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Effects of licorice (*Glycyrrhiza uralensis* F.) commercial extract on the biodistribution of the radiopharmaceutical sodium pertechnetate, radiolabeling of blood constituents and on some biochemical parameters in Wistar rats

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This study investigated the influence of a licorice (*Glycyrrhiza uralensis*) commercial extract on the biodistribution of the radiopharmaceutical sodium pertechnetate, on the radiolabeling of blood constituents and on selected biochemical parameters of Wistar rats. The animals were treated with licorice for 7 days and the assays were performed. A biodistribution assay was performed by administering sodium pertechnetate and determining its activity in organs and tissues. Blood samples were also withdrawn from the animals, the radiolabeling procedure was carried out and the biochemical parameters determined. A decrease of the radiopharmaceutical uptake was found in bladder and testis. No changes on the radiolabeling of the blood constituents neither on the biochemical parameters were found. In conclusion, licorice showed effect on the biodistribution of the sodium pertechnetate in rats. Moreover, as the licorice has not interfered on the Technetium-99m radiolabeling of blood constituents (depends on the presence of a reducing agent), this finding reinforces the antioxidant property of the licorice. Although this study was carried out with rats treated with licorice commercial extract, a precaution is suggested in the interpretation of nuclear medicine examinations with the radiopharmaceutical sodium pertechnetate involving the excretory system in patients that are undertaking licorice.

Key words: Licorice, *Glycyrrhiza uralensis*, biodistribution, radiopharmaceutical, sodium pertechnetate, interaction, rats.

INTRODUCTION

In nuclear medicine, technetium-99m (^{99m}Tc) is the most widely available radionuclide to label radiopharmaceuticals

for diagnostic in the single photon emission computed tomography (SPECT). ^{99m}Tc-radiopharmaceuticals have an expected distribution in target organs and tissues that have allowed the measurement of physiological processes, the identification of altered biological activity and changes related to various diseases through SPECT images (Saha, 2010).

Sodium pertechnetate ($Na^{99m}TcO_4$), a chemical form of ^{99m}Tc, is utilized as radiopharmaceutical to be administered intravenously, with the most uptake expected by the thyroid, stomach, lungs, intestines, salivary glands and choroid plexus of the brain (Saha, 2010). Moreover, Pettit et al. (1989) reported that an important fixation of the radiopharmaceutical is done in various organs of rats in a few minutes after the administration of the sodium pertechnetate. $Na^{99m}TcO_4$ has also been used in procedures to label blood constituents using the stannous chloride as a reducing agent (Saha, 2010).

It is known that interactions of radiopharmaceutical with drugs can alter its biodistribution and pharmacokinetics (Saha, 2010; Hesslewood and Leung, 1994). These drug interactions, which have an impact on image quality in the nuclear medicine examinations by competing with the radiopharmaceutical for binding sites for example, can lead to false negative results (Santos-Oliveira et al., 2008; Vallabhajosula et al., 2010). If this drug interaction is unknown, it is possible that the occurrence of a misdiagnosis and/or the necessity in repeating the examination, will increase the radiation dose to the patient and the staff (Bernardo-Filho et al., 2005; Vallabhajosula et al., 2010).

Natural products, as medicinal herbs, contain mixtures of various pharmacologically active compounds, that may also have the potential to interfere with the biodistribution of the radiopharmaceuticals and/or its radiolabeling (Santos-Filho et al., 2007; De et al., 2008, 2009). Several studies have reported that the treatment of rats with natural and synthetic products can bring modifications in the biodistribution of $Na^{99m}TcO_4$ in organs and tissues (Santos-Filho et al., 2007; De et al., 2008; Cekic et al., 2011; Rocha et al., 2011; Souza et al., 2011; Uçar et al., 2013) and alter the labeling of blood constituents with ^{99m}Tc (De et al., 2009; Uçar et al., 2013). Moreover, Bustani et al. (2009) have reported that the ingestion of chocolate can interfere on the labeling of blood constituents in human beings. In consequence of these findings, experimental models with radiopharmaceuticals could be useful for the evaluation of possible biological effects of natural products, as in the interactions with radiopharmaceuticals.

