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Bacteriolysis Destruction for *S. Aureus* and *E. Coli* Peptidoglycan Cell Wall by Metal Salts and Metal-Based Compounds/Alloy Materials

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Abstract

Antimicrobial and bacteriolytic PGN cell wall destruction, hydrolysis, decomposition, and cleavage activities by metal salts, metal-based compounds/alloy materials have been extensively elucidated against *S. aureus* and *E. coli*.

Anti-microbial activity on metal salts: The antibacterial activity of Cu^{2+}-treatment against Staphylococcus aureus was the most effective. Zn^{2+}-treatment possessed a great antibacterial activity against *S. aureus* even, Cu^{2+} possessed the most effective antibacterial that treated with Zn^{2+}, Fe^{2+} and Fe^{3+} possessed activity against Klebsiella pneumoniae a slight antibacterial and activity.

Anti-microbial activity on metal-based compounds: Metal-based antibacterial compounds such as silver-based antibacterial compounds, gold-based antibacterial compounds, gallium-based antibacterial compounds, copper-based antibacterial compound have a greater understanding of the properties, which give metal-based agents having higher antibacterial activity and lower toxicity will provide a successful toolkit.

Anti-microbial activity on metal-based alloy materials: Fe-, Zn-, Co-, Ti-based alloys, and other metals had been investigated under the bacterial capability method with bacterial suspension, immersion and incubation of different times, which include Co-, Fe-, Mg-, Ti-, and Zn-based alloys, and some few other metal-based alloy systems, were analyzed in detail cell wall/membrane disruption mechanism and an effort to comparatively evaluate the antibacterial and mechanical response of the different alloys developed so far was made.

Antimicrobial mechanism for metallic ions with their ligands on metal salts and metal-based compounds/metal complexes, and metal-based materials against *S. aureus* and *E. coli* may be thought that various biological aspects of the metal based drugs/ligands entirely depend on the ease of cleaving the bond between the metal ion and the ligand, in which the interactive relationship between ligand and the metal and the efficacy of the various organic therapeutic agents can often be metal-based compound/metal complexes and metal-based material as antimicrobial agents enhanced upon coordination with a suitable metal ion and the donor sequence of the ligands because different ligands exhibit different biological properties.

Keywords: Copper (II) and Zinc (II); Copper Nitrate and Zinc Sulfate; PGN Biosynthesis; Autolysin and Elongation; Zinc Salts; Metal Compounds, Fe-, Zn-, Co-, Ti-Based Alloy Materials; Metal-Based Nanoparticle Materials

Abbreviations

AMR=Anti-Microbial Resistance; DNA=Deoxyribonucleic Acid, Eps=Endopeptidase; PGN=Peptidoglycan; PGRPS=Peptidoglycan Recognition Proteins; PTEN=403 amino acids; LYS1=Lysozyme1; MBC=Minimum Bactericidal Concentration; MIC=Minimum Inhibitory Concentration; OM=Outer Membrane; PRRs=Pattern Recognition Receptors; TG=Transglycosylase; TP=Transpeptidase; ROS=Reactive Oxygen Species

Introduction

Bacterial Peptidoglycan (PGN) cell wall destruction has been elucidated on the basis of the

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results obtained from halo antibacterial susceptibility tests in metals nitrate and sulfate solutions against Staphylococcus Epidermidis, in which from halo-antibacterial susceptibility tests of metallic ion concentration of 100 mM/L against Staphylococcus epidermidis, the order of bacterial effect for the metal nitrate solutions is as follows, $Cu^{2+}>Zn^{2+}>Ag^{+}>Pb^{2+}>Al^{3+}$, and the other, in the metal sulfate solutions, the antibacterial effect order is found to be $Zn^{2+}>Cu^{2+}>Ag^{+}>Al^{3+}$ [1].

Antibacterial metal ions agents were seen due to transfer of antibiotic resistance genes by plasmids also known as Resistance Transfer Factors or R-factors that metal complexes are used to show synergistic activity against bacteria like copper & chlorhexidine on dental plaque bacteria, silver nanoparticles & cephalexin against *E. coli* & *S. aureus* [2].

