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Review of copper and copper alloys as immune and antibacterial element

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Abstract: This review discussed the relationship among copper, human, and bacteria. Copper plays an important role in human immunity. Copper can boost human immune defense reactions at recommended intake level. The content mainly focused on copper antibacterial activity and copper antibacterial mechanisms. Conclusions stated that copper antibacterial activity is affected by copper homeostasis mechanisms in bacteria, adhesion, humidity, strain specificity, and manufacturing methods of antibacterial agents. For the preparation of particle antibacterial agents and surface antibacterial agents, this review discussed several manufacturing methods, such as sol−gel, cold spray, and biosynthesis belonging to chemical synthesis, physical synthesis, and biological synthesis, respectively. Sol−gel method contributes to the preparation of particle agents and surface agents. Cold spray technique is utilized in synthesis of surface copper agent. Biosynthesis is a novel technology which can be applied in nanoparticle agent preparation.

Key words: immunity; toxicity; antibacterial activity; copper homeostasis; adhesion; humidity; strain specificity; antibacterial agents; mechanisms

1 Introduction

With the increasing desire of public health, more and more elder, middle-aged and even young people visit hospitals and are treated by invasive medical devices such as drug events and surgical operations [1]. Such behaviours increase the risk of health care-associated infections (HCAIs), which becomes the most common cause of patients' illness during hospitalization. In the entire hospital environment, bed rails, door handles, computer accessories, instruments, curtains, and other surfaces are often contaminated by bacteria, fungi, and viruses. Many medical devices are not disposable. The whole medical procedure needs to be concerned including device recycling, sorting, sterilization and disinfection, and maintenance. It is necessary not only to maintain invasive equipment sterile, but also to eliminate HCAIs as well [1]. At the beginning, metals and their compounds failed to catch as much attention as organic medicine, until YOSIOKA and ZAIZEN [2] investigated the antibacterial effect of copper by adding copper ions into 8-hydroxyquinoline against *Mycobacterium smegmatis*, because copper ions can chelate with phenazine derivative which boosted the killing bacteria efficiency. But they only discussed the copper chelating effect without discussing bulk copper killing mechanism. However, since multidrug-resistant bacteria existed [3,4], the desire of antibacterial agents increased dramatically. Figure 1 shows the development of antibacterial and the antibacterial resistance [5].

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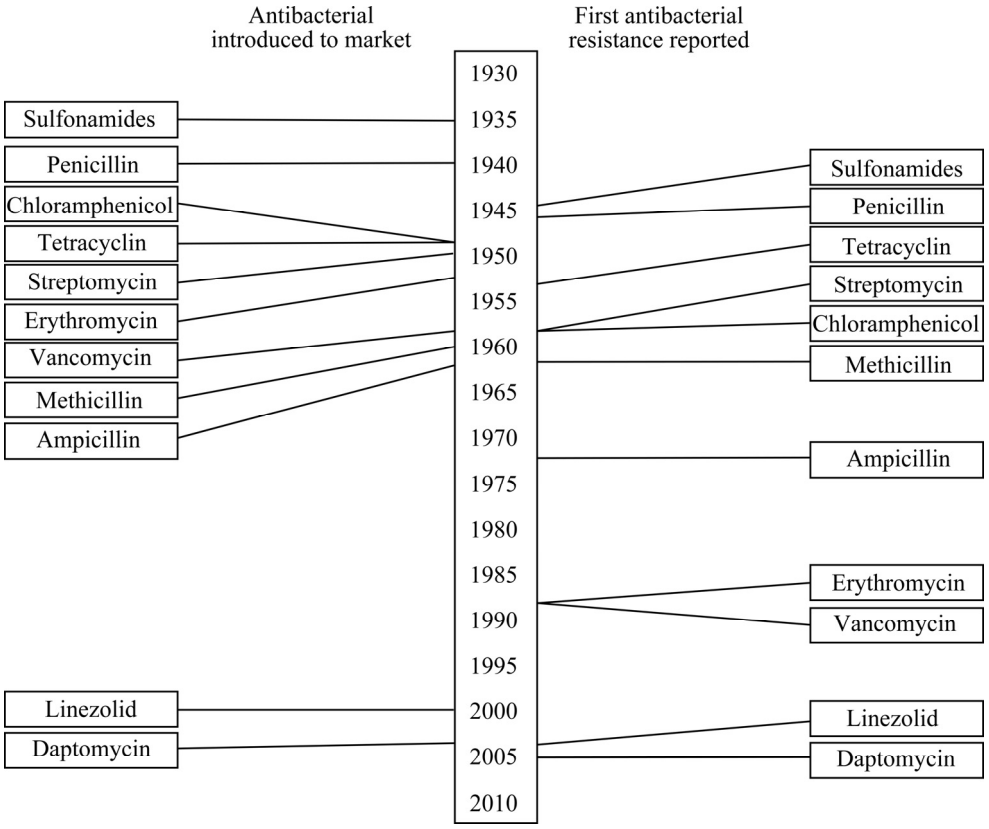

Fig. 1 Timeline representing sequence between introduction of antibacterial and antibacterial resistance [5]

Most of the antibiotics would be resisted in half-decade. DYE et al [6] declaimed that multidrug-resistant bacteria were a growing hazard to human health universally and one of the strategies to beat them could be considered as selecting a metallic substitute for an antibiotic. O'CONNELL et al [5] summarized the current strategies against multidrug-resistant organisms once they mentioned antimicrobial peptides (AMPs). AMPs carrying an overall positive charge, as part of product of immune response, concentrate on the membranes of bacterial cells which bear negative charges [7,8]. This antimicrobial effect due to electronic attraction induces the idea of metallic ions contact killing-microbial mechanisms.

Among the metallic materials, silver (Ag) and copper (Cu) are effective antibacterial agents, which have high efficacy against a variety of microorganisms, especially for super bacteria with multidrug resistance [9]. In particular, silver material has always been the first choice for many antibacterial studies [10,11], and recent studies have shown that the performance of copper under ordinary conditions (normal temperature and humidity) is even better than that of silver [12,13].

Cu as an antifouling agent is widely used in water treatment membranes, antibacterial textiles, and heating, ventilation and air conditioning systems or other high-touch surfaces [14−16]. At the beginning of the COVID-19 epidemic exploration, DOREMALEN et al [17] pointed out that coronavirus lives on copper surface for 4 h, on cardboard for 1 d, and on plastic for 3 d. All the research demonstrated that copper has great potential of killing microbial even though copper is an essential element and microbe has a strategy to maintain copper homeostasis.

In this work, hypotheses and mechanisms of killing microorganisms of copper were discussed. As one of the natural nutrients available from daily supplement, copper participates in immunity-related enzymes synthesis [18]. This paper briefly mentioned the role of copper in immune response, its toxicity, and microorganisms' strategy of copper homeostasis. Copper antibacterial activity as surface agent and particle agent was introduced. Considering the conflict between corrosion rate and antimicrobial efficiency [19,20], the impact factors of copper ions release such as adhesion, humidity, strain specificity and manufacturing

methods were also discussed. However, the review is impossibly comprehensive, as for completing such an exhaustive review in such a tremendously enormous field would be an all but impossible task. Figure 2 represents the relationship among copper, human and bacteria.

