Effect of an extract of *Aloe vera* on the biodistribution of sodium pertechnetate ($Na^{99m}TcO_4$) in rats[1]

Efeito de um extrato de *Aloe vera* na biodistribuição do pertecnetato de sódio ($Na^{99m}TcO_4$) em ratos

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ABSTRACT

Purpose: *Aloe vera* is a tropical plant popularly known in Brazil as *babosa*. We have investigated the effect of aqueous extract of *Aloe vera* on the biodistribution of $Na^{99m}TcO_4$ and laboratorial parameters in *Wistar* rats. **Methods**: Twelve animals were divided into treated and control groups. In the treated group, *Aloe vera* was given by gavage (5mg/mL/day) during 10 days. The control group received sorbitol by the same way and period. One hour after the last dose, we injected 0.1mL of $Na^{99m}TcO_4$ by orbital plexus. After 60 min, all the animals were killed. Samples were harvested from the brain, liver, heart, muscle, pancreas, stomach, femur, kidneys, blood, testis and thyroid and the percentage of radioactivity (%ATI/g) was determined. Biochemical dosages were performed. **Results**: There was a significant increase of %ATI/g in blood, femur, kidneys, liver, stomach, testis and thyroid and also in blood levels of AST and ALT. A significant decrease in levels of glucose, cholesterol, triglycerides, creatinine and urea occurred. The statistical analyses were performed by Mann-Whitney test and T-Student test ($p<0.05$). **Conclusion**: The aqueous extract of *Aloe vera* facilitated the uptake of $Na^{99m}TcO_4$ in organs of rats and it was responsible to a high increase of levels of AST and ALT.

Key words: Aloe. Plants, Medicinal. Radioisotopes. Sodium Pertechnetate Tc 99m. Technetium. Rats.

RESUMO

Objetivo: *Aloe vera* é uma planta tropical popularmente conhecida no Brasil por "babosa". Investigou-se o efeito de extrato aquoso do *A. vera* na biodistribuição do pertecnetato de sódio ($Na^{99m}TcO_4$) e em parâmetros laboratoriais de ratos *Wistar*. **Métodos**: Doze animais foram divididos em 2 grupos: tratado e controle. No grupo tratado, o extrato de *A. vera* foi administrado via oral (5mg/mL/dia) por 10 dias. O grupo controle recebeu sorbitol do mesmo modo. Uma hora após a última dose, ambos receberam 0,1mL de $Na^{99m}TcO_4$ via plexo orbital. Após 60 minutos, os animais foram sacrificados. Foram retiradas amostras do cérebro, fígado, coração, músculo, pâncreas, estômago, fêmur, rins, sangue, testículos e tiróide e determinou-se o percentual de radioatividade por grama (%ATI/g) de cada uma. Dosagens bioquímicas foram realizadas. **Resultados**: Houve um aumento significativo do %ATI/g no sangue, fêmur, rins, fígado, estômago, testículos e tiróide e nos níveis sanguíneos das enzimas AST e ALT. Ocorreu uma diminuição significativa dos níveis de glicose, colesterol, triglicérides, creatinina e uréia. Análises estatísticas foram feitas pelos testes de Mann-Whitney e T-student ($p<0,05$). **Conclusão**: O extrato aquoso de *A. vera* facilitou a captação do $Na^{99m}TcO_4$ em órgãos de ratos e foi responsável pelo aumento dos níveis de AST e ALT.

Descritores: Aloe. Plantas Medicinais. Radioisótopos. Pertecnetato Tc 99m de Sódio. Tecnécio. Ratos.

[1]Research performed at Experimental Radiobiology and Antiparasitic Assays Laboratory, Federal University of Rio Grande do Norte (UFRN), Brazil.

