Green Synthesis, Characterization of Copper and Copper Oxide Based Nanoparticles Using Plant Extracts and Their Biological Activity

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Abstract:

Recent development in nanoscience and nanotechnology has contributed to the wide applications of metal and metal oxides nanoparticles in several field of sciences, research institutes and industries. Among all metal oxides, copper & copper oxide nanoparticles has gained more attention due to its distinctive properties and applications. The high cost of reagents, equipment and environmental hazards associated with the physical and chemical methods of synthesizing opper & copper oxide nanoparticles has been a major setback. In order to puffer solution to the aforementioned challenges by reducing environmental pollution and production of cheaper nanoparticles with good properties and efficiency, this review focus on collection of comprehensive information from recent developments in the synthesis, characterization and applications from previous scientific findings on biological method of synthesizing opper & copper oxide nanoparticles due to the acclaimed advantages of been cheap, environmentally friendly, convenient and possibility of been scale up in into large scale production reported by numerous researchers. Our finding also support the synthesis of opper & copper oxide nanoparticles from plant sources due to relative abundance of plants for the production of reducing and stabilizing agents required for opper & copper oxide nanoparticles synthesis, potential efficiency of plant biomolecules in enhancing the toxicity effect of opper & copper oxide nanoparticles against microbes, prevention of environmental pollution due of nontoxic chemicals and degradation effectiveness of opper & copper oxide nanoparticlessynthesized from plant sources. Furthermore, this study provide useful information on the rapid synthesis of opper & copper oxide nanoparticles with desired properties from plant extracts.

Keywords: Green synthesis, Copper & Copper oxide Nanoparticles, Antimicrobial activity.

1. Introduction:

Nanoparticles (NPs) are materials ranging in size from 1–100 nm, with unique properties compared to bulk materials. Their higher surface-area-to-volume ratio is a very important unique property that allows them to be used in different fields of chemical, food, electronic, and healthcare industries. Copper is one of the indispensable micro elements obligatory for the growth and development of plant. It can be present as Cu^{2+} and Cu^{+} under natural conditions. Optimum concentration is regularly involved in the plants, ranging from 10^{-14} to 10^{-16} M. In addition to many of its important functions such as cell wall metabolism and protein regulation, it also acts as secondary signaling molecule in plant cells. It takes part in the mitochondrial respiration, photosynthetic electron transport, iron mobilization, hormone signaling, oxidative stress response, and also acts as co-factor for many enzymes [1]. In recent years, the development of an efficient "green" chemistry method for synthesizing metal NPs has become a major focus of researchers. Green synthesis of Cu and CuONPs is more advantageous than chemical and physical synthesis as it is a clean, nontoxic, cost-effective, and environmentally friendly approach. It bypasses the use of harsh, toxic, and expensive chemicals [2] and, instead, utilizes biological entities like bacteria [3], yeasts [4], fungi [5], algae [6], and plants. Among all these natural organisms used in the green synthesis of Cu and CuO NPs, plants rich in bioactive compounds can serve as a reducing, stabilizing, and capping agent during NP synthesis; this makes them the best choice. They are nonpathogenic to humans, and the downstream processing steps are simple [7]. Unlike some bacterial and fungal strains that produce the NPs intracellularly, plant-mediated NP synthesis yields the NPs in the mixture solution, which can be easily obtained by filtering, rinsing, and drying [8]. The size, morphology, and stability of NPs can also be easily optimized for medicinal and pharmaceutical usage using this green method [9,10]. In this review, we focus on the updates of Cu and CuO NPs synthesized from plants and their medicinal application.

Metallic nanoparticles are multifunctional in nature and hence finds huge number of applications in various sectors for environmental, biomedical and antimicrobial, solar power generation and catalytic causes[11]. Application of plant extracts to synthesize copper and its oxide nanoparticles is a green chemistry methodology which establishes strong relationship between natural plant material and nanosynthesis[12]. It has been reported in the past study that copper, gold and silver nanoparticles exhibited excellent antimicrobial activity against various disease causing pathogens. In recent years, copper nano particles (Cu NPs) have gained significance due to their multifunctional uses in industries and medicine. However, other nanoparticles, such as platinum, gold, iron oxide, silicon oxides and nickel have not shown bactericidal effects in studies with Escherichia coli [13]. The antibacterial study on E. coli and Bacillus subtilis using Cu and Ag NPs, revealed the fact that Cu exhibited superiority over Ag [14]. Cu NPs have wide applications as heat transfer systems [15] antimicrobial materials [16], sensors [17], and catalysts [18]. In addition, copper and its compound have been applied as antifungal, antiviral, and molluscicidal agents. The synthesis of Cu NPs by using extracts of various plants found all over the globe have been reported by many researchers in the past [19,20]. It is essential to develop clean, reliable, biocompatible, cheap, and nontoxic green method of nanoparticle's synthesis. Many plants parts or whole plants have been used for the green synthesis of Cu NPs [21] due to the presence of large number of bioactive compounds in plants. The extracts of plants Neriumoleander [22], Punica granatum [23], Aegle marmelos [24] & Ocimum sanctum, [25] Zingiber officinale [26] have been efficiently applied for this purpose.

Copper oxides by themselves are hazardous, and in order to remove this toxicity and make them suitable for human consumption, they are refined through a series of procedures that include treatment with plant extracts and some animal fluids. Thus, synthesizing nanoparticles from medicinal plants will benefit their application in the biomedical arena. Additionally, the natural antibacterial capabilities of plant extracts increase the qualities of green nanomaterials generated utilizing plants. It is vital to develop a diverse array of antimicrobials that are both affordable andreadily available.

Plants are abundant and can be used to synthesize nanomaterials. The flowchart in Figure.1 illustrates the overall procedure for the production and application of Cu/CuO-based nanomaterials.

