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The Assessment of a Fruit Extract (*Sechium edule*) on the Bioavailability of Radiopharmaceutical Sodium Pertechnetate in *Wistar* Rats with Diabetes Induced by Streptozotocin

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We evaluated the influence of a chayotte(*Sechium edule*) extract (macerated) and diabetes status on the bioavailability of $^{99m}TcO_4Na$. In this study, in the biodistribution analysis, the $^{99m}TcO_4Na$ (0.3 mL) was administrated into female *Wistar* rats (diabetes and no diabetes induced) which had drunk or not the extract (macerated) for 7 days. After 10 min, animals were sacrificed, the organs were isolated, the radioactivity determined in a well counter and the percentages of radioactivity (%ATI) in the organs was calculated. The analysis of the results has indicated an increase in the %ATI in the group treated with chayotte extract (0.0040±0.0010 to 0.0060±0.0010). In the diabetes group it was observed a decreased in the %ATI (0.0040±0.0010 to 0.0030±0.0010) as well as in the diabetes group treated with chayotte extract (0.0040±0.0010 to 0.0020±0.0003). Due to the %ATI in the muscle it was verified that there was an increase of the %ATI in the group treated with chayotte extract (0.0090±0.0040 to 0.0230±0.0070) and in the diabetes group treated with chayotte (0.0090±0.0040 to 0.0180±0.0230). It was observed a difference between the group treated with chayotte to the diabetes group (0.0230±0.0070 to 0.009±0.0040) and between the diabetes group to the diabetes group treated with chayotte extract (0.0090±0.0040 to 0.0180±0.0230). Related to %ATI in the spleen by the light of the results it was detect a difference in the uptake of sodium pertechnetate between the group treated with chayotte extract to the diabetes group treated with the referred extract (0.0290±0.0013 to 0.0480±0.0160). Due to the biodistribution it was related that an extract of eggplant was capable of altering the bioavailability of $^{99m}TcO_4Na$ 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 $^{99m}TcO_4Na$, as a tip, we speculate that the referred extract when metabolized in the liver may produce reactive metabolites with oxidant properties linked to the stress which is generated by diabetic status, this fact could justify by the increase of %ATI in the brain, muscle and spleen which probably may be due to the producing of AGEs in diabetes status.

Key words: Chayotte, red blood cells, biodistribution, technetium-99m, diabetes, radiopharmaceutical

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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 labelled with radionuclide to be used as radiopharmaceuticals (Chandra, 1998). Technetium-99m-labeled human serum albumin scintigraphy is helpful to localize the protein-losing origins and surgery is an effective treatment for Cronkhite-Canada syndrome with protein-losing enteropathy (Tseng *et al*., 2005). The introduction of the short half-life radionuclide technetium-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; 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. Traditional Chinese herbal medicines (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 cutaneous inflammation and to the cauterize the sores. The infusion of the leaves which contains a substance with cardiovascular properties is 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 $^{99m}TcO_4Na$. Related to Savage *et al*. (2005) insulin resistance is a major player in the pathogenesis of the metabolic syndrome and type 2 diabetes and yet, the mechanisms responsible for it remain poorly understood. Magnetic resonance spectroscopy studies in humans suggest that a defect in insulin-stimulated glucose transport in skeletal muscle is the primary metabolic abnormality in insulin-stimulated tyrosine phosphorylation of insulin receptor substrate-1 and its associated phospatidylinositol 3-kinase activity. A number of different metabolic abnormalities may increase intramyocellular/intrahepatic fatty acid metabolites; these include increased fat delivery to muscle/liver as a consequence of either excess energy intake or defects in adipocyte fat metabolism and acquired or inherited defects in mitochondrial fatty acid oxidation. Understanding the molecular/biochemical defects responsible for insulin resistance is beginning to unveil novel therapeutic targets for treatment of the metabolic syndrome and type 2 diabetes. According to Roush (1996) it is suggested that oxidative stress may be resulted by the exposition to some drugs, ionizing radiation and deficiency of folic acid. Insulin resistance, characterized by an inexorable decline in skeletal muscle glucose utilization and/or an excessive hepatic glucose production, constitutes a major pathogenic importance in a cluster of clinical disorders including diabetes mellitus, hypertension, dyslipidemia, central obesity and coronary artery disease. A novel concept suggests that heightened state of oxidative stress during diabetes contributes, at least in part, to the development of insulin resistance (Bitar *et al*., 2005). Cardiovascular disease (CVD) and diabetes are growing public health burdens and remain one of the leading causes of morbidity and mortality in Canada (Heart and Stroke Foundation, 2003). It has become increasingly evident that individuals who present