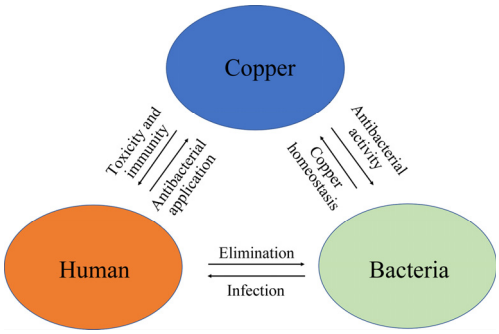

Fig. 2 Relationships among copper, human and bacteria

2 Copper and immunity

2.1 Copper in animal immunity

Creature cannot live and breed without nutrients which are usually considered as a critical role in immunity, such as energy, protein, vitamins (A, E, C, B6, B12, folic acid and choline) and minerals (Cu, Se, Zn, Co, Mn and Fe) [21]. With Cu(I)/Cu(II) redox couple in biochemistry, copper establishes its role in various biochemical reactions including electron transfer, respiration, nervous functions, wound healing, and protein activation [22,23]. Cu is not only effective in antibacterial, but also has a certain positive effect on the level of creature immune system. SENTHILKUMAR et al [24] utilized nutrients of different copper levels to investigate lamb's entire immune response and copper-dependent enzyme activity of lamb. The result showed that enzyme activity, humoral immune response and cell mediated immune response increase with inorganic copper concentration under observable toxic level. Researchers [25,26] reported that copper/zinc-loaded montmorillonite has a positive effect on suppression of genic expression of inflammation of intestinal integrity in pigs. However, the conclusion of copper used in human immunity cannot be drawn arbitrarily relying on animal research. BOYNE and ARTHUR [27] reviewed the use of animal simulations and human cells in petri dishes to assess the role of copper in immune responses. Based on their research, in the case of severe copper deficiency, the number of neutrophils in human peripheral blood decreased. Not only that, but under the premise of an obvious and slight lack of copper, their ability to produce superoxide dismutase (SOD) which could kill nucleic acids and kill ingested microorganisms has also declined. These indicators are usually considered as part of immune response to infections [21,28,29].

2.2 Copper in human immunity

As a dietary supplement, copper acts like cofactor of cuproenzymes which contain one or more copper atoms [30], for instance, ceruloplasmin (CP) [31], Cu/Zn-SOD [32], and cytochrome c oxidase (COX) [33]. CP contributes 40%−70% to copper in serum [34], participating in energy production, controlling iron and copper homeostasis, influencing connective tissue synthesis, iron ions transfer, and neurotransmitter synthesis [31,35,36]. HELLMAN et al [37] concluded that CP is synthesized in hepatocytes containing six copper atoms with three spectroscopically different types of sites, and the critical step of the synthesis was to occupy all types of copper-binding sites. This uncovered the incorporation of copper in human CP and revealed the vulnerable and accurate mechanism of CP formation. KELLEY et al [38] examined the effect of a low-copper diet on several indexes of immunity in 11 young men in a metabolically controlled trial. The result did not prove that Cu-enriched environment has a positive effect on proliferative response, while Cu-deficient environment resulted in immune reactions deficiency [38]. Nevertheless, CP is an acute phase protein motivated by infection due to bacteria. Thus, the serum copper will increase after bacterial invasion [39,40]. This phenomenon can oxidize Fe^{2+} to Fe^{3+}, which can bind with reactive oxygen species (ROS) [41,42], consuming essential Fe element to starve invaders [43]. CP generation resulting in microbial growth inhibition is called nutritional immunity.

Furthermore, skin is the largest organ in human body and the first line of immunity defence. Copper nanoparticles (Cu-NPs) have been proved to have positive effect on forming vascular endothelial growth factor (VEGF) and stimulating proliferation of skin cells by stimulation of revascularization and re-epithelialization [44,45].

From the above analysis, a conjecture might be induced that in some cases, copper ions would have antibacterial effects and have a positive effect on the human immune system. Systemic copper can not only stimulate immunity response, but also be the host's weapon against pathogens.

3 Copper antibacterial activity and toxicity in human

Copper has 29 electrons whose theoretic electron configuration is Ar $4s^2 3d^9$. Actually, the distance between fulfilled orbital and atomic nucleus is much smaller than that between incompletely filled orbitals. As a result, the practical electron configuration is Ar $4s^1 3d^{10}$ [46]. This unique property plays a great role in biochemistry. More specifically, copper cations stay stable in the Cu(I) (Ar $4s^0 3d^{10}$) state and will be transformed into the Cu(II) (Ar $4s^0 3d^9$) oxidation state in water. The standard potential of the Cu(I)/Cu(II) redox couple is E_0'=−261 mV [47]. As for coordinating to the protein, the redox potential of copper varies from 200 to 800 mV. Unbound copper cations will participate in Fenton-like reaction, generating the hydroxyl radical OH•, which will result in the oxidative damage of any cellular macromolecule [48]. However, the key factors of antibacterial effect of copper perform differently as surface and particle agents [49]. Generally, this part presents copper as surface agent, particle agent, and copper toxicity in human, respectively.

3.1 Copper as antibacterial agent

3.1.1 Copper as antibacterial surface agent

A lot of research has shown that killing microorganism efficiency and ability of copper coupons increase with the increase of its content [50−52]. Copper-based alloys were responsible for elimination of microorganisms [50,52−55]. Table 1 summarizes the copper content and the lowest effective concentration of some copper-based alloys. NOYCE et al [50] investigated several copper alloys (61−95 wt.% Cu) vs. *E. coli* O157 at different temperatures (22 and 4 °C). At 4 °C, only copper content beyond 85 wt.% obviously reduced the amount of *E. coli* O157. At 22 °C only the highest copper alloy (95 wt.% Cu) completely annihilated *E. coli*. WILKS et al [51] investigated the survival of *E. coli* O157 on copper-based alloys surface at 20 and 4 °C, respectively. They demonstrated that pure Cu obliterated all *E. coli* O157 at both temperatures, and the lowest copper content to eliminate *E. coli* was 65 wt.% at 20 °C. WEAVER et al [52] evaluated the survival of *Clostridium difficile* on five copper alloys surface (65−100 wt.%), and the result demonstrated that copper content beyond 70 wt.% significantly reduced the number of *Clostridium difficile*. On the contrary, unlike antimicrobial activity, the corrosion resistance and durability decrease with increasing copper content [51]. WILKS et al [51] investigated other copper-based alloys, such as Cu−Ni alloy and Cu−Ag alloy, which displayed higher corrosion resistance and higher durability.