Glycyrrhiza uralensis, also known as *gan cao* or licorice, is an ancient medicinal herb. In traditional Chinese medicine (TCM), it has been used in combination with other herbal ingredients to harmonize and improve the effects of herbal remedy due to the traditional concept that it is useful to moderate and harmonize the characteristics of other herbs (Chinese Pharmacopoeia Commission, 2008). It is also commonly used to treat a variety of ailments such as sore throat, cough, palpitation, dyspepsia, peptic ulcers and diverse poison (Chen and Chen, 2004).

As many other medicinal herbs, licorice is both utilized as herbal medicinal product or food supplement, and is promoted as health enhancing product. It is also present in food industry as flavouring and sweetening agents (Nomura et al., 2002; Isbrucker and Burdock, 2006; Lin et al., 2009) for its characteristically sweet taste.

A large number of chemical components has been isolated from licorice, including triterpene saponins, flavonoids, isoflavonoids and chalcones, with glycyrrhizin normally being considered to be the main biologically active component (Asl and Hosseinzadeh, 2008; Zhang and Ye, 2009). Licorice or its bioactive compounds have been demonstrated to possess some biological activities such as antioxidant, hepatoprotector, anti-inflammatory, antispasmodic, immunomodulatory, anti-cancer and antidiabetes. It has also the ability to interact with other drugs (Asl and Hosseinzadeh, 2008).

Although it is possible to find many investigations with the licorice, there are no reports about the licorice intake and the sodium pertechnetate distribution and its effect on the radiolabeling of blood constituents. Therefore, the aim of this study was to investigate the influence of a licorice (*G. uralensis*) commercial extract on the biodistribution of the radiopharmaceutical sodium pertechnetate. The effects of the licorice consumption on the *in vitro* radiolabeling of blood constituents with ^{99m}Tc and biochemical parameters of Wistar rats were also investigated.

METHODOLOGY

Preparation of *G. uralensis* extract

The extract used in this study is a brown, sweet herbal commercial concentrated granules of root and rhizome of *G. uralensis* (*Gan Cao*, E-fong, lot number 08055431, validity 04/2013, China) produced in accordance with the Good Manufacturing Practice of State Food and Drug Administration of China (SFDA). The experiments were performed during the validity of the product.

In the preparation of *G. uralensis* aqueous extract, 50 ml of boiled saline solution (NaCl, 0.9%) was added to 2 g of the extract and was homogenized. The preparation was centrifuged (450 g, 15 min) in a clinical centrifuge (Bio Eng, BE- 4004, São Paulo, Brazil) and the supernatant removed was considered to have 40 mg/ml of the extract. A spectrophotometric analysis (Analyser 800M, São Paulo, Brazil) of the diluted extract on 25% was carried out and the absorbance was determined to each 10 nm in the range 400 to 700 nm. The absorbance at 440 nm was considered the marker of the quality control to the preparation of the extract. All the fresh prepared extracts used in the experiments must have the optical

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density of 0.598 ± 0.028 at 440 nm.

Animals

Male healthy Wistar rats (3 to 4 months old, 250 to 350 g of weight) were used in this investigation. The animals were maintained under environmental conditions (25 ± 2°C, 12 h of light/dark cycle), with water *ad libitum* and normal food. All the experimental procedures followed the Ethical Guidelines of the Instituto de Biologia Roberto Alcantara Gomes, Universidade do Estado do Rio de Janeiro, Brazil, approved with the protocol number CEUA/005/2011.

Animal treatments

Wistar rats were treated by gavage either with a fresh *G. uralensis* aqueous extract (40 mg/kg) or with saline solution (0.9% NaCl), as control group, for 7 days, at 24 h intervals. All animals were fasted for 12 h before the experiments. At the eight day, the biodistribution assay was carried out. Other animals were used in evaluating the labeling of blood constituents and determining the biochemical parameters following the same treatment of the rats with the extract.

