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Hydrogen sulfide is a Janus-faced molecule with many beneficial and toxic effects on the animal health. In ruminants, rumen fermentation plays a vital role in the digestion and absorption of nutrients. During rumen fermentation, the production of hydrogen sulfide can occur, and it can be rapidly absorbed into the body of the animals through the intestinal wall. If the production of hydrogen sulfide concentration is higher in the rumen, it can cause a toxic effect on ruminants known as poliomyelitis. The production of hydrogen sulfide depends on the population of sulfate-reducing bacteria in the rumen. In rodents, H2S maintains the normal physiology of the gastrointestinal tract and also improves the healing of the chronic gastric ulcer. In the gut, H2S regulates physiological functions such as inflammation, ischemia?reperfusion injury and motility. In this review article, we summarize the toxicity occurrence in the body of animals due to high levels of hydrogen sulfide production and also recent progress in the studies of physiological function of H2S in the gut, with a special emphasis on bacteria-derived H2S is discussed in this review.

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Abstract: Hydrogen sulfide is a Janus-faced molecule with many beneficial and toxic effects on the animal health. In ruminants, rumen fermentation plays a vital role in the digestion and absorption of nutrients. During rumen fermentation, the production of hydrogen sulfide can occur, and it can be rapidly absorbed into the body of the animals through the intestinal wall. If the production of hydrogen sulfide concentration is higher in the rumen, it can cause a toxic effect on ruminants known as poliomyelitis. The production of hydrogen sulfide depends on the population of sulfate-reducing bacteria in the rumen. In rodents, H_2S maintains the normal physiology of the gastrointestinal tract and also improves the healing of the chronic gastric ulcer. In the gut, H_2S regulates physiological functions such as inflammation, ischemia–reperfusion injury and motility. In this review article, we summarize the toxicity occurrence in the body of animals due to high levels of hydrogen sulfide production and also recent progress in the studies of physiological function of H_2S in the gut, with a special emphasis on bacteria-derived H_2S is discussed in this review.

Keywords: rumen; hydrogen sulfide; ruminants; fermentation; animal health

1. Introduction

The crucial life-supporting role of hydrogen sulfide (H_2S) has developed from microorganisms to plants, invertebrate, vertebrate, and, lastly, to mammals [1]. H_2S has only been known as a poisonous gas and ecological hazard. Earlier studies have shown that in animals, H_2S is the most poisonous gaseous signaling molecule, after nitric oxide and carbon monoxide [2]. Recently, H_2S was recognized as the third most physiologically significant gasotransmitter and plays a crucial role in various cell signaling pathways. H_2S is an endogenous signaling molecule that may establish using protein sulfhydration to control different physiological functions. Hydrogen sulfide is also a byproduct of dietary sulfate metabolism by gut bacteria [3]. An increasing number of research studies have established hydrogen sulfide gas as an important cytoprotectant and redox modulator. In addition, H_2S has a pleiotropic impact on the physiology of animals [3]. Consequently, a more important function of hydrogen sulfide was recognized as protecting from oxidative stress and ischemia–reperfusion injury by various mechanisms, for example, maintaining the level of glutathione (GSH) and directly

suppressing mitochondrial reactive oxygen species (ROS) [4]. H_2S also inhibits cytotoxic CD8+ T cells, though this happens at what we currently consider to be a supraphysiological level of hydrogen sulfide [2]. Production of hydrogen sulfide in mammalian tissue has been known for a long time, but it was primarily ignored as metabolic waste. A significant level of hydrogen sulfide has been detected in mammalian tissue from human, cow and rat in the range of 50–160 um [1]. Emerging studies have shown that H_2S can serve as a potential barrier against antibiotics and oxidative stress [3,5]. In addition, hydrogen sulfide has been found to regulate several antioxidant enzymes such as ascorbate peroxidase (APX), catalase (CAT), super oxidase dismutase (SOD) and glutathione reductase (GR) [6]. H_2S also plays a vital role as an intracellular gaseous transmitter in various physiological and pathologic mechanisms in rodents [7]. In addition, H_2S plays a crucial role in the physiological function and maintenance of the gastrointestinal tract. In the rat colon, it regulates the secretion of calcium ion through activating the Ca^{2+} and ATP sensitive K^+ [8]. In addition, rats treated with H_2S improved the healing of a chronic gastric ulcer [9,10].

