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Chemolithotroph Bacteria: From Biology to Application in Medical Sciences

Elham Kazemi[1], Saiedeh Razi Soofiyani[2,3], Hossein Ahangari[4], Shirin Eyvazi[5], Mohammad Saeid Hejazi[1,3], Vahideh Tarhriz[3*]

Abstract
Chemolithotrophs are specific bacteria that utilize inorganic compounds as their energy source. These bacteria as the main source of organic molecules have more advantages in various sciences. Unlike phototrophic and organotrophic bacteria which generate their energy via the fascination of sunlight or oxidation of complex organic molecules, chemolithotrophic bacteria can exploit unconventional sources of energy, including various industrial wastes. Therefore, chemolithotroph bacteria play a key role in the remediation of micropollutants such as synthetic hormones, pharmaceutical residues, and sanitary wastes. In addition, secondary metabolites including organic acids, enzymes, and antibiotics derived from these bacteria can be used as pharmaceutical compounds. It seems that the discovery and study of the novel chemolithotrophic bacteria and investigation of their features can be helpful in medical and pharmaceutical sciences. Accordingly, it was attempted to present a comprehensive review on chemolithotrophic microbes, their energy sources, and their applications.
Keywords: Chemolithotroph bacteria, Secondary metabolites, Enzymes, Medical sciences

Introduction

Chemolithotrophic bacteria with the ability to use inorganic sources were discovered by Winogrсобытий, one of the modern microbiology pioneers, in late 1880 (1). The *litho* is a word with a Greek root meaning stone, thus this group of bacteria is called stone eaters (2). Chemolithotrophy is defined as the oxidation of the inorganic substance for cell biosynthesis (3). The main characteristic of chemolithotrophic microorganisms is the ability to grow in an unfavorable environment, and these microorganisms are widespread in archaea and bacteria domains (4). Chemolithotrophic bacteria use inorganic compounds such as elemental sulfur, ammonia, and iron (II) as an electron donor and a source of energy for their growth and maintenance. These bacteria are classified into four main groups based on their electron donors and the carbon source (1,5). The first group is obligate chemolithotroph which uses only inorganic compounds as an energy source and carbon dioxide (CO_2) as a carbon source and cannot grow in organic media (6). *Thiomicrospira* and its several species are examples of obligate chemolithotroph bacteria (7). The second group is the facultative chemolithotroph or mixotroph, which can use both organic and inorganic compounds as an energy source and obtain carbon from CO_2 or other organic carbon sources. Several species of thiobacilli, *Thiosphaera pantotropha*, and *Paracoccus denitrificans* belong to the facultative chemolithotroph group (8). The third group is chemolithoheterotrophs, which oxidize inorganic compounds to generate energy although they are unable to fix CO_2. Some species of *Thiobacillus* and *Beggiatoa* belong to this group (9). The fourth group is chemoorganoheterotrophs, which oxidize inorganic compounds while they obtain no energy from this reaction. *Thiobacterium* and *Thiothrix* are included in this group (10). This review study summarizes the details of chemolithotrophical bacteria and their ability to use various energy sources, especially industrial wastes. Moreover, the study focuses on useful compounds, which are produced by chemolithotrophic bacteria and their applications in medical and pharmaceutical industries and therapeutic applications.

Obligate Chemolithotroph Bacteria

Obligate chemolithotroph bacteria obtain their energy from the oxidation of chemical inorganic elements such as sulfur or the reduction of elements such as ammonia, nitrite, iron, and ferrous iron. The stored energy in the chemical bonds of inorganic compounds is released during oxidation. The bacteria consume the obtained energy in addition to the CO_2 to make sugar and carbohydrate. They live in extreme conditions of pH, temperature, and