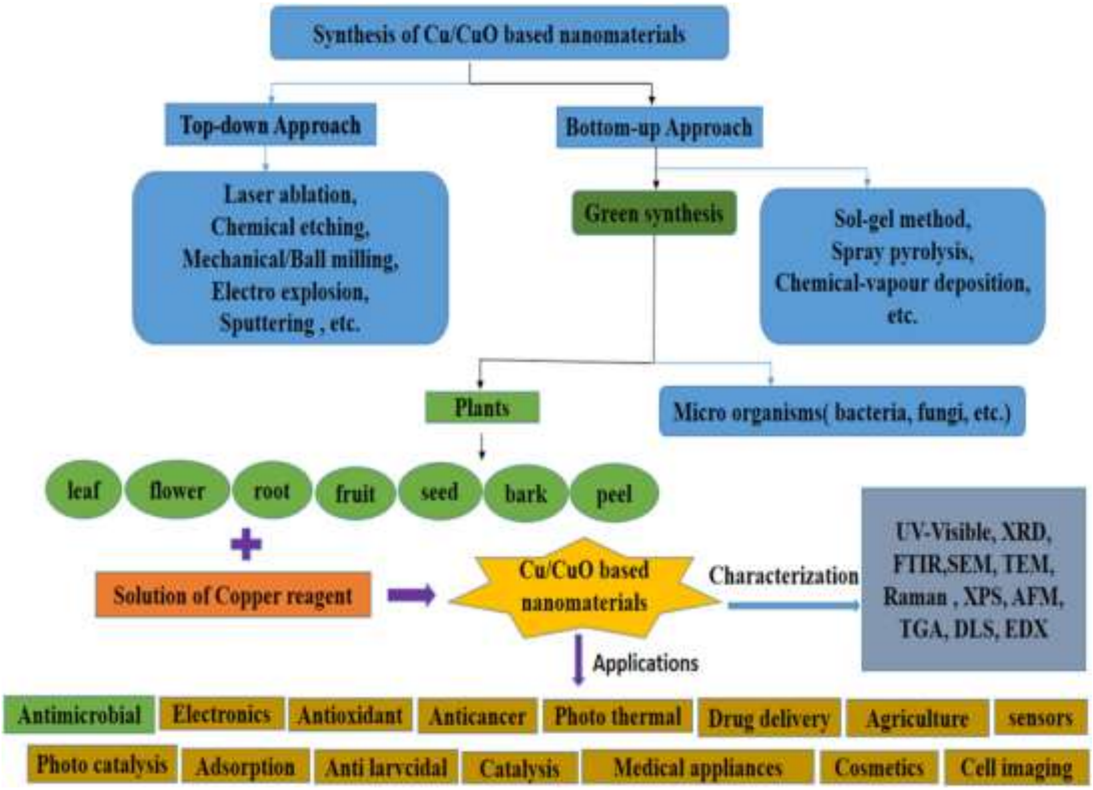

Figure. 1. Flowchart representing the biosynthesis of Cu/CuO based nanomaterials.

2. Biosynthesis of Cu/CuO based nanomaterials:

Plants consists of large number of biologically active compounds and hence, most of the plants have proven record for their anthelmintic, antitumor, antimutagenic, antibacterial and fungicidal properties. The synthesis of metallic NPs involves simple mixing of metal solution with extract of plant. Nanoparticles are produced in the medium due to reduction of metal ions. The scheme of synthesis of metallic NPs is as shown in Figure 2.

2.1. Materials

Many earlier investigations revealed that Cu NPs can be synthesised by the application of most common precursor copper salts namely, cupric acetate (monohydrate) ($(CH_3COO)_2Cu\cdot H_2O$)[27]19, Copper chloride di-hydrate ($CuCl_2$. $2H_2O$)20[28] and Copper sulfate pentahydrate ($CuSO_4.5H_2O$). [29]21 Various factors such as concentration, pH, temperature, influence the nature and properties of synthetic Cu NPs as well as CuO NPs.The reduction of copper ions to get stable copper nanoparticles can be attributed to the presence of biologically active compounds present in the leaf broth of Azadirachta indica [30].22 It was found in this study that the rate of production varied linearly with percentage of leaf broth. The other optimum conditions for the synthesis are; $[CuCl_2]$ =7.5 X 10^{-3} M, pH =6.6 and temperature = 85^{o}C.

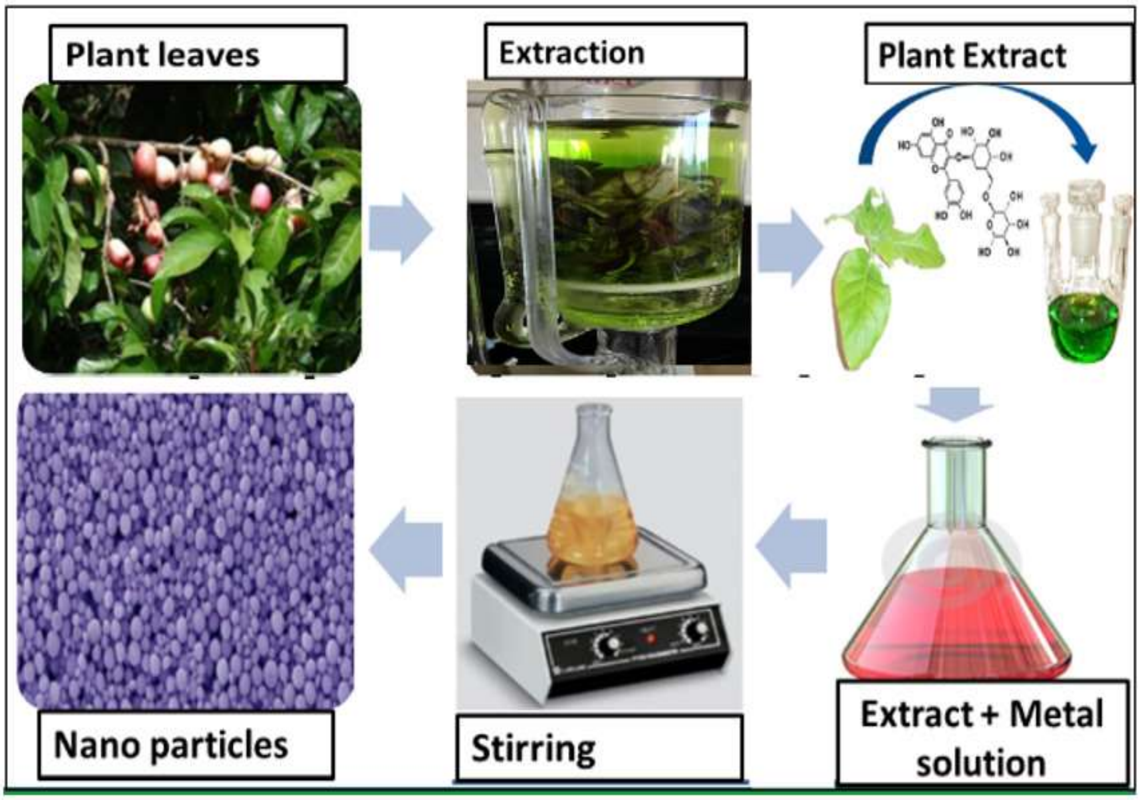

Figure. 2: A schematic diagram of green synthesis of metal nanoparticles from plant extracts

2.2. Methods

The fresh/dried powder of plant parts is dispersed in distilled water.In the majority of cases, distilled water is used as the solvent. Now it isboiled at different temperatures according to the volatile nature ofphytochemicals present in the plants, which can be accomplishedthrough various extraction procedures. Now the extract is centrifugedand filtered out using a muslin cloth and Whatmann No. 1 filter paper. Aparticular volume of the filtered extract is measured out and is mixedwith the precursor solution of particular volume and molarity [31]. Achange in colour indicates the creation of nanoparticles, which is trackedusing a UV–Visible spectrum. The overall flow chart for the synthesis of Cu/CuO-based nanoparticles is depicted in Figure. 1.

