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ISSN: 2348-1900
Plant Science Today
http://www.plantsciencetoday.online

OPEN ACCESS

Review Article

Effects of medicinal plants on radiolabeling and biodistribution of diagnostic radiopharmaceuticals: A systematic review

Pegah Khosravian[1], Saeid Heidari-Soureshjani[2*], Qian Yang[3]

[1] Medical Plants Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran
[2] Cellular and Molecular Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran
[3] Institute of Pharmacy and Molecular Biotechnology, University of Heidelberg, Heidelberg, Germany

Article history

Received: 25 February 2019
Accepted: 27 March 2019
Published: 01 April 2019

Editor

Dr. K. K. Sabu
Jawaharlal Nehru Tropical Botanic Garden and Research Institute
Thiruvananthapuram, India

Publisher

Horizon e-Publishing Group

****Correspondence***

Saeid Heidari-Soureshjani
heidari_1983@yahoo.com

Abstract

Radiopharmaceuticals are drugs that contain radioisotopes used for diagnostic and therapeutic purposes. There are evidences that medicinal herbs and their constituents can modify the radiolabeling, biodistribution, and pharmacokinetics of radiopharmaceuticals through drug interaction. To have an overview of the effects and the underlying mechanisms of medicinal plants on the radiolabeling and bioavailability of radiopharmaceuticals, we conducted this study to summarize the current findings in this field. The scientific literature was systematically collected from databases and analyzed. Studies showed that medicinal plants and their constituents can alter radiolabeling and biodistribution via several mechanisms. Interactions with proteins in red blood cells at the same sites, chelating action of stannous and pertechnetate ions, antioxidant action impeding or decreasing stannous ion oxidation, direct oxidation of stannous ions, generation of reactive oxygen species (ROS) which oxidize stannous ions and damage induced in the cell membrane. Most the medicinal plants can decrease the radioactivity of radiopharmaceuticals, but some of them like *Peumus boldus, Punica granatum, Nectandra membranacea, Mentha crispa, Rosmarinus officinalis* and derivatives such as eugenol and epigallocatechin gallate have increasing effects. In addition, altering feature in some of them is tissue dependent.

Keywords: Medicinal plants; Radiolabeling; Biodistribution; Radiopharmaceuticals

Citation: Khosravian P, Heidari-Soureshjani S, Yang Q. Effects of medicinal plants on radiolabeling and biodistribution of diagnostic radiopharmaceuticals: A systematic review. Plant Science Today 2019;6(2):123-131. https://doi.org/10.14719/pst.2019.6.2.513

Indexing: Plant Science Today is covered by Scopus, CAS, AGRIS, CABI, Google Scholar, etc. Full list at http://www.plantsciencetoday.online

Introduction

In the traditional medicine, many approaches such as aromatherapy, hypnotherapy, yoga, massage therapy, use of medicinal plants, etc. have been used for diagnosing and treatment of patients (1-7). These approaches are more safe than the methods that have been used in modern medicine. Medicinal plants are one of most commonly used approaches for treatment of diseases that their effects have been indicated in the various studies (8-14). Although medicinal plants can be effective, inexpensive, and efficient treatments for various disorders and frequently used by human beings (15-22), sometimes the biological effects of these natural medicines are not fully known. For example, several studies showed that the biodistribution, radiolabeling or the pharmacokinetics of radiopharmaceuticals can be modified by some medicinal plants (23-27). If drug interactions on biodistribution and labeling are not addressed, poor image quality and misvisualization in nuclear medicine tests could lead to misdiagnosis with a possible need to repeat the test, therefore so increasing the radiation complication to the patient and the staff. Consequently this problem cause mistreatment in the patients (28).

