

PJN

ISSN 1680-5194

PAKISTAN JOURNAL OF
NUTRITION

ANSI*net*

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The Effect of a Chayotte (*Sechium edule*) Extracts (Decoct and Macerated) on the Labeling of Blood Elements with Technetium-99m and on the Biodistribution of the Radiopharmaceutical Sodium Pertechnetate in Mice: an *In vitro* and *In vivo* Analysis

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Abstract: The biodistribution of radiopharmaceutical used in diagnostic imaging can be altered by a wide variety of factors. If unknown, the drug interaction with radiopharmaceuticals can lead to misdiagnosis or the necessity to repeat the examination, increasing the dose to the patient. The constituents of herbal products can cause adverse effects. Although natural products are widely used as food or as medicines for humans they can alter the labeling of blood constituents with technetium-99m (^{99m}Tc) as well as the bioavailability of the radiopharmaceutical sodium pertechnetate ($^{99m}\text{TcO}_4\text{Na}$). ^{99m}Tc is one of most used radio nuclide in nuclear medicine and in basic research. Some authors described that natural and synthetic drugs may alter the process of radio labeling. *Sechium edule* (chayotte) is a vegetable very spent in the human nutrition as the popular medicine due its properties such as the diuretic and the hypotensor effects. We evaluated the influence of a chayotte (*Sechium edule*) extracts (decoct and macerated) on the radio labeling of blood elements and on the bioavailability of $^{99m}\text{TcO}_4\text{Na}$. In this study, blood was withdraw from *Wistar* rats and the aliquots of blood were incubated with the chayotte extracts decoct and macerated, 0.1g/mL during 1 hour. After that, blood was incubated with stannous chloride (SnCl_2) for 1 hour together with the adding of ^{99m}Tc in each breaks of 15min until 1 of incubation with SnCl_2 . In each 10 min an aliquot of blood was taken and then plasma (P) and blood cells (BC) were isolated, also precipitated with trichloroacetic acid (TCA 5%) and soluble (SF) and insoluble fractions (IF) were separated. For the biodistribution analysis, the $^{99m}\text{TcO}_4\text{Na}$ (0.3mL) was administrated into male *Wistar* rats which had drunk or not the extract (macerated) for 60 days. After 10 min, the animals were sacrificed, the organs were isolated, the radioactivity determined in a well counter and the percentages of radioactivity per gram (%ATI/g) in the organs was calculated. For the radio images analysis, the animals were treated with the extracts (macerated and decoct) during 15 days, after this period of time, it was administrated doses of $100\mu\text{Ci}$ of $^{99m}\text{TcO}_4\text{Na}$ in the ocular plexus of the animals. The images were obtained after 10min. The qualitative analysis of the images was done. The analysis of the results has demonstrated that the extracts have increased the labeling of blood elements with ^{99m}Tc which was incubated together with SnCl_2 , in the times 0 and 30 min to decoct extract (time 0 min: labeling in the C: from 37.97 ± 0.31 to 59.70 ± 0.56 ; and in the FIC: from 61.76 ± 0.75 to 73.15 ± 0.37 ; time 30min: labeling in the C: from 84.06 ± 0.91 to 94.75 ± 0.87 ; and in the FIC: from 76.72 ± 0.26 to 85.37 ± 0.67) and in the times 15 and 30 min to macerated extract (time 15min: labeling in the C: from 29.04 ± 0.31 to 50.13 ± 0.82 ; time 30min: labeling in the C: from 75.39 ± 0.77 to 83.42 ± 0.51). The %ATI/g was altered in the thyroid (from 4.57 ± 0.58 to 2.03 ± 1.33); lung (from 0.84 ± 0.25 to 0.21 ± 0.02); stomach (from 5.19 ± 1.34 to 2.03 ± 0.60) and blood (from 50.07 ± 3.36 to 32.25 ± 2.32). In the qualitative analysis it was observed an decreased in the performance of the images related to the stomach region. Due to the biodistribution it was related that an extract of eggplant was capable of altering the bioavailability of $^{99m}\text{TcO}_4\text{Na}$ different of a cauliflower extract which has not been able to alter it. It is possible to suggest that some components of chayotte extracts present an oxidant power able to alter the biodistribution of $^{99m}\text{TcO}_4\text{Na}$, as a tip, we speculate that the referred extract metabolized in the liver may induce the generation of reactive metabolites with oxidant properties, this fact could justify the alteration of the uptake in the organs.