2.3 Green approach synthesis:

Formation of greenly synthesized copper nano particles capped with T. cordifolia (Cu NPs@Tc) was also reported [32].23 Synthesis of Cu nanoparticles has been successful with extracts of various parts of plant species that include, Citrus medica Linn. (Idilimbu) juice, [33]24 Ziziphus spina-christi (L.) Willd, [34]25 Asparagus adscendens Roxb. Root and Leaf, [35]26 Eclipta prostrata leaves, [36]27 Ginkgo biloba Linn, [37]28 Plantago asiatica leaf, [38] 29 Thymus vulgaris L, [39]30 black tea leaves [40]31, Terminalia catappa leaf [41] 32 and many more [42-33-77 presented in Table 1.

The organic hydrocarbon part of citron 24 facilitates the protection of copper. The antioxidant nature and acidic property of citron also prevents oxidation of copper as the protons present in the medium influence electro-deposition of copper at low pH range. Cu colloid formation of non-oxidized Cu NPs was observed with uv-absorption peak at 565 nm during the green synthesis of Cu NPs by Eclipta prostrata leaves extract.27The reduction of Cu^{2+} ions to Cu NPs by the phenolics and other chemicals of Thymus vulgaris L. leaf extract was reported.30 These biomolecules cogently reduce copper salts but also avoid agglomeration. The hydroxyl and ketonic groups of phenolic compounds bind to metals and show chelate effect. Flavonoids can directly scavenge molecular species of active oxygen. Antioxidant action of flavonoids resides mainly in their ability to donate electrons or hydrogen atoms.The reduction of copper ions to give Cu NPs was attributed to the phenolic compounds present in the Rheum palmatum L. root extract.51 The extract constituents believed to function both as reducing and capping agents in the stabilization of prepared Cu NPs.

The bioactive molecules present in the Carica papaya leaves extract61 also found toreduceprecursor copper sulphate to form copper oxide nanoparticles.In the similar way CuO NPs were also synthesised by using plant extracts of Aloe vera33, Oak fruit hull (Jaft),34 Ixoro coccinea leaf,35 Syzygium alternifolium (Wt.) Walp,36 Ferulago angulata (schlecht) boiss,37Rosa canina fruit,38 Azadirachta indica,39 Olea europaea leaf extract,40 Malus Domestica leaf extract,41 Bauhinia tomentosa leaves extract,42 Moringa oleifera leaves Extract,44 Abutilon indicum leaf extract,47 Eclipta prostrata leaves extract,48Euphorbia Chamaesyce leaf extract50 and many more as given in Table 1.

Table 1: Various plants extracts used in the synthesis of Cu and CuO NPs and their applications

Sr, No .	Plant	Image	Precursor	Size, morphology, surface plasmon vibration (SPV)	Applications	Ref
1	Syzygium aromaticum bud		Cupriacetate (monohydrate) ((CH3COO)2Cu· H2O)	-12 nm, spherical SPV@ <580 nm	Antimicrob ial properties	38
2	Stachys lavandulifoli a		Copper chloride di-hydrate (CuCl22H2O)	80 ± 8 nm, near spherical, SPV@ ~ 590 nm	antibacteri al activity	39
3	black bean		Coppersulfate pentahydrate (CuSO4.5H2O)	~26.6nm, spherical, hexagonal and uneven shapes,	anticancer activity	40
4	Azadirachta indica leaves		Cupric chloride di-hydrate (CuCl2. 2H2O)	48nm, cubical,SPV@ ~ 506 nm	-	41

5	Tinospora cordifolia		Copper chloride (CuCl2(II))	50–130nm, spherical, SPV@~250 nm	Catalytic Degradation	42
6	Citrus medica Linn. (Idilimbu) juice		Copper sulphate (CuSO4)	33nm, SPV@ ~ 631 nm	antimicrobial activity	43
7	Ziziphus spina-christi (L.) Willd		Copper sulphate (CuSO4)	8–15nm, spherical, SPV@ ~ 551 nm	triphenylmethanedye and antibacterial assay	44
8	Asparagus adscendens Roxb. Root and Leaf		Copper sulphate (CuSO4)	10–15 nm, Spherical, SPV@ ~ 500 to 700 nm	Antimicrobial Activities	45
9	Eclipta prostrata leaves		Copper acetate (Cu(OAc)2)	31±1.2nm, spherical hexagonal and cubical SPV@ ~ 565 nm	antioxidant and cytotoxic activities	46
10	Ginkgo biloba Linn		Copper chloride ($CuCl_2$)	15-20nm, spherical, SPV@560 to 580 nm	catalytic activity	47
11	Plantago asiatica leaf		Cupric chloride di-hydrate, (CuCl2·2H2O)	7–35nm, spherical, SP V@ 565 nm	catalytic activity	48
12	Thymus vulgaris L.		Copper sulphate (CuSO4)	various sizes, sheeted,SPV @ ~ 520 nm	catalytic activity (MB)	49
13	Black tea leaves		Copper sulphate ($CuSO_4$)	26–40nm, Spherical,	antibacterial, antifungal aflatoxin B_1	50
14	Terminalia catappa leaf		Copper sulphate pentahydrate	21–30 nm, Spherical,	Antibacterial test	51

