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Review Article

A comprehensive review on biogenically synthesized inorganic nanoparticles and their applications in anticancer activities

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ABSTRACT

The progression in nanotechnology has revolutionized the biomedical sciences for diagnosis and treatment of diseases like cancer. There have been many kinds of nanomaterials but Inorganic nanomaterials have been considered potential candidates for anticancer activities due to their high biocompatibility, less toxicity, high stability, and high precision in targeting affected cells. Several synthesis approaches have been used to prepared these nanoparticles, such as physical, chemical, and biogenic methods. Due to higher toxicity and adverse effects of chemical methods, eco-friendly way such as biosynthesized inorganic nanomaterials have attained much attention for multiple application particularly treatment of diseases. This review presents a comprehensive and updated knowledge (2015-2023) regarding the cancer treatment. The article first categorizes biogenically synthesized inorganic nanoparticles into three main groups: metallic nanoparticles, metal oxide nanoparticles, and quantum dots and then successful stories related to cancer treatment. This will also provide very effective platform for researchers and academia to detail the biogenically synthesized inorganic nanoparticles' morphology, their characterization, targeted cancer cells.

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1. Introduction

Cancer is considered a primary cause of death around the world. The Global Cancer Observatory (GLOBOCAN) estimates the cancer mortality for cancer research, and their report estimated that 19.3 million new cancer cases were reported, and almost 10.0 million cases cancer-related deaths occurred in 2020 [1]. Globocan reported that 11.7% of cases were related to female breast cancer, lung cancers contributed 11.4%, colorectal-related cases reported 10.0%, prostate cases contributed 7.3%, and stomach cancer reported 5.6% of total cases. According to their report, lung cancer-related death was reported at 18%, colorectal contributed 9.4%, liver cancer related were reported at 8.3%, stomach contributed 7.7%, and female breast cancer-related deaths were reported at 6.9% of the total death-related cases [2]. The number of cancer patients is expected to increase to 21.6 million in 2030 and 13.0 million cancer-related deaths [3]. The most widely used cancer treatments are radiation therapy [4,5], chemotherapy, immunotherapy [6], and surgical treatment [7–9]. However, anticancer treatment such as chemotherapy has certain drawbacks such as non-targeting, off-target toxicity, high cost, and long time. Another problem with conventional chemotherapy treatment is chemotherapeutic agents causing toxicity on healthy cells [10]. Multidrug resistance due to overexpression of P-glycoprotein (P-pg.) in the cancer cell (e.g., NCI-60 tumor cell lines) is also a significant drawback in traditional anticancer treatment. The expression of P-pg. was detected in more than 50% of NCI-60 tumor cell line [11]. The drug should be precisely targeted to the tumor cell to solve these challenges with traditional chemotherapeutic cancer treatment effectively. Nanotechnology is being used rapidly to ensure efficient drug delivery with precise targeting of tumor cells without affecting the healthy cells. The advancement in nanoparticles (NPs) has promising applications in various fields, especially in medical applications such as the diagnosis and treatment of cancer [12]. Due to the unique size, shape, high biocompatibility, and ability to target affected cells with high precision, NPs are recently used against cancer in clinical trials [13–15].

Nanoparticles (NPs) with one or more dimensions in the range between 1-100 nm have gained a lot attention because of their distinctive functions and interesting properties and are especially applicable in different biomedical domains such as antibacterial, antifungal, drug delivery, and cancer therapy [16–19]. There are three different methods to synthesized NPs: Biogenic synthesis [20–23], Chemical synthesis [24–27], and Physical synthesis [28–32]. Physically method of NPs synthesis is costly technologies, longer time span, dispersed particle size distribution, and high energy consumption to maintain pressure and temperature [33–37]. In case of chemically synthesis process, such as gold (Au), and silver (Ag), and many more showed toxicity and severely damaged the environment [20] and are not suitable for therapeutic applications, and are particularly hazardous to human beings [38]. Apart from these two methods, the biological synthesis method is safer for fabricating NPs and favorable for using ambient conditions for synthesis [21–23], especially in NPs used in cancer therapy [39]. Recent studies have shown that biologically synthesized NPs are safer, less toxic, cheaper, and eco-friendly [40,41]. Biogenic NPs are superior compared to chemical and physically synthesized nanoparticles in terms of safer synthesis, less toxicity, and an economically benign process [42,43]. The earlier methods are more complicated, outdated, costly, produce hazardous waste, and are less precise in targeting the affected cells [44]. Biogenically synthesized nanoparticles have a better surface area, superior catalytic reactivity, and better contact with enzymes and metal salts because of their bio-carrier (e.g., bacteria) matrix [45]. The biogenically synthesized NPs

hardly affect the natural environment and human health because, in this method, non-toxic and low-cost naturally occurring materials are used to synthesize the NPs [46][i]. These materials include plant extracts, microorganisms, and polymers that occur naturally. In the biogenic synthesis of NPs, the capping, and reducing agents are the biological entity's phytochemicals [5,40] that act as capping and reducing agents [41,47–49].

Phytochemicals are naturally occurring eco-friendly chemicals and are considered non-toxic to human life. Another reason for the advancement of the biogenic synthesis of NPs is that surfactants used as capping agents in chemical synthesis pose hazardous effects on human life as they are very difficult to remove, not degradable, and detrimental to the environment as well [50]. These capping agents are typically used to functionalize and stabilize the NPs as well as control the morphology, size, and surface modifications. Therefore, due to these limitations of toxic chemicals, NPs using biomolecules as the capping agent has gained attention recently due to their non-toxic properties [48]. The biogenic synthesis of NPs can be classified into two approaches: intracellularly and extracellularly, according to the location of NPs formation [51]. In the intracellular approach, the ions are transported into microbial cells in order to produce NPs in the presence of enzymes. In contrast, the extracellular approach is based on the process of trapping the metal ions on the cell surface and the reduction of ions in the presence of enzymes [52].

Until now, various biogenic sources have been used to synthesize NPs for biomedical applications such as antibacterial [53], anticancer [54], antifungal [55], etc. The commonly used bioresources for synthesizing NPs are plant extracts, bacteria, algae, and fungi strains [56–59]. For example, gold NPs with size ranging from 4 nm to 7 nm were synthesized using amino acid as a capping and reducing agent [60]. In another study, the authors used plants and microbial metabolites as capping and reducing agents to synthesize NPs biologically with required traits and high efficiency [61]. Other studies used different kinds of microorganisms such as *Sargassum wightii* [62], *Candida utilis* [63], *Lactobacillus kimchicus* [64], *Bacillus subtillis* [65], *Fusarium oxysporum* [66], *Colpomenia sinuosa and Pterocladia capillacea* [67] to synthesize the NPs of different size and shape for various biomedical applications including cancer therapy.

This article provides a comprehensive review of the current research trends in the biogenic synthesis of inorganic NPs and their applications in anticancer activities and drug delivery. The review categorizes the biogenically synthesized inorganic NPs through metallic NPs, Metal Oxide NPs, and Quantum Dots and presents a brief overview of their synthesis approach. This is followed by the discussion of biosynthesis mechanisms such as biogenic synthesis using plant extracts, fungi, yeast, and bacteria. Next, the applications of these NPs in drug delivery and anticancer activities are presented, mainly providing comprehensive data about characterization techniques, morphology, biological means for synthesis, and targeted cancer cells. The biomedical application of inorganic NPs, explicitly focusing on anticancer activities, has been briefly discussed.

Biosynthesis of inorganic Nanoparticles using microorganisms and plant

In biogenic synthesis, green materials (i.e., biogenic mass/extracts) are used to synthesize nanoparticles instead of expensive and toxic chemicals. In contrast to chemically synthesized NPs, the cytotoxicity and phytotoxicity of the biogenically synthesized NPs are significantly less, which can be employed in biomedical applications [68]. In the biogenic synthesis of the NPs, biological sources are used instead of chemical extracts, such as fungi, plants, algae, yeast, bacteria viruses, actinomycetes, etc., which help reduce the metal ion and stabilize the NPs [69]. Generally, the synthesis of NPs requires a medium, a precursor (*i.e.,* the origin of NPs), a reducing agent (*i.e.,* reduces the metallic ion), and stabilizing agent [49]. However, most of the above-mentioned components use toxic chemicals that generate harmful waste [70]. To overcome these issues, many researchers use the biogenic approach to synthesize NPs using various kinds of phototrophic eukaryotes. These phototrophic eukaryotes include algae, microbes, plants, fungi, and other biocompatible agents [71] [72]. **Figure 1** represents

the generalized depiction of the biogenic synthesis of NPs. Fungi and bacteria can be used to produce NPs with intracellular and extracellular production. Mathivanan et al. [73] used *lacteobacillus kimchicus* to synthesize gold nanoparticles, while in another study, Ameen et al used *Cupriavidas sp*. to synthesize Ag NPs through the extracellular synthesis approach [74] [75].

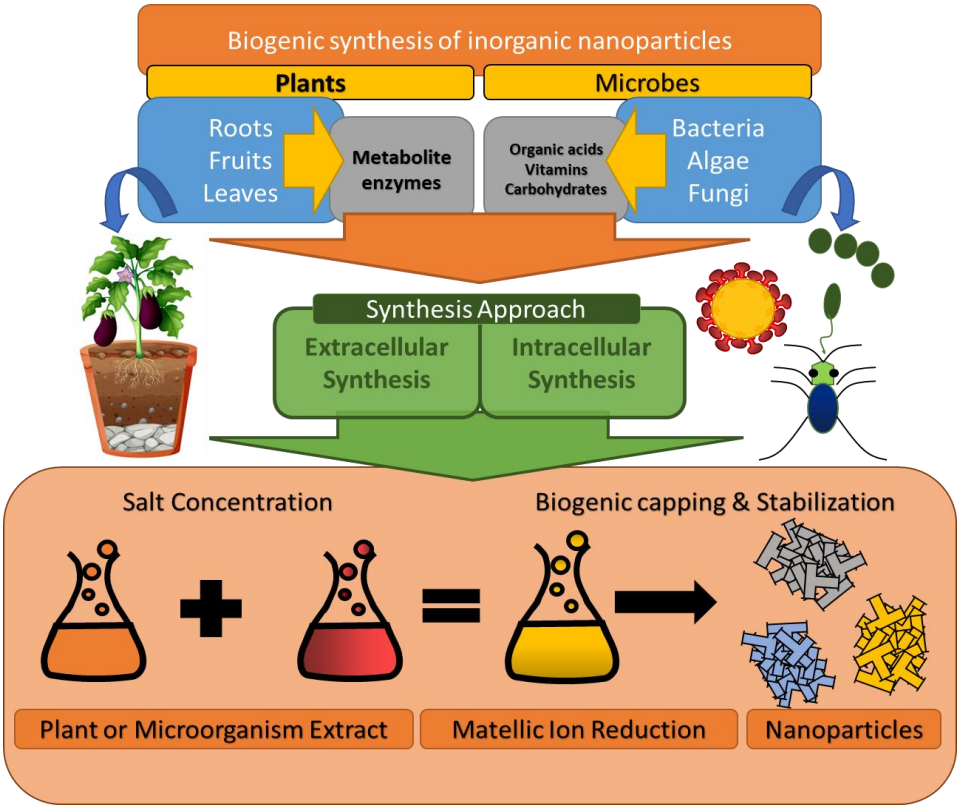

Figure 1. A Schematic Illustration of Biosynthesis of Inorganic Nanoparticles and their Biomedical Applications.

Extensive efforts have been put into synthesizing the NPs biologically for anticancer activities. Due to the unique size and morphology of the biogenically synthesized NPs, these NPs are effective treatment and drug carriers in cancer therapy. Ag NPs synthesized using *Aspergillus terreus* are used in anticancer and antibacterial activities [76]. The authors used an extracellular approach to synthesize the Ag NPs for biomedical applications. In another study Mourdikoudis et al., the authors used the *Cystoseira baccata algae* to synthesize the Au NPs. Gold NPs synthesized using plant extracts are also proven effective against cancer. Jeyarani et al., reported Au NPs biosynthesis methods using *Gelidium pusillum* extracts with the size of 12 ± 4.2nm. Their synthesis of Au NPs produces spherical-shaped NPs proving effective against anticancer activities [77].

