oxygen species (ROS), nitric oxide (NO), and carbon monoxide (CO) signaling cascades in plants and microbes. This review summarizes and clarifies the history of hydrogen agronomy and describes recent progress in the field. We also argue that emerging hydrogen agriculture will be an important direction in the new agriculture. Further, we discuss several scientific problems in hydrogen agronomy, and suggest that the future of hydrogen agronomy depends on contributions by multiple disciplines. Important future research directions of hydrogen agronomy include hydrogen agriculture in special environments, such as islands, reefs, aircraft, and outer space.

Key words: Hydrogen gas (H₂); Hydrogen agronomy; New agriculture

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1 Introduction

Many years ago, the significance of hydrogen gas (H₂) to human life became apparent. As early as in 1937, Paneth (1937) reported that the tropospheric mixing ratio of H₂ in the atmosphere was about 0.5 ppmv (parts per million by volume), equivalent to 34.5 ppbw (parts per billion by weight). Although the content of hydrogen is very low, it plays an important role in maintaining oxidation state of earth atmosphere (Constant et al., 2009). H₂ affects almost

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every aspect of our lives. For example, due to its high energy density and ability to store and retain energy after combustion, H₂ has been widely used, especially in the energy industry (Árnason and Sigfússon, 2000) for applications such as hydrogen-powered fuel cell vehicles (Dresselhaus and Thomas, 2001).

The sources of atmospheric H₂ are diverse. According to previous work (Novelli et al., 1999; Constant et al., 2009), photochemical oxidation reactions of methane (CH₄) and non-methane hydrocarbons (NMHC) are the largest sources of H₂ in atmosphere (about 19 Tg/year (1 Tg=1×10¹² g)). In addition to photochemical oxidation reactions, biomass combustion (about 16 Tg/year) and the fossil fuel industry (about 15 Tg/year) are close secondary and tertiary sources of atmospheric H₂ (Novelli et al., 1999). H₂ is also generated from nitrogen-fixing legumes, as a type of byproduct during nitrogen (N₂) fixation (Novelli et al., 1999). The proportion of electrons utilized to generate H₂ in the root nodule nitrogenases is about 40%–60% (Schubert and Evans, 1976). H₂ circulates all across the globe. The whereabouts of H₂ entering the earth atmosphere are also diverse. Previous research found that H₂ was consumed mainly by soil microbes, and oxidized by hydroxyl radicals (Ichimasa et al., 1989; Derwent et al., 2001; Constant et al., 2009). About 80% of atmospheric H₂ (about 56 Tg/year) is absorbed by soil, through a microbial-mediated process (Constant et al., 2009). Because H₂ is consumed by soil microorganisms adjacent to the nodules, relatively little soil H₂ gets into the atmosphere (about 3 Tg/year) (Novelli et al., 1999; Constant et al., 2009). The 56 Tg/year of soil H₂ represents significant energy, about 8 EJ/year. Because this energy source is taken up by soil microbial populations, it is not surprising that H₂ has biological effects on agricultural systems.

Although the production and release of H₂ from algae, plants, microorganisms, and animals have been reported, the biological functions of H₂ were long unknown (Gaffron, 1939; Gest and Kamen, 1949; Renwick et al., 1964; Czerkawski, 1972). Dole et al. (1975) reported positive effects of high-pressure H₂ on skin cancer in mice, which is the earliest report of medical hydrogen research recognized by the scientific community. Later, Ohsawa et al. (2007) found that inhaling 2% to 4% (volume/volume ratio, v/v) of H₂ can protect against ischemic brain damage in rats

by selectively reducing toxic reactive oxygen species (ROS), including hydroxyl radicals and peroxy nitrite anions. These findings sparked a new wave of research on H₂.

By 2019, 42 scientific research institutions in China had participated in research on hydrogen biology, and a landmark event is the establishment of the Center of Hydrogen Science at Shanghai Jiao Tong University (Shanghai, China). The new center is headed by Prof. Wen-jiang DING, Academician of Chinese Academy of Engineering. In order to expand commercial applications of H₂, some companies have also begun to focus their attention on hydrogen medicine and hydrogen agriculture.

In the history of hydrogen biology, hydrogen medicine was ahead of hydrogen agronomy. The effects of H₂ as an anti-oxidant (Ohsawa et al., 2007), anti-inflammatory (Zhao et al., 2013), and anti-apoptotic agent (Liu et al., 2015) have been elucidated by several animal models or small-scale clinical trials (Ohta, 2014; Lu and Sun, 2018). Moreover, H₂ can not only inhibit tumors (Dole et al., 1975; Saitoh et al., 2008), but it also has positive effects on oxidative stress-related diseases, such as ischemia reperfusion injury (Ohsawa et al., 2007), acute ischemic disease (Du et al., 2014), Parkinson's disease (Fu et al., 2009), Alzheimer's disease (Hou et al., 2018), and atherosclerosis (Song et al., 2012). Although the hypothesis of H₂ as a selective antioxidant is widely accepted, in some cases, it also still questioned by academia, and the molecular mechanisms underlying anti-oxidation, anti-inflammatory, and anti-apoptosis effects of H₂ in medicine need to be further elucidated (Ge et al., 2017; Shen and Sun, 2019). More importantly, the potentially important development of hydrogen agronomy cannot be ignored.