			($CuSO_4$ $5H_2O$)			
15	Rheum palmatum L.		Copper chloride ($CuCl_2$)	10–20 nm, Spherical, SPV@ ~ 250–300 nm	catalytic activity	52
15	Aloe vera extract		Copper sulphate $CuSO_4$	15 and 30 nm, dispersed, versatile and spherical, SPV@ ~ 265 and 285 nm	-	53
16	Oak Fruit Hull (Jaft)		Copper acetate (Cu(CH3COO)$_2$)	34nm, quasi-spherical, SPV@ ~ 590 nm	Photocatalytic Degradation (Violet 3)	54
17	Ixoro coccinea leaf		Copper sulphate $CuSO_4$	80–110 nm, Spherical, SPV@ ~ 191 nm	-	55
18	Syzygium alternifolium (Wt.) Walp.		Copper sulphate pentahydrate ($CuSO_4$ $5H_2O$)	17.5 nm, spherical, SPV@ ~ 285 nm	Antiviral Activity	56
19	Ferulago angulata (schlecht) boiss		Copper acetate ($Cu(CH_3COO)_2$)	~44nmSPV @~ 554 nm	Photocatalyticdegradation of Rhodamine B	57
20	Rosa canina fruit		Cupric acetate, $Cu(OAc)_2$	Spherical15-25SPV@ ~ 262 nm	C-N Ullmann couplingreactions	58
21	Azadirachta indica		Copper nitrate Trihydrate ($Cu(NO_3)_2.3H_2O$)	28-35 nm, spherical SPV@~262nm	Antibacterial activity (E. coli)	59
22	Olea europaealeaf		Copper sulphate $CuSO_4$	20–50 nm, Spherical, SPV@ ~ 289 nm	toxicity activities	60
23	Malus Domestica leaf		Copper sulphate $CuSO_4$	18 - 20 nm, spherical and crystalline, SPV	antibacterial,antioxidant, DNA	61

24	Bauhinia tomentosa leaf		Copper sulphate $CuSO_4$	22-40nm, Clustered & spherical, SPV@ ~ 384 nm	antibacterial	62
25	Moringa oleifera Leaves		Copper sulphate pentahydrate ($CuSO_4\ 5H_2O$)	6 and 61 nm	Nitrates Removal	63
26	Abutilon indicum leaf		Copper(II) nitratetri hydrate ($Cu(NO_3)_2.\ 3H_2O$)	nm range agglomerated hexagonal wurtzite, SPV@ ~ 725nm	Antimicrobial, antioxidant and photocatalytic dye degradation activities	64
27	Eclipta prostrata leaves		Cupric acetate, $Cu(OAc)_2$	31±1.2nm, face-centered cubic structure, SPV@ ~565 nm	antioxidant and cytotoxic activities	65
28	Calotropis procera		Copper sulphate pentahydrate ($CuSO_4\ 5H_2O$)	15–20 nm, quasi-spherical, SPV@ ~ 565 nm	adsorptive of Cr(VI)	66
29	Euphorbia Chamaesyce leaf		Copper chloride ($CuCl_2$)	~ 36–40 face-centered cubic nm, Spherical (fcc), SPV@ ~ 325 nm	catalytic activity (4nitrophenol)	67

3. Formation mechanism for the synthesis of Cu/CuONPs from plant extracts

Green synthesis of CuONPs using plant extracts as the source of electron generation for the reduction of copper salt display some advantages over the use of microbes because it does not require cell culture maintenance and it can be scaled up for large-scale synthesis. The formation of CuONPs occurs with an observable change in the color of the extract when copper salt was added. Several studies have revealed that the phytochemicals in the plant extracts first form complexes with the iron salts and then reduce the ions to form nanoparticles. The biomolecules in the plants extracts usually react with copper ion to cause reduction which subsequently transform into CuONPs [63, 64]. The probable mechanism involved in the synthesis of CuONPs is represented with the following equations.

$$Cu^{2+} + \text{plant extract} \rightarrow [\text{Cu/plant extract}]^{2+}$$

$$[\text{Cu/plant extract}]^{2+} \xrightarrow{\text{heat}} [\text{Cu(OH)}_2\text{/plant extract}]$$

$$[\text{Cu(OH)}_2\text{/ Grass Extract}] \xrightarrow{\text{incubation}} \text{CuONPs}$$

4. Effect of reaction parameters on the biosynthesis of Cu/CuO nanomaterials:

4.1. Effect of pH:

pH value helps in the determination of the level of acidity and basicity on a solution. Report had shown the influence of varying pH value on the synthesis CuONPs and other metallic oxide nanoparticles. Significant influence of pH on size and texture of some nanoparticles biosynthesized from plant extracts have been reported [65]. Also, variation of the pH value have been adopted in controlling the shape and size of the synthesized nanoparticles [66]. Solution medium with pH values ranging from 7 to 9 has been considered as the optimum condition for the synthesis of nanoparticles from Aeromonas hydrophila extract [67].

4.2. Effect of type of plant extracts and concentrations:

The synthesis of CuONPs using plants extract depend majorly on types of biomolecules found in plant extracts and the volume used [68]. The volume of plant extracts used in the synthesis of nanoparticles influence the duration of synthesis. Previous study had shown that the higher volume of extract used, the faster the rate of synthesis because more chemical constituents are available in the solution which bind with the precursor to effect rapid bio-reduction and stabilization of nanoparticles [69]. To attain an optimum condition for the green synthesis of CuONPs the ratio of the volume of plant extract must correspond to the concentration of copper precursor used [70]. The yield of CuONPs depend largely on the volume of extract used for synthesis [71]. Findings have proved that volume and kind of extract used for synthesis of nanoparticles have huge influence on their morphological properties and biological activities [72].

4.3. Effect Time:

The incubation time of nanoparticles synthesized using plant extract has been examined to influence the morphological properties and qualities of nanoparticles [73]. Other factors such as storage conditions and exposure to light also affect the reaction time of CuONPs. Long time incubation period has been stated to cause aggregation and shrinkage of particles [74].

4.4. Effect of temperature:

Temperature have been considered as one of the crucial parametersthat influences the synthesis of metallic oxide nanoparticles. The temperature recommended for the synthesis of CuONPs and other metallic oxide nanoparticles using plant extracts is in the range of 25–100 C [75]. However, the synthesis of CuONPs at room temperature is more rampant due to the volatility of some secondary metabolites found in plants extracts. The effect of temperature of reaction solution on the morphological identity of nanoparticles has been reported [75]. Findings from the green synthesis of metallic oxides from plant extracts have shown rapid and complete synthesis at higher temperatures. However, higher temperature has been reported to cause poor synthesis of nanoparticles due to inactivation of biomolecules liable for the reduction of the iron precursor [76].