2. Biogenic Synthesis of Inorganic NPs

Inorganic NPs are considered potential candidates for diagnostics and therapeutic systems in oncology, including tumor imaging, drug delivery, and enhancing radiotherapy [78–80]. Due to the promising results in the preclinical evaluation stages, these nanoparticles may be taken to the advanced clinical evaluation as reported by Huang et al [81].

Inorganic NPs cover various substances such as metal, metal oxide, and metal salts. Ag NPs are currently being used in many applications such as antibacterial activities [82–84], anticancer, and drug delivery, whereas Au NPs are widely used for biochemical applications due to their catalytic activities. Quantum dots with sizes between 1-10 nm are currently being explored for a wide variety of applications, including cancer therapy and

diagnostics of various cancers owing to their excellent optical, electrochemical, and catalytic properties. At the same time, the usage of metal oxides such as TiO_2 Al_2O_3 MnO_2, CeO_2, and NPs of iron oxides (e.g., Fe_2O_3 and Fe_3O_4) is currently increasing in biochemical applications [85–88]. Silicon (Si) and SiO_2 NPs are also being explored because of their high surface characterization and intrinsic surface reactivity [89]. Among the inorganic NPs, this review paper presents the most widely used inorganic nanoparticles and their application in cancer therapy, biomedical application for protein expression, enzymes analysis and drug delivery [90]. In the following, we briefly overview the biogenic synthesis of inorganic NPs using fungi, bacteria, plant extract, and yeast as in **Figure 2**.

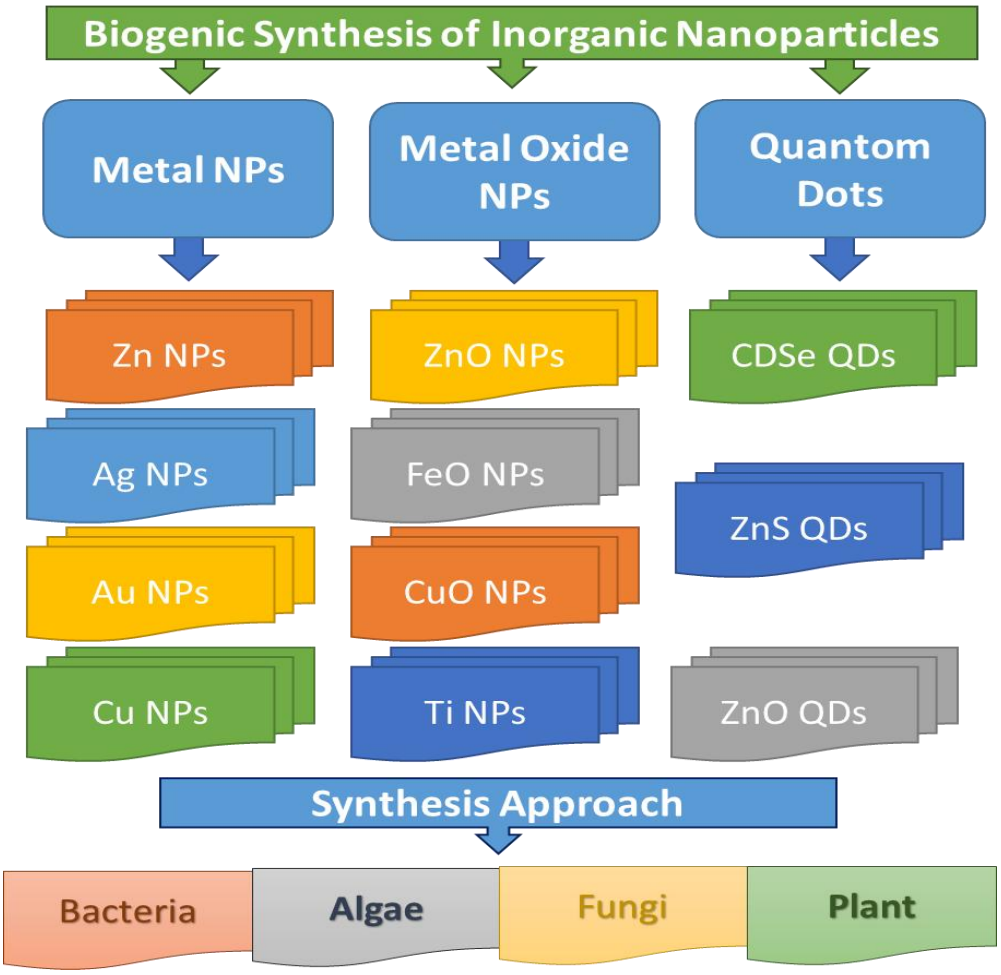

Figure 2. Taxonomy for the Biogenic Synthesis of Inorganic Nanoparticles (NPs).

2.1. Biogenic Synthesis of Ag NPs and their Application in Cancer Therapy

In the following content, we overviewed the recently proposed biogenic synthesis methods of silver NPs using fungi, bacteria, algae, and plant extracts.

2.1.1. Biogenic Synthesis of Ag NPs using Fungi Strain

Fungi are used in multiple biomedical applications, including enzyme productions, drug discovery, identification of new compounds and nanotechnology [91]. Fungi and their derivates are actively used to produce metallic nanoparticles for agriculture, industrial and biological application [92]. Due to economic feasibility, ease to scale up and processing, and mycelia in the fungi-based synthesis approach, it provides a feasible surface area.

NPs production based on fungi-based biosynthesis uses a biomineralization mechanism that helps to reduce the metal ions. Various NPs such as Au, Ag, Se, Cu, and Zn are identified as important metal ions that can be synthesized using fungi for various biomedical applications, including cancer therapy [93,94]. Different kinds of fungi strains such as *Aspergillus, Trichoderma, Fusarium, and Verticillium* have been used to synthesize metal NPs [95–98]. These NPs having different sizes and morphology can be produced by using different types of fungi. For example, the *Fusarium* [99] and *Humicola sp.* fungus strains can be used to synthesize the AgNPs and AuNPs. They concluded that various *fusarium* strains showed cytotoxicity using normal and cancerous cells. In another, example, *Fusarium solani* mediated AuNPs showed strong cytotoxicity on cervical cancer cells (HeLa) and human breast cancer (MCF-7) cancer cell lines. The research work of Tahira et al. presented a fungal-mediated synthesis of silver NPs and briefly studied the anticancer property against human lung cancer (A549) cells through apoptosis. The author synthesized the AgNPs using the endophytic fungus, which was isolated from the medicinal plant named *Catharanthus roseus (Linn.)*. Similarly, *Botryosphaeria rhodina* was used to synthesize the Ag NPs demonstrating the potential of fungus-mediated NPs to be used against cancerous cells. The efficacy of the Ag NPs from *Botryosphaeria rhodina* was tested on A549 cells. The experimental result showed that the Ag NPs effectively scavenged free radicals and induced apoptosis hallmarks in lung cancer cells under *in vitro* conditions [100]. In the biogenic synthesis of silver NPs using microorganisms, fungi strains are preferred over bacteria due to their better tolerance and metal accumulations [101]. The synthesis approach can either be extracellular or intracellular. In the intracellular approach, the precursor has added the mycelial culture and co-opted with the biomass of fungi. While on the other hand, in the extracellular approach, the metal precursor is added to the aqueous filtrate, which is a biomass molecule. However, this method does not require any protocol for the release of nanoparticles from the cell [102]. At the same time, the intracellular approach does need protocols to release the nanoparticles using chemical, filtration, or centrifugation to disrupt the biomass and release the NPs. Many researchers used intracellular and extracellular methods to synthesize Ag NPs using different types of fungi strains [103][104] [105][106]. Fungi-mediated Ag NPs are actively used in anticancer activities; for example, El-Sonbaty used the *Agaricus bisporus* fungi strain to synthesize the silver nanoparticles for cancer therapy [107]. Same as in another study, Manivasagan et al. used *Nocardiopsis sp. MBRC-1* to synthesize the Ag NPs and studied the antitumor effect [108]. *Aspergillus* fungi strained was used to synthesize the Ag NPs by the authors [109]. They studied the evaluation of *Aspergillus*-mediated Ag NPs against human breast adenocarcinoma cell lines (MCF7). A more detailed summary of the applications of Fungi strained-based biogenically synthesized Ag NPs are presented in **Table 1.**

2.1.2. Biogenic Synthesis of Silver NPs using Bacteria Strain

Bacteria have been proven as an excellent bioagent for the cost-effective, facile, and less toxic synthesis of silver NPs. Various bacterial strains have been actively used for the synthesis of Ag NPs. For example, the most commonly known bacteria used for synthesizing Ag NPs are *Massilia sp, Cedecea sp, Citrobacter spp, Streptomyces,* and *Cyanobacteria Desertifilum sp.* [110–112]. Ag NPs particles can be synthesized using bacteria in two ways. The synthesis can be done via an extracellular approach or through an intracellular approach. Microorganisms, including bacteria, synthesize various intracellular and extracellular biomolecules such as enzymes, proteins, amino acids, and organic materials [113]. Bacteria-mediated synthesis of Ag NPs uses the reduction and oxidation technique in which the metal ions are reduced in the presence of microbial enzymes. Following the reduction of metal ions, suitable extracellular and intracellular biomolecules of bacteria are served as capping agents [114]. *Bacillus sp KFU36 is* used to synthesize the Ag NPs for their application in anticancer activities [115]. The study demonstrates that the Ag NPs synthesized from *Bacillus sp. KFU36* can easily cross the endothelium and accumulate in the tumor, which induces tumor cell apoptosis. This indicates excellent anticancer activities.

Although, the resultant of Ag NPs had different size ranging from 15-40 nm. Ranjani et al. used an extracellular approach to synthesize Ag NPs from *Nocardiopsis flavascens RD30* to analyze the *in vivo* toxicity on *Swiss albino mouse, Artemia salina, and Chloroccocum humicola.* Spherically shaped Ag NPs were synthesized from *Nocardiopsis flavascens RD30* under sunlight irradiation. The size of the nanoparticle was recorded at the wavelength of 550 nm [116]. The study of Bakhtiari-Sardari et al. demonstrated the anticancer activity of Ag NPs synthesized using *Streptomyces sp. OSIP1 and Streptomyces sp. OSNP14*. These bacterial-mediated Ag NPs were the size of 8-15 nm produced by *OSIP1*, and *OSNP14,* respectively, and exhibited strong anticancer activity against *mouse colorectal carcinoma cells* (CT26) [117]. Further, the detailed synthesis of Ag NPs from bacterial strains and their applications in drug delivery and anticancer activities are given in **Table 1.**

Table 1. Recent Advancements in Biogenic Synthesis of Silver NPs and their Application in Cancer Therapy.[1]

