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Metallic Cu(II)- and Zn(II)-Ions Mediated Bacteriolytic Peptidoglycan Cell Wall Destructions and Artificial Intel-ligence-Bacterial Detective Heavy Metals against *S. Aureus* and *E. Coli*

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ABSTRACT

Cu(II)- and Zn(II)-ions can suppress PGN syntheses transpeptidase (TP)/transglycosylase (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 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.

Antimicrobial activity on metal-based alloy materials: The antibacterial activity of Cu^{2+}-treatment against Staphy-lococcus 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.

Fe-, Zn-, Co-, Ti-based alloys, and other metals had been investigated under the bacterial capability method with bacte-rial 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.

Metallic ions-induced anti-bacterial activity observations or detections by artificial intelligence (AI) techniques: AI employing has great promise for the design of antimicrobial peptides (AMPs), in which AI is now leading to rapid progress, expanding anti-infective drug discovery, enhancing our understanding of infection biology, and accelerating the development of new diagnostics. In recent advances in AI, AI-driven antimicrobial discovery encompasses a diverse set of computational strategies tailored to different data modalities, antimicrobial classes, and translational objectives that AI approaches applied to the discovery of small-molecule antibiotics and antimicrobial peptides, emphasizing model architectures, data requirements, validation strategies, and AI-based for the detection and removal of heavy metals (HMs) from environments.

Antimicrobial mechanism for metallic ions with their ligands: 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 met-al-based material as antimicrobial agents enhanced upon coordination with a suitable metal ion and the donor se-quence of the ligands because different ligands exhibit different biological properties.

Abbreviation

AMR: Antimicrobial resistance, AI: artificial intelligence, DNA: deoxyribonucleic acid, Eps: endopeptidase, HMs: heavy metals, PGN: peptidoglycan, PGRPs: peptidoglycan recognition protein, PTEN: 403 amino acids, LYS1: Lysozyme1, MBC: minimum bactericidal concentration, MIC: minimum inhibitory concentration, OM: outer membrane, PRRs: pattern recognition receptor, TG: Transglycosylase, TP: Transpeptidase, ROS: reactive oxygen species.

Introduction

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 [1].

Bacteriolysis of *S.aureus* PGN cell wall by Cu^{2+} ions is caused for the inhibition of PGN elongation due to damages of PGN synthetic TG/TP and activation of PGN autolysins. The other, bacteriolysis of *E.coli* outer membrane cell wall by Cu^{2+} ions is attributed to the destruction of outer membrane structure and to the inhibition of PGN elongation due to the damage of PGN biosynthesis TP and the activation of PGN autolysins [2].

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 was 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 [3].

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 antimicrobial resistance (AMR) [4].

Artificial intelligence (AI) using has great promise for the design of antimicrobial peptides (AMPs) that AMP- 29 shows selective antifungal activity against Candida glabrata *in vivo* antifungal efficacy in a murine skin infection model. The proposed approach offers a pipeline for designing diverse AMPs to counteract the threat of antibiotic resistance [5].

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's like copper & chlorhexidine on dental plaque bacteria, silver nanoparticles & cephalexin against *E. coli* & *S. aureus* [6].

Recently, Antimicrobial activity of copper alloys as Cu-Zn, Cu-Ni, Cu-Sn, Cu-Al-Ni alloys against microorganisms is attention specially that the experimental conditions play a major role in the results obtained and differences between studies make comparison difficult [7].

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 [5], 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. [8].

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 [9].

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 [10]. 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 [11].

