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A study on drug delivery tracing with radiolabeled mesoporous hydroxyapatite nanoparticles conjugated with 2DG/DOX for breast tumor cells

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Abstract

BACKGROUND: Mesoporous nanoparticles have a great potential in targeted therapy approaches due to their ideal properties for encapsulation of various drugs, proteins and also biologically active molecules.

MATERIAL AND METHODS: We used mesoporous hydroxyapatite (HA) nanoparticles as a drug carrier and developed radiolabeled mesoporous HA containing of 2-deoxy-D-glucose (2DG) and Doxorubicin (DOX) with technetium-99m (^{99m}Tc) for imaging in *in vitro* and *in vivo* studies.

RESULTS: 2DG and DOX in presence of mesoporous HA nanoparticles more reduced the fraction of viable cells in the MDA-MB-231, MCF-7 human and MC4-L2 Balb/c mice breast cancer cells. The radiochemical purity of the nano-2DG-DOX complex with ^{99m}Tc was calculated to 96.8%. The results of cellular uptake showed a 44.77% increase in uptake of the [^{99m}Tc]--nano-2DG-DOX compared to the complex without nanoparticles ($p < 0.001$).

CONCLUSIONS: Radioisotopic imaging demonstrated a high biochemical stability for [^{99m}Tc]-nano-2DG-DOX complex. The results demonstrated that [^{99m}Tc]-nano-2DG-DOX, may be used as an attractive candidate in cancer imaging and treatment managing.

KEY words: 2-deoxy-D-glucose, breast cancer, doxorubicin, nanoparticle, targeted therapy, ^{99m}Tc

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Introduction

In the past decades, tremendous efforts have been devoted to design and functionalize a wide variety of chemical nanoplatforms such as liposomes, polymeric micelles, and also magnetic, gold and carbon nanostructures. The nanopharmaceutical systems, as tumor-targeting carriers, were studied in selective antineoplastic drug delivery and noninvasive imaging of tumors by imaging techniques [1–4]. Mesoporous nanoparticles have attracted much attention due to their tailorable structures, high specific surface areas, large pore volumes and proper encapsulation of drugs, proteins and other biologically active molecules [1, 2].

Hydroxyapatite (HA) is another category of nanoplatforms, which seems promising for effective delivery system of drugs and biological molecules. Some characteristics of this nanoparticle such as biocompatibility, bioactivity, diverse morphologies, non-toxicity and loss of mutagenicity has made it one of the most efficient systems suitable as a drug carrier [2, 3, 5]. Delivery of chemotherapeutics to cancer cells with the goal of reducing toxic effects on healthy tissues is of critical importance. Although, development and optimization of various strategies for improvement of this new delivery approach is a major challenge for future cancer targeted imaging and therapy [1, 4, 6–9]. Various targeting ligands have been conjugated to HA nanoparticles, which have shown proper tumor cell targeting and enhanced therapeutic efficacy *in vitro*. Mesoporous HA has many advantages over other drug delivery

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systems including high drug loading capacity, controllable drug release system and co-delivery of two or more drugs and also therapeutic modalities in combination therapy [2, 10].

Combination of chemotherapeutics is a particularly encouraging approach for optimizing cancer therapy. The combination of 2-deoxy-D-glucose (2DG), structural analogue of glucose, and doxorubicin (DOX), a commonly used anticancer chemodrug, have shown a significant cell toxicity on cells with a rapid dividing capacity (T47D) compared to 2DG or DOX alone [11–13]. Also it was found that 2DG and DOX loaded with mesoporous HA could enhance the susceptibility of breast cancer cells to chemotherapy and radiotherapy [2, 10].

Recent researches on nuclear medicine imaging have focused on development of novel radiopharmaceuticals with improved properties to provide a better imaging results in a variety of diseases including cancer. Molecular imaging is a non-invasive procedure for functional medical imaging in the detection, diagnosis and monitoring response to therapy at cellular level in the living subjects [14–16]. PET and SPECT imaging techniques have been proven to be useful in detecting of malignancies in the initial stages [17]. ^{99m}Tc is the most frequently used radioisotope regarding to its ideal physical (T1/2 = 6 hours, gamma energy 140 keV) and chemical properties. This radioisotope represents as an attractive candidate for labeling a wide variety of chemical structures including nanoparticles [4, 18, 19].