In any case, the natural and physiological significance of this chemical in endogenous hydrogen sulfide digestion has not been completely determined. Hydrogen sulfide is oxidized successively in the mitochondrion to thiosulfate and afterwards to sulfite, with the end result under physiological conditions being sulfate [11].

Hydrogen sulfide and its different ionic forms are highly toxic forms of sulfur. In the rumen, microbes produce sulfide—and if the diet contains more sulfate—the microbes produce a greater quantity of sulfide. In the rumen, dietary sulfur can be compressed into hydrogen sulfide. Hydrogen sulfide is a type of gas and its accumulation in ruminants may create some kind of toxic effects on the animals. It may cause some disorders, such as poliomyelitis [12]. In ruminants, poliomyelitis causes neuropathological conditions, leading to neural metabolic disorders, as, change in the level of thiamine, water deprivation, sodium ion toxicosis, higher intake of the sulfur and lead poisoning [13]. Hence it is important to regulate the production of hydrogen sulfide in the rumen. In this review article, we summarize the toxicity occurrence in the body of animals due to high levels of hydrogen sulfide production as well as also recent progress in the studies of the physiological function of H_2S in the gut. A special emphasis on bacteria-derived H_2S is discussed in this review.

2. Hydrogen Sulfide Toxicity in Rumen

Hydrogen sulfide's effects on respiration are similar to that of hydrogen cyanide [14]. Hydrogen sulfide and its ionic particles are extremely lethal and have an strong effect on animals. Rumen fermentation produces hydrogen sulfide, which is quickly absorbed through the intestinal wall and making animal sensitive to the toxin hydrogen sulfide. The production of hydrogen sulfide depends on the sulfur concentration in the diet [15]. If the sulfur is provided to animals in the form of sulfate—or the concentration of sulfur in the diet is greater—the microorganisms in rumen use the sulfate to synthesize sulfides, which increases hydrogen sulfide levels in the rumen of the animals. This extreme absorption and production of sulfide in rumen causes a toxicological effect on the health of the ruminants [16]. Abe et al. (1996) [17] reported that hydrogen sulfide may act in the brain as a neuromodulator. Gould et al. (1997) [13] also stated that usually, when the concentration of hydrogen sulfide exceeded 2000 mg/L it may cause the poliomyelitis, and death may occur if animals are not cured timely. Many studies also reported that greater production of hydrogen sulfide levels could cause sulfur-induced poliomyelitis (S-PEM) in animals. Lewis et al. (1954) [18] reported that hydrogen sulfide concentration below 471.2 mg/L in rumen did not cause toxic and side effects on the health of animals.