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

In this mini-review article, bacteriolytic PGN cell wall destruction and clearance are elucidated under the basic concept of Cu(II)- and Zn(II)-ions induced suppressive PGN biosynthesis, activated PGN autolysin, and PGN elongation inhibition, in which Cu- and Zn-ions mediated antimicrobial activities and metallic Al-detective bacterial investigations by metal-based alloys materials have been extensively discussed against *S. aureus* and *E. coli.*

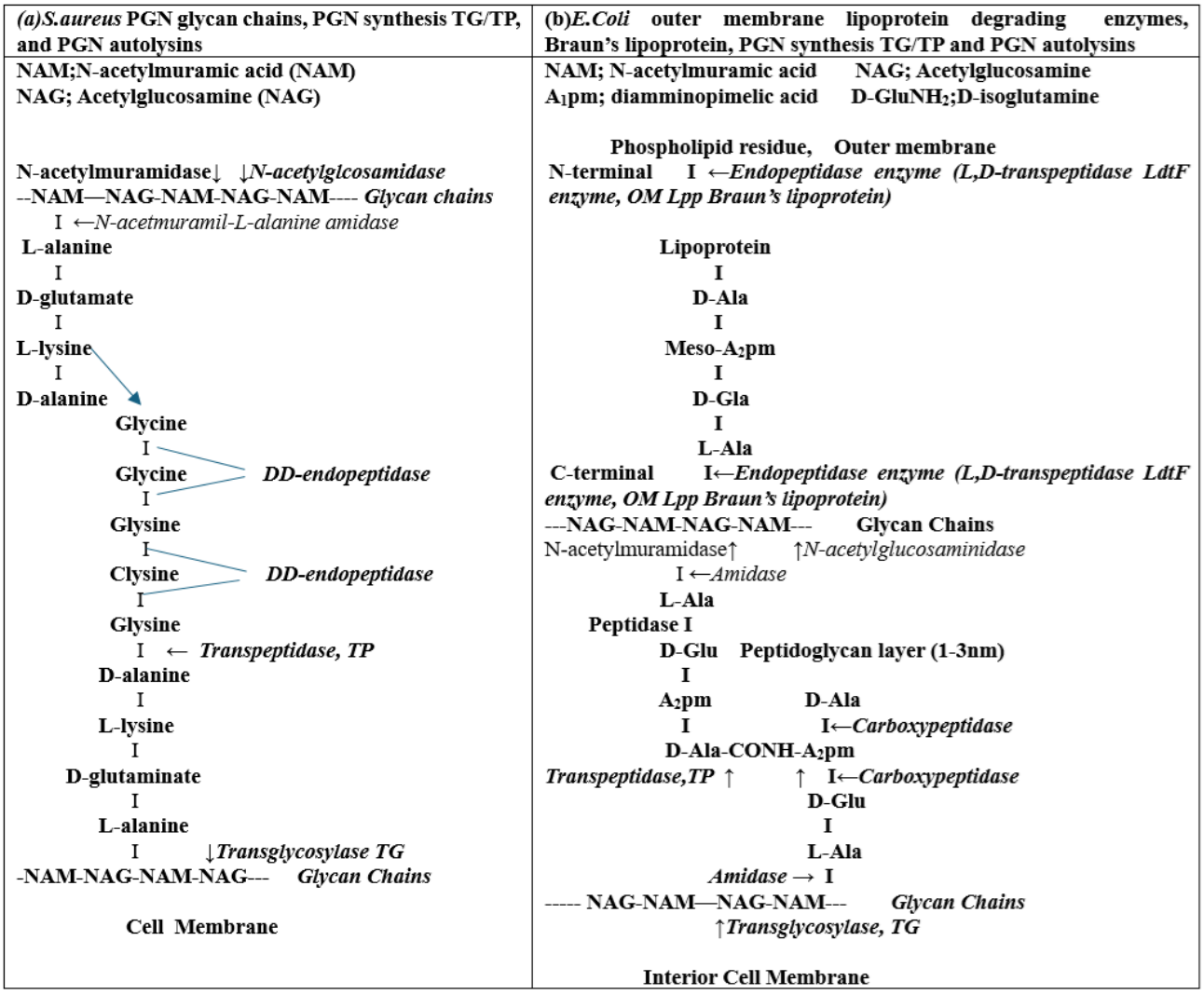
Discussion

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, 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 [12,13].