Table 1 Copper content and the lowest effective content of some copper-based alloys

Copper content/wt.%	Lowest effective content/wt.%	Ref.
61−95	85 (4 °C); 95 (22 °C)	[50]
0−100	65 (20 °C)	[51]
65−100	70	[52]

HUTCHISON et al [56] investigated Cu ions release of commercially pure Cu, Cu−4.5Sn−0.1Zn, and Cu−9.7Sn−0.1Zn (wt.%) in artificial perspiration. The result demonstrated that the sequence of Cu ions release in artificial perspiration from high to low amount was Cu−4.5Sn−0.1Zn, followed by Cu−9.7Sn−0.1Zn, and then Cu. The interesting part was that the composition of Cu−4.5Sn−0.1Zn promoted anodic dissolution, increased Cu ions release, and had the highest overall corrosion rate. Meanwhile, Sn content of Cu−9.7Sn−0.1Zn inhibited overall corrosion rate yet boosted Cu release due to SnO_2 film generation and enhanced dissolution effect [56]. QUARANTA et al [55] and HUTCHISON et al [56] challenged the idea of pure copper with the highest antimicrobial efficiency and presented the idea of balancing corrosion and ion release.

Taking all this information into account, the critical factor of antibacterial efficiency of copper as surface agent is Cu ions release rather than copper content.

3.1.2 Copper as antibacterial particle agent

Copper particles especially Cu-NPs display novel properties compared with conventional copper-based alloys. RUPARELIA et al [57] prepared Cu-NPs by wet chemical synthesis and discovered that Cu-NPs and Ag nanoparticles (Ag-NPs) kill different bacteria with superior efficiency, respectively. For example, Cu-NPs displayed higher antibacterial efficiency than Ag-NPs as for reducing *Bacillus subtilis* [57]. Combination of Ag-NPs and Cu-NPs may give rise to more complete bactericidal effect against mixed bacterial population. TAMAYO et al [58] compared the antibacterial activity of Cu-NPs with Ag-NPs in polyethylene, and the result showed that the former releases much more ions than the latter, even the latter has higher efficiency. For instance, the ions release rate of Cu-NPs was 203 times faster than that of Ag-NPs in polymer for 24 h of incubation and with 5 wt.% nanoparticles [58]. Generally, Ag-NPs have superior antimicrobial efficiency and outstanding corrosion resistance. However, Cu-NPs are easily tolerable as an essential element, and sometime, Cu-NPs can substitute Ag-NPs as biosafe material. BAKINA et al [59] utilized electrical exploration of wire to synthesize Cu/Fe bimetallic nanoparticles in argon medium, and Cu/Fe-NPs displayed the supreme antibacterial activity among Fe-NPs, Cu- NPs and their mixture, and they were competitive with Ag-NPs. Besides, other literatures [41,60,61] explained that the excellent antibacterial activity of Cu−Fe bimetallic nanoparticles is contributed by synergistic Cu^{2+} ions and Fe^{3+} ions release, which is lack of direct data to confirm. Cu^{2+} can penetrate membrane protein and damage DNA, and Fe^{3+} ions are considerable to bind with ROS [60,61].

Minimum inhibitory concentration (MIC) as one of the most critical characterizations to express antibacterial property needs to be considered. MIC is commonly defined as the lowest concentration required for an antibacterial solution to inhibit the visible growth of bacteria after 24 h incubation. For instance, BALELA and AMORES [62] observed that MIC of Cu-NPs for *E. coli* and for *S. aureus* is around 0.596 mg/mL. However, the MIC can only characterize antibacterial agent in nanoscale with specific amount and volume. Meanwhile, if copper displays as surface antibacterial agent (such as door handle), MIC needs to be modified not only because the droplet or perspiration volume is hard to determine, but also the bacteria incubation time is not fixed due to random touching surface interaction.

3.2 Copper toxicity in human

Copper is one of the cofactors of CP, and its active sites play a critical role in CP synthesis as mentioned previously [35]. However, beyond the tolerance level, the essential element could change into venomous copper. MACOMBER and IMLAY [63] revealed that even without O_2^- or H_2O_2, active copper ions inactivated enzymes by targeting iron-sulfur clusters. Based on their work, those clusters coordinating thiolate or inorganic sulfur ligands were the primary target of copper which would replace iron atoms. KARLSSON et al [64] observed higher membrane damage induced by Cu-NPs than CuO-NPs, which might link with corrosion rate. HEDBERG et al [65] confirmed that Cu-NPs corrosion reactions resulted in cell membrane damage, and they compared Cu-NPs ions release rate in biological and inorganic media. They observed that biological media boosted Cu-NPs corrosion rate and ion release rate, while higher Cu-NPs antibacterial activity was observed in inorganic media compared with the same mass of Cu ions. Table 2 represents the FDA recommended daily allowances (RDA) and the tolerable upper intake level for copper (UL) without health problems [66,67].

Table 2 Recommended daily allowances (RDA) and tolerable upper intake level (UL) ($\mu g \cdot d^{-1}$) [66,67]

Age		>19	14−18	9−13	4−8	1−3
Male	RDA	900	890	700	440	340
	UL	10000	8000	5000	3000	1000
Female	RDA	900	890	700	440	340
	UL	10000	8000	5000	3000	1000
Pregnancy	RDA	1300	1000	−	−	−
	UL	10000	8000	−	−	−
Lactation	RDA	1300	1000	−	−	−
	UL	10000	8000	−	−	−

For the balance of copper toxicity and boosting immunity, and the balance of corrosion rate and killing bacterial rate, the optimum release rate of

copper ions must be determined. For instance, 0.596 mg/mL of Cu-NPs could destroy *E. coli* and *S. aureus* after 24 h incubation [62]. Assuming that one 19 year-old male only takes Cu-NPs solution as daily nutrient supplement, and the maximum amount of daily intake is around 16.7 mL. Considering there are abundant food sources of copper, the absorption of antibacterial copper agent by skin, glands, and mucosa could raise the risk of copper intoxication.

4 Mechanisms behind copper vs micro-organisms

Before discussing copper, the hydroxyl radical OH· generated by Fenton-type reaction, is usually confirmed as ROS like H_2O_2. Copper participating cycle reactions below generate ROS, such as OH· and H_2O_2 [20,68].

$$Cu^{+}+H_2O_2 \rightarrow Cu^{2+}+OH^{-}+OH\cdot \quad (1)$$

The generated hydroxyl radical is considered to cause cell membrane damage.

$$2Cu^{+}+2RSH \rightarrow 2Cu^{2+}+RSSR+2H^{+} \quad (2)$$

$$2Cu^{+}+2H^{+}+O_2 \rightarrow 2Cu^{2+}+H_2O_2 \quad (3)$$

Copper ions can also act as the catalyst of biochemical reactions, such as sulfhydryls.

WARNES et al [69] reported that Cu(I)/Cu(II) redox couple and superoxide not including OH· play the major role in contact killing mechanism in most cases. Thus, this chapter majorly discussed the mechanisms of copper bactericidal activity and microbial copper homeostasis.

4.1 Mechanisms of copper antibacterial activity

In Section 3.1, ion release rate and nano-particles affinity to cell membrane are considered as the key factors of antibacterial copper. In a word, whether surface or particle agent, the bactericidal effect is activated after contacting. The contact killing mechanism is one of the major hypotheses of surface agent copper against microorganisms. For copper ions, Fig. 3 represents the four stages of contact killing [20].