Several research groups have found that H₂ has important biological effects on crops. Dong et al. (2003) put forward the concept of "H₂ fertilization," which was a milestone in the advancement of hydrogen agronomy. H₂ can change the structure of microbial communities and ultimately promotes soil fertility by promoting community growth of beneficial microorganisms. Thus, the essence of H₂ effects in agronomy is as a type of special biofertilizer. In this role, H₂ produced from symbiotic *Rhizobium leguminosarum* had been shown to promote crop rotation (Golding and Dong, 2010). Furthermore, some studies

suggested that H₂ might enhance plant tolerance towards abiotic and biotic stresses (Xie et al., 2012, 2014; Jin et al., 2013; Zeng et al., 2013; Su et al., 2018), and improve the quality of vegetables and fruits (Hu et al., 2014, 2018; Su et al., 2014).

With support from the Ministry of Science and Technology of the People's Republic of China, hydrogen agronomy is developing quickly. By 2019, 85 projects on hydrogen biology have been supported by the National Natural Science Foundation of China (Shen and Sun, 2019), of which nine were related to hydrogen agronomy. From the perspective of species, these hydrogen agronomy projects focused on alfalfa (*Medicago sativa*) (Cui et al., 2013, 2014; Chen et al., 2014; Su et al., 2018) and several horticultural plants, such as tomatoes (*Solanum lycopersicum*) (Zhang et al., 2019) and marigolds (*Tagetes erecta*) (Zhu and Liao, 2017). Hydrogen agronomy is related to a diverse range of physiological functions, including plant responses related to abiotic stress (Xie et al., 2012, 2014, 2015; Cui et al., 2013, 2014, 2020; Jin et al., 2013, 2016; Xu et al., 2013, 2017; Zeng et al., 2013; Chen et al., 2014, 2017; Wu et al., 2015; Dai et al., 2017; Su et al., 2018), root development (Lin et al., 2014; Zhu et al., 2016; Cao et al., 2017; Zhu and Liao, 2017), and quality of agricultural products (Hu et al., 2014, 2018; Su et al., 2014; Zhang XY et al., 2018; Su et al., 2019; Zhang YH et al., 2019). A long list of obvious and significant questions in the field of hydrogen agronomy awaits deeper scientific investigation.

2 Hydrogen agronomy: laboratory-based research

2.1 Agricultural status in China

Food is the fuel of life. As important sources of food, agriculture is one of the foundations of social development, and occupies an important position in

people's lives. According to data from the National Bureau of Statistics of the People's Republic of China, the agricultural output and its gross output value keep sustainable increase (Table 1). However, pressures from increasing population, reduction in arable land, extreme weather, and increasing demand for cereals like maize (*Zea mays*), for both fodder and fuel, are important factors restricting the development of agriculture in China (Pimentel, 1996; Lewandrowski et al., 1997; Lesk et al., 2016; Nicolopoulou-Stamati et al., 2016).

Soil plays a key role in agricultural development and biodiversity of agricultural production systems (Maeder et al., 2002; Young and Crawford, 2004; Mijangos et al., 2006; Melman et al., 2019; Qaswar et al., 2020). Soil degradation is a serious problem not only in China but also throughout the world. Crop acreage during last 6 years in China shows a volatile trend, and maize and rice are the first and second major crops (Fig. 1), based on data released by the Ministry of Natural Resources of the People's Republic of China and the United States Department of Agriculture. Although the main reasons for reduction in crop acreage include ecological land transfer and agricultural structure adjustment, according to official findings, the potential contradiction between growing population and cropland cannot be easily ignored. As we all know, modern agriculture is closely integrated not only with traditional planting and breeding industries, but also with secondary industries, including manufacturing and food processing, and with tertiary industries, such as transportation, technology, and information services (Macrae et al., 1993; Li et al., 2018; Lytos et al., 2020). Hydrogen agronomy has also no exception.

2.2 Hydrogen agronomy needs to be developed

Although the core of both hydrogen agronomy and hydrogen medicine is human health, the practices

Table 1 Gross output value of agriculture and agricultural product output in China

Year	Gross agricultural output value (billion CNY)	Grain output (1×10 ⁴ t)	Fruit output (1×10 ⁴ t)	Tea output (1×10 ⁴ t)	Meat output (1×10 ⁴ t)
2013	4894.39	63 048.20	22 748.10	188.72	8632.77
2014	5185.11	63 964.83	23 302.63	204.93	8817.90
2015	5420.53	66 060.27	24 524.62	227.66	8749.52
2016	5565.99	66 043.51	24 405.24	231.33	8628.33
2017	5805.98	66 160.72	25 241.90	246.04	8654.43
2018	6145.26	65 789.22	25 688.35	261.04	8624.63

Data source: the National Bureau of Statistics of the People's Republic of China (<https://data.stats.gov.cn/easyquery.htm?cn=C01>)

