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A Thorough Overview of the Science Endophyte Mediated Silver Nanoparticles for Cytotoxic Activities

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A B S T R A C T

Healthy plant tissues are the host of unique microorganisms called 'Endophytes'. These microbes live inside these tissues in part or throughout their life history without causing obvious symptoms of infection in host plants. Endophytes are considered as a novel type of microbial source that can produce a variety of bio constituents, have great values for research and broad prospects for drug development. Nanoparticles are defined as particulate dispersions or solid particles with assize in the range of 10-100nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Cancer is significant worldwide health problem generally due to the lack of widespread and comprehensive early detection methods, the associated poor prognosis of patient diagnosed in later stages of the diseases and its increasing incidence on a global scale. Several drawbacks have been stated with the use of marketed anticancer medicines such as drug resistance, adverse effects, toxicities and even costs. Due to these several limitations, searching for novel anticancer medicines from medicinal plants is becoming an active area of research.

Keywords: Endophytes, *Aspergillus flavus,Nanoparticles, Cancer*

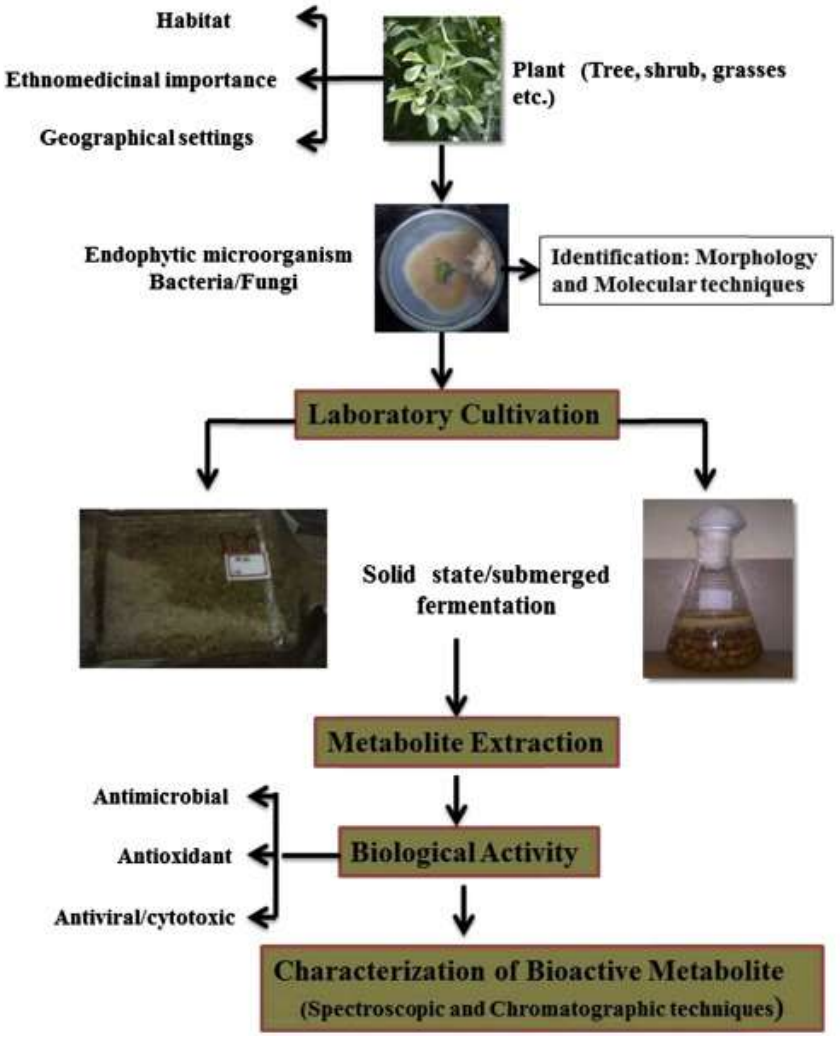
INTRODUCTION:

Every known plant species contains microbial endophytes. Endophytes are special because of their capacity to enter and flourish in plant tissues, exhibiting complex interactions inside the host plant. The presence of endophytes is known to affect a number of essential host plant functions[1].The mysteries of the mysterious endophytic fungi are starting to come to light. Similar to diseases, they are able to control the host to establish their ideal environment[2].The ability of endophytes to produce phytohormones, fixing nitrogen, antagonistic substances, and enzymes—all of which are crucial in helping plants respond to biotic and abiotic stress—has sparked an increasing interest in their potential to alleviate a variety of plant stresses, including biotic stress (like pathogenic microbes) and abiotic stress (like drought and salt stress)[3]. By generating secondary active chemicals that shield the plant from diseases like insects and fungi, the endophytic microbial community can promote plant growth. Additionally, endophytes can manufacture extracellular enzymes that are essential for their colonization within the plant host. By generating phytohormones, microbial endophytes can function as agents that promote plant growth. They can also help plants flourish in contaminated soils by breaking down harmful substances[4]. Additionally, endophytes have the ability to alter host metabolites, which may influence plant growth, adaption, and proliferation. This is a more intriguing and perplexing subject that needs further research. Since it can help uncover the gray areas of endophytes about which little to nothing is known, the effect of endophyte interaction on the host genome was examined[5]. Abiotic stress brought on by high temperatures restricts crop productivity and poses a risk to the environment. Heat stress has the greatest detrimental impact on plant development and metabolism of all the abiotic stimuli, including temperature, salinity, drought, and exposure to heavy metals. Heat stress is defined as temperatures higher than 75 °F. Plants limit growth, development, and physiological cellular metabolism when temperatures rise above their typical range. Heat stress degrades the quality of plants and increases their morbidity and death[6-8]. When salinity first appears, it can be viewed as a water stress that causes less leaf expansion, which in turn causes total inhibition of cell division and stomatal closure. Prolonged exposure causes premature leaf senescence, which lowers photosynthetic activity and eventually kills crop plants[9]. Endophyte colonization and the metabolite secretion that follows have also been linked to increased rates of photosynthesis (Sclerotinia sclerotiorum), plant cell chlorophyll content, trichome and stomata density on plant tissues (Beauveria bassiana), antioxidant enzyme activity, callose deposition, cell lignification, and phytoalexin accumulation (Diaporthe liquidambaris)[10-11]. Herbaceous crops, grasses, and woody trees are among the plant species that have endophytic bacteria; frequent genera include Pseudomonaceae, Burkholderiaceae, and Enterobacteriaceae[12]. Plant–endophyte relationships can be uncovered using a variety of methods, including metagenomics, microarrays, next-generation sequencing, comparative genomics, genome sequencing, and metatranscriptomics[13]. The use of plants and the microorganisms they are associated with to remediate a site is known as phytoremediation. It is an in situ, solar-powered remediation technology that requires little site disturbance and maintenance, which makes it inexpensive and widely accepted. Because the conventional remediation options currently available are often costly and environmentally invasive, phytoremediation proves to be a valuable alternative, particularly for the treatment of large contaminated areas with diffuse pollution. However, there are still a number of hurdles to large-scale applications of phytoremediation, such as the levels of contaminants (being toxic for the organisms involved), the bioavailable fraction of contaminants

(being too low), and, in certain cases, the evapotranspiration of volatile organic pollutants from soil or groundwater to the atmosphere[14-15]. Although some can infiltrate cells, endophytic bacteria often populate intercellular gaps. Stems, roots, leaves, fruits, bulbs, and seeds are all sources of these creatures. Some of them promote plant development, offer defense against biotic and abiotic stress, make it easier for nutrients to be absorbed from the soil and aid in the assimilation of nitrogen from an agricultural and biotechnological perspective, each of these characteristics is crucial[16-21].

