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Artigo

# Effects of a tomato (*Solanum lycopersicum*) extract on the labeling of blood constituents with technetium-99m

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**RESUMO:** "**Efeitos de um extrato de tomate (*Solanum lycopersicum*) na marcação de constituintes sangüíneos com tecnécio-99m".** O tomate (*Solanum lycopersicum*) é o segundo vegetal mais produzido e consumido no mundo, tendo sido indicado para prevenção e tratamento de câncer, asma e arteriosclerose. Constituintes sangüíneos marcados com radionuclídeos têm sido usados em procedimentos na medicina nuclear. Dados têm mostrado que alimentos e drogas podem alterar a marcação de constituintes sangüíneos com tecnécio-99m ($^{99m}$Tc). Este estudo avaliou a influência de um extrato de tomate neste procedimento de radiomarcação. Sangue heparinizado (*Wistar* rats) foi incubado *in vitro* com diferentes concentrações de um extrato de tomate e a marcação com $^{99m}$Tc foi realizada. Plasma (P) e células sangüíneas (CS) foram separadas permitindo o isolamento das frações solúvel (SF-P/SF-CS) e insolúvel (IF-P/IF-CS) por precipitação e centrifugação. A radioatividade nos constituintes sangüíneos (P, CS, IF-P, SF-P, IF-CS e SF-CS) foi determinada e a porcentagem de radioatividade (%ATI), calculada. O extrato de tomate usado, nas maiores concentrações (2,00 e 4,00g/mL), reduziu significativamente ($p < 0,05$) a %ATI na IF-P, embora este extrato não tenha modificado a radiomarcação da CS e fixação da radioatividade na IF-CS. Em conclusão, nossos dados sugerem que os compostos químicos presentes no extrato aquoso de tomate teriam algumas propriedades capazes de alterar a fixação do $^{99m}$Tc nas proteínas plasmáticas.

**Unitermos:** *Solanum lycopersicum,* Solanaceae, constituintes sangüíneos, tecnécio-99m.

**ABSTRACT:** Tomato (*Solanum lycopersicum*) is the second most produced and consumed vegetable in the world. It has been indicated in the prevention and treatment of cancer, asthma and atherosclerosis. Blood constituents labeled with radionuclides have been used in procedures in nuclear medicine. Data have shown that food and drugs can alter the labeling of blood constituents with technetium-99m ($^{99m}$Tc). This study evaluated the influence of a tomato extract on this radiolabeling procedure. Heparinized blood (*Wistar* rats) was incubated *in vitro* with different concentrations of a tomato extract and $^{99m}$Tc-labeling was performed. Plasma (P) and blood cells (BC) were separated following soluble (SF-P/SF-BC) and insoluble (IF-P/IF-BC) fractions isolation by precipitation and centrifugation. The radioactivities on blood constituents (P, BC, IF-P, SF-P, IF-BC and SF-BC) were determined and the percentage of radioactivity (%ATI) was calculated. The tomato extract used at the highest concentrations (2.00 and 4.00g/mL), reduced significantly ($p < 0.05$) the %ATI in IF-P, although this extract did not modify the radiolabeling on BC, neither the radioactivity fixation on IF-BC. In conclusion, our data suggest that the chemical compounds present in the aqueous tomato extract could have some properties capable of change the fixation of $^{99m}$Tc on plasma proteins.

**Keywords:** *Solanum lycopersicum,* Solanaceae, blood constituents, technetium-99m.



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## INTRODUCTION

Tomato (*Solanum lycopersicum*) is the second most produced and consumed vegetable nationwide and it is a rich source of lycopene, beta-carotene, folate, potassium, vitamin C, flavonoids, and vitamin E (Willcox et al., 2003; Bose and Agrawal, 2007). Over 80% of the lycopene in the American diets come from tomato itself and tomato-derived products such as ketchup, tomato paste and sauce (Everson and McQueen 2004). Some epidemiological and experimental data suggest an inverse relation between intake of tomato and risk of cancer at various anatomical sites, especially prostate and colon (Thomson and Ali, 2003; Etminan et al., 2004; Canene-Adams et al., 2007). Besides its potential role in preventing and treating cancer, tomato intake has also been studied for use in the prevention of atherosclerosis (Rissanen et al., 2002; Frederiksen et al., 2007), reduction of asthma symptoms (Neuman et al., 2000; Wood et al., 2004) as hypolipidemic effect (Gonçalves et al., 2006a,b), inhibitor of the angiotensin converting enzyme (Barbosa-filho et al., 2006), present spasmolytic activity (Oliveira et al., 2006), hypoglycemic activity (Barbosa-Filho et al., 2005) and decrease of DNA strand breakages of cells of the immune system (Riso et al., 1999; Porrini et al., 2005; Riso et al., 2006). The importance of these plants has promoted their inclusion in Brazilian Pharmacopoeia (Brandão et al., 2006; 2008).