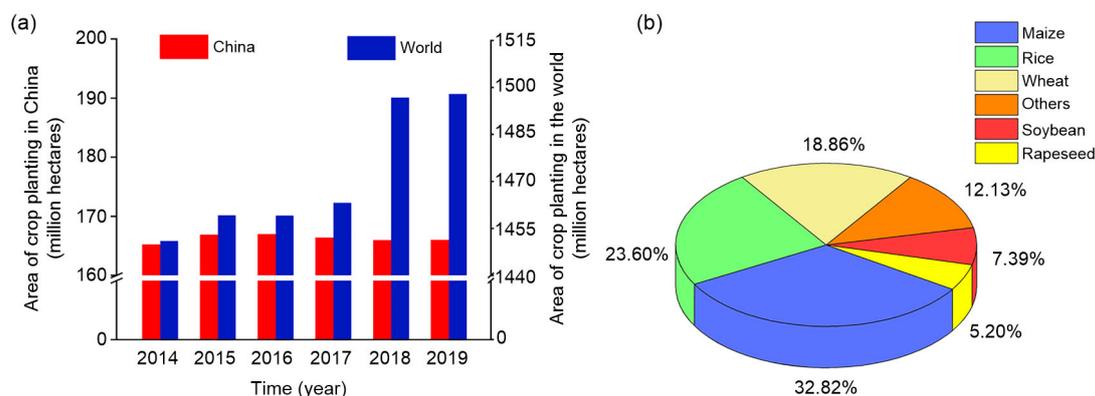


Fig. 1 Changes in crop area under cultivation in China and the world between 2014 and 2019 (a) and proportion of area devoted to cultivation of various crops in China in 2019 (b)

Data sources: the National Bureau of Statistics of the People's Republic of China (<https://data.stats.gov.cn>) and the United States Department of Agriculture (<https://apps.fas.usda.gov/psdonline/app/index.html#/app/downloads>)

of these two programs are different, including targets, methods of H₂ supply, and degree of difficulty (Table 2). The ultimate practical goal of hydrogen medicine is human health (Ohta, 2011, 2014). Unlike hydrogen medicine, hydrogen agronomy is not only a laboratory-based research study, but also has potential applications for agricultural production, dubbed hydrogen agriculture, with the goal of growing food in an affordable, healthy, and sustainable manner for human beings (Shen and Sun, 2019).

Traditional agriculture consumes a large volume of agrochemicals, especially fertilizers and pesticides (Lowry et al., 2019). As a gaseous signaling molecule, H₂ has been studied extensively in recent years. Hydrogen agronomy focuses mainly on the molecular mechanisms underlying hydrogen-rich water (HRW)- or H₂-increased yield and/or H₂-improved quality of agricultural products (Wang and Wei, 2016; Ren PJ et al., 2017; Shen and Sun, 2019).

Additionally, we should be aware of the problems probably caused by the application of H₂ on human society. In particular, H₂ is used for clean energy in industry, and future development of hydrogen economy in agriculture could also result in more anthropogenic emissions of H₂. In developing hydrogen agriculture, the influence of increasing global H₂ concentration in atmosphere cannot be easily ignored. Therefore, the impact of hydrogen economy on human beings and the planet should be carefully evaluated in the near future.

3 Hydrogen agronomy: past and present

Generally speaking, both hydrogen medicine and hydrogen agriculture address the biological effects of H₂ and its corresponding applications. Discoveries related to the research targets and mechanisms in hydrogen agronomy are summarized below (Fig. 2).

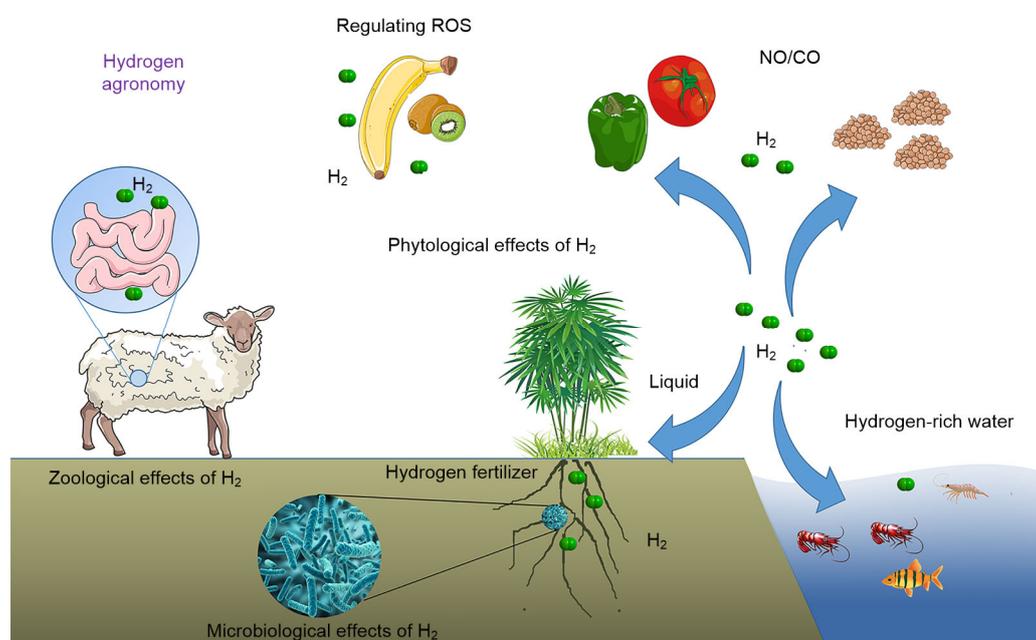
3.1 H₂ biosynthesis

H₂ biosynthesis occurs mainly in plants and microbes. Gas chromatography (GC), hydrogen-specific sensors, and spectrophotometric methods are normally used to determine H₂ in biological contexts (Shen and Sun, 2019). H₂ production was first observed in bacteria (Stephenson and Stickland, 1931). Subsequently, release of H₂ was also found in green algae (Gaffron, 1939). In algae and microbes, H₂ production depends mainly on hydrogenase (typically [Ni-Fe] and [Fe-Fe] hydrogenases) and nitrogenase (Das et al., 2008). [Ni-Fe] hydrogenase is mainly present in some sulfate-reducing bacteria (Yagi and Higuchi, 2013), and [Fe-Fe] hydrogenase is found in anaerobic prokaryotes such as clostridia and sulfate reducers; among eukaryotes, [Fe-Fe] hydrogenase has been found in some anaerobic eukaryotes (including fungi, ciliates, and trichomonads) and some green algae, including *Chlamydomonas reinhardtii* (Lubitz et al., 2014). In addition, a third type of hydrogenase, [Fe] hydrogenase, has been found in methanogenic

