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Review on biosynthesis of copper oxide nanoparticles and their antibacterial activity

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ABSTRACT

In last few decade, several research attempts in the field of nanoscience and nanotechnology due to its distinctive physicochemical and biological properties. Nanoparticles type like copper oxide nanoparticleshas has most attracted due to their multifarious in biological properties and especially suitable in the area of nanomedicine and biomedical sciences. The metal and metal oxide nanoparticles can be synthesized various approaches such as physical, chemical and biogenic methods. Physical and chemical syntheses of nanoparticles are easily obtained desired structure and high purity of the materials. However, physicochemical techniques are high expensive of regents and equipment consume high energy as well as release of high hazards chemicals to the environmental system, which leads to environmental pollutions and hazards to the human and also aquatic animals. In contrast the biogenic synthesis methods are low cost-effective, reliable, eco-friendly and simple way to synthesis of metal oxide nanoparticles. In this review focused on biogenic mediated (Plant, bacteria and fungi) synthesis of copper oxide nanoparticles for their biomedical application of antibacterial activity.

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1. Introduction

In current few decades, considering the wide rage applications of metal oxide nanoparticles have played an important role in the pharmaceutical, biomedical, environmental and textile industries. Thus important reasons have been worldwide increased in investment in the field of nanotechnology based development. Metal and metal oxide nanoparticles of silver, gold, zinc and copper oxide, zinc oxide as well as iron oxide have been effectively used several biomedical applications of pharmaceutical, antimicrobial, anticancer, drug delivery, agriculture and also included environmental wastewater treatment (Folorunso et al., 2019; Akintelu et al., 2019a-c; Khatereh et al., 2019). Traditionally, the nanoparticles have been synthesis followed two approaches methods of physical, chemical, microwave, sol gel, sonochemical, irradiation, thermal decomposition, quick precipitation and hydrothermal have reported, which has been using chemical precursor for reducing and stabilizing agents to form of metal and metal oxide nanoparticles (Wang et al., 2010; Zhu et al., 2014; Lee, et al., 2018). Another green synthesis method has been used biomolecules based liquids, which is act as capping and reducing of metal oxide nanoparticles. In this techniques have been using of less chemical solvents and moreover, faster and feasible synthesis method. Recently, several researchers and scientist have focusing on biological rout synthesis of metal oxide nanoparticles such as copper oxide nanoparticles which good exhibit biological and photocatalytic activity than those obtained from metal nanoparticles have been reported.

