Indonesian Journal of Pharmacy

VOL 30 (2) 2019: 91 – 97 | RESEARCH ARTICLE

Pharmacokinetics Interaction and Biodistribution of 5 Fluorouracil with Radiopharmaceuticals ^{99m}Tc-Glutathione for Cancer Diagnostic in Mice Cancer Model

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Info Article

Submitted: 11-03-2019
Revised: 15-05-2019
Accepted: 12-06-2019

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ABSTRACT

Radiopharmaceutical ^{99m}Tc-Glutathione has been developed for cancer diagnostic in nuclear medicine. Interactions between chemotherapy drugs and radiopharmaceuticals can altered radiopharmaceuticals performance. Drug interaction 5-fluorouracil (5-FU) with a radiopharmaceutical ^{99m}Tc-Glutathione in mice cancer model has been proven in pharmacokinetics study. The biological half-life distribution of ^{99m}Tc-Glutathione for cancer model mice when administrated with 5-FU become longer to 0.340±0.121h if compared with ^{99m}Tc-Glutathione. Biological half-life elimination for cancer model mice given with ^{99m}Tc-Glutathione is 72.712±2.427h. Administration of 5-FU makes the biological half-life elimination of ^{99m}Tc-Glutathione shorter to 17.030±3.459h. Biodistribution study of 5-FU continued with ^{99m}Tc-Glutathione for cancer model mice showed higher physiological uptake in the kidney was observed (39.77±2.70%ID/g) for ^{99m}Tc-Glutathione has lower uptake on kidney (29.55.3.73 %ID/g) with $p<0.05$. Based on calculation on cancer model mice with colon cancer compared with muscle, shown target/non-target (T/NT) ratio 2.93 for 5-FU continued with ^{99m}Tc-Glutathione has ratio 0.42. Low ratio T/NT may affect to poor organ visualization for cancer diagnosis. Acute toxicity study has shown drugs safety for clinical purpose. The knowledge about chemotherapy drug interaction with a radiopharmaceutical is important to have a correct diagnosis of the patient on clinical application.

Keyword: 5 Fluorouracil, ^{99m}Tc-Glutathione, Drug-Radiopharmaceutical Interaction, Cancer Diagnostic, Nuclear Medicine.

INTRODUCTION

Cancer is an important cause of death with high morbidity in human. The Global Cancer Statistic indicate in 2018, there are 18.1 million new cases and 9.6 million deaths from cancer. The cumulative risk of incidence of cancer indicates that 1 in 8 men and 1 in 10 women will develop cancer in a lifetime (Bray *et al.,* 2018). Based on Basic Health Research in Indonesia 2007, cancer is the 7th cause of death among all cases with national prevalence is 4.3 for 1000 population. The leading cancer case are breast cancer, cervical cancer, lung cancer and colorectal cancer (Wahidin *et al.,* 2012).

A radiopharmaceutical is a pharmaceutical that contains radioactive isotopes that used for diagnostic purposes and treatment of human diseases (Saha and Gopal, 2010). Radiopharmaceuticals usually don't have pharmacologic effects, unlike conventional drugs. When radiopharmaceutical is used for therapeutic purposes there are some exceptions. Radiolabeled particles have some potential mechanical issues such as the embolic effect of ^{99m}Tc-macroaggregated albumin and ^{90}Y-resin particles. A sufficient number of particles ^{99m}Tc-macroaggregated albumin need to be administered to avoid a non-uniform spatial distribution of radioactivity in lung region. Excess of the particles can produce acute toxicity, especially in patients with severe pulmonary hypertension (Marti, 2013).

5-Fluorouracil is an analog of uracil with a fluorine atom at the C-5 position in place of the hydrogen atom. Mechanism of action 5-Fluorouracil (5-FU) has rapidly entered the cell using the same facilitated transport mechanism as uracil then catabolized primarily in the liver. 5-FU has been used for more than 40 years in the treatment of colorectal cancer. This drugs administered intravenously for a clinical procedure and has been used in a variety of different schedules to determine the optimum dose and method. The overall response rate has a good result as a single agent for treatment of both advanced and early-stage colorectal cancer (Longley *et al.,* 2003).