Production of the secondary metabolites (SM) from endophytic fungi (EF):

Co evolution is a concept that describes the biochemical interactions between endophytes (EFs) and their host plants. Which is believed to shape the production of SMs. These SMs play a crucial role in endophyte-host communication for mutual adaptation and orientation to different environments. There are three main schools of thought on the relationship between the biosynthesis pathway of common SMs and the evolution of symbiosis between endophytes and their hosts[22]. They also stimulate the production of several phytochemicals like alkaloids, flavonoids, terpenoids, saponins and phenols[23].These fungi produce various secondary metabolites with anti-cancer, anti-nematode and antibiotic activities[24-25].



Schematic representation of isolation of bioactive Secondary Metabolites From Endophytic Fractions

Aspergillus:

One of the most well-known filamentous fungus in the *Ascomycetes* (family *Trichocomaceae*) is *Aspergillus*. According to the World of Microorganisms Information Center (WDCM), there are around 378 species members of the *Aspergillus* genus are highly aerobic fungus that thrive in oxygen-rich conditions, yet many of them can also thrive in situations that are deficient in essential nutrients.6. Numerous species have also been successfully grown under a broad range of salinities (0–34%), pH (2–11), and temperatures (10–50 °C). They are endophytes, saprophytes, parasites, and human pathogens in nature, and they share morphological and microscopical traits with aspergillums. Historically, morphological, physiological, and biochemical techniques were used to identify and categorize Aspergillus species. Lately, molecular methods including restriction fragment length, random amplified polymorphic DNA (RAPD), and ribosomal DNA (rDNA) sequence analysis[26-27].

Numerous active secondary metabolites, including butenolides, alkaloids, terpenoids, cytochalasins, phenalenones, ρ-terphenyls, xanthones, sterols, diphenyl ether, and anthraquinones derivatives, which are crucial to the pharmaceutical and commercial industries, have been demonstrated to be produced

by endophytic Aspergillus species. Different endophytic Aspergillus species generated compounds that exhibited a range of biological activities, including antiviral, antibacterial, anti-inflammatory, and anti-cancer properties. The natural products that were separated from several endophytic Aspergillus species and showed a range of bioactivities are the main topic of this review. Table S1 in the ESI listed other endophytic Aspergillus metabolites that were not bioactive.† The name, Aspergillus species, chemical nature, isolation source, and references were all included in this table. The time frame covered by this review is January 2015–December 2019[28-29].

The fungus *Aspergillus* has a significant impact on the health of people, animals, and plants all across the world. *Aspergillus* species are employed in biotechnology to generate a variety of biomolecules because of their exceptional metabolic diversity. *Aspergillus* spores can cause asthma and other allergic responses in people and animals, in addition to their pathogenic effects. There are around 330 species in this genus that are found in many regions and have the potential to be harmful[30-31].

***Aspergillus flavus*:**

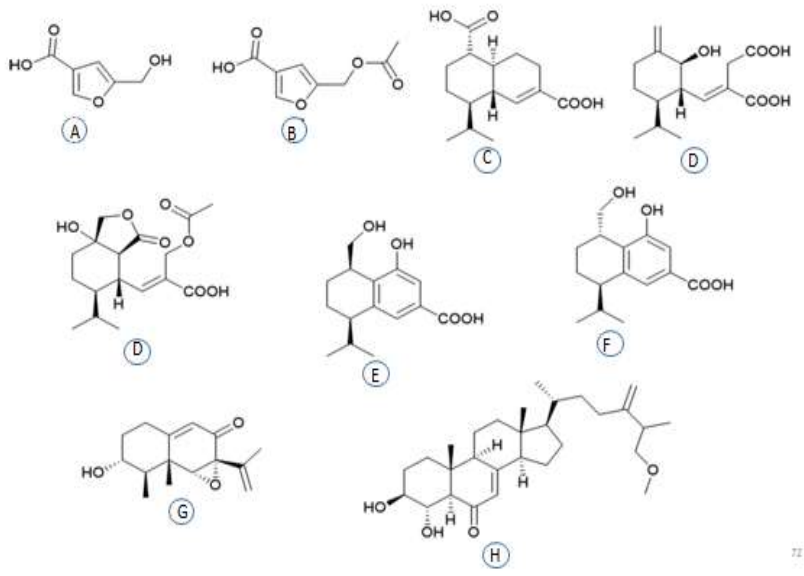
Aspergillus species are members of the *Trichomaceae* family and the *Ascomycota* phyllum. Species are distinguished by their physical traits and color. Colonies are flat, granular, downy to powdery, and frequently have radial grooves when viewed macroscopically. In contrast to other widely seen *Aspergillus* species, such as *A. fumigatus, A. niger, A. nidulans,* and *A. terreus*, the colony surface is initially yellow but eventually turns dark yellowish green. The hyphae of *A. flavus* branch at a 45° angle and are septate and hyaline. The conidiophores end in vesicles at the apex after emerging from supporting hyphae. Over the distal end of the phialides, the conidiophores of *A. flavus*, which have a diameter of μm, are organized in a radial chain. Sclerotria are microscopic structures that divide into loose columns and have a diameter of nm.

The vesicle is 20–45 μm long and 15–20 μm long (up to 800 A. flavus), and the phialides are rough and colorless. They can be uniseriate and directly attached to the vesicle, or they can be biseriate and attached to the vesicle via a supporting cell called a metula (8 μm wide).13.A. flavus h. in vitro. It grows well on Sabouraud dextrose agar or Czapek Dox and malt extract at 37 A. Its primary growth is by apical hyphal extension, which may be somewhat slower than that of °C. Conidia germination takes place at around 24 A. Apical hyphal extension is the primary growth mechanism, and it may proceed more slowly than that of A. fumigatus. According to laboratory observations, growth reaches a plateau after 24 hours and exhibits other growth characteristics comparable to those of A. fumigatus. Similar research has not been done for A. flavus, despite the fact that the rate of hyphal extension has been linked to aggression in A. fumigatus[22-38].

Compared to A. nidulans, A. flavus, a typical fungal species in Flavi, is more helpful for comprehending developmental processes in the section . Aspergillus nidulans and species of the Aspergillus section Flavi have the ability to produce an asexual specialized structure known as a conidiophore. However, the specific morphology of metabolites and asexual and sexual developmental structures differs. The primary distinction is that A. nidulans generates cleistothecia encircled by a large number of Hülle cells, whereas the majority of species in the Aspergillus section Flavi produce dark-colored sclerotia with ascospore-bearing ascocarps . A. flavus produces uni- or biseriate conidiophores according to conidiophore morphology, but A. nidulans produces biseriate conidiophores[39-40].

