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Research

Nanopartices With Zinc Based Nanomedicine Aprocheseswith Nanoparticle in Prostate Cancer Therapy

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Abstract

Prostate cancer remains a significant global health challenge, necessitating innovative therapeutic approaches. In recent years, nanotechnology has emerged as a promising avenue for cancer management. Among the various nanoparticles, zinc oxide nanoparticles (Zn ONPs) have gained attention due to their unique properties and potential applications in prostate cancer treatment. Elevated zinc levels appear to have a protective effect against prostate cancer, while zinc concentrations are significantly lower in prostate cancer tissues compared to healthy prostate tissue, suggesting zinc's important physiological role in the prostate and its potential as a preventive or therapeutic agent. The normal prostate accumulates high levels of zinc, which is essential for inhibiting specific metabolic pathways and supporting normal glandular function. Multiple studies have shown a marked reduction (around 60–80%) in prostate tissue zinc levels in cancerous tissue compared to benign or healthy tissue. Zinc inhibits citrate oxidation in the prostate, affecting energy metabolism in the cell. Loss of zinc accumulation (through decreased transporter activity, such as ZIP1) is observed in prostate cancer cells, enabling tumor progression by facilitating altered metabolism and growth. Zinc also has anti-proliferative and pro-apoptotic effects, including the activation of specific cell signaling pathways that suppress tumor growth. High dietary zinc intake and tissue zinc levels are correlated with reduced prostate cancer risk and mortality. However, excessive long-term supplementation may increase the risk of aggressive forms of prostate cancer. Monitoring and possibly restoring zinc homeostasis in prostate tissue could be considered as part of strategies for prostate cancer prevention or therapy, but further large-scale studies are warranted.

Keywords: Prostate Cancer, Zinc Oxide Nanoparticles (ZnO NPs), Nanomedicine, Drug Delivery Systems, Radiosensitizers ($ZnFe_2O_4$ Nanoparticles), Apoptosis and Anticancer Activity.

INTRODUCTION

Globally, prostate cancer is a major source of illness and death. Effective diagnosis and therapy are still difficult to come by, despite scientific advancements. The science of nanotechnology has shown great promise in providing creative approaches to cancer treatment. Zinc oxide nanoparticles (Zn O NPs) in particular have attracted interest because of their special qualities and possible medical uses.[14]

Nanoparticles

When the size of the material becomes closer to the atomic scale, its characteristics alter. This is because the material's surface atoms dominate its performance as a result of the surface area to volume ratio rising. When comparing nanoparticles to bulk materials like powders, plates, and sheets, their extremely tiny size results in a very significant surface area to volume ratio. Because they are tiny enough to contain their electrons and induce quantum effects, this property allows nanoparticles to have surprising optical, physical, and chemical capabilities. The MTT test was used to examine the possible anticancer activity of the CUR loaded zinc oxide NPs on the rhabdomyosarcoma RD cell line, and the resazurin assay was employed to evaluate the cytotoxic effects of the NPs on human embryonic kidney cells. Zn O structures' high aspect ratio was thought to contribute to the NPs' enhanced cytotoxicity (Perera et al., 2020). It was noted in a different investigation that the manufacture of zinc oxide nanoparticles involved the usage of egg albumin. By using the MTT test to determine anticancer activity on MCF-7, the method significantly decreased cellular viability and caused significant cytotoxic, Gene expression research (RT-PCR) and western blot analysis revealed that the prepared NPs induced ROS, which significantly downregulated the expression of the anti- apoptotic gene Bcl-2 while increasing the regulated transcription of mRNA levels of apoptotic genes such as p53,bcl-2,caspase-3,and caspase-9. The results indicated that MCF-7 gene expression was particularly inhibited by the nano system through ROS-induced cell death and cytotoxicity.[37]