Key words: Chayotte, red blood cells, biodistribution, technetium-99m, *in vivo*, radiopharmaceutical

Introduction

In nuclear medicine, radioactive tracers, called radiopharmaceuticals, are employed in the study of blood flow, metabolism and morphology of an organ (Carlsson, 1995). Because of the very attractive physical characteristics of technetium-99m (^{99m}Tc), several

chemicals and cellular structures have been labeled with radio nuclide to be used as radiopharmaceuticals (Chandra, 1998). The introduction of the short half-life radio nuclide technetium-99m (Tc-^{99m}) as sodium pertechnetate in 1960 paved the way for a convenient method of radio labeling and makes it the radio nuclides

of choice for most diagnostic procedures in nuclear medicine (Saha, 1998). The red blood cells (RBC) labeled are used for measurement of red cell volume and detection and localization of gastrointestinal bleeding and other purposes. This labeled process depend on optical stannous chloride concentration and can be done using either *in vivo* or *in vitro* methods, or by a combination of both (Callahan and Rabito, 1990; Kuehne and Reuter, 1999). Free pertechnetate is distributed throughout the vasculature and interstitial fluid and it is concentrated in the stomach, intestinal tract, thyroid and salivary glands (Narra *et al.*, 1994). However, many factors, as drug therapy, radiation therapy, dietary conditions, besides pathological process could affect the biodistribution of the different radiopharmaceuticals (Britto *et al.*, 1998; Spicer *et al.*, 1999; Mattos *et al.*, 2000; Diré *et al.*, 2001; Gomes *et al.*, 2002; Aguiar *et al.*, 2002; or the labeling of blood constituents (Bernardo-Filho *et al.*, 1994; Oliveira *et al.*, 1997; Sampson, 1996; Vidal *et al.*, 1998; Oliveira *et al.*, 2000; Braga *et al.*, 2000; Oliveira *et al.*, 2002; Santos-Filho, 2002; Oliveira *et al.*, 2003; Nigri *et al.*, 2002). This also requires the repetition of the examination procedure resulting in the unnecessary irradiation to the patient (Oliveira *et al.*, 1997). An increasing number of people in the world are using traditional herbs medicines. Natural medicines may contain potentially toxic ingredients and contaminants such as heavy metal. In traditional Chinese herbal medicines (TCHM) may contain non-steroidal anti-inflammatory and anti-histamine drugs, steroids and oral hypoglycaemic agents (Kam and Liew, 2002). TCHM have been reported to cause serious hematological adverse effects (Azuno *et al.*, 1999). *Sechium edule* (chayotte) a subtropical vegetable with potent diuretic action, is a cucurbitaceus species which is used as food or as medication in popular medicine. It was reported a case of severe hypokalemia pregnancy and that a chayotte preparation was implicated, as the potassium level returned to normal, without recurrence of hypokalemia, once the ingestion of this vegetable was stopped. The medicinal use of chayotte enclose the relief of diseases related to the kidneys, circulatory system, intestinal and coetaneous inflammation and to the cauterize the sores. The infusion of the leaves and of the skin bear a substance with cardiovascular properties indicated to the pulmonary ailment and intestinal inflammation (Jensen and Lai, 1986; Flores, 1989). Gordon (2000) described the hypotensor effect of chayotte. Diré *et al.*, 2001 have noticed that chayotte extract (macerated) was capable of altering the morphology of red blood cells in a qualitative analysis. In a *in vitro/in vivo* study, Diré *et al.*, 2002 observed that the extracts (decoct and macerated) of chayotte were not capable of altering the radio labeling of blood elements although they were able to alter the labeling of blood constituents in the treated animals with the referred extracts. Moreno *et al.* (2002), demonstrated that an extract of *Ginkgo biloba*

has been altered the radio labeling of blood elements in an *in vitro* analysis as well as the biodistribution of $^{99m}\text{TcO}_4\text{Na}$. In this assessment we have evaluated the influence of a chayotte extracts on the labeling of blood constituents with ^{99m}Tc and on biodistribution of $^{99m}\text{TcO}_4\text{Na}$.

Materials and Methods

Characterization of the chayotte sample: Chayotte was purchased from a local market in Rio de Janeiro city, RJ, Brazil. To prepare the extract, 50 g of skin of chayotte were mixture with 500 mL of water in an electric extractor. This preparation was filtered and this extract was considered 100%.

