# Biodegradation of antibiotics: the balance between good and bad

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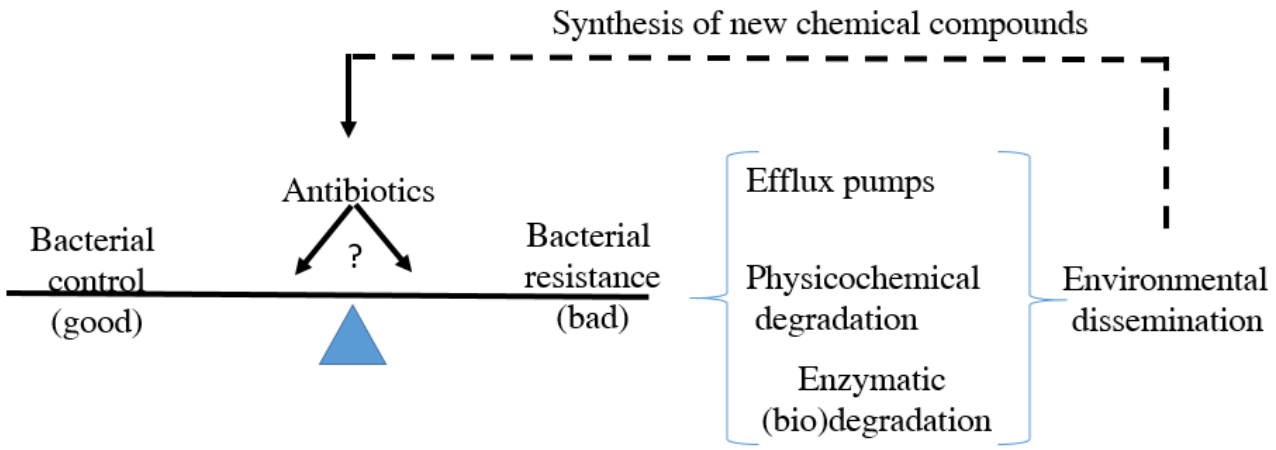
*The worldwide population rise corroborated with the raise of the health-care standards have generated an escalation of the antibiotic production and uncontrolled usage. The subsequent effects of this escalation have led to an increase of the antibiotic resistance rates, Romania is in the top of the EU countries regarding the antibiotic resistance rates, and to a continuous presence in the environment, including the aquatic environment. Unfortunately, the present design of the classical WWTPs is not optimized for the efficient removal of antibiotics since these compounds may have highly soluble and polar molecular structures. Instead, antibiotics removal using microorganisms could be an ecofriendly solution to this environmental issue, as long as their antibiotic degradation structures are not more toxic than the antibiotic itself.*
*In the present review, we focus on the environmental presence and biodegradation of the most commonly used antibiotics as well as on their biodegradation, based on bacterial model, monitored by mass-spectrometric methods.*

***Keywords:*** *biodegradation, antibiotics, bacteria, degradation pathway, antibiotic resistance*




The penicillin discovery by Fleming in 1928 was a turning point in the medicine and pharmacology fields, but the quest of finding chemical compounds with microbial growth inhibition activity started long time before.
In 1871 J. B. Sanderson and his coworkers reported a mold strain, *Penicillium*, with bacterial growth inhibition effect, but the actual effect was effectively proved by E. Duchesne in 1897. First reports on penicillin were in 1938, but soon after that, 1939-1940, S. Waksman and R. Dubos reported over 20 potential antibiotics. Since then there is a continuous race between antibiotic resistance and synthesis of new chemical compound with antibacterial effect.