5. Characterization of Cu & CuO NPs:

Since the applications of CuONPs depend largely on their properties, the need for their characterization therefore remain essential. Theimportant characterization techniques used for determining the properties synthesized Cu & CuONPs are discussed below;

5.1. UV-visible (UV-Vis) spectroscopy:

UV-visible spectroscopy is a molecular spectroscopy that is based on Bouguer Lambert Beer law principle for its operation. This technique measures the Plasmon resonance and total oscillations of conduction band of electrons in conjunction with electromagnetic waves. It is also used for absorption measurements of fluids and several other materials [77]. In UV-visible spectroscopy analysis, a beam of light splits in two in which 50% of beams analysis the compound or solution in the transparent cell and the other 50% of the beam analysis the reference material parts. In the cause of the analysis, the solution absorbs light at a specific wavelengths, this wavelength is referred to as the surface plasmon resonance (SPR) of the material analyzed [77]. For CuONPs, the surface plasmon resonance is in the range of 200–350nm [78]. Findings has demonstrated that the type of extract, pH, temperature and method of synthesis affect the SPR of CuONPs which further influence it morphological properties [79, 80]. UV-visible spectroscopy reveals crucial information about the size, structure, stability and aggregation of the CuONPs [81]. Findings on detailed application of UV as characterization tools in green synthesis of CuONPs are summarized in Table 2.

5.2. FTIR spectrophotometer:

FTIR spectrophotometer operates in long wavelengths in order to identify different functional groups associated with NPs. The FTIR spectral reveals functional groups present in extract containing NPs [82]. At a specific resonant frequencies, the incident light from FTIR will cause an absorption when it come in contact with a vibration frequency of the group or bond corresponding to the same frequency. The shape of molecular potential energy, vibronic coupling and mass of an atoms are accountable for absorption of particular energy. The observed differences in the FTIR spectrum of different compound or molecule is traceable to the unique arrangement of atoms [83]. The peaks corresponding to O–H, C=O, C–N, C–H, C=C are the prominent peaks associated with CuONPs. Several scientific findings had ascribed the absorption at 3000–3350 cm^{-1} to N–H of amine or O–H of alcohol/phenol [84]. Absorption peaks in the range of 820–880 cm^{-1} have been attributed to aromatic C–H bending [84]. A strong absorption peak at wavelength 2900-3000 cm^{-1} was credited to C–H [85]. The absorption band observed at wavelength 1600–700 are traceable to CuO [86]. The absorption band at 1600–1790 are linked to –C=O of carbonyl [87]. Reports on the comprehensive applications of FTIR in green synthesis of CuONPs are summarized in Table 2.

5.3. Size and morphological analysis:

Size and morphological behavior are the most important parameters to investigate in nanoparticles because they influence the usefulness of CuONPs. The characterization equipment and techniques popularly used for size and morphology analysis are discussed as follows;

5.4. Scanning tunneling microscopy (STM):

This technique gives comprehensive information about the surface of CuONPs [88]. It is used for size estimation, morphological study andtopography. It equally offers the advantages of wide range application for all forms of metals and semiconductor [88]. Quantum tunneling is the working principle guiding STM, Images are produced as variation of tunneling current tip causes movement across the surface. The growth of CuONPs has been measured with STM.

5.5. Atomic force microscopy (AFM):

AFM is used for the estimation of morphological properties such as size, roughness surface and texture [89]. AFM is different from other electron microscopes techniques because it is only used for the 3D characterization of NPs. It is capable of generating information about the geometry and magnetic behavior of nanoparticles. However, its scanning speed is slow compared to other microscopic techniques, it also produce in accurate topography especially when the probe is not dull [90]. Several morphological evaluation of biosynthesized CuONPs via AFM are showed in Table 2.

5.6. Transmission electron microscopy (TEM):

TEM is regarded as the best among other electron microscopy techniques for the determination of morphological identities of CuONPs and other metal nanoparticles [91]. In TEM technique beams of energetic electrons are transmitted through an ultra-thin sample and interfaces from which a picture is shaped [92]. The improved form of TEM with higher resolution that allows imaging of the crystallographic structure at nuclear scale is termed high resolution transmission electron microscopy (HRTEM) [93]. Reports obtained from the morphological evaluation of biosynthesized CuONPs using TEM and HRTEM are represented in Table 2.

5.7. Scanning electron microscopy (SEM):

SEM is used for morphological characterization of CuONPs. It is limited in some morphological analysis because it produces limited information regarding the true population and average size distribution [94]. SEM has been reported to damage some nanopolymer. Therefore, for an effective morphological analysis using SEM, the NPs must be capable of withstand vacuum pressure [95]. Another retrogression about this technique is that it very expensive and slow. Other results showing the morphological characterization of biosynthesized CuONPs via SEM are represented in Table 2.

5.8. Dynamic light scattering (DLS):

DLS is sometimes referred to as quasi-elastic light scattering. It performs the function of size determination and aggregation of NPs [96]. This technique is very fast, sensitive and can estimate the size of a particle on both nano and macro scale but it also have some limitation because the size of an individual particle cannot be obtained from an aggregate. The speed of DLS is dependent on particle size; small particles are very as characterization tools in CuONPs biosynthesis are showed in Table 2.

5.9. X-Ray diffractometer (XRD):

XRD is used for structural and crystallinity analysis of synthesized CuONPs [99, 100]. X-ray diffraction analysis have revealed that CuONPs is a face-centered cubic phase in agreement with standard powder diffraction card JCPD file No. 48–1548. The average crystallite size of CuONPs are estimated using Debye Scherrer formula [101].

$$D = 0{:}9\lambda/\beta\cos\theta$$

where d = size of Cu-NPs (nm), λ = X-ray wavelength, β = full width at half maximum of the diffraction peak and θ = measured Bragg angle. The diffraction peaks at 2θ value of 31.6^0, $45.^04$, 56.4^0, 66.3^0 and 75.2^0that indexed planes (110), (112), (202), (220) and (004), respectively, was used to characterize the monoclinic structure of CuONPs [102, 103]. Several findings on the structural and crystallinity analysis of biosynthesized CuONPs using XRD are represented in Table 2.

6. Applications of Cu/CuO nanomaterials:

CuONPs synthesized using plant extracts have been reported to exhibit numerous applications in many fields. Some applications of CuONPs are discussed below as showed in Figure 3.

