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The Environmental Fate of Azithromycin: From Pharmacology, Resistance to Advanced Oxidative Degradation

Zhuoyun Xu

Guanghua Qidi Education, Shanghai, China
jolinxu1105@hotmail.com

Abstract. This work models the degradation of azithromycin in water using a Fenton-based process integrated with an artificial neural network and facilitated by particle swarm optimization. The best conditions for 99.9% removal efficiency were predicted, which would allow the characterization of five key degradative by-products. Antimicrobial activity was significantly reduced after only 4 hours post-treatment, evidenced by the total loss of activity. Therefore, this study supports that the optimization represents a thorough, pragmatic, and promising reassessment for the removal of persistent pharmaceutical contaminants from water.

Keywords: Azithromycin degradation, Antibiotic resistance, Fenton oxidation, Pharmacological mechanisms, Clinical applications

1. Introduction

Azithromycin (AZM), a common clinical antibiotic, has raised concerns about environmental persistence and probable toxicity. Degradation pathways of azithromycin in aquatic media are key elements in assessing the drug's environmental fate since conventional treatment and disposal methods, including adsorption, filtration, and ozonation, fail to remove most pharmaceutical residues. The advanced oxidation processes, with special attention to the Fenton oxidation, have emerged as one of the most promising methods in degrading persistent organic contaminants. This method also revealed that hydroxyl radicals are the main oxidizing agents responsible for the destruction of recalcitrant pollutants. In the present work, the artificial neural network integrated with particle swarm optimization was used for the development of azithromycin degradation. The work was carried out to assess the optimal degradation conditions and to evaluate the efficiency of azithromycin removal along with its by-products from aqueous solutions.

2. Pharmacological mechanism of action

Azithromycin belongs to the macrolide class of antibiotics. Its mechanism of action is to reversibly bind to the 50S subunit of bacterial ribosomes, inhibit peptidyl transferase activity, block protein synthesis, and thus inhibit bacterial growth and reproduction. More specifically, azithromycin binds

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to the 23S rRNA at position 2058 (Escherichia coli numbering), effectively blocking translocation of aminoacyl-tRNA from the A to the P site, leading to premature termination of protein synthesis and subsequent suppression of bacterial growth [1]. The result is effective inhibition of bacterial growth with little or no effect on human cells, thus displaying significant selective toxicity.

Besides anti-protein synthesis function, growing evidence supports that azithromycin has much broader antimicrobial actions-inhibiting bacterial adhesion, invasion, and toxin production; interfering with biofilm formation; and enhancing host immune responses. Several, such as azithromycin's broader antibacterial spectrum, may be one of the reasons. In vitro, aerobic Gram-positive and -negative pathogens pose great susceptibility to azithromycin, Streptococcus pneumoniae, Streptococcus pyogenes, and Staphylococcus aureus having very low MICs. Such broad-spectrum activity is practically of great value in empirical therapy, mainly during the initial phase of undiagnosed infections. Furthermore, atypical pathogens, such as Chlamydia, Mycoplasma, and Legionella, as well as intracellular bacteria such as Helicobacter pylori and Neisseria gonorrhoeae, are sensitive to azithromycin [2]. Thus, azithromycin is important in treating infections with atypical pathogens, such as atypical pneumonia and some sexually transmitted diseases.

However, it needs to be considered that azithromycin has relatively higher MICs and lower antimicrobial activity against certain anaerobic bacteria, including Peptostreptococcus and Bacteroides fragilis. On this account, one should be very prudent regarding the type of pathogen while prescribing azithromycin, and for anaerobic infections, alternative or adjunctive antibiotic therapies may be required. Beyond his classical inhibition of protein synthesis, the pharmacological profile of azithromycin includes many other mechanisms, such as inhibition of bacterial adhesion, invasion, toxin production, and biofilm formation, as well as the modulation of host immune functions. Such a broad variety of actions may be responsible for the clinical effectiveness of azithromycin and give several ways to its further development and improvement. The X-ray crystal structure of a bacterial ribosome–macrolide complex showed that the antimicrobial mechanism of azithromycin involves binding at the growing peptide in a trough of the 50S subunit, where it inhibits protein biosynthesis [3].