Here, the nano-2DG-DOX complex was labeled with ^{99m}Tc for an uptake study of breast cancer cells.

Materials and methods

General

The working solutions of 2DG and DOX (purchased from Sigma-Aldrich Co., UK and Sobhan Chemotherapeutics Co., Iran, respectively) were prepared by dissolving 1M DOX in PBS to a final concentration of 1 μM and 2DG to 0.5 mM. 2DG and DOX were loaded with 10 mg/mL of mesoporous HA with a_s, BET = 141 (m2g-1), $r_{p,peak}$ (Area) = 4.03 (nm) and total pore volume (P/P0) = 0.5001 (cm3g-1) in room temperature. An optimum concentration of 200 ppm and 5 ppm for 2DG and DOX was found as a suitable loading and releasing profile with mesoporous HA, respectively [2, 3, 20]. MDA-MB-231 cell line was purchased from National Cell Bank of Iran (Pasteur Institute, Iran) and MCF-7 and MC4-L2 cell lines were provided from Iranian Biological Resource Center (IBRC, Iran). The animals were also purchased from the Pasteur Institute, Iran.

Radiolabeling with ^{99m}Tc

The labeling process was done in the three repetitions by addition of 200 μg $SnCl_2$ ($2H_2O$) to 2 mL of 2DG/DOX loaded mesoporous HA as reducing agent, and then adding 1ml of generator-eluted $^{99m}TcO_4^-$ (aqueous pertechnetate solution, 1000 MBq activity) and incubating at room temperature for 60 minutes. The resulting ^{99m}Tc-complex was filtered through a 0.2-μm pore syringe filter. Radiochemical purity was examined by R-TLC [21], using Whatman filter paper grade 3 as the stationary phase, acetone and 0.9% saline solution as the mobile phase [5]. The strips of the filter were cut after elution in appropriate time and counted with a gamma counter (Leybold, Germany). The stability of [^{99m}Tc]-nano-2DG-DOX was also assayed three times with the R-TLC method following incubation at room temperature for 1, 4 and 24 hours.

Cell culture and treatment

MCF-7 adenocarcinoma (ER+), MB-MDA-231 carcinoma (ER-) [22, 23] and MC4-L2 (ER+) breast cancer cells were used in this study [24]. The cell lines were cultured in RPMI-1640 media supplemented with 10% heat-inactivated (50°C, 30 minutes) fetal bovine serum (FBS), penicillin (100 U/mL), streptomycin (100 μg/mL), and amphotericin B (0.25 μg/mL) at 5% CO_2 and 95% air in a humidified 37°C incubator [11].

MTT cell viability assay

MB-MDA-231 (7×10^3 cells/well), MCF-7 (10×10^3 cells/well) and MC4-L2 (8×10^3 cell/well) cell lines were incubated in 96-well plates each containing 200 μL of the supplemented cell culture media for 24 hours at 37°C and 5% CO_2. The cells were divided in 8 groups in triplicates: blank, DOX, 2DG, 2DG/DOX, all in presence and absence of the nanoparticles, and also nanoparticle alone, all in triplicates. The rate of cellular proliferation was measured following 24 hours treatment with MTT assay. Briefly, 50 μL of 2 mg/mL MTT (3-(4, 5-dimetylthiazol-2-yl)-2, 5-diphenyltrazolium bromide) (Roche Diagnostics GmbH, Mannheim, Germany) was added to each well. The cells were incubated at 37°C and 5% CO_2 for 4 hours and then the media was discarded and 200 μL of dimethyl sulfoxide (DMSO) was added to each well to solubilize the colored Formazan product and then 25 μL Sorenson's buffer was added to each well as solubilizer buffer. Finally, the absorbance was read using an ELISA plate reader (Biotech, Bad Friedrichshall, Germany) at 570 nm wavelength. All the calculated data were analyzed relatively to the untreated cells and then normalized [11].

