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Gold nanoparticles employed in pancreatic cancer remedy

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A B S T R A C T

Nanoparticles (NPs) constitute a main curiosity in the scientific community, as evidenced by a growing body of research that has revealed encouraging findings. Nano-oncology is a comparatively recent field of study that reveals new perspectives for cancer diagnosis and treatment. This technology can also play an essential role in targeting malignant cells. In this article, we showed the progressive development of the targeted, nanoparticle-based drug delivery system in the remedial application of pancreatic cancer. The treatment of pancreatic cancer (PC) remains a great challenge, as studies have shown that nanoparticles can be used alongside chemotherapy factors that further their effectiveness while decreasing their toxicity. Increasing the effectiveness of nanoparticle therapy may improve clinical outcomes in pancreatic cancer patients. Nanomaterials, particularly gold nanoparticles (AuNPs), have singular physicochemical characteristics, like tiny size, significant surface reactivity, big surface area to mass ratio, having surface plasmon resonance (SPR) sets, simple functionalization of surface and biocompatible, In this article, we will be discussing how the distinctive characteristics of AuNPs in the delivery of targeted medication for pancreatic cancer led to the surge efficiency of conventional chemotherapy for cancer- ill.

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Introduction

Cancer is a complex disease that may attack an individual's body and experience a mutation of self-protection, a leading cause of mortality worldwide. The malignant or constantly developing cancer cells can be metastatic [1].

Based on this, several research efforts are being made to reduce the growing incidence of cancer [2]. With results based on many factors including genetic background, environmental stimuli, stage of the tumour at the phase of diagnosis, clinical reaction to therapy, and most significantly, the sort of tumour, alcoholism, obesity, smoking, prolonged exposure to sunlight is considered to be the primary risk factor for the development of cancer [3, 4].

Pancreatic cancer (PC) is a tumour of the pancreatic gland that has an elevated malignancy incidence and an elevated infection rate globally. The difficulty of an early diagnosis leads to a drop in prognosis, with a total 5-year rate of survival below 10% [5]. Furthermore, approximately 80% of pancreatic cancer patients forfeit the chance of surgical removal due to vascular conquest and\ or malignancy away from diagnosis. The most common supplementary treatments are chemotherapy and radiotherapy, but they usually have harmful side effects and are frequently ineffective because medication interactions with cells and tissues are not specific and due to poor solubility or unfavorable biodistribution. Another factor is the complicated tumour microenvironment [6]. In addition, PC has a weak responding to radiotherapy and chemotherapy due to a decline in blood supplies, dense connective tissue stroma, and higher reflect of multidrug-resistant genes [7]. Not much progress has been made in implementing immunotherapy into the pancreatic cancer therapy plan, despite it is effectiveness in treating several other carcinomas [8]. This cancer requires newer, more creative therapeutic methods [6]. The U.S. Joint Committee on Cancer Control (AJCC) categorized pancreatic cancer into four phases depending on disease intensity. Phase zero pancreatic cancer only affects the cells in the highest layers of the pancreatic canal, whereas phase four pancreatic cancers circulate to other body portions [9].

Pancreatic cancer sorts

According to the types of cells involved, pancreatic cancer can be categorized into two main categories. These are adenocarcinoma, a type of cancer that develops in the tissue of the glands or pancreatic channels cells lining pancreatic channels to promote digestive juice production. Adenocarcinomas constitute the predominant form of pancreatic cancer. Occasionally, these cancers are touted as external tumour of excretion, and endocrine pancreatic cancer is a pathological condition characterized by the emergence of cancer cells into the pancreatic tissue that produces hormones [8, 10]

Cancer diagnosis and therapy research using nanomedicine and nanotechnology has advanced in recent years in ways that have never been seen before, and many different cancer treatment options have been put forth [5, 11]. Multifunctional substances known as theranostics have been developed due to advancements in nanotechnology for cancer treatment [12]. The goal of developing a unique strategy to overcome cancer resulted in the advancement of efficient and preventive treatment approaches; yet, a great deal of research has been directed toward a wide comprehension of the molecular mechanisms that underlie the evolution of pancreatic cancer in individuals [6, 13]

A variety of structures including dendrimers, liposomes, micelles, solid lipid nano molecules, silicon and carbon nanostructures have undergone testing for medication delivery applications. Nanoparticles can interact intracellularly and extracellularly with biological molecules despite being smaller than human cells by 100 to 10,000 times.

