Current Advances in Copper MOF as a Potential Third Generation Antibacterial Agent

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Summary: Due to the lack of and high cost of antibacterial medications against resistant bacteria, infectious diseases are the leading cause of death worldwide, especially in low- and middle-income nations. Infectious diseases include viral, parasitic, bacterial, and fungal ones, with bacterial being the most prevalent. The need for the creation of new and effective antibacterial agents is critical because the overuse of antibiotics and the resulting rise in antibiotic resistance persists today. In this context, a number of metals and metal oxides, metal oxide nanoparticles, and metal-organic frameworks (MOFs) are regarded as third-generation antibacterial agents with improved properties in comparison to conventional bactericidal agents and are thought to be a successful remedy to the drug resistance problem. In this review the antibacterial potential of metal nanoparticles, copper and copper oxide nanoparticles, MOF, Cu-MOF, Cu-MOF nanofiberous membrane and Cu-MOF films is explored. The mechanism of these material as antibacterial agent was found as Cu ions release, ROS generations and both Cu metal ions and ROS generations. Based on the performance Cu-MOF, Cu-MOF nanofiberous membrane and Cu-MOF film are the promising third generation antibacterial agent.

Keywords: Cu-MOF; Nanofibers membrane; Antibacterial agent; ROS generations; Antibacterial mechanism.

Introduction

Around the globe, foremost cause of death is the infectious diseases exclusively in the countries with low and middle income because of unavailability and high-priced antibacterial drugs against resistant bacteria. The viral, parasitic, bacterial and fungal are the infectious diseases and among them bacterial are the most common ones. Bacteria are the microscopic creatures present in various environments. Each specific bacterium is responsible to cause specific disease. The different disease causing bacteria are; *Pasteurella multocida* is a non-spore forming, Gram-negative belongs to family *Pasteurellaceae.* It usually transmits by respiratory routes and cause rhinitis and pneumonia. Enterotoxaemia is caused by *Clostridium spiroforme* which is Gram-positive spore-forming anaerobe whereas *Clostridium piliforme*, Gram-negative, spore-forming filamentous organisms is responsible to cause tyzzer's disease. Salmonellosis belongs to genus *Salmonella* are facultative anaerobes and are Gram-negative. These bacteria are transmitted through contaminated food after ingestion and characterized by diarrhea. *Mycobacterium avium* and *M. tuberculosis* causes tuberculosis characterized by inflammation of liver, lungs, digestive tract and lymph nodes whereas *Mycobacterium leprae* or *M. Lepromatosis* bacteria cause chronic illness known as leprosy. These bacteria belong to genus *Mycobacterium. Fusobacterium necrophorum* is Gram-negative, non-spore-forming anaerobic bacteria that cause skin infection known as Schmorl's disease and mainly begins as an inflammation of subcutaneous tissues of head and neck characterized by necrosis and ulceration**. [**1-4**]** The unpretentious record of herbal products as antibacterial agent helps a lot to study the natural product extracted from plants along with their potential to fight against bacteria. Essential oils and its constituents are the most important components of medicinal plants having broad-spectrum anti-microbial characteristics. **[**5-7**]**. Most commonly when infections become more life threatening, antibiotics were used to treat bacterial diseases for too long like clindamycin works effectively for gram-positive bacteria, cephalexin is bactericidal and binds to penicillin-binding proteins, ciprofloxacin deals with gram-negative bacteria and showed active results for *P. aeruginosa*, andamoxicillin is credibly used for both gram-negative and gram-positive bacteria especially use to treat animal bite wound. These remote drugs were further improved by preparing their analogues but their applications are limited as bacteria get resistant to them due to their excessive use **[**8, 9**]**. In bacteria, resistance is evolved by the exchange of genetic materials between

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each other and also undergoes transfer of plasmids. In order to identify the extent of antibiotic-resistant infections, we must consider the degree of its consumption **[**10**,** 11**].** These drug-resistant bacteria then subjected to new class of treatment known as bacterial quorum sensing signaling that involve the use of anti-QS agents as alternative to antibiotics. The QS signals of bacteria interfere in variety of physiological processes and comprises of auto inducing peptides, acyl-homoserine and autoinducer-2. These three of QS signals plays significant regulatory rules in growth and infection of bacteria but these QS signals are still in preclinical phase for clinical trials **[**12**]**. In addition, infections caused by drug-resistant bacteria can be treated by photosensitization, modification of bacterial phenotype and bacteriophage therapy **[**13**]**.

As antibiotics abuse and its resistance is a still a serious issue from last decades, so development of novel and efficacious antibacterial agents was imperative. In this regard, various metal and metal oxides, their nanoparticles and metal-organic frameworks (MOFs) are considered as third generation antibacterial agent with enhanced properties as compared to traditional bactericidal agents and considered to be an efficient solution to the drug resistance issue as shown figure 1.

0-D nanomaterials

The spherical-like materials with excellent stability and dispersing ability are included in this class of nanomaterials and are appealing due to high surface area for instance fullerenes, metal-based nanoparticles, polymeric NPs and graphene quantum dots **[**16**,** 17**]**.

1-D nanomaterials

These nanostructures are linear-based and have excellent capacity to load functional agents in addition to stability. Nanowires, nanorods, nanofibers and nanotubes are included in this class of nanomaterials with photo-triggered therapeutic effects and deviant thermal, optical, mechanical and magnetic properties. Copper based 1-D materials are widely studied to maximize their biocompatibility and most specifically, copper based coordination polymer nanofibers showed excellent antibacterial effects with generation of ROS and release of copper ions **[**18**,** 19**].**