Cellular uptake assay

For an uptake study, MCF-7, MDA-MB-231 and MC4-L2 cells were seeded in 12-well plates containing 80,000 cells per well. The plates grouped in control and treated including; ^{99m}Tc, [^{99m}Tc]-nanoparticle, [^{99m}Tc]-2DG-DOX and [^{99m}Tc]-nano-2DG-DOX, respectively. The activity was 0.037 MBq in the treatments. After incubation for 4 hours (due to T1/2 = 6 hours ^{99m}Tc) at 37°C, the cells were washed with phosphate-buffered saline (PBS) three times and then trypsinized to form the cell suspensions. The suspension was placed in the gamma counter and the uptake of the cells was determined [21, 25].

^{99m}Tc-2DG/DOX Imaging

All invasive procedures were done while the animals were under anesthesia (1 ml/kg i.m. of a solution containing 13 mg of Ketamine and 86 mg of Xylazine per mL).

The aim of *in vivo* study was to trace differential uptaking of the [^{99m}Tc]-nano-2DG-DOX also ^{99m}Tc after intravenous injections by carrying out a scintigraphic imaging in normal Balb/c mice weighting 20–30 grams. The dorsal and ventral images were obtained with a triple head digital SPECT gamma camera (IRIX Marconi; Philips, USA) equipped with LEHR collimators (Matirx: 128 × 128, Mag: 3.2, Pixel Size: 1.46 mm and Time: 5 minutes). The images were acquired two hours after injection of 0.2 mL of the radiolabeled complex (3.7 MBq of [^{99m}Tc]-nano-2DG-DOX) and also 0.2 mL ^{99m}Tc (3.7 MBq) alone through the tail vein of the animals.

Statistical analysis

All the data were expressed as means ± standard error of the mean (SEM). One-way analysis of variance (ANOVA) was used to compare differences among the treated groups. A Student's t-test was performed for comparisons of the treated groups also with and without nanoparticles. Data analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 16.0 for Windows (SPSS Inc., Chicago, Illinois, USA). A probability value of less than 0.05 was considered statistically significant.

Results

Results on ^{99m}Tc labeling of nano complex 2DG/DOX

Results of R-TLC showed a high efficiency of the nano-2DG-DOX complex labeling, with the mean percentage of 93.367 ± 3.61% for all the labeling times with the highest percentage up to 96.8% (Fig. 1) for 1 hour ($p = 0.09$). The stability of the complex reached to 96.1% when $^{99m}TcO_4^-$ was added to nano-2DG-DOX at room temperature after 1 hour (Fig. 2). The percentage of stability of the nano complex was obtained 90.467 ± 5.06 for the assay times of 1, 4 and 24 hours (all $p < 0.001$).

Results on cytotoxic effects of the treatments on MDA-MB-231, MCF-7 and Mc4-L2 breast cancer cell lines

The results of cell viability analysis in the three types of treats in presence and absence of nanoparticle on the cell lines have been summarized in Table 1. Treatment of the cells for 24 hours with a combination of 2DG and DOX have shown a significant cell killing effects in MDA-MB-231 cells (65.2 ± 6.56%) compared to 2DG alone (81.5 ± 2.89%) ($p < 0.001$), and MC4-L2 cells (50.2 ± 1.04%) compared to 2DG (85.7 ± 4.06%) or DOX (71.8 ± 1.75%) alone ($p < 0.001$) than in the control whereas no significant difference in MCF-7 cells ($p > 0.05$). Incubation of the cells with the nano drugs for 24 hours reduced the fraction of viable cells compared to the drugs alone ($p < 0.001$).

The differences in viability of the treatments labeled with ^{99m}Tc were not significant compared to the unlabeled [MDA-MB-231 ($p = 0.893$), MCF-7 ($p = 0.870$) and MC4-L2 ($p = 0.963$)].