Action of metallo-antimicrobials (e.g., metal compounds/complexes, alloys, organometallics, metal nanoparticles, and metal-drug conjugates) may raise concern over their potential side effects owing to the low selectivity toward pathogens and host, which appears to be the biggest obstacle for downstream translational research and combination therapy through repurposing metallodrugs with antibiotics, and the optimization of their absorption route through formulation to achieve a target-oriented delivery will be a powerful way to combat Anti-Microbial Resistance (AMR) [3].

The antibacterial effect of the Zn (II) complexes of metal coordinated zinc (II) complexes with iminopyridine as an organic ligand and different inorganic ligands: chloride, nitrate, and acetate were studied against planktonic bacterial cells of Staphylococcus aureus (Gram positive) and Escherichia coli (Gram-negative) strains, in which shows a moderate biocide activity in both types of planktonic bacteria, and arises from the metal complexation to the Schiff base Citation. The crucial effect of the metal with Zn (II) improving the activity of Cu (II) counterparts and the impact of the inorganic ligands was not significant for the antibacterial effect but was relevant for the complex solubility, as proof of concept of topical antibacterial formulation, the most lipophilic Zn (II) complex and confirmed a sustained release for 24 h in a vertical cell diffusion assay [4].

Bacteriolytic mechanism for Ag^{+}, Cu^{2+}, Zn^{2+} ions, respectively, induced *S. aureus* is clarified that bacteriolysis and destruction of *S. aureus* PGN cell wall occur by inhibition of PGN elongation through metallic Ag^{+}, Cu^{2+}, Zn^{2+} ions-induced PGN inhibitory Transglycosylase (TG) and Transpeptidase (TP) syntheses (TG for Zn^{2+}) and PGN activated major autolysin of amidase. The other, bacteriolytic mechanism for Ag^{+}, Cu^{2+}, Zn^{2+} ions, respectively, induced *E. coli* is found that bacteriolysis and destruction of *E. coli* cell wall occur by disruption of *E. coli* Outer Membrane (OM) structure with OM lipoprotein-endopeptidase activation, and by inhibition of PGN elongation through inhibitory TG and TP syntheses (TG for Zn^{2+}) and PGN activated major autolysins [5].

In $Cu(NO_3)_2$ solution, antibacterial $Cu(NO_3)_2$ solution is used the antimicrobial activity of a novel, plasma-cured 2.5% (w/v) $Cu(NO_3)_2$-containing sol-gel surface was performed as sol-gel coatings, the plasma curing led to a gradient in cross-linking with the highest values at the top of the coating [6], the other, in $ZnSO_4$ solution, $ZnSO_4$ different concentrations of zinc sulfate were found to have antibacterial effect against multidrug resistant *Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Proteus spp*. [7].

Bacterial clearance was improved in mice pretreated with PGN that the effect of PGN pretreatment was not due to any LPS contamination by showing that exposure to the Gram-positive bacterial cell wall component peptidoglycan also induces cross tolerance to LPS and non-specifically enhances innate immune function in that PGN-pretreated mice had increased resistance to Gram-negative bacterial challenge [8]. The other, bacterial PGN cleavage and hydrolysis plays important roles for anti-bacterial functions that zinc induced bacterial PGN cleavage is composed of decomposition and hydrolysis, in which bacterial killing occurs by PGN cell wall destruction through balanced reaction between PGN suppressive biosynthesis and activated autolysin. PGN cleavage is involved that AmiA distinguishes PGN mostly by the peptide, and cleavage is facilitated by a zinc-activated water molecule [9].

Peptidoglycan (PGN) recognition proteins (PGRPs) are pattern recognition receptors of the innate immune system that bind and, in some cases, hydrolyze bacterial PGN hydrolysis by Zn^{2+}-containing PGRPs [10].