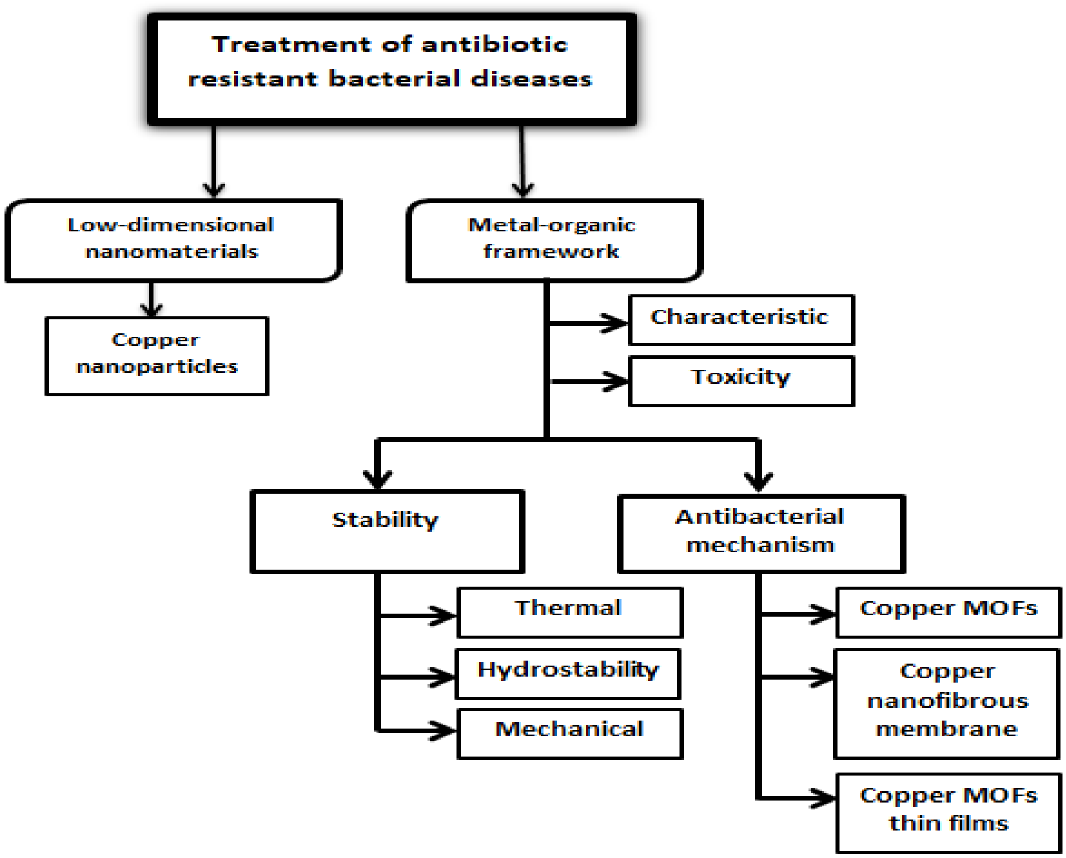

Fig. 1: Major keys topics discuss in this review.

2-D nanomaterials

To manage the limitations of 1-D nanomaterials such as loading capacity, 2-D nanomaterials with sheet/layered-like structures were synthesized having large surface area and combined PDT/PTT functionality. Moreover, 2-D nanomaterials have combined advantages of 0-D and 1-D nanomaterials and provide synergistic effects when co-loaded with them. Particularly for antibacterial effects, explored 2-D materials include transition metal oxide, graphene based and transition metal hydroxide. Among these, graphene oxide has inherent antibacterial activity due to ROS generation and damaging the cell membrane of bacteria by physical interaction [16,20].

3-D nanomaterials

The class of these materials is the assembly of 0-D, 1-D and 2-D nanostructure and any of the dimensions is not confined to nanoscale. They have supramolecular structure and have highly-complex composite products. These include nanoclusters, nanocones and nanoflowers. In 3-D nanostructures, skeleton-like nanostructures that are the foremost one are metal-organic framework (MOFs) and covalent organic framework (COFs). They have the characteristic of biocompatibility and present appreciable antibacterial activity. The proposed and most possible antibacterial mechanisms are diffusion-directed lipid oxidation, formation of ROS, interference in cation transport and membrane depolarization [16, 21, 22].

Copper and copper oxide nanoparticles as antibacterial agent

In past decade, rapid progress in the field of nanotechnology urges the researchers to investigate the antibacterial effects of metal and metal oxide nanoparticles to suppress the bacterial growth and known to be efficient fungicides [23]. In this regard, copper and copper oxide nanoparticles are of potential use as they present various features such as economical, supreme electrical conductivity, ease of accessibility and stability of copper oxide to be mixed with polymers [24, 25]. The antibacterial mechanisms of copper and copper oxide nanoparticles were reported in literature. Khani *et al* studied the effects of *Ziziphus spina-christi* fruit extract as reducing agent for copper nanoparticles synthesis and investigated the antibacterial activity against *E.coli* and *S.aureus* whereas potency was dependent upon the size of nanoparticles [26, 27]. Copper oxide nanoparticles synthesized by electro reduction methods were used to evaluate antimicrobial activities and degree of inhibition of bacterial growth was dependent on the nanoparticles concentration. Perforation of cell wall was observed as the result of interaction of bacteria with nanoparticles [28]. To add, antibacterial effects of biosynthesized copper oxide nanoparticles from papaya leaf extract was evaluated against *Ralstonia solanacearum*. Results showed strong effects with disturbed ATP production when nanoparticles interact with bacterial cell lines [29].

Metal-organic frameworks as antibacterial agent

To overcome the weaknesses of previous antibacterial agents, MOFs as emerging 3D materials are studied meticulously. Metal-organic frameworks are the porous hybrid solids and the most propitious structures becauseof the presence of active centers that are stabilized by the stronger chemical bonds. MOFs are the form of coating to the nanometer particles in a way that active metal particles are stabilized with organic ligands to prevent its interaction with outer environment [30].