In stage (a), copper dissolves from the agent surface, and ions release; Stage (b) represents bacterial copper homeostasis works after copper ion concentration increases and then the membrane fails; Stage (c) describes that copper ions and generated ROS cause cell damage; Stage (d) represents DNA degradation in bacteria after copper ions invasion.

Cu-NPs are believed in changing cell membrane permeability by their affinity [70], producing ROS or releasing copper ions which cause oxidation damage to cell [71], and disrupting DNA replication [72]. For instance, CHATTERJEE et al [73] observed the filamentation in bacteria and dissipation of cell membrane potential treated by Cu-NPs. The cell membrane potential played a critical role in cell division by influencing division proteins. The dissipation of cell membrane potential is the symbol of bacterial division. Thus, the discovery by CHATTERJEE et al [73] verified the antibacterial mechanism of Cu-NPs.

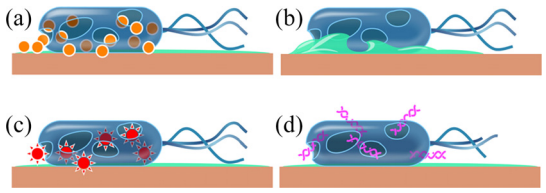

Fig. 3 Four stages of contact killing [20] (Stages (a−d) represent copper dissolution and ions release, bacterial copper homeostasis and cell membrane failure, cell damage caused by copper ions and ROS, and DNA degradation, respectively)

The mechanisms of two different agents exhibit high similarity and synergy. However, the concept of bacterial DNA degradation caused by copper ions invasion is controversial. Copper ions were believed in attacking certain nucleotide sequence in DNA [74,75]. However, QUARANTA et al [55] reported that there was no DNA destruction and reported the same mutation level of *E. coli* on copper surface and on stainless steel surface. Intracellular copper ions protect DNA in *E. coli* instead of causing genotoxicity [76] and no DNA fragmentation on dry copper surface was observed [77]. As a result, QUARANTA et al [55] challenged the idea of copper ions genotoxicity and stated that the DNA fragmentation was a secondary phenomenon without relation to copper ions. However, those intracellular copper ions exist in periplasmic cuproenzymes in bacteria as the main force to protect DNA destruction and to resist copper ions intrusion [69]. LAHA et al [78,79] observed DNA damage in Gram-negative and Gram-positive bacteria caused by ROS, which was generated by CuO-NPs.

4.2 Mechanisms of copper homeostasis in bacteria

Copper as one of the cofactors of many proteins of aerobic organism participates in a great number of redox reactions in bacteria. For instance, copper performs respiration and metal-binding protein function in bacteria [80,81]. However, copper could be toxic to aerobic life forms once beyond its allowance level. Obviously, the tolerance upper intake level for copper of human is far beyond its acceptable level of bacteria [58,67]. Besides, bacteria already have developed the strategies to face with copper-enriched environment, which is called copper homeostasis in bacteria. Almost all strain bacteria, whether pathogenic bacteria or isolated environmental bacteria, have copper resistance.

Copper homeostasis in bacteria was first observed by the phenomena of copper resistant gene point mutation [82]. Generally, cuproproteins in bacteria such as Cu/Zn SOD and COX stay in extracytoplasm/periplasm, and not in cytoplasmic space [42,83]. Cuproproteins usually fix at the membrane, thus copper ions transfer and delivery systems are regulated by extracellular cuproproteins via transmembrane transport. There are many regulation mechanisms: (1) chemical modification and ligands transformation; (2) controlling outer and inner membrane ions channel of transporter proteins; (3) managing transporter proteins abundance to change transport overall rates.

Figure 4 represents the copper homeostasis mechanisms in *E. coli*. There are two major protein systems in *E. coli* called Cu-effusing (Cue) system and Cu-sensing (Cus) system against copper [84]. According to Refs. [85−89], in Cue systems, when Cu(I) penetrates into cytoplasmic space, copper-responsive metalloregulatory protein (CueR) as the cytoplasmic sensor will start autophosphorylation and hydrolyze ATP to stimulate Cue systems gene expression. CueR utilizes hydrolysis energy to activate copper efflux P-type ATPase (CopA) which moves Cu(I) from cytoplasm to periplasm, and to activate CueO oxidizing Cu(I) to less toxic Cu(II). In Cus systems, CusS (histidine kinase) as the periplasmic sensor once detecting Cu(I) rising will activate itself and CusR (transcriptional regulatory protein) will stimulate Cus systems gene expression, finally extra Cu(I)/Cu(II) will be excreted by inner and outer membrane components of protein complex (CusA, CusB and CusC).

There is interesting information of schematic diagram of copper homeostasis mechanisms in *E. coli*. First, Cue and Cus systems respond differently. Cue system charges cytoplasm and periplasm homeostasis. Cue is responsible for transporting excessive copper complex from cytoplasm to periplasm and oxidizing Cu(I) to less toxic Cu(II). While Cus system takes charge for polluting copper ions from cell to extracellular. Second, Cue and Cus systems respond in sequence. Cue system responds at first, once Cue system is overwhelmed, Cus system starts the response. Third, both CueR and CusS sensors respond to Cu(I) not Cu(II). This phenomenon can be explained by Cu(I) toxicity and Cu(I) effect on other metals involved [90]. A precise examination of copper homeostasis mechanisms is beyond the scope of this review.

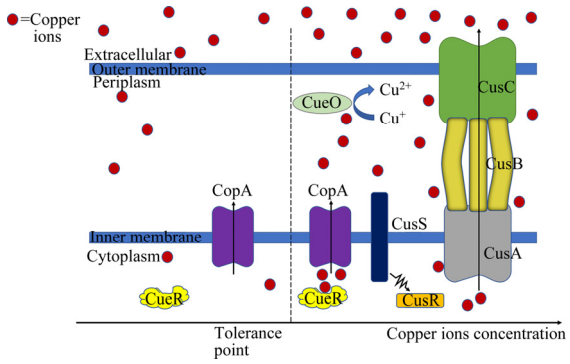

Fig. 4 Schematic diagram of copper homeostasis mechanisms in *Escherichia coli* (*E. coli*)

5 Factors responsible for copper antibacterial efficiency

In Section 3, we briefly presented surface and particle agent with different copper contents, which is hard to determine the optimum amount. However, based on the discussion mentioned above, copper ions release instead of copper content controls antibacterial activity. Thus, the issue of influencing copper antibacterial efficiency turns into that of influencing copper ions release. There are many factors influencing antimicrobial efficiency, such as temperature, sanitizer and surface free energy. In this chapter, we discussed impact characteristics under HCAIs circumstances.

5.1 Adhesion

Adhesion is usually considered as the first

character of antibacterial activity. To investigate the antibacterial properties of copper, there are two methods to evaluate its merit. One method applies a drop of suspension containing bacteria and buffer solution on specimen surface. The other way needs no suspension while employing a nutrient agar plate instead to determine the inhibition zone. For instance, IBRAHIM et al [91] employed two methods to evaluate antibacterial activity of copper surface and copper powder, respectively. The basic common idea of both approaches is agent attachment to bacteria. Basically, the attachment takes two steps [92]. On the first step, long-range interactions, such as the motility or Brownian motion, and/or gravitational force, drive the bacteria movement. Till the microorganisms reach the surface, approximately less than 5 nm, electrostatic charge, van der Waals attraction, ionic and dipole interactions, hydrophobic interactions and other short-range force take over as the driving force [92,93].