NPs have been used in medicine and can be linked to fat or the formation of polymers for the packaging of drugs to increase solubility and transmittance, as well as plug the drug for the target cells resulting in higher therapy competence [14]. It is the most prominent characteristics include the tendency to stay steady in the physiological ecology and the ability to passively target of pancreatic cancer cells by enhancing transmittance and retention. Nanoparticles can build up within tumour capillaries because of weakness in lymphatic discharge in tumours. They possess sufficient sizes to flee anatomy through the kidney while being tiny enough to avoid the removal of phagocytic by Kupffer and spleen cells. Nanotechnology is, therefore, a major topic of interest because of its impact on many fields including biology, chemistry, and medicine, where treatment of pancreatic cancer is mostly based on chemotherapy and radiation, as well as surgical, where current research shows in nano-oncology promising future results [15].

Gold/Au nanomaterials are receiving the greatest interest mong mineral nanoparticles such as Au, Cu, Ag, and Fe due to their biocompatibility, straightforward preparation, and settling [16, 17]. Specifically, gold nanoparticles (GNPs), exhibit chemical, physical, visual, and electronic properties that set them apart from other nanoparticles used in biomedical applications. These attributes are applicable for imaging, diagnosis, treatments, regulation managing surgery, targeting specific radiotherapy sites, and delivery of drugs. As a result gold nanoparticles can function as a carrier to transport medicines and genes to the target tumour site can significantly enhance the efficacy of the active compound, the ability to configure steady compounds with DNA and little overlapping RNA (siRNA) [2, 18, 19, 20, 21, 22].

GNPs have increased in use in biomedical studies have a variety of surface functions at the cell level, are simple to surface-modify, and demonstrate colloidal stability [23]. Biomolecules like antibodies and peptides have the possibility of altering the GNPs' surface properties. The application of (GNPs) is known as an important treatment in the detection and therapy of pancreatic cancer due to their simple synthesis, special optical features, significant biocompatibility, tunable shape and size, and surface plasmon resonance (SPR) features [24].
Despite all the advantagesthat gold nanoparticles offer, many issues still need to be resolved, one drawback is that some proteins are adsorbed by GNPs, which makes them unstable. To prevent this, they are often covered by a single hydrophilic biocompatible layer of dendrimer a polymer-like, polyethylene glycol polylysine, or polyethyleneimine (PEI). Another trouble that could come up is the maintenance of these entities by the macrophages and other reticuloendothelial system (RES) cells once inside the body. The issue is inhibiting GNPs from being internalized by RES cells, in vivo, so that they can remain within the body longer while the RES discards stranger particles. The NPs' size playes a significant role in this matter. It has been noted that particles of small size stay in the bloodstream for significantly longer in comparison to larger NPs [25].
The endoplasmic reticulum, mitochondria, and the nucleus are the main common regions to perform their effects. GNPs act through the drug's toxicity, gene expression modulation, or immediate toxicity upon the nuclear site, while GNPs may yield ROS, stimulate autophagy, or change the membrane potential upon the mitochondrial site [3].
Different ways were used to create GNPs, such as (1) the Brust protocol (1994), which involves transferring the ions of gold from water solution into an organic state before reducing them with borohydride to create smaller GNPs. (2) the Turkevich technique (1951), wherein sodium citrate was used to reduce gold chloride to create gold particles that are between 15 and 30 nm in size 36 (3) the microemulsion procedure, which reduces gold salt in the aqueous cores of inverted micelles and (4) the sowing protocol, in which gold seed particles was used to grew GNP under a poor reducing agent [2]. Gold constitutes a system that contains an equal number of positively charged ions (that have a rigid placement) and conduction electrons (free-moving) [26].
This article aims to highlight the most recent studies showing the role of gold nanoparticles in the administration of PC from detection to therapy phase and then focuses on how to deliver the targeted drug to cancer cells using nanotechnology [27].