with a cluster of metabolic disorders, known as the metabolic syndrome, are at an increased risk of developing both CVD and type 2 diabetes. Some studies suggested that maternal diabetes can affect the embryology environmental and this fact could help to elucidate that the oxidative stress may be related to the disturb of the gene expression which is essential in the control of the ontogenetic processes. Bruce (2003) has described that aging is accompanied by decreased specific activity in many enzymes, altered heat stability and increased carbonyl content of proteins. The nonenzymatic reaction of carbohydrates with amino groups of proteins (glycation) can give rise to Advanced Glycation End-products (AGEs). These AGEs increase with aging and are implicated in diabetes, eye disorders and amyloid accumulation. Many extracellular matrix proteins exhibit increased cross-linking with age. Sohal and Weindruch (1996) have described that oxygen-derived species can react with macromolecules in a self-perpetuating manner; they create free radicals out of subsequently attacked molecules, which in turn create free radicals out of other molecules, thereby amplifying the effect of the initial free radical attack. Reactive oxygen species appear to play a role in regulating differential gene expression. According to Basta *et al.* (2004) in the vasculature, the principal pathological consequence of AGE interaction with endothelial surface RAGE (receptor to AGEs) in the induction of intracellular reactive oxygen species. The generation of. which seems to be linked, at least, in part, to the activation of NAD(P)H-oxidase system. These ROS would in turn activate the redox-sensitive transcription nuclear factor, a pleiotropic regulator of. many response-to-injury genes. This signal transduction cascade can be blocked by antibodies directed against either RAGE or against AGEs themselves. In this assessment we have evaluated the influence of a chayotteextract and diabetes induced status on the biodistribution of $^{99m}TcO_4Na$.

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 mixtured 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 acethylcholinestarase 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 10 min. 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 (50 g) of the chayote skin which were triturated in a liquidizer with 500 mL of water. The animals were treated during 7 days. In the control the animals just have received water backwards cahyotte extracts.

Radio labeling process

Biodistribution procedures: It was performed 4 groups in the experimental, each group with 4 animals. The chayotte extract (macerated) was administrated (replaced by water in the treated group with chayotte and in the diabetic group treated with chayotte) during 7 days. The control group has received water like to the diabetic group. After that, $^{99m}TcO_4Na$ (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, ovary, uterus and blood) and counted in a well counter. The %ATI was calculated by the counting of the %ATI in each organ through a well counter machine. The statistical analysis were performed by Tukey test ($p<0.05$).

Diabetes induction: The injection of Streptozotocin was realized in the ventral region next to the alba line with a unique dose of 30 μg kg^{-1} by body weight dissolved in saline solution or in a same volume of citrate (control group). In a period of 2 h after the injection the rats were maintained without water and after that it was added sugar high quantities in their drinking during 1.5 h. After 48 h of. the induction it was performed the rate of sugar tests by tail puction. It was considered diabetic the rats with rate of sugar rates above 180 dg dL^{-1}.

RESULTS

The Fig. 1 has shown the effect of a chayotte extract and diabetes in the bioavailabity of sodium pertechnetate radiopharmaceutical. Towards the analysis of the results it was verified an alteration on the biodistribution of the sodium pertechnetate radiopharmaceutical in the brain,