Nanotechnology

Nanoparticles (NPs) are used in the emerging and promising field of nanotechnology to support illness investigation and therapy (Farrokhzad & Langer, 2009; Ferrari, 2005; Petros & DeSimone, 2010). Because of their size and remarkable surface to volume ratios, NPs provide solutions for the current problems in malignant growth therapies. The main factors influencing NPs' biodistribution in vivo are their size, shape, and surface characteristics (Alexis, Pridgen, Molnar, & Farrokhzad, 2008). By using nanotechnology, the ease with which nanostructures cooperate at the molecular level has put nanotechnology in the forefront of medicine. NPs can be customized to a specific application. Regardless of their small size, NPs can be stacked with atoms or DNA in curative and investigative agent's biomarkers that were significantly more sensitive than those found using the traditional enzyme-linked immunosorbent test (ELISA) technique. Because prostate cancer may be detected with only traces of biomarkers, the sensitivity of the nanoparticle attached detectors is linked to cost-effectiveness. Additionally, increased sensitivity makes it easier to check for prostate cancer using urine rather than blood. Blood serum collection is associated with patient disobedience and demands a high level of expertise. Due to their exceptional specificity and sensitivity, particular nanotechnology-based detectors can effectively reduce the overdiagnosis and underdiagnosis of cancer. They can also be used to monitor illness for individuals who may be at risk of recurrence following recovery. The traditional approach cannot be used as a point-of-care by the general public since it requires expert execution. Therefore, the majority of cutting-edge MRI and CT diagnostic systems for prostate cancer used magnetic nanoparticles (MNPs) as their precursor contrast agents. MNPs can be employed as ultrasmall SPIOs (USPIOS) or as superparamagnetic iron oxides (SPIOS). Numerous efficacious clinical trials have been conducted, leading to improved biocompatibility and decreased toxicity. The US FDA has authorized iron-oxide based MNPs as MRI contrast agents. Additionally, experiments were conducted to connect cationic lipid nanoparticles with SPIOs in order to overcome their limited effectiveness. A new non- invasive imaging method for prostate cancer called novel photoacoustic imaging (PAI) typically combines the effects of ultrasound and laser light. Based on the mechanistic technique of surface plasmon resonance to increase the absorption, some metallic nanoparticles, such as gold nanoparticles, can be a miraculous source of PAI. Prostate- specific antigen (PSA) can also be used in conjunction with nanotechnology to detect prostate cancer at the molecular level because both are possible targets for nanoparticles.[8]

Prostate cancer

In the United States, over 161,000 new instances of prostate cancer were detected in 2017. This makes it one of the most prevalent cancer diagnoses for males. 1)proliferation factors, androgen, and their corresponding receptors are some of the components that regulate the proliferation of prostate cancer cells. 2) The most often mentioned alteration, a rise in autocrine and paracrine growth factor loops, is highly associated with the advancement of prostate cancer. 3) It has been shown that growth factors, such as epidermal growth

factors (EGF), transforming growth factors (TGF)-α and β, fibroblast growth factors (FGF), and IGFs, are overexpressed in advanced prostate cancer [4]. In the first stages of prostate cancer, androgens are necessary for the survival and growth of cells. 4) With a median response duration of approximately 18 to 24 months, androgen ablation's usefulness in treating advanced prostate cancer is limited. Global cancer statistics show that prostate cancer is the second most common cancer, Type and the fifth leading cause of cancer mortality in me2) prostate cancer diagnoses, prognoses, and treatment, alongside standard clinical frameworks may therefore better support prostate cancer outcomes. Usually, the prostate's glandular cells are the source of prostate cancer. It can proliferate slowly or quickly, destroying neighboring tissues and travelling far (metastasis). Asymptomatic prostate cancer is common in its early stages. A growing tumor may cause the following symptoms: Symptoms of the urinary tract include increased frequency, urgency, a weak stream, or trouble beginning or ending urination. Type of prostate cancer 1) All prostate cancer cause are adenocarcinomas ,2) small cell carcinoma., 3) another neuroendocrine tumor 4) sarcoma.[3,11]

Synthesis of ZnFe2O4 Nano particles

Using Zn(NO3)2•6H2O and Fe(NO3)3•9H2O in the presence of ethanol, ZnFe2O4 nanoparticles were created [35]. To do this, 298 mg of Zn(NO3)2•6H2O and 808 mg of Fe(NO3)3•9H2O were added to 80 mL of ethanol, and the mixture was agitated at 400 rpm for 30 minutes. The combination was then sealed and heated to 180 °C for 12 hours in a stainless steel autoclave lined with Teflon. Next, room temperature was reached by cooling the combination. ZnFe2O4 powder was produced and dried in an oven at 60 °C for 24 hours. It was washed many times with distillated water (purity of≥98%). For the material characterization stage, ZnFe2O4 nanoparticles were dissolved in ethanol and distilled water; however, the appropriate quantity of the nanoparticles was dissolved in culture media to achieve the appropriate concentrations for the biological tests (refer to the following).[20]