Copper is an important element for plants, animals and humans. About 2-4 mg minimum amount of copper has required daily intake of human life, but it must be uptake from dietary sources of food and drink (Raha et al., 2020; Bost et al., 2016). The copper oxide is major function of cofactor and many enzymes involved in regulation of cell signaling pathway, neuropeptide synthesis, antioxidant defense, and triggering human immune system and also inhibit of pathogens (Latorre et al., 2019). Copper have been stimulated and regulated of immune cells such as neutrophils, macrophage and helper T cells in the human immune system (Georgopoulos et al., 2001). In furthermore, copper is essential mineral nutrition for the plant growth and important key role of various biochemical and physiochemical pathways, and it also act as enzymes cofactor to functioning synthesis of proteins such as cytochrome c oxidase, amino oxidase and plastocyanin (Castillo-Duran et al., 1988; Ghaderian et al., 2012; Sifri et al., 2016. Recently, several methodologies have been focused the biogenic synthesis of copper oxide nanoparticle on the utilization of plant aqueous extracts such as *Carica papaya* (Sankar et al., 2014), *Ruellia tuberosa* (Vasantharaj et al., 2019), *Malva sylvestris* (Awwad et al., 2015), *aloe vera* (Kumar *et al.*, 2015) and *Gloriosa superba* (Naika et al., 2015). In addition bacterial (*Escherichia coli* (Singh et al., 2010), *Morganella morganii* (Ghasem et al., 20117), *Pseudomonas stutzeri* (Zarasvand et al., 2016), *Gluconacetobacter hansenii* (Araújo et al., 2018), fungi (*Aspergillus terreus* (Mousa et al., 2020), *Trichoderma asperellum* (Saravanakumar et al., 2019) and actinomycetes biomass have been using for the biogenic synthesis of copper oxide nanoparticles. The plant extract contains both primary and secondary metabolites product of phytocompounds can act as reduce the metal ions to form of nanoparticles. Primary metabolites such as proteins, lipids, carbohydrates (simple sugars and polysaccharides), while secondary phytocompounds comprise flavonoids, alkaloids, terpenes, glycosides, acetogenins and tannins etc. In currently, several researchers have been reported on utilization of naturally derived polysaccharide compounds of gum, pullulan, hydroxypropyl, Arabic, curdlan and pectin for the synthesis of silver or gold or zinc oxide nanoparticles. General biomedical applications of biogenic synthesized copper oxide nanoparticle such as antimicrobial antifungal, anticancer, antibiotics, antioxidants, drug delivery and anti-fouling (Maqbool et al., 2017; Mohammed et al., 2018). In addition, industrial uses gas sensor, thermo sensing, catalytic, magneto resistant materials, synthesis of inorganic nanosize composites, textile industries and environmental remediation (Fatah et al., 2018; Venkatachalam et al., 2018) etc. This review mainly focused on provision scientific findings of biogenic synthesized copper oxide nanoparticles from various biological resources (plants, bacteria, fungi and actinomycetes) and their antibacterial applications.

2. Phytocompounds mediated synthesis of copper oxide nanoparticles

The synthesis of copper oxide nanoparticles have been widely using aqueous plant extracts than compared to the different biological fabrication sources of bacteria, fungi, algae and actenomycetes, but there are some limitation the using of microorganisms for the synthesis of metal and metal oxide nanoparticles (Ijaz et al., 2017). The major problems of microbial mediated synthesis of copper oxide nanoparticles due to their risk of toxicity, isolation and incubation process of the microbial culture as well as large scale production. Hence, the research scientists are mainly focused on plant aqueous extracts are ideal source for the production of copper oxide and other metal oxide nanoparticles. Plant extract contains of phytocompounds can mediated fabrication of copper oxide nanoparticles is an easy and safe, simple process, low energy consumptions, good biological properties and biocompatibility (Awwad et al., 2015). In this technique, the precursor solution is mixed with the plant aqueous extracts, and the reaction takes 2 to 3hrs at incubated room temperature to complete the reaction. The plants have different phytocompounds of secondary metabolic such as flavonoids, terpenoids, tannins, phenols and proteins that act as capping and reducing agents for the conversion of metal salt into the copper oxide nanoparticles (Asemani et al., 2019).

The plant leaf extract of *Aloe barbadensis Miller* was added to the copper sulfate solution and incubated under the stirring at room temperature for 7hrs. The color change of the solution was visually observed from greenish brown to darkish brown which indicated the formation of copper oxide nanoparticles. The physicochemical characterization of synthesized copper oxide nanoparticles were observed by UV-vis, FTIR, XRD, TEM and SEM with EDX analysis. The surface morphology of copper oxide has revealed spherical with average particles size range of 20nm. The FTIR spectrum of synthesized copper oxide nanoparticles have exhibited the presence of phenolic, terpenoids and proteins compounds that have indicated the responsible for the stabilizing and reducing of formation of nanoparticles (Gunalan et al., 2012). Similar research reported the use of *Punica granatum* peel extract for the fabrication of copper oxide nanoparticles. The peel extract was prepared and added into the vessel containing copper salt (copper acetate monohydrate) under the magnetic stirring at 37°C for 10 mint. After that incubation primary identification of the color change was visualized darkish brown which has indicated the formation copper oxide nanoparticles. Synthesized copper oxide nanoparticles were characterized by UV-Vis, FT-IR, XRD and SEM analysis. Surface morphology of the synthesized copper oxide nanoparticles was revealed spherical in shape with an average size of 40 nm. FTIR analysis was determined the presence of bioactive compounds of alcohol, phenol, and amines which responsible for reducing and stabilizing of synthesized copper oxide nanoparticles (Ghidan et al., 2016). The similar research reported by