There are many impact factors influencing bacterial adhesion. Excluding environmental factors, bacterial accumulation is an unignorable factor. Obviously, the formation of bacterial community can reduce the environmental and physical damage. For instance, the residential bacteria on lettuce increase the risk of getting noroviruses [94]. Roughness is another factor. Scratches, grooves, and other defections in microscale on the surface contribute the bacterial adhesion. On the contrary, smooth surface or surface with unmatchable size with bacteria can reduce the binding potential of bacterial attachment [92]. Furthermore, bacteria with hydrophobic surface prefer agent with hydrophobic surface, meanwhile bacteria with hydrophilic characteristics favour the hydrophilic surface and the surface with electron charge [92,93].

5.2 Humidity

In laboratory, the most conventional way to study contact killing is inoculating cell suspensions to specimen or applying Cu-NPs suspensions directly. While this might be unmatchable in health care circumstances. HCAIs usually happen on the high-touching surface, such as door handle, curtain and chair, which belong to “dry” environments. As a result, an alternation dry test method is to swab the suspension on the specimen surface allowing liquid to evaporate in seconds [77].

GRASS et al [20] summarized contact killing of microbes by copper surface under wet or dry conditions. Microbes killed by moist copper surface or suspensions usually took hours. While dry coupons or thin film applied with cotton swabs eliminated microorganisms within few minutes. However, they did not investigate this difference.

SANTO et al [77] did further comparisons between dry copper and copper under humid conditions. They claimed that the copper accumulation was much faster from dry copper surface than from wet copper surface. In other words, bacteria applied to copper surfaces absorbed a great amount of copper ions. Compared with GRASS et al [20], SANTO et al [77] precisely demonstrated the copper accumulation effect on cell membrane damage instead of DNA degradation.

It was hard to provide realistic suggestion for HACIs based on the laboratory tests under wet or dry conditions. However, very rare study investigated the relative humidity (RH) effect on copper antibacterial efficiency [12,95]. MICHELS et al [12] settled control experiments under RH of 90%, 24%, and 20% at 20 and 35 °C, respectively. However, after 24 h incubation, there was no observation of copper coupons with dramatic differences of reduction in live *Staphylococcus aureus* at 20 or 35 °C. OJEIL et al [95] investigated the temperature, incubation time and relative humidity effects in a UK hospital. The experiment temperature was settled at 20 and 37 °C. After 24 h incubation, all copper coupons at all temperatures and relative humidity exhibited extremely antibacterial activity (>4$\log_{10}$ reduction in viable bacteria). There was no statistical difference at 37 °C and RH of 100%. Meanwhile, all copper coupons in short incubation period (within 30 or 60 min) exhibited higher antibacterial efficiency at 20 °C and RH 40% than 20 °C and RH 50% [95].

5.3 Strain specificity

Different strains of bacteria are sensitive differently to copper agent. Table 3 summarizes the copper resistance of different types of bacteria.

From Table 3, various microbes have different sensitivity to copper agents. For instance, Gram-positive bacteria exhibited higher copper tolerance than Gram-negative bacteria. PENG et al [101]

Table 3 Copper resistance of different bacteria strains

Type	MIC/Killing time	Method	Ref.
S. Enteritidis	12 mmol/L	$CuCl_{2(aq)}$	[96]
S. Typhimurium S 9	14 mmol/L	$CuCl_{2(aq)}$	[96]
S. Typhimurium S 19	12 mmol/L	$CuCl_{2(aq)}$	[96]
S. Typhimurium S 20	12 mmol/L	$CuCl_{2(aq)}$	[96]
Escherichia coli	45 min	C28000, 60%Cu	[97]
Escherichia coli	30 min	C11000, 99.90%Cu	[97]
Escherichia coli	0.596 mg/mL	Cu-NPs[a]	[62]
Staphylococcus aureus	0.596 mg/mL	Cu-NPs[a]	[62]
Clostridium difficile	6 h	C11000, 100%Cu, (purified spores)	[52]
B. cereus SWSD1[b]	12 mmol/L	$CuSO_{4(aq)}$	[98]
Bacillus PRSDM[c]	12 mmol/L	$CuSO_{4(aq)}$	[98]
Clostridium sporogenes	10−25 mg/L	$Cu^{2+}_{(aq)}$	[99]
A. calcoaceticus	3.87 μg/mL	Cu-NPs[d]	[100]
K. pneumoniae	1.93 μg/mL	Cu-NPs[d]	[100]
C. albicans	1.93 μg/mL	Cu-NPs[d]	[100]
S. aureus	3.87 μg/mL	Cu-NPs[d]	[100]

a: Cu-NPs electrodeposition synthesized by CuO suspension; b: Isolated from stagnant effluent water solid sample of copper mine; c: Isolated from plant root soil from copper mine; d: Cu-NPs chemical synthesized by copper sulfate solution and sodium alginate under gamma radiation

reported that *Ochrobactrum* MT180101 with copper resistance can have a potential in dealing with electroplating wastewater. Besides, microbes also play roles in corrosion generation and propagation. LUO et al [102] declaimed that the ion release rate of copper surface in the presence of *E. coli* was higher than that of pure copper surface. *E. coli* community as ions reservoirs dissolved and removed protective oxide (Cu_2O) layer from copper surface.

5.4 Manufacturing methods

There are abundant manufacturing methods for copper agent synthesis. In summary, all fabrication methods depend upon two ideas: one is splitting raw material from the macroscopic structure into the appropriate scale; the other is to build up atoms in nanoscale to appropriate size. In this chapter, several fabrication procedures are introduced.

5.4.1 Sol−gel method

Sol−gel approach is a conventional approach for wet chemical synthesis of nanocomposites. Figure 5 represents the schematic illustration of sol−gel process and different products of different stages.

Sol−gel process requires a chemical solution or sol as an initial precursor, processing reactions with dopant particles to generate gelatinous network polymers or gel. As a wet chemical synthesis, sol−gel process is powerful at nanocomposite synthesis, as well as to generate organic−inorganic complex dispersion [103,104].