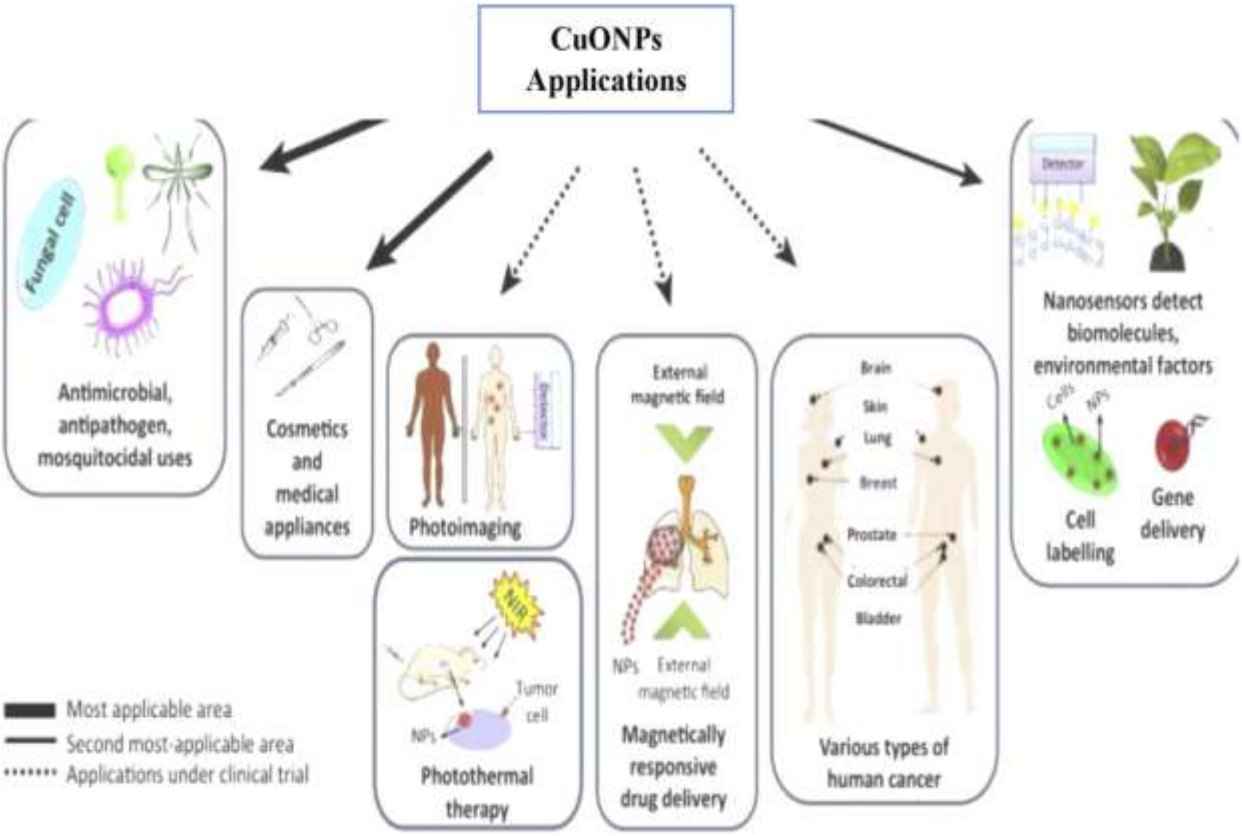

Figure 3. Flow chart showing some applications of CuONPs.

6.1. Antibacterial application:

The inhibitory antibacterial potential exhibited by biosynthesized CuONPs against both gram-positive and gram-negative bacterial strains had been studied [134]. The antibacterial activities of phytosynthesized CuONPs from the extract of Tecoma castanifolia leaf displayed reliable bactericidal activity that may be useful in biomedical applications [135]. Previous study have shown that the biomolecules of plant extracts used in CuONPs synthesis promote greater antibacterial efficacy against Gram-positive and Gram-negative bacterial strains. The increase in the antibacterial efficacy of CuONPs has been linked with the biomolecule (terpenoids) found in the extract during the capping process [136] The antibacterial analysis of CuONPs obtained from the agar well diffusion technique against both gram positive bacteria (Streptococcus mutans and Staphylococcus aureus) and gram negative (Pseudomonas aeroginos, Klebsiella pneumonia and Escherichia coli) showed the toxicity of CuONPs in destroying the growth of tested pathogens. The bactericidal effectiveness of CuONPs has been traced to the development of highly reactive oxygen species such as (OH, H_2O_2 and O^{2-}) on the surface of the CuONPs which causes the death to the bacteria [125]. Reports on the antibacterial activities of CuONPs are summarized in Table 4.

6.2. Probable mechanism for the toxicity of CuONPs against bacteria:

The presence of CuO produces reactive oxygen species which interact with bacterial cell membrane to aid the penetration of CuONPs into the bacterial cell. The disturbances caused by CuONPs in the cell membrane of the bacterial causes some malfunctions in the bacterial cell which results into the inhibition of the growth of the bacterial species which might finally lead to their death [137]. The smaller size of CuONPs (nanometer) compare to the pore size of bacterial cells (micrometer) allows the easy penetration of CuONPs into the cell membrane without any interference [138]. The destruction of the bacterial membranes by CuONPs could be via production of reactive oxygen species and radicals or by direct cell damage since superoxide and hydroxyl radicals are produced by metal oxides (CuO) [139]. The abundance of carboxyl and amines groups on bacterial cell surface could possibly attract Cu^{2+} ions towards the cell [139, 140, 141]. Therefore, the probable antibacterial mechanism can be associated with gene toxicity, mechanical damage or oxidative injury. The probable antibacterial toxicity is showed in Figure 4.