The tomato effects may be related mainly to lycopene which acts on biological mechanisms altering the oxidant status and could be responsible for its positive protective actions (Everson and McQueen 2004; Bose and Agrawal, 2007). Normally, the amount of lycopene in the tomatoes is not always the same and it can vary from 5 mg/kg in the yellow tomatoes to 50 mg/kg in the red tomatoes. Reddish foods, such as watermelon, papaya and pink grapefruit may also contain lycopene, but at lower concentrations than in tomatoes (Boyle et al., 2003).

Several theories are being explored to explain the lycopene effects on the prevention of cancer. Lycopene consumption is inversely related to insulin growth factor levels, a factor linked to a greater risk of prostate cancer (Boyle et al., 2003; Jatoi et al., 2007). A second proposed mechanism of lycopene action includes both inhibition of tumor growth by decrease or loss in junctional cell communication (Kucuk et al., 2002; Telef et al., 2006). However, the most widely accepted theory is the antioxidant effects of lycopene acting as a scavenger for singlet oxygen, hydrogen peroxide and nitrogen dioxide that are associated with DNA damage and the development of cancer (Hadley et al., 2002; Bose and Agrawal, 2007). This theory is also used to explain the beneficial effects of lycopene on asthma and atherosclerosis (Neuman et al., 2000; Rissanen et al., 2002; Frederiksen et al., 2007).

Technetium-99m ($^{99m}$Tc) has been the most utilized radionuclide in clinical nuclear medicine procedures (single photon emission computed tomography - SPECT) (Early and Sodee 1995; Harbert et al., 1996). It has been also used in various studies in basic scientific research, as to label biological and chemical structures used as radiopharmaceuticals (Oliveira et al., 2002; Welling et al., 2002).

Labeled red blood cells (RBC) with $^{99m}$Tc has come into wide use in clinical nuclear medicine for several important applications, including imaging of cardiovascular system (Niemeyer et al., 1995), peripheral arterial blood flow (Harel et al., 2005), evaluation of gastrointestinal bleeding (Wong et al., 2004; Zaman et al., 2004; Olds et al., 2005), measurement of red cell volume (Hladik III et al., 1987), hepatic hemangiomas (Artiko et al., 2004, Verdu et al., 2005), renal carcinoma (Cortes et al., 2003) and splenic reticuloendothelial system (Jin et al., 2004; Slart et al., 2004).

The use of medicinal plants or natural products for treatment of various diseases has increased in the last decades (Everson and McQueen 2004; Barbosa-Filho et al., 2008), justifying the use of accepted experimental models to study some biological properties of various natural products (Reiniger et al., 1999; Fonseca et al., 2005; Freitas et al., 2007).

Natural or synthetic drugs, as well as labeling conditions, can have effect on the labeling of blood constituents (Lima et al., 2002; Frydman et al., 2004; Fonseca et al., 2005; Jesus et al., 2006; Fonseca et al., 2007). The aim of this study is to evaluate the interference of different concentrations of an aqueous tomato extract on the labeling of blood constituents with $^{99m}$Tc.

## MATERIAL AND METHODS

### Animals

Adult male *Wistar* rats (3-4 months, 250-350 g) were maintained in a controlled environment. The animals had free access to water and food and ambient temperature was kept at 25 ± 2 ºC. The experimental protocol was approved (CEA/115/2006) by the Ethical Committee of the Instituto de Biologia Roberto Alcantara Gomes, Universidade do Estado do Rio de Janeiro.

### Preparation of tomato extract

Tomato, as fruit, was purchased in a local supermarket. To prepare the extract, 4 g of tomatoes (without bark and seeds) were ground in 1 ml NaCl 0.9%. The crude extract was filtered and centrifuged (clinical centrifuge, 2000 rpm, 10 min) to obtain the final extract. This fraction of the extract was considered 4g/mL.