SUBHA et al [105] utilized sol−gel method to synthesize the copper ferrite nanoparticles. RUPARELIA et al [57] prepared Cu-NPs, Ag-NPs and Cu−Ag nanocomposites via sol−gel method. Sol−gel process not only produces nanoparticles, but also has the potential in ultrafine inorganic fibers production [106,107]. There are various advantages of sol−gel methods such as the low processing temperature [108], and adjustable chemical composition, which are useful in medical coating and the particle size distribution by sol−gel method ranging from 1 μm to 1 nm [109]. The major drawbacks of this method are the expensive precursors and metallic alkoxides, and the gas generation in precursor fibers during calcination [107,108]. To avoid gas producing effect, researchers turn to combine other technologies with calcination such as dip coating process [110,111]. GOLLWITZER et al [110] reported that copper-doped titanium dioxide coating on medical implants of Ti6Al4V alloys prepared via sol−gel process had influence on the adhesion reduction of staphylococci and copper ions release against bacterial infection, without causing serious cytological incompatibility. Although calcination was performed after copper ions were incorporated into the sol, the surface roughness ranged from 3 to 5 nm due to dip coating procedure. MATHEW et al [112] prepared titanium dioxide coating with copper dopant via sol−gel and calcination against Gram-positive and Gram-negative bacteria under visible light illumination. Besides, they observed Cu^{+}/Cu^{2+} ions introduction. MOONGRAKSATHUM et al [111] declaimed that photocatalytic titanium

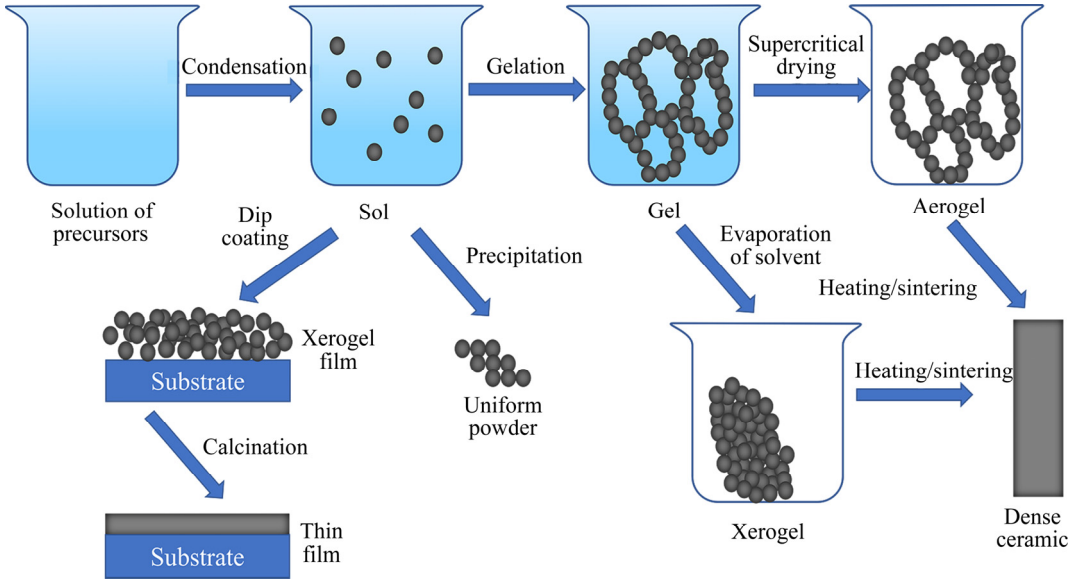

Fig. 5 Schematic illustration of sol−gel process and different products of different stages

dioxide thin films with copper integration were synthesized via peroxo sol−gel method and dip-coating process with no subsequent calcination process needed. Copper complex existed in the form of copper oxide on the surface of titanium dioxide, and this photocatalytic thin film performed high antibacterial activity against *E. coli* after UV-A irradiation [111]. EL HAMZAOUI et al [104] utilized sol−gel route for the preparation of ionic copper-doped optical fibers, and they observed that steady Cu^{+} oxidation state existed in pure silica core under UV-C irradiation.

Although, EL HAMZAOUI et al [104] did not investigate the antibacterial activity of copper-doped optical fibers, they provided a potential approach for a remarkable stability of Cu^{+} oxidation state in pure silica core. It should be noticed that the antibacterial mechanisms of copper-doped photocatalysts presented by MATHEW et al [112] and MOONGRAKSATHUM et al [111] are different from copper as antibacterial agent. The antibacterial activity of copper-doped photo-catalysts can be explained by density functional theory which emphasized that the introduction of Cu^{+} and Cu^{2+} ions reduced the band gap and created oxygen vacancies because doped Cu^{+} and Cu^{2+} ions replaced Ti^{4+} in TiO_2 lattice [111,112].

5.4.2 Cold gas spray coating

Considering the mechanisms of copper contact killing bacteria and the difficulty of producing bulk copper-based alloy, researchers turn to another approach to produce samples or surface modification. Thus to date, more and more studies are performed on coatings. Figure 6 represents the schematic diagram of the cold spray process.

In cold gas spray (CGS) process, high-pressure carrier gas was carried with feedstock powders with particle size normally between 10 and 100 μm at supersonic velocity onto a substrate. During the collision, a great part of kinetic energy was transferred into the formation of severe plastic deformation and mechanically interlocking or interlinking with each other, thereby forming a thin dense deposit. Figure 7 represents the surviving MRSA on different gas spraying deposition surfaces [113].

Compared with plasma and wire arc spraying process, cold spraying method has a supreme antimicrobial efficiency. Figure 8 represents the particle velocity and working temperature of thermal spray processes [113].

There are many outstanding advantages of CGS, such as strong bonding between coating and

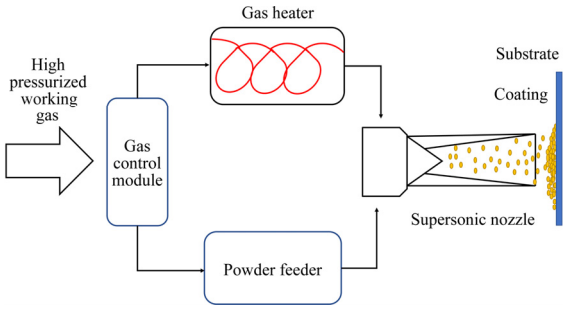

Fig. 6 Schematic diagram of cold spray process

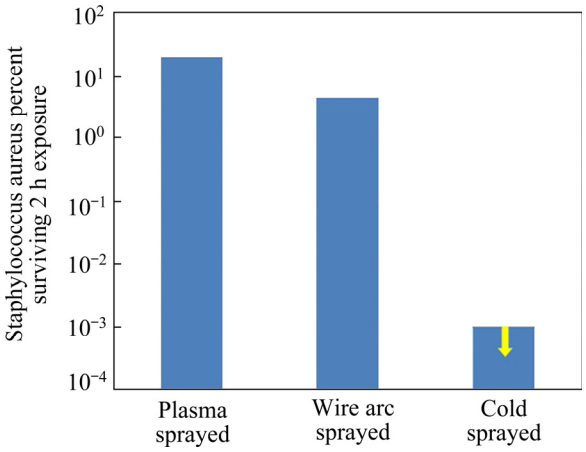

Fig. 7 Percent of MRSA surviving after exposing to various copper surfaces [113]

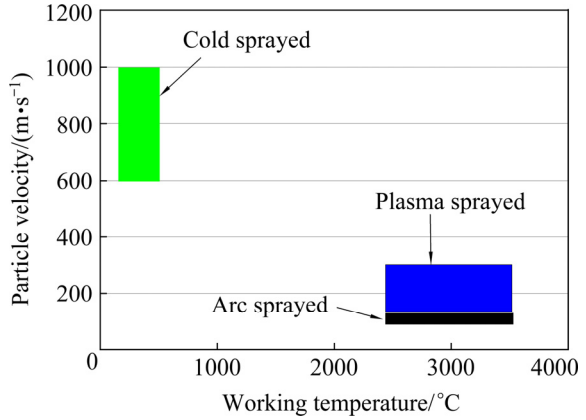

Fig. 8 Working temperature and particle velocity of various spray techniques [113]

substrate, low processing temperature [113], no oxidation, no nitriding, no decarburizing, low porosity, effective spraying nanomaterial and biocompatible material (hydroxyapatite), compressive stress and ultrathick (5−50 mm) coatings can be produced without adhesion failure [114].