2.1. Anti-inflammatory effect

Azithromycin's anti-inflammatory effects are observed in immune and epithelial cells. Azithromycin activates immune and epithelial cells, modulating ERK1/2 signaling via the oxidative burst in neutrophil degranulation and phagocytosis [4]. There is subsequent secretion of AP-1, NF-kB, inflammatory cytokines, and mucins, which together contribute to most of azithromycin's anti-inflammatory effects. In macrophages, azithromycin inhibits pro-inflammatory cytokines induced by lipopolysaccharide through an AP-1 target, increases cell phagocytosis, strengthens lysosomes against oxidative stress, and promotes M2 macrophage polarization [5, 6]. It could also inhibit T cell activity via interfering with calcineurin signaling, mTOR, and NF-kB activation [7]. In vitro, azithromycin decreased mucus production and increased epithelial barrier thickness and decreased metallo activity after bacterial lipopolysaccharide challenge, thus reducing inflammatory signaling and cellular integrity loss, thus maintaining the epithelial barrier functional and integrity [8]. Other studies indicated that azithromycin protects against sulfur dioxide-induced airway epithelial injury and inflammatory responses [9].

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2.2. Epidemic regulatory effect

Azithromycin is widely believed to exhibit a variety of immune modulating effects closely related to its anti-inflammatory activity. For instance, in experimental models of Pseudomonas aeruginosa pulmonary infection and lipopolysaccharide-induced inflammation, azithromycin has been shown to diminish, among other things, macrophage inflammatory proteins, myeloperoxidase, TNF-α, and IL-1β, altered macrophage activity, hence [10]. Other macrolides, such as azithromycin, modulate immunity mainly by binding to and inhibiting calcineurin phosphatase in T cell activation. This inhibits eosinophils and other immune cell subpopulations, including basophils [11]. Azithromycin also inhibits p65 translocation, thus preventing its activation and that of the NF-kB downstream effector in lung epithelial cells. The overall consequence is reduced IL-8 production in these cells [12-14]. Furthermore, azithromycin has intracellular effects on MAPK in mammalian cells, focusing on the ERK1/2 and NF-kB pathways. These pathways are related to inflammatory cytokine expression, cell proliferation, and mucin secretion, thus giving one possible mechanism by which azithromycin may exert immune-regulatory effects. Notably, the impact of COVID-19 on the human immune system has also been correlated with the ERK1/2 and NF-kB pathways, which would explain the immune-modulatory effect of azithromycin in patients with COVID-19 [15]. Due to its immune regulatory action, azithromycin has been helpful in treating several chronic pulmonary diseases, such as CF, non-CF bronchiectasis, COPD, chronic sinusitis, sepsis, and diffuse pan-bronchiolitis [16].

2.3. Antiviral effect

Azithromycin does possess antiviral properties, and it has been found to act synergistically with other antiviral agents. Mounting clinical and scientific evidence supports the view that azithromycin is active against many viruses, such as respiratory syncytial virus [17], Ebola virus [18, 19], Zika virus [20], H1N1 influenza virus [21], enteroviruses [22], and rhinoviruses [23]. In vitro study results investigating the possible antiviral activity of azithromycin suggest that it has an IC50 against the above viruses, except for H1N1 influenza, within a range of 1- 6 μmol/L [24]. In a screening study of 2177 compounds against Zika virus, azithromycin was again found to reduce both viral proliferation and cell damage in glial cell lines and human astrocytes [25].

3. Drug resistance mechanism

In the past few decades, with azithromycin increasingly being used in clinical practice, more and more patients have developed problems regarding bacterial resistance, which poses problematic parts of less treatment success. Besides decreasing treatment success, azithromycin may cause failure of the treatment and recurrence of the disease, increase healthcare costs and inflict more pain on patients. The main mechanisms of azithromycin resistance are:

3.1. Ribosomal methylation modification

It is one of the main mechanisms of azithromycin resistance. Methyltransferases (methylases)

mediate the methylation of the 23S rRNA, position 2058 in the ribosome. As the affinity of azithromycin for the ribosome reduces, resistance is conferred [26]. That modification directly impacts the drug target site and prevents effective binding and action. Thus far, most known methylases belong to the erm family; over 40 genes exist in them, with ermB and ermA being the

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most prolific members. Between strains, such genes can be transferred by plasmids, transposons, and other mobile genetic elements. That represents a major pathway through which bacteria acquire azithromycin resistance. Transferring such genes ensures that the rapid dissemination of resistance occurs between bacterial species, complicating the whole picture of resistance.