Researcher was identified 5-FU induce senescence cell in both cell types. Signaling pathways were activated by senescence cells that lead to the production and release of cytokines, chemokines, and growth factors to induce neighboring cells to enter senescence. 5-FU also have a possible mechanism to manifestations of cardiotoxicity. In the other hand suggest potential prevention strategies to reduce these severe side effects of an otherwise very useful drug family for the treatment of numerous cancers (Focaccetti *et al.,* 2015). Wongso and Zainuddin (2013), prove that ^{99m}Tc-Glutathione effectively reaches the cancer organ at 3h post-injection with a concentration of 0.95% ID/g. The imaging test results also showed the highest accumulation of ^{99m}Tc-Glutathione at 3h post-injection and high values of renal system.

Effect of cancer chemotherapeutics drugs interaction with radiopharmaceutical has been studied for some drugs. Doxorubicin interaction with ^{99m}Tc-DTPA was observed, mean activity in rat urinary system decreased while a significant increase in liver uptake. (Razaq *et al.,* 2017). Mahendra *et al.,* (2018) were observed interaction of NSAID drugs such as meloxicam and sodium diclofenac increased clearance of ^{99m}Tc-MDP in the blood and decrease uptake on the bone of rats. To our knowledge, there has been no report of preclinical study interaction 5-FU with radiopharmaceutical ^{99m}Tc-Glutathione. Thus, we aimed to investigate the biodistribution, pharmacokinetics and acute toxicity study in normal and cancer model mice.

MATERIAL AND METHODS

Glutathione (Sigma Aldrich), 5-Fluorouracil (Kalbe Farma), $SnCl_2$ (Sigma Aldrich), $Na^{99m}TcO_4$ was eluted from the commercial ^{99}Mo/^{99m}Tc generator (Polatom), Acetone, NaCl, TLC-SG (Bioscan), aquabidest (IPHA Laboratories), 3MM Whatmann chromatography paper and pH Universal indicator were obtained from E.Merck. The Equipment used too radioactivity counting were are Single Channel Analyzer with NaI(Tl) detector (Ortec).

Animal

Thirty four male Balb/C mice, 28 days old from PT Biofarma, Tbk Bandung, Indonesia were housed in polypropylene cages (38X30 cm) at constant temperature (26±1ºC) and humidity (60±5%) with a 12h dark cycle. The mice were feed standard (CP505) and water ad libitum then divided into two groups. Group I normal mice; group II cancer model mice induce with Azoxymethane (Sigma Aldrich) and DSS 2.5% (Sigma Aldrich). All protocol was approved by the ethics committee for the care and use of laboratory animal (KEPPHP BATAN) under protocol number 002/KEPPHP-BATAN/VII/2018. Mice in Cancer model group were induced intraperitoneal by Azoxymethane (AOM) dissolved in 0.9% Sodium Chloride with doses 10mg/kg BW. After one week of induction, mice were given standard feed and ad libitum water. Mice were given Dextran Sodium Sulfate 2.5% in drinking water for one week and then no further treatment for 18 weeks (Tanaka *et al.,* 2003).

Preparation of ^{99m}Tc-Glutathione

Preparation of Glutathione dry diagnostic kit was performed with 20mg Glutathione dissolved in 1mL aquabidest while stirring, 0.3mL of $SnCl_2.2H_2O$ (1mg/mL of HCl 0.01N) was added. The pH adjusted to pH 7, stirred for a few minutes and filtered. The mixture was dried using Freeze Dryer for 22 hours and stored at about 4°C. Labeling reaction of the ^{99m}Tc-Glutathione complex was performed with added 2.5mL of pertechnetate into glutathione dry kit and the mixture was shaken for a few seconds and left to react for 5min at room temperature. The radiochemical purity of ^{99m}Tc-Glutathione complex was assessed by TLC using a TLC-SG with two solvent, NaCl and dried acetone (Zainuddin and Maula, 2010).