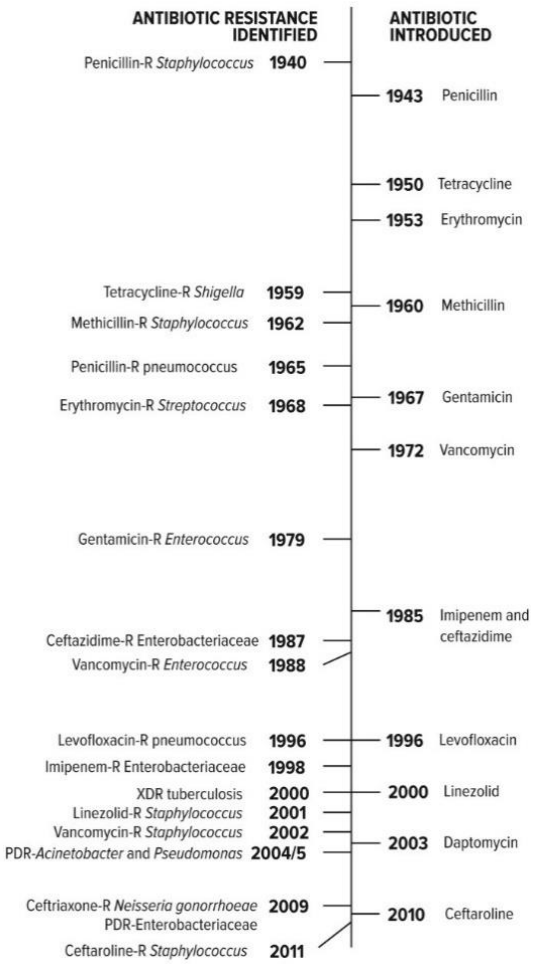



**Fig. 1.** Timeline of antibiotic resistance and new antibiotic synthesis [1]

At the present, a growing number of chemical compounds with more and more specific antimicrobial activity, antibiotics, have been continuously synthetized for human, animal and plants health. There are many classes of antibiotics regardless of their natural, synthetic and semi-synthetic origin [2] with a very well characterized antibacterial effect (Table I) [3] and subsequently there are largely used due to their benefic effects, up to 2,000,000 tons of antibiotics (AB) consumption per year, according to Centers for Disease Control and Prevention in 2015.

*Antibiotics structural characterization*

From a structural point of view antibiotics can be divided into several types of chemical structures. Logically, this classification is co-related with their mechanism of action (bactericidal, bacteriostatic, bacteriolytic) and their spectrum of activity (types of controlled bacteria). The most important classes of antibiotics are summarized in Table 1. A brief description of some of these classes of antibiotics is presented in the following paragraphs together with their structural characteristics which are given in Figure 2.

**Beta-lactams** are one of the most used classes of antibiotics containing a beta-lactam ring which consists of a 3-carbon and 1-nitrogen atom ring and a ketone group.

These antibiotics interfere with proteins essential for synthesis of bacterial cell wall [4]. Some of the most prescribed representatives are Penicillins (Penicillin G, Penicillin V, Oxacillin, Ampicillin, Amoxicillin), Cephalosporines, Monobactams (Aztreonam), and Carbapenems (Imipenem, Meropenem, Ertapenem).

**Macrolides** are large molecules containing a 14 to 16 membered macrolide ring (macrocyclic lactose ring). They inhibit protein synthesis by bacteria leading sometimes to cell death. Some of the most

important Erythromycin, Azithromycin and Clarithromycin [5].

**Tetracyclines** are antibiotics with 4 condensed hydrocarbon rings (6 carbon atoms). Tetracycline was discovered in 1945 by Benjamin Duggar from a soil bacterium of the genus *Streptomyces*. Tetracyclines may be obtained by biosynthesis (1st generation), semi-synthesis (2nd generation), or by chemical synthesis (3rd generation). Significant representatives of the 1st generation are Tetracycline, Chlortetracycline and Oxytetracycline, while for the 2nd generation drugs like Doxycycline, Lymecycline are important.

All tetracyclines target the ribosome from bacteria disrupting addition of amino acids to polypeptide chains during protein synthesis inside ribosome, preventing in this mode bacterial growth. Tetracyclines have a very broad spectrum of activity with bacteriostatic effect for aerobic and anaerobic bacteria both gram-positive and gram-negative. Over time, many bacteria have become resistant to Tetracyclines reducing in this mode their activity spectrum [6].

**Quinolones** interfere with bacteria DNA replication and transcription. These molecules contain condensed aromatic rings with a carboxylic acid group attached and in many cases a fluorine atom. Significant representatives of this class of antibiotics are Ciprofloxacin, Norfloxacin, Levofloxacin, Ofloxacin, Nalidixic acid and so on. Additional rings and different chemical moieties extend the spectrum of antimicrobial activity. Also, these structural modifications of the quinolones have improved bioavailability of the drugs increasing also activity spectrum and drug potency. Quinolones are prescribed for the treatment of urinary, respiratory tract and systemic infections caused by both gram-positive and gram-negative bacteria [7].

