DATA SCHEMA DESIGN IN CANCER TREATMENT BASED ON NANO PERSPECTIVES

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Abstract

In recent years, most human beings are affected by a disease called cancer. Early-stage detection of cancer leads to successful treatment for cancer patients. However, the rapid growth of Nano-HAp technology provides high precision, specificity, sensitivity, and multiplexed measurement to detect cancer cells with biomarkers using in-vivo and in-vitro imaging. Nano-HAp develops nanomedicine products to improve therapies against cancer. An efficient systematic pharmaceutical treatment of cancer tumors is a cytotoxic chemotherapy drug developed at a local drug delivery site. In this paper, nanoparticles and targeted systems have been investigated with clinical data to create a nano HAp schema for cancer-affected patients. Substantiate that anti-Cancer DOX (Doxorubicin) and cornerstone drug therapy of osteosarcoma and carcinoma treatment, shows a chemical reaction to Hydroxyapatite (HAp) of nano-HAp (nHAp), PEG (Polyethylene glycol), PBS solution (Phosphate Buffer Saline), FBS serum (Fetal Bovine Serum), (Sulphate doped HAp) nanosphere via the liposome of osteosarcoma and carcinoma cells where the environment creates and binds the nanoparticle drugs to release the drugs in the mitochondria and cytotoxicity in the HAp system delivery. In addition, chemotherapy and nHAp could be used as an intracellular delivery of nanoparticles which are used to destroy the cancer cells. Furthermore, nanoparticles potentially increase the safety of tumor measures and maintain the nano-HAp drug delivery database in tumor-targeting cancer therapy.

Keywords: Osteosarcoma, Carcinoma, Nano-HAp, Hydroxyapatite, Doxorubicin, Drug delivery, Nano-HAp Database Schema

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DOI: - 10.48047/ecb/2023.12.si5a.0154

I. Introduction

Bone cancer is one of the highly solid malignant tumors, mainly, they will be affecting only kids and youngsters. Lung cancer and breast cancer also affect many humans all over the world especially women affected by breast cancer. Nano HAp (doxorubicin, cytotoxicity, sulfate doping) standard protocol treatment is the backbone of drug delivery and has significantly improved the affected individuals' prognosis [1]. However, for responders and non-responders, the individuals can respond poorly, and the option is few members. Cancer Studies have shown that approximately 45- 60% of osteosarcoma, 50 % of lung cancer, and 80 % of breast cancer. The current chemotherapy protocol exhibit cancer patients a poor response with a five-year inferior survival of 45% - 55%, with a 5-year survival inferior of 45% - 55% [2], and the treatment of intensifying regimen by adding more drugs do not improve outcome but increases toxicity in patients [3, 4].

The accurate spatial and temporal drug release to target areas and enhanced cell drug absorption can greatly and effectively improve chemotherapy. Unfortunately, the limitations of the majority of the stimuli induced by chemotherapy drug delivery platforms predominate. Internal stimuli-responsive medication delivery systems, for instance, are unable to administer drugs precisely at the right dosage and target areas. The human body's bones or surrounding tissues may obstruct external stimuli like ultrasound and light, which have limited penetration into tumors.

The temperature-responsive system may experience substantial negative effects from potential tumor metastasis. Cancer tissues have a lower microenvironment pH than healthy tissues and blood, which affects the internal stimuli-responsive medication delivery mechanisms. For tumor-targeting therapy, pH can be used using nanomaterial-based drug carriers in pH drug delivery platforms. [5–7].

There is an unmet need to effectively administer cytostatic to the tumor tissue in a targeted manner to enhance the nano HAp materials outcome and limit side effects. The primary component of teeth and bones is hydroxyapatite (HA), and elemental calcium phosphate, with the chemical formula Ca10(PO4)6(OH)2, which have been thoroughly researched for a variety of clinical purposes. [8].

HAp can be synthesized and reduced to nanoparticle size. The benefit of having a relatively larger surface area than nanoparticles in a defined volume and size is that it significantly improves an agent's loading characteristics, thus it increases drug delivery capacity in the anti-tumor effect of nHA and its cytotoxicity cancer cells in-vitro [9–11].

A wide range of inorganic nanomaterials has been reported as new drug carriers for drug delivery applications, including gold nanoparticles [12-14], graphene [15], carbon nanotubes [16-19], MoS2 quantum dots [20-22], silica nanoparticles [23-25], carbon dots [26], and others. Nonetheless, the majority of these nanomaterials-based drug nanocarriers have poor degradability in the human body, potentially resulting in long-term toxicity. Because of its excellent biodegradability, biocompatibility, and bioactivity in the human body, hydroxyapatite (HAp) stands out as a promising nanocarrier [27-29].

