

Hydrogen sulfide toxicity in the gut environment: Meta-analysis of sulfate-reducing and lactic acid bacteria in inflammatory processes



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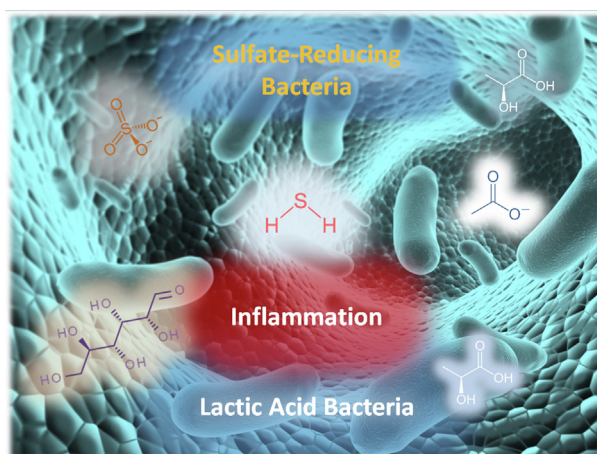
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HIGHLIGHTS

- Sulfate-reducing bacteria are the main producer of hydrogen sulfide in the gut.
- High concentrations of hydrogen sulfide are involved in gut inflammation.
- Lactic acid bacteria can be sensitive to hydrogen sulfide.
- Meta-analysis revealed a relationship between gut inflammation and sulfate-reducing bacteria.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Hydrogen sulfide is the final product of sulfate-reducing bacteria metabolism. Its high concentration in the gut can affect adversely bowel environment and intestinal microbiota by toxicity and pH lowering.

Aim of Review: The aim of the review was to give observations related to the properties of bacterial communities inhabiting the gut, with the emphasis on sulfate-reducing bacteria and lactic acid bacteria.

Key Scientific Concepts of Review: The conduction of meta-analysis was another goal, since it gave statistical observation of the relevant studies. The review literature consisted of more than 160 studies, published from 1945 to 2019. Meta-analysis included 16 studies and they were chosen from the Web of Science database. The systematic review gave important information about the development of gut inflammation, with emphasis on sulfate-reducing and lactic acid bacteria. Oppositely from sulfate-reducing bacteria, probiotic properties of lactic acid bacteria are effective inhibitors against inflammatory bowel disease development, including ulcerative colitis. These facts were confirmed by the conducted meta-analysis. The results and observations gained from the systematic review represent the emphasized

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importance of gut microbiota for bowel inflammation. On the other side, it should be stated that more studies in the future will provide even better confirmations.

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Introduction

Inconceivable diversity of life is the property of the nature that is a fascinating human for life. Sulfate reducing bacteria (SRB) is also representing fascinating property of nature since it can survive in very unique and unfavorable environments [1]. They are influencing, both positively and negatively, in numerous ways terrestrial and marine ecosystems [2]. Sulfide reacts with organic and inorganic compounds causing much damage in industries. On the other hand, sulfide can be very useful in biotechnological approaches [1,2]. It means that understanding of the processes included in sulfate-reducing metabolism can lead to better usage of the SRB in biotechnology, same as for finding more effective elimination due to their negative impact on certain industrial and environmental issues.

SRB are also present in the gastrointestinal tract of humans and animals [3–7]. They can significantly influence the gut environment since they are producing hydrogen sulfide and at the same time they are competing for nutrients. Hydrogen sulfide interferes in the colonocytes with metabolic processed and it damages the intestinal mucosa [8–11]. Consequently, SRB can be a cause for the initiation of the inflammation that can lead to bowel diseases such as ulcerative colitis (UC) [12–16].

On the other hand, ulcerative colitis is considered a multifactorial disease with unclear etiology. Ulcerative colitis treatments include following approaches: immunomodulatory, diet and immunosuppressive [17–21]. It is important to stress out that none of these approaches can be considered an absolute solution. This fact somehow explains the importance of better understandings environment and processes around bowel disease, such as ulcerative colitis, including also SRB.

The aim of the review is to observe and give important comments related to the properties of bacterial communities inhabiting the gut, with the emphasis on sulfate-reducing bacteria found in this anoxic habitat. The review also provides the overview of the studies that included microbial profiles of healthy subjects and individuals with intestinal bowel diseases. Consequently, meta-analysis was conducted for better overview of IBD occurrence.

Methodology

This study was a systematic review describing relationship between sulfate-reducing and lactic acid bacteria present in the same communities. The literature used in the review consisted of studies found in qualified databases: Web of Science, Scopus, Medline/Pubmed, and Google Scholar. The studies included in the review were published in time range from 1945 to 2019. A combination of keywords and details were used for the search procedure. A flowchart of used literatures is presented in Fig. 1. Heterogeneity was expressed by the I^2 test, where the higher I^2 represents higher heterogeneity.

The Review Manager Software (number 5.3 developed by Cochrane Collaboration) was used for meta-analysis conduction. In the included studies the data consisted of the studies dealing with relationships between SRB and IBD, same as between LAB and IBD. Heterogeneity was represented by I^2 test; higher I^2 represented indicated higher heterogeneity.

The human intestinal microbiome

Bacteria, *Archaea* and *Eukarya* are all present in the gastrointestinal tract of the adult human. The highest number of bacteria is present in the human intestine, compared with any other ecosystem. These microorganisms colonizing the gut of humans are called “gut microbiota”. This number exceeds 10^{14} and as an illustration can serve the fact that 10 times lesser numbers of cells and 100 times lesser total genome formed human body [22–24]. The importance of the gut microbiota has been confirmed by numerous studies that showed its role in the protection against pathogenic and opportunistic microorganisms. On the other hand, the disrupted equilibrium of gut microbiota can be related to certain infections [25].

Gaining nutrients and energy from the diet is the main function of the human gut microbiota. Not absorbed parts of the diet are transferred to the distal gut and there interact within metabolism processes. Primary fermenters, such as *Bacteroides*, degrade proteins and carbohydrates. In this process are produced short-chain fatty acids (e.g., propionate, acetate, and butyrate) and gases (e.g., H_2 and CO_2). These fermentation products are not used only by host, other gut microbial members used them as sources of carbon and energy [26].

Large and various microbial communities are present in the intestine and colon. That number has been evaluated to be from 400 to 1500. It should be emphasized that for many of them there is not known technique for the cultivation [27]. Considering bacterial species, several important phyla can be found in the human intestine. The main representatives are following strains: *Clostridium*, *Blautia* (*Streptococcus*, *Lactobacillus*, *Faecalibacterium*, *Eubacterium*, *Roseburium* and *Ruminococcus*), *Bacteroidetes* (*Bacteroides*, *Prevotella*), *Firmicutes* which are predominant, *Actinobacteria* (*Bifidobacteria*, *Atopobium* and *Collinsella*) and *Proteobacteria* (*Escherichia*) (Fig. 2).

New bacteria, such as *Christensenella* or *Hugonella massiliensis* are present too. The stability of a healthy gut is affected also by *Archaea*, *Methanobrevibacter* (large methane producer) *Eukarya* (yeast *Candida*), viruses and bacteriophages. The importance of gut microbiota can be seen through the fact that it is often called “organ” [27,28]. Intestinal microbiome is providing us vitamins, regulated lipid metabolism and producing short chain fatty acids, serve as resistance against gut pathogens and many other vital cell function [29].

Recent studies are also indicating connections between the gut microbiome and nervous system of the host. These interactions are based on the communication by the vagus nerve or also systems including immunology and endocrinology with neuroactive chemicals produced by microorganisms. These connections are mainly focused on anxiety and depression. Neurotransmitters produced by microorganisms lead to the possible mechanism of microbial influence on the brain and human behavior. Probiotic lactic-acid bacteria can serve as an example of neuroactive microbial substances producers (Table 1). Though, these mechanisms are still unclear, beside progressive documentations produced by recent scientific studies. Certainly, more studies in this field are necessary [30–32].

The changes in the intestinal microbiome composition (dysbiosis) can also lead to the higher prevalence of intestinal diseases, including inflammatory bowel disease, cancer and

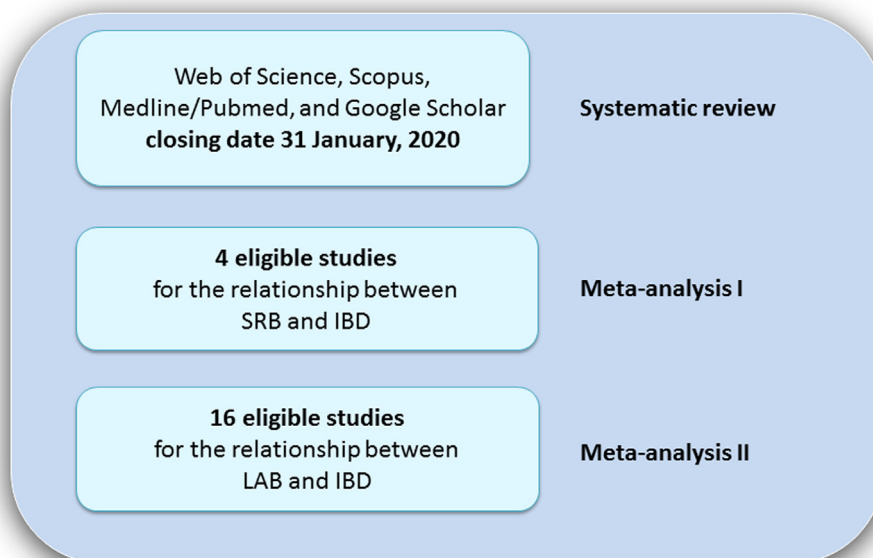


Fig. 1. A flowchart of the literature searches for the systematic review, including meta-analysis I and II.