The role of GNPs in pancreatic cancer therapy

GNPs work as outstanding delivery systems for chemotherapy. Cytotoxic medicines can be incorporated into the gold nanoshell cores, distributed throughout the matrix of nanoparticles, and subsequently adsorbed onto the GNP surfaces through chemical conjugation or electrostatic interactions. GNP-drug formulations can be delivered to specified organs through both active and passive targeting that decreases non-selected delivery to ordinary cells [28]. Permeable vasculatures and poor lymphatic drainage distinguish tumour tissue blood vessels. The increased permeability and retention impact allows the passive delivery of cytotoxic drugs*via* nanoparticles to tumour cells. Cytotoxic medication delivery employing nanoparticles leads to prolonged tumour retention and enhanced therapeutic benefits [2, 28].

A clinical trial employing the formulation (Aurimune) CYT-6091 was carried out by Libutti *et al*, in 30 people with terminal solid organ carcinoma, three of whom had pancreatic cancer. CYT-6091 is composed of gold nanoparticles that are conjugated with recombinant tumor necrosis factor (TNF) on their surface, together with thiolated polyethylene glycol. In the three individuals diagnosed with pancreatic adenocarcinoma, CYT-6091 was found to specifically target tumour tissue. Microscopic examination of tumour biopsies and the neighboring normal tissue showed that the three individuals with pancreatic adenocarcinoma had between 0–2 nanoparticles in healthy tissues and 5–6 nanoparticles in the tumour organs. Harmful effects were seen, no signs of lymphopenia, lack of blood owls and no significant liver enzyme or electrolyte disturbances. According to this study, chemotherapeutic substances can be delivered to the necessary cancer tissue with the aid of colloid gold nanoparticles and recombinant tumor-targeting agentsthat are specifically targeted at the pancreatic cancer regions [14, 29].

NPs may be bound with the therapeutic either by chemical (covalent or non-covalent) binding or physical enveloping. The application of a prodrug method involves the diversion of the therapy molecule into an inert state or its binding to a binder that is exclusively cleaved within the cancer cells or the tumour microenvironment [24]. There are pathophysiological differences between healthy and cancerous cells, like acidic pH, and the high expression of numerous cellular ingredients. Thiol groups can be used to bind active molecules on the surface of gold nanoparticles, it is an exciting solution to ensure that the given molecule will find a way into the cell. Intracellular release is allowed by the activity of glutathione (GSH) an antioxidant that accumulates to a level of 10 mM, within the cell. This molecule is responsible for the removal of free radicals and keeps the oxidation balance and cell reduction due to the ability to decrease the bonds of disulfide. GSH "replaces" conjugated substances on the AuNP surface within the cell, enabling their effective release [24, 30].
In addition, the drug's release or activation may be influenced by environmental elements such as temperature or light. Thus, using cellular features supports the biological relationship control of medication launch and activity, while external inputs allow for spatiotemporal organization. Combining the two strategies could noticeably increase anticancer treatment selectivity [30].

Delivery of targeted drug for PC utilizing gold nanoparticles

The most progressive method of transporting substances is known as targeted drug delivery (TDD) which enhances the effectiveness of active substances in a given region, whereas simultaneously, a decrease in the impact on the intact cells is observed. Nanotechnology has proven its effectiveness in the TDD mechanism, with a proposition stating that the privacy of nanoparticles increases as their size decreases [25, 31]. Certain markers have a tendency to undergo chemical change or linked to the NPs surface to directly engage with receptors of the cell surface and quickly permeate the layers of the cell membrane [3, 32].

The ideal treatment approach is to deliver different medications specifically to the main tumour **(**Figure 1), or to the site of the malignant tumour, the targeted delivery of medications by nanoparticles is projected to significantly decrease the potion of anticancer drugs with the best specificity, enhanced effectiveness, and toxicity of low [10, 33].