The presence of toxic compounds was evaluated and we did not find them in the extracts of chayotte used in our experiments. The method to verify the presence of these toxic products is based on inhibition of acetylcholinesterase in the presence of the pesticides (Cunha Bastos *et al.*, 1991). In this method, brain acetylcholinesterase is utilized as an *in vitro* detector of organophosphorus and carbamate insecticides. Briefly, a preparation of acetylcholinesterase was obtained after extraction of a rat brain microsomal fraction with Triton X-100 and was incubated with the extract of chayotte. Enzyme assay was performed by a potentiometric method based on the formation of acetic acid in the incubation mixture (preparation of acetylcholinesterase and extract of chayotte)

Preparing of the extract: To prepare the decoct of chayotte, this vegetable (50 g) was put in an Erlenmeyer with 500 mL of water and it was boiled on slow heat for ten minutes. After that, the solution was filtered and the watery extract was obtained. The same procedure was taken with the preparing of the macerated extract. It was used the skin (50g) of the chayote skin which were triturated in a liquidizer with 500 mL of water. The animals were treated during 15 days. In the control the animals just have received water backwards chayotte extracts.

Radio labeling process: Samples of heparinized blood (0.5mL) from *Wistar* rats were incubated with the extracts (0.1 g/mL) during 1 hour. Elapsed this time it was added 0.5 mL of stannous chloride (1.2 $\mu\text{g}/\text{mL}$), as $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (Reagen, Quimibrás Indústrias Químicas SA, Brazil) during 1 hour. Together with SnCl_2 ^{99m}Tc (0.1 mL), as sodium pertechnetate, recently milked from a $^{99}\text{Mo}/^{99m}\text{Tc}$ generator (Instituto de Pesquisas Energéticas e Nucleares, Comissão Nacional de Energia Nuclear, Brazil), was added in each breaks of 15 min. After 10 min of incubation in each interval (times: 0, 15, 30, 45 and 60 min) an aliquot of blood was taken and centrifuged (clinical centrifuge). Plasma (P) and blood cells (BC) were separated. Samples (20 μL) of P and BC were also precipitated with 1 mL of trichloroacetic acid (TCA) 5% and soluble (SF) and

insoluble fractions (IF) were separated. The radioactivity in P, BC, IF-P, SF-P, IF-BC and SF-BC were determined in a well counter. After that, the percentage of radioactivity (%ATI) was calculated and experimental data was analyzed (Mann Whitney test, n = 5).

Biodistribution Procedures: The chayotte extract (macerated) was administrated (replaced by water in the treated group) to the *Wistar* rats (n = 4) during 60 days. The group (n = 4) has received water. After that, $^{99m}\text{TcO}_4\text{Na}$ (0.3 mL, 3.7 MBq) was injected by ocular plexus. The animals were sacrificed and their organs were isolated (thyroid, brain, muscle, lung, heart, spleen, kidney, stomach, intestine, liver, bone and blood) and counted in a well counter. The %ATI/g was calculated dividing the %ATI in each organ by the mass of each organ. The statistical analysis were performed by Mann-Whitney test (p<0.05).

Acquisition of Images in Gamma Chamber to glide (Siemens model ZLC 370S, 1983, softer 1985): The images had been recorded in double record face model 3M and impresses in video graphic to printer up-870MD. The animals had been treated or not with the extracts (decoct and macerated) during 15 days. Doses of $100\mu\text{Ci}$ of $^{99m}\text{TcO}_4\text{Na}$ had been prepared in syringes of insulin of 1 mL. 0.3 mL had been injected by plexus ocular and after 10 min the images had been made. The qualitative analysis was performed.

Results

The Fig. 1 and 2 have shown the effect of a chayotte extract (decoct) on the distribution of the radioactivity on the blood elements. The analysis of the results to the extract indicates that there is an increase in the uptake of ^{99m}Tc in the times: 0 min by the C (from 37.97 ± 0.31 to 59.70 ± 0.56); FIC (from 61.76 ± 0.75 to 73.15 ± 0.37) and 30 min C (from 84.06 ± 0.91 to 94.75 ± 0.87); FIC (from 76.72 ± 0.26 to 85.37 ± 0.67).