Thus, bacterial PGN cleavage may be consisted of decomposition, hydrolysis, and PGN inhibitive elongation.

In this mini-review article, bacteriolytic PGN cell wall destruction is elucidated under the basic concept of main Cu (II)- and Zn (II)ions induced suppressive PGN biosynthesis, activated PGN autolysin, and PGN elongation inhibition, in which antimicrobial PGN destruction, hydrolysis, decomposition, and cleavage activities of metal salts and metal-based compounds/alloy materials are extensively discussed against *S. aureus* and *E. coli* peptidoglycan cell wall.

Experimental halo inhibitory zone test results for copper nitrate ($Cu(NO_3)_2$) and zinc sulfate ($ZnSO_4$) solutions.

Characteristics of copper nitrate ($Cu(NO_3)_2$ and zinc sulfate ($ZnSO_4$) solutions is a strong acid or strong electrolyte that such as zinc is redox-inert and has only one valence state of Zn (II). In proteins, the coordination is limited by His, Cys, Glu, and sulfur donors from the side chains of a few amino acids.

In zinc sulfate solution is dissociated into aqua zinc ion $[Zn(H_2O)_6]^{2+}$ and sulfuric ion $(SO_4)^{2-}$. Aqua zinc ions are liable to be bound to ligand L having negative charge. The sulfuric ion has bactericidal inactivity [11].

Halo antibacterial susceptibility test procedure had been performed that this method is characteristics of finding of inhibitory halo zone measurements as less qualitative antibacterial activity assay. Halo antibacterial tests have been carried out for the zinc sulfate aqueous solutions against Staphylococcus epidermidis. The other, the antibacterial reagents were prepared metallic ions 100 mM/L aqueous solutions from metallic salt reagents, wherein the crystalline powders of metallic salts of 0.01mol are dissolved in distilled water of 100 cc, preparing metallic ion concentration of 100 mM/L as antibacterial reagents (crystalline powders of 0.005 mol for zinc, copper, silver, and aluminum sulfates were used) [1].

Discussion

Antibacterial mechanism of Cu(II)- and Zn(II)- ions induced PGN cell wall bacteriolytic destruction due to suppressive PGN biosynthesis TP/TG, activated PGN autolysins, and inhibitive PGN elongation against *S. aureus* and *E. coli*

Figure 1 (a), (b) shows *S. Aureus* and *E. Coli* surface molecular structures, PGN chains, PGN syntheses TG/TP, and PGN autolysins,

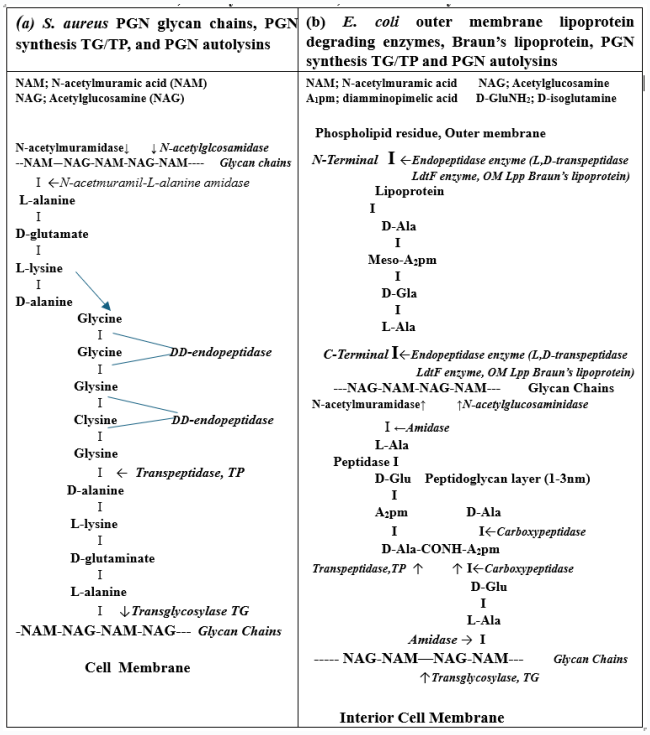

Figure 1 (a) and (b): *S. aureus* and *E. coli* surface molecular structures,PGN chains, PGN syntheses TG/TP, and PGN autolysins.

in which Table 1 indicates *S.* aureus PGN cell wall syntheses TG/TP and four PGN autolysins, and *E. coli* PGN cell wall syntheses TG/TP and five autolysins [12-14].