Results on cellular uptake

Uptake of [^{99m}Tc]-nano-2DG-DOX, in MDA-MB-231, MCF-7 and MC4-L2 breast cancer cells was significantly increased compared to the [^{99m}Tc]-2DG-DOX and ^{99m}Tc (with and without nanoparticle) groups when analyzed 4 h after the treatments (Fig. 3) ($p < 0.001$).

[^{99m}Tc]-nano-2DG/DOX Imaging

Radioisotopic images of the normal Balb/c mice with [^{99m}Tc]--nano-2DG-DOX and ^{99m}Tc alone were presented in Figures 4 and 5.

Discussion

In this study, a complex of mesoporous HA nanoparticle with 2DG and DOX was prepared and labeled with ^{99m}Tc. The radiochemical purity and also stability assays of the labeled nano complex were performed by R-TLC method at room temperature in 1, 4 and 24 hours intervals and the highest purity and also stability was found for 1 hour labelling. The treatment reduced

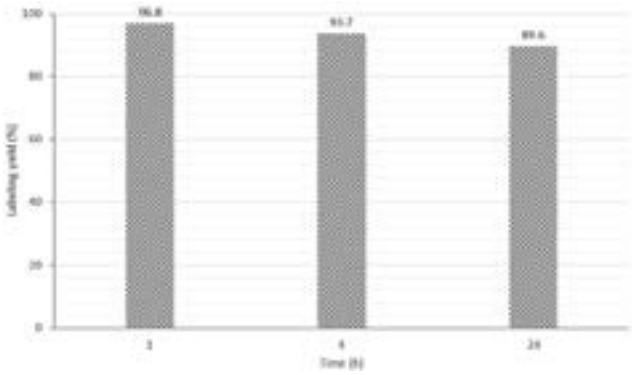

Figure 1. Labeling yields of [^{99m}Tc]-nano-2DG-DOX assayed by R-TLC method

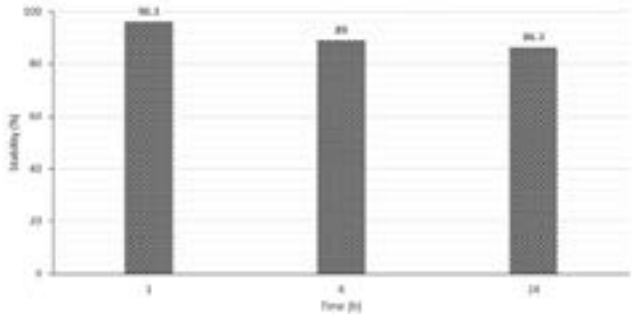

Figure 2. Stability of [^{99m}Tc]-nano-2DG-DOX assayed by R-TLC method

Table 1. The results on viability of MDA-MB-231, MCF-7 and MC4-L2 cells following treatment with mesoporous HA nanoparticles with and without DOX and 2DG. The cells were cultivated for 24 hours under the standard growth conditions

Cell Line	Cell Viability [%]						
	2DG[a]	DOX[b]	2DG + DOX	Np[c]	2DG+NP	DOX+NP	2DG+DOX+NP
MDA-MB-231	81.5 ± 2.89	67.7 ± 2.66	65.2 ± 6.56	91.4 ± 3.94	49.1 ± 2.27	48 ± 2.76	39.8 ± 2.89
MCF-7	92.2 ± 1.89	77.5 ± 2.5	88.5 ± 7.94	93.6 ± 1.89	52.4 ± 1.73	54.4 ± 10.99	66.1 ± 8.31
MC4-L2	85.7 ± 4.06	71.8 ± 1.75	50.2 ± 1.04	98.5 ± 3.6	59.5 ± 1.87	52.6 ± 1.27	55.4 ± 3.08