To explain the bond formation in cold spray process, many hypotheses were proposed. BALA et al [114] stated that plastic deformation may disrupt thin surface films, such as oxides, and provide intimate conformal contact under high local pressure, thus permitting bonding to occur. SCHMIDT et al [115] proposed the strong bonding between coating particles and the substrate or the deposited layer in cold spray process, which is related to the abnormal strain rise and stress collapse due to the plastic deformation at the interface. The main mechanism postulated for bonding of metals onto metals is adiabatic shear instability (ASI), which occurs when the particle softening overcomes its work hardening and forms a metal jet containing the coating and substrate material under stress collapse [114−116]. The metal jet disrupts thin surface films. However, the ASI mechanism is more effective on the bonding formation between particles and substrates than that between particles and layers. ASSADI et al [116] built the finite element model and discovered that the strain distribution and temperature were inhomogeneous, inducing that oxide films were not incompletely eliminated by the metal jet, which means ASI induced metal jet effect was one part of interface bonding. CHAMPAGNE et al [117] investigated the bonding mechanism between copper particles and aluminium substrates in cold spray, and they proposed a hypothesis that the bonding mechanisms whether between particles and deposited particles or between particles and substrates were the results of particle penetration, interfacial heating, and metal jet. HUSSAIN et al [118] investigated the bonding formation between copper particles and aluminium substrates. Based on the ASI theory, they proposed an additional hypothesis called interlocking, which represents extruded lips of substrates generated by incident particles trap impinging particles. This phenomenon creates the mechanical interlocking between particles and substrates. HUSSAIN et al [118] mentioned that the bonding in cold spray process was the result of ASI induced metallurgical bonding and interlocking induced mechanical bonding. The bonding mechanisms in cold spray process play an important role in nanometre coating production. It is known that there are three approaches to achieve the nanometre cold spray coating: (1) nanocrystallization; (2) nanocrystalline feedstock powder [119]; (3) nanomaterials to boost metal matrix composites (MMC) coating [120]. Figure 9 represents dynamic recrystallization in deposited particles during cold spraying [121]. Nanocrystallization in cold spray is the result of stress collapse. However, the layer in nanoscale is usually the first layer of the coating (i.e., particles deposit to substrates). Besides, the adhesion of cold spray coating decreases with the increase of coating thickness. SINGH et al [122] investigated the effect of electroplated interfaces on the bonding mechanism in cold spray process. Compared with copper electroplated interface, electroplating nickel

had a higher affinity for forming metallic bonds with copper and steel substrate, respectively [122]. This higher affinity results in better mechanical interlocking and metallurgical bonding. On the contrary, copper electroplated interface with a lower affinity to share electrons with steel could segregate coating from the substrate [122].

5.4.3 Biosynthesis

Cu-NPs are less toxic than copper ions, especially for nanocomposite carrier for drug release [123]. Although biosynthesis of nanoparticles by microbes is the by-product of the resistance to metallic antibiotic, its low cost and eco-friendly characteristics still receive much attention and biosynthesis metal nanoparticles have been reported in literature [124,125]. Figure 10 shows the schematic diagram of bacteria biosynthesis and represents that metal elements have been biosynthesized [126]. Many investigations reported that bacteria with copper resistance were isolated from copper mine or copper contaminated soil [98,127,128]. Furthermore, some micro-

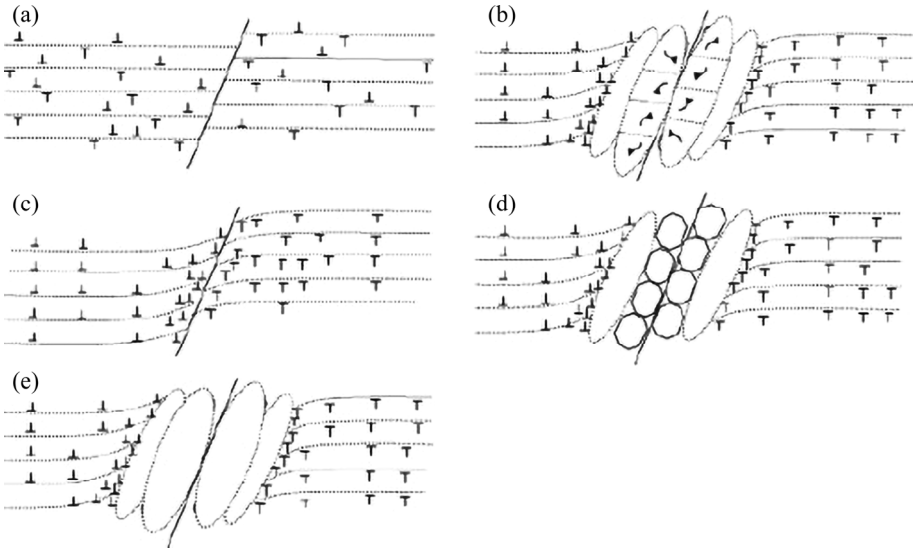

Fig. 9 Schematic diagram showing proposed mechanism of dynamic recrystallization in deposited particles during cold spraying [121]: (a) Substrate with low dislocation density before spraying; (b) Dislocation density with spraying processing; (c) Formation of elongated subgrains observed due to accommodated dislocations; (d) Dynamic recrystallization (Elongated subgrains were divided into equiaxed subgrains); (e) Formation of ultrafine grains

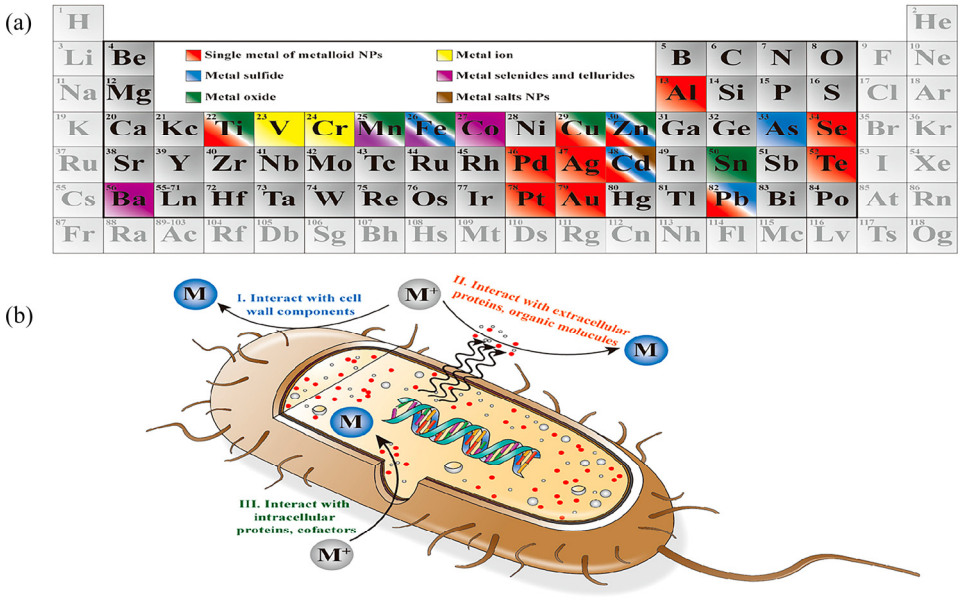

Fig. 10 Periodic table of biosynthesis elements (a), and schematic diagram of bacteria biosynthesis containing intracellular and extracellular process (b) [126]