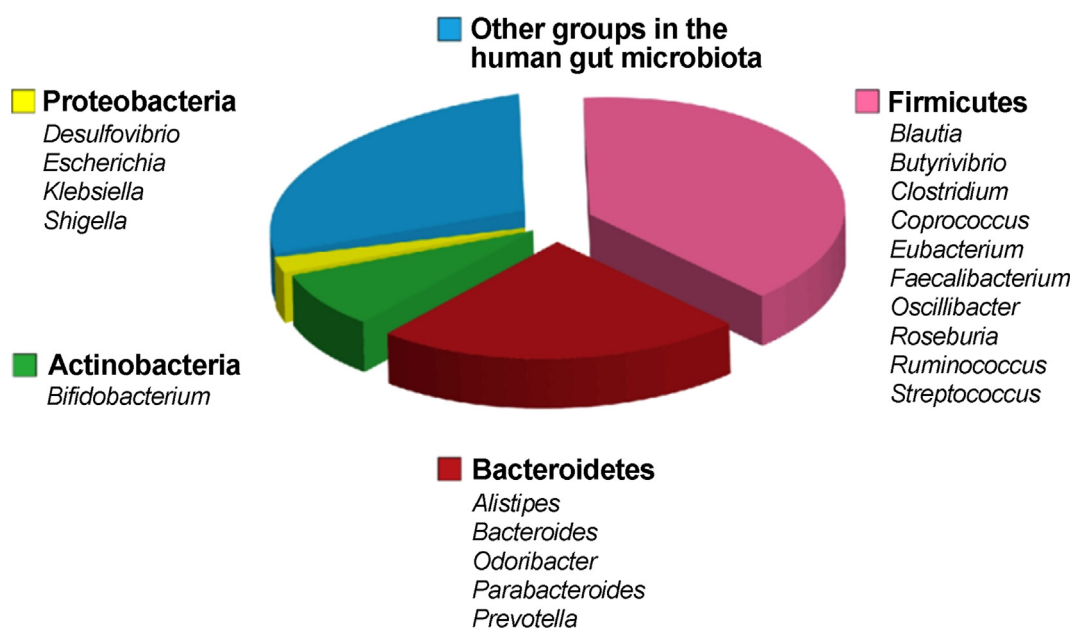


Fig. 2. The main human intestinal bacterial genera [27].

Table 1

Example of neurotransmitter production by bacteria [30].

Genus	Neurotransmitter
<i>Bifidobacterium</i> spp.	Gamma-aminobutyric acid (GABA)
<i>Lactobacillus</i> spp.	Acetylcholine, dopamine, GABA, histamine, serotonin
<i>Lactococcus</i> spp.	Dopamine, histamine, serotonin
<i>Streptococcus</i> spp.	Dopamine, histamine, serotonin
<i>Enterococcus</i> spp.	Histamine, serotonin

diabetes. It means that the handle of the gut microbiome is necessary to maintain human health [27]. Diarrheal diseases (caused by various infectious agents: viruses, bacteria and protozoan pathogens) are a cause of acute gastroenteritis. Acute gastroenteritis includes intestinal villi deletion, intestinal

permeability is enhanced, toxin production and immune cell infiltration [33].

Probiotic bacteria, such as *Bifidobacterium*, can eliminate certain diarrheal diseases. Bifidobacteria pose the genes encoding a specific carbohydrate transporter that serves as the host protection against enterohemorrhagic *Escherichia coli* O157:H7. *E. coli* O157:H7 produces shiga toxin that is transported from the intestine to the bloodstream and causes the death. A higher production of acetate by certain bifidobacteria can induce specific gene expression that leads to increase permeability of the epithelial layer which is the cause of cell death by O157:H7 [34]. Fig. 3 is showing not enough acetate production by non-probiotic bifidobacteria.

Epithelial cell death is caused by O157:H7 infection. The hosts with probiotic bifidobacteria produce enough acetate amounts

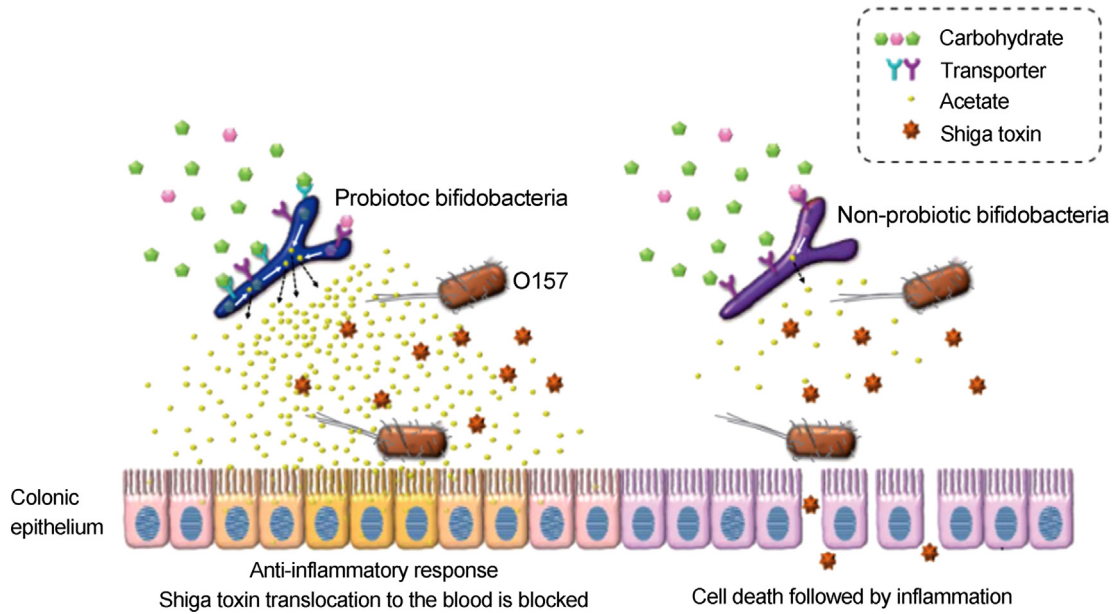


Fig. 3. Schematic introduction of the overall mechanisms of host (mice) protection by bifidobacteria from O157 lethal infection [34].

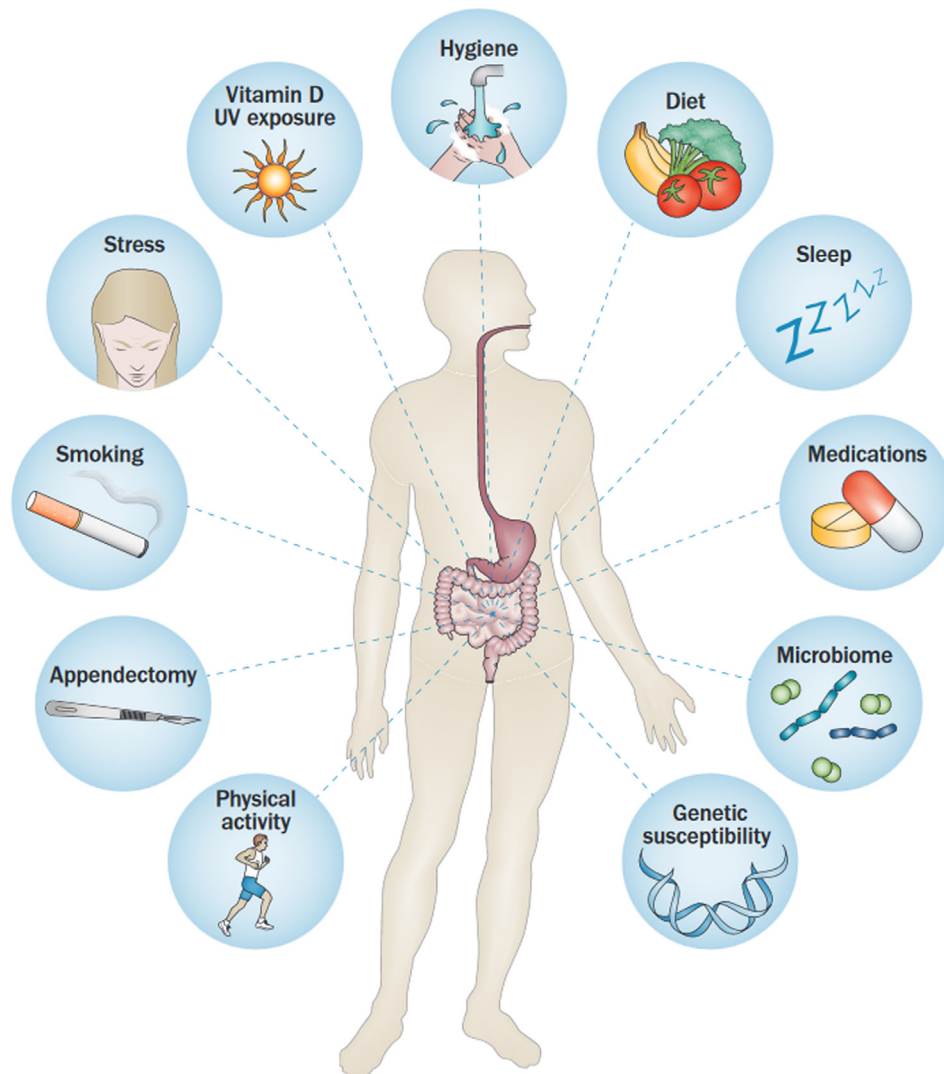


Fig. 4. Factors influencing formation of IBD [35].