ROLE OF ZINC

The peripheral zone (about 70%), the core zone (about 25%), and the transition zone (about 5%)make up the typical human prostate. The peripheral zone is the main factor in the link between zinc levels and the onset of cancer. Zinc levels in the central gland are often far lower than those in the peripheral zone. Zinc-accumulating cells are therefore found in the typical glandular secretory epithelial cells of the peripheral zone but not in the central gland. Zinc levels in the core gland of a patient with benign prostatic hyperplasia (glandular BPH) are markedly elevated and frequently higher than those in the normal periphery zone. It is thought that BPH originated in the transition zone. The generation and secretion of unusually high quantities of citrate is one of the peripheral zone glandular epithelium's primary functions. Similar to other soft tissues, the glandular secretory epithelium in the peripheral zone accumulates significant quantities of zinc, often up to ten times greater. When one considers that mammalian cells often contain mechanisms that prevent the buildup of high zinc levels particularly mobile reactive zinc, which can have lethal effects the uniqueness of this role becomes even more evident. Therefore, what makes these highly specialized secretory epithelial cells capable of performing their function? The explanation is that inhibiting m-aconitase activity requires a high concentration of zinc in mitochondria. This stops the citrate from oxidizing, causing it to build up and secrete. Inhibiting citrate oxidation and m-aconitase is fatal in other mammalian cells. This highlights the distinct characteristics of the highly specialized prostate secretory epithelial cells. High zinc levels might have a protective role in prostate cancer. Zinc supplements could potentially be considered as a therapeutic or preventive intervention1.In vivo studies have demonstrated the effective and therapeutic role of zinc administration in prostate cancer models.[4,6]

MTT assay

Radiation, MTT dye was added to each well and the mixture was incubated for four hours at 37 °C. After that, the medium that contained the MTT was taken out and replaced with 100 µL of DMSO each well in order to dissolve the formazin crystals. With a reference wavelength of 620 nm, the absorbance at 590 nm was measured using an ELISA micro plate reader. The formula used to compute the cell viability percentage was cell viability (%) = [(optical density (OD) of the sample − OD of the medium) / (OD of the cell control − OD of the medium] × 100. At least three replications of each biological experiment were conducted. For P-values b0.05, the differences were deemed significant. It should be noted that, despite the importance of researching the potential toxicity of ZnFe2O4 nanoparticles on normal human cells, testing the nanoparticles' effects on normal human cells was prohibited by institutional guidelines and ethical laws at Iran University of Medical Sciences.[36,37]

METHODS

One of the greatest quantities of zinc in the body is found in normal prostate tissue, and mechanistic research suggests that zinc is crucial for prostate health. While the exact function of zinc in the pathophysiology

of prostate cancer is unknown, research shows that zinc may inhibit the angiogenic and metastatic capacity of prostate cancer cells. A meta-analysis that demonstrated substantial evidence of study heterogeneity indicated a 10% increase in risk of prostate cancer for total zinc consumption, but not for supplementary zinc intake. In a population assumed to have adequate zinc levels, we postulated that long-term, high-dose supplementation with zinc might raise the risk of aggressive prostate cancer.[24]

Statistical analysis

The hazard ratios (HRs) and 95% confidence intervals (CIs) for the relationship between using zinc supplements and prostate cancer risk were calculated using Cox proportional hazards models. The model employed the following variables for stratification: age in months and calendar year at the start of follow-up for each 2-year questionnaire cycle; person-time was calculated from the return of the baseline questionnaire until the date of prostate cancer diagnosis, death, or end of follow-up, whichever came first.* We assessed the zinc supplement based on length (never use, previous use of any duration, 1-4, 5- 9, 10-14, ≥ 15 years) and dose (never-user, past-user, 1-24, 25-74, ≥ 75 mg/day). Race, family history of prostate cancer, prostate-specific antigen (PSA) testing in a prior cycle, and PSA testing in more than 50% of prior cycles were all included in the multivariable model. * Current weight, height, height, smoking, intense exercise, total caloric intake, red meat, meals based on tomatoes, seafood, total zinc consumption without supplements, and history of prostatitis or peritonitis.