Development history of MOFs

Coordination and zeolite /solid-state chemistry are known to be a parent field for the evolution of metal-organic frameworks. Coordination polymers are the labeled compounds formed by association of metal ions bridged with organic ligands (linkers) and became an interesting field in 1990. Around 1995, the term MOFs was well known and popularized by Umer Yaghi. In 1997, gas sorption properties of 3D MOFs was investigated at room temperature and synthesis along with detailed study of MOF-5 and HKUST-1 was done in 1999 and in other following years. Moreover, after 2002, flexible and nonflexible MOFs (MIL-47 and MIL-53) were also studied following the concept of isoreticular chemistry to further enhance the strength properties and applications. MOFs can be formed by using various methods namely hydrothermal method, sonochemical method, microwave-assisted technique, electrochemical synthesis and mechanochemical synthesis. For industrial applications, the use of MOFs is bit challenging and depend upon production procedure and its inherent characteristics. The synthesis of MOFs on laboratory scale must require the consideration of issues such as (1) price and accessibility of starting material, (2) reaction conditions, (3) necessity of having greater product yield, (4) use of minimum amount of solvent, and (5) prevention from impurities. These synthesis parameters not only affect the phase formation but also responsible to regulate the morphology of crystals[31, 32, 33].

Influence of the composition and synthesis on MOFs

MOFs as the latest class of porous solids has variety of applications and its composition can be tunable by varying organic ligands and metal ions. The classes of ligands involve are phosphonates, imidazolates, phenolates, sulfonates, pyridyl amines. The physiochemical properties of the solid can be varied and is represented by functionalization of organic linker. For biomedical applications, bio friendly constituents of MOFs are the major requirement to ensure the stability of MOFs. Furthermore, toxicity while dealing with MOFs is very rare and the acceptable toxicity is only due to metals. For bio applications, host-guest interaction, hydrophobicity/hydrophilicity and pore size are the considerable parameters. Moreover, major contributions in the chemistry of MOFs are its pore's reactivity enhancement by addition of organic units and metal-organic complexes by the reaction with linkers known as post synthetic modification of MOFs and synthesis of multivariate MOFs to generate a complexity within the pores of MOFs [34-39]. In addition, characterization of remarkably stable and porous MOFs can be done by traditional methods depends on periodic structure, high temperature sensitivity and their surface area. Brunauer-Emmett-Teller method that is used to determine MOF's specific surface area. The powder X-ray diffraction technique is suitable to study structural features and other structural differences of MOFs prepared from various methods. The growth of MOFs can be observed with liquid cell transmission electron microscopy and it proves to be the excellent tool to identify the change of size of particle with alteration of synthetic conditions. Thermal stability as the significant property of MOFs is analyzed by TGA which measures the % mass loss as a function of temperature whereas active sites of MOFs are analyzed by X-ray absorption spectroscopy [40-42].

Characteristics and applications of MOFs

MOF is a porous structure with open framework having potential voids and is known as coordination polymers or polymeric membranes. These are synthesized by the self-assembly of metal cations as nodes and polydentate organic brigands as bridges resulting in one, two or three dimensional structures. The basic building blocks of MOFs can be arranged in various ways and join together with different types of bonding namely hydrogen bonding, electrostatic interaction and metal coordination. Moreover, variety of metal centers (Ag, Zn, Co, Cu) and organic ligands (derivatives of carboxylic acid, phosphonic acid and imidazolates) can lead to formation of sizes, topologies and pore structure. Customarily, the development of MOFs can be considered as a strategy to imitate inorganic components such as zeolites because these structures do not allow us to control functionalization and size of pores. The internalization of MOFs and preservation of its overall structure (pore size and crystal morphology) is possible only by its size control in range of nanometers [30, 43, 44, 45]. MOFs with tunable porosity, high surface area, simple synthesis routes and conformable physical and chemical properties as the captivating material from last two decades can be utilize in different applications such as adsorption in aqueous solutions, gas adsorption for air purification, disinfection of water and removal of toxic pollutants, as catalysts (photocatalysts, electrocatalyst and biocatalyst) by tailoring the porous MOFs and incorporation of catalytically active nanoparticles, as biosensors, super capacitors, fuel cells, as antibacterial and anticancer agents, for photocatalytic hydrogen production and last but not the least is in drug delivery systems and for the control of its amount and release rate in the body because of the biocompatibility, high drug loading and controlled release of drugs by MOFs [46-50].

Cytotoxicity of MOFs

Besides of extraordinary importance of MOFs, its cytotoxicity is also predominant. Researched toxicity data is still rare but studies were performed in vivo to evaluate toxicity of various MOFs against cancer cell lines (HeLa cells) and mouse macrophage cell line (J774) by MTT assay. Different MOFs on the basis of their composition and structural features were employed for toxicity studies and it was inferred that Fe-MOFs showed toxic effect on heap tocarcinoma cell line. It was concluded that toxicity of MOFs depends upon nature of metal, hydrophilic-hydrophobic balance and the organic linker. In order to formulate less toxic MOFs, composition is a highlighting parameter. Therefore, choice of reactants having low cytotoxicity is preferably used to synthesize MOFs having minimum toxic effects [51].

Stability of MOFs

MOFs as evolving class of porous materials in-spite of various applications proved to be inappropriate for use under harsh conditions due to instability problems which ultimately limits its functionalities and commercialization. The stability of

MOFs depends of miscellaneous factors like metal ions, coordination geometry between metal-ligand, hydrophobicity of surface of pores and organic ligands. For chemical stability, both operating conditions as external factor and MOF structure as internal factor plays a significant role [52] hydrolytic stability.

To understand whether the material is water-stable means to study its ability to withstand laboratory air, appropriate humidity and to look for maintenance of porosity in the material. The water vapor is the major one to which chemical stability of MOFs is related and become the greater concern. The coordination bond between metal-ligand is the major concerning point and its strength is the potential index of hydrolytic stability because hydroxyl group and protonated linker is generated by process of hydrolysis. Bon *et al* reported the categories of MOFs according to stability after water exposure such as thermodynamically stable MOFs, high kinetically stable MOFs, low kinetically stable MOFs and unstable MOFs. It was inferred that after the long-term exposure to water, thermodynamically stable MOFs can withstand and potentially used for various applications for example Al-MOFs and Cr-MOFs while on the contrary, kinetically stable MOFs can be used for industrial application and easily stand up to high humidity conditions for instance UiO-66 and DUT-67 [53-55].