Biogenicaly Synthesized Nanoparticles, Size Shape and Targeted Cells						
Year	**Synthesis approach**	**NPs**	**Size**	**Shape**	**Targeted cancer cells**	**Ref**
2023	Plant (Premna integrifolia)	Ag NPs	35	Spherical	Hep G2	[137]
2023	Plant (Salvia verticillate and Filipendula ulmaria extract)	Ag NPs	40-70	Spherical	HCT-116	[138]
2023	Plant (Cleome rutidosperma leaf extract)	Ag NPs	14.07	Spherical	Epidermoid carcinoma	[139]
2022	Plant (Conocarpus Lancifolius)	Ag NPs	5-30	Spherical	MDA MB-231	[140]
2022	Plant (Sambucus ebulus)	Ag NPs	35-50	NM	AGS and MCF-7	[141]
2022	Plant (Phoenix dactylifera)	Ag NPs	14	Spherical	A549 cells	[142]
2022	Plant (Hylocereus undatus)	Ag NPs	10-50	Spherical	HepG2	[143]
2021	Annual meadow grass (poa annua)	Ag NPs	60.90-36.66	Spherical	SCC7	[144]
2019	Bacteria (Endophytic Bacteria)	Ag NPs	83-176	Spherical	HeLa cell line	[145]
2019	Bacteria (Lactobacillus rhamnosus GG)	Ag NPs	233	Spherical	MCF-7	[146]
2018	Bacteria (leptolyngbya jsc -1)	Ag NPs	10-100	Spherical	HT-29	[147]
2021	Marine algae (Ulva Lactuca extract)	Ag NPs	8-14	Spherical	HCT-116	[148]
2021	Marine algae (Chaetomorpha Ligustica)	Ag NPs	8.8	Spherical	HCT-116	[149]
2020	Algae (Chaetomorpha linum)	Ag NPs	284	Spherical	HCT-116	[150]
2023	Fungi (Penicillium brasilianum NP5)	Ag NPs	25.32	Spherical	25.32	[151]
2022	Fungi (Aspergillus Niger)	Ag NPs	50-500	Spherical	HeLa cell line	[152]
2021	Fungi (XY-YS and LPP -12Y)	Ag NPs	21.38	Spherical	H1975 and A579	[153]

[1] *All tables report the data published from 2018 to 2023. NM stands for not mentioned.*

2.1.3. Biogenic Synthesis of Silver NPs through Plant Extracts

In the green synthesis of NPs, unlike the chemical approach, the stabilizing and reducing agents are derived from plants. As plants mediated synthesis provides free capping, reducing and stabilizing agents to reduce the overall cost of formulations. The process of plant-mediated Ag NPs synthesis begins with the plant extracts mixed with the silver nitrate ($AgNO_3$) solutions. The change in color of solutions over a specific period of time indicates the formation of Ag NPs [22,118,119]. The $AgNO_3$ solutions have positive ions; it converts to a zero-valent state when the plant extracts are added. The plant extract acts as a reducing agent. After that, the nucleation process begins, and the immediate growth phase is started. Then the AgNPs with different shapes and sizes are produced. Many key factors affect the synthesis process and formation of NPs, such as pH scale, the concentration of green extracts, reaction time, temperature, and concentration of $AgNO_3$ [120].

Plant-mediated Ag NPs are emerging to counter cancer efficiently. Cancer-affected cells dodge apoptosis and continue to propagate. There are two approaches, intrinsic and extrinsic approaches, available for activation of programmed apoptosis. The plant-mediated Ag NPs using the bioactive fraction of *Pinus roxburghii* exhibited cytotoxicity against lungs and prostate cancer [121]. The apoptosis was examined *via* DNA damage and mitochondrial depolarization through an intrinsic approach. Singh et al. studied the potentials of Ag NPs synthesized from *Phyllanthus emblica leaf* extracts against cancer activities [122]. The synthesized AgNPs were used against *Hepatocellular carcinoma (HCC)* cancer. The seed extracts of the plant *Sterculia foetida L*. were used to synthesize Ag NPs and demonstrated their capabilities in tackling *cervical carcinoma* [123]. The research work of Aygün et al. exploited the use of leaf extract of the plant *Rheum ribes* to synthesize the AgNPs [124]. They used the greenly synthesized Ag NPs of size 18.2 nm against the *MDA-MB-231* breast cancer cells. Biogenically synthesized Ag NPs have been studied for human breast cancer in recent years and found to be efficient. Chandra et al. used the leaf extracts of *Artocarpus integer* to synthesize the Ag NPs [125]. They used the UV–Visible, Fourier transform infrared (FTIR) transmission electron microscopy (TEM), and thermal gravimetric analysis (TGA) for characterization. Their experimental results proved that *Artocarpus integer*-mediated Ag NPs act as an effective technique to tackle cancerous breast cells. The Ag NPs produced from their experiment were spherical in shape with a size of 5.76- 19 nm. Studies have been conducted to evaluate the effect of Ag NPs against *Lung carcinoma*, such as the study of [126], shown the effectiveness of biosynthesis of Ag NPs using *Capparis zeylanicu* leaf extracts against *Lung carcinoma*. They produce spherical-shaped Ag NPs from leaf extracts of *Capparis zeylanicu* with a size of 28 nm. The authors used Ultraviolet–visible spectroscopy (UV–Vis), FTIR, scanning electron microscopy (SEM), TEM, and X-ray crystallography (XRD) for the characterization, and their experimental results showed that the Ag NPs induced apoptosis. Another study by Nayaka et al. showed the effectiveness of biogenically synthesized Ag NPs against [127]. Human lung cancer (A549) cancer cell line from the aqueous extract of seed of *Zanthoxylum rhetsa*. They used UV–Vis., atomic force microscopy atomic force microscopy (AFM), TEM, SEM, EDX, XRD, and FTIR for characterization. The experimental results showed that the *Zanthoxylum rhetsa* seed-mediated Ag NPs synthesis with a size range between 10-68 nm was effective against cancerous cells. Due to the Ag^+ ion interacting with the cell membrane, protein, DNA, and RNA lead to cell death. Similarly, greenly synthesized NPs are used against hepatic cancer. Satsangi used the Gum of the *Asafoetida* plant to synthesize the Ag NPs to be used against hepatic cancer [128]. The Asafoetida-mediated Ag NPs demonstrated their antiproliferative ability. The author used the aqueous extract to produce spherical-shaped Ag NPs ranging from 90-95 nm.

The leaf of *Cucumis prophetarum* was used to synthesize the silver NPs in the work done by Hemlata et al. Their study concluded that the leaf-mediated Ag NPs from *Cucumis prophetarum* were effective against breast and liver cancer cells. The AgNPs from this experiment exhibit apoptosis and cytotoxicity against cancerous cells. They used the UV–Vis, FTIR, SEM, and TEM to characterize the Ag NPs and produced spherical, granulated, and ellipsoidal-shaped AgNPs [129]. Botcha and Prattipati used the leaf of the plant *Hyptis suaveolens* [130].

Their experimental study found that the *Hyptis suaveolens* mediated AgNPs interfered with protein, nitrogen base, and DNA and caused apoptosis. The authors briefly studied the AgNPs characterization and cytotoxicity evaluation against MDA-MB-231 and PC-3 Cells. A recent study by Gul et al. used Annual meadow grass (i.e., *Poa annua*) in the green synthesis of AgNPs and studied the cytotoxicity of resultant AgNPs against the murine cancer cell line (SCC7) cancer cell line [132]. **Figure 3. (a)** represents the Schematic of EDL-encapsulated AgNPs oral administration and cancer therapy mechanism of AgNPs-EDL@Starch. While **Figure 3b** represents Schematic illustration for eco-friendly and low-cost approach for the synthesis of AgNPs using phytoconstituents of the *P. annua* extract to form a biocompatible nano-drug delivery system with the loading of bio-drug. The latest green synthesis using various plants of AgNPs and their application in cancer therapy and drug delivery is presented in **Table 1**.

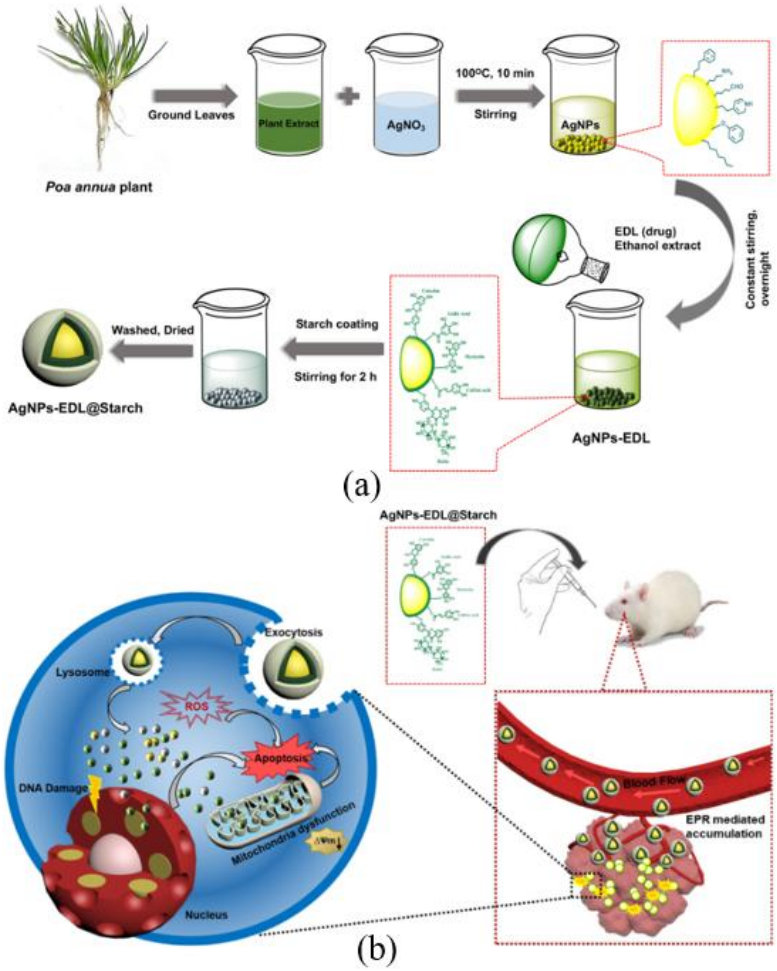

Figure 3. (a) Schematic of EDL-encapsulated AgNPs oral administration and cancer therapy mechanism of AgNPs-EDL@Starch. These core–shell nanoparticles can be internalized via endocytosis and accumulate in lysosomes, where the generation of reactive oxygen species (ROS), DNA damage, mitochondrial dysfunction, and ultimately lead to the apoptosis of cancer cells. (b) Schematic illustration for eco-friendly and low-cost approach for the synthesis of AgNPs using phytoconstituents of *P. annua* extract to form a biocompatible nano-drug delivery system with the loading of bio-drug. Reproduced with permission [131].

2.1.4. Biogenic Synthesis of Silver NPs using Algae strains

Like fungi, bacteria, and plants, algae can also be used to synthesize AgNPs. The synthesis of AgNPs using algae strains can be done either through an intracellular or extracellular approach. Various algae strains have been

used for the synthesis of metallic NPs, including AgNPs such as *Desmodesmus, Scenedesmus, picoplankton, Rhodophyta, and Tetraselmis kochinensis*. NPs produced from these algae strains are used for various biomedical applications, including drug delivery and cancer therapy [133]. Due to the ability of hyperaccumulation of the heavy metal and converting them to the new variable form, the alga has been used to develop different nanomaterials. The authors used *Polysiphonia* to synthesize the AgNPs having a spherical shape with a size of 25 nm to study the potential anticancer activities [134]. They used FTIR, SEM, TEM, and EDX for the characterization of the AgNPs. Their experimental results demonstrated that the *Polysiphonia* mediated AgNPs are effectively toxic against breast cancer MCF-7 cell lines. Elgamouz et al. did a study on synthesizing the AgNPs using *Noctiluca scintillans* and produced spherical-shaped AgNPs with the size of 4.5 nm. The characterization was done through DSL, SEM, EDS, UV, and high-resolution transmission electron micro (HRTEM). The study confirmed that the AgNPs synthesized through *Noctiluca scintillans* caused a 50% reduction in MDA-MB-231 human breast adenocarcinoma tumor cell growth [135]. Marine Algae *Chaetomorpha linum* was also used for AgNPs synthesis [136]. The experimental result proved that the AgNPs synthesized using the *Chaetomorpha linum* was used effectively against the human colon cancer cells (HCT-116). The algae-mediated NPs exhibited apoptosis against the HCT-116 colon cells, and their apoptotic effect was analyzed by MTT assay. They used Dynamic light scattering (DLS), XRD, FTIR, and TEM for the characterization of the NPs. In another study, the authors exploited the cytotoxicity of *Amphiroa rigida*-mediated AgNPs. The *Amphiroa rigida-mediated* NPs were characterized by spectral as well as microscopic analysis. They used UV–visible spectrum and X-ray diffraction characterization for characterizations. They briefly studied the cytotoxicity effects of AgNPs against the MCF-7 human breast cancer cells. More applications of algae-mediated Ag NPs in cancer therapy and drug delivery are given in **Table 1.**

2.2. Biogenic Synthesis of Au NPs and their Application in Cancer Therapy

In the following, we overview the recently proposed biogenic synthesis methods of Gold NPs using fungi, bacteria, algae, and plant extracts.