Pharmacokinetics study

Mice were divided into two groups (n=3) group I normal mice (^{99m}Tc-Glutathione and 5-FU continued with ^{99m}Tc-Glutathione) and group II cancer model mice (^{99m}Tc-Glutathione and 5-FU continued with ^{99m}Tc-Glutathione). Mice were treated with 5-FU 0.1mL, after five minutes gave a

single intravenous injection in the tail vein with ^{99m}Tc-Glutathione 0.1mL with radioactivity 100µCi. Blood collection in time interval 15min, 30min, 1, 2, 3, 4, 5, 6, 24, 25, and 26h. Blood collected from the tail vein and weighing with an analytical scale. The radioactivity of the blood sample was measured using Single Channel Analyzer with NaI(Tl) detector. After radioactivity counting, the percentage of total injection dose (%ID) in blood were calculated. Pharmacokinetics parameter of ^{99m}Tc-Glutathione was performed using PK Solver 2.0 (Zhang *et al.,* 2010).

Biodistribution study

The experiment was performed on Balb/C mice weighing approximately 25g. Mice were divided into normal group and cancer model group (^{99m}Tc-Glutathione and 5-FU continued with ^{99m}Tc-Glutathione). The 5-FU was injected into tail vein of the animal (0.1mL), after 5min then ^{99m}Tc-Glutathione was given 100µCi into vein tail. Then after one hour mice were euthanized and the tissue of interest was collected. All tissue and blood were weighed and counted for radioactivity using single channel analyzer with NaI(Tl) detector. The percent of radioctivity per gram of tissue weight (%Injected activity/g tissue) was determined using the following formula :

$$\%ID = \frac{\text{Counts per gram organ}}{\text{Counts dose given}} \text{ X } 100\%$$

Toxicity study

Healthy Balb/C mice were divided into two groups, normal and cancer model (n=5). The 5-FU was injected into tail vein of the animal (0.1mL), after 5min then ^{99m}Tc-Glutathione was given 100µCi into tail vein and animal activity was observed shortly after being injected 1, 2, 3, and 24h, up to 14 days. The following parameters were evaluated mortality, clinical observation of animal was performed for sickness symptoms due to treatment. Change in their appearance (piloerection, kyphosis, disheveled fur), behavior (grooming or nesting) and activity (altered exploring) (Silveira *et al.,* 2016).

Data analysis

All average values are given as mean ± standard deviation. The comparison of pharmacokinetics parameter and biodistribution of ^{99m}Tc-Glutathione and 5-FU with ^{99m}Tc-Glutathione in normal mice and cancer model mice was determined using t-test. The acceptable probability for a significant difference was $p<0.05$. Data were analyzed using SPSS 24 software.

RESULT AND DISCUSSION

Radiopharmaceutical has a quality requirement in the application for in vivo study. The quality requirement is clarity, sterility, non-pyrogenicity, pH and radiochemical purity. In this study, radiochemical purity testing was performed using two ascending chromatography system**.** Radiochromatogram of ^{99m}Tc-Glutathione, where aceton used as a mobile phase, ^{99m}Tc-Glutathione and $^{99m}TcO_2$ stayed at the origin (Rf=0) while $^{99m}TcO_4^-$ moved with the solvent to give Rf=1 (Figure 1). Radiochromatogram of ^{99m}Tc-Glutathione where saline solution used as a mobile phase $^{99m}TcO_2$ stayed at the origin (Rf=0) while ^{99m}Tc-Glutathione and $^{99m}TcO_4^-$ moved with the solvent to give Rf =1 (Figure 2). Result of this test showed that ^{99m}Tc-Glutathione had 99.27% radiochemical purity (n=3).

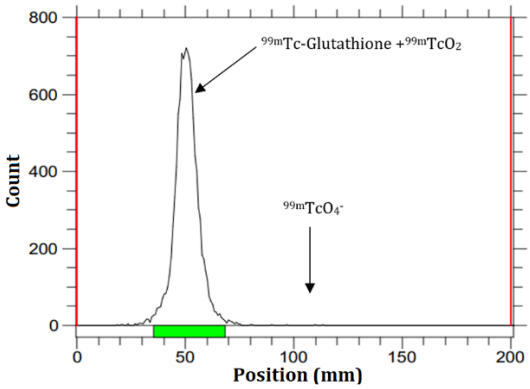

Figure 1. Radiochromatogram of ^{99m}Tc-Glutathione using acetone as mobile phase.