Radiopharmaceuticals are applied for drugs labeled with radioactive tracers for therapeutic or diagnostic purposes in medicine. Radioactive labels are radioactive compounds in which one or more atoms have been replaced by a radionuclide so by virtue of its radioactive decay and they used for direct cell labeling. Radioisotopes such as carbon, phosphorus, hydrogen, sulfur, and iodine have been applied widespread to trace the path of biochemical reactions (29). Radioactive tracers are used for diagnostic procedures and can be used in a number of tests. For example, technetium-99m (99mTc), in autoradiography and nuclear medicine, including positron emission tomography (PET), single photon emission computed tomography (SPECT) and scintigraphy (30). In addition, radioactive tracers are used to track the distribution of substances within a cell or tissue (31,32). Radiopharmaceuticals have a wide range application in diagnostic nuclear medicine procedures such as lung perfusion and ventilation, brain blood flow, thyroid scan and thyroid uptake, bone, liver, brain scan, hepatobiliary, pancreas, and kidney scans, bone marrow, cardiac imaging procedures, localization of gastrointestinal bleeding, tumor localization studies, and non-imaging studies of blood volume and iron metabolism (33). The radiolabeling of blood constituents is widely used and has great importance in nuclear medicine for both diagnostic imaging and targeted radionuclide therapy (34). Several studies have suggested that radiolabeling of blood constituents with radiopharmaceuticals could be performed to evaluate the biological effects of medicinal plant extracts (23,35,36). Besides, some the synthetic drugs and medicinal herbs can alter the biodistribution of radiopharmaceutical and the analysis of scintigraphic images and physicians must be cautious about this problem (24,37). Hence, this study was conducted to review the effects and mechanisms of medicinal plants, their derivatives and compounds on radiolabeling and bioavailability of diagnostic radiopharmaceuticals.

Search strategies

The words radiopharmaceutical, alongside with, radiolabeling, biodistribution and bioavailability in combination with some herbal terms such as *medicinal plant*, *phyto** and *herb** were used to search for relevant publications indexed in the Institute for Scientific Information (ISI) and PubMed.

A standard form was designed, which included items such as the aim or the title of the study, intervention, outcome, variables, journal name, period, and number. The article's contents that were relevant to this study were recorded on the form and entered into the study upon agreement of the researchers involved in this study. Then the plants and the plant-based products that were reported to be effective in labeling and distribution of diagnostic radiopharmaceuticals were selected. The articles whose full texts were not accessible, studies with neutral effects, non-English language articles, review articles, and studies that were not related to the purpose of this study were excluded after all researchers in this study agreement was achieved. Fig. 1 illustrates how the articles were selected for final analysis.