Mechanical stability

The applications of MOFs to be use in engineering field under vacuum or pressure is the major factor to study the mechanical stability of MOFs. The partial collapse of pores and phase change may occur by the instability of pores. Consequently, solvent exchange and solvent evacuation methods were adapted to avoid structural distortion. For the eminent activation of MOFs, exchange of solvents of high surface tension with the lower ones like liquid carbon dioxide and n-hexane is the most adapted technique. Under acidic conditions, MOFs are highly stable having higher oxidation state metal and carboxylate linkers but under basic environment it may decompose. In contrast, low-valency metal ions resist strong basic conditions. Therefore, for certain applications various criteria should be consider under specific operating conditions [56-58].

Thermal stability

The breakage of bond between node and linker of MOFs accompanied by linker combustion is the major cause of thermal degradation. The other various forms of MOFs include linker dehydrogenation, melting, dehydration of node-cluster and MOFs amorphization. The major contributing factors to thermal stability are bond strength of node-linker and the connection of number of linkers to node. With a view to enhance the thermal stability, we must consider the bond strength of metal-ligand and it can be increased by altering the constitution of linker pendant groups. Thermal stability is the applicable indicator of resistance to variety of stresses therefore it can analyze by the thermogravimetric analysis and in situ powder XRD [59, 60].

This review summarizes the potential application of Cu-MOFs as efficacious antibacterial agent due to notable biological properties of copper.

Copper MOFs as antibacterial agent

Currently, the porous network of metal cations and organic ligands with its wide applications is rapidly developing because of its high surface area and outstanding chemical and physical properties. For biomedical applications of MOFs, it must be ensure that metal ions and ligands to be used as constituents of MOF should be stable, biocompatible and nontoxic [61]. Among variety of MOFs developed, this review aims to elaborate the antibacterial activity of Cu-MOFs.

Copper as essential element have several important functions in human body as it regulates growth and development, act as major component of enzymes used for the metabolism of glucose, cholesterol and other catalytic reactions and have strong antibacterial properties [62-64]. In 1990s, after the emanation of multi-drug resistant bacteria, researchers focused to elaborate and practice the antibacterial properties of copper and its related compounds and considered it as foremost antimicrobial agent. It was reported that copper and its compounds kill pathogenic bacteria up to 99.9% in a period of 2h [65]. Vincent *et al* discussed the antibacterial effects of copper as nanoparticles on various bacterial strains such as *Bacillus subtillis* and *Salmonella choleraesuis*. From different studies on antibacterial activity of copper NPs, it was found that the potential results showed are due to release of copper ion and the size of nanoparticles plays a significant role because they have large surface area and higher ability to penetrate into the cells [66, 67]. In addition to these nanostructures, copper MOFs also proved to exhibit promising antibacterial activity due to active metal centers stabilized by chemical bonds. The factors that lead to bacterial cell death are the release of metal ions, generation of ROS that leads to rupture of cell wall of bacteria. The eminent feature of copper-based MOFs is their easy approach of fabrication along with supreme chemical stability, biocompatibility and redox activity **[**68**,** 69**].**

Kornblatt *et al* [70] found that Cu(II) ions regulated the activity of proteins which crucially responsible in the wound repair process which led potential new targets for therapeutic intervention on scars wounds.

Rauf *et al*., synthesized the coordination polymer of copper(II) based on thiophene-2,5-dicarboxylate ligand that showed higher antibacterial activity against *E.coli* and *S.aureus* because of molecular physiology of copper ions transport. Researches discussed the basic antibacterial mechanism of copper(II) compounds such as they cause disruption of cell membranes by toxic hydroxyl radical (ROS) and cause leakage of cell content at membrane level to destroy the bacterium. Furthermore, structural variation of ligands contributes to antibacterial mechanism by control release of ions. The synthesized compound namely $[Cu(TDC)(H_2O)_2].H_2O$ where H_2TDC is thiophene-2,5-dicarboxylic acid was characterized by XRD and TGA and antibacterial activity was measured by colony count method and minimal inhibitory concentration (MIC). The results of antibacterial activity of $[Cu(TDC)(H_2O)_2].H_2O$ were evaluated and MICs were measured by optical density and was in the range of 150-200 µg/mL against *E.coli* and *S.aureus*. It is estimated that number of growth colony *S.aureus* is smaller than *E.coli* and synthesized MOF is potentially active against *S.aureus* than *E.coli*. The percentage of inhibition at 250 µg/mL showed 99.9% against *S.aureus* and 99.7% against *E.coli* in contrast to copper nanoparticles with percentage inhibition of 23.0%. The tremendous antibacterial potential was due to slow copper ions release and formation of reactive oxygen specie **[**71**].**

Usefi and his co-workers investigated the antibacterial activity of two-dimensional structure of copper coordination polymer with 2-Amino-4-methylpentanoic acid against *E.coli* and *S.aureus*. The nanostructured compound $[Cu(\mu_2\text{-}Amp)_2]n$ **1** was sonochemically synthesized and antibacterial potential was evaluated by zone of inhibition method. The two different samples of **1** were prepared in which **A** involves the drop wise addition of copper nitrate mentioned in the article and **B** involves immediate addition of copper nitrate. Both samples **A** and **B** showed zone of inhibition of 15mm and 12mm against *S.aureus* whereas no inhibition zones were observed against *E.coli.* Moreover, 1 was responsive to Gram-positive bacteria and higher antibacterial results were shown by A because of stable morphology of 1 nanosheet. The results indicated that antibacterial mechanism is due to release of metal ions and is dependent on morphology and size therefore, decrease in size of **1** exhibited efficient activity and known to be biocompatible **[**72**].**