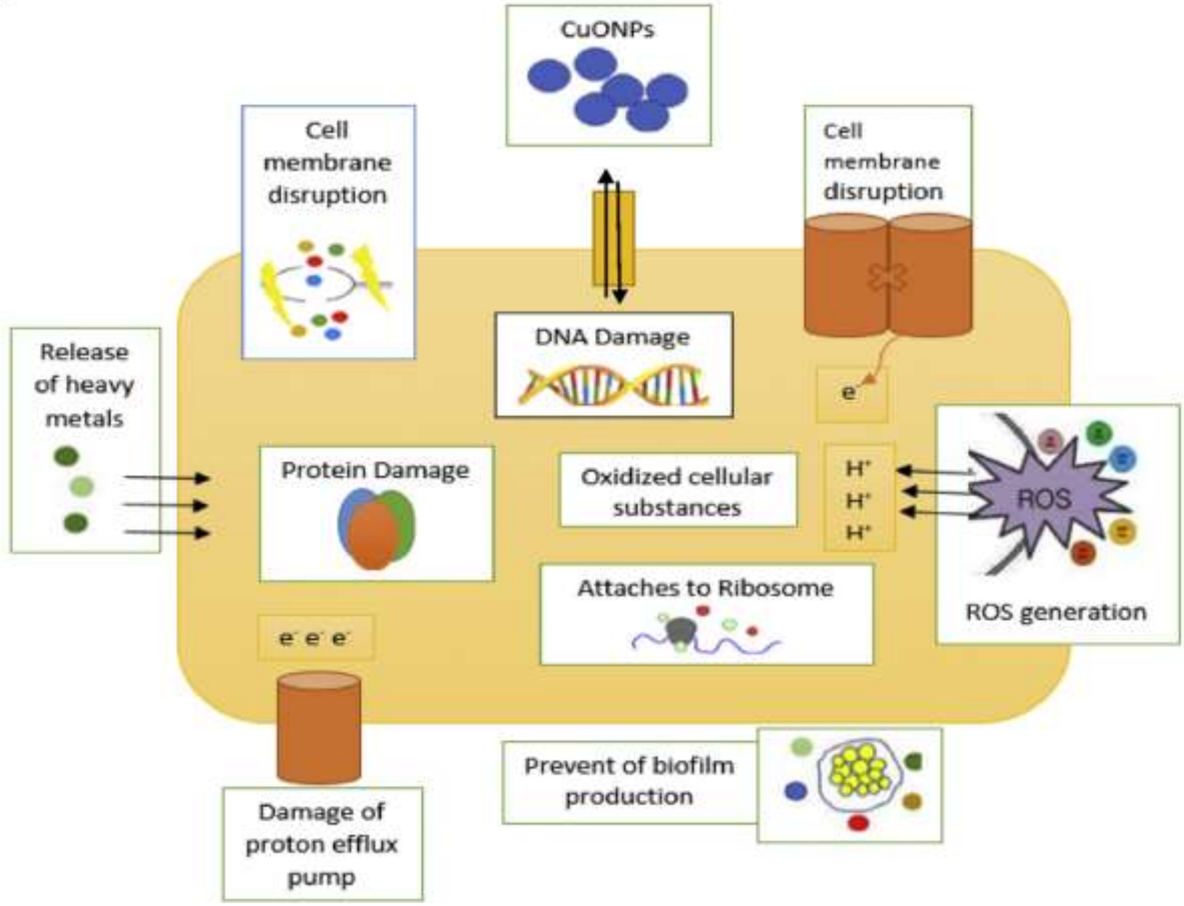

Figure 4. Probable mechanism of CuONPs toxicity against bacteria.

6.3. Anticancer application

The anticancer investigation of CuONPs biosynthesized using the extract of black bean via the sulforhodamine-B assay revealed some alteration in the mitochondrial structure when incubated with CuONPs, the growth of cervical carcinoma cells were also greatly reduced when treated with CuONPs [142]. Report have shown that CuONPs mediated from Ficus religiosa had potential anticancer efficiency against the growth of A549 adenocarcinomic human alveolar basal epithelial cells [143].

The recommendation of CuONPs in development and design of delivery carriers for cancer cell targeting due to demonstrated prominent toxicity accentuated as oxidative

stress damage and DNA damage in cancer A549 lung cells has been made [119]. The cytotoxicity of CuONPs mediated from the leaf extract of Pterolobium hexapetalum against human breast cancer cell line (MDA-MB-231) clearly showed enhanced effectiveness [118]. Stating the importance of toxicity analysis in selecting nontoxic nanoparticles with distinctive biological activities, report on the invitro toxicity investigation of phytosynthesized CuONPs reveals that they exhibit better toxicity efficacy that are beneficial in biomedical application when compared with chemically synthesized nanoparticles [145].
The report from the toxicity evaluation of CuONPs mediated from Olea europaea via animal model using 25 healthy male albino mice reveals that the CuONPs induces weight loss and exhibited dose-dependent toxicity [146]. Several studies have shown the cytotoxicity of CuONPs against cancer cell growth [147, 148, 149]. Literature reports on the anticancer potency of CuONPs are summarized in Table 4, while the probable mechanisms of CuONPs induced cytotoxicity in cancer cell lines is presented with Figure 5.

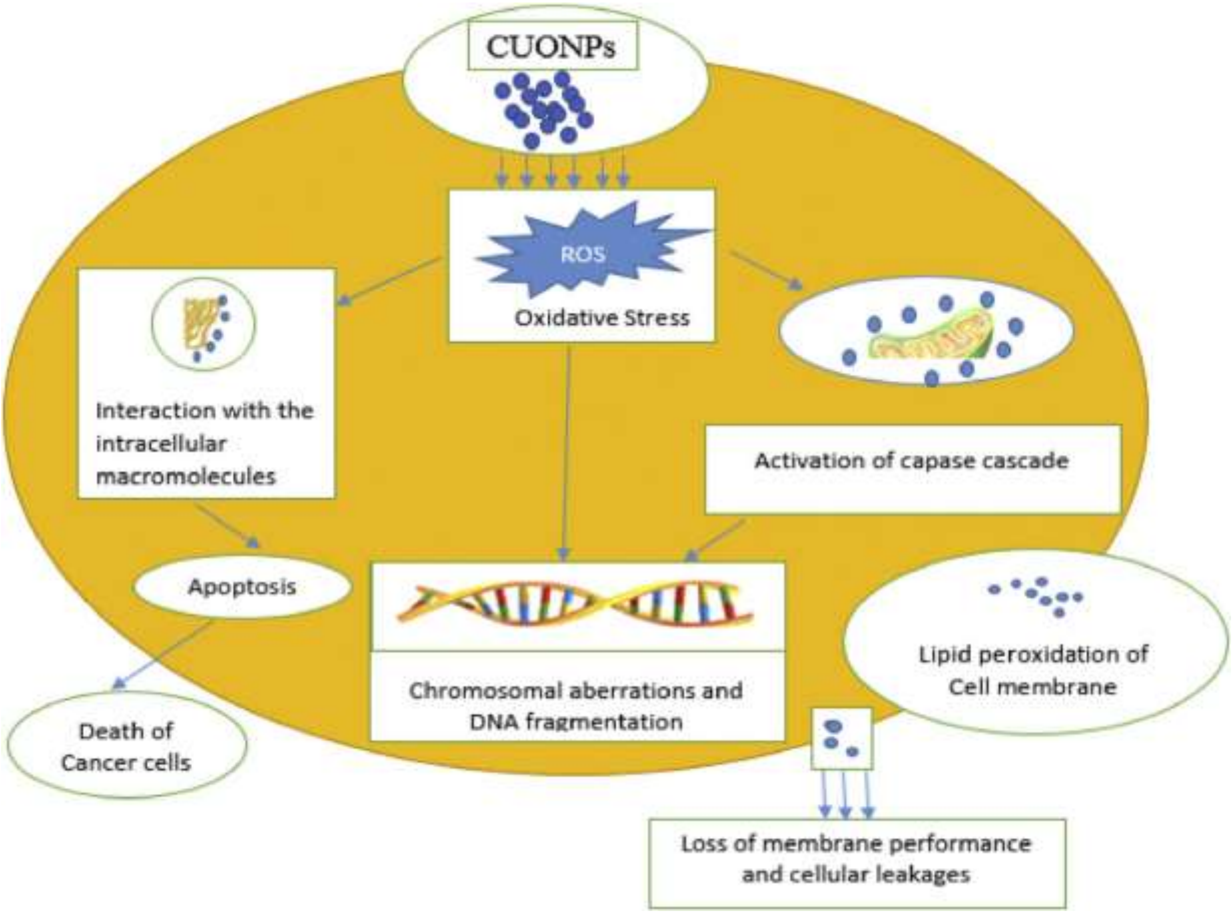

Figure 5. The probable mechanisms of CuONPs induced cytotoxicity in cancer cell lines