Table 1. Plant phytocompounds mediated synthesis of copper oxide nanoparticles

Plants name	References
Cordia sebestena	Prakash et al., 2018
Hibiscus rosasinensis	Rajendran et al., 2018
Ocimum basilicum	Rajesh et al., 2018
Quercus	Sorbiun et al., 2018
Ferulago angulata	Mehr et al., 2018
Moringa oleifera	Galan et al., 2018
Tridax procumbens	Selvan et al., 2018
Zingiber officinale, piper nigrum and piper longum	Shah et al., 2019
Zea mays L.	Nwanya et al., 2019
Saccharum officinarum	Mary et al., 2019
Psidium guajava	Singh et al., 2019
Juglans regia Walnut	Asemani et al., 2019
Caesalpinia bonducella	Sukumar et al., 2020
Phoenix dactylifera	Mohamed et al., 2020
Cedrus deodara	Ramzan et al., 2020

using of *Olea europaea* (Sulaiman et al., 2018)and *Citrofortunella microcarpa* (Rafique et al., 2018) leaf extract to the synthesis of copper oxide nanoparticle it potential antimicrobial activity of pathogenic bacteria. Recent literature of plant source mediated synthesis of copper oxide nanoparticles are shown in Table 1.

2.1. ***Bacteria mediated biogenic synthesis of copper oxide nanoparticles***

In recently, many researchers significantly focus on the bacterial synthesis of nanoparticles, including copper oxide. Bacterial through an intracellular or extracellular protein mediated synthesis of metal oxide nanoparticles have producing wonderful morphologies with nanoscale dimensions Bacterial synthesized nanoparticles have potential biological properties and their antibacterial activity. The advantage of this technique likes an easily cultured, short generation time, high stability, mild experimental condition, easily mutated at the genetic level and high yield of nanoparticles productions (Narayanan et al., 2010). Commonly metal and metal oxide nanoparticles have high toxic concentration, during the nanoparticles synthesis bacterial culture added into that environment condition which converting the toxic metal ions into non-toxic metal oxides. Bacterial oxidative stress has produced several biomolecules that contains of thiol groups (Zarasvand et al., 2016; Kouhkan et al.m, 2020). The bacterial mediated fabrication of copper oxide nanoparticles, these biomolecules act as capping and stabilizing of the nanoparticles. In several scientific reported the biogenic method of bacterial synthesis of different metal and metal oxide nanoparticles such as Au, Ag, Co, Fe, CuO, and CeO respectively. Hassan et al., 2008., have been reported copper oxide nanoparticles synthesis by using of Gram negative bacteria of *Serratia* sp. The synthesized nanoparticles were physicochemical characterization by using of UV-Vis, FTIR, XRD, XPS and TEM. The FTIR spectrum was confirmed the different functional groups of biomolecules on the surface of bioinspired copper oxide nanoparticles. Biomolecules of proteins can act as capping and reducing as well as stabilizing of nanoparticle. The TEM image was revealed polydispersed shaped and average size range between 10-30 nm of the synthesized nanoparticles. Researchers have been recently reported bacteria mediated synthesis of copper oxide nanoparticles are shown in Table 2.

Table 2. Bacteriological mediated synthesis of copper oxide nanoparticles

Bacterial strain	**References**
Escherichia coli	Singh et al., 2010
Morganella psychrotolerans	Shobha et al., 2014
Halomonas elongata	Rad et al., 2018
Proteus mirabilis	Eltarahony et al., 2018
Streptomyces	Omran et al., 2020
Streptomyces MHM38	Sarah et al., 2021

Other similar research reported, Gram negative bacteria of *Morganela morganii* has also been performed the synthesis of copper oxide nanoparticles. Bacteria mediated synthesized nanoparticles have been characterized by XRD, FESEM, XAFS, and EDS. FESEM images were observed surface morphology of copper oxide nanoparticles showed spherical with size range of 10 nm. To synthesize nanoparticles have been performed biomedical application of antibacterial activity, it showed potential bactericidal activity of various bacterial pathogens (Ghasemi et al., 2017).