2.2.1. Biogenic Synthesis of Au NPs using Fungi Strain

Recent studies have proposed various biosynthesis techniques to produce silver, gold, iron, and copper (Cu) NPs from microorganisms such as fungi, algae, bacteria, and plant extracts. The earlier studies have proven that microorganisms and inorganic materials have had direct or indirect interaction. Therefore, the microorganisms-mediated NPs synthesis should be regarded as a viable option. The microorganism-mediated NPs are synthesized bottom-up approach where the NPs are formed as part of detoxification. These processes are carried out by biomolecules of microorganisms such as protein, enzymes, and sugars. The synthesis of Gold NPs can be done through intra or extracellular methods. In the intracellular method, the NPs are synthesized inside the fungal cell by treating its biomass with some precursors. On the other hand, the extracellular methods include the process of treating the fungal filtrate or extracts with specific precursors [154]. For example, the Au NPs were synthesized using *Penicillium chrysogenum* through intracellular techniques [155]. Same as another study by the authors [156] used *Verticillium luteoalbum* to synthesize Au NPs through an intracellular approach. While economically viable, many researchers have used the extracellular approach to synthesize the Au NPs using fungal strains such as *Nigrospora oryzae* [157] and *Neurospora crassa*[158].

Due to the efficacy of fungal-mediated AuNPs in biomedical applications, researchers used fungal strains to synthesize the AuNPs for cancer therapy. For example, Munawer et al. used *Cladosporium sp* to synthesize AuNPs for its application against MCF-7 cancer cells [159]. Their experiment produced AuNPs in a spherical shape with a size of 5–10 nm. The *Cladosporium sp*-mediated Au NPs showed *in vitro* anticancer and *in vivo* antitumor activities.

Figure 4 shows the TEM analysis of mycoAuNPs produced using *Cladosporium sp* and apoptotic activity of MycoAuNPs on EAC cells. In another study, Acay used *Morchella esculenta* to synthesize the Au NPs and studied their antibacterial, antimicrobial, and cytotoxic behavior [160]. The *Morchella esculenta*-mediated Au NPs with a size of 15nm have shown strong cytotoxicity against A549 and HepG2 cell lines. The AuNPs synthesis using the *Cladosporium* fungi strain was investigated by Munawer et al. and studied the photodegradation, *in vitro*, anticancer activity, and *in vivo* antitumor as shown in **Figure 4(a-e)** [159].

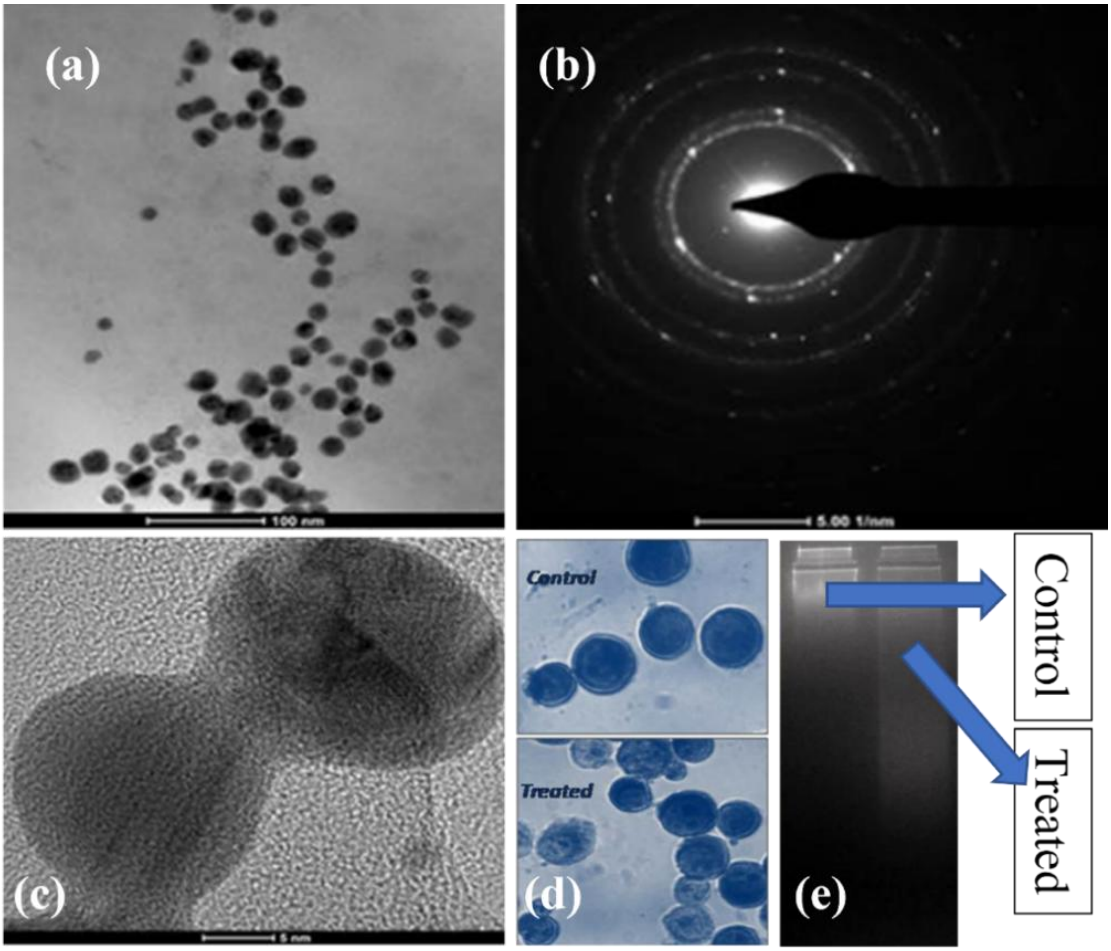

Figure 4. TEM analysis of Cladosporium sp-mediated AuNP: (a) TEM micrograph at 100 nm magnification, (b) SAED pattern, (c) HRTEM image (d) and Apoptosis on EAC cells: (d) Giemsa staining, and (e) DNA fragmentation assay. Reproduced with permission [159]

They used FTIR, XRD, TEM, and UV–Vis spectroscopic for characterization. Their study produced AuNPs of size 5–10 nm and showed strong anticancer activities against breast cancer cell line MCF-7 (IC50 38.23 µg/mL). While Saravanakumar et al. exploited the potential of *Trichoderma*-mediated AuNPs against cancer cells [161]. Their *Trichoderma*-mediated AuNPs showed cytotoxicity against A549 cancer lines and brain tumor LN229 cell lines. The characterization of AuNPs in this study was done using FTIR. *Fusarium solani* was used to synthesize the AuNPs to study their anticancer activities against human cervical cancer cells and breast cancer cells. These biogenically synthesized AuNPs exhibited cytotoxicity on cervical cancer cells and the MCF-7 cell line. The characterization was done using UV, FTIR, SEM, and XRD. The characterization through SEM indicated that the average diameter of the AuNPs with a range of 40-45 nm. The latest biosynthesis methods of AuNPs and their application in cancer therapy are reported in **Table 2.**

Table 2. Biogenic Synthesis of Au NPs and Their Application in Cancer Therapy.

Biogenicaly synthesized nanoparticles, size shape, and targeted cancer cells						
Year	Synthesis approach	NPs	Size	Shape	Targeted cancer cells	Ref
2023	Plant (Satrureja rechingeri Jamzad)	Au NPs	15.5	Spherical	A2780CP	[191]
2023	Plant (Champia parvula)	Au NPs	20	Round	Lung cancer	[192]
2023	Plant (Pistacia vera hull)	Au NPs	20-35	spherical	MCF-7 and AGS-3	[193]
2023	Plant (Haloxylon salicornicum)	Au NPs	8.1	spherical	Sw480, Sw620, HCT-116 and Caco-2	[194]
2022	Plant (Camellia Sinensis L.)	Au NPs	NM	NM	PC3 Cell Lines	[195]
2022	Plant (Verbascum speciosum Schrad)	Au NPs	118	spherical	HepG2	[196]
2022	Plant (T. Capensis)	Au NPs	10-35	Polygonal	MCF7 Cancer Cell	[197]
2022	Plant (Hibiscus and Curcumin)	Au NPs	20	Spherical	HCT-116 And MCF7 Cells	[198]
2021	Plant (Argemone Mexicana L.)	Au NPs	20-40	Spherical	Colon Cancer Cell Line (HCT15)	[199]
2020	Fungi (Fusarium solani)	Au NPs	40-45	Spindle	MCF7 And HeLa	[200]
2020	Fungi (Fungus Aspergillus flavus)	Au NPs	12	Spherical	A549 Cell	[201]
2020	Fungi (Aspergillus terreus)	Au NPs	8-20	Spherical	MCF7 Cells, HepG2	[202]
2020	Fungi (Cladosporium)	Au NPs	5-10	Spherical	MCF7	[203]
2020	Fungi (Fungus Morchella Esculenta)	Au NPs	16.51	Cubic	A549 And HepG2 Cell Lines	[204]
2020	Bacteria ((Vibro Alginolyticus)	Au NPs	100-150	Irregular	Colon Cancer Cells (HAC-7)	[205]
2019	Bacteria ((Caulerpa Racemosa)	Au NPs	13.7-85.4	Spherical and oval	HT29 Cells	[206]
2019	Bacteria (Paracocccus Haeundaensis)	Au NPs	20.93	Spherical	A549 And AGS Cancer Cell Lines	[207]
2023	Algae (red algae Halymenia pseudoforesii)	Au NPs	27	Cubic and rectangular	A549	[208]
2021	Algae (Dictyosphaeriumnsp.)	Au NPs	7.9-10.3	Spherical	HCC1954 and HCT116	[209]
2021	Algae (Mastocarpus Stellatus)	Au NPs	14.3	Spherical	THP-1 Cells	[210]
2021	Algae (Undaria sp.)	Au NPs	10	Spherical	Non-Small Lung Cancer Cells (H-460 cell line)	[211]
2020	Algae (Brown algae s. ilicifolium)	Au NPs	20-25	Spherical	Breast Cancer Cell Line (MDA-MB-231)	[212]

2.2.2. Biogenic Synthesis of AuNPs using Bacteria Strains

In contrast to the conventional chemical and physical synthesis techniques, the production of AuNPs from biosynthesis methods does not necessitate an increase in pressure and temperature. The biosynthesis schemes generally use the following steps to synthesize AuNPs biogenically: the biogenic extracts from bacteria, fungi, or

plants are added to $HAuCl_4$ salt solution and mixed well as an initial step. The change in color of the solution indicates the formation of AuNPs. In the first step, Au^{3+} is reduced to $Au^{0.}$ In the second step, agglomeration and stabilization form AuNPs. The biogenic synthesis of Au NPs through bacteria can be done with both intra and extracellular approaches. The extracellular approach is the most widely used compared to intracellular synthesis. Various bacterial strains such as *Stenotrophomonas maltophilia*, *Pseudomonas putida*, *Escherichia coli*, and *Pseudomonas fluorescence* can be used to synthesize the AuNPs [162], [163]. The biosynthesis of AuNPs in these bacteria is associated with an *NADPH-dependent reductase* enzyme that converts the Au^{3+} to Au^{0}.