organisms can accumulate free copper ions and generate metal nanoparticles. TIWARI et al [98] reported that the particle size of Cu-NPs biosynthesized by copper-resistant *Bacillus cereus* was less than 100 nm and the distribution was better than conventional industry production due to the exocellular protein coating around.

Unlike digging and isolating copper-resistant strain from copper contaminated soil, EL-BATAL et al [100] selected *Pleurotus ostreatus* fermented Fenugreek and natural polysaccharides (citrus pectin, chitosan, and sodium alginate) to investigate the potential of biosynthesis. During their research, the powder of *Pleurotus ostreatus* fermented Fenugreek and natural polysaccharides were added into copper sulfate solution under gamma irradiation, respectively [100]. The result showed that utilizing *Pleurotus ostreatus* fermented Fenugreek and natural polysaccharides was an eco-friendly biosynthesis method. The particle size distribution concentrated at 25−36 nm and the ultrafine Cu-NPs exhibited high antioxidant and antimicrobial activity. However, EL-BATAL et al [100] lacked evidence to prove that fermented Fenugreek powder acted as the same as natural polysaccharides like capping agents and the mechanism of biosynthesis was not clear enough.

CHEN et al [129,130] observed and investigated mechanisms of *S. maltophilia* for Cu(II) biosorption. Their work indicated that bacterial cell walls were the main adsorption sites for copper especially the carboxyl, hydroxyl and phosphate groups on the bacterial surface. Besides, absorbed Cu(II) was transformed and deposited into Cu(I) and Cu by natural *S. maltophilia* or removed via calcium and phosphorus metabolism by surface-esterified *S. maltophilia* [129].

6 Summary

(1) The roles of copper in human immunity and toxicity were discussed. Despite the different tolerance levels of human and bacteria for copper, the absorption of dissolved copper ions from copper agent could be poisonous.

(2) Copper as antimicrobial agents can be divided into surface agent and particle agent. For surface agent, the crucial factor of antibacterial activity is ion release rate instead of copper content. The critical factors of particle agent are ion release rate and nanoparticle affinity to the cell membrane.

(3) The mechanisms of contact killing of copper are presented. The review discusses the controversial part of DNA degradation and presents copper ions release as the core of killing mechanisms. The impact factors of copper antibacterial efficiency are stated, including humidity, adhesion, strain specificity and synthesis method of copper agent.

(4) Copper-doped alloys or coatings do have influence on antibacterial activity; however, the mechanisms are different. When copper acts as antibacterial agent, contact killing mechanism plays the role in antibacterial activity, such as copper ions release and the affinity of copper nanoparticles to membrane protein. When copper exists in photocatalytic species, photo-induced inactivation such as ROS rather than chemo-toxic killing of bacterial cells results in antibacterial activity. In this case, copper can reduce the band gap and increase the photocatalytic efficiency.

(5) Copper complex toxicity is universal to all organisms, while Cu-NPs are more toxic than copper ions. Cell membrane damage induced by Cu-NPs is higher compared with CuO-NPs. Cuprous ion is more toxic than divalent copper ion.

(6) This review discussed several manufacturing methods, such as sol−gel, cold spray, biosynthesis from chemical synthesis, physical synthesis, and biological synthesis. Sol−gel method contributes to particle agent and surface agent preparation. Cold spray technique is utilized in the surface copper agent synthesis. Biosynthesis technology is another promising technology that can be applied in nanoparticle agent production.

7 Prospects

(1) This review presented the antibacterial activity of copper. Moreover, due to the coronavirus disease (COVID-19) pandemic, copper received more and more attention as a metal-based antimicrobial regimen [131,132]. Faced with virus mutation, the absence of specific remedies and vaccine adverse reactions, copper-based bulk material and nanomaterial have great potential in COVID-19 elimination.

(2) In this overview, some biochemical and bioinformatics terms were cited, such as SOD, COX and CP. Especially, it could not be ignoble

when summarizing the antibacterial activity of copper and its active sites in proteins. However, this overview briefly introduced the importance of copper in enzymes and immunity system, which needs to be investigated in future work.

(3) Unlike novel copper agents tested in the laboratory, health care setting is usually equipped with old copper agent to guarantee copper antibacterial activity over a long time. Furthermore, impact factors of copper ion release come from material properties, corrosion conditions, and even strain specificity. Some studies have focused on bacterial effects on corrosion procedures. Those complicated and long-term studies need more precise and deeper investigations over years.

(4) Copper as antibacterial agent received much attention. In fact, unlike other unnecessary elements with antibacterial activity, more Cu ions are needed to reach the same antibacterial efficiency. Organisms already developed the mechanisms to balance Cu ions homeostasis. Before the copper-based antibacterial agents are widely commercially utilized, the result of copper shock selection such as selective sweep should be carefully considered.

(5) Microbes establish homeostasis mechanisms for copper encounter. In this review, the copper homeostasis mechanism of *E. coli* was discussed. Some research about the sensor proteins inhibitors or blockade of ion-effusing channels may raise concerns.

(6) Many researchers investigated the dopant effects on copper-based antimicrobial alloy without considering surface modifications or manufacturing methods, which plays important roles in improving antimicrobial effects and reducing cytotoxic effects. Besides, except for chemical and physical synthesis, biosynthesis is another promising method for nanoparticle production.

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铜及铜合金作为免疫和抗菌元素的综述

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摘 要：讨论铜与人、细菌之间的关系。铜在人体免疫中发挥重要作用。在推荐摄入量下，铜可以增强人体的免疫防御反应。本文主要讨论铜的抗菌活性和抗菌机制。结论表明，铜的抗菌活性受细菌中铜稳态机制、粘附、湿度、菌株特异性以及抗菌剂制备方法的影响。对于颗粒抗菌和表面抗菌材料，讨论几种制备方法，如溶胶−凝胶法、冷喷涂法和生物合成法，分别属于化学合成、物理合成和生物合成法。溶胶−凝胶法有助于颗粒抗菌和表面抗菌材料的制备；冷喷涂技术可以应用于表面抗菌铜的合成；生物合成是一种可应用于纳米颗粒抗菌剂制备的新技术。

关键词：免疫；毒性；抗菌活性；铜稳态；粘附；湿度；菌株特异性；抗菌剂；机制

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