2.2. Mycological mediated synthesis of copper oxide nanoparticles

In last few years, many researchers have been focused on fungal mediated synthesis of copper oxide and metal as well as metal oxide nanoparticles. It compared to other microorganisms, fungi mediated synthesis of nanoparticles have an easy, economic effective and high potential method. In addition flow pressure, aeration, agitation and other conditions in the bioreactor or any other growth chamber compared to bacteria (Narayanan et al., 2010; Shankar et al., 2003). The microbial cell-free bioactive compounds have act as capping, reducing and stabilizing agents for biogenic synthesis of nanoparticles. The *Trichoderma* species has produced different type of bioactive metabolites such as polyketides, diketopiperazine, terpenes, pyrones, glycolipids and enzymes, but which not involved in the biogenic synthesis of metal and metal oxide nanoparticles. Two major pathways of fungi mediated synthesis of nanoparticle like as extracellular and intracellular. The intracellular rout synthesis of nanoparticles inside the fungal species, the size of nanoparticles could be smaller, good dispersity and desired dimensions than compared to extracellular method. Extracellular pathway fabrications of nanoparticles have many advantages. In this method, cell free metabolic compounds act as reducing and stabilizing agents for synthesized nanoparticles (Ahmad et al., 2005; Mukherjee et al., 2001).

Fungal mediated synthesis of copper oxide nanoparticles by using of white-rot fungus *Stereu hirsutum.* The biomolecules are extracted from the fungal culture (without mycelium) and added into the different concentration of copper salts ($CuCl_2$, $Cu(NO_3)_2$, and $CuSO_4$ and incubated at 25 °C for 7 days under the shaker (100 rpm). The color change was visually observed dark brown that confirmed the fabrication of copper oxide nanoparticles. In furthermore, purified and characterized the synthesized nanoparticles by using of different techniques such as UV-vis, FTIR, XRD and TEM. The TEM results revealed spherical shaped and dimension range of 5-20 nm (Cuevas et al., 2015). In similar research reported by El-Batal et al. (2019), the bio-inspired synthesis of copper oxide nanoparticles by using of *Penicillium chrysogenum.* The identification of nanoparticles was characterized by UV-Vis, FTIR, XRD, DLS, TEM and SEM with EDX. The TEM and SEM images were revealed spherical morphology and their size range of 9.7 nm. The FTIR analysis was also confirmed the presence of an amide functional group that was involved capping, reducing and stabilizing of copper oxide nanoparticles. Antimicrobial activity of synthesized copper oxide nanoparticles were investigated different plant pathogenic bacteria and fungi specie. The high potential antimicrobial activity against revealed *Fusarium oxysporum* followed by *Alternaria solani*, *Aspergillus niger* and bacteria of *Ralstonia solanacearum* and *Erwinia amylovora* In furthermore, several researchers have been reported fungal mediated synthesis of copper oxide nanoparticles are shown in the Table 3.

Table 3. Mycological mediated synthesis of copper oxide nanoparticles

Fungal strain	References
Aspergillus oryzae	Mosallam et al., 2018
Pleurotus ostreatus	El-Batal et al., 2018
Trichoderma asperellum	Saravanakumar et al., 2019
Aspergillus terreus	Mousa et al., 2020
Penicillium chrysogenum	El-Batal et al., 2020
Aspergillus niger	Sadaf et al., 2020
Neurospora crassa	Feixue et al., 2021

3. Antibacterial activity

In currently, nanobiomaterial based therapies have been applied to several diagnostic and treatment of diseases and newly formation of drugs for against novel disease (Applerot et al., 2012). The biogenic syntheses of copper oxide have been investigated antibacterial activity of several pathogenic bacterial strains have discussed in the review section. The research reports revealed, copper oxide nanoparticles are highly toxic to against pathogenic bacteria of human and animals.