Biodistribution of the radiopharmaceutical $Na^{99m}TcO_4$

The animals of the control and treated group (n=4, each treatment) were anesthetized with sodium thiopental (60 mg/kg intraperitoneal). Then, 0.3 ml (3.7 MBq) of $Na^{99m}TcO_4$ (Rebello et al., 2008; Souza et al., 2011) recently milked from a $^{99}Mo/^{99m}Tc$ generator (Instituto de Pesquisas Energéticas e Nucleares, Comissão Nacional de Energia Nuclear, São Paulo, Brazil) was administered in the venous orbital plexus. The rats were sacrificed in a CO_2 gas chamber after 10 min of the administration of $Na^{99m}TcO_4$. Selected organs/tissues (thyroid, stomach, duodenum, adrenal gland, kidney, liver, pancreas, brain, bone (femur), lung, heart, spleen, muscle tissue (soleus), prostate, seminal vesicle, bladder, testis and blood) were withdrawn. The internal contents of the stomach, duodenum and bladder were removed and all the organs and tissues were weighed.

The samples were put in specific and appropriate tubes in the same conditions. The radioactivity in each organ/tissue was counted in a well gamma-counter (Gamma C-12, DPC Medlab, Los Angeles, CA, USA). The well gamma-counter energy window was adjusted to the gamma-ray emission energy of the ^{99m}Tc (140 keV). The intervals among the counting of the various samples were extremely reduced and the decay of the ^{99m}Tc did not interfere on the measurements of the radioactivity in the various samples. Moreover, all the samples were measured just at the end of the assay. The percentage of radioactivity incorporated per gram of tissue (%ATI/g) was determined as described elsewhere (Santos-Filho et al., 2007).

Labeling of blood constituents with ^{99m}Tc

Blood was withdrawn by cardiac puncture from the Wistar rats under anesthesia by sodium thiopental (60 mg/kg, Thiopentax) to the radiolabeling and the biochemical analysis. Then, the animals were sacrificed in a CO_2 gas chamber. Heparinized blood samples (0.5 ml, n=5 for each treatment) were incubated for 60 min with 0.5 ml of freshly prepared solution of $SnCl_2$ (1.2 mg/ml, Sigma Aldrich, USA), as reducing agent. In sequence, 0.1 ml of ^{99m}Tc (3.7 MBq) as sodium pertechnetate (Rebello et al., 2008; Souza et al., 2011), was added and incubated for other 10 min. Afterward, the samples were centrifuged (5 min, 250 g) in a clinical centrifuge (Bio Eng, BE-4004, São Paulo, Brazil) to plasma (P) and cells (BC) separation. Aliquots (20 µl) of P and BC were also precipitated with 1 ml of trichloroacetic acid (5%) and insoluble (IF) and soluble fractions (SF) were separated by centrifugation in a clinical centrifuge (5 min, 250 g). Radioactivity in P, BC, IF-P, SF-P, IF-BC and SF-BC was determined in a Gamma C-12 gamma counter (Gamma C-12, DPC Medlab, Los Angeles, CA, USA). All the samples were measured just at the end of the assay and the percentage of radioactivity incorporated (%ATI) on each fraction was calculated (Bernardo-Filho et al., 1983).

Biochemical parameters analysis

To biochemical parameters analysis, 4 ml of whole blood of each animal was collected and the analysis of glucose, serum total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, urea, creatinine, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase were performed in automated equipment (COBAS INTEGRA 400 plus, Roche, Basel, Switzerland).

Statistical analysis

The data are presented as their respective mean and standard deviation. The values of each assay were submitted to BioEstat 5.3 software (Belém, Brazil) through unpaired two-tailed Student's *t* test. The significance level of $P<0.05$ was adopted.

RESULTS

Table 1 shows the effect of the *G. uralensis* on the biodistribution of the radiopharmaceutical $Na^{99m}TcO_4$ (%ATI/g) in Wistar rats that either received (treated group) or did not receive (control group) the referred extract. An important finding is that the licorice extract significantly altered ($P<0.05$) the %ATI/g in the bladder. Although a significant decrease in the %ATI/g was found in the testis of the rats, this alteration was very small in comparison with the control group. In addition, the data indicated that the radioactivity was slightly decreased (not significant) in most of the analyzed organs.

Table 2 shows the effect of the *G. uralensis* on the distribution of radioactivity in blood cells and plasma compartments, as well as in the insoluble and soluble fractions isolated from blood cells and plasma samples. The results indicate that the extract did not alter the distribution of ^{99m}Tc in the blood (blood cells and plasma) compartments. Moreover, the fixation of the radiotracer in the macromolecules precipitated by the trichloroacetic acid (soluble fraction) of plasma and blood cells samples was not also altered due to treatment with the licorice extract.