As a result, HAp has found widespread use in drug delivery, bioimaging, dental implants, and other biomedical applications. Folic acid (FA) has been reported as a bioactive agent for selective drug delivery toward cancer cells for specific tumor-targeted drug delivery applications because FA can recognize cancer cells via positive targeting and thus improve the cellular uptake of drug carriers. [30, 31].

This work is focused on schema and system designing for nano HAp-based cancer therapy. Thus, drug loading and controlling to deliver drugs using the chemical structure of nano Hap might improve its killing of cancerous tumors in the body and increases nanomaterials to facilitate its clinical data and further treatment for cancer patients. The rest of the paper is organized as follows: Section II describes Nano Materials. Section III explains the Proposed Nano HAp Database Schema. Section IV shows the Results and Discussions. Finally, the Conclusion is given in Section V.

II. Nano Materials

A. Preparation of DOX and HAp

To prepare for the in-vitro evaluation and binding of DOX to HAp [32], 2 mL tubes were filled with 10 g DOX dissolved in Phosphate-Buffered Saline (PBS), and 1 mL tube containing nHA of varying sizes (10, 20, 40, and 80 mg). All of the nanotubes were mixed for 24 or 48 hours at 200 rpm. The particles were centrifuged after the chemical reaction, and the supernatants were collected. After that, the nanoparticles were thoroughly washed by resuspending them in PBS 1 mL 5

times. The concentration of DOX in the supernatants. 40 mg nHA was used for a 48-h reaction period to explore and maintain the relationship between binding the amount of DOX, and the dose of DOX was varied (10, 50, 100, 200, 400, and 800 g). The same volume of both nHA was measured in an Eppendorf tube to compare any differences in DOX binding affinity to nHA. 10 g DOX dissolved in 1 mL PBS was mixed and bound for 48 hours. To investigate the effect of proteins on DOX-HA binding, nHA particles (40 mg) were exposed to Fetal Bovine Serum (FBS) for 1 hour before being washed three times with PBS and reacted with DOX solution (100 g/mL). nHA particles were exposed to PBS for 1 hour as a control [32]. Figure 1 depicts a schematic study design evaluation of Nano HAp binding using DOX and HAp. [32].

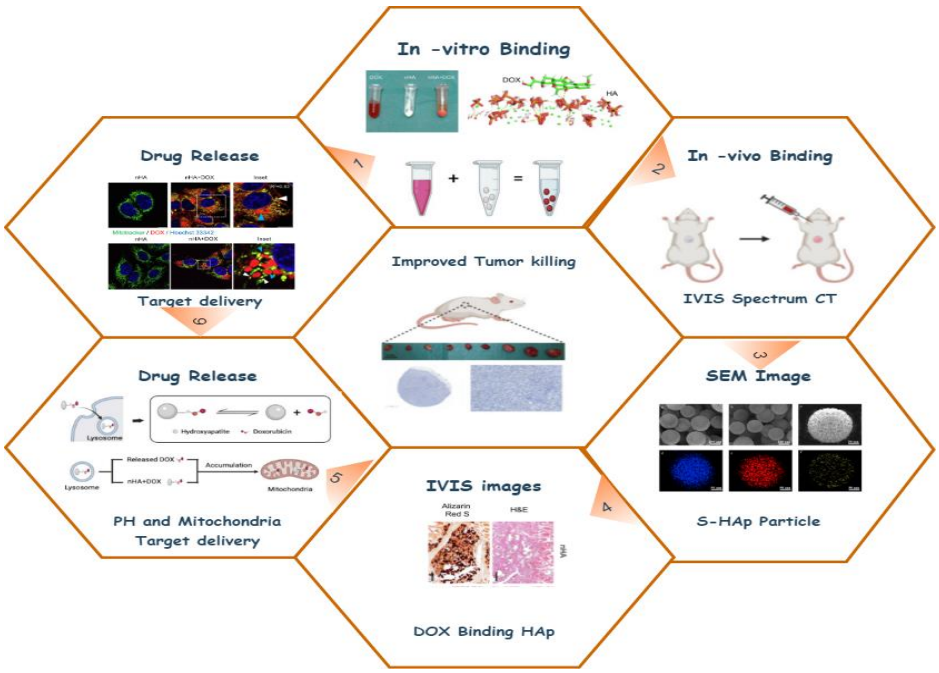

Fig. 1 Schematic Study Design of Nano HAp Material

B. Nano-HAp Material

Nano HAp-based nanomaterial was synthesized by chemical solutions using $Ca(NO_3)_2.4H_2O$ and $(NH_4)_2HPO_4$ as implemented in Sudip Mondal et al. A suspension of 0.24M of $Ca(NO_3)_2.4H_2O$ (23.6 g $Ca(NO_3)_2.4H_2O$ in distilled water with 350 mL) was mixed and maintaining the temperature at 40oc. Finally, 250 mL distilled water in (NH4)2HPO4 has added with $Ca(NO_3)_2.4H_2O$ solution. This experiment adjusted pH to 11 using an NH4OH solution. The Chemical reaction follows the formula given below [34].