Introduction

There is currently particular interest of people on medications that either are or contain components of natural origin. The use of certain plants as phytotherapy has been a millennial practice in folk medicine. Its use has gained enormous popularity around the world, as modern medicine is beyond the reach of many people. *Aloe vera* is a tropical plant easily grown in hot and dry climates and popularly known in Brazil as *babosa*. Referred to as a 'miracle' plant, *Aloe vera* possesses confirmed curative or healing actions. A total of 360 *Aloe* species (commonly accepted as *Aloe vera*) are growing in the dry regions of North American, Europe and Asia. These plants were demonstrated to contain a yellow exudate (composed mainly of anthraquinone derivatives) that has been used for centuries as a purging agent. It has a clear mucilaginous gel (consisting principally of polysaccharides) that has been used since ancient times to treat burns and other wounds where it is thought to be able to enhance the healing rate and to reduce the infection risk[1,2,3,4]. This plant is also used for various medicinal (useful in X-ray burns, dermatitis, cutaneous leishmaniasis, antiviral and anti-inflammatory activities, anti-cancer, antidiabetic, macrophage activation, cardiac stimulatory activity and others)[1,3,4], cosmetic and nutraceutical purposes[5]. It has been suggested that the extract of this plant promotes healing of diseases through the complex synergistic interaction of many substances, including alkaloids, saponins, fatty acid materials, glycoproteins, resins, sterols, gelonins, minerals, vitamins (A, C, and E) amino acids, enzymes and other small constituent molecules[5]. In spite of its wide pharmaceutical use, there are few data on *Aloe* toxicity.

Nuclear medicine is the medical specialty that uses radioactive isotopes to diagnose through images or therapy. Among the many diagnostic tools that can be used in tropical diseases, scintigraphy images are widely used in the anatomic and functional analyses of organs and systems[6]. For most applications in diagnostic nuclear medicine the use of the isotope technetium-99m (^{99m}Tc), is preferred. Technetium-99m is a short-lived isotope, present in chemically microscopic amounts and has minimally damaging radioactive emission that is close to optimal for use with today's imaging instruments. Thus a great deal of the chemistry done in the design of diagnostic radiopharmaceuticals has been technetium chemistry[6].

Several natural or synthetic drugs can interfere with the biological behavior of radiopharmaceuticals, used in scintigraphy examinations, or on the labeling of blood constituents with technetium-99m[6,7,8]. They can change the biological effect of the radiopharmaceutical and their interaction can lead to hypo or hyper uptake of radiopharmaceuticals in a particular organ, causing incorrect diagnosis or misinterpretation of results. Repeated scintigraphy may result in unnecessary radiation for patients[6,7,8].

Although *Aloe vera* is a natural product used by many people, orally or topically, little is known about its action mechanism, its effects on host cells and toxicity. Thus, it is important to study the effect of this natural product on the biodistribution of the radiopharmaceutical sodium pertechnetate in laboratory animals subjected to chronic treatment with this product. In the present study, we investigated the effect of aqueous extract of *Aloe vera* on the biochemical analyses and biodistribution of the sodium pertechnetate in *Wistar* rats.

Methods

The animals were obtained from Center of Health Sciences of the Federal University of Rio Grande do Norte (UFRN), Brazil, and they were housed in groups with free access to food and water, maintained under constant environmental conditions (23±2ºC; 12h/12h of light/dark cycle). Studies were performed in healthy male *Wistar* rats (weight range: 180–250 g). Twelve animals were randomly divided into two groups (treated and control groups) of 6 animals each one. These experiments were performed according to local regulations for animal experimentation (approved by the Ethical Committee for Using Animals of UFRN, with the number CEUA/213/2008).