[a]2DG — 2-deoxy-D-Glucose; [b]DOX — Doxorubicin; [c]NP — Nano Particle

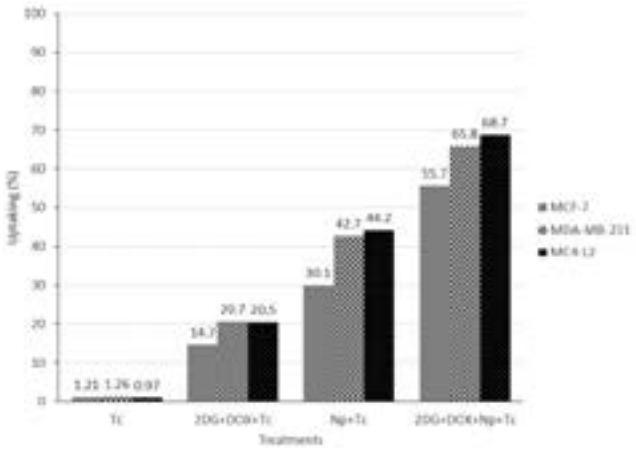

Figure 3. In vitro cellular uptake of [^{99m}Tc]–2DG/DOX and also ^{99m}Tc with and without nanoparticle in MDA-MB-231, MCF-7 and MC4-L2 cells

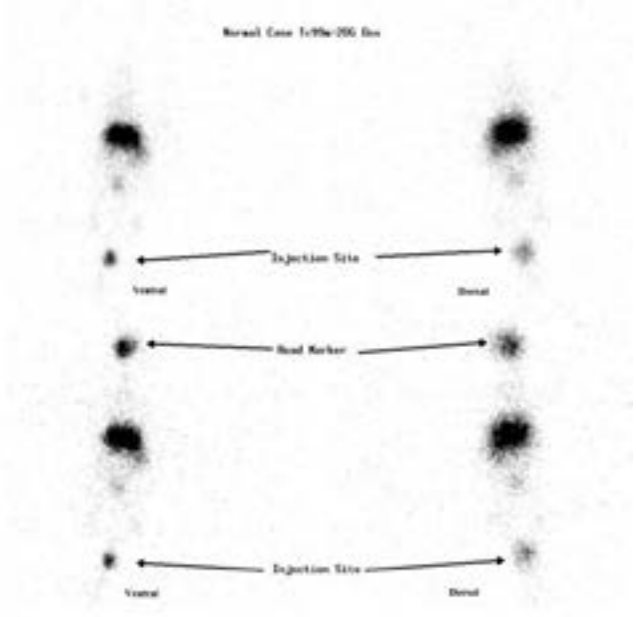

Figure 4. Planar imaging obtained at 2 hours after administration 3.7 MBq of [^{99m}Tc]-2DG/DOX in the normal Balb/c mice. There was no sign of radioactivity in thyroid and salivary gland, or gastric mucosa

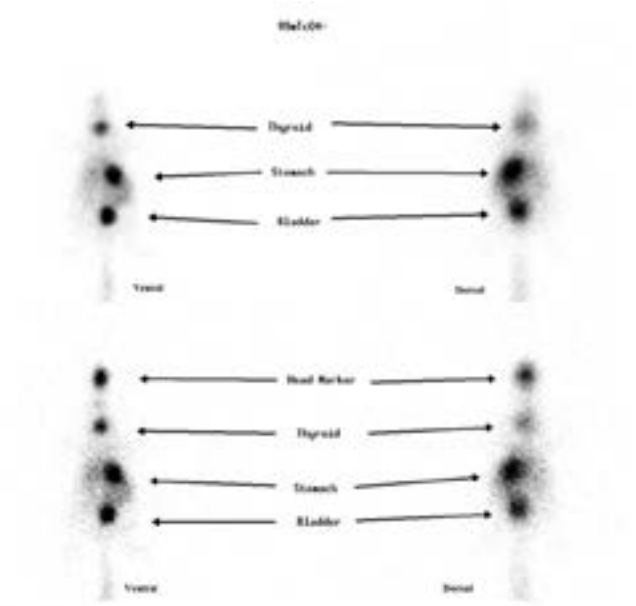

Figure 5. Planar imaging obtained at 2 hours after administration 3.7 MBq of ^{99m}Tc in the normal Balb/c mice

viability in the cells was significant compared to the untreated controls ($p < 0.001$). Also the cellular uptake of [^{99m}Tc]-nano-2DG-DOX was calculated to 65.8%, 55.7% and 68.7% in the three cell lines, respectively, at room temperature 4 h after the treatment *in vitro*. In radioisotopic imaging studies, the percentages of reduced [^{99m}Tc]--nano-2DG-DOX uptake was found 96.56%, 84.57%, and 80.10% in salivary glands, stomach and bladder of normal Balb/c mice, respectively, compared to ^{99m}Tc alone 2 hours after the injection.