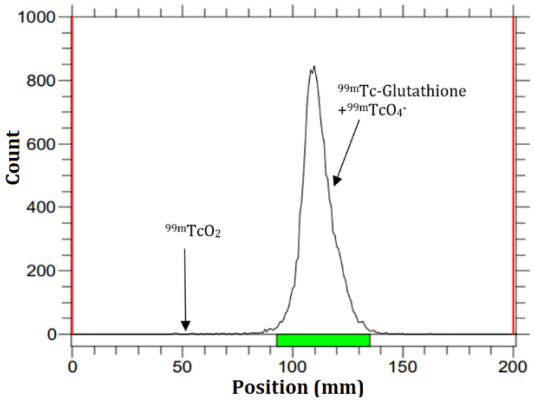

Figure 2. Radiochromatogram of ^{99m}Tc-Glutathione using 0.9% NaCl as mobile phase.

Table I. Pharmacokinetics parameter of ^{99m}Tc-Glutathione and interaction of 5-FU with ^{99m}Tc-Glutathione in normal and cancer model mice.

Pharmacokinetics Parameter	Normal Mice		Sig.	Cancer Mice		Sig.
	^{99m}Tc-Glutathione	5-FU + ^{99m}Tc-Glutathione		^{99m}Tc-Glutathione	5-FU + ^{99m}Tc-Glutathione	
K12	0.001±0.001	0.001±0.001	NS	0.003±0.003	0.017±0.027	NS
K21	0.134±0.275	0.033±0.027	S	0.067±0.099	0.019±0.017	NS
Cmaks	6.132±5.161	3.299±0.879	NS	2.436±0.569	3.766±2.677	NS
t1/2 α	0.004±0.001	0.347±0.225	NS	0.003±0.000	0.340±0.121	S
t1/2 β	5.310±1.050	11.497±2.827	S	72.712±2.427	17.030±3.459	S
AUC 0-inf	12.264±10.322	6.931±1.181	NS	4.343±1.159	7.533±5.355	NS

NS : Not Significant; S : Significant

This ^{99m}Tc-Glutathione radiopharmaceutical confirmed to United States of Pharmacopoeia, which state that the radiochemical purity has to be greater than 95%. The solution was clear and colorless with pH = 7.

Pharmacokinetics study

The pharmacokinetic study was performed to determine changes in pharmacokinetics parameter of ^{99m}Tc-Glutathione in Balb/C mice which have been previously treated with ^{99m}Tc-Glutathione and 5-FU continued with ^{99m}Tc-Glutathione. The result (Table I) that the administration of 5-FU and followed with ^{99m}Tc-Glutathione affected the pharmacokinetics parameter of ^{99m}Tc-Glutathione I.V. injection in blood both normal mice and cancer model.

The result of t-test for pharmacokinetics parameter (Table I), in normal mice there was significant difference $p<0.05$ for biological half-life elimination of ^{99m}Tc-Glutathione when administrated with 5-FU become longer to 11.497±2.827 h. Biological half-life distribution and elimination of ^{99m}Tc-Glutathione for cancer model mice when administrated with 5-FU also changed, biological half-life distribution become longer to 0.340±0.121 hours and biological half-life elimination become shorter to 17.030±3.459 hours compared with ^{99m}Tc-Glutathione single administration 72.712±2.427h.

Administration of 5-FU followed with ^{99m}Tc-Glutathione I.V. injection also change $AUC_{0\text{-}inf}$ value (area under the curve) and $C\text{-}_{max}$ (peak concentration) from normal and cancer model mice compared with ^{99m}Tc-Glutathione but not significantly different ($p>0.05$) based on statistical analysis. ^{99m}Tc-Glutathione and combined with 5-FU has the same absorption rate for normal and cancer model mice.

Radioactivity half-life of radiopharmaceutical in blood can be approximated by two phases. The first is distribution half-life that is during radioactive material spreads throughout various organs or tissues, reaching organ specific concentrations. The second is elimination half-life, the material is eliminated by biochemical processes and physical radioisotope decay (Shuryak and Dadachova, 2015).

The localization mechanism of ^{99m}Tc-Glutathione has never been clarified but in general ^{99m}Tc-Glutathione increased in blood flow and capillary permeability are the main mechanism. The blood clearance and wash out of ^{99m}Tc-Glutathione from tumoral and another tissue was not rapid because protein binding at the site of localization might occur for the prolonged retention of ^{99m}Tc-Glutathione on target tissue (Ercan and Senekowitsch-schmidtke, 2000), it has been proven in cancer model mice showed the biological half-life elimination (t1/2β) become prolonged. Administration of 5-FU continued with ^{99m}Tc-Glutathione in cancer model mice also made the blood clearance faster may occur because of 5-FU binding the site of localization in the organ but the mechanism it has not been clear.