Fresh *Aloe vera* (L.) Burm. F. (Liliaceae) leaves were collected and processed from a single garden plant. The identification of the plant, voucher no. 3479, was done by the herbarium of the Department of Botanic, Ecology and Zoology of UFRN to obtain a fresh extract for experiment during this work. The extract was obtained from leaves of this plant (300g) by using 2500 mL of distilled water at 70–80 ºC for 2 h. The mixture was agitated over the mechanical shaker for 12 h. The resulting mixture was filtered and the filtrate concentrated from the extract was redissolved in sorbitol solution to obtain a concentration of 30 mg/mL for use in the study. In the treated group, a single dose (5mg/mL/day) of aqueous extract of *Aloe vera* was administered to each rat by gavage during 10 days. The control group received sorbitol solution by the same way and period. One hour after the last dose, we injected 0.1 mL of $Na^{99m}TcO_4$ (3.7 MBq) via orbital plexus. The $Na^{99m}TcO_4$ was eluted in a $^{99}Mo/^{99m}Tc$ generator (Institute of Energy and Nuclear Research, National Commission of Nuclear Energy, São Paulo, Brazil). After 60 minutes, all the animals were quickly killed under anesthesia with xylazine (20 mg/kg) and ketamine (50 mg/kg), by intraperitoneal via. Samples were harvested from the brain, liver, heart, muscle, pancreas, stomach, femur, kidneys, blood, testis and thyroid. The tissue samples were washed in 0.9% saline, weighed on a precision scale and the percentage of radioactivity per gram of tissue (%ATI/g) was determined in an automatic gamma counter. The efficiency of the gamma counter was 86%, as specified by the manufacturer. Before the administration of $Na^{99m}TcO_4$, it was withdrawn 2 mL of whole blood from each animal and the biochemical dosages were performed in automated equipment. Data were presented as mean ± standard deviation. The percentage of radioactivity per gram (%ATI/g) was determined by dividing the percentage of total radioactivity of each sample by its weight in grams. The ATI%/g was compared using the non-parametric Mann-Whitney test and the biochemical parameters by T-Student test, considering the level of statistical significance at $p<0.05$ in both tests.

Results

Table 1 shows the relationship between the uptake (%ATI/g) of the $Na^{99m}TcO_4$ on the *Aloe vera*-treated group (n=6) and on the sorbitol-control group (n=6), 60 min after administered of the $Na^{99m}TcO_4$. The analysis of the results shows a significant ($p<0.01$) increase of the uptake of radioactivity in blood, femur, kidneys, liver, stomach, testis and thyroid. The results also reveal no significant alteration of the %ATI/g in brain, heart, muscle and pancreas.

TABLE 1 - Effect of aqueous extract of *Aloe vera* on the %ATI/g in organs of *Wistar* rats after 60 min injection of radiopharmaceutical ($Na^{99m}TcO_4$)

Organs	ATI/g		p-value
	Control	*Aloe vera*	
Blood	0.0010±0.0004	0.0060±0.0009	0.0001**
Brain	0.0018±0.0005	0.0020±0.0000	0.0001
Femur	0.0003±0.0001	0.0013±0.0003	0.0001**
Heart	0.0053±0.0006	0.0054±0.0001	0.0002
Kidneys	0.0002±0.0001	0.0034±0.0006	0.0001**
Liver	0.0004±0.0000	0.0040±0.0007	0.0004**
Muscle	0.0059±0.0023	0.0063±0.0001	0.0001
Pancreas	0.0225±0.0153	0.0313±0.0005	0.0001
Stomach	0.0012±0.0007	0.0207±0.0038	0.0001**
Testis	0.0001±0.0001	0.0012±0.0001	0.0004**
Thyroid	0.0003±0.0002	0.0251±0.0127	0.0001**

Mean±DP. **, $p<0.01$

Table 2 shows the effect of the *Aloe vera* on the laboratorial parameters of *Wistar* rats (n=6) and on the control group (n=6), before the administration of the $Na^{99m}TcO_4$. The analysis of the results shows a significant ($p<0.05$) increase of blood levels of the hepatic enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and a significant decrease ($p<0.05$) of blood levels of glucose, cholesterol, triglycerides, creatinine and urea.