Bacteriolysis of *S. aureus* PGN cell wall by Cu^{2+} ions and Zn^{2+} ions are thought to be due to inhibition of PGN elongation owing to the damages of PGN both synthetic TG/TP and the activations of PGN major autolysin of AmiA. For the sake of growth of *S. aureus* PGN cell wall, there is necessarily required for the adequate balance between PGN biosynthesis and PGN autolysin. When the balance is broken to be become imbalanced, bacteriolysis and destruction of the cell wall should occur. Hence, it became apparent that PGN cleavage and hydrolysis of *S. aureus* PGN cell wall by Zn^{2+} ions are caused by inhibition of PGN elongation due to inactivation of PGN Transglycosylase (TG) or Transpeptidase (TP) and enhancement of PGN activated autolysin of amidases. The other, bacteriolysis of *E. coli* cell wall by Cu^{2+} ions occurs by disruption of outer membrane structure due to degradation of lipoprotein at N-, C-terminals, damage of PGN syntheses TG and TP enzyme, and activations of PGN major autolysins. Furthermore, deletion of PGN autolysin also becomes bacteriolytic factor [5].

By the reaction of Cu^{2+} and Zn^{2+} ions with *S. aureus* surface, Cu- and Zn-protein complexes are formed on the ground that are due to formation of S-atom containing Cu-, Zn-cysteine complex in bacteria [15].

Cu^{2+} Ions induced bacteriolysis of *S. aureus* PGN cell wall by inhibition of PGN elongation through inhibitive TG/TP enzymes and PGN activated major autolysins [16]. Bacteriolysis by balance deletion between synthesis enzyme and decomposition enzyme (autolysin) in PGN cell wall: For the sake of growth of *S. aureus* PGN cell wall, there is necessarily required for the adequate balance between PGN synthesis and PGN autolysin [17].

Zinc may be shown to inhibit PGN biosynthesis TG that the bactericidal activity of Zn^{2+}- dependent Peptidoglycan Recognition Proteins (PGLYRPs) is salt insensitive and requires N-glycosylation of PGLYRPs, namely, zinc may be shown to inhibit PGN biosynthesis TG, but these limited PGLYRPs don't be applicable for Gram-negative bacteria [18].

Zinc ions can inhibit PGN biosynthesis TG against *S. aureus* that zinc regulates PGN biosynthesis, in which Zn^{2+} ion can inhibit PGN synthetic enzymes that Zn^{2+} ions are most commonly coordinated by cysteine, followed by histidine, aspartate, and glutamate that Zn-cysteine complex in bacteria, and the Zn^{2+} chelation represents a potential therapeutic approach for combating biofilm growth in a wide range of bacterial biofilm-related infections [19].

Wall teichoic acids are spatial regulators of PGN cross-linking biosynthesis TP, however, it is not explicit whether zinc ions could inhibit both TG and TP enzymes of the PGN, wherein due to uncertain relation between wall teichoic acids biosynthesis and PGN biosynthesis [20].

Zinc can inhibit PGN biosynthesis that zinc inhibition of phosphoglucomutase results in decreased capsule biosynthesis and Zinc intoxication also is observed to disrupt or inhibit PGN biosynthesis [21].

Metalation of Zn^{2+} enzymes are activated by Zn^{2+} metalation *via* Zn^{2+} transporters with that Zn(II) disrupts this coordination, resulting in depression of heme synthesis but continued repression of catalase that Zn (II) intoxication leads to intracellular heme accumulation from measurement of heme content of crude extract of cells treated with zinc concentration 50 μM Zn (II) [22].

