Mujibullah Sheikh / Afr.J.Bio.Sc. 6(5) (2024). 7026-7050 **ISSN: 2663-2187**

https://doi.org/ 10.33472/AFJBS.6.5.2024. 7026-7050

African Journal of Biological Sciences

A Review of Aloe Vera in Green Synthesis: A Comprehensive Analysis of Ag- and Cu-Codoped ZnO Nanoparticles and Their Antibacterial Properties

Mujibullah Sheikh[1*], Hellen Yayra Dzoagbe[1], Mrunal Deshmukh[2]

[1]Department of Pharmacology Datta Meghe College of Pharmacy DMIHER (Deemed to be University), Wardha, Maharashtra, INDIA.

[2]Department of Pharmaceutics, Datta Meghe College of Pharmacy DMIHER (Deemed to be University), Wardha, Maharashtra, INDIA,

Correspondence:

Mr. Mujibullah Z. Sheikh

Department of Pharmacology, Datta Meghe College of Pharmacy DMIHER (Deemed to be University), Wardha-442001, Maharashtra, INDIA.

Email: mujib123sheikh@gmail.com

Mobile No: +91-9325348838

Article History
Volume 6, Issue 5, 2024
Received: 15 May 2024
Accepted: 22 May 2024
doi: *10.33472/AFJBS.6.5.2024. 7026-7050*

ABSTRACT

Aloe vera, one of the most versatile medicinal plants, has been widely popularized in the field of green synthesis due to its phenomenal characteristics. This can be further discussed in the present review paper concerning the comprehensive analysis of Ag and Cu codoped ZnO nanoparticles and their potential benefits. The use of aloe vera extract as a source for green synthesis is a viable and environmentally friendly choice for traditional chemical reconstruction approaches. In this review, the primary properties of codoped nanoparticles are reviewed based on their structure, optics, and morphology, which promote their physicochemical properties in comparison to those of doping-free nanoparticles. This article investigates how the synergistic effect of codoped ZnO manifests improved catalysis, disinfection, and photocatalysis. Moreover, the review also covers the potential applications of these promising nanostructures in many fields, such as environmental remediation, biomedical applications, and energy storage devices. The outcome of this review paper will add value to the increasing literature based on the potential of aloe vera-mediated green synthesis for the development of composite materials for various advanced functional materials as a sustainable and eco-friendly solution.

Keywords: Aloe vera, green synthesis, Nanoparticles, Ag and Cu codoped ZnO, Antibacterial properties

1. INTRODUCTION

Ag and Cu have attracted significant interest because of their flexible oxidation state and almost vacancy-free electronic arrangement. The superior biocidal and immediate antifungal activities of Ag and Cu also promoted their use. These advantages combine when Ag and Cu are doped with ZnO. ZnO delivers improved dual antifungal and antibacterial activity. The green synthesis of Ag- and Cu-codoped ZnO produced through plant extracts contained relatively high concentrations of Ag and Cu, respectively. This composition is required for the synthesis of Ag and Cu codoped ZnO nanoparticles. The leaves of Camellia sinensis, seeds of Coriandrum sativum, and wetland scurf-pea roots were used as ZnO precursors to tailor the surface and properties of ZnO [1]. The morphological transformations and defects in doped ZnO are inherent characteristics that are responsible for acceptable antimicrobial and antibacterial sensitivity. Different forms of Zingiber officinale, Capsicum annuum, Olea europaea, and Eruca sativa have been sterically generated for the crystal structure modulation of doped ZnO. The attainment of polymorphs and unambiguous crystal structures for doped ZnO nanoparticles is a pressing need for antibacterial effectiveness, and these structures assume a basic role when Ag and Cu are doped [2].

The potential of Aloe vera in green synthesis was studied in Ag and Cu codoped ZnO nanoparticles with unique properties. The synthesis of Aloe vera leaf extract allowed the creation of ZnO NPs with antibacterial and antifungal properties for various applications [3]. The Codoped ZnO NPs could be characterized by a band gap of ≈3.2 eV, enabling the creation of tunable optical properties for diverse uses [4]. Another example is a survey dedicated to silver-doped ZnO nanoparticles synthesized using Gymnema sylvestre leaf extract. The results revealed significant antimicrobial activity, which could prevent the development of harmful microbes. Consequently, such nanoparticles could be used for different therapeutic needs. The use of natural extracts of plants such as Aloe vera or Gymnema sylvestre could aid in the synthesis of various types of functional nanomaterials since the method is both efficient and adaptable [5].

Among the well-recognized plants, Aloe vera is known for its acute pharmacological advantages and remarkable potential in the field of dermatology and has become a valuable fresh material for green synthesis. Recent investigations of noble metal nanoparticles have revealed that plant extracts, which are rich in physiologically active compounds, can be used to produce extracellular polymeric nanoparticles. One of these plants is Aloe vera. The present exploration suggests an eco-friendly, timely, and quick method based on photographs that represent the synthesis of silver nanoparticles utilizing Aloe vera extracts as a gel reductant [6].

The synthesized Ag-NPs were well characterized using multiple techniques. TEM, UV–Vis, FTIR, and DLS were used for the characterization. Based on the TEM micrograph analysis, the prepared Ag-NPs were found to be spherical and varied in shape, with an average size of 50-100 nm. The UV–Vis spectrum also showed an absorption peak at 450 nm due to the SPR of the Ag-NPs [7]. The antibacterial activity also validated the significance of Ag-NPs prepared from Aloe vera due to their inability to exert any toxicity on *Pseudomonas aeruginosa* and *E. coli*. Taken together, our results demonstrate the potential therapeutic potential of the Aloe vera-assisted green synthesis of Ag-NPs for generating Ag-NPs with excellent antimicrobial and cytotoxic properties for various medicinal applications [8]. This review lays the groundwork for the broad examination of Aloe vera extract-assisted green synthesis of Ag and Cu codoped ZnO nanoparticles, which explores its structural, optical, electrical and antibacterial activities and has been implemented in several fields [9].

In the last few years, transition metal doping of ZnO has become a potential step to alter its optical and electrical properties, such as through an excellent approach. Transition metal ions are inserted into ZnO crystals under suitable conditions, which boosts their performance for numerous applications in optoelectronics, biomedicine, and electronics. The doping of ZnO with Ni, Co, Sn, Al, Ag, Cu, Sr, Mg, and Mn substantially altered the characteristics of the ZnO nanoparticles. This approach provides perfect applications for the future [10].

Various nanomaterials have been codoped into ZnO nanoparticles to improve their performance and sustainability. Most studies have shown that Mn and Co, Fe and Co, and Ni and Co codoped ZnO nanoparticles present enhanced antimicrobial, photocatalytic, and ferromagnetic activities compared with those of pure and mono-doped ZnO nanoparticles [11]. Overall, codoping with Ni and Cu, Y and Cu, and Al and Cu also improved the dielectric constant, ferromagnetism, and optical properties, which could be beneficial for optoelectronic device fabrication. Conversely, codoped ZnO nanoparticles with Al and Ag, Ni and Ag, and Y and Ag showed excellent electrical, optical, and photocatalytic properties [11], [12].

NPs have a large range of applications; thus, zinc oxide NPs, which are based on a variety of properties, have become one of the most commonly used devices in science. ZnO nanoparticles, because of their strong optical and electrical properties, are good for use in some of the most commonly used optoelectronics, such as photovoltaic devices, solar cells, light-emitting diodes, biomedical imaging devices, optical waveguides, sensors, and laser devices [13]. In some cases, ZnO nanoparticles might be used as DNA biosensors, protein detectors, immunochemistry and enzymatic biosensors for research and biomedical analysis. In addition, the possibility of targeting ZnO nanoparticles to certain types of cancer cells allows detection and imaging of the process of cancer progression using methods such as fluorescence imaging, photoacoustic imaging, and various other nanoparticle systems. Moreover, ZnO nanoparticles are used for antibacterial action [14]. In many cases, their surface is coated onto the designated surface to avoid bacterial growth and hence reduce infection. From the perspective of energy storage, ZnO nanoparticles play a crucial role in solar cells, supercapacitors, and batteries, among other technologies, that facilitate the development of sustainable sources of energy. Moreover, their use has extended to applications in wound healing, water and air purification and dentistry, demonstrating their ability to act as antimicrobial agents against various bacterial strains. Due to their low-cost synthesis, chemical inertness, and low toxicity to human cells, ZnO nanoparticles are potential candidates for biological applications such as Nano genetics and drug transportation [15].