Table 2 Differences in research methods between hydrogen medicine and hydrogen agronomy

Program	Research model	Method of H ₂ supply	Degree of difficulty	Reference
Hydrogen medicine	Rat	Inhalation of H ₂	Difficult	Ohsawa et al., 2007
	Rat	Injection of hydrogen-rich saline	Difficult	Zhao et al., 2013
	Rat	Injection of hydrogen-rich saline	Difficult	Wang et al., 2011
	Rat	Drinking HRW	Easy	Fu et al., 2009
	Mice	Feeding magnesium hydride	Easy	Kamimura et al., 2016
	Human	Drinking HRW	Easy	Kang et al., 2011
Hydrogen agronomy	<i>Hypsizygos marmoreus</i>	Watering HRW	Easy	Zhang et al., 2017
	Rice	Soak in HRW	Easy	Xu et al., 2013
	Kiwifruit	Soak in HRW	Easy	Hu et al., 2014
	Tomato	Soak in HRW	Easy	Lu et al., 2017
	Lisianthus	Watering HRW	Easy	Su et al., 2019

HRW: hydrogen-rich water

**Fig. 2 Hydrogen agronomy: targets and mechanisms**

The targets of hydrogen agronomy mainly include plants, animals, and microbes. Hydrogen gas (H₂) can influence reactive oxygen species (ROS), nitric oxide (NO), and carbon monoxide (CO) signaling in organisms. In addition, the soil microbial community composition and structure can be changed by soil hydrogen treatment, and the hydrogen-treated soil can improve plant growth

archaea (Vogt et al., 2008). For nitrogenase, H₂ is a byproduct of nitrogen fixation in rhizobia (Golding and Dong, 2010).

Although metabolic synthesis of H₂ has been demonstrated in microbes, algae, and higher plants, the mechanisms of H₂ generation still need further investigation. Su et al. (2019) discovered that the photosynthetic electron transport chain was related to H₂ production. The generation of H₂ was reduced

by suppressing above process using pharmacological approach.

Some researchers are currently focusing attention on the relationship among environmental stress, phytohormones, and hydrogen production. Many studies have found that the production of H₂ from plants can be induced by drought, osmotic stress, salt damage, and heavy metal stress (Cui et al., 2013; Zeng et al., 2013; Jin et al., 2016; Chen et al., 2017).

Phytohormones are also associated with hydrogen production. H₂ production from plants can be induced or influenced by auxin, abscisic acid, and ethylene (Zeng et al., 2013; Xie et al., 2014; Cao et al., 2017). Since H₂ production is quickly induced in response to abscisic acid signaling, it cannot be easily ruled out that hydrogen production may be a non-enzymatic process. We also speculate that H₂ production and emission might be associated with energy metabolism in chloroplasts and mitochondria. The involvement of H₂ in the signaling pathways of various phytohormones (Shen and Sun, 2019) suggests the possibility that H₂ may be a “universal signaling molecule.”

3.2 Beginning of hydrogen agronomy: hydrogen fertilizer?

The essence of hydrogen agronomy in the narrow sense has been previously regarded as “hydrogen fertilizer.” Unlike traditional fertilizers that supply nutrients (N, P, and trace nutrients), “hydrogen fertilizer” exerts the roles of fertilizer in the soil through supplying H₂ (Dong et al., 2003; Golding and Dong, 2010). This “hydrogen fertilizer” is not a nutrient but exerts its beneficial effects through other mechanisms. In the forms of HRW and H₂ gas, H₂ is the protagonist of hydrogen agronomy, and its potentials in the production, transportation, storage, and sales of agricultural products have been repeatedly demonstrated (Hu et al., 2014, 2018; Xu et al., 2017; Ji et al., 2019; Zhang et al., 2019).

Previous research has found that the rates of oxygen and carbon dioxide uptake in soils are influenced by H₂ (Dong and Layzell, 2001). Further work demonstrated that soil uptake of H₂, especially near nodulated legume roots, dramatically modifies microbial populations (McLearn and Dong, 2002; Dong et al., 2003; Stein et al., 2005), by selectively enhancing the populations of plant growth-promoting rhizobacteria (PGPRs). This phenomenon is used to explain the benefits of using legumes in crop rotation with wheat and other non-legumes (Kirkegaard et al., 2008). The weight of fixed nitrogen in one hectare of legume crop is about 200 kg per season; meanwhile, the volume of H₂ produced during above process is about 240 000 L (Dong et al., 2003). The evolution of H₂ from roots of nodulated grain legumes fluctuates between 0.06 and 0.51 mmol/(h·g nodule dry weight) (Angus et al., 2015). Therefore, it is not difficult to

understand that H₂ can exert tremendous biological effects in agriculture.