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**Table 1.** Commonly used classes of antibiotics

| Antibiotic class | Type | Target |
|---|---|---|
| Aminoglycosides | Bactericidal | Inhibit protein synthesis |
| Beta-Lactams | Bactericidal | Inhibit cell wall synthesis |
| Glycopeptides | Bactericidal | Inhibit cell wall synthesis |
| Lincosamides | Bactericidal | Inhibit protein synthesis |
| Macrolides | Bacteriostatic | Inhibit protein synthesis |
| Nitrofurans | Bactericidal | Inhibit nucleic acid synthesis |
| Amphenicols | Bacteriostatic | Inhibit protein synthesis |
| Phosphonates | Bacteriostatic | Inhibit cell wall synthesis |
| Polyether ionophores | Bacteriostatic | Disrupt cellular permeability |
| Quinolones and fluoroquinolones | Bactericidal | Inhibit DNA replication |
| Rifamycin | Bactericidal | Inhibit nucleic acid synthesis |
| Sulfonamides | Bacteriostatic | Inhibit folic acid synthesis |
| Tetracyclines | Bacteriostatic | Inhibit protein synthesis |

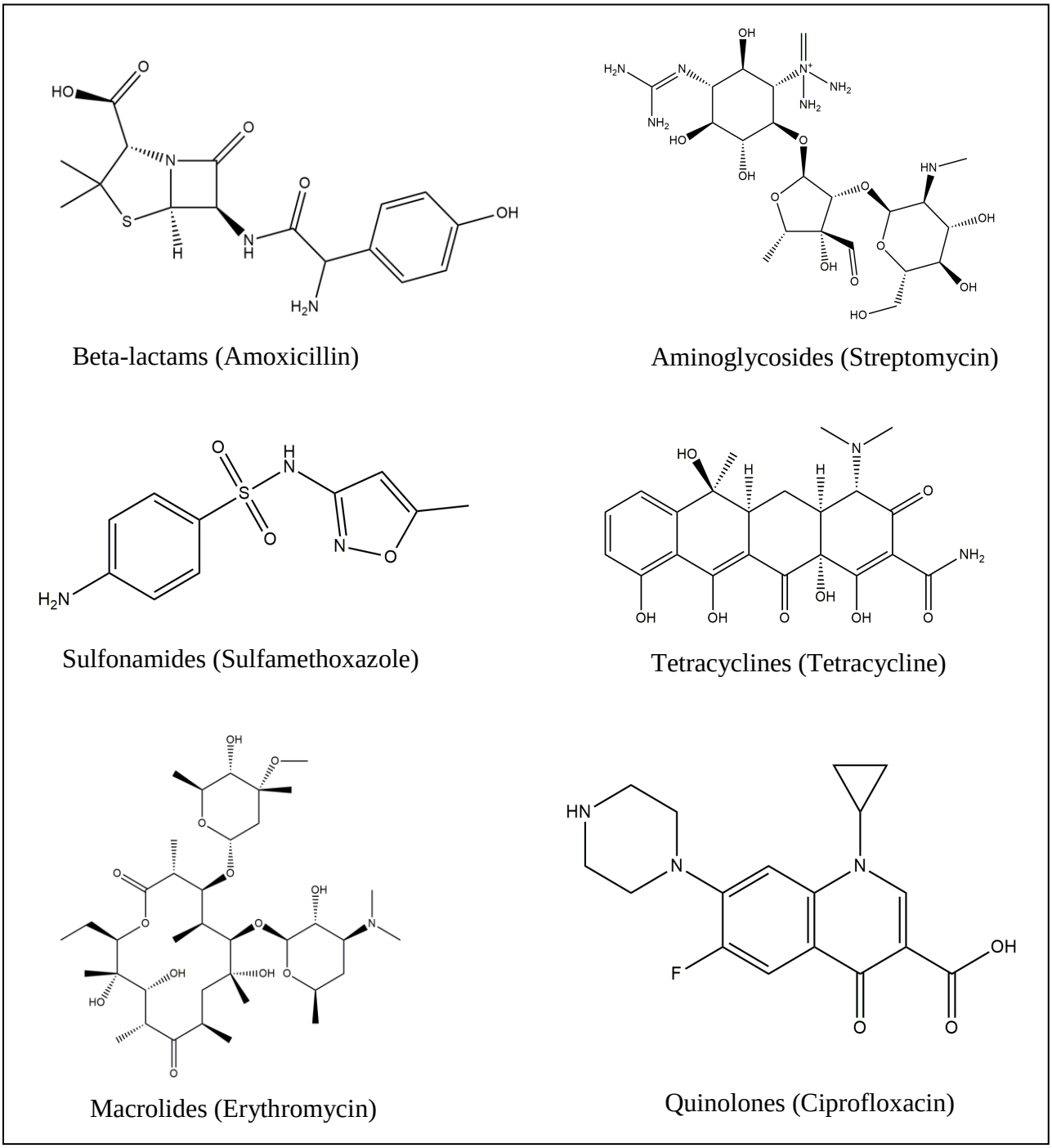


**Fig. 2.** Structural representation of some of the most important classes of antibiotics.

**Aminoglycosides** are another important class of antibiotics which act by inhibiting the synthesis of proteins by bacteria leading generally to cell death [8]. Important representatives of aminoglycosides are Streptomycin, Neomycin, Kanamycin, Tobramycin and Gentamycin.

Their structure is usually made of 3-amino sugar (glycoside) rings which are linked together by glyosidic bonds. Aminoglycosides are active against aerobic gram-negative bacteria such as Pseudomonas, Acinetobacter and Enterobacter. Aminoglycosides are generally used to treat complicated intra-abdominal, urinary tract infections, and respiratory tract infections.

Another important group of antibiotics is represented by **Sulfonamides** which were the first class of commercially available antibiotics. These drugs inhibit both gram-positive and gram-negative bacteria such as

*E. coli*, *Salmonella*, *Chlamydia trachomatis* [9]. Main members of this class are: Sulfamethoxazole, Sulfadiazine, Sulfamethazine, Sulfadimethoxine, Sulfanilamide, Sulfoxazole, etc. From structural point of view, Sulfonamides have a common sulfonamide group grafted on different hydrocarbon structures (aliphatic or aromatic in nature). These antibiotics are given to treat urinary tract infections, septicemia, meningitis and so on.