A spectrophotometric analysis (Analyser, 800M, São Paulo, Brazil) of the extract was carried out.

The absorbance at 455 nm was considered the marker of the quality control of this extract. All the prepared extracts to be used in the experiments must had the optical density of 0.05 ± 0.004 (Figure 1).

### *In vitro* radiolabeling of blood constituents

Heparinized blood (500 µL) was withdrawn by heart puncture from *Wistar* rats and incubated with 100 µL of different concentrations of a tomato extract (0.05, 0.50, 1.00, 2.00 and 4.00 g/mL) or with a saline solution (0.9% NaCl) alone, as control, for 1 hour (room temperature). Afterwards, 500 µL of stannous chloride (1.20 µg/mL) was added and the incubation continued for further 1 hour. After this period of time, 100 µL of $^{99m}$Tc (3.7 MBq) as sodium pertechnetate ($Na^{99m}TcO_4$), recently milked from a $^{99}$Mo/$^{99m}$Tc generator (Instituto de Pesquisas Energéticas e Nucleares, Comissão Nacional de Energia Nuclear, São Paulo, Brazil) were added and the incubation was continued for 10 minutes. These samples were centrifuged in a clinical centrifuge (1500 rpm, 5 min) and aliquots of 20 µL of plasma (P) and blood cells (BC) were isolated. Another aliquots of 20 µL of P and BC were separated and precipitated with 1.0 mL of trichloroacetic acid (5%) and centrifuged (1500 rpm, 5 min) to isolate soluble (SF) and insoluble fractions (IF). The radioactivity in P, BC, SF-P, IF-P, SF-BC and IF-BC was determined in a well counter (Packard, model C5002, Illinois, USA) and the percentage of radioactivity (%ATI) was calculated as described elsewhere (Bernardo-Filho et al., 1994).

### Statistical analysis

Data were reported as (means ± standart deviation) of %ATI and compared to the treated (n = 10 for each extract concentration) and control group (n = 10) by One way analysis of variance - ANOVA, followed by Bonferroni post test, with a $p < 0.05$ as significant level. InStat Graphpad software was used to perform statistical analysis (GraphPad InStat version 3.00 for Windows 95, GraphPad Software, San Diego California, USA).

## RESULTS

The Figure 1 shows the absorption spectrum of the tomato extract used in the experiments. The pattern of the absorption spectrum presents the highest measure of the optical density (0.055 ± 0.004) at 455 nm. This parameter has allowed us controlling the experimental conditions of preparation of the extracts and used as markers.

The Figure 2 shows the ATI% in blood cells (BC) and plasma (P) compartments from blood treated with different concentrations of tomato extract. The analysis of these data indicates that tomato extract has not altered the distribution of radioactivity in these two compartments (BC and P).

The Figure 3 shows the ATI% in insoluble (IF-P) and soluble (SF-P) fractions isolated from plasma separated from whole blood treated with different concentrations of tomato extract. The analysis of this data indicates that tomato extract has significantly ($p < 0.05$) reduced the radioactivity fixation in IF-P in the two highest concentration studied (2.00 and 4.00 g/mL).

The Figure 4 shows the ATI% in insoluble

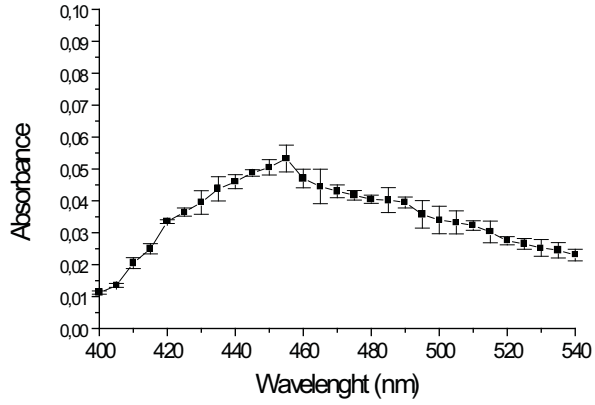


**Figure 1.** Absorbance spectrum of an aqueous tomato extract. To prepare the tomato extract, 4.0 g (without bark and seeds) were ground in 1 mL NaCl 0.9%. The crude extract was filtered, centrifuged (2000 rpm, 10 min) to obtain the final extract and stored at -18 ºC. This preparation of the extract was considered 4 g/mL.