A. nidulans generates *sterigmatocystin*, which is a precursor to aflatoxins but not aflatoxins themselves, whereas the majority of species in the *Aspergillus* section *Flavi* produce aflatoxins as secondary metabolites. New information about the growth and metabolism of *A. flavus* has been published as a result of a number of recent investigations. Thus, the purpose of this study is to outline the functions of developmental regulators in *A. flavus* and investigate the distribution of developmental regulators in *Flavi* strains. Asexual development-related developmental regulators are thoroughly explained[41-42].

Chemical constituents of Aspergillus flavus:



Two furan derivatives identified as 5-hydroxymethylfuran-3-carboxylic acid (**A**) and 5-acetoxymethylfuran-3-carboxylic acid (**B**) were isolated as a result of fermentation of the culture of *A. flavus*, the endophyte hosted in the stem of *Cephalotaxus fortunei*. Both furans exhibited antibacterial activity against *Staphylococcus aureus* with MIC values of 31.3 and 15.6 μg mL^{-1}, respectively. Moreover, 5-acetoxymethylfuran-3-carboxylic acid (**C**) showed moderate antioxidant activity with an IC_{50} value of 237 μg mL^{-1}, while 5-hydroxymethylfuran-3-carboxylic acid (**A**) displayed weak antioxidant activity with an IC_{50} value of 435 μg mL^{-1} using 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radicals assay.

The sesquiterpenoids; (1*S*,6*R*,7*R*,10*S*)-aspergilloid D (**D**), (1*S*,6*S*,7*R*)-aspergilloid E (**E**), (1*S*,6*S*,7*R*,10*S*)-aspergilloid E (**F**), (7*R*,10*R*)-aspergilloid G (**G**), (7*R*,10*S*)-aspergilloid H (**F**) and sporogen AO-1 (**G**) along with the sterol 3β,4α-dihydroxy-26-methoxyergosta-7,24(28)-dien-6-one (**G**) were isolated from the endophyte *A. flavus* associated with the leaves of the toxic medicinal plant *Tylophora ovata*. All isolated compounds at 10 μM demonstrated hepatoprotective effect on acetaminophen (APAP)-induced damage model of HepG2 cells. They improved the HepG2 cell survival rates from 24.0% (APAP, 8 mM) to 33.2–41.6%. Furthermore, the sterol 3β, 4α-dihydroxy-26-methoxyergosta-7,24(28)-dien-6-one (**G**) exhibited cytotoxicity against MCF-7 breast cancer cells with an IC_{50} value of 2.6 μM.

NANOPARTICLES:

The word “nano” derived from the Greek term “nanos” which show the meaning of dwarf or enormously small. The word “nano” is used in nanotechnology which reveal a billionth of meter. Nanotechnology comprises of novel approaches for the synthesis, designing and manipulation of elements at a small scale of 1 to 100 nm. Nanoparticles contain particular physiochemical properties because of high surface to volume ratio and nano size[43].

Nanoscience has emerged a multidisciplinary field and attracted inputs from different branches of sciences like physics, chemistry and biology with reference to applications and synthesis protocols. Biology-based methods offers different advantages relative to physical and chemical means like being devoid of any toxic wastes and high energy requirements, making them economical, eco-friendly and simple[44-45]. The synthesis of nanoparticles in the size range of 1-100 nm has surpassed the limitations of biological barriers and gained impetus in the advanced research field[46].

The synthesis of nanoparticles (NPs) particularly metal nanoparticles, has significantly impacted the research field due to their flexibility to manipulate size, shape, structure, optical properties, and assembly and thus obtaining nanoparticles of desired physiochemical characteristics. Metallic nanoparticles including gold, copper, zinc, iron, silver, graphene, titanium, magnesium and platinum have been used for the nanofabrication and showing their potential applications in industries, medicine, chemical engineering, bio imaging, biocatalysts, cosmetics, and antimicrobial agents[47].

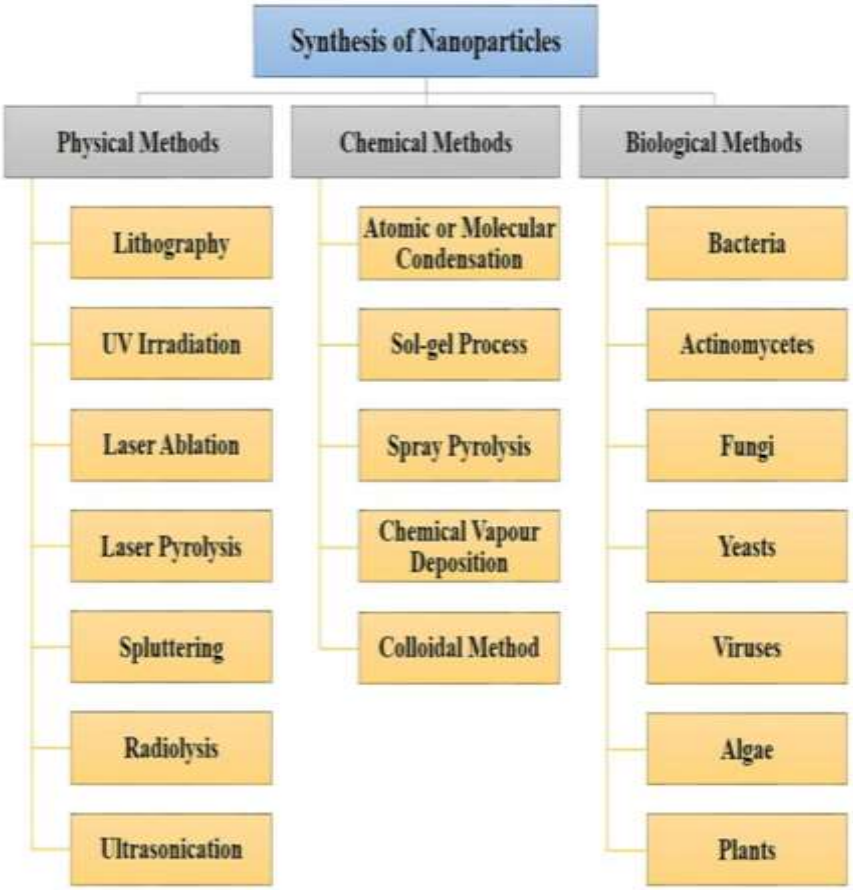
However, silver metal has been widely used for the synthesis of nanoparticles due to its exceptionally unique chemical stability, catalytic properties, and conductivity[48-49]. Silver has long been recognized for its intrinsic antimicrobial potential and therefore, extensively employed for medicinal purposes[50-51].

3.3.1 Different methods of Synthesis of Nanoparticles[52]:

I. Physical Methods

II. Chemical Methods

III. Biological methods



Different methods of Synthesis of Nanoparticles

3.3.1.1 Physical approach of AgNPs synthesis[53]:

The physical methods play a major role in NPs synthesis. The main NPs synthesis procedures are top-down (automatic grinding of a large number of metals) and bottom down (metal reduction, electrochemical process) method.

3.3.1.2 Chemical approach of AgNPs synthesis[54]:

The best aware method for AgNPs fabrication is a chemical reduction process. In common, diverse amount of reducing agents like $NaBH_4$, $Na_3C_6H_5O_7$, $C_6H_8O_6$, $NaBH_4$ and other reagents are used for Ag+ to metallic silver reduction, as followed by accumulation into oligomeric groups and these clusters ultimately form the metallic colloidal AgNPs.