The bacteria-mediated AuNPs has much biomedical application such as antibacterial, antiviral, and anticancer. Dhandapani et al. 2021 used *Nigella sativa* and *Curtobacterium proimmune K3* to synthesize the AuNPs [164]. They evaluated the anticancer activity of AuNPs synthesized from *Nigella sativa and Curtobacterium proimmune K3*. Their experimental result confirmed the exhibition of cytotoxicity against human gastric *adenocarcinoma (AGS) cells*. Their study used XRD, FT-IR, SAED, TEM, DLS, and EDX to characterize the AuNPs. The physicochemical characteristics of AuNPs were polygonal- or elliptical-shaped and sized in the range of 20–50 nm. The research work by Jafari et al. demonstrated the cytotoxicity and antibacterial activities of AuNPs synthesized using *Micrococcus yunnanensis strain J2*[165]. The authors used UV–visible spectroscopy, TEM, SEM, XRD, TGA, and FTIR methods for the characterization of AuNPs. The average size of the spherically shaped NPs was reported at 53.8 nm. Their experimental results revealed that the bacterial-mediated AuNPs exhibited significant cytotoxicity against cancer cell lines of the human brain, likely glioblastoma (U87), fibrosarcoma (HT1080), pheochromocytoma (PC12), colorectal adenocarcinoma (Caco2), breast cancer (MCF7), and epithelial-like lung carcinoma (A549). Another study found that the AuNPs synthesized from *Mycobacterium sp. were* effective against (HeLa) Cervical and HUVEC cancer cell lines. Their synthesized AuNPs size was reported between the range of 5-55 nm. They used FTIR technique for the characterization of AuNP in their studies. Marin microbes such as *Vibrio alginolyticus* are recently used for the synthesis of AuNPs as Shunmugam et al. used *Vibrio alginolyticus* in their study to synthesize the AuNPs for their application in anticancer and antioxidant activities [166]. The morphological analysis was done using SEM and TEM. The significant anticancer activity of *Vibrio alginolyticus*-mediated AuNPs against colon carcinoma was confirmed through an MTT assay. Same as the apoptotic-mediated cell death was also confirmed using fluorescence analysis. More recently proposed biogenic synthesis of Au NPs for anticancer activities is reported in **Table 2**.

2.2.3. Biogenic Synthesis of AuNPs through Plant Extracts

Biogenic Synthesis of NPs through plant extracts is becoming more popular due to their availability, low cost, environmentally more friendly, and non-toxic nature. Many different kinds of plants are currently being used to synthesize AuNPs, such as *Terminalia catappa* [167], *Cinnamomum camphora* [168], *and Pelargonium graveolens* [169], *Medicago sativa* [170], and many more. The synthesis of AuNPs is done for different biomedical applications, including cancer therapy and antifungal, anti-bacterial, and immune therapy. For example, Santos et al. used *Hevea brasiliensis* plant extract to synthesize the AuNPs in order to study the cytotoxicity and genotoxicity of cancer cell line (CHO-K1) cells. Their plant-based synthesis approach produced spherical and triangular-shaped AuNPs with a size of 50 nm. They used FTIR and XRD for the characterization of the AuNPs. The study found that the AuNPs synthesized from *Hevea brasiliensis* exhibited strong cytotoxicity against CHO-K1 cells [171]. Studies have shown that *Benincasa hispida*-mediated AuNPs possess anticancer activities, as Saqr et al. demonstrated that the potential of *Benincasa hispida*-mediated AuNPs for cancer treatments [172]. The authors used AuNPs to study the anticancer activities against HeLa cancer cells. Their experimental results confirmed that the *Benincasa hispida*-mediated AuNPs were effective against HeLa cancer cell lines. The AuNPs shape was spherical with an average size of 23 nm. FTIR, Ultraviolet–visible spectroscopy (UV-VIS), TEM, and dynamic light scattering were

used to characterize the AuNPs. The work done by Botteon et al. exploited the *Brazilian red propolis*-mediated AuNPs anticancer activities [173]. Their plant-mediated AuNPs have shown strong anticancer activities against the bladder (T24) and prostate (PC-3) cancer cells. These AuNPs were characterized through FTIR, SPR, and TGA. The shape of these NPs was reported as rods, triangular, pentagonal, and hexagonal. At the same time, the size was reported in the range of 8-15 nm. *Curcuma wenyujin*-mediated AuNPs were proven to be effective against the renal carcinoma (*A498)* cancer cell line [174].

Curcuma wenyujin mediated AuNPs apoptotic effect was also studied against human renal cell carcinoma A498 cells. Their experimental result reported the formation of spherically shaped AuNPs with a size of 200 nm. The characterization was done using the Ultraviolet–visible spectroscopy (UV-Spec), DLS, FTIR, SAED, TEM, EDAX, and AFM analysis. Balasubramanian et al. used the *Jasminum auriculatum leaf extract* to synthesize gold NPs [175]. Their study found that the *Jasminum auriculatum*-mediated AuNPs were effective against the HeLa cell line. The physiological analysis found that the AuNPs were spherical in shape with a size ranging from 8-37 nm. The characterization was done through TEM and SEM. The research work done by Lava et al. revealed that the *Lobila nicotianifolia*-mediated AuNPs were proven effective against the lung cancer (A459) cell line [176]. The physiology of the produced AuNPs was reported as spherical with a size of 80 nm. UV-vis spectroscopy, TEM, SAED, FTIR, and XRD were used to characterize the AuNPs. The anticancer activities of the *Orchid*-mediated gold NPs were studied by Yas et al. Their study reported that the *Orchid*-mediated AuNPs showed strong anticancer activities in breast cancer (AMG-13) cell lines [177]. The AuNPs in their study were reported spherical in shape with a size ranging from 14- 50 nm. TEM, FTIR, UV-Vis, and AFM were used to characterize the produced AuNPs. Patra et al. evaluated the potential of being anticancer in the HeLa and human embryonic kidney cell lines (HEK293) cancer cell line of the *Piper betle*-mediated AuNPs [178]. Their study found that the AuNPs synthesized from *Piper betle* exhibited strong anticancer activities in both cancer cell lines. UV–Visible spectroscopic, TEM, EDX, and X-ray were used for the characterization of the AuNPs. The latest advancement in plant-mediated AuNPs and their application in cancer therapy are reported in **Table 2.**

2.2.4. Biogenic Synthesis of AuNPs using Algae Strains

Another interesting source for gold NPs synthesis is through algae strains. NPs from different algae strains can be produced via extracellular and intracellular approaches. Various algae strains, such as *Turbinaria conoides* [179], *Chlorella Vulgaris* [180], *and Galaxaura elongata* [181], have been used to synthesize AuNPs for different biological applications. Biological entities present in algae have not been extensively explored than the plant extracts, fungi, and bacterial mediated synthesis of AuNPs. The functional group and metabolites in the algae cell wall reduce the metal salt into NPs. In the biosynthesis process, it is devised as a nano factory for NPs. Many researchers used algal-mediated AuNPs for their application in cancer therapy. González-Ballesteros et al. used *Cystoseira baccata* algae strain to synthesize the gold NPs [182]. The anticancer activities of *Cystoseira baccata*-mediated AuNPs against the human colon adenocarcinoma Caco-2 and (HT-29) were explored. The characterization of AuNPs of spherical-shaped polycrystalline NPs of diameter 8.4 ± 2.2 nm was done using UV–vis spectroscopy, TEM, HRTEM, STEM, and zeta potential measurements. Their experimental results confirmed the exhibition of apoptosis in colon cancer cells. Another study used *Undaria sp.* to synthesize AuNPs and studied the effect on the viability of human non-small lung cancer cells [183]. The characterization of AuNP confirmed that the particle size was approximately 10 nm. Their study confirmed that the AuNPs synthesized and stabilized by the algae were able to decrease the cancer cell viability. Amina et al. synthesized AuNPs using *Dictyosphaerium sp.* extracts to study the *in-vitro* application of their antiproliferative activities [184]. The characterization was done using UV–Vis spectroscopy, zeta potential analysis, FTIR, X-ray, and XRD [87,185–188]. The characterization confirmed the formation of spherically shaped AuNPs with an average size of 7.9 ± 2.4 nm. The study found that

the *Dictyosphaerium sp.*-mediated AuNPs exhibited strong antiproliferative activities in colorectal cancer cell line (HCT-116) and breast cancer cell line (HCC1954). In recent studies, *Turbinaria decurrens*-mediated AuNPs were found to be effective against lung cancer A549 cell lines [189]. The resultant AuNPs were sized between 10.07-19.72 nm. The study of Algotiml et al. exploited the potential of Red Sea Seaweeds-extracted gold NPs and their antibacterial and anticancer activities [190]. They used the *Ulva rigida*, *Cystoseira myrica*, and Gracilaria foliifera as capping and reducing agents for the synthesis of gold NPs. The algal-mediated gold NPs showed strong anticancer activity against MCF-7 cell lines in human breast adenocarcinoma cells. More recently proposed algae-mediated Au NPs and their anticancer applications are reported in **Table 2.**

2.3. Biogenic Synthesis of Copper & Copper Oxide NPs and their Application Cancer Therapy

In the following, we overview the recently proposed biogenic synthesis methods of Cu and CuO NPs using fungi, Bacteria, Algae, and plant extracts.

2.3.1. Biogenic Synthesis of Cu NPs and CuO NPs using Fungi Strains

Copper has various oxidation states such as Cu^0, Cu^+, Cu^{2+}, and Cu^{3+} and these oxidations exhibit a different reaction through one or two-electron pathways. The CuNPs have distinctive properties such as high catalytic activity and high stability against high temperatures. They can produce the same or higher results than other expensive particles such as Au and Ag NPs. Due to the unique properties like high surface area, high conductivity, and low electrochemical migration of CuNPs have many applications [213][214]. The production of NPs through biogenic synthesis is classified as a bottom-up approach. Three essential things to be considered while synthesizing the CuNPs through a biogenic approach are the choice of solvent medium, reducing agent, non-hazardous capping, and reducing agent [215]. Several fungi strains, such as Noor et al., used *Aspergillus niger* to synthesize the CuNPs to study the anticancer, antibacterial, and antidiabetic activities [216]. Their study found that the *Aspergillus niger*-mediated CuNPs exhibited a significant cytotoxicity effect against human hepatocellular carcinoma cell lines (Huh7). They used the UV–visible spectrophotometer, FTIR, and Zetasizer for the characterization of the CuNPs. Another study considered *Agaricus bisporus* to synthesize the CuNPs[217]. Sriramulu et al. used *Agaricus bisporus* -mediated CuNPs against the human colon cancer cell line (SW620). Their study found that the CuNPs synthesized from *Agaricus bisporus* exhibited strong cytotoxicity against human colon cancer cell line SW620. The resultant CuNPs were characterized by XRD, TEM, TEM, and EDAX.