6.4. Catalytic application:

Metallic and metal oxide nanoparticles has been reported to exhibit good photocatalytic efficiency [150, 151, 152, 153]. The photocatalytic degradation assessment of green synthesized CuONPs on RB dye revealed 94% degradation efficiency to the fifth cycle, which demonstrates the durability of the phytosynthesized CuONPs rendering it a good photocatalytic agent [154]. Furthermore, the comparative catalytic study of CuONPs and zinc oxide nanoparticles

(ZnONPs) for basic violet 3 degradation indicated that ZnONPs exhibited higher catalytic activity than CuONPs. The degradation of basic violet 3 proceeded with pseudo-first-order kinetics [120]. CuONPs synthesized using Thymus vulgaris leaf extract was reported as an outstandingly heterogeneous catalyst used in N-arylation of amines and indoles due to the remarkable percentage yield of N-arylated products obtained. The recovery and recycling of the catalyst for auxiliary catalytic reactions without ant loss in activity was also attained [155]. The photocatalytic analysis of CuONPs mediated from Aloe Vera leaves under solar simulator light irradiation indicated that CuONPs completely degraded methylene blue in 10 min. This high activity is traceable to the phyto-constituents in Aloe Vera leaves [156]. More findings on the catalytic efficiency of CuONPs has been reported [157]. The schematic representation of the degradation mechanism of CuONPs is showed in Figure 6.

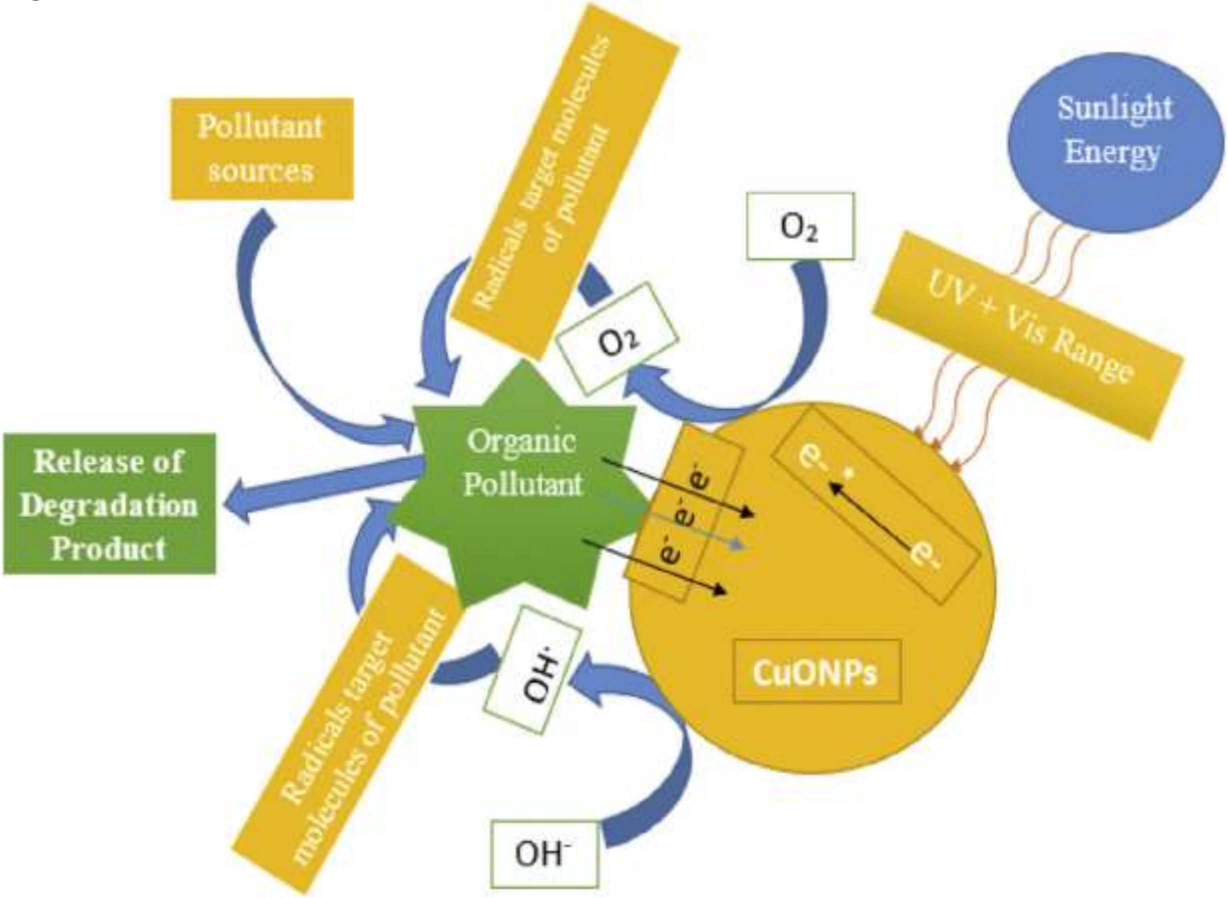

Figure 6. A schematic representation of degradation of some pollutants using the CuONPs.

7. Conclusion:

The method used in the synthesis of CuONPs predominantly affect the ecological identities as well as their physiochemical and morphological properties, which can influence their biological and catalytic applications. We discuss elaborately the biological method of synthesizing CuONPs from plant which offers great opportunity to medicinal institutes and other industries due to its biological activity and mode of synthesis.

The principal application of CuONPs in biomedical and waste treatment is attributed to their antimicrobial efficiency which depend largely on the morphological properties.

The recent characterization techniques used in examining the identities of CuONPs are well highlighted. The efficiency of biosynthesized CuONPs as anticancer, antioxidant, antibacterial and effluent treatment has been properly discussed. The mechanism of synthesis and toxicity are well explicated. To improve the biological applications of CuONPs more research work should focus on possible route of minimizing CuO-NPs' toxicity while maintaining and improving their biological efficiency.

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