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Medicinal Plants and Radionuclides: A Review

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ABSTRACT

Medicinal plants and/or phytopharmaceuticals include flavonoids, terpens, saponins, tannins, alkaloids, glycosides, resins, volatile oils, and others compounds that provide various effects on human body: positive or not. Biocomplex of natural plants are common used in Nuclear Medicine and their effects on radionuclides are insufficient knowledge. The natural products and synthetic drugs can make effects on exams of S*ingle Positron Emission Tomography – SPECT* shows false prognostic. Synthetic drugs as anaesthetic sodium Phenobarbital, an Amantadine, Vincristine, Mitomycin-C, an Acetaminophen, Acetylsalicylic acid and Dipyrone (antipyretic and analgesics drugs), an antiseizure drugs, a Glucantime, Zinc-oxid-e*ugene, Phytic acid*, others, and natural products as an extract of *Cauliflower*, *Buzhong yi qi wan* complex, *Propolis, Uncaria tomentosa, Mentha crispa, Psidium guajava, Maytenus ilicifolia, Matricaria recutita, Thuya occidentalis, Paullinia cupana, Harpagophytum procumbens, Solanum melongena, Cinnamomum zeylanicum, Cymbopogoncitratus, Maytenus ilicifolia, Baccharis genistelloides, tobacco, and foods as a tomato, Punica granatum, Sechium edule, clove,* and others, shows effects on the radionuclides and their reductors stannous chloride. Here, we discuss the effects of these plants/phyto-pharmaceuticals/synthetic drugs and their compounds on the labeling of red blood cells by sodium pertecnetate, their mechanism of action, and applications of the Nuclear Medicine.

KEY WORDS: Nuclear Medicine, Phytopharmaceuticals, Radionuclides, Sodium pertecnetate, Medicinal plants.

INTRODUCTION

Plants and drugs by plants extract are an important part of our everyday diet, and their constituents and their nutritional value have been intensively studied for decades (1). The influence of drugs on the labeling of red blood cells and plasma proteins with technetium-99m (99mTc) has been reported. Any drug, which alters the labeling of the tracer, could be expected to modify the disposition of the radiopharmaceuticals(2).

In the present study we evaluated the plants extracts effects on radiopharmaceuticals, as sodium pertechnetate (Na99mTcO4), methylenediphosphonic acid (99mTc-MDP), glucoheptonate acid (99mTc-GHA) and others used in Nuclear Medicine – a review of the articles studied these effects.

In the principle database in world, Pubmed database, we find exactly 79 articles about drugs, natural or synthetic, and stannous chloride/technetium-99m used in nuclear medicine procedures. These articles, analyzed by focus in natural drugs and synthetic drugs showed the data below (table 1). Other focus unconsidered.

The authors of these articles, refers the importance of the compounds of various drugs and foods. The flavonoids, terpens, saponins, tannins, alkaloids, glycosides, resins, volatile oils, and others compounds that provide various effects on human body: positive or not.

However, the drugs synthetic have been studied for decades, but the natural products, as plants or as food, don't have a assortment of studies. It is necessary more investigation about the effects of the natural plants on daily life.

The Nuclear Medicine growth up on last time ago and these knowledge, about the possible effects on the labeling of the radionuclides it's very necessary. So, the plants related by authors showed some effects inhibitors the labeling. The principal focus had been the 99mTc radionuclide as Na99mTcO4, or 99mTc-MDP, or 99mTc-GHA and it's reduced agent stannous chloride ($SnCl_2$).

The natural products and synthetic drugs can make effects on exams of S*ingle Positron Emission Tomography – SPECT* shows false prognostic.