3. Hydrogen Sulfide Production Pathway in Rumen

3.1. Hydrogen Sulfide Production in Rumen

The production of H_2S in the rumen is depending on the availability of sulfate reduction by ruminal sulfate-reducing bacteria. In the rumen, so many bacteria, fungi and protozoa are present, some bacteria are sulfate-reducing bacteria (SRB) and these bacteria are anaerobic. These bacteria can reduce sulfate into hydrogen sulfide in the rumen of the animals [19], and the reaction is demonstrated in Figure 1. Lewis et al. (1954) [18] verified that in the rumen of sheep, sulfate could be reduced into hydrogen sulfide. It was also confirmed in the in vitro trial that substance-reducing particles in fermentation broth could be reduced by the use of numerous sources, for example, ethanol, glucose, malic acid, citric acid and lactic acid. Though in 1960, the first strain of SRB was isolated, research on sulfate reduction in the rumen was conducted during the 1953. Desulfovibrio is SRB major strain that was found in the rumen by Howard et al. [20]. Cummings et al. (1995) [21] conducted research on steers fed high sulfate diet and concluded that there was no upsurge of SRB population, but the capability to decrease sulfate in the rumen was boosted. The source of sulfur (S) performs a vital role in the use of S and the concentration of H_2S in the rumen of ruminants—especially in an increased dietary S in total mixed ration. Availability of S for ruminal reduction is more useful than total S in the diet since the differences in ruminal H_2S concentration is successfully evaluated in ruminal protein sulfur and ruminal S availability (RAS) intakes instead of total intake of S [22]. Following an in vitro technique, the individual ingredients can be used to predict the coefficient of RAS. Meanwhile, the intake form can be controlled by the concentration of H_2S in the ruminants. The organic source of S is methionine and can be absorbed easily as amino acids. This makes it unavailable for the reduction in the rumen to sulfide and the reverse is true; thus, the inorganic source of S is vulnerable to be metabolized in the rumen to form other dangerous compounds, including H_2S. Therefore, the concept of RAS is vital to predict H_2S concentration in the rumen instead of focusing the available S in the diet [23].
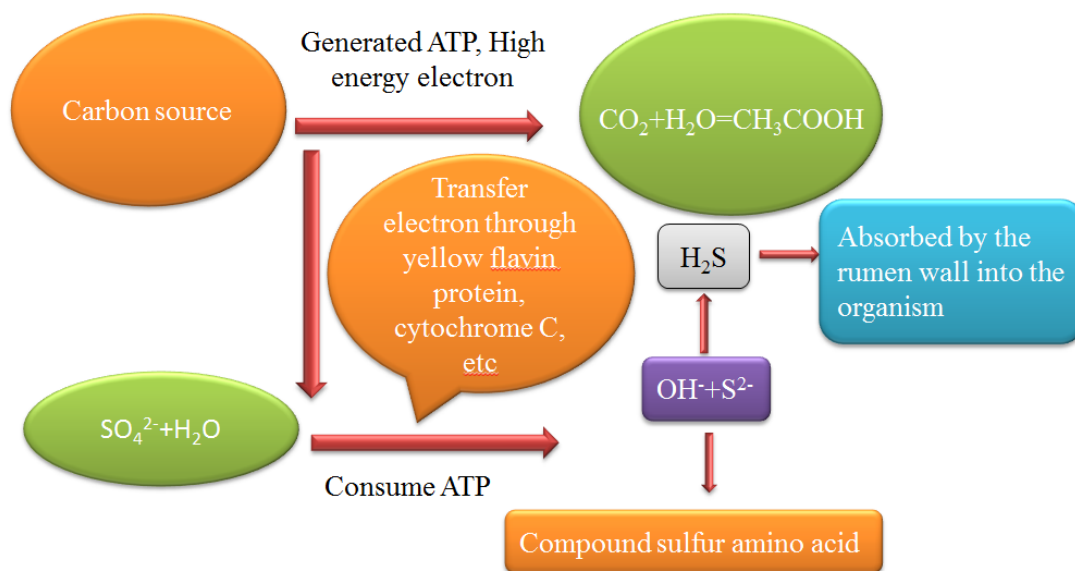

Figure 1. Sulfur-reducing bacteria use the sulfate to produce hydrogen sulfide.

3.2. Sulfide-Reducing Bacteria and Methanogens Relationship in the Rumen

There is an interactive and competitive relationship among methanogens and SRB. SRB and methanogens compete with each other for the requirement of the hydrogen for metabolism through anaerobic reactors [24]. Correspondingly, in the rumen, as SRB reduce sulfate to sulfide and methanogens reduces CO_2 to produce CH_4. SRB can also competitively attach to hydrogen ions.

In the rumen, SRB's compatibility with methanogens depends mainly on the sulfate levels [25,26]. If sulfate levels exceed a certain concentration in the rumen, the production of methane can be decreased. Nevertheless, when the concentration of sulfate becomes very low, a mutually beneficial and symbiotic association develops through hydrogen generation among methanogens and SRB, signifying 'interspecific transfer of hydrogen. Reducing the level of sulfates in the rumen by SRB can make SRB a source of hydrogen sink [27]. Taking into account the two considerations of thermodynamics and matrix affinity, SRB has an advantage in competing with methanogens for hydrogen [28]. However, few studies have shown that methanogens cannot contest with SRB for hydrogen, though SRB and methanogens coexist [29,30]. The absolute benefit of SRB in the use of hydrogen is similarly verified by the kinetic parameters of the potential difference. The hydrogen ion is more inclined towards SRB, since the energy provided by the sulfates is greater. SRB has a low value of usable critical level for hydrogen relative to methanogens. Hence, the lower level can be used by SRB as opposed to that of methanogens. Furthermore, the temperature is also a significant aspect of the rivalry among methanogens and SRB for hydrogen. SRB dominates under moderate temperature circumstances (37 °C); however, methanogens have significant advantages in high-temperature settings (55 °C) [31]. Erin et al. (2011) reported that the level of H_2S in rumen of same diet cattle were change due to the change in the SRB population in the rumen of each cattle [32].