Zinc ions-induced bacterial cell wall functions PGN inhibitive synthesis enzymes of TG and TP against *S. aureus*, in which zinc ions inhibit PGN biosynthesis and zinc disrupts PGN biosynthesis in bacterial cell wall [23]. The zinc intoxication on S. pneumoniae, observing disruptions in central carbon metabolism, lipid biogenesis, and peptidoglycan biosynthesis. Thus, copper(II) and zinc(II) mainly regulate PGN biosynthesis TG/TP, inhibit PGN synthetic enzymes and copper and zinc intoxications can inhibit PGN biosynthesis TG against *S. aureus*.

PGN cleavage by copper-containing autolysin and by zinc-containing autolysins amidase: AmiE, Rv3717, AmiA

Copper(II) can cleave and inhibit polymerization of glycan chains

Table 1: *S. aureus* PGN cell wall syntheses TG/TP and four PGN autolysins, and *E. coli* PGN cell wall syntheses TG/TP and five autolysins.

S. aureus PGN syntheses and PGN autolysins		*E. coli* PGN syntheses and PGN autolysins	
PGN syntheses TP/TG	PGN four autolysins	PGN syntheses TP/TG	PGN five autolysins
Transglycosylase, TG	*N-acetylmuramidase* *N-acetylglucosaminidase*	Transglycosylase, TG	*N-acetylmuramidase* *N-acetylglucosaminidase*
Transpeptidase, TP	*N-accetylmuramyl-L-alanine amidase* *DD-endopeptidase (Lysostaphin)*	Transpeptidase, TP	*Amidase* *Carboxypeptidase* *Endopeptidase*

bonding and cross-linking of side peptide that Cu^{2+} ions inhibit polymerization of glycan chains, forming copper complex, in which is partial action sites of glycan saccharide chains.

Copper-complexes on saccharide chains may be ·—NAG-(NAM-Cu-2O-2N-NAG)-NAM—· that Cu^{2+} ions inhibit cross-linked reaction by peptide copper complex formation bonding to side peptide chains.

$Cu2^{2+}+2LH \rightarrow CuL_2+H^+$

Peptide copper complex may be 3N-Cu-O, Cu (Gly-L-Ala) H_2O that specially, Cu^{2+} ions react with cross-molecular penta glycine $(Gly)_5$, copper-glycine complex may be formed.

Amino acid: $Cu^{2+}+Gly^- \rightarrow Cu(Gly)^+$,$Cu\ (Gly)^++Gly^-\rightarrow Cu(Gly)_2$,

Peptido: Cu^{2+}+GlyGly → Cu(GlyGly),Cu(GlyGly)+Gly^- → $Cu(GlyGlyGly)^-$ [24].

Zn PGN cleavage by zinc-containing autolysin is involved that PGN cleavage by zinc-containing autolysin amidase; AmiE, Rv3717, AmiA that Zinc(II) can cleave bacterial PGN protein that As PGN cleavage by Staphylococcal autolysin, zinc dependent metalloenzyme AmiE is efficient as prevention of the pathogen growth [25]. The other, Zn^{2+} binding AMIDASE Rv3717 showed no activity on polymerized PGN and however, it is induced to a potential role of N-Acetylmuramyl L-alanine Amidase [26]. Zinc(II) can cleave bacterial PGN protein that As PGN cleavage by Staphylococcal autolysin, zinc dependent metalloenzyme AmiE is efficient as prevention of the pathogen growth [27].

Anti-microbial activity on metal salts

Antimicrobial activities of zinc chloride, zinc citrate, zinc sulphate and zinc gluconate were assessed against Staphylococcus aureus that zinc sulphate exhibited relative less antibacterial activity while zinc gluconate was found to possess the least activity in comparison to other three zinc salts. Zinc gluconate was devoid of antifungal activity whereas the other salts showed antimycotic activity but, it was significantly lower than their respective activities against tested bacterial strains [28].

