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Therapeutic approaches of silver nanoparticles against pancreatic cancer

Aarti Sharma[1], Largee Biswas[2], Annu[1], Dishu[1], Simran Bhati[1], Aakash Mathur[3]* & Disha Mittal[1]*

[1]Department of Life Sciences, School of Biosciences and Technology; & [3]School of Basic Sciences, Galgotias University, Greater Noida-203 201, Uttar Pradesh, India

[2]Nanobiotech lab, Department of Zoology, Kirori Mal college, University of Delhi- 110 007, Delhi, India

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Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive malignancy, and conventional therapeutic approaches have not produced substantial clinical advantages, with invasive surgery being the sole curative option for patients in the early stages of the illness. It is among the most aggressive and lethal carcinomas, with a five-year survival rate of fewer than 11%. Despite advances in traditional therapies including surgery, chemotherapy, and radiation, the likelihood of survival is still poor due to late-stage detection, extensive stromal barriers, and intrinsic chemoresistance. The recent development in nanotechnology has opened new opportunities for targeted therapy, with silver nanoparticles (AgNPs) showing considerable potential due to their unique physicochemical properties, such as high surface reactivity, localized surface plasmon resonance (LSPR), and ability to penetrate tumour microenvironments. This review investigates AgNPs synthesis approaches, with an emphasis on chemical and green approaches. Green synthesis, which uses plant and algae extracts, provides a sustainable, biocompatible, and environmentally friendly alternative with increased therapeutic value. AgNPs' biological efficacy against PDAC is demonstrated via many molecular routes. AgNPs also show potential as drug carriers for targeted delivery, combating multidrug resistance, and improving the efficacy of traditional medicines through synergistic action. AgNPs shows cytotoxic effects on pancreatic cancer via various mechanism including paraptosis, autophagy and apoptosis. This review consolidates our understanding of AgNPs-mediated therapeutic processes and emphasizes their translational promise in addressing the challenges of current pancreatic cancer treatments. Future research should focus on refining AgNPs design for clinical safety, effectiveness, and targeted administration, opening the path for nanomedicine-based pancreatic cancer treatments.

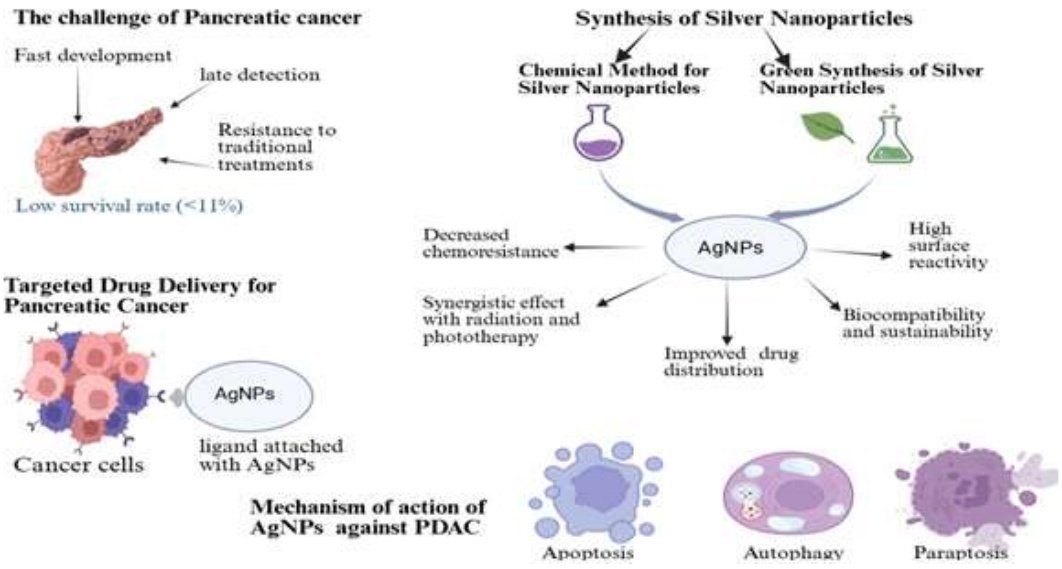
Keywords: Apoptosis, Green synthesis, Nanoparticles, PDAC

Pancreatic cancer (PC) is still one of the most aggressive and fatal cancers, with a 5-year survival rate of less than 11% despite breakthroughs in medical oncology and surgical therapies. It accounts for around 3% of all cancers and 7% of all cancer deaths, making it globally the seventh highest cause of cancer-related mortality. The most prevalent histological subtype is pancreatic ductal adenocarcinoma (PDAC), which is distinguished by fast development, late detection, and resistance to traditional treatments such chemotherapy and radiation[1].

This disease has a poor prognosis because of its aggressive local growth and early systemic spread. Only 10–15% of individuals present with local disease, whereas 25–30% present with regional illness and about 50–60% present with distant metastatic disease. The tumour's resectability determines the course of treatment and prognosis for individuals with local or regional illness. According to studies incomplete resection is known to have a negative impact on survival, approaching those who arrive with metastatic illness[2].