4. Factors Affecting the Production of Rumen Hydrogen Sulfide

4.1. Dietary Sulfur Levels Influence the Production of Hydrogen Sulfide in the Rumen

Sulfur supplementation in the diet and their use in the rumen have been positively associated with the level of generated H_2S [23]. Likewise, another study reported a linear upsurge of H_2S level in the rumen, with dried distillers' grains (feed high sulfur level) increasing in total mix ration [33]. The soluble forms of dried distillers' grains (DDGS) have been intensively utilized in ruminant production; however, excessive use of it quickly results in the accumulation of toxic H_2S gas in the rumen. This condition further resulted in a brain disease called polioencephalomalacia. Studies postulated dietary alterations could mitigate H_2S production, since acidic rumen condition favored H_2S gas development [12]. Hence the concentration of sulfur in the diet of a ruminant has been closely linked to the development of rumen H_2S. Therefore, it becomes useful to examine the influence of dietary roughages and concentration of sulfur on the production of H_2S in the rumen.

The concentration of H_2S in rumen reaches a normal daily range after 6 to 10 h of providing feed, and it reaches its limit after some days of incessant providing feed to bulls at 0.2 percent and 0.7 percent dietary sulfur levels [15,34]. H_2S levels in the rumen of cows peaked around 500 mg/L of sodium sulfate 15 to 35 days after drinking the water [35]. Drewnoski et al. (2012) [15] demonstrated that in steers, a greater amount of concentrate and sulfur (0.8 percent sulfur level) in the diet increased the development of rumen H_2S and the extreme H_2S produced in rumen between 10 to 35 days after providing the greater concentration of sulfur in the diet. The maximum tolerable limits of sulfur recommended by NRC for beef cattle [36] and dairy cattle [37] are 0.4% and 0.3% in non-high-concentrate and high-concentrate diets, respectively. However, the use of additives has been focused by many researchers to reduce H_2S production in the rumen [38,39]. At a ruminal pH of 6.5, the production of H_2S gas is deemed to be favorable; however, once the pH drops to (~5.5), it is expected to be at an optimal hydrogen gas production from glucose [40].

An increased ruminal pH creates unfavorable conditions for H_2S gas production by reducing the production of volatile fatty acid (VFA). The lignin-containing roughages (such as hay) are digested at a lower rate compared with starch found in concentrates. May et al. (2010) reported that the fraction of lignin that is indigestible was found to increased ruminal-fluid pH by decreasing the production of VFA [41].

Supplementing minerals such as molybdenum (Mo) in ruminant diets affects ruminal H_2S production. Excessive intake of S by ruminants overproduce free sulfide (S_2) in the rumen, which interferes with cellular processes and hence bind hydrogen to form a compound called toxic H_2S gas. This resulted in poor performance in ruminants and S-induced polioencephalomalacia (PEM). The molybdenum (molybdate) interacts with S in the rumen to form various isoforms of thiomolybdate, which are either absorbed or passed through the gastrointestinal tract [42]. The Mo impedes sulfate (SO_4)-reducing bacteria without interfering with fermentation in the rumen; this then prevents the activation of SO_4, which is catalyzed by ATP sulfurylase [36]. Ruminal fermentation also produces S_2, but Mo was found to inhibit the production of S_2 [27]. Reports by Huber et al. (1971) and Walter et al. (2004) prescribed that supplementing 100 mg Mo/kg DM does not reduce animal performance [43,44]. An in vitro experiment showed inhibition of H_2S gas production when ≥100 mg/kg Na_2MoO_4 was added to fermentations with 2500 mg/kg SO_4 [45]. Molybdate was found to impede SO_4-reducing bacteria that specifically produce H_2S gas in the rumen [46]. Therefore, supplementing Mo could adequately bind excess ruminal S without forming toxic concentrations. Previous findings displayed that the concentration of H_2S in the rumen of sheep was approximately 0.52 g/m^3 when the total mix ration comprises of 0.71% sulfur and 60% DDGS [47]. In contrast, it was 1.07 g/m^3 (more than two times that of the former) when the amount of sulfur in the diet up to 0.84%, with the similar content (60%) of DDGS [48]. Dietary sulfur content (provided through water and feed), feeding approaches and variations in diets were analogous between the two findings. However, variations in H_2S concentrations maybe because of flora variations caused by a change in the sulfate concentration in the rumen. The additional potential reason may be the various types of sulfur that occur in the diet, but in each diet, the types of sulfur (sulfates, amino acids) were not measured.