3.2. Efflux pump mechanism

Active efflux pumps can expel azithromycin from the cell, further decreasing the intracellular concentration of the drug and, thus, yielding resistance. This could be the case for azithromycin and may give rise to cross-resistance for other antibiotics. Most efflux pumps responsible for the macrolide-class antibiotics belong to the ATP-binding cassette transporter superfamily and the major facilitator superfamily. Important examples include msrA from Staphylococcus aureus and mefA/E from Streptococcus pneumoniae, which both provide an important contribution to azithromycin resistance. Regarding the involvement of efflux pumps in multidrug resistance, one pump can be involved in the efflux of several antibiotics.

3.3. Ribosomal mutations

Mutations at the 23S rRNA positions 2058 and 2059 in bacterial ribosomes are also related to azithromycin resistance. Such mutations affect the site of azithromycin binding and prevent its adequate action from being realized. This mechanism is prevalent in strains of Helicobacter pylori and many species of Legionella [27], though it is less common in clinical isolates. Despite being scarce, high-level resistance usually develops from such mutations, dramatically impacting treatment efficacy.

3.4. Other mechanisms

Studies have shown that the bacteria may develop limited resistance to azithromycin through the production of inactivating enzymes to degrade the drug or by changing the permeability of the cell wall and membrane [28]. However, these mechanisms are not common in clinically resistant strains. Though this is not the major pathway through which azithromycin resistance develops, it attracts valuable attention. The major mechanism of azithromycin resistance is ribosomal methylation and efflux pump. Other multiple resistance mechanisms may be present in different species; that is, resistance development is a continuous phenomenon. The presence of multidrug resistance mechanisms complicated the resistance issue; thus, one strategy is hard to implement. Therefore, the need to enhance surveillance of azithromycin resistance, rationalize drug usage, and postpone the emergence and spread of resistant strains in order to properly guide clinical treatment and maintain therapeutic efficacy cannot be overemphasized. Specific measures in this regard include resistance monitoring networks, rational drug usage guidelines, education of health professionals and the general public on proper drug usage, and development of new antibiotics and combination therapies.

4. Clinical application

4.1. Respiratory infection

Lower respiratory tract infections often present with symptoms like cough, sputum production, dyspnea, and chest pain. Many children also complain of generalized fatigue. Epidemiological evidence suggests that children suffer from 6 to 8 respiratory infections a year, with accompanying

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symptoms of a condition often exacerbating an already existing condition with the highest episode leading to severe complications, such as asthma or pulmonary edema. Thus, this necessitates a focus on the prevention and early management of respiratory infections among pediatric patients. After an azithromycin course for a respiratory infection, it gets rapidly engulfed by white blood cells and is, therefore, able to reach the site of inflammation with concentrations far higher than those in noninflamed tissues and thus enhance its antimicrobial activity. Thereafter, in those situations where blood drug levels decline, it can also be released from white blood cells, whereupon maintenance of therapeutic concentrations is permitted, and its duration of action is increased. In such cases, a single dose administered at 24 to 48 hours is generally adequate to establish blood concentrations that are efficient. Azithromycin has been shown to be efficient, in both prophylaxis treatment forms, against infections by Streptococcus pneumoniae and Haemophilus influenzae types and is thereby one of the characters used in anti-infective treatments in children during periods where there is a high incidence of influenza.

4.2. Skin and soft tissue infections

In recent times, the common pathogens associated with skin soft tissue infections include Staphylococcus aureus and various Streptococcus species. In comparative studies, a single dose of azithromycin over 3-5 days in pediatric SSTIs has been found to produce comparable results to a 7–10-day course of erythromycin, dicloxacillin, or cloxacillin. However, these two drugs are more effective and their duration shorter. More recent studies show that azithromycin achieves a better bacterial eradication rate and therapeutic efficacy about 90% in pediatric SSTIs, equal to flucloxacillin, cloxacillin, cefalexin, dicloxacillin, and erythromycin [29]. Azithromycin exerts its antibacterial action by binding to the 50S subunit of the bacterial ribosome and blocking the activity of transferase enzymes, which inhibits protein synthesis in pathogenic bacteria, such as Staphylococcus aureus and Streptococcus, ultimately resulting in the death of the bacteria.

4.3. Urinary tract infection

At present, azithromycin has been included by both the WHO and the FDA as a first-line treatment for non-gonococcal urethritis and chancroid. Azithromycin binds to the 23S rRNA of the ribosomal subunit in the pathogens causing UTIs, such as Gram-positive cocci, Mycoplasma, and Chlamydia, and thus tRNA cannot smoothly bind to the ribosomal subunit. This results in adding new amino acids to the growing polypeptide chain, and thus, when bacterial protein synthesis is halted, bacterial growth and replication are inhibited. However, during treatment, if the child has developed a UTI with Gram-positive cocci, Mycoplasma, or Chlamydia, it will be treated with azithromycin. For those with E. coli and other pathogens, azithromycin is generally not advised . Particularly, in a clinical scenario of a pediatric UTI, it should be a prerequisite to requesting a midstream urine for culture and antimicrobial susceptibility testing. It will point out the specific bacterial pathogen involved, which, therefore, allows the practicability of shelling out the most appropriate medication.