$10\ Ca(NO_3)_2.4H_2O + 6\ (NH_4)_2HPO_4 + 8\ NH_4OH \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 20\ NH_4NO_3 + 20\ H_2O$ (1)

The nanoparticle-based cancer cell treatment analysis with SEM and TEM images using nano HAp is shown in Figure 2.

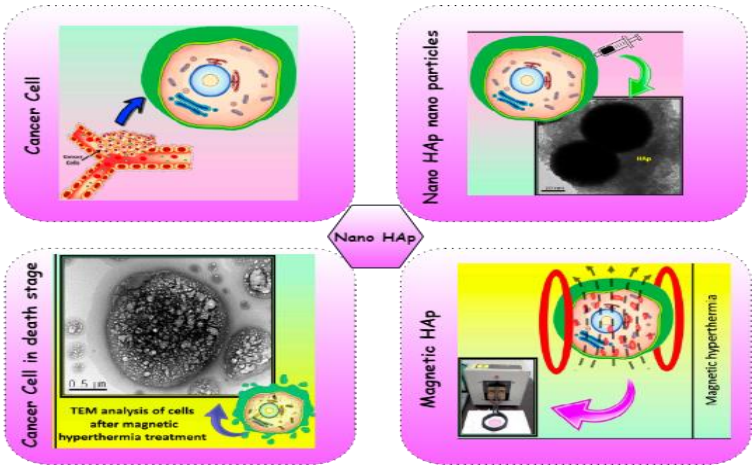

Fig. 2 Nano HAp based Cancer treatment

C. DOX synthesis to HAp

The first stage of nanoparticles is used to prepare the DOX solution and HAp solution. DOX is presented in orange or red color and nano HAp solution is presented in white color. When mixing DOX solution with nano HAp powder and dissolved in PBS solution. After mixing the solution, the white color HAp turned pink, and DOX turned lighter color after five times washing, it did not change the color of DOX. It has been an indirect sign of DOX interaction with HAp. The highest DOX is a 40 mg dose binding with nano HAp 10 mg in 24 hours. Binding the relationship between DOX and nano HAp to explore and increase binding DOX (10, 50, 100, 200, 400) being 91.8%. HAp with protein serum did not affect the DOX binding in pre-treatment.

D. Intercellular ingestion of nHAp loaded with DOX

The human tissue experiments of nHA+DOX, nHA-DOX, S-Hap / PEG/ FA / DOX, p53 / CD / NHAP, and PEGFP / PEI were prepared by mixing the correct solution and measuring the tumors in various experiments at different hours, and injecting human cells and killing the tissues. To make the storage of solution for tissue experiment.

E. Tumor detection in vivo and in vitro imaging

Live tumor detection investigates in vivo and in vitro imaging. In vitro composite chemicals preparation of drug materials and release of the drugs through cytotoxicity and vitro spectrofluorometer in SEM microstructure and composition material FTIR and XRD. It was tested with MTT and released the cytotoxicity drug. In vivo imaging is divided into two types, one is preoperative chemotherapy and postoperative chemotherapy. In preoperative performs 18 days of tumor growth and tested with tumor volume, PET-CT image, and Histology H&E. Finally postoperative performs one week in early response and three weeks of tumor growth and tested with tumor volume, PET-CT image, and Histology H&E, CD31, Ki 67 as shown in Figure 3 [35].