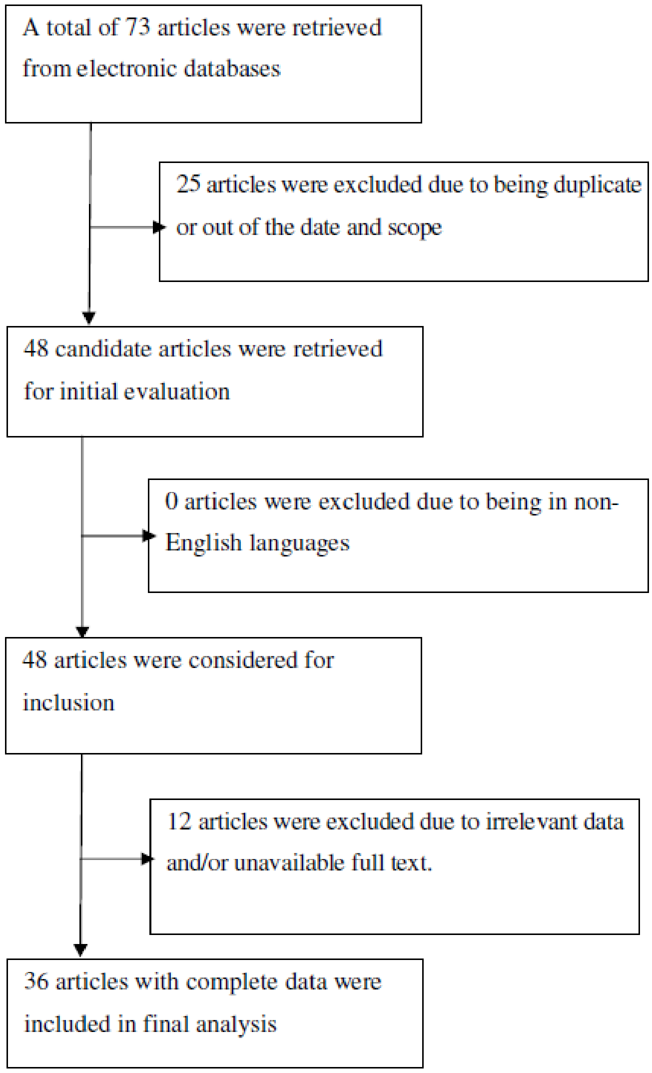

Fig. 1. Flowchart of the process of selecting the articles for final analysis

Results

The previous studies indicated that that medicinal plants and their derivates can alter radiolabeling and biodistribution. Most the medicinal plants could decrease the radioactivity of radiopharmaceuticals, but some of plants such as *Peumus boldus, Punica granatum, Nectandra membranacea, Mentha crispa, Rosmarinus officinalis* have increasing effects (Table 1).

In addition, there are some phytochemicals and herbal combinations that affect radiolabeling and biodistribution of radiopharmaceuticals (Table 2).

Several factors that categorized in physical and chemical factors may affect drug delivery and the radiolabeling of a chemical compound (65-68). For instance, pharmaceutical variables, such as sedimentation problems or instability of the cell chelator, choice of anti-coagulant, level of stannous ion and oxidation of radiopharmaceuticals, difficulties with collecting sufficient cells, or problems may arise which are patient-related (drug interference or the presence of disease) can affect the radiolabeling and misdistribution of radiopharmaceuticals (69). Medicinal herbs and constituents can reduce the labeling and distribution of diagnostic radiopharmaceuticals in several ways (Fig. 2). Interactions with the blood constituents protein at same sites of radiopharmaceuticals binding and disrupted the radiolabeling efficiency. The other way is direct inhibition (chelating action) of the stannous and pertechnetate ions (23). Because chelator activity has an important pharmacokinetic role in the development of labeling and bioavailability of radiopharmaceuticals targeting (70). Both the antioxidant and oxidant agents (or generation them in chemical interaction) in medicinal plants, in turn, can reduce the cell's labeling. Direct oxidation with the presence of oxidant agents or generation of free radicals that could oxidize the stannous ion (62). In addition, medicinal plants have polyphenols that are micronutrients with antioxidant activity. On the other hand, RBC labeling procedure with radiopharmaceuticals such as ^{99}mTc depends on the presence of stannous (+2) ions (40). Antioxidant property of medicinal plants can block the action of stannous ions, antioxidant action impeding or decreasing the stannous ion oxidization and binding to them in labeling and fixation procedure; so decreasing the binding of radiopharmaceuticals in plasma proteins (23,71). The last way is an alteration of the plasma membrane structure and receptors or changing in the transport systems of stannous and pertechnetate ions into cells. So, they alter the transport of ions (stannous and pertechnetate ions) through the cellular membrane (23,58). Pertechnetate anions across membranes of human blood constituents have a vital role in radiolabeling. The pertechnetate anion may reach the interior of the blood cells constituents (stannous and pertechnetate ions pass through the membrane) via the band-3 anion transport system (72). In other words, medicinal plants and their derivatives act in the transport of the pertechnetate ion via the cellular membrane of determined organs (73). The herbs chemical compounds can alter the blood cells membrane morphology (59), and it is one of the altering mechanisms of radiopharmaceutical labeling on the cells. Another result of this study suggests that the medicinal herbs and their components can act on the biodistribution of radiopharmaceuticals in specific organs (28).