1.1. Overview of Green Synthesis

The green synthesis of antibiotics refers to a sustainable and eco-friendly process of nanoparticle production from biological materials in the fight against antimicrobial resistance. In particular, the use of different plant extracts, bacteria, fungi, yeast, and algae in the process of nanoparticle synthesis has been widely selected as a cost-effective, simple, and environmentally friendly approach for preventing the production of harmful materials. Among the nanoparticles that have attracted much interest in terms of green synthesis are silver nanoparticles, as the resistance of microorganisms to antibiotics is a global challenge [16]. Specifically, concerning the preparation of antibiotics, green synthesis aims to reduce and exclude the use and production of harmful materials through the use of green chemistry philosophy. Using bacterial and fungal species, as well as plant extracts, the synthesis of AgNPs was developed both intracellularly and extracellularly because many bacterial strains can reduce metal ions and produce nanoparticles

[17]. This method allows not only the generation of nanoparticles with desired characteristics but also decreases the negative anthropogenic influence and stimulates a green approach to the production of antibiotics [18].

Therefore, the green synthesis of nanoparticles for antibiotic use supports the development of environmentally friendly and safe chemical products and processes. The 12 principles of green synthesis, such as waste minimization, using safer solvents, and reducing synthesis time, are aimed at minimizing the production of chemical substances that harm the environment [16]. Thus, in line with the major goal of green synthesis for the development of safer and environmentally friendly chemical products, green synthesis is a promising method for the preparation of antibiotics; this method is much simpler, takes less time, is one step, is less expensive and preserves or enhances the physical and chemical properties of nanoparticles [19]. Green synthesis is an essential practice in the war against the threat of antimicrobial resistance. In particular, it promotes the advancement of inorganic chemistry, innovations in chemical technologies and solutions, and the effective combatting of multidrug-resistant microorganisms. Green synthesis enables the realization of the growing need for novel nanostructures using available biological resources and facilitates the prevention of environmental damage by using traditional methods of synthesis. This chemical technology enhances the production of antibiotics responsibly and efficiently and eliminates the threat to humanity caused by antimicrobial resistance [20].

Greener synthesis principles of sustainability, energy efficiency, low toxicity, minimal harm to ecosystems, and the use of renewable resources as the procedure by which researchers synthesize various compounds, including antibiotics, must influence the production of these compounds. The continuous development and use of green synthesis approaches for the development of antibiotics present a means of changing the landscape of how antibiotics are developed. This will help ensure greener and more sustainable pharmaceutical practices in the future.

1.2. Anatomy and Characteristics of Aloe Vera

Aloe vera, a Liliaceae plant succulent, is recognized as the primary source of several antiseptics, including lupeol, salicylic acid, urea nitrogen, cinnamonic acid, phenols, and sulphur. The aloe vera plant was discovered more than 5,000 years ago and has been christened the “silent healer,” “evergreen,” or “miracle plant” by the natives of Xanthii. Aloe vera is, in reality, one of the most versatile and useful plants on the planet. It has been a popular part of modern and traditional medicine for centuries and an essential element in pharmaceutical formulations [21]. The application of aloe vera in cosmetics, food processing, medicine, and a wide range of products demonstrates its importance in multiple industries. Aloe vera is an amazing succulent plant of the Liliaceae family that has attracted the attention of many researchers, scientists, and health enthusiasts. Several researchers have studied the strong antimicrobial properties of aloe and have used aloe to treat various medical disorders [22]. In addition to being an antiseptic agent, aloe is known for its strong anti-inflammatory and antioxidative capabilities [23]. It is thus widely used as an ingredient in skincare and cosmetic products. Aloe not only is miraculous in the medical field but also provides numerous benefits when it intrudes into the culinary world. The plant uses plant leaves from gel-like flesh to prepare various foods and drinks to increase the flavor of foods and increase their nutritional value [24].

Aloe vera is a plant of economic and medicinal importance that has unique anatomical and genetic characteristics. For example, the whole-genome sequence containing 86,177 coding genes has undergone adaptive evolution in genes associated with drought stress response and circadian rhythm [25]. Morphological studies of Aloe vera accessions revealed variations in the length and width of the leaves and stems. The most effective micropropagation technique for plant regeneration has been standardized [26]. Water availability affects the anatomical and physiological features of Aloe vera and hence its productivity and water use efficiency [27]. Historically, the numerous bioactive compounds in Aloe vera, including aloins and polysaccharides, have made Aloe vera a miracle plant because of its healing, anti-inflammatory, and antidiabetic properties.

Aloe vera is a succulent plant in the genus Aloe and is one of the most popular plants worldwide. The plant is popular for its anatomy and many other characteristics. The plant leaves are thick, fleshy and colored green to gray–green. They can measure 60–100 cm (24–39 in) long and 3–5 cm wide. The leaves are arranged in a rosette, and they have serrated margins and small white teeth. Flowers appear on a spike of up to 90 cm in height, each with an ovary approximately 1 cm long. The corollas of the tawny flowers are pendulous and yellowish tubular [28]. The anatomy of the Aloe vera leaf consists of three fundamental layers: rind, latex, and gel. The rind is the outer ingredient that is high in proteins and carbohydrates; latex is the middle membrane of the leaf and contains a bitter yellow sap made up of glycosides and anthraquinones, while the gel is the inner layer, which is 95% water and full of bioactive molecules such as lignans, phytosterols, polyphenols, and anthraquinones. Acemannan is a large proportion of gel polysaccharide in the leaves for gland profiling. This gel is used topically for a variety of commercial items, including skin lotions, makeup, ointments, and gels, as well as minor chemical and thermal burns, cuts, canker sores, ash, and windburn [29].

1.3. Traditional and Medicinal Uses

Aloe vera, an adaptable herbal plant, has been widely employed for traditional and medicinal purposes in several cultures [30], [31], [32], [33]. The healing of aloe vera initiates tissue granulation, acts as an anti-inflammatory and antiseptic agent, and is a rich source of bioactive compounds such as flavonoids, anthraquinones, and phytosterols [34]. It plays a central role in immune system modulation, wound healing, and inflammation reduction. Aloe vera gel and latex, which include more than 300 species, are used in strengthening cosmetics, medicine, and food products owing to their antimicrobial, antioxidant, and antidiabetic characteristics. The traditional importance of aloe vera in medicine represents a beneficial contemporary commercial example that demonstrates the medicinal potential of Aloe vera.

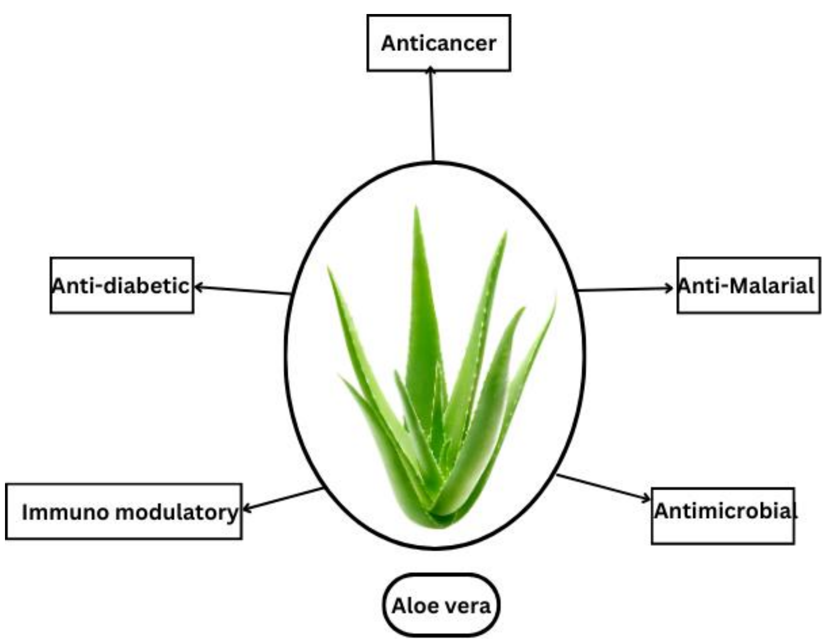

Figure 1: Traditional and medicinal uses of aloe vera

Internally, Aloe vera has been shown to cure a broad spectrum of conditions, such as ulcers, gastritis, diabetes, cancer, headaches, arthritis, and immune system diseases. It also acts as a viable laxative, assisting in overall digestion and bowel regulation. The detoxification, antiseptic, and immune-enhancing abilities of the plant are also well established, making it a valuable all-round tonic. Aloe vera contains vital vitamins such as B12, as well as vitamins A, C, and E; contains all amino acids; and contains numerous minerals. Aloe vera gel should be used by pregnant children and women while taking medication [35]. The medicinal uses of Aloe vera also include ailments or signs related to abrasions, burns, insect bites, rashes, herpes, urticaria, fungal infections, vaginal infections, conjunctivitis, and allergic reactions. It is an active component for keeping the skin hydrated and good-looking in unclothed or dry-skin conditions, mitigating acne and sprains, providing sunburn skin soothing and preventing X-ray burns. Other uses of Aloe vera solutions include frostbite, shingles, psoriasis, marks of defeat, flaws, aging, and furrows. This implies that this plant can fight almost all the body’s problems.