4.4. Other infections

4.4.1. Ordinary infection

Azithromycin's extensive use encompasses pediatric acute pharyngitis, pediatric chlamydia trachomatis infections, toxoplasmic encephalitis, scrub typhus, pediatric gastroenteritis, and others.

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Chlamydia trachomatis infection in children is a chronic, infectious disease mainly due to the bacterium Chlamydia trachomatis. Until recently, chlamydial infections in children were treated with the application of tetracycline eye ointment. This mode of treatment requires prolonged use and application into the eyes, which is inconvenient for children and makes this option less acceptable to patients. The most likely consequence of such a situation is an interruption in the course of the medication that has been prescribed, making ineffective any medication that may have been used. On the other hand, it is easy to administer a single oral dose of azithromycin, and satisfactory results are obtained after one dose in treating pediatric Chlamydia trachomatis infections.

The main pathogens in pediatric acute pharyngitis are Strep and Staph species, and azithromycin inhibits both types efficiently. High concentrations of azithromycin after oral administration go into the pharyngeal lymphatic tissues via systemic circulation, which provides much potential for benefit in the treatment of acute pharyngitis.

4.4.2. Special infection

It can, in some cases, have serious complications like the ones involving liver or kidney functions in children. Initial management of scrub typhus is empirically done with chloramphenicol and doxycycline. These have been associated with several adverse events, such as nausea, vomiting, drowsiness, and anorexia. Some children cannot tolerate the side effects and discontinue the medication. Current evidence supports the efficacy of azithromycin treatment; it is given at doses of 100 mg for those weighing less than 15 kg, 200 mg for those between 15 and 25 kg, and 300 mg for those more than 30 kg. All the doses are considered optimal and have provided good therapeutic results. Scrub typhus involves an infection of the blood and liver cells, causing an immune response followed by pathological changes that will eventually make one sick. Azithromycin crosses the bacterial cell membrane and inhibits protein synthesis in scrub typhus organisms. Inside the organism, azithromycin binds to the ribosomes in the bacterial cytoplasmic membrane and interferes with protein synthesis, disrupting cell function and preventing the organism from metabolizing and growing normally. Second, azithromycin inhibits the replication of scrub typhus DNA by inhibiting bacterial DNA polymerase activity, thus impeding DNA synthesis and replication. Further, such prevention of cell division and proliferation leads to the death of scrub typhus organisms.

5. Adverse reaction

Azithromycin generally exhibits good overall tolerance, with a low incidence of adverse reactions. The most common side effects are gastrointestinal symptoms, such as nausea, vomiting, abdominal pain, and diarrhea, which are usually mild and resolve on their own after discontinuation of the drug. Allergic reactions are the next most frequent, typically presenting as rashes and itching, with more severe cases potentially leading to angioedema or anaphylactic shock. Additionally, a small number of cases have reported central nervous system reactions (such as dizziness, headaches, and blurred vision), cardiovascular reactions (such as palpitations and electrocardiogram changes), and liver-related reactions (such as elevated liver enzymes) [30].

It should be noted that the FDA has warned about the possible risk of serious arrhythmias, up to and including cardiac arrest, in association with azithromycin, especially among older patients, those with hypokalemia, and those receiving concomitant antiarrhythmic therapy, which further increases the risk [31]. In this context, the electrocardiographic changes and levels of electrolytes should be monitored in those with a history of cardiovascular disease and other risk factors while considering prescribing azithromycin. The use of azithromycin among pregnant and nursing mothers should be

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considered, and the doses in children, the elderly, and those with liver or renal impairment are adjusted based on the latter's condition. Azithromycin may also increase the sensitivity of skin to light; therefore, during treatment, patients are advised to avoid exposure to sunlight or ultraviolet radiation as much as possible.

6. Synthesis process

Azithromycin,as shown in Scheme 1, is a semisynthetic, 15-membered macrolide antibiotic originating from erythromycin A through a series of oximation, Beckmann rearrangement, reduction, and N-methylation reactions [32].