Compared with normal mice group, 5-FU administration followed with ^{99m}Tc-Glutathione causing the half-life elimination (t1/2β) to be longer, this is probably due to 5-FU causes retention of ^{99m}Tc-Glutathione and radioactivity become prolonged on the blood.

Biodistribution study

Biodistribution of ^{99m}Tc-Glutathione and 5-FU in normal and cancer model mice were studied at 1h post-injection to evaluate the accumulation of radiopharmaceutical. Based on data for normal mice higher physiological uptake of

^{99m}Tc-Glutathione in the kidney was observed in this work (36.88±6.89%ID/g) it was so administer level 5-FU continued with ^{99m}Tc-Glutathione (44.20±7.74%ID/g). The second organ with the highest accumulation was the bone, (7.71±1.58%ID/g) and (10.10±4.28%ID/g) respectively. Lower uptake in other organ 1 hour after injection: was muscle (1.13±0.76%ID/g) (0.94±0.40%ID/g), hearth (1.87±1.03%ID/g) (1.70±0.84%ID/g), and stomach (1.77±0.45 %ID/g) (3.73±2.75%ID/g). Administration of ^{99m}Tc-Glutathione compared with 5-FU followed with ^{99m}Tc-Glutathione change the biodistribution value for organ in normal mice but not significantly different based on statistical analysis with p>0.05.

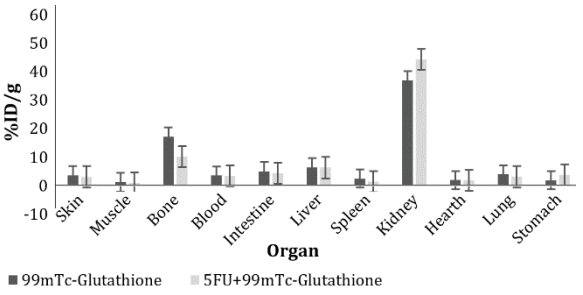

Figure 3. Biodistribution of ^{99m}Tc-Glutathione and 5-Flurouracil with ^{99m}Tc-Glutathione in normal mice (1h).

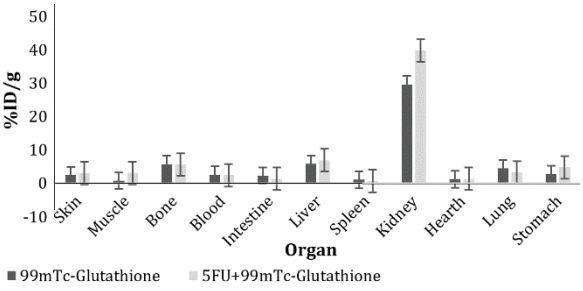

Figure 4. Biodistribution of ^{99m}Tc-Glutathione and 5-Flurouracil with ^{99m}Tc-Glutathione in cancer model mice (1h)

Administration of 5-FU followed with ^{99m}Tc-Glutathione for cancer model mice (Figure 4) showed higher physiological uptake in the kidney. The uptake in kidney was observed (39.77±2.70%ID/g). However when ^{99m}Tc-Glutathione was administered with 5-FU, the uptake of glutathione was lower (29.55.3.73 %ID/g). The present work shows that some accumulation of ^{99m}Tc-Glutathione on the organ. Intestinal accumulation on normal mice due to biliary excretion of the agent and in cancer model mice the agent delivered to cancer tissue. Blood and extravascular fluid compartment also contribute to distribution to all organ.

The result of t-test between normal and cancer model group for organ showed there was no significant difference in biodistribution between administration of ^{99m}Tc-Glutathione and 5-FU followed with ^{99m}Tc-Glutathione p>0.05 for normal mice. Biodistribution of ^{99m}Tc-Glutathione on cancer model mice showed data was significantly different increased the ^{99m}Tc-Glutathione level to the kidney. High concentration on kidney due to the metabolism of ^{99m}Tc agents on renal system. Administration of 5-FU increased the retention of ^{99m}Tc-Glutathione on kidney and reach high concentration. 5-FU interaction with ^{99m}Tc-Glutathione based on biodistribution study compared data in both normal and cancer mice do not affect the physiologic state of the target organs.