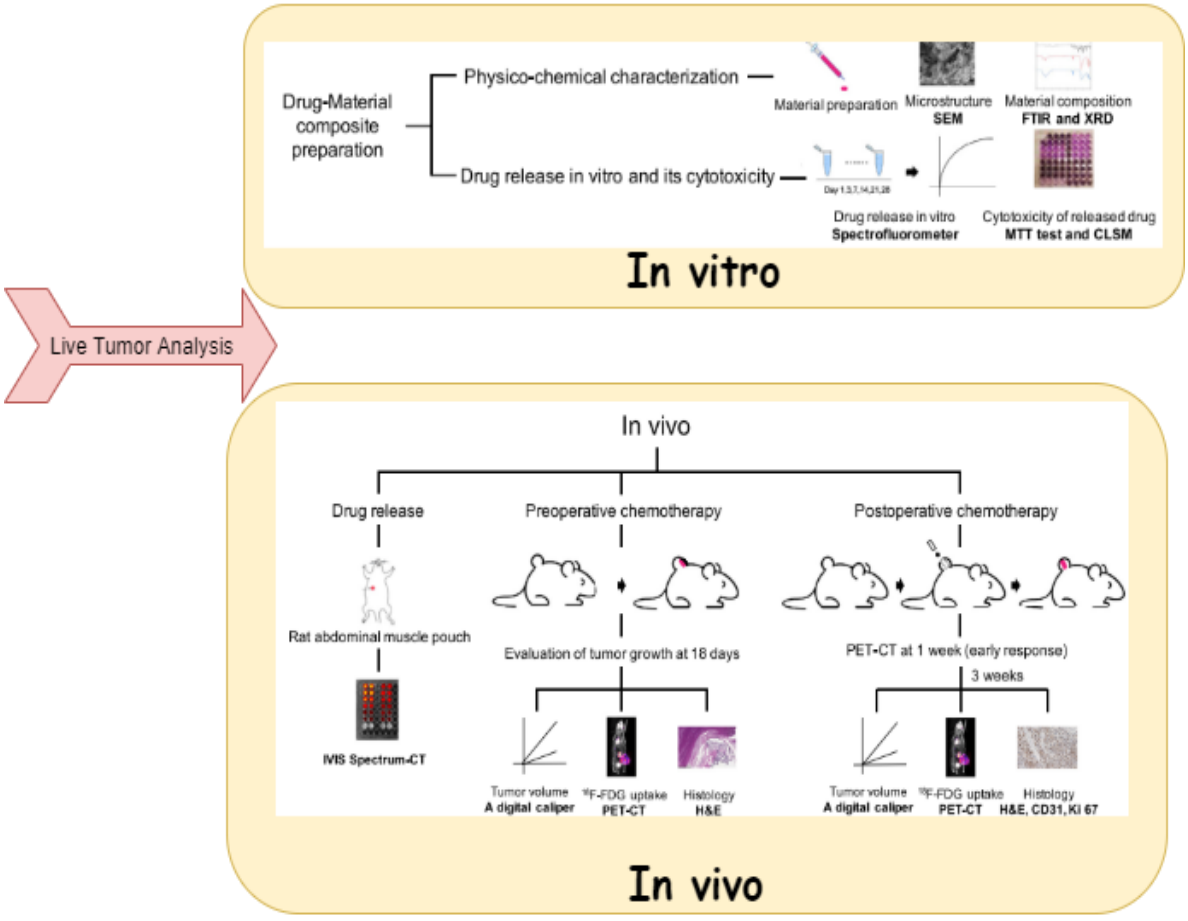

Fig. 3 In vitro and In vivo live tumor analysis

F. S-HAp/PEG/FA/DOX particle synthesis

S-HAp/PEG/FA/DOX particles were loaded in DOX by mixing them with DOX solution (0.2 mg/mL, 5mL and Suspension of S-HAp/PEG/ FA/DOX (5mg/mL, 5mL, PBS solution in dispersed at 7.4, dark magnetic stirring for 24 hours). Finally, the S-HAp/PEG/FA/DOX mixture was centrifuged, and the concentrations of DOX in the supernatant were determined using UV-V spectroscopy (Shimadzu, UV3600). To achieve the highest drug loading capacity, experiments were carried out with different concentrations of DOX (0.2, 0.4, 0.6, 0.8, and 1 mg/mL) on both S-HAp/PEG/FA and HAp/PEG/FA. The following equation could be used to calculate the DOX loading capacity.

$$DOX = \frac{m(Total\ numberof\ DOX) - m(DOX\ suspension)}{m(Drug\ carrier)}\ X\ 100\%$$

Finally, in the cytotoxicity study, the drug load in the delivery drug system at the DOX of one mg/mL was used to release the drugs.

G. Cytotoxicity of nHAP / DOX release

Human cell 143B (1x104 cells/ well), 96 well plate cells. Medium complete cell described above and it contains nHA of 25 μg/ mL or nHA -DOX (25-100 μg/ mL, 0.575-2.3 μg/ mL).

This nano solution was given to cells for 24h, after incubation and seeding. A positive control is used as a DOX containing (2.3 μg/ mL) medium. The biocompatibility to explore the HA particles was given to the cells 143B and MC3T3 cells. Different solution concentrations of 50, 100, and 200 μg/ mL were used for 2 days.

H. Drug targeting and drug release

Create the intracellular mitochondria-targeted delivery system used to deliver the DOX and HAp binding drugs to the human cell 143B and analysis with in vivo imaging. The SEM images show the size and shape of the tissues in concentration solutions given a period. The tumor volume and weight were measured with all the samples and given the drugs in target delivery at the time point.