The combination of 2DG and DOX was reduced cellular viability to some extent in slowly growing MCF-7 cells, while a significant cell killing was induced in rapidly dividing cells including MDA-MB-231 and MC4-L2 (Table 1). These results confirmed previous studies on growth inhibition and cytotoxicity of combined 2DG/BSO and also 2DG/DOX in MDA-MB-231 [22] and MCF-7 [13] cells. However, mesoporous HA nanoparticles alone was shown non-toxic effects on the three cell lines (Table 1). Meanwhile, mesoporous HA nanoparticles containing 2DG or DOX and also in the combination decreased the cell viability 24 h after the treatments. The results on viability confirmed the previous study on the reducing viability of magnetic mesoporous HA coated by SPIONs nanoparticles, containing DOX and 2DG, on T47D and SKBR3 cell lines [2, 10]. The Minor differences with our findings may related to the difference sensitivity of the studied cell lines.

The [^{99m}Tc]-nano-2DG-DOX exhibited an excellent labeling efficiency (> 93.37%) (Fig. 1). In addition, the difference on nano complex cellular uptake compared with [^{99m}Tc]-2DG-DOX, [^{99m}Tc]--nanoparticle, and ^{99m}Tc alone was obtained 63.4%, 18.6%, 39%, and 1.15%, respectively (Fig. 3). Therefore, it suggests an increased uptake capability in human and mice breast cancer cells. The obtained results are in agreement with the previous studies on the radiolabeling, uptaking and also biodistribution of [^{99m}Tc]-DTPA-DG [21], [^{99m}Tc]–2-[(3-carboxy-1-oxopropyl)amino]-2-deoxy-D-glucose [26], [^{99m}Tc]-DOX loaded nanoparticles [27] and [^{99m}Tc]-nano hydroxyapatite [5]. Our results on the labelling and cell uptaking of [^{99m}Tc]-nano-2DG-DOX could confirm the claim that the radiolabeled nanoparticle is an attractive candidate in cancer therapy, owing to its great potential for radioisotopic imaging study [4, 18, 28, 29].

Furthermore, the radioisotopic imaging study of [^{99m}Tc]--nano-2DG-DOX in the normal Balb/c mice was performed to ascertain whether the organ uptake of the nano complex was perfusion related. The images were also acquired with ^{99m}Tc alone in the normal mice 2 hours after injection. The difference on [^{99m}Tc]--nano-2DG-DOX uptake in thyroid, salivary gland and gastric mucosa compared to ^{99m}Tc alone (Fig. 4), indicating the related suitable bio-stability may provide a differential absorption for further tumor study *in vivo*.

Conclusions

In this study, we demonstrated the potential of mesoporous HA nanoparticles as the drug carrier in enhancing tumor targeted delivery of 2DG and DOX in breast cancer cells. The [^{99m}Tc]-nano-2DG-DOX exhibited an excellent stability and target specificity *in vitro* and also *in vivo*. There are needed some more studies to suggest [^{99m}Tc]-nano-2DG-DOX as a candidate in cancer imaging.