^{99m}Tc-Glutathione is higly water soluble complex with a negative charge and could be secreted through the renal tubule if it posses anionic properties. Interaction of drug with radiopharmaceutical may arise as a result of a variety of factors including the pharmacological action of the drug, physiochemical interactions between drugs and radiotracers, and competition for binding sites for example. Diseases induced by drugs, which may be potentiated by a radio-pharmaceutical, would also be considered an adverse event (Oliveira *et al.,* 2008).

5-FU is anticancer drug that has been used to treat various type of malignancies cancer. This drug was catabolized to inactive metabolites by dihydropyrimidine dehydrogenase (DPD), cytotoxic effects on tumor cells and normal tissues through anabolic actions. 5-FU was inhibiting DNA synthesis which in turn affect RNA transcription and function. The 5-FU metabolite, fluorodeoxyuridine mono-phosphate (FdUMP), forms a ternary complex with thymidylate synthase (TS) and 5,10-methylene tetrahydrofolate (CH2THF), thereby inhibiting the synthesis of DNA (Miura *et al.,* 2010).

Several studies have investigated used ^{99m}Tc-Glutathione as a tumor-specific imaging agent. Cancer cell if compared with normal cell posses higher Reactive Oxygen Species (ROS) level and enhanced antioxidant system (Woo *et al.,* 2014). Ercan & Senekowitsch-schmidtke (2000) was observed that ^{99m}Tc-Glutathione has a significant increase in tumor uptake at 1h post-injection with tumor 3.27±0.80% injected dose/g. Uptake may

decrease at 3h post-injection, because of Glutathione mechanism of action.

Availability of ^{99m}Tc-Glutathione to be used in cancer patient under treatment of 5-FU is not recommended if we compare between the target and non-target. Based on calculation on cancer model mice with colon cancer compared with muscle shown target/non-target (T/NT) ratio 2.93 whereas, if 5-FU followed by ^{99m}Tc-Glutathione has ratio 0.42. Low ratio T/NT may affect to poor organ visualization for cancer diagnosis.

Toxicity study result

No death or clinical sign of peracute toxicity was observed in normal and cancer model groups during the 14-days study period. All the animals seemed healthy throughout the course of the study. No signs of distress, morbidity, injury or changes in behavior shortly after being injected with 5-FU and ^{99m}Tc-Glutathione, 1, 2, 3, 24 hours, and 14 days.

CONCLUSION

The knowledge about chemotherapy drug interaction with a radiopharmaceutical is important to determine the correct diagnosis of the patient in clinical application. The present work was designed to study 5-FU interaction with ^{99m}Tc-Glutathione both in normal and cancer model mice. Change in pharmacokinetics parameters occur in 5-FU administration followed by ^{99m}Tc-Glutathione especially in the biological half-life of cancer mice, the biological half-life elimination becomes longer and biological half-life biodistribution become faster. Biodistribution studies show that 5-FU administration followed by ^{99m}Tc-Glutathione does not change the uptake of ^{99m}Tc-Glutathione in normal mice but in cancer model mice the uptake in kidney significantly increased. Further study is needed to understand the cellular mechanism for 5-FU interaction with ^{99m}Tc-Glutathione.

ACKNOWLEDGMENT

Authors acknowledge PSTNT BATAN for research financial support and wish to thank Mr.Ahmad Sidik as a technician in Laboratory Animal PSTNT-BATAN.

REFERENCES

Bray F., Ferlay J., Soerjomataram I., Siegel RL., Torre LA. and Jemal A. 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Can J For Clin*, *68*(6), 394-424. https://doi.org/10.3322/caac.21492.

Ercan MT., Senekowitsch-Schmidtke R. and Bernatz S., 1999. Biodistribution of 99m Tc-glutathione in mice with osteosarcoma : effect of gamma irradiation on tumour uptake. *Research in Experimental Medicine*, 359–367.

Focaccetti C., Bruno A., Magnani E., Bartolini D., Principi E., Dallaglio K. and Albini A. 2015. Effects of 5-fluorouracil on morphology, cell cycle, proliferation, apoptosis, autophagy and ROS production in endothelial cells and cardiomyocytes. *PloS one*, *10*(2). https://doi.org/10.1371/journal.pone.0115686.