Afterward, when ruminants consumed more sulfur in diet, a considerable quantity of H_2S was produced in rumen under the action of SRB. In rumen, SRB may decrease the sulfate level in the rumen, but excess sulfate levels more than 576 mg/L can impair SRB's capability [49]. The dietary sulfur levels can be indicated to affect H_2S development by controlling SRB in the rumen.

Therefore, DDGS, as a quality feedstuff, can be utilized by ruminal microbes as an effective CP source hence can influence the production of H_2S in the rumen. In addition,, other forms of dietary manipulation may be active in alleviating H_2S production [12].

4.2. Rumen pH Influences the Production of Hydrogen Sulfide

In ruminants, higher dietary sulfur levels decrease the pH of rumen [50]. The change of sulfide to H_2S is a procedure which depends on pH. Morine, Drewnoski and Hansen (2014a) reported that the concentration of H_2S in rumen was negatively associated with pH 6 h after feeding on Days 7, 14, 21, 29 and 84 [51]. There was a clear adverse association among H_2S level and pH in the cattle rumen when the cows provided a total mix ration with sulfur 0.45 percent, and the reduction in sulfide to H_2S can be encouraged when the value of pH in rumen decreases [45]. Higher pH helps to decrease the production of H_2S by dropping the activity of SRB in batch anaerobic digestion of wastewater sludge in the slaughterhouse; however, till today, there is no investigation conducted on the activity of SRB in the rumen below this pH [52,53]. The finding of the association among the concentration pH of rumen and H_2S are not similar. Moreover, Uwituze et al. (2011) [54] reported that intakes comprising 30 percent DDGS (0.65 percent sulfur and 0.42 percent) augmented the level of H_2S in the rumen through in vivo digestion experiment with increased rumen pH in Angus steers. It can be shown that under this experimental condition, there was a positive association between the pH of rumen and concentration of H_2S. To date, though, not all studies have exposed a close association between the concentration of H_2S gas and ruminal pH in ruminants. Earlier findings demonstrated that sulfur affected the concentration of H_2S in rumen (beef) and evaluated that the pH of rumen can only change 12 percent of H_2S levels in rumen, whereas the intake of ruminal protein sulfur may contribute 58 percent of changes in rumen H_2S level [23]. Based on the above findings, the use of rumen pH as a predictor of bovine rumen H_2S concentration was suggested to be problematic.

4.3. Dietary NDF Content Influences the Production of Hydrogen Sulfide in Rumen

There are many factors which affect the rumen pH that is not associated directly with dietary sulfur levels and rumen pH factors, such as dietary NDF, that affect rumen H_2S development. Morine et al. (2014) [53] reported that the level of H_2S in rumen reduced linearly with the upsurge in dietary roughage neutral detergent fiber (rNDF) content (4 percent, 7 percent or 10 percent), whether fed with bromegrass hay or cornstalks. Enhancing the supply of hay in the diet from 5% to 12% (DM basis) reduced H_2S levels by approximately 2000 mg/L; rumen H_2S level reduced linearly with the upsurge in dietary content of rNDF ($p = 0.004$), 6 h on Day 14 after providing a total mix ration. Thus, more rNDF diet, will decrease the production of rumen H_2S. Though the particular mechanisms of S-PEM disease are not clear yet, it is understood that animals fed more quantity of concentrate in total mix ration faces a higher hazard of this infection compared to those provided higher forage supplementation in total mix ration [55]. This proposes that increased content of sulfur in total mix ration, while animals eat a more forage quantity in the total mix ration, may reduce the potential threat of toxicity induced by sulfur through modifying the population of SRB in rumen. Though, scarce studies on the influence of NDF content in total mix ration on H_2S of rumen, so more experimental confirmation, particularly on mechanism of the S-PEM, is required.

4.4. Effect of Ruminal Hydrogen Sulfide on Ruminants Health/Beneficial Impact of Hydrogen Sulfide on Animals

Ruminant diets containing excess S can be harmful to animal health because it triggers ruminal production of H_2S and subsequently resulting in toxicity. Though, sulfur is regarded as an essential element of ruminant nutrition. However, excessive intake of sulfur can decrease animal production and causes respiratory problems, as well as enteric and encephalic problems [13,56]. Overproduction of ruminal hydrogen sulfide directly resulted in the development of polioencephalomalacia [57]. Cattle growth is also severely affected by subacute intoxication caused by ruminal hydrogen sulfide [58]. In ruminant livestock in regions with high-S drinking water, exhibited poor performance and S-PEM). As much as the problems of ruminal hydrogen sulfide exist in ruminant production, nutritionists also tried several ways to curb the situation. Supplementing Mo improves the health and performance of steers, given a high-fiber diet and high-S drinking water [58].

