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Review

Impact of metal coordination on the antibiotic and non-antibiotic activities of tetracycline-based drugs

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ABSTRACT

The tetracycline family of antibiotics possesses, in addition to the advantages of a broad-spectrum of action, low toxicity, and the fact that they can be administered orally, a very interesting chemical structure with several metal coordinating sites. This ability to chelate metal ions dictates their pharmacological profile. The species that inhibits bacterial growth is a complex with magnesium ion, which acts by impairing protein synthesis through binding to the 30S ribosomal subunits. The appearance of bacterial resistance to tetracycline and derivatives has compromised their use in the treatment of bacterial infections. The most commonly found mechanism of bacterial resistance to tetracyclines also involves metal chelation: a membrane-associated protein in the resistant bacteria acts as an antiporter by coupling the efflux of a monocationic metal complex with tetracycline out of the bacterial cell to the influx of one proton. Interestingly, this mechanism can be overcome by administering the drug as metal complexes with some divalent metal ions, such as Pt^{2+} or Pd^{2+} ions. The discovery of non-antibiotic activities of doxycycline, minocycline and chemically modified tetracyclines, such as the inhibition of matrix metalo-proteinases or the induction of cellular apoptosis, restored the interest in this long-standing family of pleiotropic drugs. The inhibition of matrix metalo-proteinases seems to result from the binding to a Zn^{2+} ion present in the structural metal center of the protein. Furthermore, transition metal complexes with tetracyclines exhibit antitumor activity and act as nucleases. In this review, we discuss the importance of metal chelation to the antibiotic and non-antibiotic activities of tetracyclines, either by coordinating to biological metal ions *in vivo* or by being administered as metal complexes.

Abbreviations: A site, acceptor site; AgNPs, silver nanoparticles; chl, chlortetracycline; cmt, chemically modified tetracycline; CD, circular dichroism; DNA, deoxyribonucleic acid; dox, doxycycline; His, histidine; IC_{50}, the concentration required to inhibit 50% of cell growth; IR, infrared spectral region; MCX-metal-tc, xanthate–metal–tetracycline complexes; MDR, multidrug resistant; min, minocycline; MMPs, matrix metalo-proteinases; MPT, mitochondrial permeability transition; mRNA, messenger ribonucleic acid; NMR, nuclear magnetic resonance; oxy, oxytetracycline; PVP, polyvinylpyrrolidone; ROS, reactive oxygen species; tc, tetracycline; tcs, tetracyclines; TG, thermogravimetry; tig, tigecycline; tRNA, transfer ribonucleic acid; UV-vis, ultraviolet and visible spectral region.

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1. Introduction

The long-standing success of tetracycline drugs is impressive considering that the first member of the family, chlortetracycline (chl), was firstly isolated from *Streptomyces aureofaciens* in 1948. In the same year, oxytetracycline (oxy) was isolated from *Streptomyces rimosus* and, in 1953, the main compound of the family, tetracycline (tc), was isolated from *S. aureofaciens*, *S. rimosus*, and *S. viridofaciens* [1]. Subsequently, semi-synthetic analogs, such as doxycycline (dox) and minocycline (min), were developed (Fig. 1) [2,3].

This was the first antimicrobial group of drugs for which the term 'broad spectrum' was used, due to its effectiveness against a wide range of infectious microorganisms, which includes both Gram-positive and Gram-negative bacteria. The clinical use of tetracycline and analogs in the treatment of bacterial infections has declined because of the emergence of bacterial resistance to these drugs. Aiming to circumvent bacterial resistance, semi-synthetic derivatives of minocycline, the glycylcyclines, were developed [4]. More recently, eravacycline, a fluorocycline, has been advanced to phase III clinical trials [5]. Nowadays, tetracyclines continue to be used in the treatment of different bacterial infections, such as urinary tract infections, acne, gonorrhea, chlamydia, eye infections, periodontitis, pneumonia, and rosacea, in the treatment of rheumatoid arthritis and in the prevention of malaria (Table 1).

Tetracycline possesses a very interesting chemical structure with many potential metal-binding sites: oxygen atoms at the C10–C12 keto-phenol system, the enolic oxygen at C3 and the nitrogen atoms at C4 and at the carboxamide group in ring A. Doxycycline has the same minimal formula as that of tetracycline: the difference between them lies in the presence of an OH group at C5 in doxycycline instead of C6 in tetracycline. Other antibiotics of the tc family contain an identical 4-ring carbocyclic structure and substituent variations at carbons 5, 6, and 7. Tigecycline (tig) contains the group N,N-dimethylglycilamide at carbon 9 of minocycline (Fig. 1) [1].