We also made adjustments for multivitamins, selenium, vitamin A, vitamin E, and the total number of supplements taken in order to account for any possible confounding from other supplements. The proportionate hazards assumption was validated by incorporating interactions between the exposure and the time scale, verifying the proportionate risks hypothesis. A continuous variable, the median of each category, was used to evaluate linear trends between categories.Multivariate models did not include an additional adjustment for a history of negative biopsy since it had no effect on the main results.[8]

Cell viability assay

The MTT test, which measures mitochondrial activity in live cells, was used to conduct the cell viability study. The cells were seeded at a density of 1×104 cells/well in 96-multiwell plates, and during 24 and 48 hours, they were fed with varying concentrations of zinc sulphate (20–100 μ mol/l). Following the treatment phase, 100 μl of RPMI 1640 containing 0.5 mg/ml of MTT was added to each well, and the mixture was incubated in CO2 at 37 °C for three hours. Following the incubation time, the medium was taken out and two PBS (phosphate buffered saline) washes were performed on the cells. The tetrazolium ring may be changed by living cells into dark blue, insoluble formazan crystals that are soluble in dimethyl sulfoxide (DMSO). These crystals can then be measured at 570 nm using an enzyme-linked immunosorbent assay (ELISA) reader. Using the following formula, the proportion of viable cells in relation to control PC-3 cells was calculated.[9]

Absorbance of treated cells/Absorbance of control cells × 100 = % cell viability

As determined by the MTT assay, zinc strongly affects the survival of PC-3 cells in a time- and dose-dependent manner (Fig. 1). In this study, the inhibition of cell viability by zinc was observed clearly in dose-dependent manner. Time response data demonstrated 50% growth inhibition at 60 μM concentration of zinc treatment for 24h.Percentage of cell viability was reduced gradually with increase in zinc concentration.Hence, 40 and 60 μmol/l zinc concentrations were used in our experiments.[14]

Radiotherapy of prostate cancer

When gamma radiation interacts with high-Z nanoparticles (used as radiosensitizers), it can intensify the photoelectric effects and/or Auger electron ejections even more. As a result, several high-Z nanoparticles (such gold and gadolinium) have been successfully employed as radiosensitizers in cancer treatment. Zinc ferrite, a normal spinel structure with (Zn)[Fe2]O4 representation in which parenthesis shows the cations in tetrahedral or A sites and square brackets contain the octahedral or B sites, has garnered the most attention among the various spinel ferrites because of its narrow band, low ordering temperature, antiferromagnetic ground state with a Néel temperature of about 10 K, and paramagnetic behaviour at room temperature. An assessment of the magnetic and biological properties of ferromagnetic glass ceramics containing ZnFe2O4 for the treatment of cancer via hyperthermia. ZnFe2O4 nanoparticles with strong magnetic properties and neuro-cytocompatibility have recently been proposed by Liu et al. for use in magnetic resonance imaging of cells. As high-zelement nanoparticles, like gold, iron oxide, and gadolinium-based nanoparticles, have been employed as radiosensitizing agents in cancer radiotherapy, ZnFe2O4 nanoparticles, which also contain high-zelements, can be suggested as an appropriate magnetic radiosensitizer in cancer therapies.[15,7]

RESULTS AND DISCUSSIONS

SEM and TEM were used to examine the morphological structures of the ZnFe2O4 nanoparticles. The results showed that the produced powders were spherical clusters with ~0.5–2 μm sizes including nanoparticles with ~10–50 nm sizes. Before any biological tests, sonication was used to break the clusters apart. The nanoparticles, which have diameters between 5 and 15 nm.[14]