Several research studies have shown that combination chemotherapy is better than individual agents for different solid tumours. The association of gemcitabine and cetuximab was employed in preclinical forms. Treatment-associated toxicities were light to moderate comprising fatigue, fever, and skin rash. These results prompted researchers involved in nanotechnology research for cancer to create alternative and more effective targeted drug delivery systems (DDS) to treat various cancers, particularly pancreatic cancer [34, 35]. A specialized method, for delivering treatment, known as a targeted delivery approach (TDA) utilizing gold nanoparticles (5 nm) was developed for treating cancer both in laboratory settings and, within living organisms. Gold nanoparticles (AuNPs) were used to fabricate this TDA.
The anticancer gemcitabine drug and the anti-epidermal growth factor receptor (EGFR) cetuximab antibody (C225) as the targeted agents. The epidermal growth factor receptor (EGFR) was selected as a target in pancreatic cancer for some reasons. EGFR is present on the cell surface and becomes active upon linking it is certain ligands, comprising transforming growth factor α (TGF-α) and epidermal growth factor [36]. Likewise, there are several reasons for selecting gemcitabine as a therapy. In addition to being the first line of chemotherapy to combat pancreatic cancer, it is also used to treat breast and ovarian cancer. It has been shown that applying this targeted delivery scheme noticeably inhibited the proliferation of pancreatic tumour cells (MIA Paca2, AsPC-1, and PANC-1) *in vitro* and the growth of orthotopic pancreatic tumour *in vivo*. This method can be applied generally to treat a range of malignancies distinguished by EGFR over-expression [37].
Coelho *et al*. studied the collaborative influence of a couple of nano-conjugates polyethylene glycol-enveloped GNPs, linked with varlitinib (GNPs-PEG-VAL) and linked with doxorubicin (GNPs-PEG-DOX) as in vitro precise delivery against cancer cells proliferation. Two pancreatic cancer cell lines (S2-013 and MIA PaCa-2) and a healthy pancreatic cell line (hTERT-HPNE) were employed in the investigation. During the 72-hour incubation period, GNPs-PEG till 1.0 nM did not cause any harm to both cell lines in the investigation. Concurrently, it was found that GNPs-PEG-DOX had risky effects, on pancreatic tumour derived cells (MIA PaCa-2) but not on other cell types. Moreover, GNPs-PEG-VAL showed toxicity towards S2–013 (derived from metastatic pancreatic tumors), and MIA PaCa–2 cells while having no impact on hTERT–HPNE cells. The experiment involved exposing the cells to DOX-PEG-GNPs for 24 hours followed by treatment with GNPs-PEG-VAL for 48 hours and comparing the results with free anticancer drugs. The combined effect of the two anticancer medications was notably stronger for S2-013 cells, only observed with the conjugates. Furthermore, compared to the toxicity of unconjugated drugs the toxicity of conjugated drug-PEG-GNPs was lower, in normal pancreatic cell lines [38].

Steckiewicz and coworkers studied the safety and anti-cancer potential of AuNPs combined with gemcitabine (GEM), doxorubicin (DOX), and cytarabine (CTA) along with reduced glutathione (GSH). They tested the cytotoxic impact, on several cell lines using the MTT assay. It was discovered that AuNPs had a concentration-dependent cytotoxic effect and had a lower impact on normal cell lines than on cancer ones, which shows the anticancer potential of the tested AuNPs [31].

Banstola et al. prepared adherent GNPs linked with PLGA microspheres loaded with paclitaxel using polydopamine to create PLGA-Ms-PTX-pD-GNPs, which was then employed in PC cell line type (PANC-1) cells with and without treatment with NIR (near-infrared red). It was discovered that using NIR increased the output of ROS (Reactive oxygen species), and decreased the levels of two crucial antioxidant enzymes, SOD2 and CATALASE. It has been shown that chemo-photothermal therapy works in conjunction to trigger cancer cell apoptosis [39].