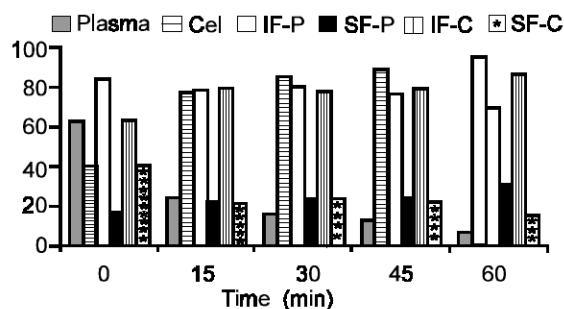


Fig. 1: Conventional labeling (%ATI) of blood elements with ^{99m}Tc - Kinetic Curve

Samples of blood from *Wistar* rats (Control) were incubated with stannous chloride and ^{99m}Tc were added. The ATI% was calculated. The results were analyzed (Mann Whitney test, n = 5).

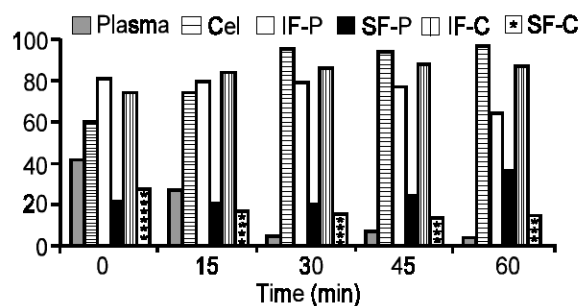


Fig. 2: Effect of chayotte extract (decoct) on the labeling (%ATI) of blood elements with ^{99m}Tc -Kinetic Curve

Samples of blood from *Wistar* rats (treated) were incubated with stannous chloride and ^{99m}Tc were added. The ATI% was calculated. The results were analyzed (Mann Whitney test, n = 5).

The Fig. 3 and 4 have shown the effect of a chayotte extract (macerated) on the distribution of the radioactivity on the blood elements. The analysis of the results to the extract indicates that there is an increase in the uptake of ^{99m}Tc in the times: 15 min by the C (from 29.04 ± 0.31 to 50.13 ± 0.82) and 30 min C (from 75.39 ± 0.77 to 83.42 ± 0.51).

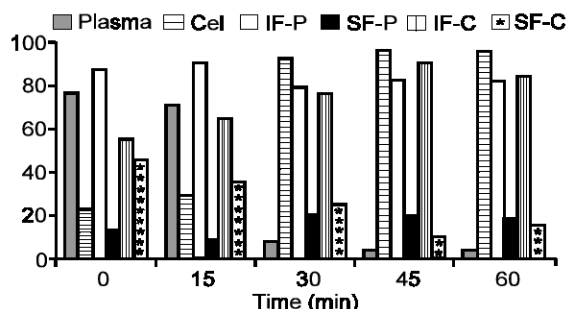


Fig. 3: Conventional labeling (%ATI) of blood elements with ^{99m}Tc -Kinetic Curve

Samples of blood from *Wistar* rats (control) were incubated with stannous chloride and ^{99m}Tc were added. The ATI% was calculated. The results were analyzed (Mann Whitney test, n = 5).

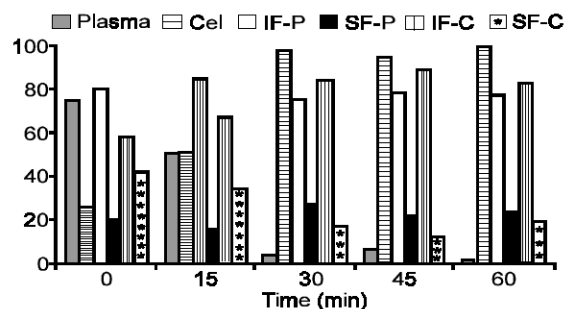


Fig. 4: Effect of chayotte extract (macerated) on the labeling (%ATI) of blood elements with ^{99m}Tc -Kinetic Curve

Samples of blood from *Wistar* rats (treated) were incubated with stannous chloride and ^{99m}Tc were added. The ATI% was calculated. The results were analyzed (Mann Whitney test, $n = 5$).