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[1]Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran. [2]Sina Educational, Research, and Treatment Center, Tabriz University of Medical Sciences, Tabriz, Iran. [3]Molecular Medicine Research Center, Biomedicine Institute, Tabriz University of Medical Sciences, Tabriz, Iran. [4]Department of Food Science and Technology, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran. [5]Department of Biotechnology, School of Advanced Technologies in Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
*Corresponding Author: Vahideh Tarhriz, Tel: +98(41) 33372256, Mobile: +98(914) 2575057, Email: t.tarhriz@yahoo.com

pressure similar to deep-sea vents in the ocean (11, 12). Low amounts of organic compounds such as sugar and amino acid inhibit the growth of obligate chemolithotroph completely or incompletely (13). Chemolithotrophs are more susceptible to inhibitors compared to heterotrophic bacteria. Definitely, the inhibitor concentration is different for each group of organisms. For example, the growth of *Thiobacillus thiooxidans* is inhibited by acetate and malate with a 0.1 Mm concentration while these organic compounds could inhibit *Thiobacillus ferrooxidans* growth with 10 Mm concentrations (14). Valine has an inhibitory effect on *Escherichia coli* K12 at a concentration of 4×10^{-5} Mm while it has an inhibitory effect on *Thiobacillus thioparus* at a concentration of 10^{-3} Mm (15). Evidence shows that some organic compounds, apart from the inhibitory effect, trigger the growth of other strains (16). Moreover, the inhibitory effect of organic compounds depends on the media and pH. For example, pyruvate with 10^{-3} M concentration inhibits the growth of *Thiobacillus thiooxidans* at the pH of 2-5 while it has no significant effect at pH 7. The toxicity degree of organic compounds on obligate chemolithotrophs relies on the electronegativity and the chain length of the compounds (16). Long-chain organic acids could be effective on the dissolving of the cellular envelope and releasing of cell components including DNA, RNA, and proteins (17).

Facultative Chemolithotroph Bacteria

Facultative chemolithotroph or mixotroph bacteria use inorganic and organic compounds as an energy source. Meanwhile, they use either CO_2 or organic carbon as the carbon source, implying that they have the ability to grow under heterotrophic and autotrophic conditions (18,19). Recent studies have shown that some groups of facultative chemolithotroph bacteria such as *Chlorella vulgaris* have more biomass and lipid productivities in heterotrophic conditions compared with autotrophic conditions (20, 21). The strain grows in a medium supplemented with carbohydrates, proteins, organic acid, and alcohol and under highly strong organic compound limitations. It could switch from chemoorgano-heterotrophic to chemolitho-heterotrophic metabolism and use molecular hydrogen as an energy source (22).

Sulfur-oxidizing Bacteria (SOBs)

Sulfur-oxidizing chemolithotrophs bacteria are found in environments which are rich in inorganic sulfur elements such as sulfide (HS^{-}), elemental sulfur (S^0), thiosulfate ($HS_2O_3^{2-}$), and sulfite (HSO_3^{2}). Sulfur–oxidizing chemolithotrophic bacteria are categorized in two types: photosynthetic SOBs and non-photosynthetic SOBs according to their sun light requirements. Photosynthetic SOBs are photo-pigment producers, and color bacteria generated in exposing to the light and non-photosynthetic SOBs are generally called colorless bacteria which are aerobic or facultative anaerobic (18). These bacterial strains commonly use oxygen as the final acceptor of electrons (Figure 1). In addition, some SOB strains use nitrate or nitrite as the final electron acceptors and can grow under anaerobic conditions (Figure 2). In this regard, Liang et al isolated a SOB that uses thiocyanate and thiosulfate as electron donors and nitrate as an electron acceptor (23). According to the pH range and the temperature of the living environment, SOBs are classified into archaebacterial and eubacteria types (17). SOB can live in environments with a wide pH range, and most known isolates are active at a neutral pH range but some of them such as *Sulfolobus*, *Acidianus infernus*, and *Sulfurococous* can grow at low pH values. On the other hand, *Thioalkalimicrobium* and *Thioalkalivibrio* can grow at pH ranges above 7.5 (24-26). Further, SOBs are able to grow in environments with temperature ranging

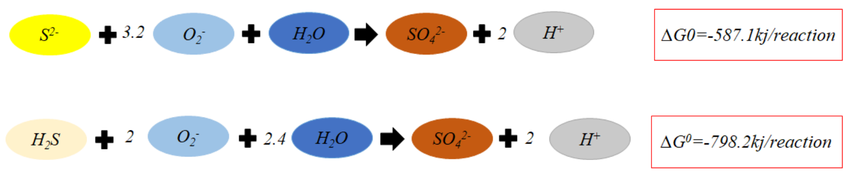

Figure 1. Photosynthetic Reactions and Final Products of Sulfur Oxidizing Bacteria Strains. Note. SOB: Sulfur-oxidizing bacteria.