One main challenge with the use of ethanol-based coproducts in ruminant nutrition is its ability to increase S concentrations in the diet [16]. Therefore, the inclusion of increased proportions of DDGS and other ethanol-based coproducts in finishing rations for ruminant production has been prohibited, partly due to changes in promoting the development of poliomyelitis and reduction in maximum ruminant output [13]. In addition, researchers reported that supplementing thiamine to ruminant diets helps to alleviate or to prevent poliomyelitis in animals [59–61]. Meanwhile, others reported that the involvement of thiamine in S-induced poliomyelitis is unclear [62]. The causative mechanisms of poliomyelitis, for instance; long-term thiamine deficiency or increased hydrogen sulfide gas concentration, may influence the chances or the efficacy by which thiamine supplementation may prevent poliomyelitis in ruminants fed with an increased dietary S. Due to this, studies have been conducted studies to determine the effective level or concentration of thiamine that is necessary to alleviate or prevent poliomyelitis. Interestingly, researchers have recommended supplementing 150 mg of thiamine/animal per day to ruminants fed increased amounts of DDGS in the diet [63]. Hence, supplementing high dietary thiamine would decrease the incidence of poliomyelitis in lambs fed increased S diets without affecting animal performance.

H_2S also plays a vital role as an intracellular gaseous transmitter in various physiological and pathologic mechanisms in rodents [10]. In addition, H_2S plays an essential role in the physiological function and maintenance of the gastrointestinal tract. In the rat colon, it regulates the secretion of calcium ion through activating the Ca^{2+} and ATP sensitive K^+ [8]. Wallace et al. [9] concluded that treatment through H_2S in rats improved the healing of a chronic gastric ulcer. In addition, H_2S prevents the gastric mucosal damage due to the use of ethanol or nonsteroid anti-inflammatory

drugs [10,64]. Magierowski et al. (2016) [64] observed that H$_2$S produced endogenously from cysteine due to the activity of cystathioninelyase, and H$_2$S acts as a vital and protective role in gastric mucosa ischemia/reperfusion lesions, H$_2$S can increase the healing process of these lesions. Furthermore, H$_2$S also protects gastrointestinal mucosal lesions induced by the aspirin. H$_2$S released from NaHS and carbon monoxide released from CO-releasing tricarbonyldichlororuthenium (II) dimer attenuate the aspirin-induced increase content of MDA considered as an index of gastric mucosal lipid peroxidation and can improve the antioxidative status of gastric mucosa due to restoration of antioxidative GPx-1 protein expression impaired by aspirin treatment [10]. Magierowski 2016 [64] reported that H$_2$S and carbon monoxide released from their donors, NaHS and CORM-2, protect gastric mucosa compromised by stress against alendronate-induced gastric damage via a mechanism involving downregulation of hypoxia-inducible factor 1α (HIF-1α), kappa-light-chain enhancer of triggered B cells (NF-kB) and proinflammatory factors inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), tumor necrosis factor-α (TNF-α) and interleukin-1 β (IL-1 β).

5. Conclusions

There are currently few studies regarding the development of rumen H$_2$S. H$_2$S is provided by the reduction of sulfate SRB in the rumen, during which a competitive association exists amid methanogens and SRB. Though, there is still a need to test if the development of H$_2$S is restrained by methanogens in the rumen. It is also important to test either level of H$_2$S in rumen increases or no longer after reaching a critical value when the amount of dietary sulfur upsurges. There is still a need to explain the relation between pH and H$_2$S development in the rumen. Supplementation of more content of rNDF in diet can decrease the level of H$_2$S in the rumen, but the correlation requires more experimental tests. Hence, further research is required to explore either increased dietary rNDF content will incessantly decrease the concentration of H$_2$S in the rumen. In addition, the endogenous production of H$_2$S in rodents improved the normal physiology of the GIT tract, particularly improves the healing of chronic gastric ulcer in rats. Finally, it is vital to accentuate the important role of GIT microbes in the physiology of the host. The effect of H$_2$S derived from bacteria on the physiology and pathophysiology of the host and is a mainly unknown, but crucial area of research. Research must be done to investigate the role of bacteria-derived H$_2$S on the biologic processes of the host. Determining how H$_2$S derives from bacteria may influence the biology of host can benefit us to understand the basic mechanism of various diseases.

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