3.3.1.3 Biological approach of AgNPs Synthesis[55].

The physical and chemical methods are greatly helpful to produce the NPs, but due to some limitations like high cost, releasing of a toxic substance into the environment and a highly time-consuming process for NP synthesis. The environment change and the increased atmospheric temperature have raised worldwide awareness to decrease the toxic waste substances hence, the biological method has gained more interest in the scientific field.

3.3.2 Versatile properties of Metal nanoparticles:

3.3.2.1 Physical Properties[56]:

1. Physical parameters like size, shape, specific surface area and aspect Ratio.
2. Agglomeration/aggregation state, particle size distribution, surface morphology/topography, crystal structure and defects.
3. Colour of materials
4. Solar energy absorption

5. Melting point

3.3.2.2 Chemical Properties[57]:

1. Structural formulas and molecular structures describe the arrangement and bonding of atoms in a chemical compound.
2. Nanomaterials composition provides details about chemical constituents, purity and impurities.
3. Nanoparticles can suspend in solutions, unlike bulk materials which sink or float.
4. Surface chemistry deals with composition, charge, tension, reactive sites, physical structure, photo catalytic properties and zeta potential.
5. Catalytic activity of nanoparticles is typically on metal surfaces with increased surface to volume ratios enhancing catalytic activity.
6. Metal particles smaller than 5 nm are of interest due to their unique catalytic properties.
7. Hydrogen storage in metals is the most important chemical application, making nanoparticles useful in such devices.

3.3.2.3 Optical Properties[58]:

1. Metal nanoparticles exhibit unique shape and size-dependent optical properties with extinction spectra dominated by localized surface plasmon resonance (LSPR).
2. The color of a metallic nanoparticle is determined by plasmonic resonance when illuminated by white light.
3. Mie theory describes characteristic light absorption of spherical metal nanoparticles, showing that absorption doesn't strongly depend on particle size in the 3-10 nm range.
4. However, particles show size dependence on the plasmon resonance band below 10 nm and disappear for particles less than 2 nm, confirming the decreasing validity of the free electron gas model assumption.
5. Semiconductor nanocrystals with luminescence activators like Mn^{2+} or Eu^{2+} are interesting candidates for improving optical properties.

3.4 Synthesis of Sliver Nanoparticles[59-60]:

3.4.1 Physical method:

Silver nanoparticles (AgNPs) can be synthesized using physical methods like evaporation-condensation and laser ablation. Both techniques produce large quantities of high-purity AgNPs without releasing toxic substances, but they face challenges such as agglomeration due to the absence of capping agents. Additionally, both methods require significant power and longer synthesis times.

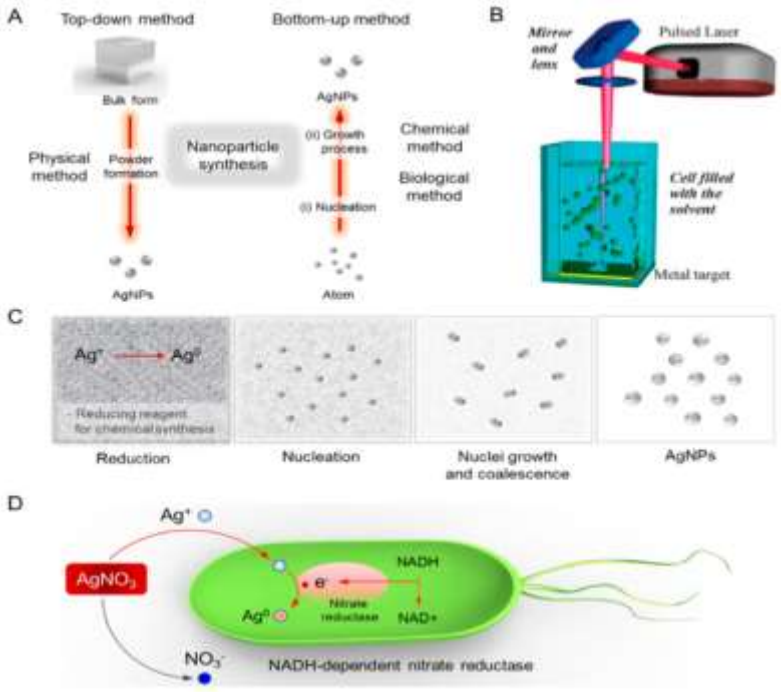
Evaporation-condensation involves a gas-phase route in a tube furnace to create nanospheres from materials like Au, Ag, and PbS. This method has drawbacks, including space requirements, high energy consumption, and extended durations for achieving thermal stability, although these can be mitigated using a ceramic heater.

Laser ablation, on the other hand, synthesizes AgNPs by irradiating a bulk metal source in a liquid environment. The properties of the resulting nanoparticles depend on various parameters. This method is advantageous as it produces pure and uncontaminated AgNPs using mild surfactants without the need for additional chemical reagents

.3.4.2 Biological Method :

The green synthesis of silver nanoparticles (AgNPs) was studied in *Verticillium* species, a type of fungus, with the hypothesis that AgNPs form beneath the cell wall rather than in solution. Ag+ ions adhere to the surface of fungal cells due to electrostatic interactions with negatively charged carboxylate groups of enzymes. As these ions are reduced intracellularly, silver nuclei form and grow through further reduction.

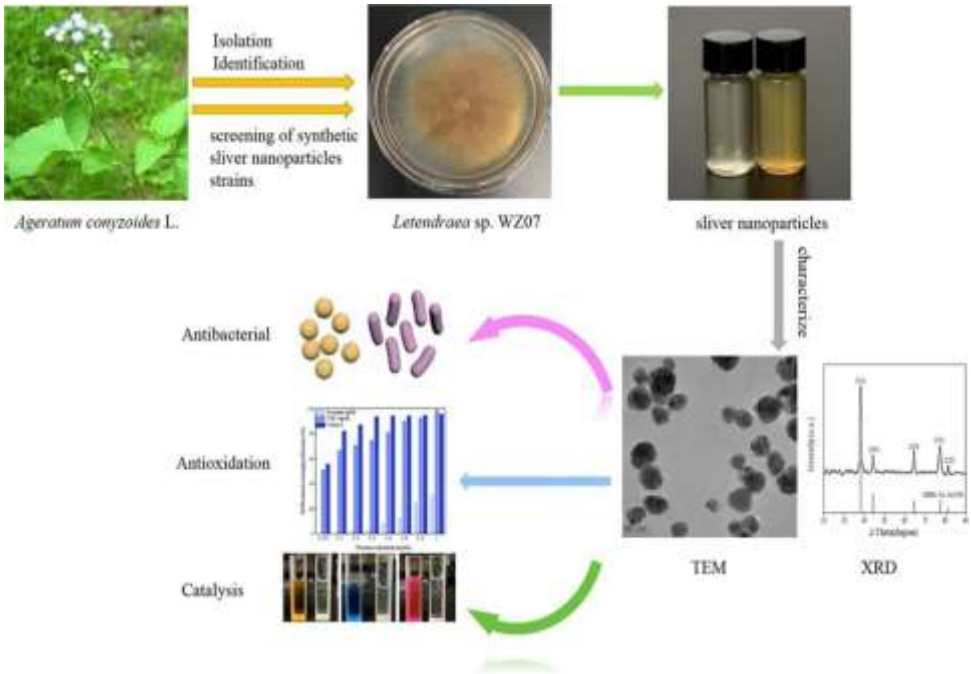
Transmission electron microscopy (TEM) analysis revealed that AgNPs formed in the cytoplasmic space, measuring about 25 ± 12 nm in diameter. Notably, the fungal cells continued to proliferate even after AgNP biosynthesis. Additionally, nitrate, commonly used by bacteria as a nitrogen source, is converted to nitrite by nitrate reductase, which utilizes reduced nicotinamide adenine dinucleotide (NADH) for this process. The role of nitrate reductase as a reducing agent is significant in the bio-reduction.