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References

1. Chen F, Hong H, Zhang Y, et al. In vivo tumor targeting and image-guided drug delivery with antibody-conjugated, radiolabeled mesoporous silica nanoparticles. ACS Nano. 2013; 7(10): 9027–9039, doi: 10.1021/nn403617j, indexed in Pubmed: 24083623.
2. Aval NA, Islamian JP, Hatamian M, et al. Doxorubicin loaded large-pore mesoporous hydroxyapatite coated superparamagnetic Fe 3 O 4 nanoparticles for cancer treatment. International Journal of Pharmaceutics. 2016; 509(1-2): 159–167, doi: 10.1016/j.ijpharm.2016.05.046, indexed in Pubmed: 27234695.
3. Aval NA, Javadpour J, Badiei A. Application of sucrose as a cosurfactant in controlling the pore diameter in the synthesis of mesoporous hydroxyapatite nanoparticles. Ceramics–Silikáty. 2015; 59(4): 311–317.
4. Psimadas D, Bouziotis P, Georgoulias P, et al. Radiolabeling approaches of nanoparticles with (99m) Tc. Contrast Media Mol Imaging. 2013; 8(4): 333–339, doi: 10.1002/cmmi.1530, indexed in Pubmed: 23613436.
5. Albernaz Md, Ospina CA, Rossi AM, et al. Radiolabelled nanohydroxyapatite with 99mTc: perspectives to nanoradiopharmaceuticals construction. Artif Cells Nanomed Biotechnol. 2014; 42(2): 88–91, doi: 10.3109/21691401.2013.785954, indexed in Pubmed: 23586417.
6. Islamian JP, Hatamian M, Rashidi MR. Nanoparticles promise new methods to boost oncology outcomes in breast cancer. Asian Pac J Cancer Prev. 2015; 16(5): 1683–1686, doi: 10.7314/apjcp.2015.16.5.1683, indexed in Pubmed: 25773810.
7. Jiang X, Xin H, Ren Q, et al. Nanoparticles of 2-deoxy-D-glucose functionalized poly(ethylene glycol)-co-poly(trimethylene carbonate) for dual-targeted drug delivery in glioma treatment. Biomaterials. 2014; 35(1): 518–529, doi: 10.1016/j.biomaterials.2013.09.094, indexed in Pubmed: 24125772.
8. Brannon-Peppas L, Blanchette J. Nanoparticle and targeted systems for cancer therapy. Adv Drug Deliv Rev. 2012; 64: 206–212, doi: 10.1016/j.addr.2012.09.033.
9. Yezhelyev MV, Gao X, Xing Y, et al. Emerging use of nanoparticles in diagnosis and treatment of breast cancer. Lancet Oncol. 2006; 7(8): 657–667, doi: 10.1016/S1470-2045(06)70793-8, indexed in Pubmed: 16887483.
10. Okarvi SM, Al Jammaz I. Synthesis and evaluation of a technetium-99m labeled cytotoxic bombesin peptide conjugate for targeting bombesin receptor-expressing tumors. Nucl Med Biol. 2010; 37(3): 277–288, doi: 10.1016/j.nucmedbio.2009.12.006, indexed in Pubmed: 20346867.
11. Aghaee F, Pirayesh Islamian J, Baradaran B. Enhanced radiosensitivity and chemosensitivity of breast cancer cells by 2-deoxy-d-glucose in combination therapy. J Breast Cancer. 2012; 15(2): 141–147, doi: 10.4048/jbc.2012.15.2.141, indexed in Pubmed: 22807930.
12. Gupta S, Farooque A, Adhikari JS, et al. Enhancement of radiation and chemotherapeutic drug responses by 2-deoxy-D-glucose in animal tumors. J Cancer Res Ther. 2009; 5 Suppl 1: S16–S20, doi: 10.4103/0973-1482.55135, indexed in Pubmed: 20009287.
13. Ahmad I, Mustafa E, Mustafa N, et al. 2DG enhances the susceptibility of breast cancer cells to doxorubicin. Open Life Sciences. 2010; 5(6), doi: 10.2478/s11535-010-0060-y.
14. Willmann JK, van Bruggen N, Dinkelborg LM, et al. Molecular imaging in drug development. Nat Rev Drug Discov. 2008; 7(7): 591–607, doi: 10.1038/nrd2290, indexed in Pubmed: 18591980.