Even with all the above advantages, it is critical to know that aloe vera has drawbacks. When used topically, it can cause redness, burning, and allergens in sensitive individuals. If taken orally, it may cause abdominal cramps, diarrhea, hepatitis, and electrolyte imbalances. This approach may even increase the likelihood of developing colorectal cancer if used in the long term. Thus, it is crucial to apply this plant under medication control for people with known allergies and pregnant or breastfeeding women [36].

2. Advancements in Aloe Vera-Mediated Green Synthesis of Ag and Cu Co-Do

Excitingly, Aloe vera has shown promising potential in the green synthesis of silver and copper nanoparticles [37]. The published journals have reported some work on the use of Aloe vera extract in the synthesis of Ag nanoparticles with which Aloe vera extract demonstrated excellent antioxidant properties and substantial anti-cervical cancer effects. Furthermore, Aloe vera has been demonstrated to be an excellent reducing and capping agent for synthesizing CuO nanoparticles, revealing antibacterial activity, and has promising photocatalytic properties [38]. Both Ag and Cu nanoparticle syntheses using Aloe vera indicate that the bioinspired and eco-friendly creation of such metals is viable and is a feasible alternative to traditional chemical techniques. Such inventions emphasize the multiple purposes and efficiency of Aloe vera in moderating green metal nanoparticle synthesis throughout all sectors.

While previous research has studied the use of Aloe vera in the synthesis of zinc oxide nanoparticles doped with silver or copper alone, the current study utilized a novel method of Ag and Cu codosing. Thus, the unique finding of this work lies in the application of Ag and Cu codoping to ZnO nanoparticles via a green synthesis method [9]. This study investigated the use of Aloe vera as a bioreducing agent for the synthesis of Ag-Cu codoped ZnO nanoparticles. The use of Ag-Cu-codoped ZnO nanoparticles, which are synthesized through an environmentally friendly method, is a distinct contribution to the literature. The literature review includes limited examples of comprehensive studies on dual-doped ZnO nanoparticles using an eco-friendly process. Thus, this study contributes significantly to the development of the current field based on the studied preparations, codoping impacts, green synthesis, and reducing agents, i.e., Aloe vera. The findings will serve a variety of sectors, namely, optoelectronics, biomedical devices, energy storage, and catalysis, which can be accessed and used for more cost-efficient and environmentally friendly technological applications.

Aloe vera-mediated green synthesis of Ag and Cu-codoped ZnO nanoparticles was achieved using Aloe vera gel extract as a reducing and stabilizing agent due to its antioxidant, antibacterial, and anticancer properties. The process was conducted using a solution with a pH of 10 and applying the coprecipitation method. This method enabled the doping of transition metal dopants of Ag and Cu into the seed ZnO nanoparticles [9]. X-ray diffraction revealed a hexagonal wurtzite structure in the nanoparticles and crystallite sizes ranging from 17-23 nm. Moreover, the lattice parameters, bond lengths, and dislocation density of the nanoparticles significantly changed due to the doping. Furthermore, EDX revealed that the Ag and Cu were successfully doped into ZnO without the addition of impurities. Transition metals were well incorporated without any excess or high centrifugal forces during agitation [38]. The morphological study indicated that there was a decrease in the agglomeration and morphological transition of the nanoparticles from columnar to globular shapes. This finding strongly indicates the effects of the dopants on the physical properties of the nanoparticles. An optical study revealed that all the samples exhibited band gaps in the range of 3.18-3.27 eV [9]. The abovementioned results confirmed that the nanoparticles are wide-bandgap semiconductors. However, the dopants shifted the spectra and resulted in increased transparency and band gap but a lower absorption coefficient in the visible region. Moreover, as the temperature increases, the electrical resistivity decreases for all the nanoparticles, with the codoped nanoparticles showing the lowest resistivity at various temperatures, thus confirming the semiconductor nature of the codoped nanoparticles. At extremely low concentrations, the particles synthesized herein were highly effective against two bacteria that were tested: gram-positive *S. aureus* and gram-negative *E. coli*. Inhibition zones were observed even at the lowest concentrations and were equal to those observed for antibiotic controls. This means that Aloe vera-assisted green-synthesized Ag and Cu codoped ZnO nanoparticles have potential applications in the biomedical, energy storage, and optoelectronic fields [39].

2.1. Ag and Cu Co-Do Synthesis Using Aloe vera

The synthesis of silver and copper codoped ZnO nanoparticles, ZnO:Ag, Cu, using aloe vera as a bioreduction agent is a major step in environmentally friendly nanotechnology. This paper discusses the codoping of Ag and Cu on ZnO NPs, which shows the possibility of using aloe vera for green synthesis [9].

For the preparation of the materials, Aloe vera leaves were collected for the study, thoroughly rinsed with deionized water to remove any contaminants, and then cut into small pieces, which were then boiled in deionized water for 20 minutes to obtain the bioactive ingredients. Thereafter, the broths were filtered to remove any solid residues and then kept in a refrigerator at 4°C to obtain the Aloe vera extract solution [40]. In the synthesis experiment, a 0.3 mol solution was prepared using 20 ml of deionized silver nitrate, which was subsequently mixed with 20 ml of Aloe vera extract solution at room temperature with rapid stirring for 30 minutes. To characterize the synthesized nanoparticles, several methods that allowed us to attain this goal were used. To determine the crystal phase, X-ray diffraction with CuKα radiation was used. For an accurate analysis of particle sizes and morphology, it was necessary to use both scanning electron microscopy and transmission electron microscopy. Finally, the optical properties of the nanoparticles can be revealed using UV–visible absorbance [41].

3. Antibacterial mechanism of ZnO NPs

There are various pathways through which ZnO NPs exert their antibacterial effects. They include the release of highly reactive oxygen species produced from the interaction between NPs and bacteria, which causes cell death as the cell walls and membranes are perforated [42]. It generates reactive oxygen species, including ·OH and $O2^{\cdot -}$, under visible light, which can intensify its antibacterial capabilities [43]. Moreover, ZnO NPs disrupt the organization of the bacterial membrane, damaging it and preventing cell division. Hence, the antibacterial action of ZnO NPs does not solely depend on the internalization of NPs in bacteria; rather, surface action, as well as cell culture media, is a substantial factor affecting the cytotoxicity of this widely studied material [44]. In conclusion, the activity of ZnO NPs against bacteria is associated with ROS formation, membrane damage, and surface action, which indicates that this material is suitable for exposure to many bacterial strains. Figure 2 shows the mechanism of action of the ZnO NPs.

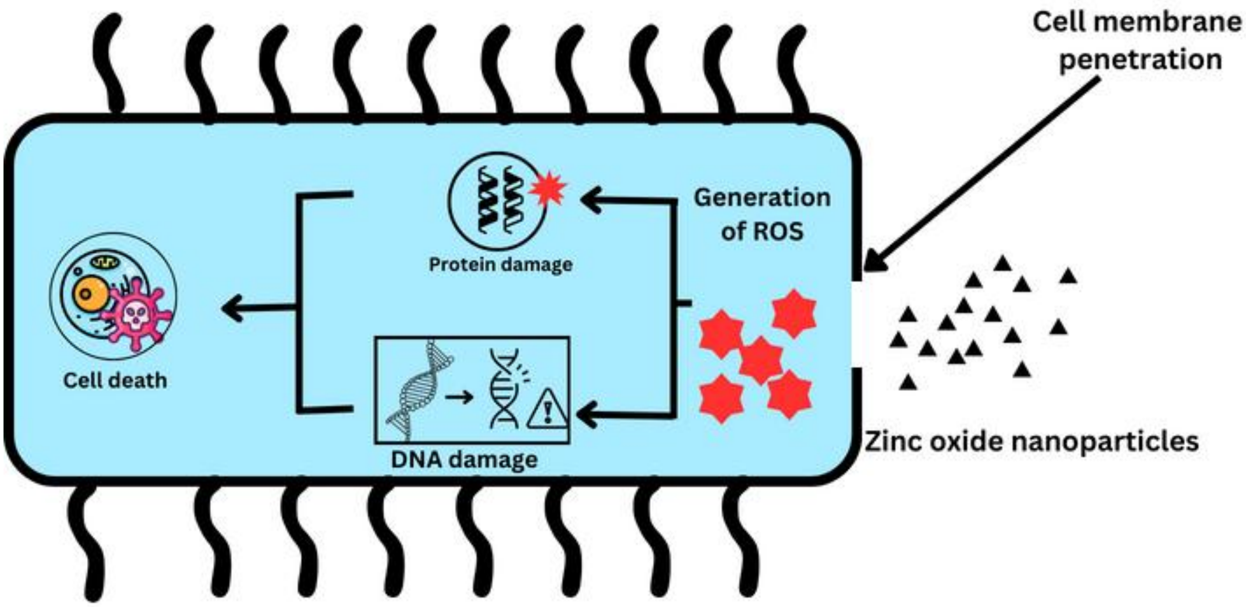

Fig. 2: Mechanism of action of the ZnO NPs

- **Reactive oxygen species:** ZnO NPs can also generate ROS upon exposure to UV/visible light. The superoxide anions, hydroxyl radicals, and hydrogen peroxide produced by ZnO NPs can ably damage the bacterial cell membrane, DNA, and proteins, leading to cell death [45], [46].
- **Zn2+ ion release:** ZnO NPs also release Zn2+ ions when they are dissolved in the bacterial medium, as do ZnO NPs dissolved in the cell culture medium. These can easily pass through the bacterial cell wall and cell membrane and attack the protein C3. It also damages the electron reservoir ability and blocks the respiratory chain [45], [46].
- **Membrane disruption:** The positively charged ZnO NPs might interact with the negatively charged bacterial cell membrane and initiate a series of reactions related to membrane damage and cell material leakage [46].