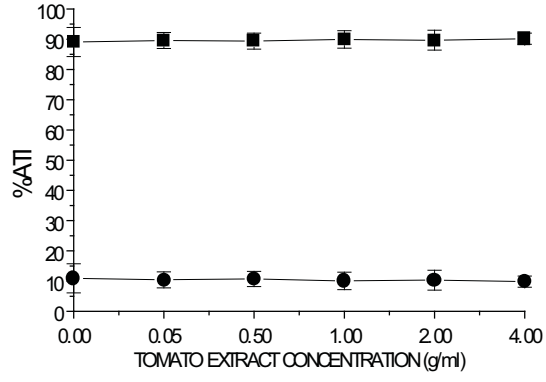


**Figure 2.** Effect of tomato extract on the distribution of the $^{99m}$Tc in the plasma and blood cells (BC) compartments in the radiolabeling procedure of blood elements. Heparinized blood samples of *Wistar* rats were incubated with different concentrations of tomato extract (1 h) and after with $SnCl_2$ (1.20 µg/mL, 1 h) and in sequence with $Na^{99m}TcO_4$ (3.7 MBq, 10 min). After centrifugation, plasma (P) and blood cells (BC) were isolated, the radioactivity was counted and the ATI% calculated. (■) P and (●) BC.

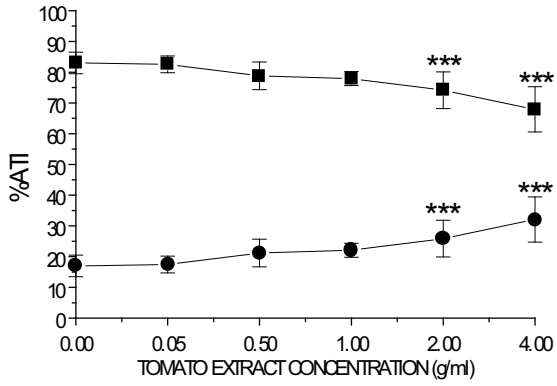


**Figure 3.** Effect of tomato extract on fixation of $^{99m}$Tc by insoluble (IF-P) and soluble (SF-P) fractions of plasma (P), in the radiolabeling procedure of blood elements. Heparinized blood samples of *Wistar* rats were incubated with different concentrations of tomato extract (1 h) and after with $SnCl_2$ (1.20 µg/mL, 1 h) and in sequence with $Na^{99m}TcO_4$ (3.7 MBq, 10 min). Insoluble and soluble fractions of plasma (IF-P and SF-P) were obtained by precipitation with trichloroacetic acid (5%) and centrifugation (1500 rpm, 5 min). The radioactivity in these fractions were counted and the ATI% was calculated. (●) SF-P and (■) IF-P. (***) $p \leq 0.001$, when compared to control group.

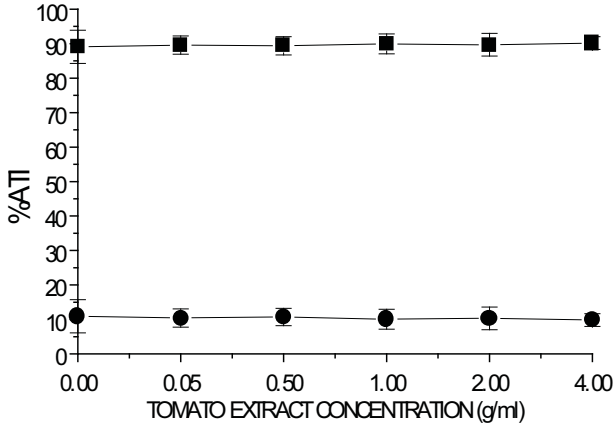


**Figure 4.** Effect of tomato extract on fixation of $^{99m}$Tc by insoluble (IF-BC) and soluble (SF-BC) fractions of blood cells (BC), in the radiolabeling procedure of blood elements. Heparinized blood samples of *Wistar* rats were incubated with different concentrations of tomato extract (1 h), after with $SnCl_2$ (1.20 µg/mL, 1h) and in sequence with $Na^{99m}TcO_4$ (3.7 MBq, 10 min). Insoluble and soluble fractions of blood cells (IF-BC and SF-BC) were obtained by precipitation with trichloroacetic acid (5%) and centrifugation (1500 rpm, 5 min). The radioactivities in these fractions were counted and the ATI% was calculated. (●) SF-BC and (■) IF-BC.