Studies have shown that Copper oxide (CuO) NPs have been proven effective in cancer therapy. Different fungal strains have been used to synthesize the CuO NPs for different biomedical applications. Saravanakumar et al. used *Trichoderma asperellum* to synthesize the CuO NPs and studied the effect of photothermolysis on human lung carcinoma [218]. Their experimental results confirmed that the *Trichoderma asperellum*-mediated CuO NPs have the therapeutic potential for *in vitro* photothermolysis. The study of Mani et al. used *Aspergillus terreus* fungal strain to synthesize the CuO NPs [219]. They studied the several bioactivities and anticancer activities of *Aspergillus terreus*-assisted CuO NPs. These endophytic fungi *Aspergillus terreus*-mediated CuO NPs were proven effective against the colon cancer cell line HT29. The anti-cancer activity on the HT29 cell line was evaluated by MTT (IC50: 22 µg/mL) and Fluorescence-activated cell sorting (FACS) analyses (32.11% cells gated in the S phase of the cell cycle). FTIR, EDAX, SEM, and CRD were used to characterize the CuO NPs. Recently proposed fungal-mediated biogenic synthesis of CuNPs and their anticancer activities in different cancer cell lines are given in **Table 3.**

Table 3. Biogenic Synthesis of Cu NPs and CuO NPs and their Application in anticancer activity

Biogenically Synthesized Nps Their Size, Shape, and Targeted Cancer Cells						
Year	Synthesis Approach	Nps	Size	Shape	Targeted Cancer Cells	Ref
2023	Plant (Hibiscus Cannabinus)	Cu & Cuo	900 and 450	Spindle	HL60	[233]
2023	Plant (Sesbania Grandiflora)	Cu & Cuo	33	Needle-Shaped	Hepg2	[234]
2022	Plant (Prunus Nepalensis)	Cu & Cuo	42.5	Spherical	Breast Cancer Cells (MCF7)	[235]
2022	Plant (Calendula Officinalis)	Cu & Cuo	19.64 -39.15	Spherical	Lung Adenocarcinoma Cell Lines	[236]
2022	Plant (Mentha Piperita)	Cu & Cuo	13.42-39. 85	NM	KYSE270, OE33, And ESO26	[237]
2021	Plant (Wrightia R. Br)	Cu & Cuo	15	Spherical	MCF7 Cells	[238]
2021	Plant (Allium Noeanum)	Cu & Cuo	10.8	Polygonal	HEC1B	[239]
2021	Fungi (Aspergillus Terreus)	Cu &Cuo	Below 100	Spherical	HT29 Cell Line	[240]
2020	Fungi (Agaricus Bisporus)	Cu & Cuo	10	Cubic	SW620 Cancer Cell Lines	[241]
2020	Fungi (Aspergillus Niger)	Cu & Cuo	500	Round	Huh-7	[242]
2019	Fungi (Trichoderma Sp)	Cu & Cuo	10-190	Spherical	A549 Cancer Cells	[243]
2021	Bacteria (Pseudomonas Silesiensis)	Cu & Cuo	32	Spherical	Wi38	[244]
2023	Spirulina platensis (Blue-Green Algae)	Cu & Cuo	3.75–12.4	Spherical	A549, HCT, Hep2 And WISH	[245]
2022	Algae (Pterocladia Capillacea)	Cu & Cuo	62	Irregular	Hepatocellular Carcinoma, Breast Cancer, And Ovarian Cancer Cell Line	[246]
2021	Algae (Sargassum Latifolium and Cystoseira Myrica)	Cu & Cuo	12 and 26	Irregular	Leukemia Cell Line (K562)	[247]

2.3.2. Biogenic Synthesis of CuNPs and CuO NPs using Bacterial Strains

In the microbial-mediated NPs synthesis, microbes tend to produce enzymes that reduce the toxic metals which cause the formation of NPs [220]. Different bacterial strains have been used to synthesize CuNPs via Intra and extracellular approaches like other microbes. Unlike other NPs, CuNPs role in cancer therapy and drug delivery is not yet explored widely. Only a few studies have reported the bacterial-mediated CuNPs role in cancer therapy. A study by Zhou et al. used *Shewanella oneidensis MR-1* to synthesize the copper sulfide NPs [221]. Photothermal therapy is an effective cancer treatment, and Copper sulfide exhibits photostability and high absorption in the infrared region. Generally, Cu sulfide was previously synthesized using a chemical approach that requires high temperatures, hydrophilic modification, and explicit stabilization. However, bacterial-mediated NPs are more stable; thus, the authors used *Shewanella*. *oneidensis MR-1*-mediated CuNPs are highly stable and exhibit

high photothermal conversion efficiency of 27.2%. Their study concluded that the CuNPs were homogenous shaped and hydrophilic with a size of ~5 nm.

Several bacterial strains were used to synthesize the CuO NPs, such as the Sonbol et al. used the *Cylindrospermum stagnale* to synthesize the CuO NPs [222]. They studied the antibacterial, anticancer, and larvicidal application of *Cylindrospermum stagnale*-mediated CuO NPs. Their study revealed that the cyanobacterium-capped CuO NPs exhibited significant cytotoxic against the HepG2 cell line. The characterization was done using UV–Vis, FT-IR, SEM, and TEM and confirmed the formation of spherical-shaped crystalline CuO-NPs. Another study by Kouhkan et al. exploited the potentials of *Lactobacillus casei Subsp. Casei*-mediated CuO NPs in cancer therapy [223]. They demonstrated the cytotoxic effects of CuO NPs against gram-negative and positive bacteria and cancer cell lines. These NPs were characterized using FTIR, XRD, TEM, EDX, and FESEM and confirmed the production of CuONPs. More bacterial-mediated Cu and CuO NPs and their anticancer activities and therapy are reported in **Table 3.**

2.3.3. Biogenic Synthesis of CuNPs and CuO NPs using Plant Extracts

Various plants were used to synthesize the Cu and CuO NPs for biomedical applications. In addition to other biomedical applications of Cu and CuO NPs, such as antibacterial and antifungal activities, these NPs have shown specific drug transport abilities and efficient photoluminescence potentials, enabling them as a potential candidate for target delivery of imaging agents and cancer therapeutical drugs. The greenly synthesized Cu and CuO are emerging as essential candidate agents for cancer therapy. Many studies have confirmed that biogenically synthesized NPs are efficient against different kinds of cancer cell lines [224]. A recent study proposed by the Biresaw and Taneja used *Prunus nepalensis* to synthesize the CuNPs and studied the anticancer activities of *Prunus nepalensis*-assisted CuNPs in breast cancer cell lines [225]. In their study, the authors fabricated CuNPs from the fruit extract *of Prunus nepalensis (P. nepalensis)*. UV–Vis, FTIR, SEM, and TEM were used to characterize the CuNPs. They confirmed the formation of NPs with an average size of 42.2 nm. The experimental result concluded that the CuNPs showed environmentally friendly anticancer activity. CuNPs were synthesized using starch collected from potatoes in a recent study [226]. They exploited the antimicrobial, anticancer, and antioxidant capabilities of starch-mediated CuNPs. The characterization was done using UV–visible, FTIR, TEM, XRD, TEM, DLS, and EDX. The result concluded the formation of spherical-shaped nanocomposites with 200 nm and CuNPs with a size of 9 nm. The study by Yaqub et al. proposed a *Zingiber and Allium sp*-mediated synthesis of CuNPs[227]. They exploited the effect of Doxycycline for anticancer and bactericidal activities. CuNPs in this study were characterized by using FTIR, UC-Vis, and XRD and confirmed the formation of CuNPs. They concluded the anticancer behavior of *Zingiber and Allium sp*-mediated CuNPs against HeLa and HepG2 cell lines by MTT assays.

Bioinspired synthesis of CuO NPs using *Syzygium alternifolium (Wt.) Walp* was proposed by Yugandhar et al. to study the antibacterial and anticancer activities [228]. Their study concluded that the CuO NPs significantly exhibited anticancer activity against breast cancer cell lines (MDA-MB-231). For the characterization of the CuO NPs, they used FTIR, XRD, DLS, Zeta, and TEM. Their study produced spherically shaped NPs with sizes ranging from 5-13 nm. Ali Thamer and Tareq Barakat study concluded that the CuO NPs synthesized from *Cordia myxa L. aqueous extract* exhibited strong cytotoxicity against breast cancer cell lines [229]. Their study observed that the inhibition rate at l00 µg/ml was 85.2 for MCF7 and 78.2 for AMJ13. The study confirmed that aqueous extract of *Cordia myxa L.* showed a toxic effect on the growth of breast cancer cells. They confirmed the strong anticancer activities of starch-mediated CuNPs in the MCF7 cancerous cell line. The recently proposed biogenic synthesis of CuNPs is reported in **Table 3**.

2.3.4. Biogenic Synthesis of CuNPs and CuO NPs using Algae Strains

The Biogenically synthesized Cu, and CuO NPs using a variety of algal strains exhibited significant results against cancer cell lines. Recent studies have reported that both copper and copper oxide NPs showed cytotoxicity against different human cancer cell lines. A recent study on the biogenic synthesis of CuNPs using *Pterocladia capillacea* [230] revealed that the red algae-mediated CuNPs have strong cytotoxicity towards hepatocellular carcinoma, breast cancer, and ovarian cancer cell lines. Their study used *Pterocladia capillacea* algae to synthesize CuO NPs. Their study produced CuO with a size of 62 nm. XRD, TEM, FTIR, and DLS were used for the characterization of CuO NPs. The algae-mediated CuO NPs showed significant cytotoxicity against hepatocellular carcinoma, breast cancer, and ovarian cancer cell lines with IC50 values of 0.40 ± 0.08, 1.50 ± 0.12, and 0.70 ± 0.09 µg/mL, respectively.

Ramaswamy et al. used *Sargassum polycystum* extracts to synthesize CuO NPs [231]. They studied the antimicrobial and anticancer activities of *Sargassum polycystum*-mediated NPs. In their study, the authors confirmed the anticancer activity of *Sargassum polycystum* algae-mediated CuO NPs was determined by MTT assays against the MCF7 cancer cell line. Another recent study synthesized CuNPs using *Undaria pinnatifida-derived fucoidan* [232] and studied their anticancer, apoptosis effect. Their study reported that the formation of NPs was circular with a size of less than 30 nm. Phull et al. study concluded that the CuO NPs inhibited HeLa cell growth with an IC50 value of 0.479 mg/mL. The (Terminal deoxynucleotidyl transferase dUTP nick end-labeling) terminal deoxynucleotidyl transferase biotin-dUTP nick end labeling (TUNEL) assays confirmed that the CuO NPs induced DNA damage and showed significant apoptosis in HeLa cancer cell lines. More recently proposed biogenically synthesized Copper and Copper Oxide NPs and their application are reported in **Table 3.**

2.4. Biogenic Synthesis of Zinc (Zn) and Zinc Oxide Nanoparticles and their Application in Anticancer Activities

In the following, we overview the recently proposed biogenic synthesis methods of Zn and ZnO NPs using fungi, Bacteria, Algae, and Plant extracts.

2.4.1. Biogenic Synthesis of Zn NPs and ZnO NPs using Fungi Strains

Many researchers have studied the capability of the fungal-mediated Zn and ZnO NPs in anticancer activities against different cancer cell lines. Researchers used various fungal strains such as *Penicillium chrysogenum, Pleurotus ostreatus, and Trichoderma harzianum (SKCGW009)* to synthesize Zn NPs and ZnO NPs. A study by El-Batal et al. used *Pleurotus ostreatus* as a reducing and stabilizing agent to synthesize the ZnNPs[248]. They studied the antimicrobial, antioxidant, and anticancer of fungal-mediated Zn NPs. The fungal-based Zn NPs were characterized using UV, TEM, DLS, XRD, and FTIR. TEM confirmed that the average diameter of Zn NPs was 46 nm. Their experimental result confirmed that the Zn NPs exhibited anticancer activity towards Ehrlich Ascites Carcinoma (EAC) and CACO (i.e., human colon adenocarcinoma). The value of IC50% was recorded at 47.5 µg/ml and 65 µg/ml. Housseiny and Gomaa explored the *Penicillium chrysogenum*-based biosynthesis technique of ZnNPs and evaluated its antimicrobial and antitumor activities [249]. The resultant NPs were characterized by using HR-TEM, DLS, and FTIR. The antitumor activity towards breast carcinoma MCF7 and HCT116 (i.e., colon carcinoma cells) was evaluated and confirmed that the ZnNPs showed antitumor activities.

Saravanakumar et al. used *Trichoderma harzianum (SKCGW009)* to synthesize the ZnO NPs [250]. The formation of ZnO NPs was confirmed using FTIR and PACE. The XRD, UHR SEM, and TEM EDS characterization reported the formation of the spherical shape of ZnO NPs with a size of 30.34 nm. Cytotoxicity analysis confirmed that the ZnO NPs were not toxic to NIH3T3 cells. The dose-dependent inhibitory effect on pulmonary carcinoma

(A549 cell lines) was confirmed. Another fungi stain named *Xylaria acuta* was used to synthesize the ZnO NPs. This study concluded the formation of ZnO NPs with a hexagonal shape, and the size was recorded between 34-35 nm. Sumanth et al. studied the anticancer assay of the synthesized ZnO NPs by cell uptake, MTT assay, and apoptosis assay [251]. The experiment confirmed that the synthesized ZnO NPs exhibited solid anticancer activity toward cancer cells at 1 µg/mL. More fungal-mediated Zn and ZnO NP synthesis and their application are given in **Table 4**.