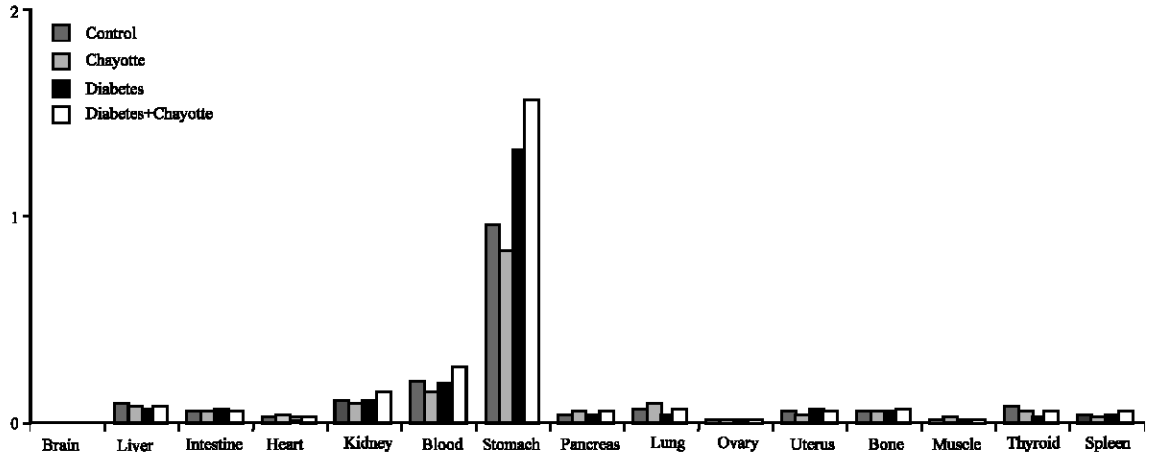

Fig. 1: Effect of chayotte and diabetes in the bioavailability of sodium pertechnetate. Female *Wistar* rats had drunk (treated group: diabetic and not diabetic) or not the extract (control group) during 7 days and after that $^{99m}TcO_4Na$ was injected by ocular plexus. The animals were sacrificed, the organs were isolated and the % ATI was determined. For blood 1 mL was considered to be equivalent to 1g. A statistical analysis (Tukey test, n = 4) was performed to compare the results

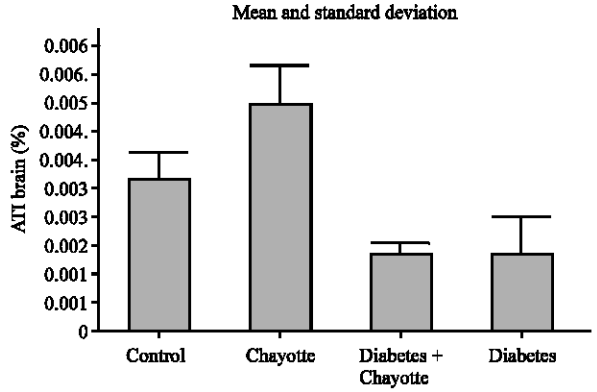

Fig. 2: Effect of chayotte extract and diabetes in the uptake of sodium pertechnetate in the brain. Female *Wistar* rats had drunk (treated group: diabetic and not diabetic) or not the extract (control group) during 7 days and after that $^{99m}TcO_4Na$ was injected by ocular plexus. The animals were sacrificed, the brain was isolated and the % ATI was determined. A statistical analysis (Tukey test, n = 4) was performed to compare the results

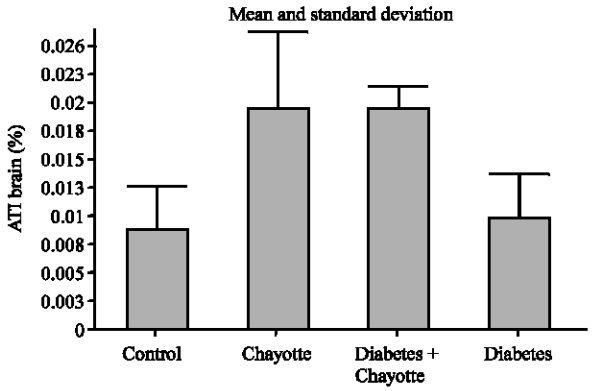

Fig. 3: Effect of chayotte extract and diabetes in the uptake of sodium pertechnetate in the muscle Female *Wistar* rats had drunk (treated group: diabetic and not diabetic) or not the extract (control group) during 7 days and after that $^{99m}TcO_4Na$ was injected by ocular plexus. The animals were sacrificed, the muscle (gastrocnemic) was isolated and the % ATI was determined. A statistical analysis (Tukey test, n = 4) was performed to compare the results

muscle and spleen. In the Fig. 2 has shown the %ATI in the brain. Due to the analysis of the results it was noticed an increase in the %ATI in the group treated with chayotte extract (0.0040±0.0010 to 0.0060±0.0010). In the diabetes group it was observed a decreased in the %ATI (0.0040±0.0010 to 0.0030±0.0010) as well as in the diabetes group treated with chayotte extract (0.0040±0.0010 to 0.0020±0.0003). In the Fig. 3 has shown the %ATI in the muscle. Related to the analysis data it was verified that there was an increase of the %ATI in the group treated with chayotte extract (0.0090±0.0040 to 0.0230±0.0070) and in the diabetes group treated with chayotte (0.0090±0.0040 to 0.0180±0.0230). It was observed a difference between the group treated with chayotte to the diabetes group (0.0230±0.0070 to 0.009±0.0040) and between the diabetes