As a result of the extraordinary coordination ability of tetracycline, its pharmacological behavior depends on metal coordination. The research group of professor Berton in collaboration with professor Kozlowski demonstrated that the fraction of antibiotic not bound to proteins in blood plasma almost exclusively occurs as calcium and magnesium complexes [22]. Inside cells, the drug is mainly coordinated to magnesium(II) ions, as $[Mg(tc)]^+$. Coordination to Mg^{2+} provides the antibiotic activity, because it is the $[Mg(tc)]^+$ complex that binds to the bacterial 30S ribosomal subunit, leading to the inhibition of protein synthesis [23,24]. Metal complexes also

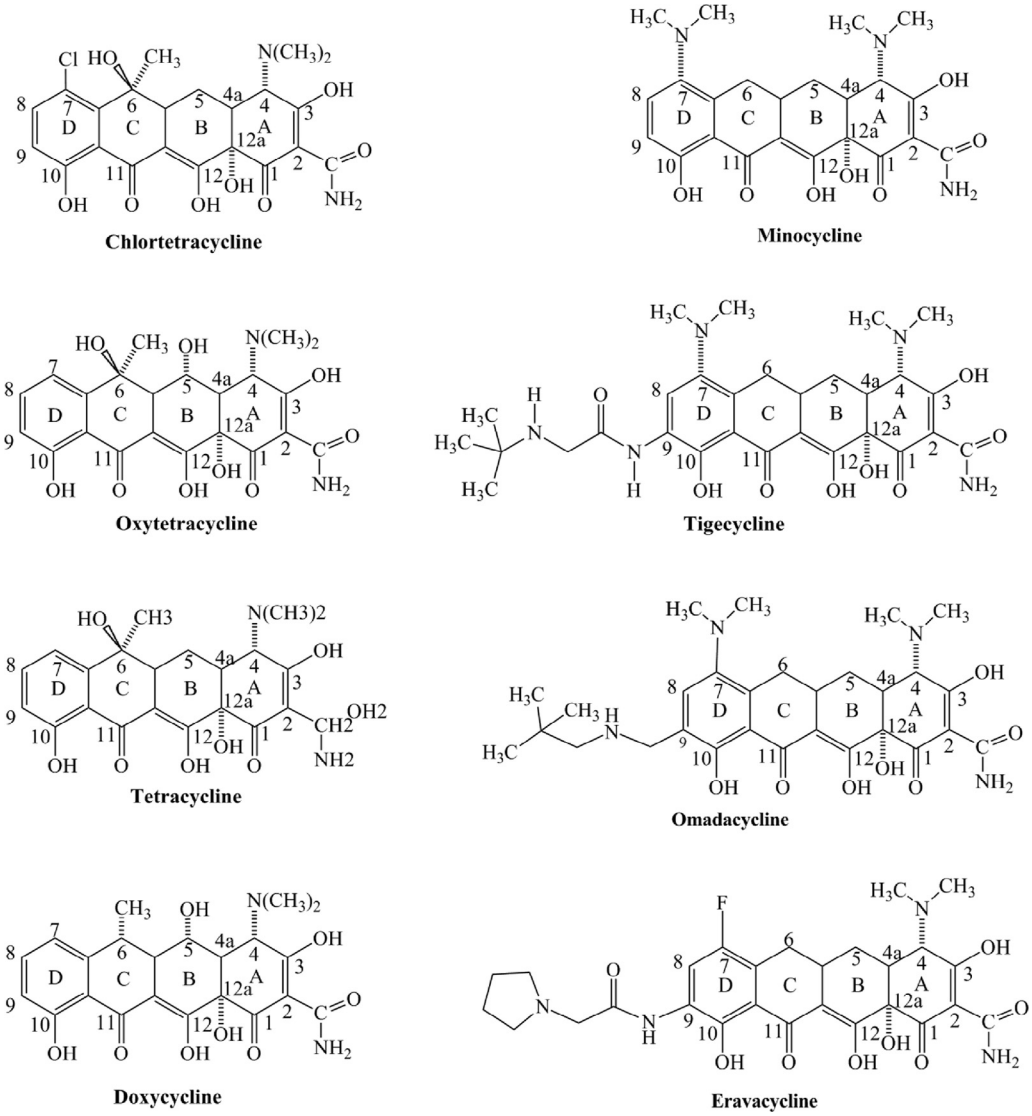

Fig. 1. Molecular structure of selected tetracyclines, tigecycline, omadacycline and eravacycline.

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