**Antibiotic resistance genes acquisition and dissemination**

In addition to the human consumption of antibiotics, they are widely used in agriculture enhancing the livestock growth, bee-keeping, and fish farming [10]. Unfortunately, the antibiotic low degree of metabolization and its high environmental reminiscence combined with a high dissipation property has become a major threat to public health by compromising bacterial infection treatments. In spite of banning the usage of antibiotics in agriculture and livestock industries in EU from 2006, a large number of world population from China and India keep using them in agriculture and livestock industries [11].

Moreover, the excessive use of antibiotics in human and animal medicine [12] over amplify the antibiotic presence in the environment and more dangerously this has triggered the selection of antibiotic resistant bacteria (ARB) and their antibiotic resistance genes (ARGs) [13]. The use of antibiotics in hospitals did not mean that humans are their only target and, unfortunately, the antibiotics have had also an impact on others not-targeted organisms [14, 15] inducing resistance in all organisms after a longtime exposure [16]. Significant quantities (30–90%) of consumed antibiotics may be eliminated unchanged or as active metabolites through urinary and/or fecal excretion [17, 18]. In spite of the fact, that hospitals from European countries discharge only 5–20% pharmaceuticals, the antibodies concentrations in hospital effluents have been 100-fold higher than those of municipal effluents [19, 20]. The antibiotics could be detected in municipal sewage water, WWTP biosolids, effluents, soil, surface waters, groundwaters, sediments, biota and drinking water [21, 22, 23].

In all those areas, especially wastewaters and WWTP, there have been a mixt of antibiotic chemical structures as well as an exchange between human and environmental bacteria could generate environmental stress and antibiotic resistance [24, 25]. The antibiotic resistance has been accentuated by the persistence of low molecular weight (< 1000 D) antibiotics which are very soluble in water bodies such as b-lactams, aminoglycosides, lincosamides, macrolides, nitrofurans, amphenicols, quinolones, fluoroquinolones, rifamycins, sulfonamides and tetracyclines [15, 26]. The wastewater treatment has not been sufficient to completely eliminate pharmaceutical compounds, including ABs [17] and the lower remaining amount released to the environment boost the antibiotic resistance process.