Diverse synthesis routes of silver nanoparticles. (A) Top-down and bottom-up methods. (B) Physical synthesis method. (C) Chemical synthesis method. (D) Plausible synthesis mechanisms of green chemistry

Green synthesis of silver nanoparticles from Endophytic fungus *Aspergillus niger*[61-62].

The synthesis of silver nanoparticles (AgNPs) involved mixing 5 ml of endophytic extract with 45 ml of 5 mM silver nitrate solution in an Erlenmeyer flask. The mixture was incubated at room temperature for 24 hours in the dark to facilitate nanoparticle formation. After incubation, the solution was centrifuged at 10,000 rpm for 10 minutes to separate the nanoparticles, and the supernatant was discarded. The resulting pellet was washed multiple times with double-distilled water to remove unreacted substances. The purified pellet containing the silver nanoparticles was then stored for further use.



Green synthesis of silver nanoparticles from Endophytic fungus

CYTOTOXICITY:

Cancer is an abnormal growth of cell in our bodies that can lead to death. It is one of the normal cell and creates and imbalance in the body[63]. Physical inactivity, obesity and diet are related to 30-35% of cancer deaths and some specific foods are related to the specific type of cancer like high salt diet causes gastric cancer, aflatoxin B1 cause liver cancer and chewing betel nut causes oral cancer[64].

Cancer cells have four characteristics that distinguish them from normal cell likely uncontrolled proliferation, loss of function because of lack of capacity to differentiate, invasiveness and the ability to metastasis[65].Genetic abnormalities found in cancer typically affect two general classes of genes such as oncogenes and tumor suppressor genes. Cancer promoting oncogenes are typically activated in cancer cells and change cells properties such as hyperactive growth and division, protection against programmed cell death, loss of respect for normal tissue boundaries and the ability to become established in diverse tissue environments. Tumor suppressor genes are then inactivated in cancer cells, resulting in the loss of normal functions in those cells, such as accurate DNA replication, control over the cell cycle, orientation and adhesion within tissues and interaction with protective cells of the immune system[66].

The toxicity and side-effects associated with cancer chemotherapy and radio therapy create new avenues for discovering and developing nontoxic agents for prophylaxis, mitigation and treatment of injury. One of the best approaches in searching novel anticancer agents from plant resources is selection of plants based on ethno medical practices and testing their efficacy and safety in light of modern science[67].

In the past two decades, systematic ethno botanical documentation has been prioritized in India and recent studies indicate that many plants used by herbal healers have been scientifically shown to possess antiviral, cancer preventive and of therapeutic value[68-69].

Epidemiology:

This report provides an overview of current cancer epidemiology, based on data from the World Health Organization and the American Cancer Society, including recent information on the frequency, mortality, and survival rates of the 15 most common cancers worldwide. Cancer presents the highest burden in terms of Disability-Adjusted Life Years (DALYs) across all diseases. The risk of developing cancer by age 74 is 20.2% overall (22.4% for men and 18.2% for women). In 2018, 18 million new cancer cases were reported, with lung (2.09 million), breast (2.09 million), and prostate (1.28 million) cancers being the most common. Except for sex-specific cancers, cancer incidence is higher in men than in women, with thyroid cancer as an exception (male-to-female ratio of 0.30). Cancer is currently the second leading cause of death worldwide, accounting for 8.97 million deaths, following ischemic heart disease. However, projections suggest it may become the leading cause of death by 2060, with approximately 18.63 million deaths. The deadliest cancers globally are lung, liver, and stomach cancers, while lung and breast cancers lead cancer-related deaths in men and women, respectively. Prostate and thyroid cancers have the most favorable prognoses, with 5-year survival rates near 100%. In contrast, cancers of the esophagus, liver, and pancreas have poor outcomes, with 5-year survival rates typically below 20%.[70-71]

Risk Factors[72-73]:

Evidence indicates that several lifestyle factors increase the risk of colorectal cancer (CRC), including being overweight or obese, physical inactivity, cigarette smoking, and alcohol consumption. Inappropriate dietary patterns, such as a diet low in fiber, fruits, vegetables, calcium, and dairy products, but high in red and processed meats, also elevate CRC risk. Additionally, factors such as the gut microbiome, age, gender, race, and socioeconomic status are known to influence the likelihood of developing colorectal cancer.

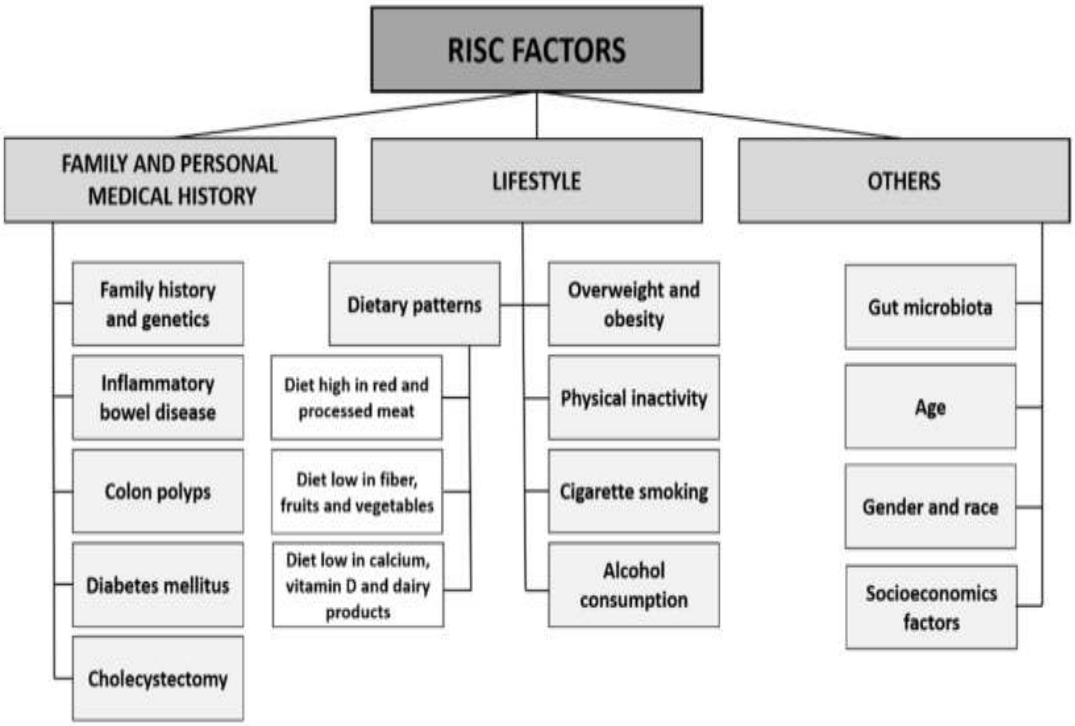
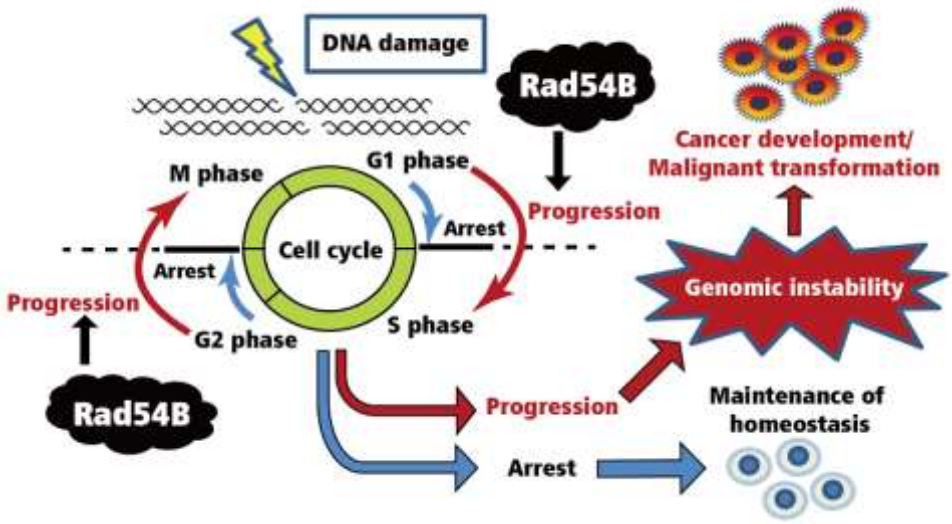