Antibacterial activity of Cu^{2+}-treatment against Staphylococcus aureus was the most effective. Zn^{2+}-treatment possessed a great antibacterial activity against *S. aureus* even. Cotton fabric treated with Cu^{2+} possessed the most effective antibacterial that treated with Zn^{2+}, Fe^{2+} and Fe^{3+} possessed activity against Klebsiella pneumoniae a slight antibacterial and activity [29].

Antibacterial effects of four zinc salts namely zinc chloride, zinc sulfate, zinc citrate and zinc acetate against *Streptococcus mutans* (*S. mutans*) and *Streptococcus sobrinus* (*S. sobrinus*) have been evaluated that zinc chloride, zinc sulfate and zinc acetate demonstrated higher MIC and MBC values against *S. mutans* compared to *S. sobrinus*, in which zinc citrate revealed the highest MIC and MBC values of 1 mg/mL and > 8 mg/mL for *S. sobrinus* and > 8 mg/mL for *S. mutans*, respectively. For *S. mutans*, zinc chloride recorded a MIC value of 1 mg/mL whereas both zinc sulfate and zinc acetate had MIC values of 2 mg/mL. MBC values for zinc chloride were 2 mg/mL, followed by 4 mg/mL for both zinc sulfate and zinc acetate. For *S. sobrinus*, zinc chloride, zinc sulfate and zinc acetate recorded MIC values of 0.125 mg/mL and MBC values of 4 mg/mL Zinc citrate exhibited higher MIC and MBC values respectively of 1 mg/mL and > 8 mg/mL for S. sobrinus and 8 mg/mL and > 8 mg/mL for S. mutans [30].

Antimicrobial activity on metal-based compounds antibacterials

Antimicrobial activity of metal based antibacterial compounds such as silver-based antibacterial compounds, gold-based antibacterial compounds, gallium-based antibacterial compounds, copper-based antibacterial compound have a greater understanding of the properties, which give metal-based agents having higher antibacterial activity and lower toxicity will provide a successful toolkit for the development of compounds that are safe and effective for systemic administration. Metal-based antibacterial compounds could become a solution for the treatment of bacterial infections resistant to antibiotics [31].

Some of the most historically relevant metal-based compounds in the field of antimicrobials are showed in the following; (A) Dicyanoaurate(I) N ☰ C-Au-C ☰ N; (B) chemical structure of auranofin, one of the currently most promising metal based antimicrobial agent; (C) silver sulfadiazine; (D) ranitidine bismuth citrate; (E) bismuth subcitrate potassium that although bismuth and silverbased antimicrobials are currently in clinical use, the immense versatility of metal based compounds, including the types of ligands, the coordination geometries and the intrinsic properties of the metallic center, make them some of the most promising antibacterial candidates for the next generation of antimicrobials, both by elucidating the mechanism of action and by unravelling non-trivial response pathways that are active. Compared to traditional techniques, omics approaches can generate an unprecedented amount of data, enable the analysis of highly complex features and providing a general overview of the underlying processes [32].

These complexes consist of a central metallic ion and a surrounding array of ligands defined as molecules or ions that have electrons available for donating towards a positively charged species such as metal ions, forming dative covalent bonds. These ligands can be pharmacological active molecules and the coordination with metals can modify the activity or they can be inactive in which most part of the studied complexes is more active than the free ligands. The effect on the microbial targets is due to the action of the complexes as it, or metal and ligand as individual species where the complexes can act as a carrier of metals and ligands across the cell membrane. Moreover, the synergistic action of metals and free ligands, information very valuable to make comparison with the activity of complexes, or include analysis of the selective action on microorganisms [33].