Table 4. Biogenic Synthesis of Zn and ZnO NPs and their Application in different cancer cell lines.

Biogenic Synthesis of Zn and ZnO NPs and their Application in different cancer cell lines.						
Year	Synthesis Approach	Nps	Size	Shape	Targeted Cancer Cells	Ref
2023	Plant (Pumpkin Seed Extracts)	Zn & Zno	50	Spherical and Hexagonal	Ovarian Cancer Cell Line	[259]
2022	Plant (Morin Catharanthus and Roseusda Citrifolia)	Zn & Zno	17.44	Spherical	MCF7	[260]
2021	Plant (Garcinia Cambogia)	Zn & Zno	11-32	Hexagonal	Kidney Cancer (A498) Cell Lines	[261]
2021	Plant (Artemisia Scoparia)	Zn & Zno	9	Spherical	Huh7 Liver Cancer Cells	[262]
2021	Plant (Amygdalus Scoparia)	Zn & Zno	29	Spherical	Hela, MCF7, LS180	[263]
2020	Plant (Lawsonia Inermis)	Zn & Zno	17.12	Cubic	MCF7	[264]
2021	Fungi (Cladosporium Tenuissimum)	Zn & Zno	Below 100	Hexagonal	Hela Cell Lines	[265]
2020	Fungi (Xylaria Acuta)	Zn & Zno	52	Hexagonal	MDA-MB 134	[266]
2019	Fungi (Aspergillus Niger)	Zn & Zno	80-130	Rod and Cluster	Hepg2	[267]
2019	Fungi (Aspergillus Terreus)	Zn & Zno	110	Spherical	HCT116	[268]
2021	Bacteria (Lactobacillus Spp)	Zn & Zno	18.6	Hexagonal	HT 29 Cancer Cell Line	[269]
2019	Bacteria (Cyanobacteria Nostoc Sp. EA03)	Zn & Zno	50-80	Star	A549 Cells	[270]
2020	Algae (Anabaena Cylindrica)	Zn & Zno	40-60	Rod	Melanoma B16F10 Cells	[271]
2018	Algae (Sargassum Muticum)	Zn & Zno	NM	NM	Hepg2	[272]

2.4.2. Biogenic Synthesis of Zn NPs and ZnO NPs using Bacteria Strains

Compared to other microbes, bacteria-mediated Zn and ZnO NPs biosynthesis for cancer therapy has not been fully explored. However, fewer studies have demonstrated the biogenic synthesis of ZnO NPs using different bacterial strains. Suba et al. used *Lactobacillus spp* to synthesize the ZnO NPs, and their results confirmed the

biocompatibility of the resultant NPs against HT 29 cancer cell lines through MTT Assays [252]. These NPs were characterized using XRD, FESEM, FTIR, EDX, and AFM. Ebadi et al. explored the anticancer activities of cyanobacterium-mediated ZnO NPs. They used *cyanobacterium Nostoc sp. EA03* to synthesize the ZnO NPs and evaluate the cytotoxicity against MRC-5 lung fibroblast cells and A549 cells [253]. The characterization was done using TGA, FTIR, SEM, TEM, EDX, and Zeta. The TEM and SEM images confirmed the formation of star-shaped NPs having an average size of 50–80 nm. **Table 4** reports the more recent biogenically synthesized Zn and ZnO NPs and their application in cancer therapy.

2.4.3. Biogenic Synthesis of ZnNPs and ZnO NPs using Plant Extracts

ZnNPs are considered an essential metallic oxide due to their biomedical applications in cancer therapy and antimicrobial activities. It has unique advantages and hence has received much recognition in pharmaceutics. Researchers have proposed several plant-mediated biogenic synthesis approaches for Zn and ZnO NPs and evaluated the anticancer activities. The *Ocimum americanum* was used by Vidhya et al. in their study to synthesize the ZnO NPs and their anticancer activity was studied [254]. Their experiment confirmed the Anti-proliferation activities at a concentration of 31.2 µg towards cancer cell line A431 through MTT assays. A recent study by Chabattula et al. used leaf extract of *Annona muricata (Am)* to synthesize the ZnO NPs [255]. The characterization confirmed the formation of the nearly spherical-shaped ZnO NPs with an average size of 80 nm. Their study found that the resultant NPs were biocompatible and hemocompatible. The study concluded that the ZnO NPs showed anti-cancer effects on 2D and 3D tumor models. They also reported the toxicity of ZnO NPs on both A549 and human T lymphoid cell (MOLT4) cells and recorded a reduction in the size of the A549 tumor. In a recent study, *Mentha mozaffarianii* was used by Ranjbar et al. to synthesize the ZnNPs greenly [256]. The ZnNPs were characterized by XRD, FE-SEM, EDX spectroscopy, and FTIR spectroscopy. The characterization by FESEM reported the formation of the spherical shape biosynthesized ZnONPs with a mean diameter of between 20–29 nm. The experiment concluded that the *Mentha mozaffarianii*-mediated ZnNPs exhibited strong anticancer activity against HeLa at IC50: 50.1 µg/ml, MDA-MD231 at IC50: 54.9 µg/ml, and LS180 at 63.4 µg/ml) cancer cell lines. **Table 4** reported more recently proposed biogenically synthesized Zn and ZnO NPs using plant extracts and their application in cancer therapy and cytotoxicity.

2.4.4. Biogenic Synthesis of Zn NPs and ZnO NPs using Algae Strains

Metal oxide-based chemotherapeutics have emerged as a promising anticancer approach. ZnO NPs synthesis using algae can be done through the extracellular synthesis approach. A study conducted by R. et al. used *Gracilaria edulis* to synthesize the ZnO NPs using the extracellular approach [257]. The characterization of the ZnO NPs was done by using UV–Visible spectroscopy, FESEM, EDX, HRTEM, and FTIR. They evaluated the anticancer capability of *Gracilaria edulis*-meditated ZnO NPs against cervical cancer cell lines (SiHa cells) through an MTT assay. The characterization confirmed the formation of hexagonal shape NPs with sizes ranging from 20 to 50 nm. Their study concluded that the ZnO NPs exhibited cytotoxic effects towards SiHa cells with an IC50 value of 35 ± 0.03 µg/ml (in a dose-dependent manner). Bhattacharya et al. proposed an algal-mediated biogenic synthesis of ZnO NPs, and anticancer activities were evaluated [258]. *Anabaena cylindrica* algae strain was used to synthesize ZnO NPs, and the result confirmed that ZnO NPs exhibited strong anticancer activities against skin melanoma (B16F10) cells. Their experimental result reported a more significant reduction in cell viability exposed to ZnO NPs. They also reported a 50% decrease in cellular viability (IC50) for *Anabaena cylindrica*-mediated ZnO NP at a 3% dose. **Table 4** reported biogenically synthesized Zn and ZnO NPs and their application in cancer therapy.

2.5. Biogenic Synthesis of Iron Oxide and Titanium Nanoparticles and their Application in Cancer Therapy

In the following, we overview the recently proposed biogenic synthesis methods of Iron Oxide and Titanium Oxide using fungi, Bacteria, Algae, and Plant extracts. Compared to other biogenically synthesized NPs, the applications of Iron oxide and Titanium oxide NPs in cancer therapy are not widely explored due to their distinct properties. However, fewer studies have been reported in different journals.

2.5.1. Biogenic Synthesis of Iron NPs and Titanium Oxide NPs using Fungi Strains

Fungi-mediated synthesis of Iron oxide NPs for cancer therapy was not reported in recent studies. However, a study by Lingaraju et al. synthesized TiO_2 NPs using *Alternaria solani* fungal strain [273]. They characterized the TiO_2 NPs using FTIR, Powder X-ray diffraction (PXRD), Differential reflectance spectroscopy (DRS), and SEM. Their study confirmed that the TiO_2 NPs showed strong cytotoxicity toward human lung cancer (A549) and human breast cancer (MCF7) cell lines. Another study by Manimaran et al. used *Pleurotus djamor* to synthesize the TiO_2 NPs [274]. They studied the antibacterial, anticancer, and histopathological effects of fungal-mediated TiO_2 NPs using *Pleurotus djamor.* Their study concluded that the *Pleurotus djamor*-mediated NPs showed 9.08–64.71% cytotoxicity at 6.25–100 µg/ml concentration against A549 cancer cells. The SEM and HRTEM characterization confirmed the formation of spherical shape NPs. The NPs size was recorded at 31 nm, and the zeta potential showed 16.4 mV. The work done by Rehman et al. exploited the potential of *Fomes fomentarius*-mediated TiO_2 NPs in antibacterial and anticancer applications [275]. The biogenic synthesis of TiO_2 was analyzed and characterized using XRD, DR-UV, FTIR, SEM, and TEM. The study confirmed that the treatment with TiO_2 NPs also exhibited significant cytotoxicity on cancer cell (HCT116 cells) viability. **Table 5** reports recently studied the biosynthesis of Iron oxide and Titanium NPs and their application for anticancer activities. A recent research work by Wani et al. used *Chaetomium cupreum* to synthesize the Iron oxide NPs and exploited the potentials of fungal-mediated iron oxide NPs [276]. The study confirmed that the treatment with Fe_2O_3 NPs exhibited strong inhibition of MCF7 tumor sphere growth at greater concentration.

Table 5. Biogenic Synthesis of Iron Oxide and Titanium Oxide NPs and their Application in different cancer Cell Lines.

Biogenic Synthesis of Iron Oxide and Titanium Oxide NPs and their Application in different cancer Cell Lines.						
Year	**Synthesis approach**	**NPs**	**Size (nm)**	**Shape**	**Targeted cancer cells**	**Ref**
2023	Plant (algae Spatoglossum asperum)	Iron oxide	16	spherical	glioblastoma cancer cells	[292]
2020	Plant (Carica Papaya)	Iron oxide	21.59	Not uniform	HeLa and BHK21	[293]
2020	Plant (Fomes fomentarius)	Tio2	100–120	spherical	HCT116	[294]
2019	Plant (Papaver Somniferum L.)	Iron oxide	38 ± 13	spherical	HepG2	[295]
2018	Algae (Albizia Adianthifolia)	Iron oxide	32–100	spherical	AMJ13 and MCF7	[296]
2018	Fungi (Callistemon Viminalis)	Iron oxide	36,26,32	spherical	HepG2	[297]

2.5.2. Biogenic Synthesis of Iron NPs and Titanium Oxide NPs using Bacteria Strains

Studies have confirmed that bacteria-mediated Iron oxide and Titanium oxide have proven significant cytotoxicity against different cancer cell lines. For example, Majeed et al. used *Proteus vulgaris ATCC-29905* bacterial strain to synthesize the Iron oxide NPs [277]. Their study has drawn a conclusion that Iron Oxide NPs synthesized from *Proteus vulgaris ATCC-29905* have proven effective against U87 MG—glioblastoma cancer cells and HT-29 cancer cells, and HT-29 cancer cells. The characterization was done using FESEM, EDX, and TEM and confirmed the formation of the spherical-shaped NPs with diameters ranging from 19.23 nm and 30.51 nm. These Iron Oxide NPs exhibited strong cytotoxicity towards U87 MG glioblastoma cancer cells and showed an IC50 value at 250 µg/ml compared with healthy L132 cells.