- **Size and morphology dependence:** variation in size and morphology. Smaller-sized ZnO NPs and ZnO NPs with more complex structures have shown better outcomes [44], [47].

In contrast to most microorganisms and unlike *Campylobacter jejuni*, which has increased sensitivity to ZnO nanoparticles, the latter serve as a suitable model for studying the molecular determinants of the bactericidal effects of nanoparticles [48]. ZnO nanoparticles disrupt bacterial DNA replication, downregulate most pneumococcal virulence-related genes, and strongly alter genes related to oxidative and general stress responses. Furthermore, ZnONPs have antibacterial effects against *A. baumannii* carbapenem-resistant RS-307 and RS-6694 [49]. Additionally, the effect of ZnONPs depends on the growth stage and is most effective at the exponential phase when directed against gram-positive and gram-negative bacteria, whereas their bactericidal activity significantly decreases during the lag and stationary growth phases. The bactericidal concentrations of the suspensions of ZnO nanoparticles were compared with fourfold higher ranges, as outlined in Fig. 4. To date, recent research has focused on specific methods for improving the antimicrobial action of nanoparticles. The general characteristics of nanoparticle organization outlined in comprehensive synthetic libraries are based on the following descriptions: type, method of synthesis, size, structure, form, presence or absence of an envelope and nucleus, and affected objects: type, biological effect, nanoparticle counts, time of action, impact from 10°C-30°C, and environmental factors [50].

Table 1: Properties, physical and chemical attributes, and biological characteristics of the ZnO nanoparticles

NO.	Size, nm	Composition of material	Type of microorganism	Concentration	Exposure time and temperature	References
1.	33	Zno	*E. coli*, S. choleraesuis, B.subtilis	10 mg/ml	48 h, 37^{o} C	[51]
2.	23.7-88.8	Zno	*S. aureus*, *E. coli*, *C. albicans*	0.25; 0.5 mg/ml	24 h, 37°C; (*C. albicans* at 28°C)	[52]

3.	22	Zno	*B. subtilis*, *S. mutans*, S. Aureus, *E. coli*, *P. aeruginosa*, *K. oxytoca*	0.0005 g (0.5 mg) weighed portions of NPs were placed in a well in agar seeded with bacteria	24 h, 37° C	[53]
4.	20-50	Zno	*S. aureus*, S. typhimurium, A. flavus, *A. fumigatus*	20-100 ug/mi	24 h, 37°C	[53]
5.	4.45 ± 0.37	Zno	*S. aureus*, *E. coli*	0.375-1.5 mg/m for *E. coli*: 0.09-0.375 mg/ml for *S. aureus* 0.5-16 mg/ml	24 h, 37°C	[54]
6.	66	Zno	*S. aureus*, Proteus sp., Acinetobacter sp, P. aerogenes, *E. coli M. luteus*, *S. aureus*, *S. pneumoniae*, *E. coli*, *P. aeruginosa*	20 pg/ml	24 h, 37°C	[55]

Characterization of several physicochemical and biological characteristics of ZnO nanoparticles has been performed in numerous experiments. ZnO nanoparticles with sizes ranging from 4.45 nm to 88.8 nm were tested on nests of microorganisms such as *E. coli*, *S. aureus*, *B. subtilis*, and *C. albicans*. The concentrations used varied from 20 pg/ml to 10 mg/ml, and the duration of the experiment ranged from 24-48 h at 37°C and 28°C. These experiments revealed the antimicrobial effects of ZnO nanoparticles on microorganism growth and viability. For instance, 33 nm ZnO nanoparticles exerted bactericidal effects on *E. coli*, S. choleraesuis, and *B. subtilis* at a concentration of 10 mg/ml after 48 hours of exposure at 37°C. ZnO nanoparticles with a size of 23.7-88.8 nm exhibited a killing ability toward *S. aureus*, *E. coli*, and *C. albicans* at concentrations of 0.25 and 0.5 mg/ml after 24 hours of 37°C and 28°C treatment. Other studies have explored the impact of fewer ZnO nanoparticles, such as 22 nm, on a wider spectrum of microorganisms, including *B. subtilis*, *S. mutans*, *S. aureus*, *E. coli*, *P. aeruginosa*, and *K. oxytoca*. NPs (0.0005 g) were loaded into a well in agar containing bacteria and incubated for 24 hours at 37°C. ZnO nanoparticles 20-50 nm in size were tested against *S. aureus*, S. Typhimurium, A. flavus and *A. fumigatus* at 20-100 µg/ml for 24 hours at 37°C.

4. Green Synthesis of Ag and Cu Co-Doped ZnO Nanoparticles

4.1. Preparation of Ag and Cu Co-Doped ZnO Nanoparticles

Extraction of Aloe vera gel: The gel from the Aloe barbadense miller was collected and washed, and the gel was removed immediately by gently cutting it with a knife and scooping it with a spoon. Equal amounts of the above-removed gel and distilled water (1:1) were mixed homogenously to form the above light green gel solution. The solution was stirred at 60°C and 1000 rpm with the help of a magnetic stirrer until the gel became pale yellow. The resulting solution was cooled to room temperature and filtered through Whatman filter paper. The filtrate of the Aloe vera gel extract was collected in a refrigerator cooled to 10°C for further use [56].

4.1.2. The precursor solutions were prepared as follows: the starting precursor salts ZnNO 3 ·6H 2 O, AgNO 3, Cu (NO 3) 2 ·3H 2 O, and NaOH were weighed and dissolved in distilled water to obtain 1 M solutions [57].

4.1.3. Nanoparticle Synthesis: Aloe vera gel extract (1:1) was used, and the precursor solution was shaken on a magnetic stirrer at 1500 rpm and 80°C. A simple 0.1 M NaOH solution was prepared, and a drop of NaOH was added to adjust the pH after regular monitoring via a pH meter reading at pH 10. After the pH reached 10, the solution was centrifuged at 4500 rpm for 8 minutes. Subsequently, the solution was washed with double-distilled water and ethanol, finally dried at 100°C and ground into a transparent powder. The powder was then calcined at 25°C for

4 hours; consequently, the final product was obtained, which was Ag and Cu codoped ZnO nanoparticles [58].

4.2. Pellet Preparation of Ag and Cu Co-Doped ZnO Nanoparticles

One gram of synthesized Ag and Cu codoped ZnO NP powder was measured and mixed with the PVA binder polyvinyl alcohol. The mixture was positioned in a pellet press and compressed up to 3 tons applied. This was followed by sintering at a temperature of 450°C. Sintering improves the density and fusion of the nanoparticles with each other, strengthening the structural integrity of the pellets. This can vary depending on the duration of sintering, the temperature of the sinter and the material characteristics of the Ag and Cu codoped ZnO nanoparticles [59], [60].

4.3. Characterization of the synthesized Ag and Cu codoped zno nanoparticles

X-ray diffraction analysis was used for structural characterization. The experiments were carried out using a Bruker D8-Advance X-ray diffractometer (Germany) equipped with Cu-Kα radiation. The scanned region was $2\theta = 30°$, and 60° to 80° was analyzed. The X-ray tube was operated at 40 kV and 30 mA. XRD analysis was used to characterize the crystal structure of the ZnO nanoparticles doped with Ag and Cu. For morphological feature characterization of the nanoparticles, scanning electron microscopy was used. Imaging and observation were performed using a Zeiss-EVO 18 microscope.