I. Statistical analysis

All the data used for the experiments to calculate the mean ± standard deviation (SD) have been presented before performing statistical analysis to check for normality. DOX binds to HA to evaluate the A student t-test was used to analyze in vitro and in vivo DOX binds and measure ANOVA (Analysis of Variance) and a comparison test was used for multiple toxicities in different groups G1 for the control group, (G2 – G4) for pre-operative chemotherapy, and chemotherapy post-operative and four different treatment defined in groups by statistical significant values followed by $p < 0.05$ based on one way ANOVA analysis was carried out Prism 8 software processing all the data[32 - 34].

III. Proposed Nano HAp Database Schema

Concerning the above-existing literature, the proposed Nano HAp database schema is designed. The clinical data diagnosed from patients with cells from bone cancer, breast, and lung cancer cells size, shapes, drug level, and therapy information are stored in the database which generates in the schema. Doctors can easily retrieve the data from the proposed schema database and generate the query. The proposed database schema contains drug-loaded levels, nanoparticle references, human cells, nanomaterials, etc. The algorithm of the Nano HAp Carci Database Schema has been used to store and maintain patient information and drug level in a database, which can update, retrieve, and modify patient information and drug information easily. Thus, it generates the data proposed schema as shown in Algorithm 1.

Algorithm 1: Bio HAp Carci Database Schema
Input: Collection of attributes based on Cancer Images
Output: Generate the schema with data query
1: Load the patient information
2: Load the Bio HAp drug level material data
3: Read the Bio HAp drugs
4: Modify the patient information
5: Store the drug data and patient data in the database
6: Update the patient data and drug information
7: Retrieve the drug level data into the database
8: Delete the particle size info
9: Maintain Carci(cancer) and Bio HAp drug information
10: Generate the Bio HAp Carci Database Schema

Proposed cancer clinical data algorithm

The proposed clinical data architecture of the Nano HAp database schema contains osteosarcoma, lung, and breast cancer which are stored in the database as shown in Figure 4

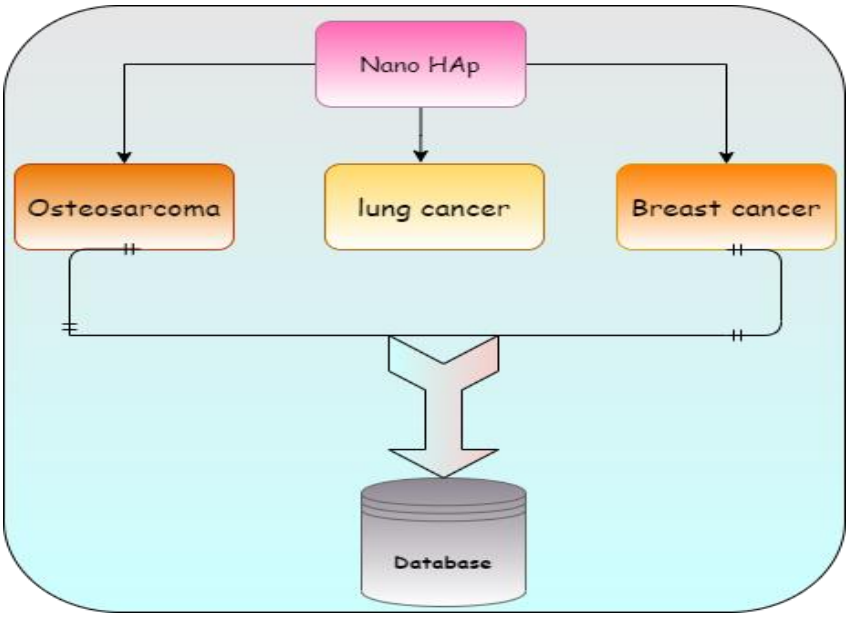

Fig. 4 Proposed cancer clinical data architecture

IV. Results and Discussions

Doctors' diagnosis of cancer tissues based on in vivo and in vitro images and Hap-based therapy (Chemotherapy) for cancer cells are used to store in the Hap-based information like patient id, the nanomaterial, primary particle size, shape, drug delivery, and the surface of the nanoparticle. In vivo and in vitro, fluorescent cancer digital images are acquired and stored in a database. Digital image processing techniques are used to measure the area of defective cancer cells and tumor size. According to the affected measured area of the cancer cells, respective size and shape can fetch the related HAp information from the database. It facilitates to development of a Nano HAp-based clinical database and delivers the HAp drugs for cancer patients. The significance of delivering Nano-HAp-related drugs to cancer patients is helpful to reduce cancer with the help of a clinical database. Nano HAp schema and system design are helpful to kill human cancer cells with the digitized world based on therapy. The proposed Carci (cancer) database schema is shown in Figure 5.