(on the left side). These transporters take carbohydrates and metabolize them. The barrier against O157:H7 infection is formed due to the acetate action [34]. Inflammatory bowel disease (IBD) can lead to many health problems: nutrient malabsorption, diarrhea and abdominal pain. IBD can be life threatening and the quality of the life is affected too. IBD is usually caused by ulcerative colitis or Chron's disease [35–37].

There are numerous people around the world affected by inflammatory bowel disease, including ulcerative colitis (UC). The prevalence of UC mainly occurs prior to age 30. The gender differences have not been observed yet. The main factors affecting the occurrence of inflammatory bowel disease are gut microbiota composition changes, the immune system responses of the host and also the overall lifestyle (Fig. 4) [35,38,39].

Several pathological findings are related to ulcerative colitis: oxidative stress, specific inflammatory mediators increase, higher concentrations of glycosaminoglycan in the mucosa, short chain fatty acids reduced oxidation, higher intestinal permeability, higher sulfide production and lower level of methylation. Geographical region, lifestyle and diet habits also affect the prevalence of UC. Developing countries have lower incidence rates in comparison with developed nations. USA, UK, Canada and Scandinavia are the countries with the highest incidence of UC (the prevalence: 1/1000). The lowest UC prevalence is in Africa. In Africa methanogens are the most dominant gut microorganisms among populations [38–40].

Sulfate and sulfite serve as food preservatives and antioxidants in the production of bread, meat, wine and dried fruits. Dietary supplement chondroitin and food additive carrageenan also contain sulfate. There is an observation that maybe higher dietary intake of these foods lead to higher incidence of UC [26,41].

UC can be grouped according to the occurrence place: proctitis (distal part), distal colitis (descending colon) and pancolitis (the whole colon). Symptoms are abdominal cramping, stool loosening and diarrhea. When the disease is more progressive, affected individuals lose weight, feel fatigued, appetite loss, rectal bleeding, fever and anemia [42]. Higher counts of SRB and increase amounts of H₂S are in correlation with UC formation. Hydrogen sulfide concentrations in healthy adult individuals range from 0.3 to 3.4 mmol/l. The free penetration of hydrogen sulfide through the cell membrane is possible due to its solubility in lipophilic solvents. Adenosine 5'-triphosphate-dependent potassium channels, DNA integrity, and activity of cytochrome *c* oxidase and carbonic anhydrase are influenced by H₂S [8,36,37,43].

H₂S is prohibiting butyrate oxidation. Colonocytes are getting 70% of energy from the butyrate derived from intestinal substrates fermentation by gut microbiota [44]. That is the reason why energy deficiency is often connected with the prevalence of UC [10,11,45].

General characteristic of sulfate-reducing bacteria

Anoxic habitats are environments where sulfate-reducing bacteria (SRB) are often found [46]. SRB are able to reduce sulfate to hydrogen sulfide and from this their ability is also derived their name. They use sulfate in the same way as aerobic microorganisms oxygen (terminal electron acceptor) [47–50].

Biologically, SRB are quite unrelated to each other (they differ in shape and optimal growth conditions), beside ability to perform dissimilatory sulfate reduction [51]. Among SRB groups there are a variety of microorganisms: *Deltaproteobacteria* (mesophilic genera *Desulfovibrio*, *Desulfobacterium*, *Desulfobacter*, *Desulfobulbus*), genus *Thermodesulfovibrio* (thermophilic gram-negative bacteria), *Desulfotomaculum* (gram-positive bacteria) and genus *Archaeoglobus* (*Euryarchaeota*) [2].

Dutch microbiologist M. W. Beijerinck in 1895 discovered SRB [51]. He isolated and also characterized the first known SRB genus

Spirillum desulfuricans (at the present time it is known as *Desulfovibrio desulfuricans*). There are also known sulfate-reducing archaea (called sulfate-reducing prokaryotes) [1].

Beside gastrointestinal tract of humans and animals, SRB inhabit environments such as fresh and marine water ecosystems, anaerobic areas of soil, wetlands, rice fields, hypersaline habitats, hydrothermal vents, biogas reactors, plant anaerobic digester and also habitats with extreme pH values [52–56].

SRB use hydrogen as an organic matter and obtain energy by oxidation. In sulfate reduction electron donors are lactate, pyruvate, malate, succinate and acetate [57]. Some strains of SRB can grow on short-chain fatty acids (including acetate), long chain fatty acids and aromatic compounds (benzoate and phenol) [48]. There is a difference among SRB in their organic compounds degradation since some of them degrade organic compounds to carbon dioxide (total degradation) and others degrade it only to acetate [51]. Sulfate is the terminal electron acceptor, but fumarate and dimethylsulfoxide can be used by some marine strains, same as sulfonates by *Desulfitobacterium* [58–61].

According to the shape, SRB can be oval, rod-shaped, spiral, vibrio-shaped, with size from 0.4 to 3 μm. They also exist as aggregates, pairs and individually. Cultivation conditions can influence the shape, for an example *Desulfovibrio* sp. can be in the spirilloid form in environments that are unfavorable [51]. The presence of oxygen also affects the morphology [62]. Consequently, morphology is not an ideal way for SRB identification. The crucial step for the experiments is the standardization of growth conditions [51].

Gram positive (that are exceptions) SRB are spore forming (*Desulfotomaculum*), while the majority are gram negative [63]. The majority of SRB are motile (they usually have a single or polar and multiple flagella). SRB can also lose their motility by losing their flagella if they are treated roughly [51]. High concentrations of hydrogen sulfide are another factor affecting the motility of *Desulfovibrio* [5,51].

SRB are declared anaerobes, though they can tolerate some oxygen during a period of time [64]. The oxygen tolerance is species dependent [65]. SRB strains isolated from North Sea survived oxygen exposure of up to 72 h. Several mechanisms explaining the capability of SRB to survive in the presence of oxygen have been described [66,67].

The key element in anaerobes cultivation is also redox potential (E_h), reaching values below – 50 mV. Redox poisoning agent that is present in the medium sodium sulfide (Na₂S) or ascorbic acid [51]. SRB strains are both mesophilic and thermophilic strains. Thermophilic strains (e.g. *Desulfotomaculum*) grow under conditions that include temperature range from 35 °C to 60 °C. The suitable pH is also species dependent [2,23]. Morphological and physiological characteristics of selected SRB genera are shown in Table 2.

Medium for SRB growth usually contains lactate (the most commonly utilized electron donors in SRB metabolism [6,68,70–72]). SRB are used as significant reducers for the elimination of the environmental pollution, since various SRB can oxidize toluene, ethylbenzene, benzene and xylene (the major compounds in aromatic fuel hydrocarbons) [47].

The reduction by the intracellular electron mediators (ferredoxin or NADH) is prohibited due to sulfate-sulfite redox couple ($E^0 = -516$ mV) which is too negative and it represents an energetically unfavorable condition. Sulfate is activated by ATP sulfurylase, a single ATP molecule is consumed and adenosine 5'-phosphosulfate (APS) is formed (Fig. 5) [73,74].

The redox couple APS-sulfite has E^0 60 mV, meaning that APS can reduce to sulfite (by APS reductase – AprAB) and ferredoxin (NADH) (two electron input is required). During APS reduction, AMP (adenosine monophosphate) is formed and then two ADP molecules (by ATP dependent adenylate kinase). Sulfate activation

Table 2
Some morphological and physiological characteristics of selected SRB genera (data according to Rabus et al., 2013 [64]).

Genus	Morphology	Optimal temperature (°C)	Electron donors			
			Lactate	Propionate	Acetate	H ₂
<i>Desulfovibrio</i>	vibrio	30–38	+	–	–	+
<i>Desulfomicrobium</i>	oval, rod	28–37	+	–	–	+
<i>Desulfotomaculum</i>	(curved) rod sporulates	30–38	±	±	±	±
<i>Desulfobulbus</i>	oval	28–39	+	+	–	+
<i>Desulfobacter</i>	oval, vibrio	28–32	–	–	+	±
<i>Desulfonema</i>	Multicellular filaments	30–32	±	+	+	±
<i>Desulfacinum</i>	oval	60	+	+	+	+
<i>Thermodesulfovibrio</i>	vibrio	65	+	–	–	+

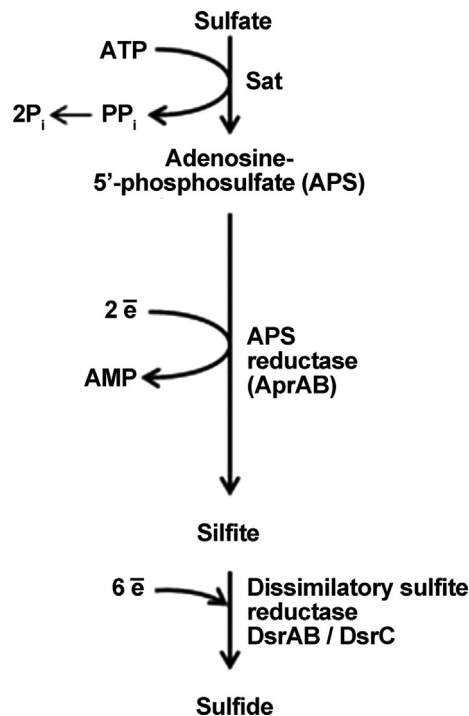


Fig. 5. The prokaryotic dissimilatory sulfate reduction [73].

needs two ATP molecules. Sulfite-sulfide redox couple has E^0 116 mV. The dissimilatory sulfite reductase DsrAB, DsrC, possibly DsrD reduced sulfite to sulfide (input of six electrons is required). Though, these processes are still not fully explained [46,73].