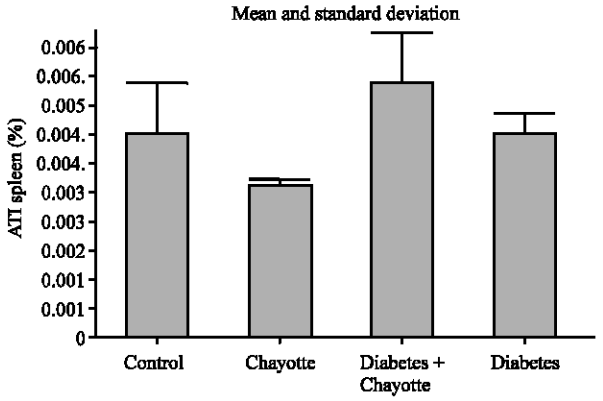

Fig. 4: Effect of chayotte extract and diabetes in the uptake of sodium pertechnetate in the spleen. Female *Wistar* rats had drunk (treated group: diabetic and not diabetic) or not the extract (control group) during 7 days and after that $^{99m}TcO_4Na$ was injected by ocular plexus. The animals were sacrificed, the spleen was isolated and the % ATI was determined. A statistical analysis (Tukey test, n = 4) was performed to compare the results

group to the diabetes group treated with chayotte extract (0.0090±0.0040 to 0.0180±0.0230). In the Fig. 4 is shown the %ATI in the spleen. In the light of the results it was detect a difference in the uptake of sodium pertechnetate between the group treated with chayotte extract to the diabetes group treated with the referred extract (0.0290±0.0013 to 0.0480±0.0160).

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 research it was noticed that chayotte extract was capable of normalizing the uptake of $^{99m}TcO_4Na$ in the pancreas in the animals treated with the referred extract. In comparison to that in the diabetes animals was noticed that the disease status was capable to induce a decrease in uptake of. the radiopharmaceutical in pancreas. 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; Hesslewood and Leug, 1994; Owunnwanne *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-labelled 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 ocidentallis* (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 *Solanun 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 $^{99m}TcO_4Na$. Santos *et al*. (2002),

reported that the extracts of *Mentha crispa 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. ocidentallis* 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. 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. We can speculate like observed by Mongelli *et al.* (1997), in a study with *Bolax gummifera* extract, that the chayotte extract when administrated to the animals due to their possible metabolization may generate reactive metabolites with oxidant properties which may be able to alter the active of cell membrane which can modify the uptake of $^{99m}TcO_4Na$ in the brain and in the muscle as it was noticed although the effect of the extract may be in association to the effects linked to the diabetes status as it was observed in the diabetes group and in the diabetes group treated with the extract. Similar effect could be seen in the muscle where there was an increase in the uptake of %ATI in the group treated with the extract and in the diabetes group treated with chayotte, added to this fact, it was noticed an opposite effect of the extract related to the diabetes status once that in comparison of the groups it may be noticed that chayotte extract promote an increase in the uptake of the %ATI in the diabetes group treated with chayotte different of the diabetes group although to the results obtained to the brain in the diabetes group treated with chayotte the results were different indicating different mechanisms of actions in the tissues. This fact may be supported due to the analysis of the spleen where the extract had promoted a decrease in the %ATI although together with diabetes status it was noticed an increase in the %ATI. The results may be support by the study in which to dissect the contribution of RAGE-ligand interaction in the pathogenesis of diabetic vasculopathy, an acute animal model of diabetes-associated hyper permeability was tested first, using reagents blocking the receptor itself or blocking the access of ligants to RAGE, by administering the decoy protein soluble RAGEs. Rats rendered diabetic with streptozotocin, after 9-11 weeks of diabetes shoed increased vascular permeability in multiple organs, especially the intestine, the skin and the kidney (Basta *et al.*, 2004).

CONCLUSIONS

Due to the results obtained in this study we can speculate that *Sechium edule* extract and diabetes status were capable of altering the biodistribution of $^{99m}TcO_4Na$ in brain, muscle and spleen. This fact could be related to the presence of compounds with oxidant properties which could be produced by the metabolization of the extract and by the generation of AGEs in diabetes. 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 who is drinking chayotte extract therapeutically.

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