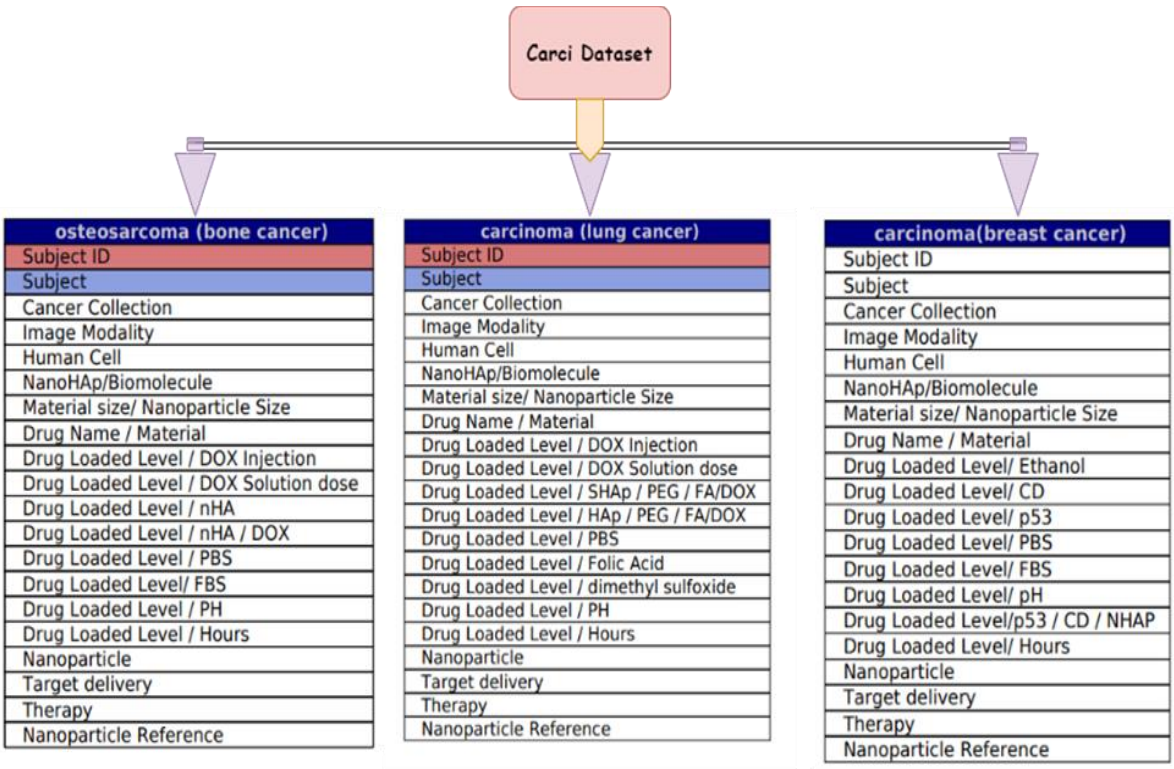

Fig. 5 Proposed Carci (Cancer) Clinical Data Schema Design

Proposed Cancer Clinical Data of Osteosarcoma cancer contains 21 attributes with attribute information are Subject ID, Subject, Cancer Collection, Image Modality, Human Cell, NanoHAp/Biomolecule, Material size/ Nanoparticle Size, Drug Name / Material, Drug Loaded Level / DOX Injection, Drug Loaded Level / DOX Solution dose, Drug Loaded Level / nHA, Drug Loaded Level / nHA / DOX, `Drug Loaded Level / PBS, Drug Loaded Level/ FBS, Drug Loaded Level / PH, Drug Loaded Level / Hours, Nanoparticle, Target delivery, Therapy, Nanoparticle Reference as shown in Table 1.