Yu *et al* studied the application of copper MOF as an effective carrier for copper sulfide nanoparticles (CuS NPs). In this study, researchers studied the effects of photodynamic anti-bacterial therapy as an efficient alternate of antibiotics to kill bacteria by production of ROS along with photothermal effects to destroy the protein structures. For inactivation of bacteria photo catalytically, near-infrared-responsive materials are the excellent antibacterial agents as they have superb penetrability. Researchers used biocompatible and economical CuS NPs as propitious NIR-responsive material to kill bacteria with HKUST-1 (copper MOF) as suitable carrier. To add, in copper MOFs, copper ions also act as a source of copper for the production of CuS NPs to simplify the synthesis process. For in vitro antibacterial activity, spread plate method was employed against *E.coli* and *S.aureus* and under 20 minutes NIR irradiation, results depict that prepared MOF effectively convert light into heat by involving the use of NIR absorbance leading to membrane damage and increasing the permeability of membrane. The generation of ROS caused the oxidation of DNA and definite enzymes where antibacterial efficiency was 99.7% for *S.aureus* and 99.8% for *E.coli* **[**73**].**

Antimicrobial fabrics based on Nylon and polyester (PET) was prepared comprising of Cu-BTC within them by Eman *et al*. The natural fabrics with Cu-BTC other than antimicrobial effects provide significant applications in removal of pesticides, purification of fuel and UV protective textiles. The synthesized fabrics were evaluated for antimicrobial activity by using disk diffusion method against bacteria (*E.coli* and *S.aureus*) and fungus (*C.albicans*). The results showed good biological effects and MIC of Cu-BTC in PET against *E.coli, S.aureus* and *C.albicans* was 60, 70 and 67mg/mL whereas for Cu-BTC in Nylon was 64, 65 and 62mg/mL **[**74**].**

Copper MOFs consisting of ligands like glutarates and bipyridyl also exhibit effective antibacterial properties and studied by Jo and his co-workers. The hydrothermal method was used to synthesized four 3D MOFs as $[Cu(Glu)_2(\mu\text{-}L)]\cdot x(H_2O)$ where Glu is glutarate and L is bpy = 4,4'-bipyridine **1,** bpa= 1,2-bis(4-pyridyl)ethane **2,** bpe= 1,2-bis(4-pyridyl)ethylene **3**, and bpp = 1,2-bis(4-pyridyl)propane **4**. The minimum bactericidal concentration (MBC) was used to evaluate antibacterial effects against five different bacterial strains and results showed that MBC values for all the prepared copper MOFs were as low as 20 µg mL^{-1}[75]. Similarly, Cu MOFs with glutarate ligands embedded in hydrogels showed excellent activity with 99.9% efficiency and these Cu-MOF hydrogels systems owing to their low cytotoxicity have potential application in cosmetics and treatment of skin problems [76].

Rubin *et al* synthesized Cu-MOF-cotton material for post synthetic modification to produce free amine for enhance physical and chemical properties and it displayed highest antibacterial activity. The layer-by-layer dip coating process was used for the growth of MOF on cotton fibers and antibacterial proficiency was investigated by standard broth dilution agar plating method against *E.coli.* The mechanism was attributed to copper ions release and this cotton fabric with MOF considered being a promising for clothing and bandages to kill bacteria and avoid the bacteria attachment onto the surface [77]. Moreover, copper MOF in composite with activated carbon (AC-HKUST-1) manifested antibacterial effects and reported in literature formulated by hydrothermal method assisted by ultrasonic.The MIC and MBC values of AC-HKUST-1 against Methicillin-resistant *S.aureus* (MRSA) were 100 and 200 µg/mL and for *P.aeruginosa* were 50 and 200 µg/mL [78].

Soltani and Akhbari [79] loaded 10% chlorhexidine (CHX) on Cu-BTC MOF against gram positive and gram negative becteria by Agar well difusion method and MIC (minimal inhibitory concentration) assay. The resultant CHX@Cu-BTC had improved antibacterial activity as compared to Cu-BTC and chlorhexidine.

It was found previously that Cu based MOF(HKUST-1) modified in term of variation of R-group of s-nitrosothiols or its environment (organic linkers) led to effect NO release. Taylor *et al*., [80] proved this hypothesis experimentally and computationally. It was proved that addition of acetyl group to CysNO decreased rate of NO release whereas methyl group increased rate of NO release. This finding can be exploited for synthesis of nanomaterials having slow, controlled and sustained drug release of highly reactive NO like molecules.

Gizer and Sahiner[81] prepared succinic acid and mercapto succinic acid based MOF with copper(II) ions SA-Cu(II) and MSA-Cu(II) respectively. The antibacterial and antifungal potential of these MOF's were applied against *Pseudomonas*,*B. subtilis*,*E.* coli and *S. aureus* bacteria to determine MIC and MBC. SA-Cu(II) MOFs exhibit 0.25 mg/mL MIC and MBC values on *B.subtilis*, 0.5 and 0.25 mg/mL MBC and MIC values on *S. aureus*, 1.0 and 0.5 mg/mL MBC and MIC values on *P. aeruginosa* and0.5 mg/mL MBC on *E. coli* respectively. On the other hand MSA-Cu(II) MOFs exhibits 0.125 and 0.031 mg/mL MBC and MIC values on *B. subtilis* and 0.5 and 0.25 mg/mL MBC and MIC values on *S. aureus.*

Han *et al* doped 10% Cu^{2+} ions into the porphyrin ring of organic linker (PCN 224) of CuMOF, which enhanced its photocatalytic property with improved antibacterialpotential by ROS generation and heat on *Staphylococcus aureus.*

Wang *etal* synthesized 2D Cu-MOF NPs by a facile single step hydrothermal method and the resultant antibacterial effect were studied on *Staphylococcus aureus.* These NSs could convert H_2O_2 into highly cytotoxic hydroxyl free radical which caused bacterial death, thereby showing a synergist antibacterial effect.

Shams *et al* prepared Cu/H_3BTC MOF which showed notable antibacterial performance against *S. aureus* and *E. coli.*Agarose gel electrophoresis (AGE) revealed that the resulting MOF could infiltrate the bacterial cells through by weakening cell membranes and preventing DNA synthesis.