Long-term exposure at lower concentration of antibiotics than their minimal inhibitory concentration (MIC) increased the bacterial DNA mutation rate of genes, the horizontal gene transfer (HGT) in the bacterial population and modulate genes expression, altogether inducing an antibiotic resistance [27, 28, 29] as well as further increasing the minimal inhibitory concentration (MIC) of antibiotics [30].

**Antibiotic resistance mechanisms**

The ARGs allowed (micro)organisms to develop resistance by avoiding a specific drug-target interaction such as DNA, RNA or protein, rejecting of antibiotics from the cell through efflux pump (Fig. 3a) and antibiotics degradation (Fig. 3b) by biotic and abiotic processes [3].

The functionality of ARGs is extended also to the survival fight between bacterian strains which naturally produce antibiotics to eliminate the competition for the same resources. The structural characteristics of cell walls (Gram positive vs Gram negative bacteria –extra outer membrane- or exopolysaccharide and extracellular DNA) as well as the bacterial aggregation in biofilms [31] prevent antibiotic to reach their targets increasing the level of resistance [32, 33]. Moreover, the biofilm is suitable environment for resistance genes acquisition and spreading among bacterial populations [34].

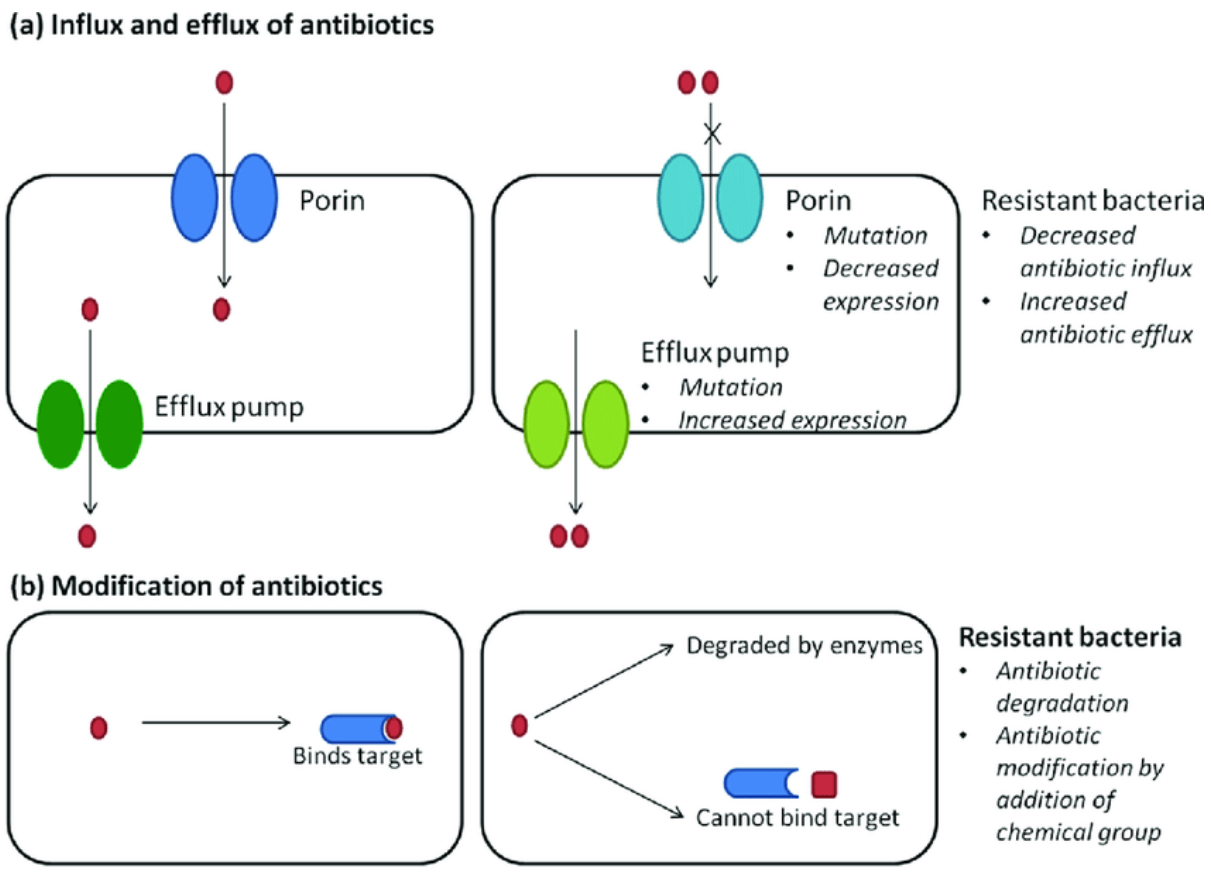


**Fig. 3.** Defense mechanisms [35]

*Efflux pumps*

One of the most efficient bacterial defense mechanisms relies on the efflux pump through which bacteria expel ingested chemical compounds, including the antibiotics (Fig. 3a). These bacterial efflux pumps may expel specific substrates or they may have a very wide specificity, transporting multiple substrates. Moreover, the bacterial efflux pump has a high mechanistic homology with the multiple drug resistance (MDR) mechanisms of Eukariotic cells. In this respect, a study showed that LmrA, an ATP-based ABC transporter, present in *Lactococcus lacis* is involved in antibiotic resistance mechanisms by pumping out amphiphilic compounds from inside the bacterium and it is homologue with P-glycoprotein, which is also an ATP-based ABC transporter involved in the resistance of tumor cells to chemotherapy [36]. Due to the high homology between bacterial LmrA and human P-glycoprotein, LmrA genes were inserted into fibroblast cells, which generated resistance effects comparable to P-glycoprotein. Also, P-glycoprotein-specific inhibitors retain their inhibitory properties on LmrA [37]. The fact that these genes of different origins are interchangeable shows that the mechanism of resistance induced by efflux pumps has been conserved from bacteria to humans.