This technique establishes the shape of the particles, their size, and the anatomy of the surface of the doped ZnO nanoparticles. Moreover, through EDX spectroscopy using the ZEISS-EVO 18 system, elemental composition and doping confirmation were performed. This analysis was essential for confirming the presence and distribution of the Ag and Cu dopants in the ZnO nanoparticle matrix. Similarly, optical properties were analyzed through the use of UV–visible spectroscopy, which involved recording the UV–Vis absorption data at 350-700 nm with a Perkin Elmer Spectrum UV/Visible spectrometer. This provided information regarding the optical absorption behavior and bandgap analysis of Ag and Cu codoped ZnO nanoparticles [5], [61].

Finally, the electrical resistivity of the synthesized nanoparticle pellets was determined by the four-point probe method. The conductance of this pellet was calculated by resistance at different temperatures ranging from 28-100°C. Finally, the determined function was used to analyze the

Mujibullah Sheikh / Afr.J.Bio.Sc. 6(5) (2024). 7026-7050

electric transport characteristics of the Ag and Cu codoped ZnO nanocomposites [5], [62]. A graphical representation of the preparation of the Ag and Cu codoped ZnO nanoparticles is shown in Figure 2.

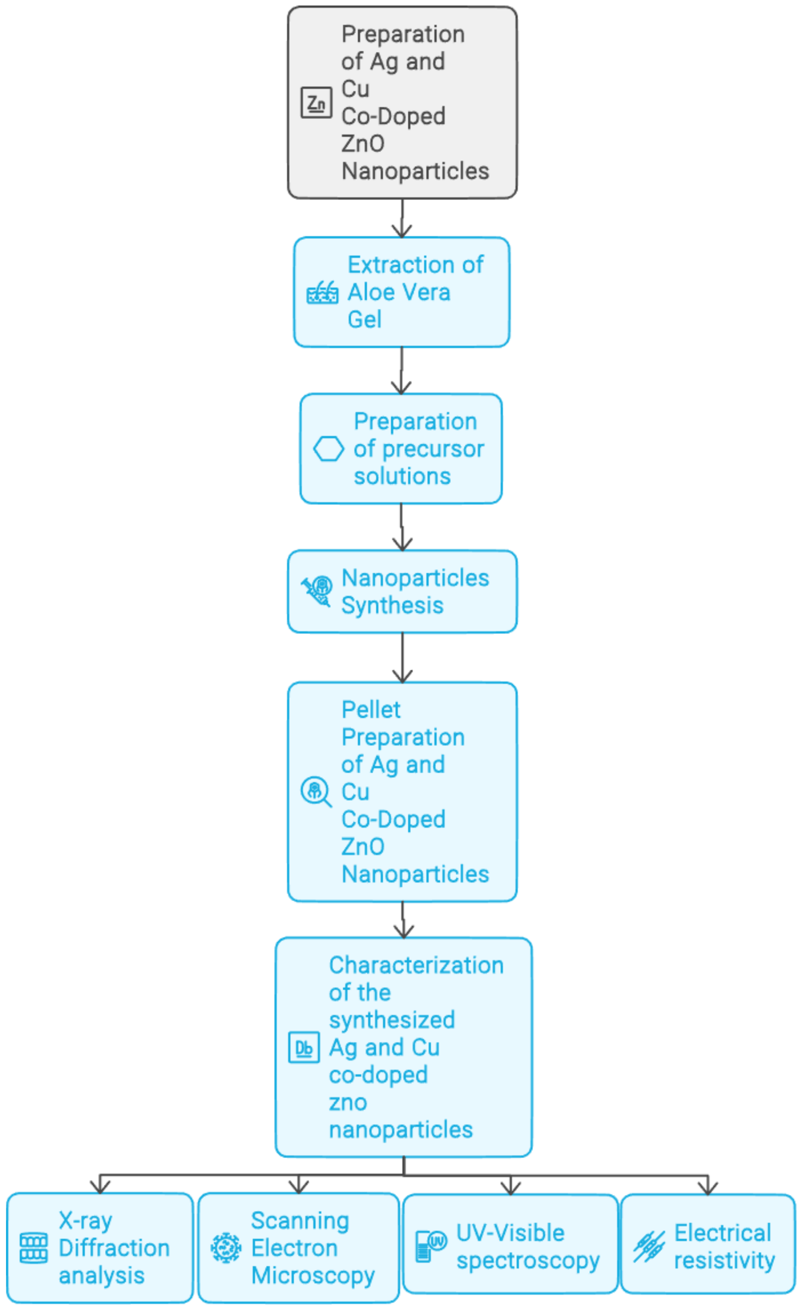

Fig. 2: Preparation of Ag and Cu Codoped ZnO Nanoparticles

5. Application of Aloe vera-mediated Ag and Cu Co-Do Synthesis in Industrial Settings

The applications of Aloe vera-mediated synthesis of silver and copper nanoparticles have been investigated in several reports in the literature. This green method is gaining popularity as an alternative to hazardous and expensive chemical synthesis methods owing to its eco-friendliness and low cost. The reducing and stabilizing effects of Ag and CuNPs on the phytochemical constituents of aloe vera, such as polysaccharides, phenolic acids, and vitamins, increase the efficiency of these nanoparticles for industrial applications. Recent studies have revealed that the aloe vera-mediated synthesis of Ag and Cu nanoparticles optimizes their stability, biocompatibility, and antibacterial performance and thus could be employed in various biomedical practices, catalysis, and environmental cleanup [63]. This study further showed that Aloe vera extracts have been widely employed in the controlled synthesis of Ag and Cu nanoparticles to control their dimensions, forms, and other industrial specifications. Additionally, green chemistry procedures have demonstrated that green chemistry is desirable because it does not necessitate the use of harmful chemical compounds, thus decreasing high-priority environmental deterioration. Moreover, in addition to investigating the synthesis, researchers have investigated the underlying mechanism, particularly the role of individual phytochemicals in both reducing and capping Ag and Cu nanoparticles [41]. By understanding the mechanisms underlying nanoparticle synthesis with Aloe vera extracts, one may increase their quality and optimize parameters for industrial synthesis. Moreover, some studies have indicated that the aloe vera-mediated synthesis of various nanoparticles exhibits scalable potential. Therefore, in industrial quantities, the Aloe vera synthesis of Ag and Cu codoses can be achieved. Additionally, researchers have used aloe vera-synthesized Ag and Cu codosing in addition to traditional nanoparticle use and explored the use of sensor technology in drug delivery systems, pharmacology and wastewater treatment [64]. The potential Aloe vera-mediated Ag and Cu codoped synthesis has been demonstrated to go beyond conventional nanoparticle production in industrial settings. Due to the versatility of Aloe vera-mediated synthesis, investigations have been conducted on the application of this method to sensor technology, drug delivery systems, and wastewater treatment. As such, Aloe vera-mediated synthesis appears to be an environmentally friendly and cost-effective approach for a wide, growing array of sector demands [65].

5.1. Antimicrobial Applications

Over the past few decades, the number of issues associated with the rapid development of antibiotic-resistant bacteria has increased, and antibiotic-resistant bacteria have quickly become a critical global health concern; hence, alternative antimicrobial agents are becoming a field of interest. In the recent past, the green synthesis approach, which uses metal nanoparticles synthesized by reductive agents and stabilizers derived from plants, has gained much attention. Aloe vera, a well-known succulent plant with beneficial medicinal properties, is one of the most studied and promising plants for the biosynthesis of Ag and Cu nanoparticles. Cu nanoparticles synthesized from Aloe vera extract have been widely used to date due to their strong antimicrobial activity against a broad spectrum of pathogenic bacterial species, including both gram-negative and gram-positive strains. The shape and size of AgNPs can be customized by regulating synthesis parameters such as temperature, extract concentration, and reaction time [66]. Surprisingly, studies have shown that compared with other morphologies, octahedral-shaped AgNPs are more effective at promoting antibacterial activity. Aloe vera-mediated AgNPs achieve increased antibacterial activity by interacting with the bacterial cell membrane, adversely affecting its functionality and leading to the formation of ROS, which eventually leads to cell death. Additionally, copper nanoparticles synthesized similarly also show potential antibacterial capabilities. Their shape and size can be manipulated by changing the pH, extract concentration, and type of copper salt precursor [67]. The antibacterial activity of CuNPs is based on copper ion release, which affects the constituents and functionality of bacterial cells by inducing oxidative stress. Interestingly, some studies have reported the antimicrobial activity of aloe vera-mediated AgNPs and CuNPs [68]. Both types of nanoparticles have been shown to have high antimicrobial activity against multiple pathogenic bacteria. Moreover, the combined effect of AgNPs and CuNPs has also been examined. Moreover, it shows improved antimicrobial action relative to that of individual nanoparticles. Green synthesis of aloe vera-extracted AgNPs and CuNPs offers several benefits. These advantages include the use of a renewable, nontoxic, and environmentally friendly reducing and capping component. More significantly, because of their antimicrobial activity, they have numerous uses, including but not limited to being utilized in wound dressings, medical devices, and water disinfection systems [64], [69].