The strikingly high mortality in this disease can be attributed to several clinical features: characteristically late diagnosis, broad resistance to targeted and cytotoxic therapies, and aggressive metastasis. Clinical symptoms preceding PDAC are often vague, and a vast majority of patients will be diagnosed with treatment-refractory systemic disease that is ineligible for surgical resection, still considered the only potentially curative therapy. Together, these factors contribute to a 5-year survival rate of only 13%[3]. Although this number demonstrates the significant challenges that remain to improve patient outcomes, it also signifies the progress made in the past two decades to bring the 5-year survival rate up from below 7%. The high mortality and aggressive nature of PC can be largely ascribed to (a) diagnostic deficiencies, (b) chronic inflammation, (c) desmoplastic stroma, (d) early metastasis, (e) KRAS signalling, (f) metabolism, and (g) rapid deconditioning[4].

*Correspondence:
E-mail: dishamittal90@gmail.com (DM);
aakash1288@gmail.com (AM)



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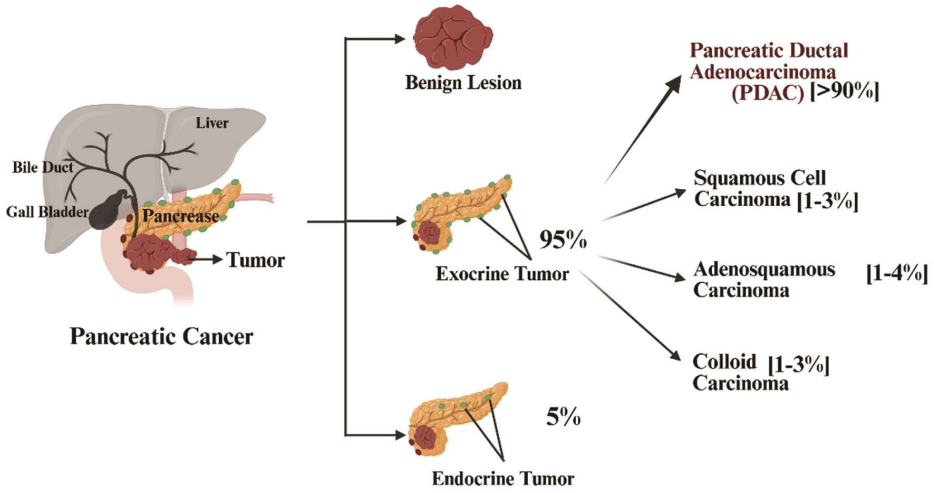

Fig. 1 — Classification of pancreatic cancer based on tumor origin and their characteristics

The integration of nanotechnology into oncology initially focused on improving drug delivery systems by utilizing nanoparticles (NP) to enhance the solubility, stability, and bioavailability of chemotherapeutic agents. However, the scope of nanotechnology has since expanded. The development of multifunctional nanoparticles now enables precise targeting of tumors, efficient drug delivery[5]. AgNPs have unique physicochemical properties, including a high surface area-to-volume ratio, which enables efficient interaction with biological systems, such as cancer cells, enhancing their therapeutic and diagnostic potential in biomedical applications. AgNPs can be passively targeted to tumor cells by leveraging the EPR effect or through surface functionalization and bioconjugation, leading to their accumulation at the tumor site and enabling anticancer activity[6]. This review seeks to investigate the manufacture, characteristics, and cytotoxicity mechanism of AgNPs against PC (Fig. 1).

Conventional therapy for pancreatic cancer

PC is often treated with radiation therapy, chemotherapy, surgery, and, in certain situations, targeted treatments. However, the therapeutic landscape remains difficult because to late-stage detection, aggressive tumour biology, and therapy resistance.

Table 1 — Various Chemotherapeutic Drugs against pancreatic cancer with their mode of action

S. No.	Drug	Study Model	Mode of Action	References
1	Gemcitabine	Clinical trials, *in vitro*, animal models	Inhibition of DNA synthesis	10,11
2	5-Fluorouracil (5-FU)	Clinical trials, animal models	Inhibits Translation and Transcription by downregulating thymidylate synthase	12,13
3	Oxaliplatin	Clinical trials, *in vitro*, animal models	Forms platinum-DNA adducts, leading to DNA cross-linking, leading to inhibition of DNA replication	15
4	Irinotecan	Clinical trials, *in vitro*, animal models	Inhibits topoisomerase I, causing DNA strand breaks, leading to cell death.	11,14
5	Nab-Paclitaxel	Clinical trials, animal models	Inhibits microtubule depolymerization, disrupting mitotic spindle formation, and inducing cell cycle arrest.	11
6	Capecitabine	Clinical trials, *in vitro*, animal models	Prodrug of 5-FU, metabolized to 5-FU in the tumour, inhibiting thymidylate synthase.	10,12
7	Erlotinib	Clinical trials, *in vitro*	Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, blocking cell signalling pathways involved in cancer cell proliferation.	13
8	Paclitaxel	Clinical trials, *in vitro*, animal models	Stabilizes microtubules, inhibiting cell division and promoting apoptosis.	13,14
9	Cisplatin	Clinical trials, *in vitro*, animal models	Forms DNA adducts, causing cross-links and inhibiting DNA replication, leading to apoptosis.	16

Surgery is now the only possibly curative therapy, however about 15-20% of individuals are eligible for resection when they are diagnosed. Surgical resection is still the only potentially effective procedure for pancreatic cancer, though only a small number of patients are eligible due to the disease's advanced phase on diagnosis. PC is frequently discovered at a late stage, after metastasis or vascular involvement has occurred, making curative treatment difficult. Surgery provides the highest chance of long-term survival for the 15–20% of patients with pancreatic cancer who have resectable tumors[7].