Colorectal cancer contributes to 10% of the commonly diagnosed cancers around the world. Around ten million colorectal cancer-related deaths were reported in 2020. Several treatments have been applied to treat colorectal cancer. Existing treatment leads to precision targeting and possesses adverse side effects. Vigneshwaran et al. synthesized TiO_2 NPs using a probiotic bacteria, *Lactobacillus* aiming to produce safe and biocompatible NPs for colorectal cancer treatment [278]. They studied the cytotoxic effects of titanium oxide in HT29 cells using MTT assays. To analyze the apoptosis-related morphology, the authors used acridine orange/ethidium bromide staining. The study concluded that the *Lactobacillus*-mediated TiO_2 showed apoptosis by activating the intrinsic apoptotic pathway and generating intracellular reactive oxygen species in HT29 cells. **Table 5** reported more recent bacteria-mediated biosynthesis of Iron Oxide and TiO NPs and their application in cancer therapy.

2.5.3. Biogenic Synthesis of Iron Oxide NPs and Titanium Oxide NPs using Plant Extracts

Green synthesis of iron oxide and Titanium Oxide NPs is exceptionally promising due to its non-toxicity and eco-friendly behavior for cancer therapy. Numerous studies have proven the effectiveness of biogenically synthesized iron and titanium oxide NPs using various plant species in cancer therapy [279] [280] [281]. In a recent study, Bhuiyan et al. used *papaya (Carica papaya) leaf extract* to synthesize the Iron oxide NPs and studied cytotoxicity in HeLa and BHK21 cell lines [282]. The characterization was done using XRD, FTIR, EDX, FESEM, and TGA. Yusefi et al. studied *Punica Granatum-mediated* iron oxide NPs potentials in cancer therapy and found that the biogenically synthesized NPs from *Punica Granatum* showed against nasopharyngeal carcinoma (NPC) cell line, and HONE1[283]. Morphological analysis of greenly synthesized iron oxide NPs confirmed that adding *Punica Granatum* peel extract decreased the size of NPs, and NPs sizes were recorded below 11 nm. The experimental result demonstrated the cytotoxicity of NPs against nasopharyngeal carcinoma.

Similarly, various plant extracts such as *Acacia nilotica* [284], *Cissusquadrangularis* [285], and *Coleus aromaticus* [286] have been used to synthesize the titanium oxide NPs for cancer therapy. Aswini et al. used *Ledebouria revoluta* to synthesize the TiO_2 NPs and studied their larvicidal, histopathological, and anticancer activities [287]. During their study, TiO_2 NPs were synthesized using *Bulb Ledebouria revoluta* extracts. The resultant NPs were characterized using FTIR, XRD, HRTEM, UV-Vis, and XRD. XRD confirmed the formation of 47 nm spherical-shaped NPs. The Anti-lung cancer activity of TiO_2 NPs confirmed using the MTT assay, resulting in an IC_{50} value of 53.65 µg/mL. More recent iron oxide and titanium oxide NPs biogenic synthesis and their applications are reported in **Table 5**.

2.5.4. Biogenic Synthesis of Iron Oxide NPs and Titanium Oxide NPs using Algae Strains

Recently, Fe_3O_4 has attracted much attention due to its distinct useful properties in various fields such as nanomedicine, optofluidic sensor, electrocatalytic, and antibacterial properties [288]. However, Salehzadeh et al.used *Spirulina platensis,* which is a filamentous multicellular blue-green alga extract, for the first time to synthesize the Fe_3O_4/Ag nanocomposites for anticancer activities[289]. Their experimental result concluded that

the Fe_3O_4/Ag nanocomposite triggers a dose-dependent cell proliferation reduction in the human breast cancer cell line (MCF7 cells) at an IC50 value of 135 µg/ml. Fe3O4/Ag nanocomposite exhibited strong cytotoxicity toward the MCF7 cancer cell line. Namvar et al. *Sargassum muticum* synthesizes Fe_3O_4 NPs [290]. Iron oxide modified with their surface morphology help to harvest the key proteins which play important role in cancer treatment [41,291]. Their study found that the *Sargassum muticum*-mediated NPs demonstrated anticancer activities in leukemia (Jurkat cells), MCF7, HeLa, and HepG2 cells.

Although titanium oxide is used for different biomedical applications, fewer studies related to algal-mediated titanium NPs application in anticancer activities were reported. Literature works have reported that numerous NPs were synthesized using algal strains. In a recent study, *Phaeodactylum tricornutum* culture was used to synthesize the Titanium NPs for cancer therapy [298]. The size of NPs under optimal conditions was recorded at around 50 nm. From the experimental results of the cytotoxicity test, the algal-mediated NPs exhibited a significant cytotoxic effect on various cancer cell lines. **Table 5** reports more algal-mediated Iron and Titanium oxide NPs and their application in anticancer activities.

2.6. Biogenic Synthesis of quantum dots and Their Application in Cancer Therapy

Generally, quantum dots are a similar group of nanoparticles having significant optical properties and can be modified with various approaches such as photochemical synthesis, microwave-assisted aqueous synthesis, irradiation methods, *etc* [83]. However, biogenic synthesis of QDs is the latest yet safe synthesis method having unique properties such as the uniform shape and size of QDs, it has a distinction among other synthesis approaches. However, the problem with QDs is the toxicity based on composition, surface modification, and other factors. Compared to QDs produced using chemical and physical approaches, biogenically synthesized QDs are more biocompatible. Several microbes and plant species have been used to synthesize QDs and evaluated their application in cancer therapy. In the following, we overview the most commonly used biogenically synthesized QDs and their application in cancer therapy.

Researchers used different types of fungal strains such as *Fusarium oxysporium* [300], *Schizosaccharomyces pombe* [301], and *Phanerochaete chrysosporium* [302], *etc.* to synthesize the QDs for different applications. Shi et al. have proposed a fungal-mediated cadmium chalcogenide quantum dots synthesis approach [303]. This study considered the *Rhizopus stolonifer* to synthesize quantum dots of cadmium telluride and cadmium sulphide. The formation of quantum dots was confirmed using PL spectroscopy, XRD, and TEM. The experimental results concluded that a significant contrast in imaging was obtained when incorporating the quantum dots in human breast adenocarcinoma Michigan Cancer Foundation-7 MCF7 cell lines. Another study by the authors used fungus fiber to synthesize N, S-self-doped carbon quantum dots [304]. Their experimental results showed that N, S-C QDs did not affect the cell viability and exhibited significant promises in cellular bioimaging.

Various studies have reported the use of bacteria-mediated synthesis approaches to synthesize different quantum dots. For example, Kominkova et al. synthesized through extracellular biosynthesis by *Escherichia coli* [305]. They analyzed the toxicity of the biogenically synthesized QDs with the QDs prepared by the microwave synthesis approach. The toxicity of QDs was evaluated on three cell lines Foreskin Fibroblast (HFF), Prostate Cancer cells (PC3), Breast Cancer cells (MCF7), and the MTT assay. Their study confirmed that the toxicity of biogenically synthesized QDs was 35% less than the QDs synthesized using the microwave synthesis approach.

QDs have low dimensions, more specifically less than 10 nm have obtained significant consideration for potential biomedical applications such as diagnostics and therapy. Researchers have synthesized QDs using extracts obtained from different parts of plants, such as roots, fruits, peels, and leaves extracts. Shivaji et al. demonstrated the capabilities of *tea leaf extract (Camellia sinensis)* in the biosynthesis of CdS QDs and their applications in bioimaging and therapeutic application in lung cancer cell lines [306]. From their experiment, they

obtained CdS QDs with the size of 2-5 nm using tea leaf extracts as a toxic-free stabilizing agent. The resultant QDs cause strong cytotoxicity against A549 cancer cells, and these CdS QDs produce high-contrast fluorescence images of A549 cancer cells, which indicates a great interaction with A549 cancer cells. **Figure 5** shows the overall process involved in Green-Synthesis-Derived CdS Quantum Dots Using Tea Leaf Extract and their application in anticancer activities. The study of the Gholami et al. explored the apoptosis effect of CdS quantum dots on MCF7 and AGS cancer cells [307]. The authors biogenically synthesized the CdS QDs through aqueous extracts of the roots of *Rhaphanus sativus L*. as a reducing and stabilizing agent of Cd and S precursor ions. The characterization was done using TEM, EDS, and FTIR techniques, and the formation of 2-7 nm QDs was confirmed. Cytotoxicity analysis of CdS QDs performed MCF7 breast cancer and AGS gastric cancer using MTT assay. Their experimental results concluded that significant inhibitory effects on treated cells in a dose-dependent manner were observed. The results also confirmed the apoptosis effect on MCF7 cells was higher than on AGS cell lines.

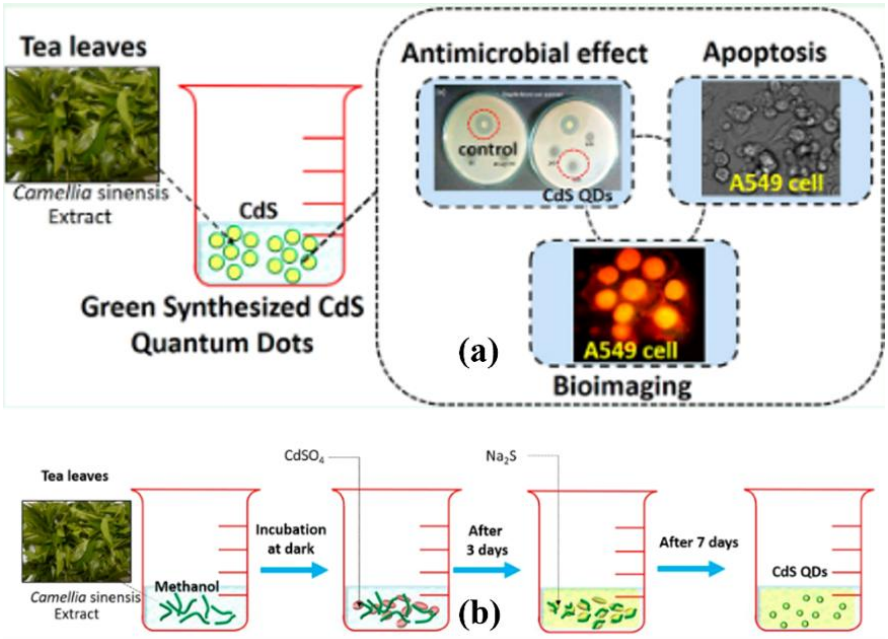

Figure 5. Schematic Diagrams of C. Sinensis Extract-mediated green CdS quantum dots synthesis. (a) Abstract level diagram of process involved in Green-Synthesis-Derived CdS Quantum Dots and their application lung cancer cell therapeutics. (b) *C. sinensis* Extract-Mediated Green CdS QDs Synthes process. Reproduced with permission [299]

3. Conclusion

Nanoparticles have gained significant attention from researchers and academia because of their exceptional chemical, biological, and optical properties. This review help researcher to focus on the toxicity and other adverse effects of synthesized NPs and their application in cancer therapy limited to some extent. However, many researchers proposed biogenic synthesis approaches for NPs, making them safer, less toxic, precision-targeting, economically friendly, and more feasible in cancer therapy. The biological synthesis technique is now preferred because it is green, easy, facile, eco-friendly, and cost-effective. Biogenic synthesis of NPs and QDs can be accomplished using naturally occurring extracts from microorganisms such as fungi, bacteria, algae, and different plant species. Plant-mediated biosynthesis has been considered a widely used method to synthesize nanoparticles among algae, fungi, bacteria, and plants. Plans are also considered to possess extraordinary efficacy as a capping agent, reducing agent, and stabilizing agent due to Phyto-molecules. These biogenically synthesized nanoparticles

have several biomedical applications such as antibacterial, antiviral, antifungal, drug delivery, and anticancer activities. However, we opted to briefly overview the application of biogenically synthesized nanoparticles and quantum dots in cancer therapy among all biomedical applications. This review provides a platform for the scientific community to get diverse materials related to the biosynthesis of inorganic metal, metal oxide nanoparticles, and quantum dots and their application in anticancer activities.

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Conflict of interest

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