



Review

Future prospects of antibacterial metal nanoparticles as enzyme inhibitor



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ABSTRACT

Nanoparticles are being widely used as antibacterial agents with metal nanoparticles emerging as the most efficient antibacterial agents. There have been many studies which have reported the mechanism of antibacterial activity of nanoparticles on bacteria. In this review we aim to emphasize on all the possible mechanisms which are involved in the antibacterial activity of nanoparticles and also to understand their mode of action and role as bacterial enzyme inhibitor by comparing their antibacterial mechanism to that of antibiotics with enzyme inhibition as a major mechanism. With the emergence of widespread antibiotic resistance, nanoparticles offer a better alternative to our conventional arsenal of antibiotics. Once the biological safety of these nanoparticles is addressed, these nanoparticles can be of great medical importance in our fight against bacterial infections.

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1. Introduction

Enzymes are biological agents which help in assisting a reaction wherein a reaction starts with a particular substrate and then converted to the desired products. Till date, enzymes are being known to assist in nearly 5000 biochemical reactions [77]. Some enzymes contain metal ions in their structure; these enzymes are called as metalloenzymes. There are some chemical species which bind to the enzymes and

make them active, these are called coenzymes. The complex of enzyme and the coenzymes is called as a holoenzyme. The inactive or non-functional enzymes are called as apoenzyme. Coenzymes bind to the apoenzymes by the means of electrostatic bonds or van der Waals forces and produce several enzymatic actions [10].

1.1. Enzyme inhibition

In general, the blocking or stopping of the enzyme action is called as enzyme inhibition. Indeed, both natural and synthetic inhibitors are available that can be effectively used in therapeutics and as medicine for controlling harmful diseases mediated by specific enzymes. Enzyme

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inhibition is mainly of two types: reversible and irreversible. In both reversible and irreversible inhibition, the inhibitor need not cover the complete binding (active) site of the enzyme. Binding of the inhibitor to any part of the enzyme or the active site results in bringing a conformational change in the enzyme resulting in distortion of the active site of the enzyme due to which the substrate does not fit in the active site and the enzyme action is inhibited.

1.1.1. Reversible inhibition

Reversible inhibition is facilitated by enzyme inhibitors which bind to the enzyme for a specific period of time and then releases itself from the active site of the enzyme. The binding causes a specific change in the conformation of the enzyme. Reversible enzyme inhibition is mainly of two types, namely competitive and non-competitive inhibition. Competitive inhibition involves the reversible binding of the inhibitor to the active site of the enzyme. In this case, the inhibitor has the same shape as that of the substrate and thus it competes with the substrate to bind at the active site of the enzyme. As a result, enzymes bind to the inhibitors and minimize the overall enzyme action of the metabolic process. In the case of non-competitive inhibition, the inhibitor does not resemble the substrate hence it does not compete with the substrate for binding to the active site of the enzyme. In this method, the inhibitor reversibly binds to any part of the enzyme. As a result, enzyme undergoes a conformational change and this results in the change in the active site of the enzyme and thus, blocks the substrate binding and inhibits the enzyme action [40].

1.1.2. Irreversible inhibition

Irreversible inhibition occurs through the binding of the enzymes either by strong covalent or non-covalent bond. In the case of a non-covalent bond, the inhibitors detach from the active site of the enzyme for a short time after the attachment and make the enzyme-free to carry out the normal reaction [28]. Irreversible inhibition is mainly caused by the help of active site-directed inhibitors. These inhibitors bind with the functional groups present at the active site or near the active site of the enzyme. As a result, the enzyme becomes unavailable for the reaction, which results in a reduction in the formation of essential products [28].

Enzyme inhibition has been regarded as an important process for regulating metabolic activities. In this review, we provide an overview of different commercially available drugs which act as an enzyme inhibitor and also provide information about how the antibacterial activity of the metal nanoparticles resembles the natural and conventional antibiotics.