The Whipple technique (pancreaticoduodenectomy) is the most often used surgical method for pancreatic head tumors. The pancreatic head, duodenum, gallbladder, and a portion of the bile duct are all removed, and the digestive system is then reconstructed. A distal pancreatectomy, which involves the removal of the distal section of the pancreas and frequently the spleen, may be done for malignancies found in the pancreas' body or tail. Despite the possibility of therapeutic outcomes, pancreatic surgery is linked with high morbidity and mortality. Recent improvements in surgical methods, such as minimally invasive approaches and robot-assisted surgery, have sought to mitigate the dangers associated with these treatments. Research has indicated that, in comparison to open surgery, robotic pancreas surgery may have benefits in terms of shorter recovery times, less blood loss, and fewer problems[9].

Chemotherapy is still the primary mode of systemic treatment for pancreatic cancer, particularly when surgical resection is not practical because of the disease's advanced stage or the prognosis. Gemcitabine, fluorouracil (5-FU), oxaliplatin, and irinotecan are the principal chemotherapy drugs used in PC, either alone or in combination (Table 1). Pancreatic cancer patients continue to have a dismal prognosis despite increases in survival with combination therapy, mostly because to the disease's aggressiveness and the emergence of chemoresistance[10]. The accepted treatment for advanced PC has traditionally been gemcitabine. It was authorized because it improved overall survival relative to optimal supportive care, with a median survival of around 6 months[11]. However, gemcitabine monotherapy frequently produces very moderate outcomes, and medication resistance is widespread. To overcome these limitations, combination regimens have been investigated, including FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin). Conroy *et al.*'s pivotal phase III study found that FOLFIRINOX significantly increased survival compared to gemcitabine alone, with a median overall survival of 11.1 months against 6.8 months, particularly in patients with good functional status[12].

According to Basu *et al.*, this combination medication may not be suitable for older or weak patients due to its increased rates of toxicity, which include neutropenia, tiredness, and gastrointestinal disorders[13]. Another frequent combination is gemcitabine + nab-paclitaxel, which was demonstrated in the MPACT trial to increase

the median lifespan from 6.7 months to 8.5 months when compared with gemcitabine alone[14].

In the treatment of PC, radiation therapy (RT) is essential, especially for individuals whose illness is locally progressed or just marginally curable. Radiation treatment is frequently used as an adjuvant to lower tumour burden, enhance local control, and increase the likelihood of effective resection in patients who are not candidates for surgery, even if surgery is still the only potentially curative option. The role of radiation in PC treatment is evolving, as is the use of SBRT (stereotactic body radiation therapy), thanks to developments in motion management, target definition, treatment planning, and imaging guiding. These methods have advanced ablative radiation therapy and dosage escalation with better quality of life, tolerable toxicity, and local control. RT is anticipated to become even more essential when new systemic medicines are produced and there is a greater emphasis on local disease management. SBRT's suitable function and interaction with systemic treatment and surgery are currently being investigated[17]. Conventional therapy has substantial limits due to the disease's aggressiveness and the development of drug resistance. Drugs used in chemotherapy such as gemcitabine and FOLFIRINOX frequently produce very minor survival improvements, with resistance resulting from the thick stromal barrier, altered drug metabolism, and genetic alterations such as KRAS. Furthermore, radiation treatment suffers from poor tumour response because of the tumour's hypoxic microenvironment and the surrounding desmoplastic stroma. These issues add to the overall dismal prognosis and highlight the need for more effective, tailored therapy.

Synthesis of silver nanoparticles

Chemical method for silver nanoparticles

The most popular technique for synthesizing AgNPs is chemical reduction, which uses both organic and inorganic reducing agents. Silver ions can be efficiently reduced to metallic silver, which subsequently aggregates into NP, using common chemicals such as ascorbate, sodium citrate, sodium borohydride, and elemental hydrogen. Trisodium citrate and sodium borohydride serve as reducing and stabilizing agents in $AgNO_3$, which is commonly used as a silver source. This results in NP of different sizes, ranging from 60 to 100 nm and 5 to 20 nm, respectively. Other mixtures, like polyvinyl alcohol and hydrazine hydrate, have also worked well for creating spherical AgNPs[18]. They have some disadvantages, too, such as high expenses, hazardous chemicals, and trouble managing particle size.