Copper MOFs nanofibrous membranes

The antibacterial potential of copper and its related compounds is driven by various toxicological effects in which reactive oxygen species produced by copper defects sites causes burst of cell leakage and become stronger by reducing the size of nanostructures. Into the bargain, the death of bacterial cell was also proposed due to interaction of nanoparticles and negatively charges cell membrane [85]. In addition to copper metal-organic framework nanoparticles, it also becomes effectively employed as nanofibrous membranes. These nanofibers can be synthesized by incorporating into polymers via electrospinning technique or can also be deposited on the surface of polymers to achieve its desired application. The electrospinning is the comprehensible technique to produce nanofibers having high surface-to-volume ratio using high-voltage power supply and present practical applications to prepare clothing with wound dressing properties [86].

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Table-1: Summary of copper MOF as antibacterial agent with mechanism.

MOFs	**ligand**	**Mechanism**	**Method**	**bacteria**	**Ref.**
$[Cu(TDC)(H_2O)_2].H_2O$	Thiophene-2,5-dicarboxylic acid	Release of copper ion and generation of destructive ROS	MIC, colony count method	*E.coli* and *S.aureus*	[71]
$[Cu(\mu_2\text{-}Amp)_2]n$	2-Amino-4-methyl pentanoic acid	Metal ion release	Zone of inhibition	*E.coli* and *S.aureus*	[72]
Copper MOF HKUST-1 (CuS@HKUST-1)	1,3,5-benzene tricarboxylic acid	ROS generation by photodynamic antibacterial therapy and release of metal ions	Spread plate method	*E.coli* and *S.aureus*	[73]
Cu-BTC in polyester and Cu-BTC in Nylon	1,3,5-benzene tricarboxylate	Release of ions	Disk diffusion method	*E.coli, S.aureus* and *C.albicans*	[74]
$[Cu(Glu)_2(\mu\text{-}L)]\cdot x(H_2O)$	Bpy, bpa, bpe, bpp	Release of metal ions	Minimal bactericidal concentration	*E.coli, S.aureus, K.pneumonia, P.aeruginosa, MRSA*	[75]
Hydrogel@Cu-MOF	Glutarate and bpe	Release of metal ions	Minimal bactericidal concentration	*E.coli* and *S.aureus*	[76]
$Cu_3(NH_2BTC)_2$	BTC	Metal ion release	Standard broth dilution agar plating method	*E.coli*	[77]
AC-HKUST-1	Benzene-1,3,5-tricarboxylic acid	Metal ions release	MIC and MIB	*MRSA* and *P.aeruginosa*	[78]
Cu-BTC loaded with chlorhexidine(CHX)	1,3,5-benzene tricarboxylate	Copper ions and CHX release	MIC and Agar Well Diffusion Method	*E.coli* and *S.aureus*	[79]
Cuccinic acid-Cu(II) and mercaptosuccinic acid-Cu(II) MOFs	Succinic acid (SA) and mercaptosuccinic acid (MSA)	Copper ions release	MIC and MIB	*Pseudomonas*, *Escherichia* coli, *Bacillus subtilis*, and *Staphylococcus aureus*	[81]
10% Copper ion doped CuMOF	H_2TCPP and benzoic acid	ROS and heat	MIC and MBC	*Staphylococcus aureus*	[82]
2D CuMOF	MI	Copper ions release	Number of Colony Forming units (CFU) plate count method	*Staphylococcus aureus*	[83]
Cu/H_3BTC MOF	H_3BTC	Copper ions release	Zone of inhibition, Time kill assay and MIC	*E.coli* and *S.aureus*	[84]

Wang *et al* studied the antibacterial performance of synthesized copper MOFs/cellulose fibers (HKUST-1/CF) composite. Copper MOF (HKUST-1) is widely studied MOF having excellent stability and large surface area whereas cellulosic fibers showed chemical activity due to rich hydroxyl groups with electronegativity. The researchers produced DMF solvent free HKUST-1/CF via green process because DMF is a toxic, carcinogenic solvent not fitted for industrial production. The antibacterial activity was evaluated by inhibition zone test against *E.coli* and *S.aureus* and the results showed visible results against both bacterial strains but composites appeared to be more effective towards Gram-positive *S.aureus.* It was found that the bacteria inhibition is due to copper ions in HKUST-1 that disrupt the structure of bacterial cell membrane or alter transmembrane potential **[**87**].**

Rauf *et al* synthesized MOF nanofibers using hydrothermal process assisted with microwave and assessed the antibacterial activity against *E.coli* and *S. aureus* using colony count method with synergistic mechanism. The prepared MOF nanofibers was copper (II) coordination polymer [Cu(HBTC)(H_2O)$_3$]. Researchers also synthesized the macro particles and compared the antibacterial efficiency with that of nanofibers. It is inferred that comparing the efficiency of nanofibers and macro particles, greater efficacy was observed with nanofibers and the percentage of inhibition for *E.coli* was 99.9% and for *S. aureus* it was 99.1%. The proposed mechanism of antibacterial activity was the release of Cu^{2+} ions and generation of (ROS) reactive oxygen species like hydroxyl radical, hydrogen peroxide, superoxide radical and singlet oxygen. The ROS rupture the individual components of bacterial cells due to its oxidative stress ultimately leads to suppression of bacterial growth and production of ROS was due to oxygen vacancies, defect sites and reforming in the crystals structure. It was attributed the nanofibers are of more potential because of the presence of large number of metal atoms at surfaces **[**88**].**

Wang *et al* scrutinized the antibacterial effects and mechanical properties of HKUST-1 incorporated into electrospun chitosan/polyvinyl alcohol fibers and these fibrous membranes produced by electrospinning showed promising effects in wound dressing to prevent from infections. For electrospinning, different polymers can be utilized but chitosan was suitably used because of its biocompatibility,antioxidant and antibacterial properties along with polyvinyl alcohol as cost-effective polymer to ameliorate the mechanical feature and spin ability of chitosan. MOFs were incorporated into these electrospun chitosan/PVA fibers as modifying agent to enhance the properties. The bacterial colony count method was used to investigate antibacterial efficiency of HKUST-1/chitosan/fibers (2cm) against *E.coli* and *S.aureus* and results showed that the kill ratio against both bacteria were 99.0% with promising skin tissue regeneration abilities **[**89]. In another study, antibacterial efficiency of Cu-BTC MOF immobilized onto cellulosic fibers was investigated by standard zone of inhibition test against *E.coli*. Rodriguez *et al* reported that the bacterium was killed when the interaction between copper (II) and cell membrane by oxidation of fatty acids and membrane proteins ultimately resulted in cell lysis [90**].**