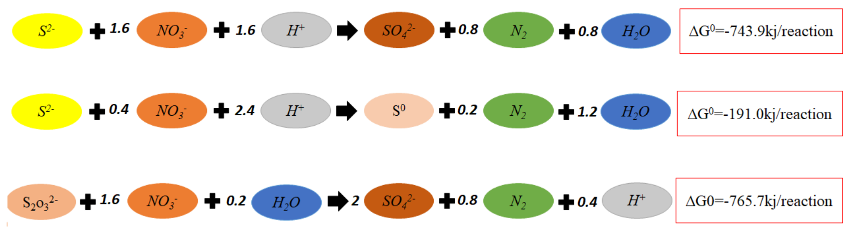

Figure 2. Anaerobic Reactions and Final Products of SOB Strains. Note. SOB: Sulfur-oxidizing bacteria.

Table 1. Growth Conditions of Some Chemolithotrophic SOB Strains

Microorganism	pH	Temperature (°C)
Acidithiobacillus thiooxidans	0.5-5.5	10-37
Acidithiobacillus ferrooxidans	1.3-4.5	10-37
Thiobacillus thioparus	4.5-7.8	28
Thiomicrospira denitrificans	7.0	22
Thiobacillus denitrificans	6.8-7.4	28-32
Thermothrix thiopara	6.0-8.5	73
Thermothrix azorensis	6.0-8.5	76-78

Note. SOB: Sulfur-oxidizing bacteria.

from 4°C to 95°C (20-22, 27). Table 1 summarizes the pH and temperature conditions of chemolithotrophic SOBs. Furthermore, SOBs were isolated from the soda lakes of different places with a pH value in the range of 9.0-11 and salt concentrations of 20-475 g/L. Sorokin et al used thiosulfate and nitrate as an electron donor and a nitrogen source, respectively, and isolated several strains of obligate lithoautotrophic SOB from different soda lakes with pH=10 in south-east Siberia (Russia) and Kenya (28). SOBs play an important role in the mineral cycle maintenance of nature. Among other chemolithotrophs, SOBs have a great chance to adapt to extreme conditions due to the high energy produced from thiosulfate oxidation to sulfate. Moreover, this group of bacteria has many applications in waste treatment, metals bioleaching, biomining, and agriculture (24). An increase in industrial wastewater, the amount of reduced sulfur compounds also increases in nature becoming a concern for public health (29). Sulfur compounds create environmental problems due to their toxicity and unpleasant odor (30). SOBs can oxidize reduced sulfur compounds in the wastewater to sulfur or sulfate which is discharged into the water (17). Bioleaching is the process through which insoluble metal sulfide changes to water-soluble metals by extremely SOB strains such as *Acidithiobacillus thiooxidans*, *Acidithiobacillus ferrooxidans*, and *Thiobacillus caldus*, and in some cases, by several archaea such as *Sulfolobus, Acidianus*, *Metallosphaera*, and *Sulfurisphaera* (31,32). Another capability of SOB is oxidizing inorganic sulfur compounds to sulfate. By the oxidation of inorganic compounds, the pH of the soil decreases and acidic conditions facilitates the solubilization of nutrients similar to phosphate for plants (33).

Ammonium-oxidizing Bacteria (AOBs)

According to Wang et al (31), these bacteria are able to use ammonia and CO_2 as energy and carbon sources, respectively (Figure 3). Some characteristics of these strains are presented in Table 2. In these types of reactions, the charge of the nitrogen atom changes from -3 to +3 when the ammonia is oxidized to nitrite (34). AOBs are responsible for one of the nitrification steps (35). Several factors such as pH, ammonia limitation, oxygen, and nitrite affect the metabolism and activity of AOBs. The oxidation causes the acidity of the environment by these bacteria as the best pH range (0.8-8.5) for the growth of AOBs such as *Nitrosomonas europaea* (36). In a pH level below 5.8, the ammonia oxidation is stopped completely because the balance between NH_3 and NH_4 completely disappears and the concentration of NH_3, which is the substrate for AOB, reduces in the acidic pH (37). Although AOB is sensitive to pH. For example, the *Nitrococcus* genus isolated from a Japanese tea field could grow in a pH range between 3.5 and 7 and optimally at a pH of 5 (38). Despite ammonia oxidization, chemolithotrophs and some heterotrophic bacteria can convert ammonia (39) although this is beyond the scope of this review. In recent decades, nitrogenous wastes have been increased due to the ranching and increasing development of nitrogen-producing industries. Therefore, biological ammonia oxidation is one of the critical factors for reducing environmental nitrogen. Ammonia oxidation is useful for waste treatment and area decontamination from toxic ammonia salts (40). Moreover, AOBs are applied in biofilter systems. They consume ammonia, CO_2, and other compounds that are available in the sewage and attach to the biofilter. They are considered as the dominant microorganism in the ammonia oxidation process for removing nitrogen-containing pollutants in various types of wastewater. However, the over-oxidation of ammonia altered the environmental pH, damaging the existing trees and plants (41). Despite these advantages, this process has several disadvantages. The ammonia oxidation causes a change in the environmental pH (42) and has a damaging effect on tree health in the forests (43).