AgNPs produced with tannic acid (TA) as a stabilizing and reducing agent are investigated kinetically and thermodynamically. Using spectro-photometric monitoring of reaction kinetics at 410 nm, the study investigates the effects of concentrations of sodium hydroxide, tannic acid, and silver nitrate on the production and development of NPs. A pseudo-first-order reaction mechanism with a stiff activated complex was suggested using thermodynamic characteristics. The process is easy to use, economical, safe for the environment, and appropriate for producing AgNPs on a big scale for possible industrial and biomedical uses[19]. To synthesize AgNPs with antibacterial and antioxidant properties, cellulosic polymers were used as effective reducing, coating, and stabilizing agents. Here, cellulosic polymers such as hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), and ethylcellulose (EC) were used to create AgNPs. Several polymeric materials were successfully used to create AgNPs with a variety of hues[20] (Table 2).

Green synthesis of silver nanoparticles

Plant extracts from bark, stems, roots, leaves, flowers, oil, fruit peels, seeds, seaweed, and citrus lemon zest are employed in all biological methods, as are microorganisms like bacteria, yeast, and fungi. The production of AgNPs using biomolecules is a pollution-free and environmentally beneficial process. By employing plant extracts or bacterial proteins as reducing agents, we could control the size, shape, and monodispersed nature of the NPs. The availability of a wide range of natural resources, a shorter time need, high density, and stability are further advantages of biological processes. The use of green chemistry meets the need for organic compounds, such as glycosides, alkaloids, tannins, phenols, terpenoids, flavonoids, or coumarin, to cover the surfaces of the NP. Three requirements must be met to maintain the value of green synthesized NPs: (i) Selecting solvent systems that are good for the environment; (ii) Using a sustainable reducing agent; and (iii) Using a suitable capping agent to stabilize NPs. Natural reducing and capping agents are employed in the biological process to create NPs without producing any hazardous byproducts[21]. Biomolecules act as reducing agents, converting Ag^+ to neutral Ag^0 by donating electrons and releasing hydrogen, acidifying the medium. These biomolecules then partially cover Ag^0, serving as capping agents. Thus, in green synthesis of AgNPs, biomolecules function both as reducers and cappers.

Table 2 — Green Synthesis of Silver Nanoparticles along with its characteristics and applications

Source Type	Biological Source	Role in Synthesis	AgNP Characteristics	Applications	References
Plant Extract	*Aconitum violaceum*	Reducing and capping agent	Spherical and triangular; <100 nm	Antibacterial, antioxidant, photocatalytic	32
Plant Extract	*Debregeasia salicifolia*	Reducing and stabilizing agent	Spherical; confirmed by UV-Vis, XRD, FTIR	Antibacterial, antioxidant, biomedical	33
Plant Extract	*Uvaria narum*	Reducing and capping agent	Spherical; confirmed by UV-Vis, XRD, FTIR	Antibacterial, anticancer, catalytic	34
Plant Extract	*Curcuma longa*	Reducing and capping agent	~5 nm; UV-Vis, XRD, HR-TEM	Antibacterial	35
Plant Extract	*Vernonia amygdalina*	Reducing and capping agent	SPR peaks 411–430 nm; UV-Vis, XRD	Antimicrobial	36
Fungal Isolate	*Fusarium nygamai* (AJTYC1)	Extracellular enzymes and metabolites	27.3–53.1 nm; UV-Vis, TEM, XRD, FTIR	Antioxidant, antimicrobial, cytogenetic	37
Fungal Isolate	Alternaria carthami (KUMBMDBT-30)	Reducing and capping agent	~97.15 nm; FTIR, SEM-EDAX, XRD, DLS	Biomedical	38
Fungal Isolate	*Phyllosticta owaniana*	Extracellular enzymes and metabolites	Spherical; UV-Vis, FTIR, SEM, TEM	Biomedical	39

Green synthesis of silver nanoparticles with algae

Algae are used primarily because of their high metal-absorbing and metal-ion-reducing capacity, somewhat inexpensive production costs, and above all their large-scale NP production capabilities. Their superior resistance to adverse climatic conditions over other microbes is another intriguing characteristic. The term "bionanofactories" refers to the ability to use both live and dead dry biomass of algae to produce NPs. Among the bioactive substances present in green algae are proteins, lipids, carbohydrates, carotenoids, vitamins, and secondary metabolites (terpenoids, phenols, flavonoids, and alkaloids), which stabilize the produced NPs by acting as a reductant and a capping agent[23]. In the extracellular pathway, a metal ion is bio-reduced to its NP on the algal cell surface; in the intracellular process, however, the bio-reduction via enzymatic activity takes place inside the cell wall and cell membrane. In one study, an aqueous extract of *Asterarcys* (a type of microalgae) was employed for the green synthesis of AgNPs through the biological reduction of silver nitrate ($AgNO_3$) under optimized conditions[24]. In another study, by measuring absorbance at 436 nm on the UV–Vis spectrum, the production of AgNPs from the dried biomass of *Chlorella ellipsoidea* was verified. The produced AgNPs are primarily crystalline and spherical in form. AgNPs had an average size of 220.8 ± 31.3 nm and a polydispersity index of 0.408[25].