TABLE 2 - Effect of aqueous extract of *Aloe vera* on biochemical parameters from *Wistar* rats

Biochemical parameters	Control	*Aloe vera*	p-value
ALT(U/L)	48.83±7.10	82.50±29.99	0.038*
AST(U/L)	85.70±14.50	101.00±38.40	0.029*
Cholesterol (mg/dL)	3.12±0.25	2.10±0.29	0.043*
Creatinine (mg/dL)	0.48±0.01	0.37±0.04	0.045*
Glucose (mg/dL)	122.67±17.92	24.67±6.69	0.005*
Tryglicerides (mg/dL)	74.83±11.43	40.00±15.39	0.014*
Urea (mg/dL)	43.83±8.16	34.66±5.71	0.048*

Mean±DP. *, $p<0.05$

Discussion

The extract of the plants promotes successful treatment of diseases through the complex synergistic interaction of many substances. *Aloe vera* extracts, possess some biological activities as analgesic, antiinflammatory, anti-cancer, anti-diabetes, macrophage activation, antimicrobial effect on gastrointestinal infections and urinary infections[1,4].

There are over 300 species of *Aloe* known, but *Aloe vera* L. is recognized as the "true *Aloe vera*" for its widespread use and purported healing powers. It has been demonstrated that a large part of the pharmacological activity of this plant is due to polysaccharides, which makes up the majority of the mucilaginous *Aloe vera* gel[3,4,5]. The popularity and use of herbal medicine products are gradually increasing. Yet, hepatic toxicity is a potential complication of these compounds that may lead to hepatic insufficiency[9,10]. On the other hand, studies of *Aloe vera* evaluating its clinical effectiveness for a variety of indications were undertaken. They found that oral *Aloe vera* might be valuable for reducing cholesterol or glucose levels[2,3,11].

We observed in our work that the aqueous extract of *Aloe vera* probably was responsible to a high increase of the levels of AST and ALT, demonstrating its hepato-toxicity. Our study also demonstrated low levels of cholesterol, triglycerides and glucose in *Wistar* rats treated orally with aqueous extract of this plant. These biochemical changes may be related to the biological and/or metabolic effects of *A. vera*. According to Patel & Mengi (2008)[11], the *Aloe vera* extract has hipolipidemic, hipoglicemic and antitrombotic activities. This fact probably explains the reduced levels of these biochemical dosages (cholesterol, triglycerides and glucose) in the treated rats.

The use of phytotherapeutic products by the world population has greatly increased in the last decades. Vegetal extracts and synthetic drugs can generate metabolites capable to promote morphological and/or physiological modifications in treated animals. Several authors have demonstrated that the biodistribution of radiopharmaceuticals may be altered by natural and/or synthetic drugs, diets and surgery[6,8,12,13,14,15]. We have previously shown that the antiparasitic drugs glucantime and mefloquine can alter the biodistribution *in vivo* of ^{99m}Tc-methylenediphosphonic acid (^{99m}Tc-MDP) in *Wistar* rats[8,12]. Besides these studies, changes on the biodistribution of the $Na^{99m}TcO_4$ in organs of the *Wistar* rats were observed after treatment with natural products such as *Artemisia vulgaris* and *Punica granatum*[8,15]. In our experiment, we demonstrated that the aqueous extract of *Aloe vera* facilitated the uptake of the $Na^{99m}TcO_4$ in organs, increasing their uptake in blood, femur, kidneys, liver, stomach, testis and thyroid of *Wistar* rats. Probably, clinical implications can be observed in cases of patients using this plant extract.

Conclusions

The results of the present study indicated that the aqueous extract of *Aloe vera* in rats has hypolipemic and hypoglycemic effects and demonstrated to be toxic to the liver. In addition, it facilitated the uptake of $Na^{99m}TcO_4$ in some organs, with possible clinical implications in nuclear medicine imaging.

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Conflict of interest: none
Financial source: none

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Received: March 04, 2009
Review: May 06, 2009
Accepted: June 10, 2009

How to cite this article
Holanda CMCX, Costa MB, Silva NCZ, Silva Júnior MF, Barbosa VSA, Silva RP, Medeiros AC. Effect of an extract of *Aloe vera* on the biodistribution of sodium pertechnetate ($Na^{99m}TcO_4$) in rats. Acta Cir Bras. [serial on the Internet] 2009 Sept-Oct;24(5). Available from URL: http://www.scielo.br/acb