Anti-microbial activity on metal-based materials

Metal-based alloys antibacterial mechanism has been proposed that killing the bacteria by direct/indirect contact with specific released metal ions or generation of Reactive Oxygen Species (ROS), both metal ions and ROS can disturb the functionality of bacteria and damage cellular components, for instance, by inhibiting protein and enzyme functions and by changing the bacteria‘s Deoxyribonucleic Acid (DNA). Antibacterial materials inhibit bacterial growth, eventually leading to bacterial cell mortality. Therefore, the antibacterial mechanisms of metals, it is fundamental to have a basic knowledge of the bacterial cell structure with particular respect to the cell wall against Gram- positive and Gram-negative bacteria structures. In the process of inhibiting pathogenic microorganisms, these four mechanisms interact and intersect and the active component, metallic Ag, Cu, Zn play the main role in inhibiting and killing pathogenic microorganisms by destroying the structure of cells [34].

Antibacterial capability of antibacterial metallic elements, Fe-, Zn-, Co-, Ti-based alloys, and other metals had been investigated including Co-, Fe-, Mg-, Ti-, and Zn-based alloys, and some few other metal-based alloy systems, were analyzed in detail cell wall/membrane disruption mechanism and an effort to comparatively evaluate the antibacterial and mechanical response of the different alloys developed so far was made. Generally, the incorporation of Cu or Ag, which are well-known antibacterial metallic elements, shows remarkable effectiveness against both Gram-positive and Gram-negative bacteria. Additionally, some few other elements like Ca, Ce, and rare earths have been investigated, and some of them show antibacterial capability [35].

As an alternative, exploring Multicomponent MoNbNiTiZr Alloy is viewed as a viable path for bettering both mechanical performance and biocompatibility, which the MoNbNiTiz alloy demonstrate its ability to resist biofilm formation in these preliminary tests can reduce the risk of implant failure caused by bacterial infections and the potential of the MoNbNiTiZr alloy for biomedical applications. Its unique microstructural characteristics, favorable mechanical properties, biocompatibility, and antimicrobial resistance make it a promising candidate for further exploration in the field of biomaterials [36].

Antimicrobial activities of metal-based nanoparticles; AgNPs, CuONPs, AuNPs, and ZnONPs such as nanoparticle material for medical and pharmaceutical applications such as antibacterial, anti-fungal, anti-viral, anti-amebial, anti-cancer, anti-angiogenic, antiinflammatory agents have been proposed as alternative over traditional antibiotics to overcome bacteria resistance against Grampositive and Gram-negative bacteria [37].

Specific metal ions such as silver, zinc, copper, iron and gold outline their distinct modes of action that the use of these metal ions and nanoparticles in tissue engineering had been employed to prevent implant failure including the most recent advances in antimicrobial research using Ag, Zn, Cu, Fe and Au ions and nano materials and the various mechanisms of action which are currently discussed in the field. Importantly, in the case of nanoparticles, the release of metal ions creates a dual-mode of action where both NPs and ions can independently cause antibacterial effects and that ROS generation and ion release are supposed to play a subordinate role in the antibacterial activity of gold and Au-NPs, while direct interaction with the cell envelope, and binding to intracellular components of the bacteria are thought to represent the key mechanisms [38].

Titanium alloy coated with carbon-based nanofilms has stronger antibacterial activity and better histocompatibility in vivo than CoCr-Mo alloy that both *in vitro* co-cultures of carbon-based nanofilm titanium alloy and Co-Cr-Mo alloy with *S. aureus* and *E. coli*, respectively, failed to form obvious inhibition zone. Fewer bacteria adhered to the novel titanium alloy coated with carbon-based nanofilms can be observed by scanning electron microscopy and fluorescence staining techniques [39].

Antimicrobial mechanism for interactive relationships of metallic ions and their ligands

Antimicrobial mechanism for metallic ions with their ligands may be thought that metallic ions and ligands in metal salts, metal-based compounds/metal complexes, and metal-based materials against *S. aureus* and *E. coli* interact with that Various biological aspects of the metal based drugs/ligands entirely depend on the ease of cleaving the bond between the metal ion and the ligand, in which the relationship between ligand and the metal in biological systems and the efficacy of the various organic therapeutic agents can often be metal complexes as antimicrobial agents enhanced upon coordination with a suitable metal ion and the donor sequence of the ligands because different ligands exhibit different biological properties [40].