Chemolithotrophic sulfur bacteria can oxidize sulfide under aerobic conditions, same as phototrophic sulfur bacteria under anaerobic conditions. Sulfate reduction is accounted to represent more than 50% of organic carbon mineralization in marine sediments. It is undisputed that sulfate reducers in sulfur and carbon cycles are of the great importance the both for the environment and living organisms [46].

These are five intestinal sulfate-reducing bacteria genera the most often prevailing in the intestines: *Desulfovibrio*, *Desulfobacter*, *Desulfomonas*, *Desulfobulbus* and *Desulfotomaculum*. *Desulfobulbus* and *Desulfovibrio* genera use the molecular H₂ as an electron donor. Approximately 66% of all colonic sulfate reducing bacteria are accounted by *Desulfovibrios* accounted for approximately 66% of all colonic SRB, while *Desulfobulbus* spp. only 16% [75].

Different substrates can be utilized by SRB in the human colon. The major electron donors are fatty acids (acetate, propionate and butyrate), amino acids (glutamate, serine and alanine), ethanol and organic acids (succinate, pyruvate and lactate). Hydrogen can be

also utilized by Acetogens (*Clostridium*, *Ruminococcus*, *Blautia*) and methanogens (*Methanobrevibacter*, *Methanosphaera*). Sulfite (with very low pH: pKa = 7.04) is released into the colonic environment and biologically active free H₂S is in the process of HS⁻ hydrolysis [9,26,40]. SRB cannot survive in environments with low sulfate concentrations, since they have a limited capacity to degrade carbon compounds. SRB has to compete for the hydrogen with methanogenic bacteria that use it more efficiently. Consequently, in human feces can be only one of these two bacteria [8].

There is a higher prevalence of SRB in patients with UC than in healthy persons. Certainly, that the presence of sulfate is influencing SRB counts. The studies that conducted experiments including feeding of animals (guinea pigs with developed UC) with sulfated polysaccharides (carrageenan and amylopectin sulfate) indicated the progression of colitis like conditions. Specific fatty acids (derived during sulfur metabolism) can also induce colitis due to their influence on colonic epithelial cells [40].

Metabolism and enzymes of SRB

Superoxide radicals and peroxides are formed in the process of sulfide reduction. The formation of aggregates is helping SRB to survive oxygen exposure or even to conduct an oxygen reduction [67]. It was observed that *Desulfovibrio* sp. have aerotaxis (cell migration to areas with the most favorable concentration of oxygen [55]). This process is caused by oxygen sensing mechanism. These cells are able to measure oxygen concentrations and redox potential of the environment due to their developed sensors [76].

Detoxification of reactive oxygen species represents another mechanism against superoxide (O₂⁻), hydrogen peroxide (H₂O₂) and hydroxyl radical (HO•). Superoxide dismutase (SOD) and superoxide reductase are scavenging superoxide anion [67]. Hydrogen peroxide is the covert product of superoxide, done by SOD. *Desulfovibrio* possess catalase that further detoxifies hydrogen peroxide [77].

Aerobic respiration was noticed in following SRB strains: *Desulfobacterium autotrophicum*, *Desulfobulbus propionicus* and *Desulfococcus multivorans* [27].

Sulfur can be utilized only in its reduced form and that is the reason why the process of sulfate reduction is very important in nature [51]. It means that sulfates, thiosulfates and sulfites are essential for life on Earth [2]. Many microorganisms can perform an assimilatory sulfate reduction, but only a few microorganisms can perform a dissimilatory sulfate reduction [78]. The final product of sulfate reduction is hydrogen sulfide (H₂S) (requiring 8 electrons) [2]. There are more than hundred compounds that can be potential electron donors for SRB [1].

Lactate or acetate, electrons and hydrogen ions are formed in the process of carbon sources oxidation [23]. Subsequent metabolism utilizes these ions. SRB reduce sulfate to hydrogen sulfide, same as aerobes reduce oxygen to water. There are many anaerobic bacteria and archaea genera that are able to utilize hydrogen sul-

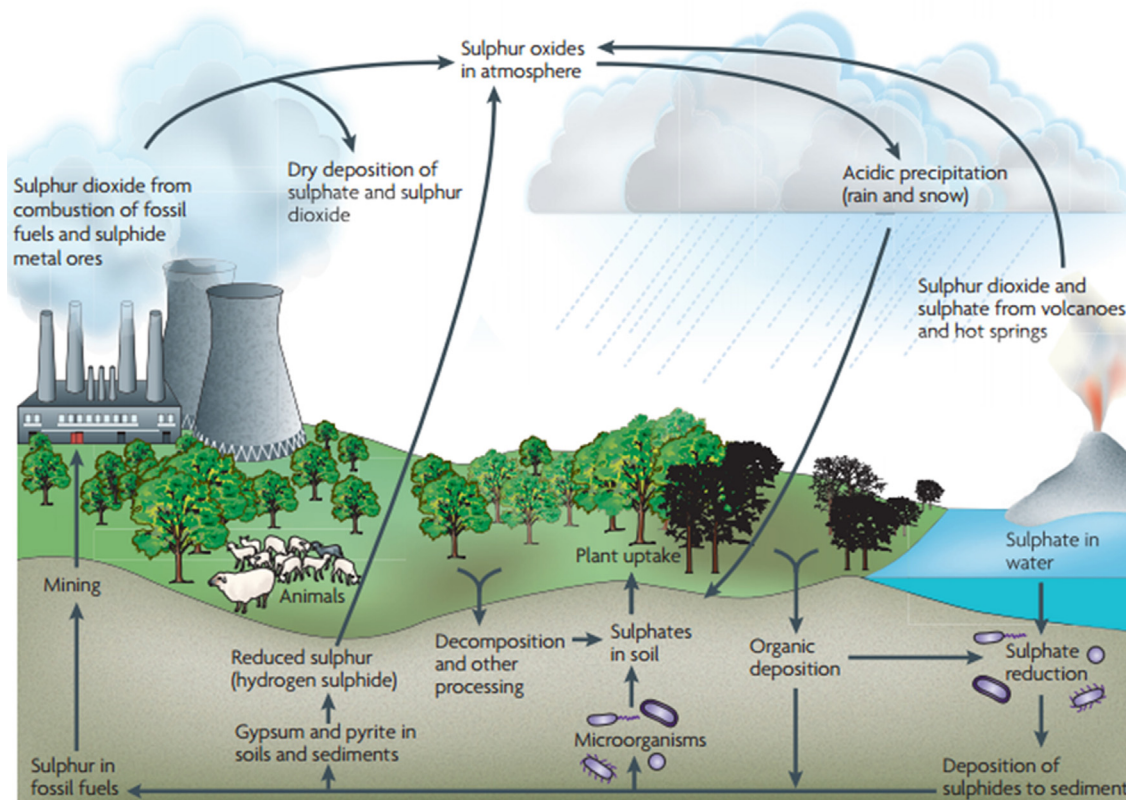


Fig. 6. The sulfur cycle by Muyzer and Stams (2008) [46]

fide from sulfate (SO_4^{2-}), elemental sulfur (S^0), thiosulfate ($\text{S}_2\text{O}_3^{2-}$), and tetrathionate ($\text{S}_4\text{O}_6^{2-}$). They are using them as terminal electron acceptors [47].

Beside sulfur containing compounds, SRB are also able to use other molecules from the environment as terminal electron acceptors, including nitrite and nitrate (some strains of *Desulfovibrio*). Some marine strains can reduce dymerhtlsulfoxide to demethylsulfide [60]. Rarely, *Desulfovibrio* strains can reduce inorganic Fe^{3+} [64].

Following stages are included in the dissimilatory sulfate reduction: sulfate transport, sulfate activation, APS reduction, sulfite reduction.

The description of sulfate transport

At the inner side of the cytoplasmic membrane, the whole process of sulfate reduction is done, since sulfate has to be transferred into the cell. H^+/Na^+ antiport is carrying out the transport. A system attenuating sulfate transport is also preventing the transport of very high sulfate concentrations (28 mM), a system attenuating sulfate transport prevents more sulfate to be transported into the cell [64].

Sulfate activation

The sulfate ion conversion to adenosine phosphosulfate (APS) is the start step of the sulfate reduction. Redox potential of the free anion pair $\text{SO}_4^{2-}/\text{SO}_3^{2-}$ is very low ($E_0 = -0.516 \text{ V}$) and sulfate ion is hard to reduce. Due to this, redox potential has to be increased. It is done by ATP sulfurylase, while consuming ATP [74]:



two of the ATP's phosphate groups are substituted by a sulfate group. Pyrophosphate is generated by this reaction. The equilibrium enzyme constant is not favorable for ATP formation [51].