Synthetic drugs as anaesthetic sodium Phenobarbital (PBBT) (3), an Amantadine (A) (4), Vincristine (V) (5), an Acetaminophen (Ac), Acetylsalicylic acid (AAS) and Dipyrone (D) (antipyretic and analgesics drugs) (6, 7), an antiseizure drugs (8), a Glucantime (G) (9), Zinc-oxid-e*ugene* (OZE) (10), *Phytic acid* (PA) (11), others, and natural products as an extract of *Cauliflower* (Cf) (12), *Buzhong yi qi wan* (BYQW) complex (13), *Propolis* (P) (14), *Uncaria tomentosa* (UT) (15), *Hypericum perforatum* (16), *Psidium guajava* (PG) (17), *Thuya occidentalis* (TO), *Peumus boldus* (PB) and *tobacco* (Tc) (18), *Harpagophytum procumbens* (19), *Paullinia cupana* (PC) (20), *Gingko biloba* (21), *Cymbopogon citratus* (C), *Maytenus ilicifolia* (MI) and *Baccharis genistelloides* (BG) (22), *and foods as a tomato* (To) (23), *Punica granatum* (PG) (24), *Sechium edule* (SE) (25), *clove* (CL) (26), and others, shows effects on the radionuclides and their reducers stannous chloride.

In order to know the mode of action of PBBT in moving adult *Schistosoma mansoni* worms from mesenteric veins to the liver, the authors labelled PBBT with 99mTc and a biodistribution studied in infected and non-infected Swiss mice was performed. The radioactivity was mainly taken up by the blood, kidney, liver and spleen. No radioactivity was found on

Qt.	Herbs	Synthetic drugs	Biocomplex of plants	Effect on Pertecnetate	Effect on stannous chloride	Effect on *E.coli*	Title	Date Year
2	*Uncaria tomentosa*			Yes	yes		Effect of oral ingestion of an extract of the herb Uncaria tomentosa on the biodistribution of sodium pertechnetate in rats.	2007
1		Acetylsalicylic acid		Yes	yes		Effect of oral ingestion of an extract of the herb Uncaria tomentosa on the biodistribution of sodium pertechnetate in rats. Acetylsalicylic acid decreases the labeling of blood constituents with technetium-99M.	2007
1	*Harpagophytum procumbens*				yes	yes	Protective effect of an aqueous extract of Harpagophytum procumbens upon Escherichia coli strains submitted to the lethal action of stannous chloride.	2007
2	*Paullinia cupana*			Yes	yes		Effect of a commercial extract of Paullinia cupana (guarana) on the binding of 99mTc-DMSA on blood constituents: An in vivo study. Effect of extract of medicinal plants on the labeling of blood elements with Technetium-99m and on the morphology of red blood cells: a study with Paullinia cupana.	2007 2002
1	*Gingko biloba*			Yes	yes		Experimental model to assess possible medicinal herb interaction with a radiobiocomplex: qualitative and quantitative analysis of kidney, liver and duodenum isolated from treated rats.	2007
1	Propolis			Yes	yes		A propolis extract and the labeling of blood constituents with technetium-99m.	2006
1	*Psidium guajava*			Yes	yes		Guava extract (Psidium guajava) alters the labelling of blood constituents with technetium-99m.	2006
1		Antipyretic drugs		Yes	yes		Influence of antipyretic drugs on the labeling of blood elements with technetium-99m.	2005
2		Glucantime		Yes	yes		The effect of Glucantime on the labeling of blood constituents with technetium-99m. Effects of the glucantime on the kinetic of biodistribution of radiopharmaceuticals in Wistar rats.	2005 2002
1	*Hypericum perforatum*			Yes	yes		Effect of Hypericum perforatum extract on in vitro labelling of blood elements with technetium-99m and on biodisponibility of sodium pertechnetate in Wistar	2005