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Thus, antimicrobial mechanism of interactive relationship of metallic ions and their ligands, in which the relationship between ligand and the metal in biological systems and the efficacy of the various organic therapeutic agents can often be metal complexes as antimicrobial agents enhanced upon coordination with a suitable metal ion and the donor sequence of the ligands.

Conclusion

(1) Bacteriolytic destruction of PGN cell wall has been clarified on the ground of the results obtained from halo antibacterial susceptibility tests of metals nitrate and sulfate solutions in metallic ion concentration of 100 mM/L against Staphylococcus epidermidis, in which the order of bacterial effect for the metal nitrate solutions is as follows, $Cu^{2+}>Zn^{2+}>Ag^{+}>Pb^{2+}>Al^{2+}$, and the other, in the metal sulfate solutions, the antibacterial effect order is found to be $Zn^{2+}>Cu^{2+}>Ag^{+}>Al^{2+}$.

(2) Cu(II)- and Zn(II)-ions mainly can suppress PGN syntheses TP/TG, inhibit PGN elongation, and enhance PGN autolysins, in which copper(II) and zinc(II) regulate PGN synthesis TG/TP, inhibit PGN synthetic enzymes, and copper and zinc intoxications can inhibit PGN biosynthesis TG against *S. aureus* and *E. coli*. PGN cleavage by copper-, zinc-containing autolysins amidase; AmiE, Rv3717, AmiA that copper(II) can cleave and inhibit polymerization of glycan chains

bonding and cross-linking of side peptide, forming copper complex, in which is partial action sites of glycan saccharide chains.

(3) Anti-microbial activity on metal salts: The antibacterial activity of Cu^{2+}-treatment against Staphylococcus aureus was the most effective. Zn^{2+}-treatment possessed a great antibacterial activity against *S. aureus* even, Cu^{2+} possessed the most effective antibacterial that treated with Zn^{2+}, Fe^{2+} and Fe^{3+} possessed activity against *Klebsiella pneumoniae* a slight antibacterial and activity.

(4) Antimicrobial activity on metal-based compounds: Metal-based antibacterial compounds such as silver-based antibacterial compounds, gold-based antibacterial compounds, gallium based antibacterial compounds, copper-based antibacterial compound have a greater understanding of the properties, which give metal-based agents having higher antibacterial activity and lower toxicity will provide a successful toolkit.

(5) Anti-microbial activity on metal-based alloy materials. Fe-, Zn-, Co-, Ti-based alloys, and other metals had been investigated under the bacterial capability method with bacterial suspension, immersion and incubation of different times, which include Co-, Fe-, Mg-, Ti-, and Zn-based alloys, and some few other metal-based alloy systems, were analyzed in detail cell wall/membrane disruption mechanism and an effort to comparatively evaluate the antibacterial and mechanical response of the different alloys developed so far was made. Generally, the incorporation of Cu or Ag, which are well-known antibacterial metallic elements, shows remarkable effectiveness against both Gram-positive and Gram-negative bacteria, which shows remarkable effectiveness against both Gram-positive and Gram-negative bacteria. Metallic Ag, Cu, Zn play the main role in inhibiting and killing pathogenic microorganisms by destroying the structure of cells.

(6) Finaly, antimicrobial mechanism for metallic ions with their ligands in metal salts, metal-based compounds/metal complexes, and metal-based materials against *S. aureus* and *E. coli* may be thought that various biological aspects of the metal based drugs/ligands entirely depend on the ease of cleaving the bond between the metal ion and the ligand, in which the interactive relationship between ligand and the metal in biological systems and the efficacy of the various organic therapeutic agents can often be metal-based compound/metal complexes and metal-based material as antimicrobial agents enhanced upon coordination with a suitable metal ion and the donor sequence of the ligands because different ligands exhibit different biological properties.

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Conflict of Interest

The author declare that they have no competing interests.

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