TABLE 1. OsteosarcomaCancerr Clinical Dataset

Subject ID	1	2	3	4
Subject	Human	Human	Human	Human
Cancer Collection	Osteosarcoma / Bone Cancer	Osteosarcoma / Bone Cancer	Osteosarcoma / Bone Cancer	Osteosarcoma / Bone Cancer
Image Modality	PET/ CT	PET/ CT	PET/ CT	PET/ CT
Human Cell	143B (1 *10 power 4 cells) and C3T3	143B (1 *10 power 4 Cells) and MC3T3	143B (1 *10 power 4 cells) and MC3T3	143B (1 *10 power 4 cells) and MC3T3
NanoHAp/Biomolecule	nHa+DOX	nHa+DOX	nHa-DOX	nHa-DOX
Material size/ Nanoparticle Size	20-50nm	20-50nm	20-50nm	20-50nm
Drug Name / Material	Anticancer Doxorubicin, Hydroxyapatite powder, nano-hydroxyapatite paste,143B human Osteosarcoma cell	Anticancer Doxorubicin, Hydroxyapatite powder, nano-hydroxyapatite paste,143B human Osteosarcoma cell	Anticancer Doxorubicin, Hydroxyapatite powder, nano-hydroxyapatite paste,143B human Osteosarcoma cell	Anticancer Doxorubicin, Hydroxyapatite powder, nano-hydroxyapatite paste,143B human Osteosarcoma cell
Drug Loaded Level / DOX Injection	0, 0.5, 1.0 and 2.0 mg	0, 0.5, 1.0 and 2.0 mg	0, 0.5, 1.0 and 2.0 mg	0, 0.5, 1.0 and 2.0 mg
Drug Loaded Level / DOX Solution dose	2.3µg /mL	1mg /mL	12.5µg /mL	12.5µg /mL
Drug Loaded Level / nHA	50µg/mL	40mg	50µg/mL	50µg/mL
Drug Loaded Level / nHA / DOX	25-100µg / mL	23µg / 23mL	25-50µg / mL	50-100-200µg / mL
Drug Loaded Level / PBS	2 mL	2 mL	2 mL	2 mL
Drug Loaded Level/ FBS	1%	1%	1%	1%
Drug Loaded Level / PH	6%	6%	6%	6%
Drug Loaded Level / Hours	24 hrs	48 hrs	24 hrs	48 hrs
Nanoparticle	Liposome	Liposome	Liposome	Liposome
Target delivery	Mitochondria / Cytotoxicity	Mitochondria / Cytotoxicity	Mitochondria / Cytotoxicity	Mitochondria / Cytotoxicity
Therapy	Chemotherapy	Chemotherapy	Chemotherapy	Chemotherapy
Nanoparticle Reference	https://doi.org/10.1016/j.mtbio.2022.100227			

Proposed Cancer Clinical Data of lung cancer contains 21 attributes with attribute information are Subject ID, Subject, Cancer Collection, Image Modality, Human Cell, NanoHAp/Biomolecule, Material size/ Nanoparticle Size, Drug Name / Material, Drug Loaded Level / DOX Injection, `Drug Loaded Level / DOX Solution dose`, `Drug Loaded Level / SHAp / PEG / FA/DOX, Drug Loaded Level / HAp / PEG / FA/DOX, Drug Loaded Level / PBS, Drug Loaded Level / Folic Acid, Drug Loaded Level/dimethyl sulfoxide, Drug Loaded Level / PH, Drug Loaded Level / Hours, Nanoparticle, Target delivery, Therapy, Nanoparticle Reference as shown in Table 2.

TABLE 2. LUNG CANCER CLINICAL DATASET

Subject ID	1	2
Subject	Human	Human
Cancer Collection	Lung Cancer / Carcinoma	Lung Cancer / Carcinoma
Image Modality	SEM images(A Scanning Electron Microscope)	SEM images(A Scanning Electron Microscope)
Human Cell	A549 / 96 well-plate	A549 / 96 well-plate
NanoHAp/Biomolecule	S-Hap / PEG/ FA / DOX	S-Hap / PEG/ FA / DOX
Material size/ Nanoparticle Size	Nanosphere 200 nm - 400 nm in diameter/ tumor size 50nm	Nanosphere 200 nm - 400 nm in diameter/ tumor size 50nm
Drug Name / Material	Sulphate-doped HAP (S- Hap), Polyethylene glycol (PEG), Folic acid(FA), Doxorubicin	Sulfate-doped HAP (S- Hap), Polyethylene glycol (PEG), Folic acid(FA), Doxorubicin
Drug Loaded Level / DOX Injection	0. 2, 0.4, 0.6, 0.8 and 1 mg /mL	0. 2, 0.4, 0.6, 0.8 and 1 mg /mL
Drug Loaded Level / DOX Solution dose	0.2 mg / mL, 5 mL	0.2 mg / mL, 5 mL
Drug Loaded Level / SHAp / PEG / FA/DOX	5 mg / mL	5 mg / mL
Drug Loaded Level / HAp / PEG / FA/DOX	1 mg/ 1 mL	1 mg/ 1 mL
Drug Loaded Level / PBS	5 mL / 7.4	5 mg/ mL / 0.2 mL
Drug Loaded Level/ / Folic Acid	100 mg	100 mg
Drug Loaded Level/ / dimethyl sulfoxide	DMSO,10 mL	DMSO,10 mL
Drug Loaded Level / PH	7.4	0.2 mL
Drug Loaded Level / Hours	24 hours	48 hours
Nanoparticle	Sulfate doping Hap nanosphere	Sulfate doping Hap nanosphere
Target delivery	Nanosphere / Cytotoxicity	Nanosphere / Cytotoxicity
Therapy	Chemotherapy	Chemotherapy
Nanoparticle Reference	https://doi.org/10.1016/j.ceramint.2020.08.015	