						rats.	
1	*Punica granatum*		Yes	yes		Assessment of the effect of Punica granatum (pomegranata) on the bioavailability of the radiopharmaceutical sodium pertechnetate (99mTc) in Wistar rats.	2003
1		Phytic acid	Yes	yes	yes	Evaluation of the phytic acid effect on the labeling of blood elements with technetium-99m and on the survival of a strain of Escherichia coli treated with stannous fluoride.	2003
1		Antiseizure drugs				Assessment of the effect of antiseizure drugs on the labeling process of red blood cells and plasma proteins with technetium-99m.	2002
1	*Solanum melongena*					Effect of eggplant (Solanum melongena) extract on the in vitro labeling of blood elements with technetium-99m and on the biodistribution of sodium pertechnetate in rats.	2002
1		Amantadine	Yes	yes		Study of the biodistribution of the amantadine labelled with technetium-99m in Wistar female rats.	2002
						Evaluation of the effect of mitomycin-C on the bioavailability of technetium-99m-labelled sodium pyrophosphate in mice.	2002
3		Mitomycin-C	Yes	yes		Effect of mitomycin-C on the bioavailability of the radiopharmaceutical (99m)technetium-phytic acid in mice: a model to evaluate the toxicological effect of a chemical drug.	2002
						The effect of mitomycin-C on the biodistribution of 99Tcm-MDP in Balb/c mice.	1998
1	*Sechium edule*		Yes	yes	yes	Effect of a chayotte (Sechium edule) extract on the labeling of red blood cells and plasma proteins with technetium-99m: in vitro and in vivo studies.	2002
1	*Cauliflower*		Yes	yes	yes	Effect of an extract of cauliflower (leaf) on the labeling of blood elements with technetium-99m and on the survival of Escherichia coli AB1157 submitted to the treatment with stannous chloride.	2002
1	*Cymbopogon citratus, Maytenus ilicifolia and Baccharis genistelloides*			yes	yes	Effect of the Cymbopogon citratus, Maytenus ilicifolia and Baccharis genistelloides extracts against the stannous chloride oxidative damage in Escherichia coli.	2001

2		Vincristine	Yes	yes	The effect of vincristine on the biodistribution of technetium-99m DTPA, GHA, and DMSA in Balb/c female mice.	2000
					A model to evaluate the biological effect of natural products: vincristine action on the biodistribution of radiopharmaceuticals in BALB/c female mice.	1999
1	*Maytenus ilicifolia*		Yes	yes	Assessment of the effect of Maytenus ilicifolia (espinheira santa) extract on the labeling of red blood cells and plasma proteins with technetium-99m.	2000
1	*Thuya occidentalis, Peumus boldus and Nicotiana tabacum*		Yes	yes	The effect of drugs on the labeling of blood elements with technetium-99m.	2000
1		Boldine		yes	Boldine action against the stannous chloride effect.	1999
1	*Peumus boldo*		Yes	yes	Effect of Peumus boldus on the labeling of red blood cells and plasma proteins with technetium-99m.	1999
1		chemotherapeutic drug	Yes	yes	Effect of a chemotherapeutic drug on the biodistribution of 99mTc-DTPA in Balb/c mice.	1998
1		radioautographic	Yes	yes	In vitro radioautographic studies of the biodistribution of radiopharmaceuticals on blood elements.	1998
1	*Nicotiana tabacum*		Yes	yes	Influence of tobacco on the labelling of red blood cells and plasma proteins with technetium-99m.	1998
1		anaesthetic sodium phenobarbital	yes	yes	Biodistribution study of the anaesthetic sodium phenobarbital labelled with technetium-99m in Swiss mice infected with Schistosoma mansoni Sambon, 1907.	1997
1		trichloroacetic acid	yes	yes	Evaluation of 99mtechnetium-radiopharmaceutical binding to blood elements using different trichloroacetic acid concentrations.	1996
1	*Thuya occidentalis*		yes	yes	Effect of Thuya occidentalis on the labeling of red blood cells and plasma proteins with technetium-99m.	1996

Pubmed - www.ncbi.nlm.nih.gov; period: 1996 - 2007; access in sep/2007. Articles: 79 in september/2007; 36 articles about 99mTc, SnCl2 and E.coli; others=43

the adult worms. They concluded that the worm shift was due to an action on the host of the PBBT (3).

Amantadine (AMA) has been described as dopamine stimulant and norepineprhine release, capable to block the N-methyl-D aspartate (NMDA) glutamatergic and nicotinic receptors, enhancing the sexual behavior of the male rats and inducing hypersexuality in humans. The aim of this study was to label and evaluate the bioavailability of the AMA labelled with 99mTc (99mTc-AMA) in Wistar female rats. They concluded that 99mTc-AMA may be used to study the bioavailability of amantadine and evaluate its effect in sexual behavior in female rats (4).