Application

Nanomaterials; Application in treatment of prostate cancer

Nanomaterials have been used in many applications during the past ten years, particularly in the treatment and targeting of illnesses. A carrier system needs to be able to transport a large concentration of medication effectively, be biocompatible, and be inert. Based on current understanding, the majority of carrier systems are unable to deliver drugs at high concentrations because of their increased cytotoxicity at the site of targeting.Consequently, many of the current therapeutic approaches are ineffective for treating cancer, particularly breast tumours in women and prostate cancer in men. One of the most prevalent illnesses, prostate cancer (PCa), requires a higher concentration of active medication to reach the organs and tissues impacted by the cancer. According to Figure, more effective drug delivery methods for a higher concentration of active pharmaceutical ingredient (API) targeting prostate tumours have been demonstrated by both organic (nanoemulsions, liposomes, niosomes, and polymeric nanocapsule) and inorganic (carbon nanotubes, gold nanoparticles, magnetic nanoparticles, silica mesoporous nanoparticles, quantum dots, and selenium nanoparticles) nanocarrier types. The ensuing nanomaterials have the capacity to increase both active and passive targeting (enhanced permeability and retention effect, or EPR) through receptor-mediated endocytosis and the decorating of nanoparticles with various ligands.[26]

Multi –application of zinc

Zn absorption from the gut and circulation in the blood and competition for albumin binding sites Zn storage in metallothionines and competition for binding sites Zn levels and prostate cancer; tissue Zn levels, distribution, and prostate cancer; mitochondrial aconitase (mACO2) and prostate Zn supplementation effects; interaction with other trace minerals, demographic, lifestyle, and comorbidity effects transgender women and prostate cancer[26]

Epidemiology of hereditary Prostate cancer

Early onset and autosomal dominant inheritance are features of HPCa, which is caused by gene mutations. According to Heidegger et al., males diagnosed under the age of 55 had a cumulative, proportion of PCa cases owing to high-risk susceptibility alleles of 43%, whereas for men beyond 85 years, the figure is just 9%. African American males have an HPCa incidence that is two and three times greater than that of European and Asian men, respectively. Lifestyle factors including food and obesity, as well as screening practices within a community's ethnic or racial group, may have an impact on this result. Likewise, there are variations in genetic aetiology among many populations. For instance, Afro-American men did not include single-nucleotide polymorphisms (SNPs) that had previously been identified in groups of white people or Asian people. According to these findings, the majority of the previously published loci found in people of European or Asian ancestry were not replicated by other genome-wide association studies (GWAS). Consequently, a new locus (SNP, rs7918885) on chromosome 10p14 has been discovered that is unique to African men. This SNP, rs7918885, is located at 10p14 inside an intron of a 360 kb centromeric long non- coding RNA (lncRNA RP11-543F8.2) encoding GATA3. Further, African American patients had higher frequencies of multiple BRCA1/2 variations of uncertain significance (VUS) than did Caucasian patients (4.6% vs. 1.6%, respectively). However, across different ethnic groups, a number of SNPs have been linked to PCa susceptibility at a single chromosomal location at 8q24 (next to the MYC proto-oncogene).[2]

Gentic counselling; guidelines for genetic test and surveillance

It is suggested that individuals with early onset aggressive PCa and a family history of PCa or other heritable cancers should be considered candidates for genetic testing since they are significant indicators of a hereditary component. As of now, there are no standardised standards indicating which individuals, or at what point in the disease, should have genetic testing done in order to be considered for active monitoring. Low prostate specific antigen (PSA) level and low grade and low volume tumour on biopsy are two commonly utilised criteria. Serine protease PSA is generated by both normal and cancerous cells. The secretion of PSA into glandular ducts occurs in healthy persons at concentrations million times greater than in plasma. In contrast, patients with PCa have PSA leakage into the extracellular space due to disruption to the secretory pathways. Serum PSA levels rise as a result, which is indicative of both inflammatory and malignant activities in the prostate. Prostate health index (PHI), a more contemporary technique for calculating PSA, incorporates PSA,

free PSA, and p2PSA4. The accuracy of PHI value is still unknown as of right now when compared to conventional PSA procedures.[15,7]

Radiation therapy

Techniques, or the other way around. Many studies have compared retroactively radical prostatectomy with radiation, although though no prospective randomised trials evaluating this topic have yet been finished. 1,238 patients who had radical prostatectomy and 609 individuals who had EBRT were included in a combined study of patients from Fox Chase Cancer Centre and the Mayo Clinic.75.ADT was given to 344 individuals undergoing radiation treatment in all. Classified as PSA. ≥20ng/ml, Gleason grade 8–10, or ≥T3 disease, all individuals had high-risk prostate cancer. The patients who received EBRT and ADT, EBRT alone, and radical prostatectomy had 10-year cancer- specific survival rates of 92%, 92%, and 88%, respectively (P=0.06). Distant metastases and cause- specific survival did not vary significantly following multivariable risk adjustment.[15,7]