The reduction of APS

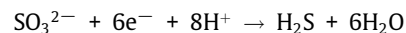
APS is converted to AMP and sulfite by APS reductase enzyme:



This redox reaction can be described as exergonic and reversible [64].

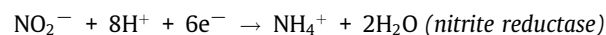
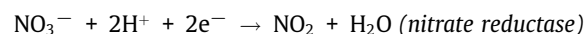
The reduction of sulfite

Out of sulfite (SO_3^{2-}) is yield sulfide (S^{2-}). Intermediates are tetrathionate, dithionate and thiosulphide ions. Six electrons from a donor are required in this reaction [51]:



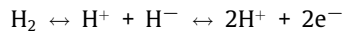
Sulfite reductase is carrying the reaction. According to absorption spectra, there are four kinds of sulfite reductases: desulfovirdin, desulfurubidin, desulfofuscidin and protein P_{582} [23]. There are group-specific. *Desulfovibrio* sp., *Desulfonema* sp. and *Desulfococcus multivorans* usually have desulfovirdin, regarded as taxonomic marker [31,64,79]. *Desulfomicrobium* species and *Desulfosarcina variabilis* have desulfurubidin [80,81]. *Thermodesulfobacterium* genus (thermophilic genus) possess desulfofuscidin [40] and protein P_{582} is found in some sporulating genera of *Desulfotomaculum* sp. [81].

Following strains can utilize nitrite and nitrate: *Desulfovibrio*, *Desulfobulbus*, *Desulfotomaculum*, *Desulfobacterium* and *Thermodesulfobacterium* [1]. In certain occasion they can even prefer them over sulfate [74]. Ammonium is the final product of nitrate by sulfate and sulfur reducers [64]. Nitrate reductase is reducing nitrate to nitrite and subsequently nitrite to ammonium by nitrite reductase:



Nitrite is inhibiting the dissimilatory sulfate reduction pathway (the last step: sulfite to sulfide reduction by sulfite reductase [41]. It means that microbial influenced corrosion can be inhibited by the growth of SRB [1].

Molecular hydrogen is oxidized to protons and electrons, reversibly:



This process is allowing generation of membrane potential and pH gradient without pump protons situated across the cell membrane [1].

Four types of hydrogenases are known: [NiFe], [FeFe], [NiFeSe] and [Fe]. These hydrogenases are interchangeable functional, and they are not distributed uniformly across *Desulfovibrio* sp. The most often found is [NiFe] type [23,83].

Periplasmic hydrogenases are transporting hydrogen ions to cytochrome c_3 . Then electrons from cytochrome c_3 are transported across the cell membrane to cytoplasmic adenosine phosphosulfate (APS) and HSO_3^- . Hmc complex (high molecular weight cytochrome c) is a protein involved in cross-membrane electron transport. This protein is associated at one side with periplasmic region of cytochrome c , and with the cytoplasmic side containing FeS-protein on the other side. Hmc protein is mostly found in *Desulfovibrio vulgaris* usually has hmc protein. *D. vulgaris* can grow only in the presence of lactate and sulfate after hmc genes removal. In this case, the growth is decreased in the presence of H_2 and sulfate only [23].

Sulfate-reducing bacteria and etiology of inflammatory bowel diseases

Spontaneous relapsing inflammation of the gut is the characterization of inflammatory bowel diseases (IBD), such as ulcerative colitis (UC) and Crohn's disease. Crohn's disease can influence each part of the digestive system, oppositely from the ulcerative colitis that affects only the large intestine [82]. The reason for this is probably acidic pH of the stomach (unfavorable environment for the SRB), while colon has a pH lower than 5.5, but in the distal part of the colon pH is neutral that is considered the optimal condition for SRB growth [23].

The categories of UC are formulated in the following way: ulcerative proctitis (colitis in the most distal colon part and the rectum), distal colitis (colitis in the descending colon down) and pancolitis (colitis of the entire colon) [42]. Diarrhea, malnutrition, abdominal pain, rectal bleeding and weight loss are the most common symptoms of IBD [83].

There was found the correlation between UC and colorectal cancer prevalence. The risk is calculated to be 20% [84,85]. Beside cancer, patients with UC can also have secondary conditions, such as osteoporosis, kidney stones, gallstones and liver disease [42]. There was also report that SRB can enter blood circulation through the intestinal wall and cause bacteremia [33].

On the other hand, SRB are not considered directly to be pathogenic for humans and animals [2,86,87]. The most often SRB occur in the intestines of humans and animals are following species: *Desulfotomaculum*, *Desulfobulbus*, *Desulfomicrobium*, *Desulfomonas* and *Desulfovibrio*, with *Desulfovibrio* (*D. desulfuricans*, *D. farfieldensis*) being the most frequently isolated [23].

The etiology of ulcerative colitis and IBD is still unclear. Environment, immune system, and genetic influences the development of chronic inflammation [55]. Patient's dietary habits and intestinal microbiome composition belong to environmental factors. The scans of the whole genome detected susceptible genes to UC occurrence; chromosome 1 and 4, though these loci have not been confirmed uniformly [88]. Cytokines with modified profiles have found to be with other inflammatory

mediators important factor influencing the prevalence of UC and Crohn's disease. Genetics is also closely related to immunity, since it immune response activates or alters gene expression [89].

The correlation between IBD and SRB presence in the gut has been found, but they are still considered an ordinary component of the normal intestinal flora (SRB is found in the digestive system of healthy people too). Healthy population has prevalence of SRB in the gut, according to literature, from 12% to 79% [8,14].

SRB cannot be considered direct pathogens, but only a possible contributing factor in ulcerative colitis development. An inappropriate response to a luminal agent is the cause for IBD [83]. During inflammation the barrier epithelium function is damaged and translocation of toxins and antigens further promotes immune response [23].

Acetate, butyrate and propionate (short chain fatty acids) are crucial for the maintenance of gut homeostasis [83]. These short chain fatty acids are produced in the gut by the fermentation of undigested dietary fibers (polysaccharides) by intestinal bacteria. Colonic cells use the oxidation of short chain fatty acids (mainly butyrate) as the major energy yielding mechanism. Apoptosis of colonic cancer cells is induced by short chain fatty acids [90]. Certainly, these processes lead to the impairment of gut homeostasis and pathogenesis of UC and consequently can further proceed to colorectal cancer [8,23].

Cells are starving due to the inhibition of butyrate oxidation that is caused by hydrogen sulfide damages on gut mucosa [42]. The experiments, including human colonocytes showed butyrate oxidation by hydrogen sulfide of 75% and 43% in the distal colon and ascending colon, respectively [11]. Decreased oxidation of short chain fatty acids is influencing gut inflammation, since studies confirmed lower butyrate oxidation levels in patients with UC than in patients within remission. The fact is also supported by the fact that 3 patients with inactive disease faced relapsed in a few weeks, had decreased butyrate oxidation [91].

Milimolar concentrations (1.0–2.4 mM) of hydrogen sulfide are commonly present in the gut. These concentrations are even beneficial for colonic mucosa since they increase the cell's respiration ability [92]. Thiosulfate is the main product of H_2S oxidation by colonic cells. Oppositely, excessive concentrations of hydrogen sulfide are toxic to SRB themselves too (by cytochrome c inhibition) [23].

The source of sulfate in the gut are food and beverages. It means that diet habits can significantly influence SRB counts in the gut, same as the whole gut microbiome composition. Daily dietary sulfate intake is approximately from 2 mmol to 9 mmol. The major amount of dietary sulfate intake is utilized, since only about 0.5 mmol per day obtains in daily fecal [41]. The dietary sources of sulfate are mostly: food additives, dried fruit (apples, apricots, raisins, dates), nuts (almonds, hazelnuts), vegetables (broccoli, brussels sprouts, cabbage), wheat bread and sausages [93]. Food commodities containing more than 80 mg/100 g of sulfate are cow milk, cheese, eggs and cruciferous vegetables [10].

The oxidation of sulfur dioxide (present in cheese, beer, canned and pickled products serving as a conservator) can be also the source of sulfate. Mucins, secreted by goblet cells of the gastrointestinal tract, and chondroitin sulfate in mammalian tissues are other sulfate sources [2]. SRB are dependent on saccharolytic bacteria in the gut, since they cannot utilize mentioned sulfate sources. Saccharolytic bacteria can disengage the bound sulfate through depolymerization and desulfatation of glycoproteins [40].

Certain drugs for UC treatment are present, though they have numerous side-effects, including vomiting, headache,

weight gain, pancreatitis, fever, and diarrhea. Non-pharmacological approaches such as diet adjustment, same as taking dietary supplements (certain minerals and vitamins) are also usually advised to be used during UC treatment [42]. Oppositely, smoking has been reported to improve UC symptoms [94]. Janus kinase (JAK) inhibitors represent a promising approach in inflammation treatment, since they are important in inflammation cascade [95].

Understanding ulcerative colitis and mechanisms included in the whole process of its development stages is of crucial importance for finding and improving the therapy of disease affected individuals. Since SRB and hydrogen sulfide are connected with UC prevalence their characterization is also important for better understanding of UC.