Vincristine has been widely used in various chemotherapeutic protocols in oncology. The purpose of this study was to evaluate the effect of vincristine on the biodistribution of 99mTc-DMSA, 99mTc-GHA, and 99mTc-DTPA in Balb/c female mice. The results could be explained by the metabolization, toxic effect, therapeutic, or immunosupressive action of the studied chemotherapeutic drug (5).

Acetaminophen (AAP), acetylsalicylic acid (ASA) and dipyrone (DIP) are antipyretic and analgesics drugs that have wide use in health sciences (6). Acetylsalicylic acid is the most widely used drug as antipyretic, analgesic, anti-inflammatory agent and for secondary prevention of thrombotic phenomena in the heart, brain and peripheral circulation. Although the experiments were carried out with rats, it is possible to suggest that AAP, ASA or DIP should not interfere with the procedures in nuclear medicine involving the labeling of blood elements with 99mTc (7).

It is estimated that about 2.5 million people only in the United States are affected by epilepsy. Labelled red blood cells (RBC) and plasma proteins (PP) are used for several evaluations in nuclear medicine and drugs affecting those labelings have previously been described. The aim of this study was to evaluate whether the most popular antiseizure drugs interfere with the 99mTc labeling process of RBC and PP. They can suggest that with this in vitro assay, at the therapeutic level of phenytoin, phenobarbital, carbamazepine and valproic acid will not interfere on the 99mTc labeling process of RBC. Interference is displayed at higher phenobarbital concentrations (2,000 microg/ml). However, humans do not tolerate this concentration. On the other hand, a decreased RBC and PP labeling efficiency with 99mTc may be expected for clonazepam at therapeutic levels(8).

In this paper, the influence of glucantime on the labeling of blood constituents with 9mTc was reported. Was probably due to products present in this drug that may complex with ions (Sn(+2) and 99mTcO4) or have a direct or indirect effect on intracellular stannous ion concentration (9).

In dentistry, the combination of the zinc oxide and *eugenol* substances produce cement (OZE) with anesthesia, analgesic, anti-inflammatory, sedative and tissue cicatrisation. The authors showed qualitative alterations on the shape of the RBC were founded and confirmed by perimeter/area ratio. In conclusion, the analysis of the results indicates that the studied solution have substances that could oxidize the stannous ion, reducing the distribution of the radioactivity on the RBC and the fixation of the 99mTc on the plasma and cell proteins. Moreover, it could also explain by alterations on the cell membrane, as showed in the morphometric parameters alterations, reducing the ions transport (10).

Phytic acid occurs in foods derived from plants. The authors have investigated the possibility that phytic acid and stannous fluoride are capable of altering the physiological properties (osmotic fragility) and morphological properties of red blood cells (RBC). Osmotic fragility was unchanged by the presence of phytic acid and stannous fluoride in the studied concentrations, but RBC morphology was modified in the presence of the studied substances. In conclusion, the alterations to RBC morphology were not sufficient to promote modifications in osmotic fragility. The results suggest that the chelating properties of phytic acid could be responsible for the observed effects (11).

Cauliflower (*Brassica oleracea L. var. botrytis*) is used in folk medicine and authors evaluated its influence on (i) the labeling of blood elements with 99mTc, and (ii) on the survival of an *E. coli* strain. They suggest that the substances present in the extract of cauliflower probably, would have redox property with different mechanisms of action. The oxidant action of the substances of the extract would not be strong enough to oxidize the stannous ions altering the 99mTc-labeling. However, the referred substances could oxidise these ions sufficiently to protect the *E. coli* culture against the lethal effect of the stannous ion (12).