**Physical-chemical degradation of antibiotics**

The abiotic degradation of antibiotics relies on adsorption, hydrolysis, photolysis, oxidation and reduction reactions [17, 38, 39]. The antibiotic susceptibility to abiotic degradation depends on their chemical structure and up to 70% of administered antibiotics could be found in the environment unchanged or degraded to different degradation products which in some cases present also antibiotic activity [40].

Some of these compounds may exert higher toxicity on the ecosystem than the antibiotics themselves [41]. The antibiotics degradation degree and rate depend on their chemical structure: in some cases, they are degraded by certain abiotic factors, and may be unaffected by others.

Tetracyclines have smaller structure than cephalexin and degrade faster by UV-light, and photolysis [42]. Overall tetracyclines, sulphonamides, tylosin, nitrofuran or (fluoro)quinolones antibiotics are sensitive to UV light, but fluoroquinolones are resistant to hydrolysis [43]. Oxygen and ozone are widely spread abiotic factors and they are involved in the sulfamethoxazole and oxytetracycline antibiotics degradation by oxidation [44, 45]. Metal ions such mercury, copper, zinc, cadmium, and cobalt are involved in beta-lactam antibiotics degradation, like Cephalosporin and Penicillin, by breakage of the β-lactam ring [46].

**Enzymatic degradation of antibiotics**

The enzymes play an important part in the mechanism of antibacterial resistance by modifying or degrading the antibiotics (Fig. 3b). Studies showed a correlation between ARG expression, antibiotic degrading enzyme production and antibiotic resistant bacteria. In addition, some studies point to the idea that ARGs involved in the expression of aminoglycoside-modifying and β-lactamase enzymes were present in the environment long before the use manmade antibiotics in a therapeutic scope [47, 48, 49] showed that β-lactamase family shared a common origin with enzymes involved in cell wall biosynthesis.

In spite of using the antibiotics and their presence in the environment, bacteria resistant to β-lactams are thriving and there are a constant presence in more and more countries [50, 51, 52].