Significance of sulfate-reducing bacteria in environment and biotechnology

Sulfur present in the atmosphere is in the form of sulfur dioxide (SO_2), and it in from three sources: geothermal vents and volcanic activity, consumed fuels and organic molecules decomposition. SRB are producing hydrogen sulfide from the consumption of organic substrates [46]. Acid rains that damage the ecosystem are formed by sulfur dioxide dissolved into weak sulfuric acid (H_2SO_4) by falling rain. This important biogeochemical process is partially influenced by sulfate reducing bacteria (Fig. 6).

The big problem in the industry is corrosion of ferrous pipes and components of constructions [1]. SRB exist in biofilm form on the surface of metals. Hydrogen sulfide binds to iron and form iron sulfide deposits that cause corrosion (releasing H_2 from the metal surface). SRB use released molecular hydrogen as a substrate and with their H_2 consumption further hydrogen dissociation from the metal is supported (Fig. 7). Consequently, SRB are attracting other molecules to bind to the metal, since on the surface, they are forming colonies [96].

Wastewater from the municipal contains sulfate ions in various amounts. SRB prevail in the wastewater even when cleaning process includes high oxygen input due to SRB property to form biofilms in anoxic environment [97]. Certainly, SRB hydrogen sulfide production depends on sulfate concentrations in the wastewater [98]. SRB biofilms inside the pipes can be treated with certain nitrite, since they are inhibited in the presence of nitrite [99,100]. Nitrate can be as sulfate the final electron acceptor for some species of *Desulfovibrio* genera. It can be reduced to nitrite with following its reduction to molecular nitrogen.

Biocide (formaldehyde, chlorine, or quaternary ammonium compounds) treatment is another way to eliminate hydrogen sulfide [101]. Promising results have been also observed with the combination of nitrite and biocide [102]. SRB can be also well inhibited by some antibiotics (gramicidin S, gramicidin D and polymyxin B) [103].

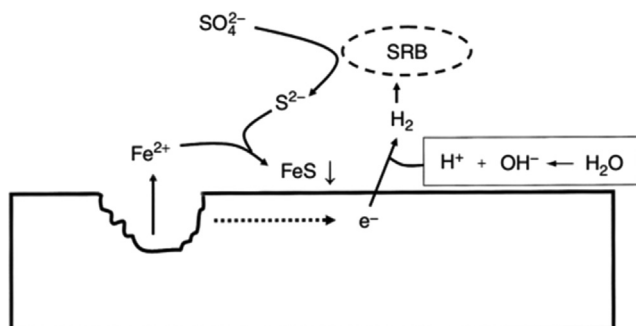


Fig. 7. Microbially-influenced corrosion by Barton and Fauque (2009) [1].

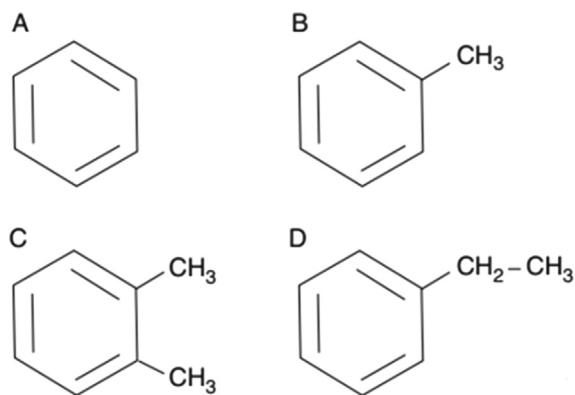


Fig. 8. Structures of BTEX compounds: benzene (A), toluene (B), o-xylene (C), ethylbenzene (D) by Barton and Fauque (2009) [1].

Aerobic bacteria cannot remediate petroleum spills due to anoxic environment. Benzene, toluene, ethylbenzene and xylene (BTEX) (Fig. 8.) structures are the major compounds in aromatic fuel hydrocarbons and several species of SRB have been reported to oxidize them [58]. If the spills are contaminated by oxygenated additives, such as ethanol, it may slow down the degradation of BTEX because consumption of oxygenated additives may be preferred by SRB over degradation of BTEX [1].

Other aromatic compounds contaminating soils and waters that can be degraded by SRB are chloroethens, nitroaromatics (trinitrotoluene) and methyl *tert*-butylether [1].

SRB belong to methylation bacteria and they are capable for inorganic mercury transformation to more toxic organic form of mercury (methyl mercury) [104]. The studies indicated that SRB are the main Hg methylators in soil and sediments (anaerobic environments) [105] (Hsu-Kim et al., 2013). Molybdates are used for the SRB inhibition in soil [104]. Though, not all SRB can methylate mercury, this property depends on the strain rather than genus or species [105]. Methyl-cobalamin compounds and acetyl-coenzyme A (acetyl-CoA) pathway are responsible for the methylation of inorganic mercury. The exceptions have been also found, since some SRB without acetyl-coenzyme A were detected to produce methyl mercury [106].

Metallurgic plants, petroleum refining industry and coal mines are releasing to the environment to cadmium, lead, zinc, arsenic and chromium [1]. SRB produce hydrogen sulfide that reacts with the cationic metals and generate highly insoluble sulfides of metal [107]. Even uranium can be reduced in a process of dissimilatory metal reduction by some SRB species [108].

Colorless aromatic amines are formed by the ability of hydrogen sulfide to degrade the $\text{N}\equiv\text{N}$ bond. This process is important for the decomposition of azo dyes (toxic organic compounds released mainly by textile industry) [1].

General characteristics of lactic acid bacteria

Lactic acid bacteria (LAB) make an integral part of the intestinal microbiota. The proper functioning of the digestive tract is influenced by LAB. Following intestinal LAB are the most often present in the intestine: *Lactobacillus* sp., *Bifidobacterium* sp., *Streptococcus* sp., *Lactococcus* sp., *Enterococcus* sp., *Pediococcus* sp., *Leuconostoc* sp. [109]. Bacterial translocation and gut infections can be prevented with the presence of certain specific LAB probiotic strains [110]. LAB occurrence is reduced during inflammatory bowel disease.

Recent studies are proving and emphasizing the importance of the intestinal microbiome for physiological and psychological processes in human and animal bodies. It has not been fully described the influence of hydrogen sulfide on LAB.

Non-spore forming, non-motile, low GC content, gram-positive rods and cocci are LAB that have fermentative metabolism and form lactic acid as the main final product. LAB are present in various environments, including human and animal intestines and surfaces of plants [111].

LAB belong to facultative anaerobic organisms. LAB are resistant to O₂ toxicity because they are not able to biosynthesize heme molecules. It means that they are not getting heme enzymes (catalases and peroxidases) that are the strongest molecules involved in hydroxyl radical scavenging. LAB possess other mechanisms to withstand oxygen exposure. Generally, LAB are considered as safe (GRAS) microorganisms. They are used as starter cultures in fermented food and beverages since they are producing specific flavor, texture and nutritional value. They are also producing bulk and fine chemicals such as lactic acid, polyols and vitamins. Due to these facts, LAB are very promising microorganisms for biotechnological applications [112]. LAB adapted their metabolism, in the style to have the most beneficial relationship as symbionts of animals and plants, serving them as a supplier of amino acids, proteins and vitamins [113].

Lactic acid fermentation is a process where the pyruvate, the product of the glycolysis, is reduced by lactate dehydrogenase with NADH to lactate or other products. In accordance with the metabolic pathways they use (Embden-Meyerhof or phosphoketolase pathway) and the resulting end-products, they are divided into two groups homofermentative or heterofermentative (Fig. 9) [114].

In terms of homofermentative bacteria (e.g. *Lactococcus lactis*, *Streptococcus salivarius*, *Lactobacillus acidophilus*), 2 mol of ATP and 2 mol of pyruvate are yielded from each molecule of glucose via the Embden-Meyerhof pathway. Using lactate dehydrogenase, pyruvate is reduced to the exclusive end-product, lactate. The second group includes heterofermentative lactic acid bacteria (e.g. *Lactobacillus fermentum*, *Lactobacillus brevis*, *Leuconostoc mesenteroides*). Several products are produced in the heterofermentative fermentation. Primarily, it is lactic acid, ethanol, acetic acid and carbon dioxide. Only one mole of ATP is yielded from 1 mol of saccharide [115,116].

Swedish pharmaceutical chemist Carl Wilhelm Scheele described lactic acid for the first time in 1780. Lactic acid was isolated from sour milk and was considered a milk component. Louis Pasteur discovered in 1857 that lactic acid is the metabolite generated during the fermentation process by certain microorganisms.

Lactic acid can be produced by microbial fermentation or chemical synthesis. In the early 1960s, lactic acid was chemically synthesized for baking industry, since heat stable lactic acid was necessary in industrial production [117].

Lactic acid can be also produced by other microorganisms: *Bacillus* (*B. coagulans*), certain species of fungi (*Rhizopus microsporus*, *Rhizopus oryzae*) and genetically modified strains of *Escherichia coli* and *Saccharomyces cerevisiae*.

There are two lactic acid isomers: L(+)-lactic acid and D(-)-lactic acid (Fig. 10). Lactic is recognized as safe (GRAS) food additive. Though, only L(-) form is safe for the consumption.

Acidosis and decalcification can occur in the case of excessive D(+) ingestion [117]. Chemical synthesis (from petrochemical resources) can produce only racemic DL-lactic acid (mixture of both L and D isomers) and only microbial fermentation can produce pure L(+)- or D(-)-lactic acid [118].