15. Rudin M, Weissleder R. Molecular imaging in drug discovery and development. Nat Rev Drug Discov. 2003; 2(2): 123–131, doi: 10.1038/nrd1007, indexed in Pubmed: 12563303.
16. Weissleder R. Molecular imaging in cancer. Science. 2006; 312(5777): 1168–1171, doi: 10.1126/science.1125949, indexed in Pubmed: 16728630.
17. Gomes CM, Abrunhosa AJ, Ramos P, et al. Molecular imaging with SPECT as a tool for drug development. Adv Drug Deliv Rev. 2011; 63(7): 547–554, doi: 10.1016/j.addr.2010.09.015, indexed in Pubmed: 20933557.
18. Ferro-Flores G, Ocampo-García B, Santos-Cuevas C, et al. Multifunctional Radiolabeled Nanoparticles for Targeted Therapy. Curr Med Chem. 2013; 21(1): 124–138, doi: 10.2174/0929867311320990218.
19. Müller C, Schibli R. Single hoton emission comuted tomograhy tracer. Molecular Imaging in Oncology: Sringer; 2013. p. : 65–105.
20. Pirayesh Islamian J, Hatamian M, Aval NA, et al. Targeted superparamagnetic nanoparticles coated with 2-deoxy-d-gloucose and doxorubicin more sensitize breast cancer cells to ionizing radiation. Breast. 2017; 33: 97–103, doi: 10.1016/j.breast.2017.03.009, indexed in Pubmed: 28351000.
21. Chen Y, Huang ZW, He L, et al. Synthesis and evaluation of a technetium-99m-labeled diethylenetriaminepentaacetate-deoxyglucose complex ([99mTc]-DTPA-DG) as a potential imaging modality for tumors. Appl Radiat Isot. 2006; 64(3): 342–347, doi: 10.1016/j.apradiso.2005.08.004, indexed in Pubmed: 16290170.
22. Andringa KK, Coleman MC, Aykin-Burns N, et al. Inhibition of glutamate cysteine ligase activity sensitizes human breast cancer cells to the toxicity of 2-deoxy-D-glucose. Cancer Res. 2006; 66(3): 1605–1610, doi: 10.1158/0008-5472.CAN-05-3462, indexed in Pubmed: 16452219.
23. Ozgur A, Lambrecht FY, Ocakoglu K, et al. Synthesis and biological evaluation of radiolabeled photosensitizer linked bovine serum albumin nanoparticles as a tumor imaging agent. Int J Pharm. 2012; 422(1-2): 472–478, doi: 10.1016/j.ijpharm.2011.11.013, indexed in Pubmed: 22101288.
24. Dória ML, Cotrim Z, Macedo B, et al. Lipidomic approach to identify patterns in phospholipid profiles and define class differences in mammary epithelial and breast cancer cells. Breast Cancer Res Treat. 2012; 133(2): 635–648, doi: 10.1007/s10549-011-1823-5, indexed in Pubmed: 22037781.
25. Liang Z, Li X, Xie Y, et al. 'Smart' gold nanoshells for combined cancer chemotherapy and hyperthermia. Biomed Mater. 2014; 9(2): 025012, doi: 10.1088/1748-6041/9/2/025012, indexed in Pubmed: 24525482.
26. Wang Y, Zhu J, Song X, et al. Synthesis and evaluation of (99m)Tc-2-[(3-carboxy-1-oxopropyl)amino]-2-deoxy-D-glucose as a potential tumor imaging agent. Bioorg Med Chem Lett. 2014; 24(16): 3882–3885, doi: 10.1016/j.bmcl.2014.06.051, indexed in Pubmed: 25001483.
27. Polyak A, Palade EA, Balogh L, et al. In vitro and biodistribution examinations of Tc-99m-labelled doxorubicin-loaded nanoparticles. Nucl Med Rev Cent East Eur. 2011; 14(2): 55–62, doi: 10.5603/nmr.2011.00016, indexed in Pubmed: 22219144.
28. Morales-Avila E, Ocampo-García BE, et al. de María Ramírez F, Radiolabeled nanoparticles for molecular imaging: Citeseer. ; 2012.
29. Assadi M, Afrasiabi K, Nabipour I, et al. Nanotechnology and nuclear medicine; research and preclinical applications. Hell J Nucl Med. 2011; 14(2): 149–159, indexed in Pubmed: 21761018.