Nitrite-oxidizing Bacteria (NOBs)

Winograsky first isolated new strains of NOBs in 1982 (44).

Table 2. Morphologic and Molecular Features of AOB Genera

Characterization	*Nitrosomonas*	*Nitrococcus*	*Nitrospira*
Phylogenetic group	Beta	Gamma	Beta
Morphologic	Short to long rods	Large cocci	Spiral
Motility	+	+	+
Gram-staining	-	-	-
DNA (mol G+C %)	45-53	49-50	54
Habitat	Soil, sewage, fresh water sediment, and marine	Fresh water and marine	Soil

Note. AOB: Ammonium-oxidizing bacteria.

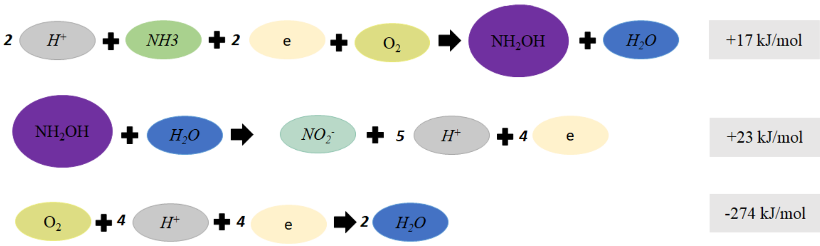

Figure 3. Reactions of AOB in O_2 Limitation and Exchanging of Physical Distribution to O2. Note. AOB: Ammonium-oxidizing bacteria.

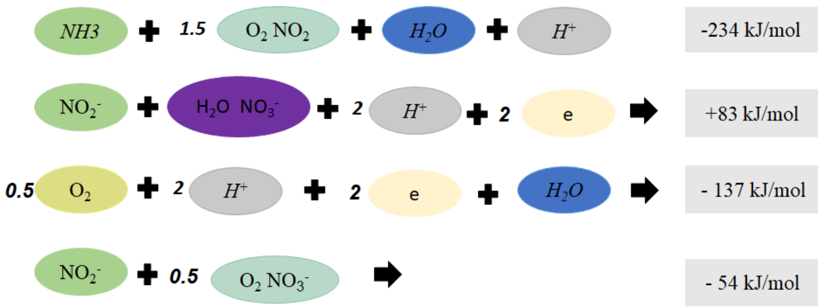

Figure 4. Converting Ammonia to Hydroxylamine by Ammonia mono Oxygenase Enzyme and Next Hydroxylamine Changing to NO_2^- by Hydroxylamine Reductase

Due to the severe growth of NOBs in laboratory conditions, the number of isolates from this group is extremely rare. Nitrite oxidizing bacteria carry out the second step of the nitrification process and use nitrite and CO_2 as energy and carbon sources, respectively (Figure 4). Generally, most NOBs are obligate lithoautotrophs although among them various groups (e.g., *Nitrobacter*) are heterotroph and use acetate (45) or pyruvate (46) as energy sources. The oxidation mechanism is different from autotrophic NOBs because they produce hydrogen peroxide by the oxidation of organic compounds (47). Although NOBs are often obligate aerobes, some of them use nitrate as an electron acceptor in oxygen inadequacy and grow in anaerobic environments such as the wastewater storage tank in the presence of sulfide (48). Different genera of NOBs are known, including *Nitrobacter*, *Nitrococcus*, *Nitrospira*, and *Nitrospina* that have various morphology and reproduction systems (49). *Nitrospina* and *Nitrococcus* are obligated chemolithotrophs while *Nitrobacter* and *Nitrospira* are facultative chemolithotrophs or heterotrophs. The difference between the four genera of nitrite-oxidizing bacteria is provided in Table 3 (50). Nitrite-oxidizing chemolithotroph can be successfully isolated from inorganic-rich media without any organic compounds. The growth of heterotrophs overcomes that of chemolithotroph bacteria in the presence of organic compounds.