Plants mediated green synthesis of silver nanoparticles

The potential of therapeutic plants among the biological sources has been particularly encouraging. It is preferable for plants to synthesize AgNPs rather than microbes. Additionally, the increased potential ability of plant extracts to synthesize NPs with better qualities is responsible for the decrease properties of secondary metabolites of plants. The reduction of Ag ions, nucleation of reduced atoms, and subsequent development and stability of NPs are the three main stages of the green synthesis of AgNPs utilizing plant extracts[26]. Silver ions receive electrons from the bioactive substances in medicinal plants, which reduces them to elemental silver. These biomolecules cap the NPs at the same time, improving stability and avoiding agglomeration. The production of AgNPs from plant extracts is demonstrated in (Fig. 2).

In a recent research, aqueous fruit extracts from *Scabiosa atropurpurea* subsp. *maritima* (L.) was used to synthesize AgNPs[27]. According to the AgNPs characterization using FTIR (Fourier Transform Infrared Spectroscopy), TEM (Transmission Electron Microscopy), XRD (X-Ray Diffraction), and UV–Vis (Ultraviolet–Visible Spectroscopy), they were uniformly spherical in shape and had average diameters between 40 nm and 50 nm. Phenolic compounds and flavonoids, the most significant phytochemicals linked to the redox potential and responsible for the antioxidant capacity[28].

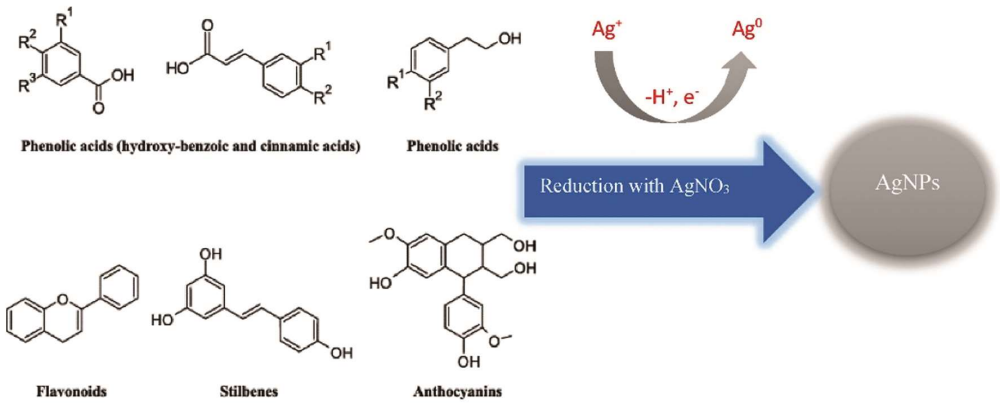

Fig. 2 — Overview of green synthesis of AgNP from plant extracts which exhibits the role of phytochemicals as reducing agent for converting AgNO3 to AgNP

Factors affecting the synthesis of AgNPs

The size and shape of AgNPs are significantly influenced by temperature,smaller and more spherical AgNPs are generally produced at higher temperatures. On the other hand, larger NPs are typically produced at lower temperatures. Kredy *et al.* also discovered that high temperatures cause the formation of tiny AgNPs. It's interesting to note that even at 40°C, *Vitex agnus-castus* leaf extract may lower Ag^+. However, the 60-80°C range was where AgNP synthesis was most effective. In general, low temperatures promote the formation of NPs, whereas high temperatures favor nucleation[29].

According to a studies pH has a critical role in regulating the stability, size, and form of AgNPs. The pH 7 is ideal for reducing Ag^+ to Ag^0, and pH 7–9 is ideal for synthesizing the most NPs. Higher pH levels have been shown in numerous investigations to accelerate the formation of AgNP. AgNPs are more spherical at alkaline pH values, and pH 8 significantly accelerates the rate of reaction. High NP yield and stability are also guaranteed by alkaline conditions[30]. Furthermore, by incorporating additional OH groups from plant extracts, a basic pH improves the reduction process. These OH groups are important stabilizing and reducing agents. The size, stability, and yield of produced AgNPs are all significantly influenced by the incubation period. AgNPs quickly generated using *Ananas comosus* extract in less than two minutes, yielding spherical NP (~12 nm). In a different investigation, *Ocimum sanctum* extract produced stable AgNPs (~17 nm), and after 15 minutes, production increased steadily. Likewise, an extract from *Origanum vulgare* shown that the yield of NPs increased with incubation time up to three hours[31]. Successful NP synthesis was indicated by color shifts from yellow to brown, which were correlated with longer reaction times and higher concentrations of NPs.

Properties of silver nanoparticles

The size and shape of AgNPs significantly influence their physicochemical and functional properties. Typically, AgNPs range in diameter from 1 nm to 100 nm, with shapes including spheres, rods, cubes, and triangular plates. The geometry directly affects their interaction with biological and environmental systems as well as their catalytic and optical behaviour. For example, spherical NP generally exhibit more uniform properties, while anisotropic shapes such as triangular or rod-like structures display multiple plasmonic modes and enhanced surface activity[40]. Moreover, the aspect ratio and edge sharpness of NPs have been shown to modulate their electromagnetic field distribution, which is critical for applications like sensing and photothermal therapy[41].