As shown in Table 3, the quantification in the plasma of some biochemical parameters in Wistar rats treated with *G. uralensis* aqueous extract was also not altered in comparison with the animals of the control group.

Table 1. Effect of the *Glycyrrhiza uralensis* on the biodistribution of $Na^{99m}TcO_4$ in Wistar rats.

Organ and tissue	Groups		
	Control (%ATI/g)	Treated (%ATI/g)	P
Thyroid	4.54 ± 3.32	3.32 ± 1.01	0.139
Stomach	2.07 ± 0.73	1.50 ± 0.25	0.187
Duodenum	0.59 ± 0.24	0.56 ± 0.34	0.874
Kidney	0.74 ± 0.15	0.62 ± 0.16	0.323
Liver	0.76 ± 0.15	0.72 ± 0.10	0.659
Pancreas	0.45 ± 0.05	0.39 ± 0.02	0.054
Brain	0.05 ± 0.01	0.05 ± 0.01	0.914
Bone (Femur)	0.19 ± 0.08	0.22 ± 0.05	0.668
Lung	0.77 ± 0.13	0.72 ± 0.09	0.547
Heart	0.36 ± 0.06	0.37 ± 0.08	0.881
Spleen	0.44 ± 0.04	0.40 ± 0.04	0.210
Muscle (Soleus)	0.11 ± 0.02	0.11 ± 0.01	0.655
Adrenal	0.12 ± 0.07	0.17 ± 0.05	0.263
Prostate	0.39 ± 0.11	0.37 ± 0.06	0.803
Seminal vesicle	0.20 ± 0.04	0.18 ± 0.02	0.598
Bladder	1.57 ± 0.60	0.77 ± 0.16	0.041*
Testis	0.18 ± 0.01	0.15 ± 0.01	0.012*
Blood	0.89 ± 0.23	0.86 ± 0.25	0.826

Wistar rats were treated with *Glycyrrhiza uralensis* aqueous extract (40 mg/kg) by gavage daily. After seven days, $Na^{99m}TcO_4$ (3.7 MBq) was administered and the animals were sacrificed. The animals organs were isolated, the mass of each organ was determined and the percentage of radioactivity per gram of each organ (%ATI/g) was calculated (1 ml of blood was considered to weight, 1 g). Animals in the control group were treated with saline (0.9% NaCl). Results are mean ± standard deviation (SD). Statistical analysis with *t* test, significance level *P < 0.05, n=4, was utilized.

DISCUSSION

The study of the effect of the treatment with licorice on the biodistribution profile of the radiopharmaceutical $Na^{99m}TcO_4$ in organs and tissues of Wistar rats was performed to try to understand better the actions of the referred herbal medicine. An important finding of this present investigation is that the %ATI/g of the radiopharmaceutical sodium pertechnetate was significantly reduced in the bladder (P<0.05) (Table 1) of rats of the group treated during one week with an extract of licorice. Although a decrease in the testis was also found with statistical significance, this reduction is considered very small. A relevant consideration is that this effect in the bladder could be associated with the possible action of a compound isolated (*Glycyrrhizin*) of the *G. uralensis* in the urinary tract as reported by Kang et al. (2003).

To further experiments, it is pointed out that due to the licorice intake (one week), the radioactivity (%ATI/g) was slightly (not significant) decreased in several of the analyzed organs and tissues isolated from the rats. In similar experiment, in general, this finding (Table 1) is in agreement with the results described to *Cassia augustifolia* (senna) (Souza et al., 2011), that is a plant in the same family (Leguminosae) of the *G. uralensis*.

In the biodistribution process, after the $Na^{99m}TcO_4$ intravenous injection, the pertechnetate ion ($^{99m}TcO_4^-$) is weakly bound to serum proteins (70 to 80%). The unbound pertechnetate ions diffuses slowly through the capillary membranes to the interstitial fluids, from where it is cleared by various organs such as stomach wall, intestines, salivary glands, thyroid, choroid plexus, sweat glands, kidneys, mucous membrane, testis, bladder wall and others (Owunwanne, 1995; Saha, 2010). Approximately 30% of the injected activity is excreted in the urine in the first 24 h (Saha, 2010).