Diagnosis to bypass conventional and Nano medicine has revolutionized the field of medicine

Treatment protocols in the treatment of notorious cancers and various intracellular diseases. The use of nanotechnology in medicine can also result in improved transmembrane penetration, improved permeability retention, greater solubility, and tailored drug delivery. Both active and passive targeting can cause nanoparticles to accumulate in the tissues of tumours. Selecting a ligand receptor that is overexpressed in tumour cells is necessary for active tumour targeting. To deliver drugs to cancer cells specifically, a specific ligand can be attached using nanocarriers and bound to the overexpressed location. Galactosamine, transferrin, and folate are a few frequent types of ligands for tumours. Drug-loaded nanocarriers can enter the tumor's leaky vasculature and accomplish passive targeting. Prostate cancer patients now enjoy higher quality of life thanks to the successful synthesis of several forms of nanomedicines, such as metallic nanoparticles, immune-conjugates, polymer–drug conjugates, polymeric nanospheres, liposomes, and nioosomes. Numerous studies looking at the application of nanomaterials in environmental applications have been published up to this point. On the other hand, creating structured, multifunctional materials with the ability to target certain illnesses and safeguard therapeutic moieties using nanotechnology is the most urgent task. Functionalities that enable movement over biological barriers and quickly achieve the intended therapeutic benefits via comprehension of the toxicological consequences of nanomedicines are related to certain nanoscale characteristics. Clinical and regulatory examination of each nanopharmaceutical must be done on a case-by-case basis due to the possible environmental effect and the need for a safety assessment of all manufacturing processes.[36,37]

Treatment

Nanomaterials have been used in many applications during the past ten years, particularly in the treatment and targeting of illnesses. A carrier system needs to be able to transport a large concentration of medication effectively, be biocompatible, and be inert. Based on current understanding, the majority of carrier systems are unable to deliver drugs at high concentrations because of their increased cytotoxicity at the site of targeting. Consequently, many of the current therapeutic approaches are ineffective for treating cancer, particularly breast tumours in women and prostate cancer in men. One of the most prevalent illnesses, prostate cancer (PCa), requires a higher concentration of active medication to reach the organs and tissues impacted by the cancer. There are two types of nanocarriers that have demonstrated greater efficacy as drug delivery systems for more active pharmaceutical agents (API) for targeting prostate tumours: organic (nanoemulsions, liposomes, niosomes, and polymeric nanocapsule) and inorganic (carbon nanotubes, gold nanoparticles, magnetic nanoparticles, silica mesoporous nanoparticles, quantum dots, selenium nanoparticles). The following nanomaterials can be used to increase passive (increased permeability and retention effect, or EPR) and active (receptor mediated endocytosis, which is achieved by coating nanoparticles with various ligands).[6,9,10,15]

CONCLUSION

Improvements in technology and improved surgical and radiation methods have improved the prognosis for individuals with "high-risk" prostate cancer, both in terms of cancer control and decreased treatment-related morbidity.Well-planned and carried out clinical trials have demonstrated these gains. The field is in a unique position to shift the paradigm even further and start pushing the boundaries of curability beyond what can be accomplished with any single or dual- modality approach because of advancements in surgical technique, radiation biology, technical advancements in radiation delivery, and our understanding of the biology of the disease. nanocarrier drug delivery to prostate cancer. To improve diagnostic efficiency, and efficacy, as well as reduce side effects in prostate cancer, nanodrug delivery systems are being used for prostate cancer diagnosis and treatment. Thanks to the introduction of targeted therapeutic agents consisting of NPs, it is possible to diagnose and treat prostate cancer simultaneously. Their easily modified surfaces ensure the

adaptability of biomolecules, thus enhancing their ability to target the specific response sites to be studied. The use of such nanoplatforms may contribute to effective molecular imaging and treatment of prostate cancer.

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