By using a straightforward one-step electrospinning approach, composite nanofibers of pectin/PEO mixes incorporating modified Cu MOFs were effectively created in order to enhance controlled drug release while minimizing the harmful effects of Cu^{2+} ions. The fact that the produced samples biocompatibility shows that the release of Cu^{2+}ions was safe. According to the findings of the antibacterial, drug release, and tensile strength tests, pectin nanofibers having 2 wt% Cu-MOF are the best sample when compared to the other samples studied. This study demonstrates a potential first step in the designing of a drug delivery system for biomedical applications [91]. Singbumrung *et al*[92] prepared Cu-BTC MOF/PVA fibers which showed excellent antibacterial effectiveness against *S. aureus.*

Allahbakhsh *et al* synthesized Cu-BTC/GO nanocomposites having different morphologies and structures and studied their antibacterial resistance against *S. aureus* and *E.Coli*. It was found that antibacterial potential of Cu-BTC/GO nanocomposite with decrease in Cu-BTC NPs size. It can be concluded that Cu-BTC/GO nanocomposites antibacterial potential can be controlled by changing the structural and surface properties of CuBTC NPs through the synthesis process.

Azizabadi *et al* prepared copper-MOF by an effective, rapid, controllable ultrasonic supported reverse micelle methodusing copper nitrate, 2,6-pyridine dicarboxylic acid and poly vinyl pyrolidine. Then, Fe_3O_4nanoparticle ascore improved physiochemical properties and stability of copper MOF. The resultant composite material had excellent antibacterial activities as compared to Cu-MOF.

Liu *et al* prepared a high antibacterial potential fibrous membrane of by 3D Cu-MOF(copper citric acid and poly lactic acid. It was then compared with commercial Cu NPs, Citric acid and Cu-MOF and found superior antibacterial properties.

Table-2: Summary of copper MOF nanofibrous membrane and its antibacterial mechanism.

MOF	polymer	mechanism	method	bacteria	Ref.
HKUST-1/CF	**cellulosic fibers**	**Release of Cu^{2+} ions and destroy cell membrane of bacteria**	**Inhibition zone test**	***E.coli* and *S.aureus***	**[87]**
$[Cu(HBTC)(H_2O)_3]$	**1,3,5-benzenetricarboxylic acid**	**Synergistic effect of ROS and metal ions release**	**MIC, bacterial reduction assay**	***E.coli* and *S.aureus***	**[88]**
HKUST-1/chitosan/PVA	**Chitosan and polyvinyl alcohol**	**Release of ions**	**Bacteria colony count method**	***E.coli* and *S.aureus***	**[89]**
Cu-BTC immobilized on cellulosic fibers	**-**	**Copper (II) interaction with cell membrane by oxidation of fatty acids**	**Standard zone of inhibition test**	***c***	**[90]**
F-HKUST incorporated on pectin electrospun fibre	**Pectin and Poly ethylene oxide**	**Copper ion release**	**Bacteria colony formation count method**	***S. aureus* and *E.coli***	**[91]**
Cu-BTC incorporated in PVA	**PVA Fibre**	**Copper ion release**	**Standard zone of inhibition test**	***S. aureus***	**[92]**
Cu-BTC /graphene oxinde nanocomposite	**Graphene oxide nanocomposites**	**Copper ion release and ROS**	**Standard zone of inhibition test**	***S. aureus* and *E.coli***	**[93]**
Fe_3O_4@Cu-MOF	**Fe_3O_4 nanoparticles**	**Copper ion release**	**Standard zone of inhibition test**	***S. aureus* and *E.coli***	**[94]**
Cu-MOF-1	**poly(lactic acid) (PLA) Fibre**	**Copper ion release**	**The growth curve method, colony count and inhibition zone**	***S. aureus* and *E.coli***	**[95]**

Copper MOFs as films

To add further, the interesting approach of using copper MOFs efficiently and to avoid instability issues is the immobilization of copper MOF (HKUST-1) as film on polyacrylamide, chitosan or fiber as solid substrate. Ren *et al* synthesized beneficial composite with bacteria killing effects and wound healing properties based on HKUST-1-loaded chitosan film (HKUST-1/CS) and characterized by XRD, FT-IR and SEM. To measure antibacterial potential against *E.coli* and *S.aureus*, disc diffusion and plate count assays were applied. The results obtained presented the higher results against *S.aureus* than *E.coli* and showed low cytotoxicity **[**96**]**.

Abbasi *et al* prepared copper MOFs nanostructures as coating on silk fibers via layer-by-layer technique that exhibited antibacterial activity against bacterial cultures. Researchers inferred that the release of copper ions as active phase to surrounding medium was the dominating factor of antibacterial activity performed against bacteria using disk diffusion method **[**97**].**

Nanofiltration membranes used for dye or salt removal requires surface modification to achieve high selectivity and antifouling activity of membranes. Mozafari *et al* synthesized polyethersulfone membrane (PES) coated with chitosan and surface was further enhanced by coating of copper MOF thin film. The binding of thin film to membrane was confirmed by SEM, EDX and water contact-angle measurement and its effectuality was investigated by it antibacterial activity against *E.coli*. The results revealed that Cu-BTC/CS immobilize 83% bacteria as compared to membrane not coated with copper MOF thin films. The proposed mechanism involves rupture of cell wall when in contact with metal ions[98]**.**

Gwon*et al*embed Cu Glu bpa MOF on polysiloxane(PS@Cu-MOF)and investigated its antibacterial potential against *E.coli*, *S. aureus* and methicillin-resistant Staphylococcus aureus(MRSA).