The present study does not allow us to comment on the direct mechanisms by which licorice consumption results in an interaction with the radiopharmaceutical or the stimulation of the bladder, that allows a decrease of biodistribution of $Na^{99m}TcO_4$. The effect of licorice would be based on its antioxidant effects (Ahn et al., 2006; Lee et al., 2010; Huo et al., 2011; Wu et al., 2011), but pertechnetate exists in circulation and on excretion in its original oxidation state and, therefore redox states do not play a significant role in the biodistribution of this radiopharmaceutical. Beside this, it is possible to speculate, by the radiolabeling and biochemical results (Tables 2 and 3) that the substances or metabolites of the licorice extract could alter the biodistribution of $Na^{99m}TcO_4$ not by an action on blood that could influence

Table 2. Effect of the treatment with *Glycyrrhiza uralensis* on the labeling of blood constituents with ^{99m}Tc.

Blood constituent	Groups		
	Control (%ATI)	Treated (%ATI)	P
P	7.99 ± 4.06	5.29 ± 2.10	0.222
BC	92.01 ± 4.06	94.71 ± 2.10	0.222
IF-P	73.39 ± 5.14	72.74 ± 5.67	0.854
SF-P	26.61 ± 5.14	27.26 ± 5.67	0.854
IF-BC	95.55 ± 0.99	95.69 ± 0.68	0.815
SF-BC	4.45 ± 0.99	4.31 ± 0.68	0.815

Wistar rats were treated by gavage, for seven days, with *Glycyrrhiza uralensis* (40 mg/kg) or saline (NaCl , 0.9%) as control. Blood samples from the treated and the control group were incubated with stannous chloride and ^{99m}Tc was added. The samples were centrifuged, and plasma (P) and blood cells (BC) were separated. Other aliquots of P and BC were precipitated with trichloroacetic acid, and soluble (SF) and insoluble (IF) fractions were also separated, the radioactivity was counted and the percentage of radioactivity (ATI%) was calculated. Results are mean ± standard deviation (SD). Statistical analysis with *t* test, significance level *P<0.05, n=5, was utilized.

Table 3. Effect of *Glycyrrhiza uralensis* treatment on the biochemical parameters of male Wistar rats.

Biochemical parameter	Groups		
	Control	Treated	P
Glucose (mg/dL)	172.8 ± 47.9	193.6 ± 98.1	0.681
Cholesterol (mg/dL)	60.2 ± 8.0	53.6 ± 2.6	0.117
HDL (mg/dL)	50.8 ± 5.8	46.6 ± 2.3	0.171
LDL (mg/dl)	7.3 ± 3.8	10.4 ± 4.8	0.399
Triglycerides (mg/dL)	82.6 ± 46.7	87.0 ± 27.1	0.860
Urea (mg/dL)	50.0 ± 7.6	42.0 ± 2.3	0.089
Creatinine (mg/dL)	0.3 ± 0.1	0.3 ± 0.1	1.000
Albumin (g/dL)	3.6± 0.3	3.6 ± 0.2	0.912
ALT (IU/L)	67.0 ± 25.6	58.8 ± 11.6	0.533
AST (IU/L)	134.4 ± 32.5	163.2 ± 78.6	0.471
Alkaline phosphatase (IU/L)	149.8 ± 52.3	145.8 ± 33.0	0.889

Wistar rats were treated by gavage for seven days with *Glycyrrhiza uralensis* (40 mg/kg) or saline (NaCl, 0.9%) as control. After seven days, blood samples were withdrawn and the biochemical parameters were evaluated. Results are mean ± standard deviation (SD). Statistical analysis with *t* test, significance level *P<0.05, n=5, was utilized.

its distribution or either generally alterations in rats metabolism. Thus, some direct physiological/pharmacological alterations (like competing with the radiopharmaceutical for binding sites for example) that can interfere in the uptake of the pertechnetate ion in bladder tissue, may be happening. Moreover, since the licorice extract is capable to decrease the %ATI/g of sodium pertechnetate (Table 1) in the bladder, it is important to speculate that some alterations in examinations in the nuclear medicine with this radiopharmaceutical might be verified. Furthermore, if the licorice compounds could influence the renal physiology (Kang et al., 2003), and the fixation of the sodium pertechnetate in the bladder (Table 1), then the licorice effect on renal imaging agents may be important, irrespective of the imaging agent (^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) for glomerular filtration rate, ^{99m}Tc-mercaptoacetyl triglycine (MAG3) for tubular function) (Saha, 2010).