The growth performance of barley, soybean, canola, and spring wheat was improved in H₂-treated soils compared with growth in untreated soils, and the tiller numbers of barley and spring wheat were increased by 36% and 40%, respectively (Dong et al., 2003). H₂ is an obligate byproduct of nitrogen fixation in legume rhizobia. Dong and his colleagues proposed that H₂, whether produced by nitrogenase or exogenously applied, could have an important “fertilization” effect in rotations with legume crops (Dong et al., 2003; Golding and Dong, 2010). H₂ may then have some functions to partly minimize the use of chemical fertilizer. The relationships between microbes in soils and plants are very close (Yang and Crowley, 2000). H₂ can change the microbial community structure and thus influence plant growth and development (Dong et al., 2003).

3.3 Research methods of hydrogen agronomy

Hydrogen agronomy is an interdisciplinary science that combines physiological, biochemical, molecular biology, genetics, and multi-omics to study the related scientific principles of hydrogen agriculture. Each method has its own unique characteristics. Integration of these various disciplines and use of multiple methods are needed to study hydrogen agronomy from multiple angles and at multiple organizational levels.

3.3.1 Physiological and biochemical approaches

Physiology and biochemistry form the basis of hydrogen agronomy research. By measuring indicators related to physiology and biochemistry, we can intuitively understand hydrogen agronomy.

Early research on hydrogen agronomy mainly focused on easily measurable parameters, such as yield, quality, and organ development. Golding and Dong (2010) found that H₂, as a “fertilizer,” promoted rotation in non-leguminous crops, including influencing yield. The role of H₂ in improving drought tolerance of alfalfa (*M. sativa*) was confirmed via pharmacological experiments (Jin et al., 2013). In addition, lateral root and adventitious root formation, as easily observed phenotypes, have been widely used to study the influence of H₂ on plant development (Zhu et al., 2016; Cao et al., 2017). Moreover, the use

of phytohormones and their synthetic inhibitors, as well as other biologically active substances, are effective experimental tools for studying hydrogen agronomy; these experiments provide strong evidence that H₂ may be an essential component of the complex signaling network (Zeng et al., 2013; Xie et al., 2014; Su et al., 2018). These physiological and biochemical approaches are effective and useful methods for studying hydrogen agronomy.

3.3.2 Molecular and genetic approaches

Molecular and genetic approaches are two important methods of biological research. Although the presence of hydrogenase in algae and certain bacteria has been confirmed, no homologous gene has been found in higher plants (Gaffron, 1939; Golding and Dong, 2010; Shen et al., 2018). Therefore, finding candidate genes encoding a hydrogenase-like enzyme is of great biological and historical significance.

At present, most molecular and genetic experiments in hydrogen agronomy have been carried out by using specific, signaling-impaired mutants including mutants deficient in ROS (Xie et al., 2014) and nitric oxide (NO) (Cao et al., 2017) signaling. In addition, the study of gene expression at transcriptional and translation levels is widely used in hydrogen agronomy. For example, Wu et al. (2015) found that HRW could regulate expression of ion transporter genes, thus alleviating cadmium toxicity in Chinese cabbage (*Brassica campestris* spp. *chinensis*). The expression of *microRNA528* (*miR528*), *miR160a*, *miR398a*, and *miR159a* is also regulated by H₂, which explains the phenotypes that alleviate aluminum stress in rice (*Oryza sativa*) seed germination (Xu et al., 2017). The expression levels of jasmonic acid and salicylic acid receptors are also regulated by H₂, indicating H₂ controls of plant resistance against disease (Zeng et al., 2013).

3.3.3 “Multi-omics” approaches

With the development of science and technology, the use of genomics, proteomics, or newly developed metabolomics technology is becoming more and more common. These approaches offer the potential of high-throughput experiment technology for hydrogen agronomy.

At present, multi-omics approaches have been used to study the mechanisms of H₂ production in

algae, and to characterize of some important genes, including *HydA1*, *HydA2*, *Sulp*, *Tla1*, *Sta7*, and *PFL1* (Xu et al., 2019). Similarly, some genes related to H₂ production have been discovered (Melis et al., 2000; Vignais et al., 2001; Volgusheva et al., 2013). Using RNA-sequencing, Cui et al. (2020) identified many differentially expressed genes in cadmium-stressed alfalfa (*M. sativa*) seedlings in the presence of HRW, including genes involved in glutathione and sulfur metabolism. More recently, Huang et al. (2020) found that metabolism-related proteins, photosynthesis-related proteins, and stress response-related proteins might play positive roles in H₂-promoted cucumber adventitious rooting by proteomic analysis.

Use of multi-omics technology allows researchers to analyze the process of H₂ metabolism and understand the changes of the entire metabolic network. Since metabolomics technology has a lot of scientific potential in higher plants, metabolomics technology is bound to advance hydrogen agronomy in the near future.

3.4 Mechanisms

Generally, the concentration of dissolved H₂ in HRW utilized in agriculture is about 78 μmol/L (10% HRW) (Cui et al., 2014; Zhu and Liao, 2017), and the H₂ content during fumigation tests is greater than 0.2 μmol/L (Hu et al., 2018). Since H₂ concentration in the troposphere is about 0.5 ppmv (equivalent to 34.5 ppbw, about 22 nmol/L H₂) (Paneth, 1937), and tropospheric H₂ can escape to upper atmosphere (Liu and Donahue, 1974), it is reasonably deduced that the lower concentration of H₂ in the atmosphere could not directly influence the performance of plants on earth. However, there is ample evidence, showing that local H₂ in the soils and plants, when endogenously produced (especially in roots of legume plants, among other sources) and/or exogenously applied, could significantly alter plant responses (Shen and Sun, 2019). Here, mechanism of hydrogen agronomy is accordingly summarized.