Proposed Cancer Clinical Data of breast cancer contains 21 attributes with attribute information are Subject ID, Subject, Cancer Collection, Image Modality, Human Cell`, NanoHAp/Biomolecule, Material size/ Nanoparticle Size, Zero potential (mV), Drug Name / Material, Drug Loaded Level/ Ethanol, Drug Loaded Level/ CD, Drug Loaded Level/ p53, Drug Loaded Level/ PBS, Drug Loaded Level/ FBS, Drug Loaded Level/ pH, Drug Loaded Level/p53 / CD / NHAP, Drug Loaded Level/ Hours, Nanoparticle, Target delivery, Therapy as shown in Table 3.

TABLE 3. BREAST CANCER CLINICAL DATASET

Subject ID	1	2	3
Subject	Human	Human	Human
Cancer Collection	Breast Cancer / Carcinoma	Breast Cancer / Carcinoma	Breast Cancer / Carcinoma
Image Modality	in vitro and in vivo experiments	in vitro and in vivo experiments	in vitro and in vivo experiments
Human Cell	Density of 1.0 x 10 power 4 cells / well (96- well plates)	Density of 1.0 x 10 power 4 cells / well (96- well plates)	Density of 1.0 x 10 power 4 cells / well (96- well plates)
Nano HAp/Biomolecule	p53 / CD / NHAP	PEGFP / PEI	PEGFP / PEI
Material size/ Nanoparticle Size	50.3nm	60 nm	156.4 nm
Zero potential (mV)	negative 21.5 mV	positive 30.8 mV	negative 16.54 mV
Drug Name / Material	plasmid 53, Candesartan (CD), Nano hydroxyapatite	plasmid 53, Candesartan (CD), Nano hydroxyapatite	plasmid 53, Candesartan (CD), Nano hydroxyapatite
Drug Loaded Level/ Ethanol	10 mg/mL	10 mg/mL	10 mg/mL
Drug Loaded Level / CD	5 mg	5 mg	5 mg
Drug Loaded Level / p53	0.1 mg/ mL	0.1 mg/ mL	0.1 mg/ mL
Drug Loaded Level / PBS	-	-	-
Drug Loaded Level/ FBS	-	-	-
Drug Loaded Level / PH	7.4	7.4	7.4
Drug Loaded Level / p53 / CD / NHAP	10, 20, 50, 100, 150, and 200 μg/ mL	10, 20, 50, 100, 150, and 200 μg/ mL	10, 20, 50, 100, 150, and 200 μg/ mL
Drug Loaded Level / Hours	24, 48, and 72 hours	24, 48, and 72 hours	24, 48, and 72 hours
Nanoparticle	p53 / CD / NHAP	p53 / CD / NHAP	p53 / CD / NHAP
Target delivery	Gene	Gene	Gene
Therapy	anti- angiogenesis	anti- angiogenesis	anti- angiogenesis
Nanoparticle Reference	10.12659/MSM.902538		

V. Conclusion

This proposed work has presented a Nano HAp database schema design which is highly useful to develop biomaterial drug delivery for cancer therapy based on existing literature [34 -36] and created the clinical data information in a nutshell. This HAp clinical data provides size, shapes, drug level, target delivery, therapy, and existing nanoparticle as mentioned in the following references. With this proposed system, doctors can easily access one place to refer to the HAp clinical database which is implemented with rats and human cells. It is observed that the human cells have been purchased in different countries and therapy has been carried out with Nano HAp drugs through Cytotoxicity (Chemotherapy) in patients to monitor the cancer patient tissue in their bodies and reduce cancer tissues stage by stage analysis within vivo and in vitro imaging, SEM, TEM images and XRD. Thus, the proposed Nano HAp schema in the biomaterial world facilitates predicting cancer in an early stage, the final stage of malignant tumor detection. Thus, the Nano HAp therapy helps to damage cancer cells of the patients to recover fast and safely to save their life.

Acknowledgment

This research was supported by the MHRD RUSA 2.0 funding under the scheme Research Innovation and Quality Improvement of Biomaterials - Nano informatics on the role of Nano - HAp in cancer diagnostics and therapy: Schema and System Design from the University of Madras.

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