(IF-BC) and soluble (SF-BC) fractions isolated from blood cells separated from blood treated with different concentrations of tomato extract. The analysis of this data indicates that tomato extract has not significantly modified the radioactivity fixation in insoluble blood cells fraction.

## DISCUSSION

It has been described that food and also natural and synthetic drugs can alter the labeling procedure with a radionuclide causing an unexpected behavior of the labeling of the blood constituents with the radiopharmaceutical (Hesslewood and Leung 1994; Sampson, 1999; Gomes et al., 2002).

The changes in the pattern observed when binding the radionuclide $^{99m}$Tc have been possible through studies carried out with natural or synthetic products interaction (Fonseca et al*.,* 2005). It seems that natural products (terpenoids, isoflavonoids, abajeru) or synthetic drugs (acethylsalicic acid, zinc oxide, eugenol,) as well as food (tomatoes, clove), are capable of modifying the blood constituents labeled with radionuclides (Hesslewood and Leung 1994; Sampson, 1999; Gomes et al., 2002).

However, to understand the modification of the bioavailability of the radiobiocomplex is quite difficult since the analysis of the natural or synthetic drugs are not provided by consistent experimental models. A model using isolated blood cells and plasma has been effectively used in order to verify the mode of action of products used daily by humans. In this model, the radiolabeling of blood constituents from *Wistar* rats have been assayed (Oliveira et al., 2002; Fonseca et al., 2005; Abreu et al., 2007; Fonseca et al., 2007) and comparisons and extrapolations of the results to the human population may be done.

The data obtained in this work shown that the tomato extract has reduced the radioactivity fixation on plasma proteins (Figure 3). Yet, the tomato extract has not modified the distribution of radioactivity between plasma and blood cells compartments (Figure 2) neither the fixation of $^{99m}$Tc on the blood cells proteins (Figure 4). Stannous ion ($Sn^{+2}$) is used as reducing agent in the $^{99m}$Tc-labeling of blood constituents and compounds or conditions that interfere with its action can alter the fixation of $^{99m}$Tc on these constituents (Hladik III et al., 1987; Bernardo-Filho et al., 1994; Moreno et al, 2002; Fernandes et al., 2005; Aquino et al., 2007). The effect of tomato extract on labeling of plasma proteins could be related to its antioxidant property disturbing the action of $Sn^{+2}$ on $^{99m}$Tc and decreasing the radioactivity uptake by plasma proteins. In fact, data have demonstrated that tomato constituents (as lycopene and vitamin C) have antioxidant effects (Hadley et al., 2002; Rissanen et al., 2002; Everson and McQueen 2004; Bose and Agrawal, 2007) and this may explain the alterations of $^{99m}$Tc-labeling plasma proteins obtained in this work.

On the other hand, in the blood, carotenoids transported by lipoproteins and, more substantially, by low density lipoproteins (LDL), suggest that the increase

in LDL resistance to oxidation during consumption of tomato juice may be, at least, partly due to increased content of lycopene (Erdman et al., 1993; Upritchard et al., 2000). In addition, it has been also related a protective effect of beta-carotene and lycopene entrapped in human albumin against the oxidative attack of electronically excited molecular oxygen on 2'-deoxyguanosine (dGuo) (Yamaguchi et al., 1999). So, these interactions between plasma proteins and tomato constituents could decrease the number of the binding sites of $^{99m}$Tc with plasma proteins and this could be related with the decrease of the radiolabeling of these proteins.

## CONCLUSION

Our data have shown that the aqueous tomato extract, in a concentration that is found in human diet, has the ability to reduce the radiolabeling on plasma proteins. Probably this occurs due to chemical substances of the tomato extract that could have action on reducing agent (stannous ion) used in the labeling process and/or the ability to interact with plasma proteins, occupying its binding sites. Although these experiments were performed in rats, the results suggest that caution should be taken with the interpretation of the data obtained from nuclear medical diagnosis and tests when patients consume tomato extracts or its derivatives in food.

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