Buzhong Yi Qi Wan (*Buzhong*) is a medicinal herbs widely used in Traditional Chinese Medicine to treat systems digest and circulation. *Buzhong* extract at the highest concentrations used (6.4 and 12.8mg/ml) in labeling of blood with 99mTc, altered significantly ($p<0.05$) the %ATI in blood constituents. Substances present in the *Buzhong* extract could alter the cell membrane and plasma and/or generation of free radicals that have oxidant properties (13).

Since ancient times propolis has been employed for many human purposes because to their favorable properties. The authors in results suggest that at high concentration the constituents of this extract could alter the labeling of plasma proteins competing with same binding sites of the 99mTc on the plasma proteins or acting as antioxidant compounds (14).

The aim of the present study was to determine the effect of the oral ingestion of an extract of the herb *Uncaria tomentosa* (cat's claw) on the biodistribution of the radiobiocomplex sodium pertechnetate (Na99mTcO4) in rats. Although these results were obtained with animals, caution is advisable in the interpretation of the nuclear medicine examination when the patient is using this herb. This finding is probably an example of drug interaction with a radiopharmaceutical, a fact that could lead to misdiagnosis of the examination in clinical practice with unexpected consequences for the patient (15).

Authors showed the effect of a hiperico extract (*Hypericum perforatum*) on the labeling of blood elements with technetium-99m (99mTc) and in the bioavailability of the radiopharmaceutical sodium pertechnetate in Wistar rats. The analysis of the results indicates that in studied extract should have substances that should oxidize the stannous ion,

reducing the fixation of the 99mTc on the erythrocytes and plasma and cellular proteins. Moreover, it could produce metabolic alterations with influence in the uptake of the radiopharmaceutical 99mTcO4Na in bone, muscle, pancreas and thyroid (16).

Psidium guajava (guava) leaf is a phytotherapic used in folk medicine to treat gastrointestinal and respiratory disturbances and is used as anti-inflammatory medicine. The data showed significant (P<0.05) alteration of ATI in BC from blood incubated with guava extract (17).

The authors have evaluated the effect of *Thuya occidentalis* (TO), *Peumus boldus* (PB) *and Nicotiana tabacum (tobacco)* (To) extracts on the labeling of RBC and plasma and cellular proteins with 99mTc. The analysis of the results shows that there is a decrease in %ATI (from 97.64 to 75.89 percent) in BC with *Thuya occidentalis* extract. The labeling of RBC and plasma proteins can be decreased in presence of tobacco. This can be due either a direct or indirect effect (reactive oxygen species) of *tobacco*. The analysis of radioactivity in samples of P and BC isolated from samples of whole blood treated with *Peumus boldus* showed a rapid uptake of the radioactivity by blood cells in the presence of the PB, whereas there was a slight decrease in the amount of 99mTc radioactivity in the TCA-insoluble fraction of plasma. This study shows that extracts of some medicinal plants can affect the radiolabeling of red blood cells with 99mTc using an in vitro technique (18).

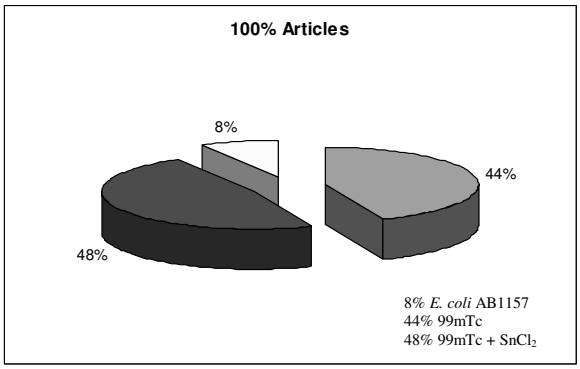
Harpagophytum procumbens, also known as Devil's Claw, is a plant used in folk medicine, as an analgesic and anti-inflammatory in cases of joint and back pain, on the treatment of degenerative rheumatoid arthritis, osteoarthritis, kidney inflammation and heart diseases. The authors showed that substances in the extract could be acting as: (i) chelator of the stannous ions, avoiding the generation of free radicals (FR), (ii) FR scavenger, protecting the cells against the oxidation, and/or (iii) an oxidant compound acting upon the stannous ions, reducing the SnCl2 cytotoxicity (19).