Aloe vera-driven green silver and copper nanoparticle synthesis has provided a new and powerful tool for the formulation of effective antimicrobial agents against rapidly spreading antibiotic-resistant bacteria. Its applicability is bolstered by the possibility of regulating the shape and size of nanoparticles and their strong complementary action when the polymerization of AgNPs with CuNPs is considered.

5.2. Biomedical Applications

The biomedical applications of Aloe vera-mediated Ag and Cu codoped synthesis have attracted increasing amounts of attention over the past several years, as they hold promise for improving the efficiency of a variety of medical treatments [9]. As previously noted, according to a study recently published in the Journal of Biomedical Materials Research, Aloe vera-mediated Ag and Cu codoped nanoparticles showed improved antimicrobial efficiency against a broad range of bacteria, including methicillin-resistant *Staphylococcus aureus*. This suggests their potential as a wound-healing material, as infection with antibiotic-resistant bacteria is a significant issue in this field. An additional study, which appeared in the Journal of Materials Science: Materials in Medicine, shed light on the value of these particles in reducing the risk of infection and improving implant biocompatibility due to their ability to decrease tissue.

6. Future considerations and challenges

The future perspective and challenges of Aloe vera-mediated green synthesis for the complete analysis of Ag- and Cu-codoped ZnO NPs are discussed above, as they are particularly focused on antibacterial performance. Further research should be emphasized to more significantly examine the stability and antibacterial activity of these NPs in comprehensive formulations in the future, as well as in vitro and in vivo systems, for instance, to achieve antibacterial performance in the workbook system and to determine whether long-term bacteria can have antibacterial effects. Some explanations need to be applied to optimize the efficacy and stabilize the results to test for disturbances from contact between various bacterial strains. The cost-effectiveness and commercial basis of the future of Aloe vera green synthesis may be another topic of interest [9].

The synthesis parameters, i.e., reaction conditions, Aloe vera contents, and dopant ratios, must be changed to balance the process robustness and agreeable productivity to reproducibly produce nanoparticles in the bulk. Furthermore, administration may also require particular checking of the cytotoxicity and biocompatibility of these nanoparticles before they are used in clinical applications. Complete biocompatibility investigations, i.e., all types of in vitro and in vivo tests, must be performed to evaluate the extended use of these nanoparticles in medical materials or treatment. Moreover, investigating the combined effects of Ag and Cu codoping and their role in the bactericidal activity of ZnO nanoparticles produced using Aloe vera may result in the creation of more effective antimicrobial agents. Recognizing the mechanism of the activity mediated by attention to these nanoparticles and their exact goals in bacterial bodies can contribute to creative research on antipathogenic techniques targeted at reaching drug immunity [37].

Conclusion

Employing Aloe vera as a reductant in the green synthesis of Ag and Cu codoped ZnO NPs is a novel, sustainable and eco-friendly strategy for antibiotic development. This method represents a greener, sustainable, less expensive and faster approach to synthesizing NPs, with notable enhancements in their physical and chemical properties, which all meet the green chemistry guidelines. The Aloe vera-mediated synthesis of silver and copper NPs has potent antimicrobial activity against multidrug-resistant bacteria and several pathogenic bacteria, showing great potential for various biomedical applications, such as wound dressings, medical implants and water treatment. Overall, the biomedical application potential of Aloe vera-mediated Ag and Cu codoped nanoparticles could significantly improve the effectiveness of existing medical treatments. In addition to accelerating wound healing and eliminating antibiotic-resistant bacteria, these nanoparticles may also enhance implant biocompatibility and reduce infection risks. Nonetheless, subsequent studies focusing on the increased stability, antibacterial properties, and biocompatibility of these nanoparticles should include more extensive trials for other purposes. In this context, continuing investigations on the combined effect of Ag and Cu incorporation and their impact on the bactericidal activity of ZnO nanoparticles are promising for the development of more effective antimicrobial agents. However, before clinical use, rigorous biocompatibility tests must be conducted.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

Funding

NI

References

[1] A. A. Mohamed, M. Abu-Elghait, N. E. Ahmed, and S. S. Salem, "Eco-friendly Mycogenic Synthesis of ZnO and CuO Nanoparticles for In Vitro Antibacterial, Antibiofilm, and Antifungal Applications," *Biol. Trace Elem. Res.*, vol. 199, no. 7, pp. 2788–2799, Jul. 2021, doi: 10.1007/s12011-020-02369-4.

[2] M. Alavi and J. F. Kennedy, "Recent advances of fabricated and modified Ag, Cu, CuO and ZnO nanoparticles by herbal secondary metabolites, cellulose and pectin polymers for antimicrobial applications," *Cellulose*, vol. 28, no. 6, pp. 3297–3310, Apr. 2021, doi: 10.1007/s10570-021-03746-5.

[3] R. S. Shinde *et al.*, "Design, fabrication, antitubercular, antibacterial, antifungal and antioxidant study of silver doped ZnO and CuO nano candidates: A comparative pharmacological study," *Curr. Res. Green Sustain. Chem.*, vol. 4, p. 100138, 2021.

[4] M. S. Nadeem, T. Munawar, F. Mukhtar, M. N. Ur Rahman, M. Riaz, and F. Iqbal, "Enhancement in the photocatalytic and antimicrobial properties of ZnO nanoparticles by structural variations and energy bandgap tuning through Fe and Co codoping," *Ceram. Int.*, vol. 47, no. 8, pp. 11109–11121, 2021.

[5] A. Gnanaprakasam, V. M. Sivakumar, and M. Thirumarimurugan, "A study on Cu and Ag-doped ZnO nanoparticles for the photocatalytic degradation of brilliant green dye: synthesis and characterization," *Water Sci. Technol.*, vol. 74, no. 6, pp. 1426–1435, Sep. 2016, doi: 10.2166/wst.2016.275.

[6] S. Medda, A. Hajra, U. Dey, P. Bose, and N. K. Mondal, "Biosynthesis of silver nanoparticles from Aloe vera leaf extract and antifungal activity against Rhizopus sp. and Aspergillus sp.," *Appl. Nanosci.*, vol. 5, no. 7, pp. 875–880, Oct. 2015, doi: 10.1007/s13204-014-0387-1.

[7] T. R. Anju *et al.*, "Green synthesis of silver nanoparticles from Aloe vera leaf extract and its antimicrobial activity," *Mater. Today, Proc.*, vol. 43, pp. 3956–3960, 2021, doi: 10.1016/j.matpr.2021.02.665.

[8] M. S. Alwhibi, D. A. Soliman, M. A. Awad, A. B. Alangery, H. Al Dehaish, and Y. A. Alwasel, "Green synthesis of silver nanoparticles: Characterization and its potential biomedical applications," *Green Process. Synth.*, vol. 10, no. 1, pp. 412–420, Jul. 2021, doi: 10.1515/gps-2021-0039.

[9] M. H. Rashid, S. I. Sujoy, M. S. Rahman, and M. J. Haque, "Aloe vera assisted green synthesis of Ag and Cu codoped ZnO nanoparticles and a comprehensive analysis of their structural, morphological, optical, electrical and antibacterial properties," *Heliyon*, vol. 10, no. 3, p. e25438, Feb. 2024, doi: 10.1016/j.heliyon.2024.e25438.

[10] P. Singh, R. Kumar, and R. K. Singh, "Progress on Transition Metal-Doped ZnO Nanoparticles and Its Application," *Ind. Eng. Chem. Res.*, vol. 58, no. 37, pp. 17130–17163, Sep. 2019, doi: 10.1021/acs.iecr.9b01561.

[11] R. Ebrahimi *et al.*, "Effects of doping zinc oxide nanoparticles with transition metals (Ag, Cu, Mn) on photocatalytic degradation of Direct Blue 15 dye under UV and visible light irradiation," *J. Environ. Health Sci. Eng.*, vol. 17, no. 1, pp. 479–492, Jun. 2019, doi: 10.1007/s40201-019-00366-x.

[12] N. M. Basith, J. J. Vijaya, L. J. Kennedy, M. Bououdina, S. Jenefar, and V. Kaviyarasan, "Codoped ZnO nanoparticles: structural, morphological, optical, magnetic and antibacterial studies," *J. Mater. Sci. Technol.*, vol. 30, no. 11, pp. 1108–1117, 2014.

[13] A. Sirelkhatim *et al.*, "Review on Zinc Oxide Nanoparticles: Antibacterial Activity and Toxicity Mechanism," *Nano-Micro Lett.*, vol. 7, no. 3, pp. 219–242, Jul. 2015, doi: 10.1007/s40820-015-0040-x.