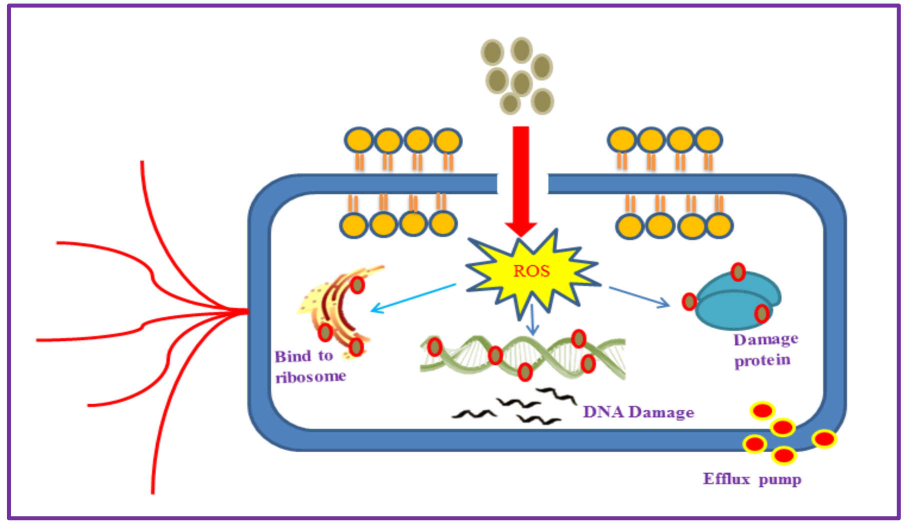

Fig.1 Mechanism of nanoparticles interaction against for pathogenic bacteria

Biogenic synthesized copper oxide nanoparticles have potential bactericidal activity against both Gram positive and Gram negative bacteria, due to their unique biological properties of size, morphology, non-toxic and biocompatibility nature of their materials (Awwad et al., 2015). The green chemistry route synthesis of copper oxide nanoparticles by using aqueous leaf extract of *Tabernaemontana divaricate* and their potential antibacterial activity was evaluated against pathogenic bacteria of urinary tract infection (UTI). The highest zone of inhibition was observed against Gram negative bacteria of *Escherichia coli* (Sivaraj et al., 2014). Similar research agreement with the biogenic synthesized copper oxide nanoparticles from *Gloriosa superba L.* extract, their antibacterial activity was investigated against both Gram positive (*Staphylococcus aureus*) and Gram negative (*K. aerogenes, P. desmolyticum, E.coli*) bacterial strains (Naika et al., 2015). The green synthesized copper oxide nanoparticles exhibit their potential bactericidal activity revealed against *E. coli* and *K. aerogenes.* Antibacterial mechanism of nanoparticles interaction is shown in the (Fig 1).

4. Conclusion

Copper oxide nanoparticles were potential biomedical applications of antibacterial, anticancer, antifungal, antioxidant and drug delivery. Copper oxide nanoparticles have been synthesized different techniques of physical, chemical and biological methods. The physical and chemical approaches are using different toxic chemical that induced hazardous to the environmental aquatic animals as well as humans. In moreover, required high energy and expensive of materials. Hence, the biological based synthesis of copper oxide nanoparticles is cost-effective, environmental friendly, low energy consumption, reliable and stable. In this review, summarized the biogenic synthesized of copper oxide nanoparticles using of different resources, and their biomedical application of antibacterial activity. To more researcher focus on improve the minimizing of toxic effect through the biological synthesis of copper oxide nanoparticles and detail defiant their antibacterial activity mechanisms.

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Conflicts of Interest: None

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