Lactic acid bacteria can inhibit certain microorganisms due to its ability to penetrate the cytoplasmic membrane in undissociated form. This is resulting in diminished intracellular pH and at the same time disruption of the proton motive force transmembrane. Lactic acid change outer membrane permeability due to its ability to gain access to the periplasmic space of gram-negative bacteria (via the porins present in the outer membrane). This process is not considered bactericidal. The penetration of other compounds such as bacteriocins, antibiotics or lysozymes to the cell occur due to the outer membrane disruption. In this way cellular metabolism can be affected may result in cell death [120].

LAB are mainly used in the food industry in dairy products, meat, vegetables, sourdough, candies, beer, wine and other alcoholic beverages [121]. They are also important in food issues concerning food storage, food quality, and food safety. The benefit of LAB is that they are forming conditions not adequate for pathogenic microorganisms such as: low pH and oxidation-reduction potential, antimicrobial compounds production, or lack of nutrients due to competition [122].

Yoghurt is the most known lactic fermentation food product. *Streptococcus thermophilus* and *Lactobacillus delbrueckii* ssp. *bulgaricus* (thermophilic homofermentative bacteria) are in a symbiotic relationship in the yoghurt production process. *Lactobacillus* have exoproteases and peptidases that degrade proteins in milk to amino acids and peptides. *Streptococcus* then used these formed amino acids and peptides. Lactic acid, formic acid and carbon dioxide are produced by streptococcus, pH is decreased and it supports *Lactobacillus* growth [123]. Rice wine, called sake, is also produced by microorganismal cooperation. *Aspergillus oryzae*, lactic acid bacteria (*Lactobacillus sakei* and *Leuconostoc mesenteroides*) and *Saccharomyces cerevisiae* are the main microorganisms in sake production [124]. Sour cabbage is produced by *Leuconostoc mesenteroides*, *Lactobacillus plantarum*, *Lactobacillus brevis*, *Pediococcus* and *Enterococcus* [125,126]. *Pediococcus* spp. and *Lactobacillus* spp. are producing authentic organoleptic properties of the unique and spontaneously fermented beer Lambik (produced by river

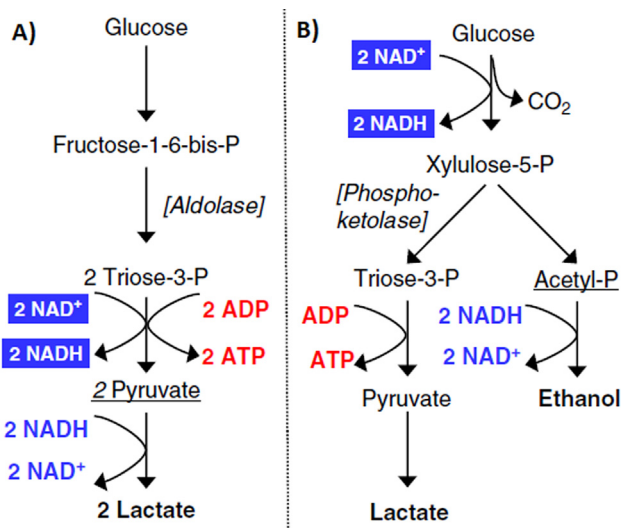


Fig. 9. Homofermentative metabolism of hexoses via the Embden-Meyerhof pathway (A) and heterofermentative metabolism of hexoses via the phosphoketolase pathway (B) [115]

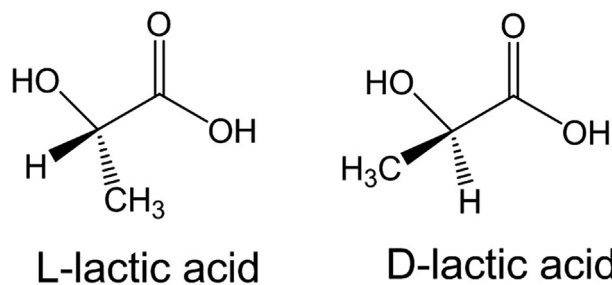


Fig. 10. Stereoisomers of lactic acid: L(+) and D(-) lactic acid [119].

Senne in Belgium) [127]. Lactic acid bacteria (*Lactobacillus*, *Leuconostoc*, *Pediococcus* and *Oeonococcus*) and yeasts naturally occur on the surface of grapes and also on must during the wine making process [128]. Silage process in agricultural industry use usually following microorganisms: *Enterococcus*, *Lactococcus*, *Pediococcus* and *Lactobacillus buchneri* [129].

LAB are also used in medicine. Probiotics have been used since the ancient times. Today, probiotics can be also found in the form of tablets, powders or beverages [130].

The scientist Ilya Mechnikov was the first person that emphasized the importance of probiotics for human health. He was

awarded with the Nobel Prize for Medicine together with Paul Ehrlich for their work in the field of immunity [110]. The most common probiotic microorganisms that possess health benefits for human health are listed in Table 3.

These are requirements that lactic acid bacteria can serve as probiotic: probiotic has to stay viable through the self-life of food commodity; they have to demonstrate a favorable effect, to resist the hard condition during the transport through the gastrointestinal tract; to adhere to the colonic epithelial cell and colonize the intestinal lumen; to produce antimicrobial substances; to be non-pathogenic and non-toxic to the host; and be associated with health benefits and intestinal microbiome stabilization [131].

Certain specific probiotic strains showed positive effects on the intestine, which might be useful for the prevention of bacterial translocation and gut infections caused by bacteria. As it is shown in the Fig. 11, direct probiotic effects include stimulation of preferred microorganisms, elimination of potentially pathogenic microorganisms by competitive growth and antimicrobial compound secretion, competitive blocking of adhesion of undesired microorganisms, and regulation of intestinal mucus production. Some strains also show ability to specifically stimulate the innate and systemic immune system.

Probiotic bacteria are able to modulate the human dendritic cell phenotype and function, influence the host immune system by pro-inflammatory cytokines reduction and anti-inflammatory cytokines induction, macrophages activation, or increase systemic and mucosal immunoglobulin A responses [110,132,133].

Table 3
The most commonly used lactic acid bacteria species in probiotic preparations by Parvez et al. (2006) [131].

<i>Lactobacillus</i>	<i>Bifidobacterium</i>	<i>Enterococcus</i>	<i>Streptococcus</i>
<i>L. acidophilus</i>	<i>B. bifidum</i>	<i>E. faecalis</i>	<i>S. cremoris</i>
<i>L. casei</i>	<i>B. adolescentis</i>	<i>E. faecium</i>	<i>S. salivarius</i>
<i>L. delbrueckii</i> ssp. bulgaricus	<i>B. animalis</i>		<i>S.</i>
<i>L. cellobiosus</i>	<i>B. infantis</i>		<i>diacetylactis</i>
<i>L. curvatus</i>	<i>B. thermophilum</i>		<i>S. intermedius</i>
<i>L. fermentum</i>	<i>B. longum</i>		
<i>L. lactis</i>			
<i>L. plantarum</i>			
<i>L. reuteri</i>			
<i>L. brevis</i>			