2. Synthetic drugs as enzyme inhibitors

A drug called difluoro methyl ornithine, which is used to treat African trypanosomiasis (sleeping sickness) works on the principle of irreversible inhibition of enzyme action. A compound called as diisopropylfluorophosphate (DFFP) is a potent inhibitor of acetylcholinesterase (ACE). It follows irreversible inhibition mechanism and binds at the active site of ACE, thereby blocking the enzyme activity to break down acetylcholine [78]. This results in accumulation of the excess amount of acetylcholine in the body and improper function of respiratory muscles leading to death due to suffocation. Similar effect is also observed by the compound malaon which is a toxic derivative from malathion which binds reversibly and then irreversibly to the active site serine and inactivates ACE leading to death due to suffocation [78]. DFFP and malathion are the prime components of the current organophosphorus nerve gases like sarin and other organophosphorus toxins. Gout is a disease caused due to over production of uric acid in the body [23]. The enzyme xanthine oxidase helps in the production of uric acid crystals in the body by its oxidase property [11]. Allopurinol is an anti-gout drug which acts on the enzyme xanthine oxidase by the mechanism of suicidal irreversible inhibition [78]. The enzyme

xanthine oxidase first converts allopurinol into its active form called oxypurinol, which thereby binds to the molybdenum sulfide complex present at the active site of the enzyme xanthine oxidase rendering the enzyme inactive. This results in less production of uric acid in the body and thus a cure for gout disease.

Methotrexate is a commonly used antimetabolite which is usually used as an anticancer drug and also for many autoimmune diseases. Methotrexate acts as a competitive inhibitor of the enzyme dihydrofolate reductase (DHFR) [78]. DHFR converts dihydrofolate to tetrahydrofolate. Being similar to dihydrofolate, methotrexate blocks the active site of DHFR thereby reducing the availability of tetrahydrofolate which acts as a carrier molecule in for carbon moieties important for anabolic pathways. Blocking the anabolic pathways results in blockage of synthesis of purine nucleotides for DNA replication [71].

Sulfanilamides are another class of drugs which belong to the sulfa drugs group. They are mainly used as antibacterial and anticancer drugs. The principle behind their activity lies in competitive inhibition. They block the folic acid synthesizing enzyme [78]. Folic acid is vitamin B9 which is required for important functions in the body. Humans and bacteria cannot synthesize folic acid in the body but it is an essential vitamin for synthesizing important compounds like methionine, DNA, RNA in the body. Hence, folic acid is supplied externally in the form of folate which is converted to folic acid by the folic acid synthesizing enzyme. Hence, sulfanilamides act as a competitive inhibitor for the substrate *p*-aminobenzoic acid and prevent it from binding to folic acid synthesizing enzyme thereby blocking the synthesis of folic acid. Unavailability of folic acid kills the bacteria as important constituents required for the growth cannot be synthesized [50].

Aciclovir, a commonly used antiviral drug, is a guanosine analog called as acycloguanosine and is used mainly for treatment of herpes simplex virus [13]. Acyclovir is converted to acycle-guanosine monophosphate by the enzyme viral thymidine kinase. This acycloguanosine monophosphate can be easily phosphorylated to acycloguanosine triphosphate (acyclo-GTP) by cellular kinases. The formed acylo GTP is a potent inhibitor of viral DNA polymerase leading to termination of DNA replication and virus inactivation [3].

Apart from the examples of the drugs mentioned above, there exist many other synthetic drugs which are being used as an enzyme inhibitor. A list of the drugs and that acts as enzyme inhibitors are provided in Table 1.

3. Conventional antibiotics enzyme inhibitors

Many newly developed antibiotics for various diseases cure by acting on the essential enzymes which are required by the bacteria or the virus to develop infection. Some of the common antibiotics which use enzyme inhibition mechanism as their tool to kill the infectious bacteria and virus are being discussed below.

The most common and widely used antibiotic Penicillin discovered in 1928 in England is a very promising antibiotic against the bacterial infection arising from *Streptococci* and *Staphylococci*. Penicillin is known to act as a suicidal inhibitor following the irreversible inhibition mechanism towards the enzyme glycopeptide transpeptidase belonging to the family of serine protease. Enzyme glycopeptide transpeptidase is required for the synthesis of the cell wall of bacteria which is essential for the growth and survival of the bacteria [78]. It cleaves the peptide linkage between the alanine residues in the polypeptide. Penicillin structure possesses a β -lactam ring that is similar to the transition state of the product formed in the cleavage reaction [53]. This helps penicillin to actively bind at the active site of the enzyme thus rendering it inactive due to which the bacterial cell wall is compromised and resulting in cell wall rupture and bacterial death. Other antibiotics like ofloxacin, ciprofloxacin, kanamycin are also expected to follow the same mechanism for killing the bacteria.

Acetylsalicylic acid commonly known as aspirin is a well-recognized anti-inflammatory and analgesic drug [47]. The mechanism of action of

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