The authors studied the influence of a commercial extract of *Paullinia cupana* (guarana) on the binding of technetium-99m-dimercaptosuccinic acid ((99m)Tc-DMSA) on blood constituents. Plasma (P) and blood cells (BC) from Wistar rats (control and treated) were separated. P and BC were precipitated with trichloroacetic acid (TCA) or ammonium sulphate (AS) and soluble (SF) and insoluble fractions (IF) isolated. The percentage of incorporated radioactivity (%ATI) in each fraction was determined. The treatment influenced the %ATI in IF-P and in IF-BC isolated by TCA precipitation (20).

The authors demonstrated that *Ginkgo biloba* extract (EGb) has been used as a medicinal herb. Several biological properties have been associated with this extract, especially, in the increase of the blood flow, in the action as platelet activating factor antagonism and in the prevention of the membrane against the damage caused by free radicals. The results showed that EGb decreased the uptake of the 99mTcO4Na in the duodenum (P<0.05). Moreover, morphometric analysis has revealed significant modifications (P<0.05) on kidney, liver and duodenum due to the cited treatment. It is speculated that the substances present in the EGb could act directly or generate metabolites capable to promote changes in organs (kidney, liver and duodenum), however, only significant alteration in the uptake of the 99mTcO4Na in the duodenum (21).

Cymbopogon citratus, Maytenus ilicifolia and Baccharis genistelloides extracts have been used in popular medicine. The authors results showed a reduction of the SnCl(2) effect on the survival of the cultures in presence of the crude extracts. The extract of M. ilicifolia showed the highest level of protection action against the SnCl(2) effect in comparison with the other extracts. This protector effect could due to the redox properties of these crude extracts. The compounds in the crude extracts could (i) chelate stannous ions, protecting them against the oxidation and avoiding the generation of reactive oxygen species (ROS), (ii) be a scavenger of the ROS generated by the SnCl(2) oxidation and/or (iii) have oxidant compounds that could oxidise the stannous ions, abolishing or reducing the SnCl(2) effect (22).

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. These experimental data suggest that the chemical compounds present in the aqueous tomato extract could have some properties capable to influence in the fixation of ^{99m}Tc on plasma proteins (23).

Punica granatum (pomegranata) is used as food or as medication in folk medicine for antiviral, anthelmintic, antifungal, antibacterial and antimicrobial activity. The authors have studied in rats, the effect of the medicinal plant *Punica granatum* on the bioavailability of the radiopharmaceutical technetium-99m-sodium pertechnetate (Na(99m)TcO4) (24).

Sechium edule (chayotte) is used as food or as medication in popular medicine. The labeling of blood elements with technetium-99m (99mTc) has been altered by drugs (synthetic and natural). Some authors have reported biological effects concerning the chayotte. In vitro study no alterations on the labeling of blood elements were found, however, we have found alterations on the fixation of 99mTc in the in vivo study, probably, due to the metabolization of chayotte capable to induce the generation of active metabolites. These results finded can be justified by therapeutic effect of this extract and/or by generation of active metabolites capable to

interfere with the biodistribution of the studied radiopharmaceutical (25).

Clove (*Caryophyllus aromaticas L.*) has been used for clinical procedures. The aim of this work was to evaluate the effects of clove extract on the labeling blood constituents with 99mTc and on the morphologic red blood cells. The results indicate that clove extract present chemical compounds that interfere with the radiolabeling of blood constituents and alter the morphology of red blood cells by oxidative/chelating actions or interacting with the cellular membrane structure (26).

CONCLUSION

Based in the data collection on Pubmed database, we conclude have few articles on relation all medicinal articles with this focus about Nuclear Medicine. These articles are insufficient studies about medicinal plants and interactions with 99mTc and stannous chloride. The Nuclear Medicine exams can be mistaken in their diagnosis. So, we discuss the deficiency on more articles and experiences with plants and synthetic drugs, on nuclear medicine kit, their mechanism of action, and applications for the humans.

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