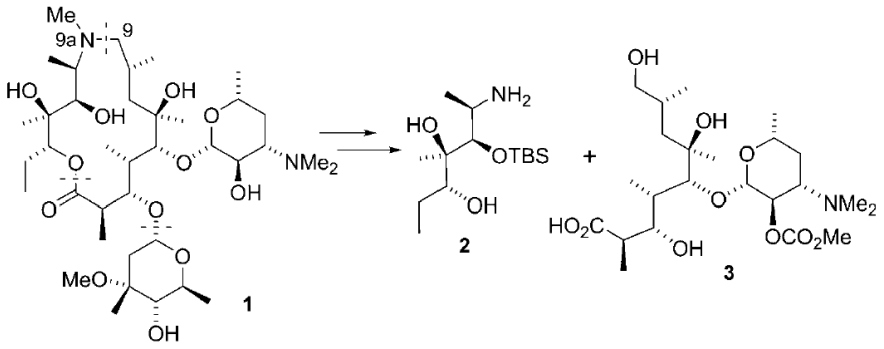


Figure 1. Scheme 1. Retrosynthetic analysis of azithromycin (1). TBS= tert-butyldimethyl-silyl

There are two main synthetic processes for azithromycin.

6.1. Chemical synthesis method

The chemical synthesis employs erythromycin as the starting material, which undergoes a series of chemical reactions, such as oxidation, oximation, reduction, acylation, and methylation, to yield azithromycin.

6.2. Genetic engineering bacterial fermentation method

The direct fermentation of azithromycin using genetically engineered microorganisms has also been studied. At present, industrial-scale production is based on its chemical synthesis, which has advantages like the availability of starting materials and the stability of product quality. On the other hand, it suffers from some disadvantages, such as being long, low-yielding, costly, and highly polluting. Fermentation with genetically engineered microorganisms, on the other hand, has a shorter fermentation cycle, higher yields, lower costs, and less pollution, and it represents the future trend in azithromycin biotechnology.

7. Azithromycin degradation

The proposed neural network coupled with particle swarm optimization succeeded in modeling and locating the optimal conditions for azithromycin degradation. The best values were [NaClO] = 200 μM, [AZM] = 35.37 mg L–1, [FeSO4] = 3.5 mg L–1, pH 2.51, and 99.9% yield predicted. Five photoproducts, Azit-DP1 to Azit-DP5, were characterized by m/z values of 357.11533, 159.06552, 146.08127, 100.07701, and 83.04969, respectively. A degradation pathway mechanism is proposed.

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According to the biotests results, AZM shows antimicrobial efficacy concentration in the medium; upon degradation, the antimicrobial efficacy declines and disappears after 4 hours of the degradation process.

Proposed biotests confirmed that the system designed is effective in removing azithromycin and its subproducts from aqueous media at low costs.

This depends on various conditions, such as temperature, pH, and other pollutants that may speed up or slow down the degradation rate. In general, azithromycin is very stable in water and could persist for several days under normal ambient conditions.

It does appear that the presence of other contaminants or microorganisms in the water leads to an enhancement in their degradation rate [33].

Various other conventional methods for degrading pharmaceutical contaminants include adsorption, filtration, precipitation, ozonation, and flocculation. However, these methods do not effectively remove the pharmaceuticals via treatment, as these residues often exhibit poor biodegradability [34].

Advanced oxidation processes (AOPs) have been successfully used to mineralize a variety of toxic, organic compounds. In principle, they are based on a generation of non-selective hydroxyl radicals, which apply to recalcitrant pollutants through fast reaction rates [35].

Among AOPs, Fenton oxidation is a convenient and effective method breaking down of various organic contaminants, which was acted based on the reaction between iron and oxidizing agents (usually hydrogen peroxide (H_2O_2)) [36].

8. Conclusion

The findings clearly indicate that optimizing the Fenton oxidation system achieves the target azithromycin concentration and reduces by-products considerably under optimal conditions. The process was modeled to yield a 99.9% removal of azithromycin, which significantly reduced its antimicrobial activity over time. The identification of five photoproducts and the suggestion of a degradation pathway provided insight into the chemical transformation that azithromycin undergoes during oxidation. It follows, therefore, that the antimicrobial effect of azithromycin will decrease during its degradation and finally disappear after four hours. This study shows that while temperature and pH may affect degradation rates, in this case, the proposed system remains a feasible low-cost and high-efficacy solution for dealing with the persistent pharmaceutical contaminants that threaten improving ecological water quality.

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