3.4.1 H₂ and ROS signaling

Studies using various animal models have confirmed the effects of H₂ or hydrogen-rich saline on Alzheimer's disease (Nishimaki et al., 2018), cell apoptosis (Guo et al., 2015), retinal light damage (Tian et al., 2013; Qi et al., 2015), and branch retinal vein occlusion (Long et al., 2019).

In animals, ROS are byproducts of oxidative phosphorylation. Excess ROS can be produced by smoking (Tanriverdi et al., 2006; Grassi et al., 2010), immobilization stress (Liu et al., 1996), and ischemia/reperfusion injury (Zhao et al., 2013). Besides their toxic effects, ROS also play an important role in cell signaling pathways, as has been shown in the previous work (Sauer et al., 2001; Kim and Byzova, 2014). In addition, the functions of H₂ are related to anti-apoptosis, metabolic diseases, and neurodegenerative diseases (Table 3). The main goal of hydrogen medicine is reduction of toxic ROS, especially selective scavenging of ROS (Ohsawa et al., 2007).

Unlike hydrogen medicine, H₂ may induce ROS signaling in plants. Xie et al. (2014) found that H₂ first rapidly induced ROS signaling (as early as 10 min after treatment) and then mobilized NO signaling to promote stomatal closure in *Arabidopsis*. Further, by using a mutant deficient in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase,

we further confirmed that NADPH oxidase-dependent ROS were downstream signaling molecules of H₂ (Xie et al., 2014).

However, there is also strong evidence that H₂ might improve the antioxidant capacity of plants and reduce ROS accumulation (24 h after stress), thereby alleviating the inhibitory effects of metal pollution on seedling growth (Cui et al., 2014; Dai et al., 2017). Moreover, H₂ can increase superoxide dismutase (SOD) activity in kiwifruit (*Actinidia chinensis*), therefore maintaining ROS at a low level (Hu et al., 2014). Additionally, H₂ enhances pyruvate kinase activity by reducing lipid peroxidation and intracellular ROS levels, thereby alleviating the damage of abiotic stress to *Hypsizygus marmoreus* (Zhang et al., 2017). Ren A et al. (2017) found that the homeostasis of ROS in *Ganoderma lucidum* can be regulated by H₂.

Overall, ROS play important roles in H₂ function in both hydrogen medicine and hydrogen agronomy. In agronomy, we propose that H₂ may quickly induce

Table 3 Mechanisms of hydrogen biology in hydrogen medicine and hydrogen agronomy

Process	Mechanism of action	Reference
Hydrogen medicine		
Hydrogen-mediated oxidative stress	H ₂ can attenuate severe burn-induced early AKI by regulating the MAPKs, Akt and NF-κB signaling pathway	Guo et al., 2015
	H ₂ can increase the antioxidant effect by activating the Nrf2 transcription system	Kawamura et al., 2013
Hydrogen-regulated metabolic diseases and neurodegenerative diseases	H ₂ can improve Alzheimer's disease caused by apolipoprotein ApoE4 mutation	Nishimaki et al., 2018
	HRW can reduce the damage of type 2 diabetes mellitus patients to glucose tolerance to a certain extent	Kajiyama et al., 2008
Hydrogen-regulated autophagy	Hydrogen-rich saline can enhance anti-apoptosis of cells by regulating Bax/Bcl-2 ratio and ASK-1/JNK pathway	Liu et al., 2015
	H ₂ can increase the expression of phosphorylated p-AMPK, AIF, Caspase 3, etc., thereby enhancing the 5-fluorouracil-induced apoptosis of cancer cells	Runtuwene et al., 2015
Hydrogen agronomy		
Hydrogen-mediated ROS signaling	H ₂ can reduce the accumulation of cadmium and mercury, improve the antioxidant capacity of plant seedlings, and reduce the accumulation of ROS	Cui et al., 2014; Dai et al., 2017
	H ₂ can maintain a low-ROS level, thereby extending the shelf life of kiwifruit	Hu et al., 2014
Interaction of hydrogen and NO	H ₂ mobilizes NO signaling to promote stomata closure, thereby improving its drought tolerance	Xie et al., 2014
	H ₂ enhances the resistance of tomato fruits to <i>Botrytis cinerea</i> by increasing the activity of polyphenol oxidase and NO content	Lu et al., 2017
Interaction of hydrogen and CO	H ₂ regulates CO, a downstream signaling molecule that depends on heme oxygenase-1, thereby improving alfalfa's drought tolerance	Jin et al., 2013
	H ₂ modulates target gene expression related to adventitious root development and auxin signaling pathway through the CO pathway, thereby promoting the development of cucumber adventitious roots	Lin et al., 2014

ROS, reactive oxygen species; NO, nitric oxide; CO, carbon monoxide; AKI, acute kidney injury; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; Nrf2, nuclear factor erythroid 2-related factor 2; ApoE4, apolipoprotein E4; HRW, hydrogen-rich water; Bcl-2, B cell lymphoma-2; ASK-1, apoptosis signal-regulating kinase 1; JNK, c-Jun N-terminal kinase; p-AMPK, phospho-adenosine monophosphate (AMP)-activated protein kinase; AIF, apoptosis-inducing factor

ROS signaling to trigger the gene expression of antioxidant genes. Afterwards, the redox homeostasis was reestablished.