Figure No 3.7 Flow chart of risk factors in the epidemiology of cancer Development[74]



Development of Cancer cell

Regulation of the cell cycle in the DNA damage response. While mechanisms exist to arrest the cell cycle upon DNA damage, Rad54B instead inactivates the mechanism of cell cycle arrest and promotes cell cycle progression, there by enhancing survival of the cells carrying genomic instability. The survival of such cells could be the first step of cancer development or malignant transformation of tumours.

Symptoms[75]:

1. Weight loss
2. Appetite loss
3. Fatigue
4. Unusual Bleeding
5. Peeing problem

6. Coughing up blood
7. Aches or pains when breathing or coughing
8. Changes in your bowel habits
9. Unexplained lumps and changes in your breasts
10. Changes to your moies

Diagnosis[76]:

1. Radiological Diagnosis
2. Cytological Diagnosis
3. Histological Diagnosis
4. Frozen section
5. Heamtogical Diagnosis
6. Immunohistochemistry
7. Molecular Diagnosis
8. Tumour markers

Natural Drugs for Treatment of Cancer[77]:

1. *Camptothecin*: To treat a Breast cancer, Colorectal cancer.

2. *Taxol*: To treat both early-stage breast cancer and advanced breast cancer.

3. *Vinca*: To treat lung cancer.

4. *Curcumin*: To treat gastric cancer

Synthetic Drugs for Treatment of Cancer[78]:

1. Abazitaxel: Stopping growth of cancer cells.
2. Paclitaxel: To treat ovarian cancer, bladder cancer and lung cancer.
3. Docetaxel: To treat prostate cancer.
4. Eribulin: To treat breast cancer and liposarcoma.

Semi-Synthetic Drugs for Treatment of Cancer[79]:

1. Polygodial**:** To treat castration-resistant prostate cancer

2. Drimenol: To treat prostate cancer.

REFERENCES:

1. Khare E, Mishra J, Arora NK. Multifaceted interactions between endophytes and plant: developments and prospects. Front Microbiol. 2018;11;9:2732.
2. Collinge DB, Jensen B, Jørgensen HJ. Fungal endophytes in plants and their relationship to plant disease. Curr Opin in Microbiol. 2022:10;69:102.
3. Zhang Y, Yu X, Zhang W, Lang D, Zhang X. Interactions between endophytes and plants: beneficial effect of endophytes to ameliorate biotic and abiotic stresses in plants. J plant bio. 2019 Feb;62:1-3.
4. Eid AM, Salim SS, Hassan SE, Ismail MA, Fouda A. Role of endophytes in plant health and abiotic stress management. Microbiome in plant health and disease: challenges and opportunities. 2019:119-44.
5. Kumar V, Nautiyal CS. Endophytes modulate plant genes: Present status and future perspectives. Curr Microbio. 2023 Nov;80(11):353.
6. Dos Santos, T.B.; Ribas, A.F.; de Souza, S.G.H.; Budzinski, I.G.F.; Domingues, D.S. Physiological Responses to Drought, Salinity, and Heat Stress in Plants: A Review. Stresses.**2022**, *2*, 113–135.
7. Haider, S.; Raza, A.; Iqbal, J.; Shaukat, M.; Mahmood, T. Analyzing the regulatory role of heat shock transcription factors in plant heat stress tolerance: A brief appraisal. Mol. Biol. Rep. **2022**, 1–15.