Surface charge, usually quantified as zeta potential, determines the colloidal stability and interaction of AgNPs with their surroundings. A highly positive or negative zeta potential (typically above ±30 mV) contributes to greater electrostatic repulsion among particles, thus enhancing their dispersion stability in suspension. It also influences cellular uptake and toxicity profiles[40]. Additionally, AgNPs exhibit strong optical absorption due to localized surface plasmon resonance (LSPR), typically observed between 400 nm and 450 nm, depending on particle size and shape. Variations in NP dimensions or the surrounding dielectric environment can induce red or blue shifts in the LSPR peak, allowing fine-tuning of their optical properties for applications in biosensing and imaging[42].

Table 3 — Role of Silver Nanoparticles in Different Cancers and their Mechanisms of action

S. No.	Role	Action Mechanism	Cancer Model	References
1	Improving Radiation Outcomes	By promoting the creation of oxidative compounds in tumor tissues, silver nanoparticles exacerbate the effects of radiation and cause cellular damage.	Brain tumours in rodent models	[52]
2	Enhancing Heat-Based Treatments	Upon light exposure, AgNPs generate localized heat that selectively targets and destroys malignant cells while sparing surrounding healthy tissue.	Melanoma in mice	[52]
3	Vehicle for Drug Transport	By assisting in the precise delivery of cancer medications to tumor areas, silver nanoparticles improve therapy efficacy while reducing damage to healthy cells.	Breast cancer (MCF-7 cell line)	[52]
4	Triggering Programmed Cell Death	AgNPs affect mitochondrial pathways, which causes malignant cells to undergo controlled death, or apoptosis.	Colon cancer (HCT116 cell line)	[53]
5	Blocking Tumour Vascularization	The tumor's growth is hindered by AgNP, which limit its availability to nutrients and prevent the growth of blood vessels that nourish it.	In vivo tumor models	[54]
6	Reversing Drug Resistance	AgNPs disrupt the functioning of drug-resistance systems, increasing the effectiveness of conventional chemotherapy drugs.	Lung cancer (A549 resistant cells)	[53]
7	Trigerring cell death	AgNPs upregulated the levels of p53 and also caused DNA fragmentation leading to cell death.	Human Breast cancer cells (MCF-7)	[26]

Role of silver nanoparticles in cancer

Nanotechnology has revolutionized cancer treatment by overcoming the limitations of conventional treatments like chemotherapy and radiation. AgNPs are a relatively new class of metal NPs that hold great promise for the study of cancer biology. NP therapies are promising avenues for therapeutically relevant drug development because of their cancer-specific targeting, reduced side effects, and powerful anti-cancer activities (Table 3). In addition, the physical-chemical characteristics and bioactivity that is highly dependent on particle size, shape, stabilizer, and production methodof AgNPs are attracting more interest in the field of cancer research[43]. Furthermore, present anticancer medications and cancer therapy combinations may benefit from the use of NPs to improve their pharmacokinetic and pharmacodynamic qualities[44].

Targeted drug delivery for cancer

There is a lot of interest in using AgNPs to treat cancer because of their special physicochemical characteristics and potential for targeted drug delivery. In cancer treatment, active targeting involves modifying drug delivery vehicles, such NP, with ligands that bind to receptors that are overexpressed on cancer cells. This approach reduces harm to healthy tissues while increasing treatment accuracy and efficacy[47]. To specifically identify and attach to receptors or antigens that are overexpressed on cancer cells, NP are combined with ligands (such as antibodies, peptides, or small molecules). This binding enhances intracellular drug delivery by facilitating receptor-mediated endocytosis[48]. The unique properties of tumour vasculature are exploited by passive targeting to enhance drugs delivery. AgNPs concentrate in tumour tissues through the Enhanced Permeability and Retention (EPR) effect, which is caused by leaky blood arteries and insufficient lymphatic drainage, which allow nanoparticles to enter and remain in the tumour microenvironment[49].

Controlled and sustained release

AgNPs can be used to encapsulate drugs for chemotherapy, reducing the frequency of dosing and associated adverse effects while maintaining therapeutic drug levels for prolonged periods of time. AgNPs can be functionalized with biocompatible polymers, such as polyethylene glycol (PEG), to increase their stability and drug loading capacities[49]. Nonetheless, the potential toxicity of AgNPs to healthy tissues necessitates careful consideration of their design and application. Studies have shown that AgNPs have dose-dependent cytotoxic effects that vary with particle size and surface chemistry. AgNPs penetrate cells and release silver ions, resulting in cell damage and apoptosis. This procedure is referred to as the "Trojan-horse" mechanism. The biodegradability and removal of AgNPs have a major impact on their safety and efficacy in clinical settings. Further research is being conducted to find AgNPs-based delivery strategies that maximize therapeutic benefits while reducing potential risks[43].