In this work, the effects of licorice intake on the *in vitro* radiolabeling of blood constituents of Wistar rats with ^{99m}Tc have also been investigated, as sodium pertechnetate form that depends on the presence of a reducing agent (stannous chloride). This study shows that the intake of *G. uralensis* for 7 days did not interfere on the radioactivity distribution between cellular and plasma compartments neither on the fixation of this radionuclide on insoluble fractions of plasma (plasma

proteins) and blood cells (blood cells proteins) (Table 2). Antioxidant capabilities of the licorice could justify this result due to a protection of the stannous ion against its oxidation. Indeed, some authors have reported the antioxidant effects of licorice extract in experimental and clinical studies (Ahn et al., 2006; Lee et al., 2010; Huo et al., 2011; Wu et al., 2011). Moreover, although there is evidence that some natural or synthetic products that could affect the radiolabeling of blood constituents (De et al., 2009; Bustani et al., 2009; Uçar et al., 2013), which was not found in the study with licorice extract. Similar result was also found within an investigation of the *C. augustifolia* extract on the radiolabeling of blood constituents (Souza et al., 2011).

In addition, alteration was not found in the biochemical parameters of healthy Wistar rats after licorice consumption (Table 3). Experimental studies, with induced diseases or injuries models, described that treatment with licorice or its compounds are capable to improve some biochemical parameters of the affected animals (Kim et al., 2006; Ko et al., 2007; Kalaiarasi et al., 2009; Aksoy et al., 2011; Huo et al., 2011). Besides this, the biochemical parameters do not seem to be altered in healthy subjects treated with licorice or its compounds, as presented in this investigation (Table 3) and in some other studies (Kim et al., 2006; Kalaiarasi et al., 2009; Aksoy et al., 2011).

Considering the findings (Tables 1 to 3), licorice (1) does not influence the uptake of ^{99m}Tc-sodium pertechnetate in thyroid, in stomach and kidneys that are important clinically due to the expected uptake of radiopharmaceutical in these organs, (2) despite being an antioxidant, it does not influence red blood cell (RBC) labeling, (3) does not interfere in the plasma concentration of various biomarkers.

In addition, it is suggested to highlight that, in the moment of the nuclear medicine examination, all patients should have to be informed about their medications (including herbal) to try to avoid possible drug interaction with radiopharmaceuticals (Hesslewood and Leung, 1994; Bernardo-Filho et al., 2005; Santos-Oliveira et al., 2008; Vallabhajosula et al., 2010).

In conclusion, putting together all the findings reported in this investigation, it is possible to verify an effect of a licorice extract in the biodistribution of the radiopharmaceutical sodium pertechnetate in rats, in which, a significant ($P<0.05$) decrease of the uptake in the bladder of Wistar rats was found. Moreover, as the licorice extract has not interfered on the ^{99m}Tc-radiolabeling of blood constituents (depends on the presence of a reducing agent), this finding reinforces the antioxidant property of this medicinal herb. Considering the results, no alteration would be expected in the concentrations of selected biochemical parameters, as it was found. Although this study was carried out with rats treated with licorice commercial extract, precaution is suggested in the interpretation of nuclear medicine examinations with the radiopharmaceutical sodium pertechnetate involving the excretory system in patients that undertake the licorice. This is an exciting area of research with important potential clinical applications.

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ABBREVIATIONS:

^{99m}Tc, Technetium-99m; **Na^{99m}TcO$_4$,** sodium pertechnetate; **SPECT,** single photon emission computed tomography; **TCM,** Traditional Chinese Medicine; **^{99}Mo,** Molybdenum-99; **%ATI,** percentage of radioactivity incorporated; **%ATI/g,** percentage of radioactivity incorporated per gram of tissue; **P,** plasma; **BC,** Blood cells; **IF,** insoluble fractions; **SF,** soluble fractions; **HDL,** high-density lipoprotein cholesterol; **LDL,** low-density lipoprotein cholesterol; **ALT,** alanine aminotransferase; **AST,** aspartate aminotransferase.

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