Kim DW., Kim WH., Kim MH., Kim CG., Oh CS. and Min JJ. 2014. Synthesis and evaluation of Tc-99m DTPA–glutathione as a non-invasive tumor imaging agent in a mouse colon cancer model. *Annals of nuclear medicine*, *28*(5), 447-454. https://doi.org/10.1007/s12149-014-0835-8.

Longley DB., Harkin DP. and Johnston PG. 2003. 5-Fluorouracil : Mechanisms of Action and Clinical Strategies. Nature review cancers, *3*(5), 330–338. https://doi.org/10.1038/nrc1074.

Miura K., Kinouchi M., Ishida K., Fujibuchi W., Naitoh T., Ogawa H. and Shibata C. 2010. 5-fu metabolism in cancer and orally-administrable 5-fu drugs. *Cancers*, *2*(3), 1717-730. https://doi.org/10.3390/cancers2031717.

Mahendra I., Daruwati I., Halimah I. and Pajrin SR. 2018. Pharmacokinetics Interaction of Non-Steroid Anti Inflammatory Drugs to 99m Tc-MDP Radiopharmaceuticals for Bone Imaging and Its Biodistribution. *Atom Indonesia*, *44*(3), 173-177. https://doi.org/10.17146/aij.2018.741.

Nurlaila Z. and Sriyani ME. 2010. Formulasi radiofarmaka 99mTc-glutation untuk diagnosis kanker. *Jurnal Sains dan Teknologi Nuklir Indonesia*, *11*(2). http://dx.doi.org/10.17146/jstni.2010.11.2.399.

Perales JLG. and Martínez AA. 2013. A portable database of adverse reactions and drug interactions with radiopharmaceuticals. *J nuclear medicine technology*, *41*(3), 212-215. https://doi.org/10.2967/jnmt.113.120626.

Razaq T., Nisar H., Roohi S., Shehzad A. and Ahmad I. 2017. Administration of 99mTc-DTPA in combination with doxorubicin alters the

radiopharmaceutical biodistribution in rats. *Iranian J.Nuclear Medicine*, *25*(2), 122-128.

Santos-Oliveira R., Smith SW. and Carneiro-Leão AMA. 2008. Radiopharmaceuticals drug interactions: a critical review. *Anais da Academia Brasileira de Ciências*, *80*(4), 665-675. https://doi.org/10.1590/S0001-37652008000400008.

Saha GB. 2010. Radiopharmaceuticals and methods of radiolabeling. In *Fundamentals of nuclear pharmacy* (pp. 83-113). Springer, New York, NY.

Shuryak I. and Dadachova E. 2015. New Approaches for Modeling Radiopharmaceutical Pharmacokinetics Using Continuous Distributions of Rates. *JNuclear Medicine*, *56*(10), 1622-1628. https://doi.org/10.2967/jnumed.115.160515.

Silveira MB., Ferreira SM., Nascimento LT., Costa FM., Mendes BM., Ferreira AV. and Mamede M. 2016. Preclinical acute toxicity, biodistribution, pharmacokinetics, radiation dosimetry and microPET imaging studies of [18F] fluorocholine in mice. *Applied Radiation and Isotopes*, *116*, 92-101. https://doi.org/10.1016/j.apradiso.2016.07.021.

Tanaka T., Kohno H., Suzuki R., Yamada Y., Sugie S. and Mori H. 2003. A novel inflammation-related mouse colon carcinogenesis model induced by azoxymethane and dextran sodium sulfate. *Cancer science*, *94*(11), 965-973.

Wahidin M., Noviani R., Hermawan S., Andriani V., Ardian A. and Djarir H. 2012. Population-based cancer registration in Indonesia. *Asian Pacific J Canc Prevention*, *13*(4), 1709-1710.

Wongso H., Zainuddin N. and Iswahyudi I. 2013. Biodistribution and Imaging of The 99m Tc-Glutathione Radiopharmaceutical in White Rats Induced with Cancer. *Atom Indonesia*, *39*(3), 106-111.

Zhang Y., Huo M., Zhou J. and Xie S. 2010. PKSolver: An add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel. *Computer methods and programs in biomedicine*, *99*(3), 306-314. https://doi.org/10.1016/j.cmpb.2010.01.007.