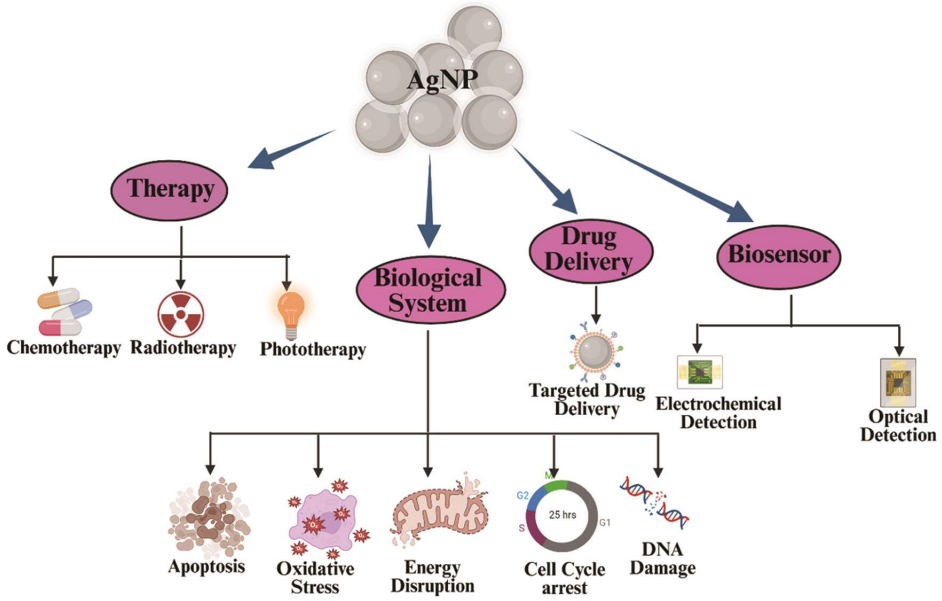

Fig. 3 — Applications of silver nanoparticles (AgNPs) in cancer therapy. AgNPs exert effects on biological systems, therapies, drug delivery, and biosensor applications

Overcoming multidrug resistance (MDR)

Multidrug resistance (MDR) is a significant barrier to successful cancer treatment, usually leading to chemotherapy failure. AgNPs have showed potential in overcoming MDR by improving the efficacy of chemotherapeutic drugs. According to research, AgNPs can operate in conjunction with other chemotherapy drugs to increase autophagy, apoptosis, and mitochondrial dysfunction in resistant cancer cells (Fig. 3). For example, when AgNPs and cisplatin were coupled, ovarian cancer cells that were previously unresponsive to AgNPs showed enhanced cytotoxicity[43].

Photothermal and photodynamic therapy

NPs that display localized surface plasmon resonance (LSPR) show potential as cancer therapy and diagnostic tools. AgNPs, one of the most widely used metal NPs, have the highest surface plasmon strength and light scattering[50]. AgNPs can also enhance photodynamic therapy (PDT) and help kill cancer cells by acting as photosensitizers that release reactive oxygen species (ROS) when light is activated. In contrast to conventional chemical and physical techniques, biogenic manufacture of AgNPs using plant extracts offers advantages such as reduced toxicity, cost effectiveness, and energy efficiency. These biogenic AgNPs have shown extraordinary anticancer activity due to their unique sizes, morphologies, and optical properties. Furthermore, the phytochemicals in biogenic AgNPs can be released into cancer cells' acidic environment, boosting their anticancer activity[51].

Mechanism of action of AgNPs against Pancreatic cancer

Induction of Paraptosis

A study using a human PDAC cell line revealed that AgNPs prevent the cancer growth by inducing a mixed kind of cell death that resembles paraptosis. Some important characteristics of this process include the production of ROS, the activation of mitogen-activated protein kinase (MAPK) pathways, and the development of cytoplasmic vacuoles because of the dilatation of the endoplasmic reticulum (ER) and mitochondria, which is different from apoptosis, which involves cell shrinkage and membrane blebbing. Unlike other cell death methods, paraptosis caused by AgNPs does not include caspase activation, DNA breakage, or visible nuclear abnormalities. Instead, autophagy-related markers such as LC3b and p62 are up-regulated. This selective elimination of PDAC cells occurs at low AgNPs concentrations while sparing non-malignant cells. Moreover, AgNPs demonstrate their potential as a supplemental agent for PC treatment, particularly in overcoming apoptosis resistance. They also cause mitochondrial damage, inhibit cell migration and colony/spheroid formation, lower proliferation markers (Ki-67, PCNA), prevent tumour xenograft growth *in vivo* with no adverse effects, and boost paraptosis markers (ALDH1L1, CHAC1)[55].

Induction of oxidative and nitro-oxidative damage

To assess the cytotoxic effect of AgNPs on human pancreatic ductal adenocarcinoma cells, Barcińska *et al.* carried out research in 2018 that included mitochondrial damage, oxidative and nitro-oxidative stress formation, antioxidant system impairment, and cell cycle disruption. Human pancreatic ductal carcinoma PANC-1 (CRL-1469) and the immortalized human pancreatic duct epithelial cell line htert-HPNE (CRL-4023) were treated with 2.6 nm and 18 nm AgNPs, respectively. The treatment of PANC-1 cells with AgNPs resulted in increased ROS generation, which was more noticeable in cancer cells than in non-cancer cells from the same tissue. Treatment with AgNPs resulted in a rise in the NOS isoforms iNOS, eNOS, and nNOS at both the mRNA and protein levels. This suggested that the formation of ROS and/or RNS, as well as the weakening of the antioxidant system, cause programmed cancer cell death. This result was linked to PANC-1 cells being stalled in the sub-G1 cell cycle phase, which is associated with programmed cell death, a low level of mitochondrial membrane potential, and abnormalities in mitochondrial ultrastructure that are characteristic of oxidative damage. Furthermore, AgNPs disrupted the antioxidant system (SOD1, SOD2, GPX-4, CAT, and SOD3) in PC cells. Barcińska *et al.* demonstrate that AgNPs-induced cell death in human PDAC involves oxidative and nitro-oxidative processes[55].