8. Perrella, G.; Bäurle, I.; van Zanten, M. Epigenetic regulation of thermomorphogenesis and heat stress tolerance. New Phytol. **2022**, *234*, 1144–1160.
9. Verma H, Kumar D, Kumar V, Kumari M, Singh SK, Sharma VK, Droby S, Santoyo G, White JF, Kumar A. The potential application of endophytes in management of stress from drought and salinity in crop plants. Microorganism. 202:08:13;9(8):1729.
10. Hartley, S.E.; Eschen, R.; Horwood, J.M.; Gange, A.C.; Hill, E.M. Infection by a foliar endophyte elicits novel arabidopside-based plant defence reactions in its host, *Cirsium arvense*. New Phytol. **2015**, *205*, 816–827.
11. Tian, B.; Xie, J.; Fu, Y.; Cheng, J.; Li, B.; Chen, T.; Zhao, Y.; Gao, Z.; Yang, P.; Barbetti, M.J.; *et al*. A cosmopolitan fungal pathogen of dicots adopts an endophytic lifestyle on cereal crops and protects them from major fungal diseases. ISME J. **2020**, *14*, 3120–3135.
12. Weyens N, van der Lelie D, Taghavi S, Vangronsveld J. Phytoremediation: plant–endophyte partnerships take the challenge. Curren opinion biotechnol. 2009:4:1;20(2):248-54.
13. Kaul S, Sharma T, K. Dhar M. "Omics" tools for better understanding the plant–endophyte interactions. Front plant sci. 2016:06:29;7:955.
14. Weyens N, van der Lelie D, Taghavi S, Vangronsveld J. Phytoremediation: plant–endophyte partnerships take the challenge. Curren opinion biotechnol. 2009:04:1;20(2):248-54.
15. Saikkonen K, Wäli P, Helander M, Faeth SH. Evolution of endophyte–plant symbioses. Trend in plant sci. 2004 Jun 1;9(6):275-80.
16. Frank, A.C.; Saldierna, G.J.P.; Shay, J.E. Transmission of bacterial endophytes. Microorganisms**:**05:2017:70.
17. Toubal, S.; Bouchenak, O.; Elhaddad, D.; Yahiaoui, K.; Boumaza, S.; Arab, K. MALDI-TOF MS detection of endophytic bacteria associated with great nettle (*Urtica dioica* L.), grown in Algeria. *Pol. J. Microbiol.* 2018, *67*, 67–72.
18. Yaish, M.W.; Al-Lawati, A.; Jana, G.A.; Patankar, V.H.; Glick, B.R. Impact of soil salinity on the structure of the bacterial endophytic community identified from the roots of Caliph Medic (*Medicago truncatula*). *PLoS ONE* 2016, *11*, e0179007.
19. Le Cocq, K.; Gurr, S.J.; Hirscg, P.R.; Mauchline, T.H. Exploitation of endophytes for sustainable agricultural intensification. *Mol. Plant Pathol.* 2017, *18*, 469–473
20. Liu, H.; Carvalhais, L.C.; Crawford, M.; Singh, E.; Dennis, P.G.; Pieterse, C.M.J.; Schenk, P.M. Inner plant values: Diversity, colonization and benefits from endophytic bacteria. *Front. Microbiol.* 2017, *8*, 2552.
21. Akinsanya, M.A.; Goh, J.K.; Lim, S.P.; Ting, A.S. Metagenomics study of endophytic bacteria in *Aloe vera* using next-generation technology. *Genom.* 2015, *6*, 159–163.
22. Y. M. Lee, M. J. Kim, H. Li, P. Zhang, B. Bao, K. J. Lee and J. H. Jung, *Mar. Biotechnol.*, 2013, **15**, 499–519
23. Alam B, Lǐ J, Gě Q, Khan MA, Gōng J *et al.*, Endophytic fungi: from symbiosis to secondary metabolite communications or vice versa. Front. Plant Sci. 2021;12(1):791033.
24. Dwibedi V, Rath SK, Joshi M, Kaur R *et al.*, Microbial endophytes: application towards sustainable agriculture and food security. Appl. Microbiol. Biotechnol. 2022;106(17):5359-84.
25. Singh VK, Kumar A. Secondary metabolites from endophytic fungi: Production, methods of analysis, and diverse pharmaceutical potential. Symbiosis. 2023;90:111-25.
26. Patil RH, Patil MP, Maheshwari VL. Bioactive secondary metabolites from endophytic fungi: a review of biotechnological production and their potential applications. Studies in Nat Prod Chem. 2016;49:189-205.
27. S. S. Ebada, M. El-neketi, W. Ebrahim, A. Mándi, T. Kurtán, R. Kalscheuer, W. E. G. Müller and P. Proksch, *Phytochem. Lett.*, 2018, 24, 88–93.
28. Y.-M. Ma, X. Liang, H. Zhang and R. Liu, *J. Agric. Food Chem.*, 2016, 64, 3789–3793.
29. P. Wang, J. Yu, K. Zhu, Y. Wang, Z. Cheng, C. Jiang, J.-G. Dai, J. Wu and H. Zhang, *Fitoterapia*, 2018, **127**, 322–327.
30. R. A. Kamel, A. S. Abdel-razek, A. Hamed, R. Reham, H. G. Stammler, M. Frese, N. Sewald, R. Ibrahim, H. G. Stammler, M. Frese, N. Sewald and M. Shaaban, *Nat. Prod. Res.*, 2018, 34, 1080–1090
31. Rashad YM, Al Tami MS, Abdalla SA. Eliciting transcriptomic and antioxidant defensive responses against *Rhizoctonia* root rot of sorghum using the endophyte Aspergillus oryzae YRA3. Scientific Reports. 2023:11:14;13(1):19823.
32. El-Sayed AS, Khalaf SA, Azez HA, Hussein HA, EL-Moslamy SH, Sitohy B, El-Baz AF. Production, bioprocess optimization and anticancer activity of Camptothecin from *Aspergillus terreus* and *Aspergillus flavus*, endophytes of *Ficus elastica*. Process Biochem. 202:08:1;107:59-73.

33. Klich, M.A. *Aspergillus flavus*: The major producer of aflatoxin. *Mol. Plant Pathol.* 2007, *8*, 713–722.

34. Krishnan, S.; Manavathu, E.K.; Chandrasekar, P.H. *Aspergillus flavus*: An emerging non-*fumigatus Aspergillus* species of significance. *Mycoses* 2009, *52*, 206–222.

35. Rudramurthy, S.M.; Paul, R.A.; Chakrabarti, A.; Mouton, J.W.; Meis, J.F. Invasive *aspergillosis* by *Aspergillus flavus*: Epidemiology, diagnosis, antifungal resistance, and management. *J. Fungi* 2019, *5*, 55.

36. Park, H.-S.; Jun, S.-C.; Han, K.-H.; Hong, S.-B.; Yu, J.-H. Diversity, application, and synthetic biology of industrially important *Aspergillus* fungi. *Adv. Appl. Microbiol.* 2017, *100*, 161–202.

37. Jin, F.-J.; Hu, S.; Wang, B.-T.; Jin, L. Advances in genetic engineering technology and its application in the industrial fungus *Aspergillus oryzae*. *Front. Microbiol.* 2021, *12*.

38. Kobayashi, T.; Abe, K.; Asai, K.; Gomi, K.; Juvvadi, P.R.; Kato, M.; Kitamoto, K.; Takeuchi, M.; Machida, M. Genomics of *Aspergillus oryzae*. *Biosci. Biotechnol. Biochem.* 2007, *71*, 646–670.]

39. Batomunkueva, B.P.; Egorov, N.S. Preparations of extracellular proteinases from *Aspergillus ochraceus* 513 and *Aspergillus allíaceus* 7dN1. *Mikrobiologiia*. 2002, *71*, 56–58.

40. Varga, J.; Frisvad, J.; Samson, R. Two new aflatoxin producing species, and an overview of *Aspergillus* section Flavi. *Stud. Mycol.* 2011, *69*, 57–80.

41. Bennett, J.W. An Overview of the Genus Aspergillus. In *The Aspergillus*; Molecular Biology and Genomics; CRC Press: Boca Raton, FL, USA, 2010;1–17.

42. Adams, T.H.; Wieser, J.K.; Yu, J.-H. Asexual sporulation in *Aspergillus nidulans*. *Microbiol. Mol. Biol. Rev.* 1998, *62*, 35–54.

43. Y. Ma, C. Ma, T. Li and J. Wang, *Nat. Prod. Res.*, 2016, 30, 79–84

44. Ovais M, Zia N, Ahmad I, Khalil AT *et al*., Phyto-Therapeutic and nanomedicinal approaches to cure alzheimer's disease: Present Status and Future Opportunities. Front Aging Neuro sci. 2018;10(1):284.

45. Shah A, Lutfullah G, Ahmad K, Khalil AT *et al.,. Daphne mucronata*-mediated phytosynthesis of silver nanoparticles and their novel biological applications, compatibility and toxicity studies. Green Chem Lett Rev 2018;11(3):318–33.

46. Rahman S, Rahman L, Khalil AT, Ali N *et al.,*. Endophyte-mediated synthesis of silver nanoparticles and their biological applications. Appl Microbiol Biotechnol. 2019;103(6):2551-69.