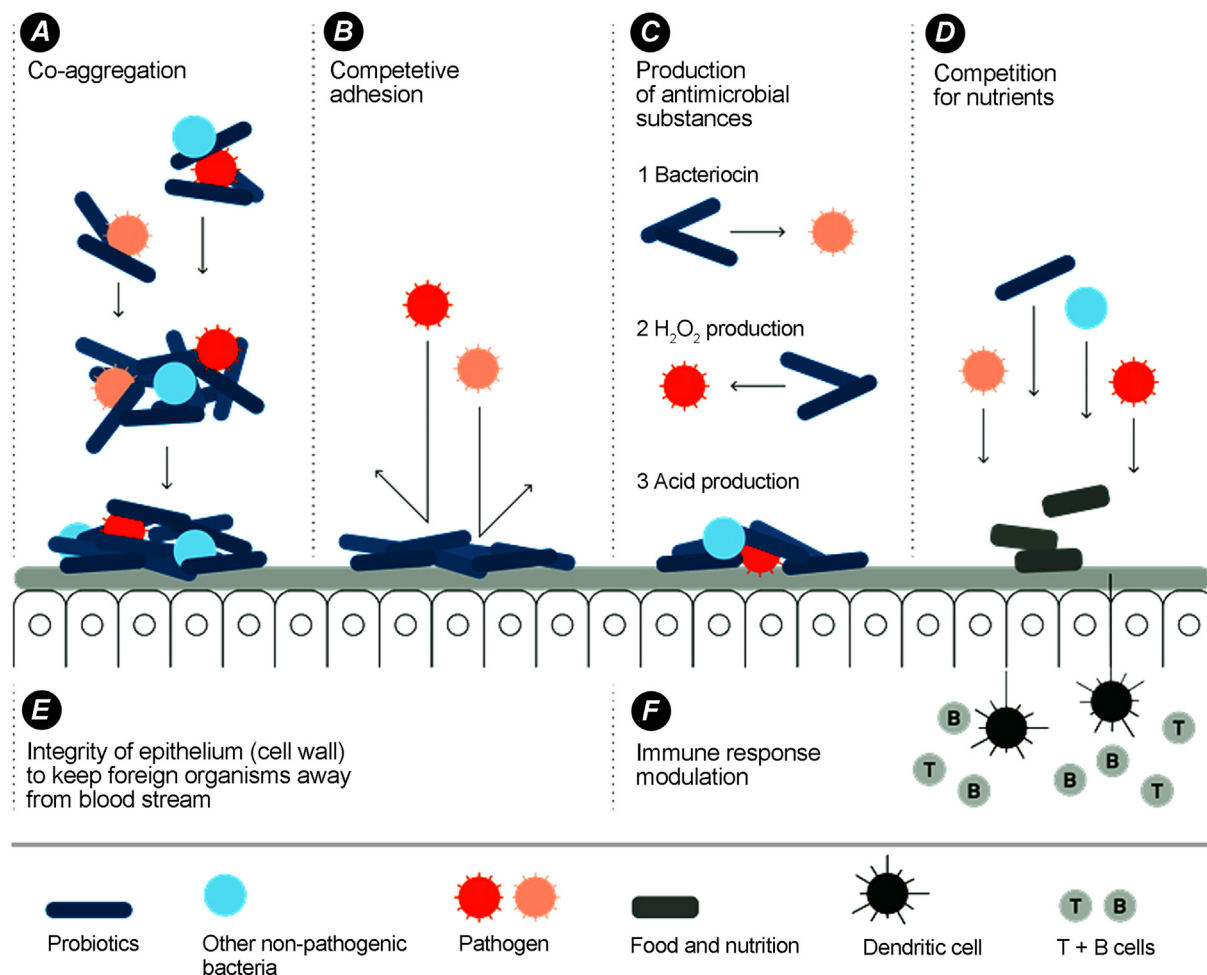


Fig. 11. Effects of probiotic bacteria on the host and their interaction with potential pathogens (adopted from: <http://bifodan.com/probiotic>. Online [2019–03–04]. Edited).

Another crucial role of LAB is associated with the vitamins production as the human body is not capable to synthesize any vitamins. LAB become to be key organisms in the production of vitamin B₁₂. This beneficial compound which has a crucial role during the process of DNA synthesis is produced only by certain bacteria, include LAB. Animals, plants or fungi are unable to synthesize vitamin B₁₂. Other vitamin involved in host metabolic processes such as DNA repair and synthesis, is folate, whose main producers are species of *Bifidobacterium* genus. Vitamin K, riboflavin, biotin, nicotinic acid, pantothenic acid, pyridoxine and thiamine are further vitamins, which are known to be produced by intestinal microorganisms in humans [24].

Various enzymes are released into the intestinal environment by lactic acid bacteria, resulting in synergistic impacts on digestion, malabsorption symptom reduction, and lactic acid production, leading to the decrease of the intestinal pH and so inhibition of invasive pathogens. Due to the bacterial enzymatic hydrolysis, bioavailability of protein and fat may be enhanced. This process can lead to higher production of free amino acids. The short chain fatty acids (SCFA) released into the intestinal environment as the end-product of fermentation, when absorbed, contribute to the available energy of the host and can increase the protection against pathological changes in the colonic mucosa. Certain SCFA concentration may also help to keep a suitable pH in the colonic lumen. This is crucial in the expression of many bacterial enzymes as well as in the carcinogen metabolism in the gut [131,134].

Meta-analysis: SRB versus IBD prevalence and probiotic treatment against UC

The studies included in Fig. 12 are showing the relationship between SRB occurrence and IBD prevalence. The occurrence of SRB in feces samples was predominant in IBD patients, but in the colon and ileum samples, SRB was more likely to occur in healthy patients [3,23,135–137]. The finding can be explained by previous results indicating SRB inhibition in an environment with hydrogen sulfide concentrations over 4 mM. It is important to be emphasized that hydrogen sulfide in the colon and ileum is produced by SRB themselves [5]. Otherwise, all studies except Coutinho et al. (2017) [13], found a significant (p < 0.05) difference between SRB occurrence in healthy people and patients with developed IBD. However, the diamond, which summarizes all studies, indicates the occurrence of SRB mainly in persons with IBD and since it does not touch the zero effect line, a significant (p < 0.05) difference was observed too.

Forest plot of studies, including treatment of patients with ulcerative colitis with probiotics are shown in Fig. 13. The studies were conducted in the way that the group was always divided into a placebo dosing control group and a probiotics group. It can be seen from the comparative studies that most of them touch the zero effect line and therefore have no significant difference except for studies by Ishikawa et al. (2003) [138], Miele et al. (2009), and Sood et al. (2009) [139], where a significant (p < 0.05) difference was noted.

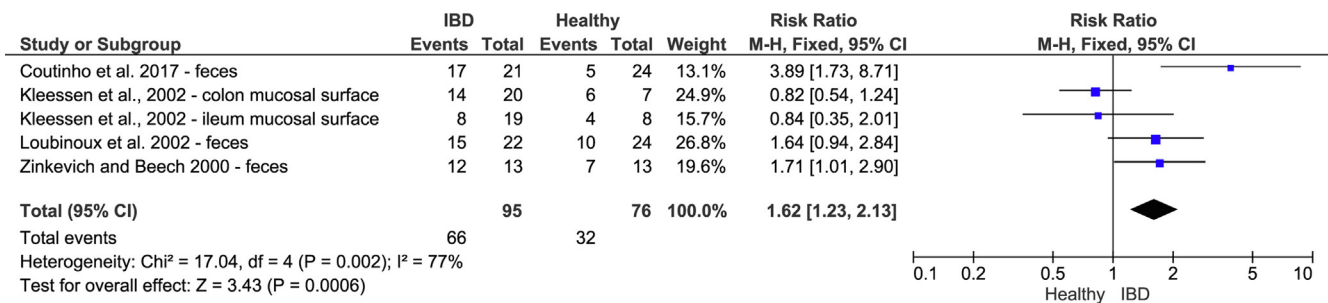


Fig. 12. Forest plot of the relationship between SRB presence and IBD prevalence.

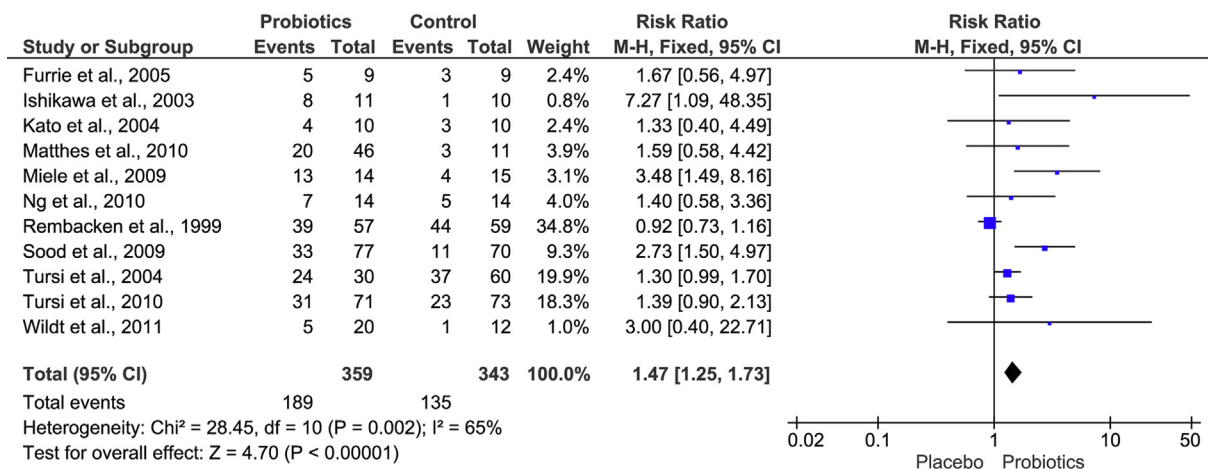


Fig. 13. Forest plot of probiotics treatment affection against UC [140–142]

All studies except the study by Remabcken et al.(1999) [21], show that the use of probiotics has an effect on the course of UC and the symptoms of the disease have been reduced during use. A diamond that summarizes all the studies indicates that the administration of probiotics to patients with UC positively affects the symptoms of the disease.

Conclusions and future perspectives

The systematic review provided important information about the human intestinal microbiome and the role of hydrogen sulfide produced by SRB. The importance can be overviewed by the fact that sulfate-reducing and lactic acid bacteria were described and characterized. The number of studies included in the review (over 140) is indicating the relevance of the review. Sulfate-reducing bacteria play an important role in the development of IBD; they are affecting the environment, same as the food chain due to the mercury methylation. Probiotic properties of lactic acid bacteria are affecting positively gut microbiota and serve as inhibitors against the development of IBD. This was confirmed by conducting meta-analysis that indicated lesser occurrences of IBD within the group of individuals that were receiving probiotics. Oppositely, higher SRB occurrence, according to conducted meta-analysis, is connected with higher IBD prevalence.

The conducted systematic review unambiguously emphasized the importance of gut microbiota for IBD development. Though, lack of studies, especially studies concerning SRB occurrence, can be misleading factor. Certainly, future studies that will have on the disposition more obtained results will lead to more corner stone conclusions in the similar systematic reviews.

Compliance with ethics requirements

This article does not contain any studies with human or animal subjects.

Declaration of Competing Interest

The authors have declared no conflict of interest.

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Author contribution to study

Dani Dordević, Simona Jančíková, Monika Vítězová, and Ivan Kuhkevych, wrote the article. All authors contributed to the conception, design and critically revised the manuscript.

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