Methane-oxidizing Bacteria (MOBs) or Methanotrophs

These microorganisms oxidize methane and few other C_1 compounds as an electron supporter for energy conservation and sole carbon sources (51). Methane monooxygenase is the key enzyme, which catalyzes the reaction of methane to methanol. CH_4 is produced in anaerobic sites by methanogenic archaea (e.g., muds, marshes, rumen, and mammalian guts). It is highly stable and methanotrophs readily use it as an electron donor for energy production. Methanotrophs reside in environments where methane is produced, including wetlands, soils, marshes, rice paddies, and even aquatic

Table 3. Morphologic and Environmental Differences of NOB Strains

Characteristic	*Nitrobacter*	*Nitrococcus*	*Nitrospina*	*Nitrospira*
Phylogenetic	α-proteobacter	γ-proteobacter	δ-proteobacter	Phylum Nitrospirae
Morphology	Short rods	Coccoid	Straight rods	Rods to spiral
Size (µm)	$0.5\text{-}0.9\times1^{-2}$	1.5-1.8	0.3-0.5 ×1.7-6.6	0.2-0.4× 0.9-2.2
Motility	+	+	-	-
DNA (mol G+C %)	59.4-62	61.2	57.7	50-56
Habitats	Fresh water, soda lake, soil, waste water, and oceans	Oceans	Oceans	Oceans

Note. NOB: Nitrite-oxidizing bacteria.

systems while not residing in maritime environments with low methane. All methanotrophs are aerobic and have methane monooxygenase enzymes (52). They utilize reduced carbon substrates containing no carbon-carbon bonds, including methane, methanol, and other methylated compounds. However, some non-methanogenic methylotrophs can use carbon-carbon bond compounds such as sugars, acids, and ethanol (53,54).

Ferrous-oxidation Bacteria (FOBs)

These groups of bacteria can live in acidic and neutrophilic, as well as aerobic and anaerobic conditions (55). Some *thiobacilli* such as *Acidithiobacillus ferrooxidans* oxidize ferrous to ferric to obtain energy (Figure 5). To oxidize the ferrous ion, it is necessary to be mixed with sulfate. In fact, sulfate is needed for ferrous oxidation (31). Hallberg et al isolated a novel iron-oxidizing bacteria (i.e., *Acidithiobacillus ferrivorans*) from metal-mine that was psychrotolerant and facultative anaerobe and could reduce iron. *Acidithiobacillus thiooxidans* as other FOBs can tolerate extreme acidity and high temperatures (growth occurs at up to 47 °C) in comparison with *Acidithiobacillus ferrooxidans. Thiobacillus prosperus* is one example of iron-oxidizing bacteria that tolerate 0.6 M sodium chloride whereas most Acidithiobacillia disappear in concentrations of 1% w/v salt (32).

Hydrogen-oxidizing Bacteria (HOBs)

HOBs can utilize gaseous hydrogen as an electron donor, oxygen as an electron acceptor for all energy productions, and carbon dioxide as a sole carbon source to grow as chemolithoautotrophs (56). All hydrogen-oxidizing bacteria contain one or more hydrogenase enzyme(s) that bind H_2 and use it to produce adenosine triphosphate. Most HOBs are facultative chemolithotrophs (34). For instance, *Aquifex pyrophilus* was found as a new phylum of the bacteria characterized by its hyperthermophilic and chemolithoautotrophic metabolism, yielding energy from the oxidation of molecular hydrogen (57). *Hydrogenobacter thermophiles* (58) and *Calderobacterium hydrogenophilum* (59) are the other genera of thermophilic bacteria which are introduced as HOBs. Scientists have shown interest in the potential of HOBs in biotechnological processes. HOB cells can synthesize valuable products such as polyhydroxyalkanoate (degradable plastics), protein, and plant growth promoters (60). For example, Volova et al showed that polyhydroxyalkanoate constitutes 85% of *Cupriavidus eutrophus* dry cell weight in the pure culture (61). Matassa et al reported that HOBs in the mixed culture can produce protein up to 71% of the dry cell weight (59). However, this issue requires further investigation.