[14] Y. Xie, Y. He, P. L. Irwin, T. Jin, and X. Shi, “Antibacterial Activity and Mechanism of Action of Zinc Oxide Nanoparticles against *Campylobacter jejuni*,” *Appl. Environ. Microbiol.*, vol. 77, no. 7, pp. 2325–2331, Apr. 2011, doi: 10.1128/AEM.02149-10.

[15] N. Babayevska *et al.*, “ZnO size and shape effect on antibacterial activity and cytotoxicity profile,” *Sci. Rep.*, vol. 12, no. 1, p. 8148, May 2022, doi: 10.1038/s41598-022-12134-3.

[16] Md. A. Huq, Md. Ashrafudoulla, M. M. Rahman, S. R. Balusamy, and S. Akter, “Green Synthesis and Potential Antibacterial Applications of Bioactive Silver Nanoparticles: A Review,” *Polymers*, vol. 14, no. 4, p. 742, Feb. 2022, doi: 10.3390/polym14040742.

[17] H. B. Habeeb Rahuman *et al.*, “Medicinal plants mediated the green synthesis of silver nanoparticles and their biomedical applications,” *IET Nanobiotechnol.*, vol. 16, no. 4, pp. 115–144, Jun. 2022, doi: 10.1049/nbt2.12078.

[18] J. E. Castañeda-Aude, J. R. Morones-Ramírez, D. A. De Haro-Del Río, A. León-Buitimea, E. D. Barriga-Castro, and C. E. Escárcega-González, “Ultra-Small Silver Nanoparticles: A Sustainable Green Synthesis Approach for Antibacterial Activity,” *Antibiotics*, vol. 12, no. 3, p. 574, Mar. 2023, doi: 10.3390/antibiotics12030574.

[19] M. Mouzaki *et al.*, “Green synthesis of silver nanoparticles and their antibacterial activities,” *Green Process. Synth.*, vol. 11, no. 1, pp. 1136–1147, Dec. 2022, doi: 10.1515/gps-2022-0061.

[20] A. Singh *et al.*, “Green synthesis of metallic nanoparticles as effective alternatives to treat antibiotics resistant bacterial infections: A review,” *Biotechnol. Rep.*, vol. 25, p. e00427, Mar. 2020, doi: 10.1016/j.btre.2020.e00427.

[21] R. Arora, P. Malhotra, S. Sundriyal, H. S. Yashavanth, R. J. Pai, and M. S. Baliga, “Medicinal Plants as Remedies for Gastrointestinal Ailments and Diseases,” in *Bioactive Food as Dietary Interventions for Liver and Gastrointestinal Disease*, Elsevier, 2013, pp. 301–311. doi: 10.1016/B978-0-12-397154-8.00033-6.

[22] G. Mahor and S. A. Ali, “Recent update on the medicinal properties and use of Aloe vera in the treatment of various ailments,” *Biosci. Biotechnol. Res. Commun.*, vol. 9, no. 2, pp. 273–288, 2016.

[23] D. Hekmatpou, F. Mehrabi, K. Rahzani, and A. Aminiyan, “The Effect of Aloe Vera Clinical Trials on Prevention and Healing of Skin Wound: A Systematic Review,” *Iran. J. Med. Sci.*, vol. 44, no. 1, pp. 1–9, Jan. 2019.

[24] M. Sánchez *et al.*, “Isolation, Activation, and Mechanism of Action of Platelet-Rich Plasma and Its Applications for Joint Repair,” in *Regenerative Medicine*, M. S Choudhery, Ed., IntechOpen, 2020. doi: 10.5772/intechopen.90543.

[25] W. Ozols-Narbona and J. Imery-Buiza, “Morphological and cytogenetic characterization in experimental hybrid Aloe jucunda Reyn. x Aloe vera (L.) Burm. f. (Asphodelaceae),” *Caryologia*, vol. 75, no. 4, Apr. 2023, doi: 10.36253/caryologia-1886.

[26] S. K. Jaiswal, A. Chakraborty, S. Mahajan, S. Kumar, and V. K. Sharma, “The genome sequence of *Aloe vera* reveals adaptive evolution of drought tolerance mechanisms.” May 31, 2020. doi: 10.1101/2020.05.29.122895.

[27] H. Silva *et al.*, “Relationships between leaf anatomy, morphology, and water use efficiency in Aloe vera (L) Burm f. as a function of water availability,” *Rev. Chil. Hist. Nat.*, vol. 87, no. 1, p. 13, Dec. 2014, doi: 10.1186/s40693-014-0013-3.

[28] P. L. Chong, A. K. Singh, and S. L. Kok, “Potential application of Aloe Vera-derived plant-based cell in powering wireless device for remote sensor activation,” *PLOS ONE*, vol. 14, no. 12, p. e0227153, Dec. 2019, doi: 10.1371/journal.pone.0227153.

[29] S. K. Sonawane, J. S. Gokhale, M. Z. Mulla, V. R. Kandu, and S. Patil, “A comprehensive overview of functional and rheological properties of aloe vera and its application in foods,” *J. Food Sci. Technol.*, vol. 58, no. 4, pp. 1217–1226, Apr. 2021, doi: 10.1007/s13197-020-04661-6.

[30] A. Mitra, M. Singh, A. Banga, J. Pandey, S. S. Tripathi, and D. Singh, “Bioactive compounds and therapeutic properties of Aloe vera- a review,” *Plant Sci. Today*, Mar. 2023, doi: 10.14719/pst.1715.

[31] L. Simanjuntak, "Giving Aloe Vera Gel (Aloe Vera) As Topical In Burns Treatment," *Sci. Midwifery*, vol. 10, no. 4, pp. 3314–3318, Oct. 2022, doi: 10.35335/midwifery.v10i4.826.

[32] . S. and D. Patel, "A review on phytochemicals composition and medicinal properties of Aloe vera plant," *Int. J. Pharmacogn. Life Sci.*, vol. 3, no. 1, pp. 50–55, Jan. 2022, doi: 10.33545/27072827.2022.v3.i1a.66.

[33] L. Isager Ahl, "Aloe Vera: En plantes rejse gennem natur- og kulturhistorien," *Kulturstudier*, vol. 13, no. 2, pp. 146–160, Nov. 2022, doi: 10.7146/ks.v13i2.134664.

[34] A. Saleem, I. Naureen, M. Naeem, H. S. Murad, S. Maqsood, and G. Tasleem, "Aloe Vera Gel Effect on Skin and Pharmacological Properties," *Sch. Int. J. Anat. Physiol.*, vol. 5, no. 1, pp. 1–8, Jan. 2022, doi: 10.36348/sijap.2022.v05i01.001.

[35] "Aloe Vera: The Miracle Plant Its Medicinal and Traditional Uses in India." Accessed: May 07, 2024. [Online]. Available: https://www.phytojournal.com/vol1Issue4/17.html

[36] R. Rajeswari *et al.*, "Aloe vera: the miracle plant its medicinal and traditional uses in India," *J. Pharmacogn. Phytochem.*, vol. 1, no. 4, pp. 118–124, 2012.

[37] P. Packialakshmi *et al.*, "Aloe Vera Extract-Mediated CuO NPs as Catalysts for the Synthesis of 4-Hydroxy-3-Methoxybenzaldehyde-Connected Piperidine Derivatives and Their Antibacterial Activity," *J. Chem.*, vol. 2023, pp. 1–14, Apr. 2023, doi: 10.1155/2023/2113151.

[38] J. Yan *et al.*, "Introducing a bionanocomposite (Ultrasound-assisted synthesis of Ag nanoparticles embedded *Aloe vera* gel) for the treatment of cervical carcinoma," *J. Exp. Nanosci.*, vol. 17, no. 1, pp. 617–630, Dec. 2022, doi: 10.1080/17458080.2022.2134562.

[39] S. Sharma and K. Kumar, "Aloe-vera leaf extract as a green agent for the synthesis of CuO nanoparticles inactivating bacterial pathogens and dye," *J. Dispers. Sci. Technol.*, vol. 42, no. 13, pp. 1950–1962, Nov. 2021, doi: 10.1080/01932691.2020.1791719.

[40] P. Tippayawat, N. Phromviyo, P. Boueroy, and A. Chompoosor, "Green synthesis of silver nanoparticles in aloe vera plant extract prepared by a hydrothermal method and their synergistic antibacterial activity," *PeerJ*, vol. 4, p. e2589, Oct. 2016, doi: 10.7717/peerj.2589.

[41] G. A. Espinel-Rubio and D. Feo-Ardila, "Territorio e identidad de resistencia en jóvenes del Catatumbo (Colombia), constructores de paces imperfectas," *Investig. Desarro.*, vol. 30, no. 01, pp. 40–68, Feb. 2022, doi: 10.14482/indes.30.1.303.661.