47. Blanco, E.; Shen, H.; Ferrari, M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nat. Biotechnol. 2015; 33(1):941−951

48. Shah, M.; Fawcett, D.; Sharma, S.; Tripathy, S. K.; Poinern, G *et al*., Green synthesis of metallic nanoparticles via biological entities. Materials. 2015;8:7278−08

49. Rauhah Ridzuan, A.; Ibrahim, S.; Karman, S.; Ab Karim, M. S *et al*., C.C.Study on electrical conductivity of graphene oxide decorated with silver nanoparticle for Electrochemical Sensor Development. Int. J. Electrochem. Sci. 2021;16:2105-57.

50. Yaqoob, A. A.; Ahmad, H.; Parveen, T.; Ahmad, A *et al*., Recent advances in metal decorated nanomaterials and their various biological applications: a review. Front. Chem. 2020;8(1):341.

51. Sim W, Barnard RT, Blaskovich MAT, Ziora ZM. Antimicrobial Silver in Medicinal and Consumer Applications: A Patent Review of the Past Decade. Antibiotics (*Basel*). 2018;10(1):7-93.

52. Sulaiman, G.; Ali, E.; Jabbar, I.; Saleem, A. Synthesis, characterization, antibacterial and cytotoxic effects of silver nanoparticles. Dig J Nanomater Biostruct. 2014;9(1):787−96.

53. Ghosh S, Ahmad R, Zeyaullah M, Khare SK. Microbial nano-factories: synthesis and biomedical applications. Front. Chem. 2021;9(1):62.

54. Evanoff DD, Chumanov G. Size-controlled synthesis of nanoparticles. 1.Silver-only aqueous suspensions via hydrogen reduction. J. Phys. Chem. B. 2004;108(1):13948-56.

55. Li B, Ye S, Stewart IE, Alvarez S, Wiley BJ. Synthesis and purification of silver nanowires to make conducting films with a transmittance of 99%. Nano letters. 2015;15(10):6722-6.

56. Nagajyothi PC, Lee KD. Synthesis of plant-mediated silver nanoparticles using Dioscorea batatas rhizome extract and evaluation of their antimicrobial activities. J. Nanometer. 2011;2(3):1-7.

57. Jamkhande PG, Ghule NW, Bamer AH, Kalaskar MG. Metal nanoparticles synthesis: An overview on methods of preparation, advantages and disadvantages, and applications. J. Drug Deliv. Technol. 2019;53(1):10.

58. Abdussalam-Mohammed W. Comparison of chemical and biological properties of metal nanoparticles (Au, Ag) with metal oxide nanoparticles (ZnO-NPs) and their applications. Adv J Chem Sect A. 2020;3(2):111-236.

59. Wang L, Hasanzadeh Kafshgari M, Meunier M. Optical properties and applications of plasmonic-metal nanoparticles. Adv. Funct. Mater. 2020;30(51):2005.

60. Pryshchepa O, Pomastowski P, Buszewski B. Silver nanoparticles: Synthesis, investigation techniques, and properties. Adv. Colloid Interface Sci. 2020;284(1):10.

61. Almatroudi A. Silver nanoparticles: Synthesis, characterisation and biomedical applications. Open life sci. 2020;15(1):819-39.

62. Naganthran A, Verasoundarapandian G, Khalid FE, Masarudin MJ *et al.,* .Synthesis, characterization and biomedical application of silver nanoparticles. Materials. 2022;15(2):427.

63. Hemashekhar B, Chandrappa CP, Govindappa M, Chandrasekhar N *et al.*,.Green synthesis of silver nanoparticles from Endophytic fungus *Aspergillus niger* isolated from *Simarouba glauca* leaf and its Antibacterial and Antioxidant activity. Inter J Eng Res Appl. 2017;7(8):17-24.

64. Parmar S, Sharma VK. Endophytic fungi mediated biofabrication of nanoparticles and their potential applications. In Microbial endophytes 2020 Jan 1 (pp. 325-341). Wood head Publishing.

65. Biesalski HK, Bueno de Mesquita B, Chesson A, Chytil F *et al*., European Consensus Statement on Lung Cancer: risk factors and prevention. Lung Cancer Panel. CA Cancer J Clin. 1998;48(2):167-76.

66. Kuper H, Adami HO, Boffetta P. Tobacco use, cancer causation and public health impact. J Intern Med. 2002;251(1):455-66.

67. Strobel G, Daisy B. Bioprospecting for microbial endophytes and their natural products. Microbiol Mol Biol Rev. 2003;67(1):491-502.

68. Prabhune M, Belge G, Dotzauer A, Bullerdiek J *et al*.,. Comparison of mechanical properties of normal and malignant thyroid cells. Micron. 2012;43(1):1267-72.

69. Berti M, Cortez D, Lopes M. The plasticity of DNA replication forks in response to clinically relevant genotoxic stress. Nat Rev Mol Cell Biol. 2020;21(1):633-51.

70. Fu B, Wang N, Tan HY, Li S *et al.*,. Multi-component herbal products in the prevention and treatment of chemotherapy-associated toxicity and side effects: a review on experimental and clinical evidences. Front Pharmacol. 2018;9(1):1394.

71. Bray F, Colombet M, Mery L, Piñeros M *et al.*,. Cancer Incidence in Five Continents Volume XI: Cancer Today. IARC Sci Pub. 2021;2(1);122.

72. Wong MC, Huang J, Lok V, Wang J *et al.*,. Differences in incidence and mortality trends of colorectal cancer worldwide based on sex, age, and anatomic location. Clinical Gastroenterology and Hepatology. 2021;19(5):955-6

73. Argirova R, Zlatareva A. Lifelong vaccination model: for a better quality of life. Biotechnol. Biotechnol. Equip. 2023 Dec 31;37(1):24-33.

74. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. Immunity. 2004;21(2):137-48.

75. Amersi, F.; Agustin, M.; Ko, C.Y. Colorectal cancer: Epidemiology, risk factors, and health services. *Clin. Colon. Rectal. Surg.* 2005;18:133–140.

76. Win, A.K.; Macinnis, R.J.; Hopper, J.L.; Jenkins, M.A. Risk prediction models for colorectal cancer: A review. *Cancer Epidemiol. Biomark.*2012;2(1)1:398–410.

77. Matthews HK, Bertoli C, de Bruin RA. Cell cycle control in cancer. Nat. Rev. Mol. Cell Bio. 2022;23(1):74-88.

78. Damhus CS, Siersma V, Dalton SO, Brodersen J. Non-specific symptoms and signs of cancer: different organisations of a cancer patient pathway in Denmark. Scand. J. Prim. Health care. 2021;39(1):23-30.

79. Shrestha A, Martin C, Burton M, Walters S *et al.*,. Quality of life versus length of life considerations in cancer patients: a systematic literature review. J.Psycho-oncol. 2019;28(7):1367-80.

80. Huang M, Lu JJ, Ding J. Natural products in cancer therapy: Past, present and future. Nat. Prod. Bioprospect. 2021;11(1):5-13.

81. Sharifi-Rad J, Ozleyen A, Boyunegmez Tumer T, Oluwaseun Adetunji *et al.,*. Natural products and synthetic analogs as a source of antitumor drugs. Biomolecules. 2019;9(11):679.

82. Beckmann L, Tretbar US, Kitte R, Tretbar M. Anticancer activity of natural and semi-synthetic drimane and coloratane sesquiterpenoids. Molecules. 2022;27(8):2501.