Application of Chemolithotrophs Bacteria

Neutralization of Pharmaceutical Residues

During the last decades, biological contaminations such as wastewater from pharmaceutical industries, detergents, and disinfectants have caused increasing damage to the environment (62). Many medicinal derivatives have been found in wastewater, and surface and underground water with different concentrations (63,64). Therefore, there is an urgent need to neutralize pharmaceutical residues using different methods as neutralization. The neutralization depends on the properties of pharmaceutical products (65). Biodegradation by AOBs is the main way for removing pharmaceutical residues (66). The bacteria use mono-oxygenase enzymes to convert aliphatic and aromatic compounds such as phenol and hydrocarbons to less hazardous compounds (67). Luo et al studied the wastewater treatment and removal of pharmaceutical compounds processing using bacteria and concluded that removal efficiency (%) differs in various medicine categories because the physico-chemical properties of products are highly different. For example, removal efficiency in wastewater treatment for anti-inflammatories such as acetaminophen was 99% while it was 23% for tramadol and cefaclor, and 98% for cefaclor (68). However, there were no efficiencies for antibiotics groups such as spiramycin. Some studies (69,70) compared the rate of elimination in nitrification and non-nitrification methods and demonstrated that the elimination by the nitrification method was significantly higher compared to the non-nitrification method (Table 4). Layton et al showed that AOBs have a significant role in removing 17α-ethinylestradiol (EE2) from wastewater by nitrification. In an aerobic condition, NH_3 changes to NH_2OH by ammonia monooxygenase (AMO) and the hydroxylamine oxidoreductase enzyme oxidizes NH_2OH to NO_2^-. The activated site of AMO contains metal ions such as CU^+ which reacts with oxygen. Oxygen is able to convert CU^+-CU^+ to CU^{2+}-CU^{2+} and attaches as the O_2^- to the ions, thus the oxygenated AMO can convert pharmaceuticals residues to oxidized products (71), the related data are illustrated in Figure 6.

Production of Secondary Metabolites

Chemolithotroph bacteria have the ability to produce different enzymes, organic acids, and other secondary

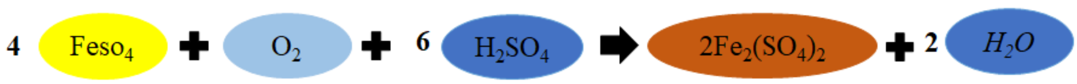

Figure 5. Second Step of the Nitrification Process of NOB and Nitrite Utilization as an Energy Source. *Note*. NOB: Nitrite-oxidizing bacteria.

Table 4. The Removal Efficiencies of Pharmaceutical Residues With and Without Nitrification During Wastewater Treatment Processes

Pharmaceutical Residues	With Nitrification (%)	Without Nitrification (%)
Iopromide	61	0
Trimethoprim	50	1
Naproxen	60	35
Gemfibrozil	41	9
Diclofenac	21	1
Bezafibrate	92	56
Ketoprofen	63	10
Fenoprofen	93.7	36
Indomethacin	89	14
Ketoprofen	90	38
Gemfibrozil	87	37
Naproxen	73	30
Diclofenac	76	25
Carbamazepine	38	12
Propyphenazone	39	5
Sulfamethoxazole	86	0

Source. (66,69,70).

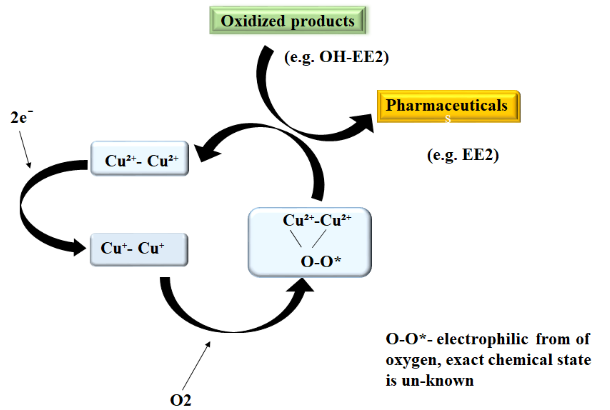

Figure 6. Oxidizing Reaction of Ferrous to Ferric in *Acidithiobacillus ferrooxidans* for Obtaining Energy.

metabolites which can be used in pharmaceutical and medical industries (72,73). It has been shown that chemolithotrophic iron- and sulfur-oxidizing bacteria including *Leptospirillum ferriphilum*, *Acidithiobacillus ferrooxidans*, and *Acidithiobacillus caldus* are the main sources in the production of glycolic acid which has a crucial role in the formulation of various skin-care products in pharmaceutical industries (74).