The Table 1 has shown the effects of the chayotte extract on the biodistribution of the $^{99m}\text{TcO}_4\text{Na}$ (%ATI/g) in the male rats which had received (0.1g/ml) or not (control group) the extract. The chayotte extract altered the uptake of $^{99m}\text{TcO}_4\text{Na}$ in the thyroid (from 4.57 ± 0.58 to 2.02 ± 1.33); lung (from 0.84 ± 0.25 to 0.21 ± 0.02); stomach (from 5.19 ± 1.34 to 2.03 ± 0.60) and blood (from 50.07 ± 3.36 to 32.25 ± 2.32).

Table 1: Effect of a chayotte extract on the biodistribution of $^{99m}\text{TcO}_4\text{Na}$

Organs	Control	Treated

	(%ATI/g)	
Thyroid	4.57 ± 0.58	2.02 ± 1.33
Brain	0.02 ± 0.01	0.01 ± 0.01
Muscle	0.08 ± 0.02	0.06 ± 0.02
Lung	0.84 ± 0.24	0.21 ± 0.02
Heart	0.22 ± 0.07	0.21 ± 0.02
Spleen	0.33 ± 0.07	0.51 ± 0.14
Kidney	0.51 ± 0.08	0.51 ± 0.14
Stomach	5.18 ± 1.34	2.03 ± 0.60
Duodenum	0.86 ± 0.16	0.60 ± 0.27
Liver	0.67 ± 0.07	0.55 ± 0.12
Bone	0.16 ± 0.07	0.16 ± 0.05
Blood	50.07 ± 3.26	32.25 ± 2.32

Male *Wistar* rats had drunk (treated group) or not the extract (control group) for 60 days and after $^{99m}\text{TcO}_4\text{Na}$ was injected. The animals were sacrificed, the organs were isolated and the % ATI/g was determined. For blood 1 mL was considered to be 1g. A statistical analysis (Mann Whitney, $n = 4$) was used to compare the results. The Fig. 5, 6 and 7 have shown the effect of a chayotte extracts (decoct and macerated) on the distribution of the radioactivity in the body of the animals. The analysis of the results to the extract indicates that there is a decrease in the uptake of $^{99m}\text{TcO}_4\text{Na}$ in the stomach region as well as in the thyroid.



Fig. 5: Control



Fig. 6: Treated decoct



Fig. 7: Treated macerated

Male *Wistar* rats had drunk (treated group) or not the extract (decoct and macerated) (control group) for 15 days and after $^{99m}\text{TcO}_4\text{Na}$ was injected. After 10 min, the animals were submitted to the gamma chamber for the obtaining of the images. A qualitative analysis ($n = 5$) was performed to compare the results.

Discussion

The distribution, uptake, retention and the elimination of radiopharmaceuticals depend on several factors, such as regional blood flow tissue metabolism and the binding to the blood elements (Hladik III *et al.*, 1987; Sampson, 1996). The labeling of blood elements with ^{99m}Tc has many applications. It is known that extracts obtained from medical plants can alter the labeling of blood elements with ^{99m}Tc as well as the morphology of red blood cells (Oliveira *et al.*, 1997; Vidal *et al.*, 1998; Reiniger *et al.*, 1999; Braga *et al.*, 2000; Oliveira *et al.*, 2000; Lima *et al.*, 2002; Oliveira *et al.*, 2002; Diré *et al.*, 2002; Capriles *et al.*, 2002; Oliveira *et al.*, 2003). The evidence that drugs can affect either the radio labeling as the biodistribution of red blood cells or the morphology of them in the context of nuclear medicine clinic has come to light only comparatively recently and it is an important factor in the interpretation of scintigraphic images. In this work it was noticed that chayotte extracts were capable of decrease the uptake of $^{99m}\text{TcO}_4\text{Na}$ in the thyroid and stomach regions in the animals treated with the referred extracts. A great number of workers have turned their attention to *in vitro* and *in vivo* evaluation of drugs in the process to label blood cells and in the biodistribution of radiopharmaceutical (Hladik III *et al.*, 1987; Hessewood and Leug, 1994; Owunwanne *et al.*, 1995; Sampson, 1996). Nigri *et al.* (2002), analyzing concentrations levels higher than the therapeutic levels in humans it was demonstrated that antiseizure drugs like phenobarbital, clonazepam and phenytoin have the capacity of altering the radio labeling of blood elements. Gomes *et al.* (2002), have demonstrated that a component of many chemotherapeutic regimens, mitomycin-C, has altered the bioavailability of technetium- 99m -labeled sodium pyrophosphate in mice.