It showed more than 80% antibacterial potyentialagainst the tested bacteria at a Conc. of 100 µg/mL with negligible cytotoxicity. Cu(II) ion released proved its stability in phosphate buffer saline solution with a negligible cytotoxicity toward mouse embryonic fibroblasts at the same concentration.

Antibacterial Mechanism of Copper-based MOFs

MOFs provide an alternative to conventional antibiotics and have the potential to address drug resistance through a variety of modes of action due to their robust structures and inherent active centers. MOFs can act as metal ion reservoirs, enabling controlled and prolonged release. This is beneficial for long-term antibacterial and antimicrobial effects[100, 101] in a variety of applications, such as textiles and medical equipment. Combining various metal ions[102] and adding antimicrobial organic linkers to MOFs creates opportunities for targeted medicinal applications and synergistic antibacterial effects[103]. The biocidal mechanisms of MOFs as well as metal/metal oxide nanoparticles (NPs)[104, 105] include the release of metal ions, which increase membrane permeability and disrupt cellular functions, leading to bacterial cell death. Synergistic effects observed in multi-metallic MOFs and hybrid NPs suggest that both metal ion release and reactive oxygen species (ROS) generation contribute to their antibacterial efficacy. This interaction of metal/ metal ion with bacterial cells can result in significant structural damage, including disruption of DNA replication and cell wall integrity, underscoring their potential as effective antimicrobial agents[106]. This mechanism is summarized in figure 2.

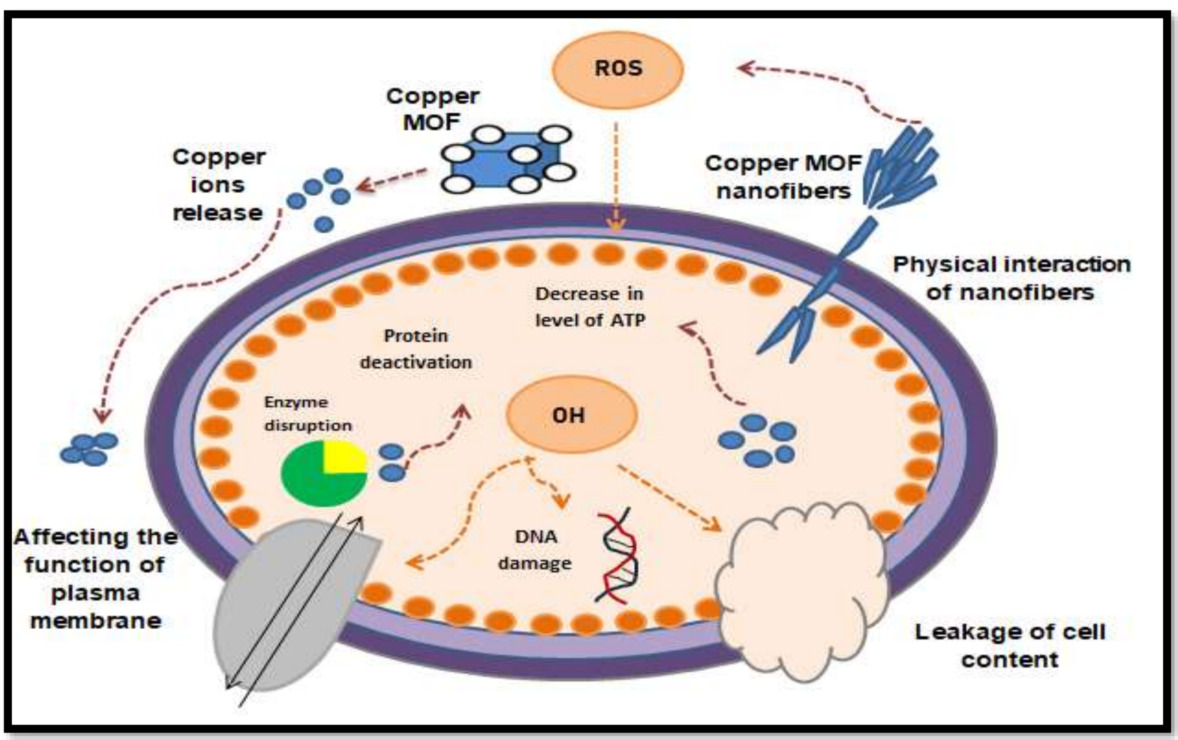

Fig. 2: Schematic mechanism of antibacterial action of copper-based compounds.

Table-3: Summary of copper MOF films and their proposed antibacterial mechanism.

MOF	polymer	mechanism	method	bacteria	Ref.
HKUST-1/CS	Chitosan	Release of Cu^{2+} ions	Disk diffusion and plate count method	*E.coli* and *S.aureus*	[96]
HKUST-1/silk fibers	Silk fibers	Slow copper ions release	Disk diffusion method	*E.coli* and *S.aureus*	[97]
PES-CS coated with Cu-BTC	Chitosan	Cell wall rupture by metal ion interaction	Fluorescence microscopy for live and dead staining	*E.coli*	[98]
PS@Cu-MOF Cu-Glubpa MOF on polysiloxes (glutarate and 1,2-bis(4-pyridyl)ethane)	Polysiloxanes	Release of Cu^{2+} ions	Colony firming units	*E.coli*, *S.aureus* and methicillin-resistant Staphylococcus aureus(MRSA)	[99]

Conclusion

Antibacterial medicines are vital part of human life now. Due to high cost, lack of availability and bacterial resistance exploration of new and promising antibacterial agents is essential. Copper metal organic frameworks "Cu-MOF" are one of t hird generation potential anti-bacterial agents whose mechanism is based on slow release on Cu(II) ions or ROS and heat or both Copper ions and ROS. By maintaining stability and minimizing cytotoxicity of Cu-MOF, it can be applied alone or as a Cu-MOF based membrane or film. Further research is required to enhance antibacterial potential of these materials by mean of their combination or changing composition.

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