3.4.2 Crosstalk between H₂ and NO

In plants, NO generation is induced by phytohormones and environmental stimuli to trigger a wide range of cellular responses. Although NO has been widely studied, the causal relationship between NO and H₂ is a matter of strong research interest in the study of hydrogen agronomy.

In Arabidopsis, NO was found to be involved in H₂-induced stomatal closure and drought tolerance (Xie et al., 2014). In addition, interaction between H₂ and NO was shown to be a factor in plant biotic stress and other abiotic stresses. For example, NO can contribute to H₂-improved osmotic tolerance in alfalfa (Su et al., 2018). Pharmacological experiments showed that H₂ can alleviate the inhibition of root growth caused by aluminum stress by inhibiting synthesis of NO in alfalfa (Chen et al., 2014). H₂ also enhances the resistance of tomato (*S. lycopersicum*) to the fungal pathogen *Botrytis cinerea* by increasing polyphenol oxidase activity and NO content (Lu et al., 2017).

Furthermore, interactions between H₂ and NO have been found in plant organ development, especially in root development. For instance, the development of lateral roots in tomato and Arabidopsis is regulated by H₂ (Cao et al., 2017). As a downstream signaling molecule, NO might participate in H₂-induced cucumber adventitious roots (Zhu et al., 2016).

These research efforts have shown several apparent interactions between H₂ and NO. As a downstream signaling molecule, NO participates in H₂-induced stress resistance, and in plant growth and development. These data strongly suggest that the interaction between H₂ and NO may be as tight as that of antigens and antibodies.

3.4.3 Crosstalk between H₂ and carbon monoxide

For plant stress tolerance, carbon monoxide (CO) is also a potential downstream signaling molecule. Previous research reported that CO might be a downstream signaling molecule for H₂ control of drought tolerance in alfalfa (Jin et al., 2013). Moreover, CO is involved in plant organogenesis induced by H₂, especially in root development (Lin et al., 2014). The

expression of target genes related to adventitious root formation and auxin signaling is mediated by H₂ in CO-dependent fashion, thereby promoting the development of cucumber adventitious rooting. Additionally, CO may participate in the adventitious root development process induced by H₂ under drought stress, and reduce the oxidative damage as well (Chen et al., 2017).

According to current research, both H₂ and CO are thought to be involved in plant stress tolerance and adventitious root development, both of which closely interact with phytohormone activity (Shen and Sun, 2019). Thus, the combination of genetic and multi-omics approaches should be adopted to reveal corresponding mechanisms in the near future.

3.5 Nanotechnology and hydrogen agronomy

Although application of HRW is an effective and safe method to exert the biological effects of H₂, the high diffusivity and the low solubility of H₂ in water normally results in several difficulties when used in hydrogen agronomy and thereafter in hydrogen agriculture.

Yang et al. (2018) packed the hydrogen-producing prodrug into a spherical mesoporous structure to increase hydrogen delivery time and to achieve higher concentrations. In addition, nanocarriers can also be modified to release H₂ in some specific areas or contexts, such as cancer cells (Zhao et al., 2018; Kou et al., 2019). Combining nanotechnology and H₂ agronomy should have great future potential.

3.6 Hydrogen agronomy in future: a challenging

Unlike the processes used in hydrogen medicine, hydrogen agronomy has its own unique mechanisms (Table 3). In addition to ROS, the functions of H₂ are closely related to those of many other gaseous signaling molecules, including NO and CO. Hydrogen agronomy is a broad field that includes beneficial roles of H₂ in plants, microbes, and animals (Fig. 2).

With the development of hydrogen science, some important papers and patents of hydrogen agronomy have been pointed out (Fig. 3). We searched hydrogen agronomy-related papers in the database of Web of Science, and found that the number of the papers shows an increasing tendency since 2012 (Fig. 4; Table S1). Among these papers, the plant studies