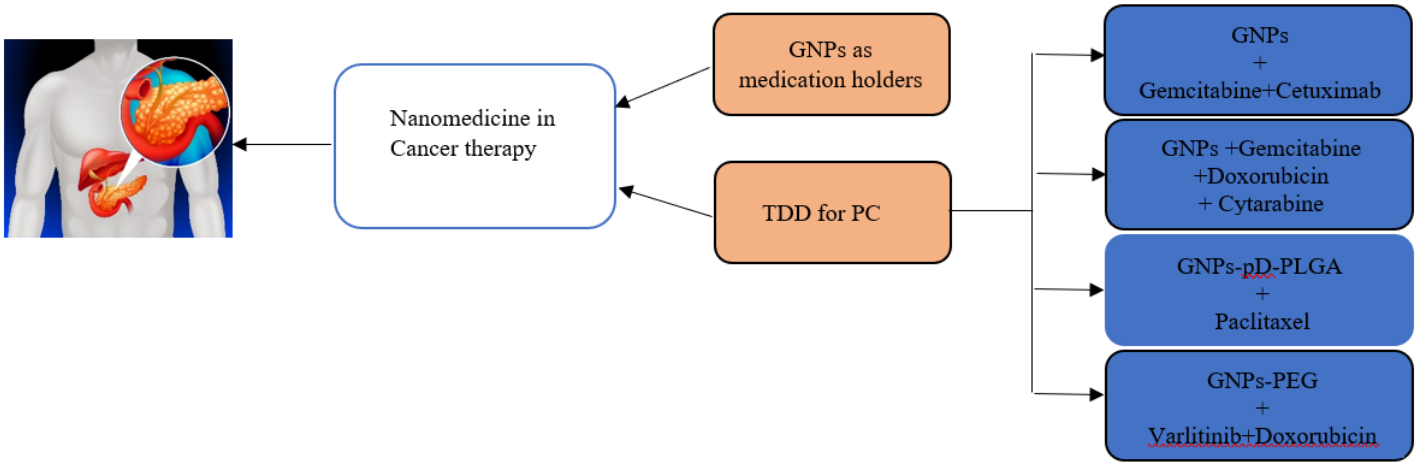

Figure 1: Various configurations of GNPs investigated in the context of pancreatic cancer

Other viewpoints about GNPs and PC

Studies have been conducted on the potential contribution of NPs to the initial diagnosis of PC or perhaps to the reversal of desmoplasia of the pancreas. Cancer detection serves as a prism through which nanotechnology is investigated. To detect CA 19-9, Alarfaj *et al*. produced carbon quantum dots coupled with Au nanocomposite, a tumor marker utilized in PC rapid screening [40]. Han and coworkers used GNPs coated with polyethylene to participate in the delivery of thermal shock protein HSP47 (targeting siRNA) and transient retinoic acid to the activated pancreatic stellate cells (PSC). This nanosystem was found to have stabilized PSC and discouraged the excessive extracellular matrix production. In this regard, drug delivery has been enhanced for tumours and at the same time enhanced the efficacy of chemotherapy [41]. Likewise, another research study disclosed that using innovative ultrasound-targeted microbubble destruction, dendrimer-enveloped AuNPs can co-deliver miR-21 inhibitor and gemcitabine to treat pancreatic cancer with significant benefits [42]. In the last years, a trend of developing gold nanoparticles has been in obtaining an effective and targeted treatment. Despite, the experimental plans showing promising results, an ideal tested part has not yet been detected with 100% bioavailability and important anti-tumour effects without side effects on the body's organs. However, scientists are making encouraging strides, putting more of an emphasis on fusing various methods and utilizing all the qualities of gold, as mentioned earlier [25].

Conclusions

Due to the fast progress of nanoscience and nanotechnology over the previous few years, a diverse range of particles with varying sizes, and forms, are presently possible to researchers. In light of the unique properties of these particles, AuNPs are of medical importance, especially in anti-cancer treatment. These particles have also been used as promising research factors and have been proven suitable for the prognosis of pancreatic cancer, motivating programmed cell death in cancer cells hence rendering pancreatic cancer cells further sensibility to chemotherapy.

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