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***	**Transglycosylase, TG**	***N-acetylmuramidase*↑**
	N-acetylglucosaminidase		***N-acetylglucosaminidase***
	N-accetylmuramyl-L-alanine amidase		***Amidase***
Transpeptidase,TP	***DD-endopeptidase (Lysostaphin)***	**Transpeptidase, TP**	***Carboxypeptidase***
			Endopeptidase



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

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 [1].

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 [14]. 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 [15].

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 [16].

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 [17].

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 [18].

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 [19].

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 [20].

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) [21].

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 [22]. The zinc intoxication on *S. pneumoniae,* observing disruptions in central carbon metabolism, lipid biogenesis, and peptidoglycan biosynthesis.

Thus, copper(II) and zinc(II) regulate PGN biosynthesis TG/TP, inhibit PGN synthetic enzymes and copper and zinc intoxications can inhibit PGN biosynthesis TG against *S. aureus.*

Antimicrobial 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 [23].

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 [24].

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 [25].

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* [2].

Metallic ions-induced anti-bacterial activity observations or detections by using AI-bacterial detective heavy metals

AI-based method for early detection of antimicrobial effects on *E. coli* has been developed that the AI model was used to determine the antimicrobial activities of the various cationic ions. The AI model accurately estimated the minimal inhibitory and minimal lethal concentrations for *E. coli,* indicating the potential of our novel methodology to be applied in microbiology [26].

Artificial intelligence (AI) is now leading to rapid progress, expanding anti-infective drug discovery, enhancing our understanding of infection biology, and accelerating the development of new diagnostics. Approaches for detecting, treating, and understanding infectious diseases, underscoring the progress supported by AI. AI also is enable to design next-generation drugs, vaccines, and diagnostics that address infectious diseases [27].

In clinical practice, AI-driven decision support systems strengthen antimicrobial stewardship by deep learning approaches accelerate antimicrobial drug discovery. AI also enhances the detection and surveillance of resistance genes through genomic and metagenomic analyses across human, animal, and environmental settings. AI applications in antimicrobial resistance (AMR) face challenges related to data quality, bias, interoperability, privacy, and clinician adoption. Subsets of AI, including machine learning (ML) and deep learning (DL), are particularly valuable relevant to AMR. The other, in healthcare, AI supports AMR management by rapidly identifying pathogens and predicting resistance pat terns, guiding optimized antibiotic prescribing, accelerating the discovery of novel antimicrobial compounds through in silico screening, and integrating clinical and environmental data to forecast emerging resistance trends. AI also can enhance diagnosis, treatment, and strategic planning, enabling healthcare systems to respond more effectively to the growing threat of AMR [28].

Recent advances in artificial intelligence (AI) and AI-driven antimicrobial discovery encompasses a diverse set of computational strategies tailored to different data modalities, antimicrobial classes, and translational objectives. AI approaches applied to the discovery of small-molecule antibiotics and antimicrobial peptides, emphasizing model architectures, data requirements, validation strategies, and emerging design paradigms, in which AI methodologies increasingly support the discovery of narrow-spectrum agents and target-specific antimicrobial peptides, reflecting a growing emphasis on minimizing resistance selection pressure and preserving microbiome integrity [29].

By AI detections of metal ions, AI-based technology is integrated for the detection and removal of heavy metals (HMs) such as Cu, Ni, Zn, Co, Fe^{+2}, Mn, Cd, Fe^{+3} and Pb from environmental and human samples the impact of HMs on the environment and human health, their detection and removal techniques, and the integration of recent advancements in AI-based technology [30].

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 [31].

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, anti-inflammatory agents have been proposed as alternative over traditional antibiotics to overcome bacteria resistance against Gram-positive and Gram-negative bacteria [32].

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 [33].

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

Cu(II)- and Zn(II)-ions can suppress PGN syntheses TP/TG, inhibit PGN elongation, and enhance PGN autolysins: 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.

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.

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