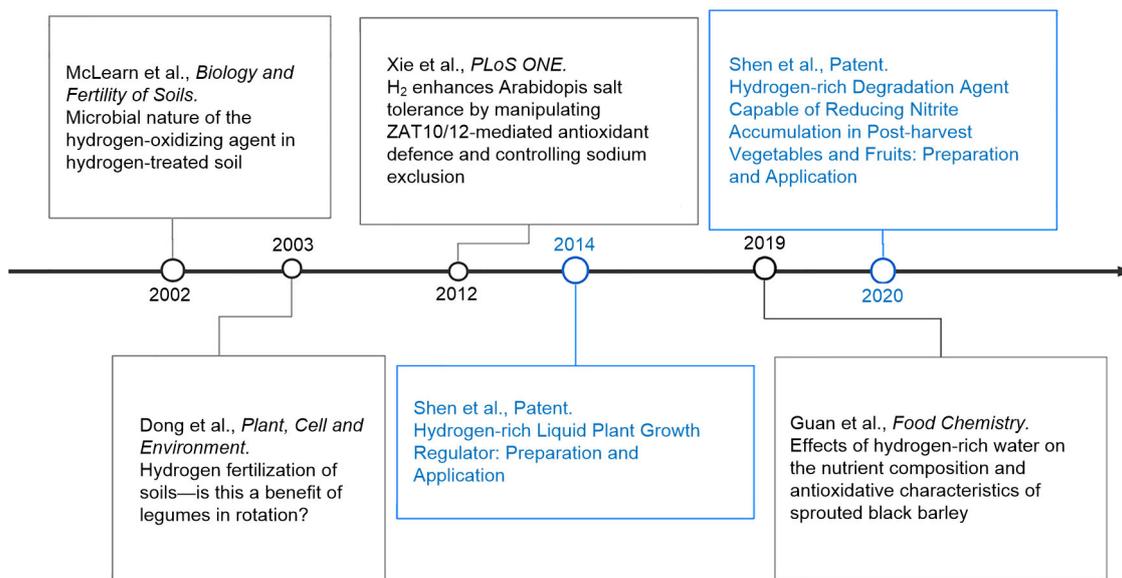


Fig. 3 Growth of research on hydrogen agronomy

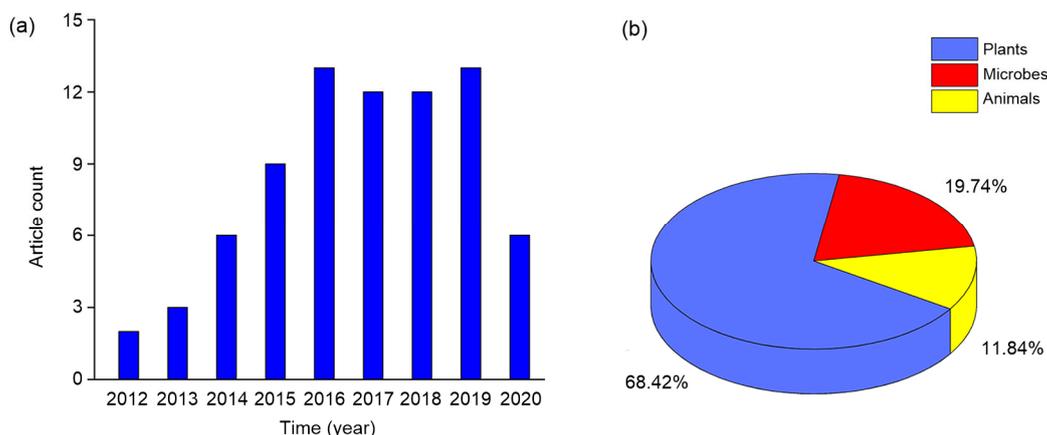


Fig. 4 Number of papers focused on hydrogen agronomy from Jan. 2012 to July 2020 (a) and the proportion of papers focused on biological effects of hydrogen on plants, microbes, and animals in the core collection section of Web of Science (b)

ranked first, at least in terms of the number of papers. More importantly, the development of hydrogen agronomy is just beginning. Although it was recently found that H₂ can alter enzyme activity (Ma et al., 2020), there is still an urgent need for basic research to fully understand the process of endogenous H₂ metabolism and its consumption in agriculturally relevant plants and microbes, and also to identify the cellular targets or receptors of H₂ and their functions.

Overall, hydrogen agronomy has developed gradually as a multidisciplinary and integrative field, and its interconnections among agronomy, medicine, chemistry, and other disciplines are apparent. Research on aquaculture and space agriculture may be the next direction in hydrogen agronomy.

Contributors

Wen-biao SHEN conceptualized and designed this study. Yue-qiao WANG and Wen-biao SHEN wrote this article. Yu-hao LIU and Shu WANG collected the data and drew the figures and tables. Wen-biao SHEN and Hong-mei DU checked the final version. All authors have read and approved the final manuscript and, therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Yue-qiao WANG, Yu-hao LIU, Shu WANG, Hong-mei DU, and Wen-biao SHEN declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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List of electronic supplementary materials

Table S1 Articles about hydrogen agronomy

中文概要

题目：氢农学：研究进展与展望

概要：农业是社会发展的基础。在人口增长、自然灾害、环境污染、气候变化和食品安全等诸多压力下，跨学科的新农业正在成为现代农业的发展方向之一。新农业不仅是大健康和新能源的基础，同时也是国家粮食安全、能源安全以及生物安全的基石。氢农学主要研究农业领域中氢气 (H₂) 生物学效应的相关机理，为从属于新农业的氢农业实践提供相关理论基础。过去，H₂生物学效应的研究主要集中在医学方面，选择性抗氧化是氢医学的主要理论依据。随后的实验表明，H₂也可以调节农作物、食用微生物和家畜的生长发育，增强它们对各种胁迫的耐受性。更重要的是，H₂还可以改变土壤中微生物的群落结构，进而调节农作物生长。使用H₂还可以提高农产品的营养价值和采后品质。研究人员还表明，H₂的生物学功能是通过调控植物与微生物等体内活性氧 (ROS)、一氧化氮 (NO) 和一氧化碳 (CO) 信号级联来介导的。本文总结了氢农学的发展历程，综述了相关研究的新进展。我们认为崭露头角的氢农业将是新农业发展的方向之一。我们还讨论了目前氢农学存在的一些科学问题，指出氢农学的未来需要结合多学科的优势。此外，例如岛礁、飞行器和外太空等特殊环境下的氢农业也将成为氢农学的重要研究方向。

关键词：氢气 (H₂)；氢农学；新农业