According to Sato and Kawaguti (75), organic acids are a key group among top platform chemicals that can be produced by microbial fermentation (Table 5). The microorganism-mediated production of the products is preferred over conventional methods due to high purity, selectivity, cost-effectiveness, and eco-friendly nature (76, 77). Organic acids are used in pharmaceutical, food, and chemical industries on a huge scale. For example, diverse salts of gluconic acid are used for the treatment of illnesses appeared by the deficiency of minerals such as zinc and iron (78) or acetic acid which is used as an effervescent in powders and tablets in combination with bicarbonates (79). Several chemolithotrophs, along with other bacteria are commonly used for the industrial production of different organic acids such as lactic, acetic, citric, succinic, and itaconic acids.

Antibiotics are the secondary metabolites of some microorganisms which help the immune system combat pathogenic bacteria (80). Antibiotics are grouped as cytotoxic or cytostatic based on their effects on other microorganisms, including the inhibition of the synthesis of proteins and the destruction of DNA, RNA, and the cell membrane (80,81). During the last decades, excessive usage of antibiotics has led to the emergence of resistant pathogenic bacteria that have many consequences (82). Two classifications of resistant bacterial strains are extremely drug- and multidrug-resistant bacterial pathogens. The US Center for Disease Control and Prevention has considered antibiotic resistance as one of the world's most important public health problems and estimated that thousands of people annually die because of infections by antibiotic-resistant bacteria (83). Therefore, most biological studies have focused on the discovery of new species of microorganism-producing safe antibiotics for humans. Chemolithotroph bacteria can be suitable candidates among the newer species of antibiotic producers and have doubled the benefits because of producing active compounds using energy sources such as wastewater released into the environment and thus the declination of pollutants such as sulfide and nitrite (24). It seems that future biotechnology studies should focus on identifying and using new strains of chemolithotroph such as *Thiobacillus* spp. which can produce new antibiotics with low-cost energy sources on an industrial scale.

Conclusions

The specific characterization of chemolithotrophs such as producing organic carbon from atmospheric carbon

Table 5. Several Chemolithotrophs Along With Other Bacteria Commonly Used for the Industrial Production of Different Organic Acids

Pharmaceutical	Producer Organism	Application	Reference
Riboflavin	*Eremothecium ashbyii*	Treatment of vitamin B2 deficiency disease	(84)
Glutamic acid	*Corynebacterium glutamicum*	MSG production, ammonia detoxification	(85)
Cobalamin	*Acidithiobacillus ferrooxidans*	Anti-anemia treatment	(86)
Vitamin C	*Agrobacterium tumefaciens*	Food, pharmaceutical industry	(48)
Pyridoxine	*Azotobacter vinelandii*	Synthesis of sphingomyelin deficiency disease	(87)
Methionine	*Rhodopseudomonas faecalis*	Copper poisoning treatment, angiogenesis	(88)

dioxide, utilizing iron (an electron acceptor or electron donor), reducing nitrogen gas to organic nitrogen (ammonium), and converting ammonium into nitrogen gas have caused enabled them for the bio-remediation of wastes and decreases in harmful agents in the environment, along with human and animal life. The isolation and identification of novel chemolithotrophic bacteria and the investigation of their secondary metabolics can be helpful for biotechnological researchers. In addition, the capability of chemolithotrophs in using low-cost energy sources, especially wastewater has double benefits in preferring them rather than other bacteria. Previous studies regarding chemolithotrophic bacteria are extremely limited and the knowledge of their metabolic mechanisms is poorly understood, therefore, comprehensive conclusions need more detailed studies on chemolithotrophs.

Authors' Contribution

The core idea of this study came from EK, VT and MSH. They also directed the other authors and analyzed the collected papers. SRS, HA, and SE wrote the manuscript in collaboration with MSH and VT. Final editing was done by VT.

Conflict of Interests

The authors declare that they have no direct or indirect conflict of interests.

Ethical Issues

Not applicable.

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