The same emerging resistance pattern it is also observed for bacteria producing carbapenemase [53, 54, 55]. Unfortunately, bacteria producing carbapenemase, cephalosporinase or oxacillinase exchange their ARG among them or with other bacteria from the environment, subsequently spreading the resistance to antibiotics to other bacterial communities and other distant geographical areas [56, 57]. Fluoroquinolone class of antibiotics is one of the most prescribed group of antibiotics worldwide. They are used for treating infections generated by aerobic gram-positive and gram-negative bacteria.

Among fluoroquinolones, some of the most important representatives are Ciprofloxacin, Norfloxacin, Levofloxacin, Ofloxacin and others. The main mechanism of action is by inhibiting DNA replication. For example, Ciprofloxacin and Ofloxacin inhibit DNA topoisomerases of bacteria, affecting thus nucleic acid synthesis. In a biodegradability study [58] the authors presented several possible bacteria biodegradation pathways (LC-MS/MS identification) of Ciprofloxacin generated by a mixed culture of *Gammaproteobacteria*, *Bacteroidia*, and *Betaproteobacteria*. Authors identified several biodegradation products of Ciprofloxacin generated by deamination (C-N bond cleavage), hydroxylation, defluorination (C-F bond cleavage), dealkylation (C-C bond cleavage) reactions. The structural changes of Ciprofloxacin are promoted by bacteria enzymatic degradation. Approximately 47% of the Ciprofloxacin amount was biodegraded by bacteria after 7 days and more than 89% the antibiotic was dissipated after 28 days of incubation.

The Sulfonamide class of antibiotic drugs are another important group of antibiotics with high volume of consumption worldwide. Among its representatives, some of the most important are represented by Sulfamethoxazole (SMX), Sulfadiazine (SDZ), Sulfamethazine (SMZ), Sulfadimethoxine (SDM), Sulfanilamide (SAD) and others. In a comprehensive review, Chen et al., describe the recent advances in understanding Sulfonamide antibiotics biodegradation by microorganisms present in natural and engineered active sludge systems [9]. The authors describe biodegradation pathway of Sulfonamides which is mainly generated by hydroxylation and acetylation reactions at the aniline or the aminated heteroaromatic groups of the sulfonamide structure. Other chemical changes arise by C-N, C-S and C-C bond cleavage, along with oxidation. As with respect to the main bacterial population able to degrade these types of compounds, the authors report *Proteobacteria* and *Acidobacteria*, *Firmicutes* and *Bacteroidetes* for Sulfamethazine (SMZ) biodegradation [59]. In the case of (Sulfanilamide) SAD biodegradation was promoted by *Firmicutes*, *Bacteroidetes*, *Bacillus* and *Chryseobacterium* genus groups [60]. Concerning activated sludge bacteria species which are able to biodegrade many of the sulfonamide antibiotics, it is worthwhile to

mention *Rhodopirellula baltica*, *Methylibium petroleiphilum*, *Micrococcus luteus*, *Delftia acidovorans*, *Oligotropha carboxidovorans*, *Acinetobacter*, and *Pseudomonas* [61]. The biodegradation rate generated by some of these microorganisms is quite high and can reach even 100% in the case of Sulfamethoxazole.

## CONCLUSIONS

Antibiotics are chemical compounds of natural or chemical synthesis origin which exhibit a microorganisms killing or growth inhibition effects. They have a variable range of bacterial specificity effect from one group of bacterial strain to many groups of bacterial strains of Gram positive and Gram negative bacteria. The beneficial effect of using antibiotics have expanded to many applications from agriculture to livestock growth and human health.

The reverse of the medal consists in producing of more and more amounts of antibiotics which are not completely processed / biodegradable and subsequently large quantities of antibiotics will reach the environment.

Uncontrolled usage of antibiotics enhanced their pollution effect and more important enhancing antibiotic resistance features. In a natural way, bacteria have an innate or acquired resistance to the antibiotics, but the misusage of antibiotics enhances the antibiotic features.

A solution to prevent the full bacterial antibiotic resistance has been to continuously synthetize new chemical compounds which are obtained by changing or adding different chemical moieties. The new molecules exert the same or higher antimicrobial effect and are efficient concerning bacteria inhibition until the latter develop adaptation mechanisms. After that we could focus on the balance between good effects versus bad effects and their solution of producing new chemical structure with antibacterial effect.

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