[42] H. Yang *et al.*, "Antibacterial Effect of Low-Concentration ZnO Nanoparticles on Sulfate-Reducing Bacteria under Visible Light," *Nanomaterials*, vol. 13, no. 14, p. 2033, Jul. 2023, doi: 10.3390/nano13142033.

[43] Brij Nandan Singh, Harshada Shah, Praful S Patil, Mohammad Ashfaq, Ankit Singh, and G. C. Upadhyay, "Zinc Oxide Nanoflakes Mechanism of Action: A Future Prospective Nanomedicine Against CRE Infections," *J. Pharm. Negat. The results*, pp. 2618–2625, Dec. 2022, doi: 10.47750/pnr.2022.13.S05.403.

[44] K. Kalra, V. Chhabra, and N. Prasad, "Antibacterial activities of zinc oxide nanoparticles: a mini review," *J. Phys. Conf. Ser.*, vol. 2267, no. 1, p. 012049, May 2022, doi: 10.1088/1742-6596/2267/1/012049.

[45] S. Jiang, K. Lin, and M. Cai, "ZnO Nanomaterials: Current Advancements in Antibacterial Mechanisms and Applications," *Front. Chem.*, vol. 8, p. 580, Jul. 2020, doi: 10.3389/fchem.2020.00580.

[46] C. R. Mendes *et al.*, "Antibacterial action and target mechanisms of zinc oxide nanoparticles against bacterial pathogens," *Sci. Rep.*, vol. 12, no. 1, p. 2658, Feb. 2022, doi: 10.1038/s41598-022-06657-y.

[47] S. V. Gudkov, D. E. Burmistrov, D. A. Serov, M. B. Rebezov, A. A. Semenova, and A. B. Lisitsyn, "A Mini Review of Antibacterial Properties of ZnO Nanoparticles," *Front. Phys.*, vol. 9, p. 641481, Mar. 2021, doi: 10.3389/fphy.2021.641481.

[48] W.-R. Li, X.-B. Xie, Q.-S. Shi, H.-Y. Zeng, Y.-S. OU-Yang, and Y.-B. Chen, "Antibacterial activity and mechanism of silver nanoparticles on *Escherichia coli*," *Appl. Microbiol. Biotechnol.*, vol. 85, no. 4, pp. 1115–1122, Jan. 2010, doi: 10.1007/s00253-009-2159-5.

[49] V. Tiwari, N. Mishra, K. Gadani, P. S. Solanki, N. A. Shah, and M. Tiwari, “Mechanism of Antibacterial Activity of Zinc Oxide Nanoparticle Against Carbapenem-Resistant *Acinetobacter baumannii*,” *Front. Microbiol.*, vol. 9, p. 1218, Jun. 2018, doi: 10.3389/fmicb.2018.01218.

[50] A. Khan *et al.*, “705. Four Superbugs Isolated From a Single Patient in the United States: *E. coli* (EC) and *K. pneumoniae* (KP) Harboring NDM-5, *P. aeruginosa* (PA) Harboring NDM-1 and Candida auris,” *Open Forum Infect. Dis.*, vol. 5, no. suppl_1, pp. S254–S254, Nov. 2018, doi: 10.1093/ofid/ofy210.712.

[51] N. M. Al-Hada *et al.*, “Downtop nanofabrication of binary $(CdO)_x$ $(ZnO)_{1-x}$ nanoparticles and their antibacterial activity,” *Int. J. Nanomedicine*, vol. Volume 12, pp. 8309–8323, Nov. 2017, doi: 10.2147/IJN.S150405.

[52] R. Khan *et al.*, “Flower-shaped ZnO nanoparticles synthesized by a novel approach at near-room temperatures with antibacterial and antifungal properties,” *Int. J. Nanomedicine*, p. 853, Feb. 2014, doi: 10.2147/IJN.S47351.

[53] A. Precious Ayanwale and S. Y. Reyes-López, “ZrO_2 –ZnO Nanoparticles as Antibacterial Agents,” *ACS Omega*, vol. 4, no. 21, pp. 19216–19224, Nov. 2019, doi: 10.1021/acsomega.9b02527.

[54] M. Saliani, R. Jalal, and E. Kafshadre. Goharshadi, “Effects of pH and Temperature on Antibacterial Activity of Zinc Oxide Nanofluid Against E. coliO157:H7 and *Staphylococcus aureus*,” *Jundishapur J. Microbiol.*, vol. 8, no. 2, Feb. 2015, doi: 10.5812/jjm.17115.

[55] A. Khezerlou, M. Alizadeh-Sani, M. Azizi-Lalabadi, and A. Ehsani, “Nanoparticles and their antimicrobial properties against pathogens including bacteria, fungi, parasites and viruses,” *Microb. Pathog.*, vol. 123, pp. 505–526, 2018.

[56] V. Chandegara and A. K. Varshney, *Aloe vera: Development of gel extraction process for Aloe vera leaves*. LAP LAMBERT Academic Publishing, 2012.

[57] R. H. Maret, “Process for preparing extracts of aloe vera,” US3878197A, Apr. 15, 1975 Accessed: May 08, 2024. [Online]. Available: https://patents.google.com/patent/US3878197A/en

[58] D. Manickam, M. Venkatachalam, and G. Parthasarathy, “Synthesis of Nano Particles From Aloe Vera Extract – Review Paper,” *Imp. J. Interdiscip. Res. IJIR*, vol. 2, pp. 1570–1575, Oct. 2016.

[59] J. Yan, “A Review of Sintering-Bonding Technology Using Ag Nanoparticles for Electronic Packaging,” *Nanomaterials*, vol. 11, no. 4, p. 927, Apr. 2021, doi: 10.3390/nano11040927.

[60] X. Dan *et al.*, “Improving the sinterability of CeO2 by using plane-selective nanocubes,” *J. Eur. Ceram. Soc.*, vol. 39, no. 14, pp. 4429–4434, Nov. 2019, doi: 10.1016/j.jeurceramsoc.2019.06.024.

[61] A. Srithar, J. Kannan, and T. Senthil, “Preparation and characterization of Ag doped ZnO nanoparticles and its antibacterial applications,” *J Adv Chem*, vol. 13, pp. 6273–6279, 2017.

[62] R. Nan *et al.*, “Facile Synthesis of Cu-Doped ZnO Nanoparticles for the Enhanced Photocatalytic Disinfection of Bacteria and Fungi,” *Molecules*, vol. 28, no. 20, p. 7232, Oct. 2023, doi: 10.3390/molecules28207232.

[63] J. Vincent, K. S. Lau, Y. C.-Y. Evyan, S. X. Chin, M. Sillanpää, and C. H. Chia, “Biogenic Synthesis of Copper-Based Nanomaterials Using Plant Extracts and Their Applications: Current and Future Directions,” *Nanomaterials*, vol. 12, no. 19, p. 3312, Sep. 2022, doi: 10.3390/nano12193312.

[64] D. Medina-Cruz *et al.*, “Aloe Vera-Mediated Te Nanostructures: Highly Potent Antibacterial Agents and Moderated Anticancer Effects,” *Nanomaterials*, vol. 11, no. 2, p. 514, Feb. 2021, doi: 10.3390/nano11020514.

[65] N. Chakraborty *et al.*, “Green synthesis of copper/copper oxide nanoparticles and their applications: a review,” *Green Chem. Lett. Rev.*, vol. 15, no. 1, pp. 187–215, Jan. 2022, doi: 10.1080/17518253.2022.2025916.

[66] K. Logaranjan, A. J. Raiza, S. C. B. Gopinath, Y. Chen, and K. Pandian, “Shape- and Size-Controlled Synthesis of Silver Nanoparticles Using Aloe vera Plant Extract and Their Antimicrobial Activity,” *Nanoscale Res. Lett.*, vol. 11, no. 1, p. 520, Dec. 2016, doi: 10.1186/s11671-016-1725-x.

[67] P. J. Burange *et al.*, "Synthesis of silver nanoparticles by using Aloe vera and Thuja orientalis leaves extract and their biological activity: a comprehensive review," *Bull. Natl. Res. Cent.*, vol. 45, no. 1, p. 181, Oct. 2021, doi: 10.1186/s42269-021-00639-2.

[68] N. Liaqat, N. Jahan, Khalil-ur-Rahman, T. Anwar, and H. Qureshi, "Green synthesized silver nanoparticles: Optimization, characterization, antimicrobial activity, and cytotoxicity study by hemolysis assay," *Front. Chem.*, vol. 10, p. 952006, Aug. 2022, doi: 10.3389/fchem.2022.952006.

[69] H. Arshad, M. Saleem, U. Pasha, and S. Sadaf, "Synthesis of Aloe vera-conjugated silver nanoparticles for use against multidrug-resistant microorganisms," *Electron. J. Biotechnol.*, vol. 55, pp. 55–64, Jan. 2022, doi: 10.1016/j.ejbt.2021.11.003.