Stimulation of Autophagy

AgNPs are becoming more well-known as potent agents that influence autophagic pathways to target pancreatic ductal adenocarcinoma (PANC-1) cells. AgNPs can cause these cancer cells to undergo both autophagic and apoptotic cell death at certain doses. The mechanism requires the activation of the tumour suppressor protein p53, a rise in the Bax/Bcl-2 ratio, and elevated levels of autophagy and necroptosis proteins such as RIP-1, RIP-3, MLKL, and LC3-II. This suggests that AgNPs cause a stress response in cancer cells, boosting autophagic flux while decreasing cell survival and proliferation. Furthermore, lysosome activation and the intracellular accumulation of smaller AgNPs, notably those about 10 nm, promote autophagic activities. The simultaneous activation of apoptosis and autophagy can greatly increase cytotoxicity in PANC-1 cells. AgNPs' autophagy-driven cytotoxic features, particularly their size, make them a viable therapeutic option against PC, perhaps increasing efficacy when combined with other chemotherapeutic drugs[56].

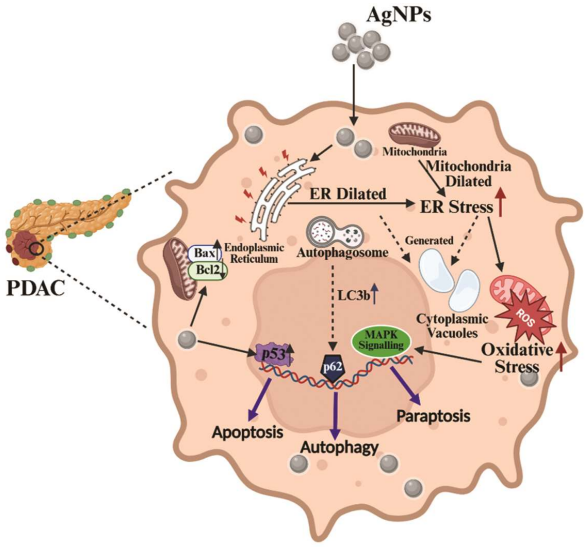

Fig. 4 — Schematic diagram of proposed mechanism of silver nanoparticle (AgNP)-induced cell death in PDAC. AgNPs trigger multiple intracellular stress responses, including endoplasmic reticulum (ER) stress and oxidative stress, as indicated by dilated ER and mitochondria, and increased reactive oxygen species (ROS). These stresses lead to the formation of autophagosomes, cytoplasmic vacuoles, and activation of stress signalling pathways. The p53 and p62-MAPK signalling axes play a central role in mediating downstream responses including apoptosis, autophagy, and paraptosis

Induction of mixed kind of programmed cell death

AgNPs have been shown to induce several pathways leading to programmed cell death in human PDAC cells, according to a study conducted on this cell line. AgNPs with diameters of 2.6 nm and 18 nm inhibited PC cell survival and proliferation in a size and concentration-dependent manner. Ultrastructural investigations showed that AgNPs absorption by cells resulted in necroptosis, autophagy, apoptosis, and mitotic catastrophe (Fig. 4). These modifications were associated with elevated levels of the pro-apoptotic protein Bax and reduced levels of the anti-apoptotic protein Bcl-2. AgNPs also significantly boosted the amounts of proteins associated with necroptosis and autophagy, including RIP-1, RIP-3, MLKL, and LC3-II, as well as the tumor suppressor p53 protein. Compared to non-tumor pancreatic cells, PC cells were more susceptible to AgNPs-induced[55].

Conclusion

PC is an important therapeutic concern due to its resistance to standard therapies and low survival rates. The introduction of AgNPs represents a new frontier in targeted cancer therapy. AgNPs have high cytotoxic effects on pancreatic cancer cells while sparing healthy tissues due to their capacity to elicit

numerous kinds of programmed cell death, including paraptosis, apoptosis, necroptosis, and autophagy. Their distinct physicochemical features enable improved drug distribution, decreased chemoresistance, and synergistic effect with radiation and phototherapies. Notably, green synthesis processes improve both biocompatibility and sustainability. However, clinical translation necessitates a thorough evaluation of NP size, stability, bio-distribution, and possible long-term toxicity. Numerous AgNP preclinical formulations are intricate, comprising multiple components, which complicates the prediction of their *in vivo* behaviour and subsequent manufacture and scale-up. Hence, continued multidisciplinary research is needed to improve AgNPs formulations and delivery methods, opening the path for more effective and less toxic PC treatment.

Conflict of interest

All authors declare no conflicts of interest.

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