In the labeling process of blood constituents with ^{99m}Tc is needed a reducing agent and probably the stannous ion would be oxidized. In *in vitro* studies was verified that

extracts of *Thuya occidentalis* (Oliveira et al., 1997), *Nicotiana tabacum* (Vidal et al., 1998), *Maytenus ilicifolia* (Oliveira et al., 2000), *Syzygium jambolanum* (Santos et al., 2002), *Stryphnodendron adstringens* (Mart.) Coville (Costa et al., 2002) and *Ginkgo biloba* (Moreno et al., 2002), possibly, would have oxidants compounds, and the labeling of blood elements decrease in the presence of these extracts. In a research was verified that *Paullinia cupana* extract was capable of altering the radio labeling of blood elements as well as to alter quantitatively the shape of red blood cells (Oliveira et al., 2002). In other *in vitro* study with *Fucus vesiculosus* extract was noticed that the referred extract has induced a qualitative alterations on the morphology of red blood cells together with alterations on the labeling of blood elements with ^{99m}Tc (Oliveira et al., 2003). In a *in vivo* studies Diré et al. (2002), have demonstrated that the chayotte extracts (macerated and decoct) were capable of altering the radio labeling of blood elements. Similar results were observed with an extract of *Solanum melongena* (eggplant) which was capable of altering radio labeling of blood elements with ^{99m}Tc as well as the bioavailability of NaTcO_4 (Capriles et al., 2002). Moreno et al. (2002), eyed that in a *in vitro* study the extract of *Ginkgo biloba* altered the morphology of red blood cells together with the radio labeling of blood elements, the opposite, was observed in a *in vivo* study which this fact may be explained by the generate of metabolites *in vivo* without direct action on the morphology of red blood cells despite the referred extract had been altered the biodistribution of $^{99m}\text{TcO}_4\text{Na}$. Santos-Filho et al. (2002), reported that the extracts of *Mentha crispera* L. (mint) and *Piper methysticum* (Kava Kava) were capable of altering the morphology of red blood cells notwithstanding mint extract has also altered the radio labeling process. Braga et al. (2000), in a *in vitro* study demonstrated that *Peumus boldus* did not alter the labeling of blood elements with ^{99m}Tc , in this same study it was observed that the extracts of *T. occidentalis* and *N. tabacum* have altered the radio labeling of blood elements as well as the morphology of red blood cells. Lima et al. (2002) in a *in vivo* study have shown that an extract of cauliflower (leaf) was not capable of altering the labeling of blood elements with technetium-99m. In other study Lima et al. (2001), demonstrated that cauliflower extract was not able to alter the biodistribution of $^{99m}\text{TcO}_4\text{Na}$. In our study we verified that the extracts have decreased the time of labeling expressing an antioxidant action. We can speculate that if the chemical compounds present in these extracts could be modified by the metabolism complexing with $^{99m}\text{TcO}_4\text{Na}$ and SnCl_2 as a chelating agent, this fact could explain the decrease in the fixation of radioactivity on the blood elements. Diré et al. (2001), in a qualitative analysis *in vivo*, have eyed that a chayotte extract (macerated) has induced alteration on the shape of red

blood cells. In this study the chayotte extracts did alter the radio labeling of blood elements as well as the shape of red blood cells, in question to this fact, we can speculate like observed by Mongelli et al. (1997), in a study with *Bolax gummifera* extract, that the chayotte extracts when they are administrated to the animals due to their possible metabolization they are not able to stabilize the active of red blood cell membrane entailing morphology alterations on the red blood cells as well as in other membranes of the different tissues it can modify the uptake of $^{99m}\text{TcO}_4\text{Na}$ in some organs.

Conclusion: Due to the results obtained in this study we can speculate that *Sechium edule* extracts are capable of improving *in vitro* the labeling of blood elements with ^{99m}Tc as well as the biodistribution of $^{99m}\text{TcO}_4\text{Na}$. This fact could be related to the presence of compounds with oxidant properties which could be produced by the metabolization of the chayotte extracts. Moreover, although our results were obtained with animals, we suggest paying attention with examination in nuclear medicine in patients under the treatment referred to popular medicine using chayotte extracts as medicine.

Acknowledgment

We thank to UERJ, CAPES, FAPERJ and CNPq for the financial support.

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