In this regards, radiolabeling and biodistribution also depend on the type of tissue (64). This can be due to differences in receptors in various body tissues. Although, some of the medicinal herbs didn't has an effect on radiolabeling of radiopharmaceuticals. Because labeling depends on the presence of reducing agent or chemical substances, so without such interfering substances, they can't interaction with the radiolabeling process (59,74).

Therefore, precaution must be considered in the interpretation of diagnostic radiopharmaceuticals results when patients are concomitant using these drugs and must be cautious about misdiagnosis and/or repetition of the examinations in nuclear medicine.

Although these results mainly were obtained with animal studies, caution must be considered in the interaction of the nuclear examination when the patient is using these medicinal herbs. So limitation in human studies was a weakness of the reviewed articles which can disturb generalizability of the study's results to the human population.

Conclusion

Studies showed that medicinal plants and constituents can alter radiolabeling and biodistribution via several mechanisms. They can interactions with the blood cells compartment proteins at same sites, chelating action on the stannous and pertechnetate ions, antioxidant action impeding or decreasing the stannous ion oxidization, direct oxidation of the stannous ions, generation of reactive oxygen species in the body that could oxidize the stannous ions and damage induced in the cell membrane. Limitation in human studies was a weakness of the reviewed articles which can disturb generalizability of the study's results to the human population. Most of them have decreasing in the radioactivity of radio pharmaceuticals, but some of them have increasing effects. In addition, altering feature in some of them is tissue dependent.

Table 1: Effects of medicinal plants on radiolabeling and biodistribution of radiopharmaceuticals

References	Plants	Study Design	Type of administration	Main outcomes or mechanisms
Oliveira et al. (25)	*Thuya occidentalis*	Experimental (*in vitro*)	Extract	Decrease in the percentage of ATI via inhibition of the transport of the ions, competition with the cited ions for the same binding sites, creating damage in blood cells (BC) membrane and possible generation of reactive oxygen species that could oxidize the stannous ion.
Reiniger et al. (38)	*Peumus boldus*	Experimental (*in vitro*)	Solution	Increasing labeling of red blood cells and increase radioactivity bound to the red blood cell (RBC).
Braga et al. (39)	*Thuya occidentalis*, *Peumus boldus* and *Nicotiana tabacum* (tobacco)	Experimental (*in vitro*)	Extract	Decrease in the percentage of ATI, *Nicotianatabacum* decreasing labeling of RBC and plasma proteins and *Peumusboldus* increase uptake of the radioactivity by blood cells but a slight decrease in the amount of ^{99}mTc radioactivity.
de Oliveira et al. (40)	*Maytenus ilicifolia*	Experimental (*in vitro*)	Extract	Decrease in the percentage of ATI on blood elements. This changes due to the presence of oxidant agents in the *Maytenus ilicifolia* extract.
de Oliveira et al. (41)	*Paullinia cupana*	Experimental (*in vitro*)	Solution	Decreasing in the uptake of radioactivity by the RBC in insoluble fractions plasma (IF-P) and in insoluble fractions blood cell (IF-BC) and also alterations in the shape of RBC was observed.
Feliciano et al. (42)	*Sechium edule*	Experimental (*in vivo* and *in vitro*)	Extract	Decrease of the radioactivity in BC, IF-BC and IF-P and slight decrease in the uptake of ^{99}mTc by BC and a strong decrease in the fixation in IF-P with the macerated *in vivo*. But *in vitro* study, no alterations on the labeling of blood elements were reported.
Vidal et al. (43)	*Nicotiana tabacum*	Experimental (*in vitro*)	Extract	Decreasing labeling of RBC and plasma proteins due to direct or indirect effect (reactive oxygen species) of tobacco by oxidation of the stannous ion, possible chelating action on the stannous and/or pertechnetate ions and possible damages caused in the plasma membrane.
Amorim et al. (44)	*Punica granatum*	Experimental (*in vitro*)	Infusion	Increase in the percentage of ATI in lungs, brain, spleen, heart, liver, stout bowel, stomach, muscle, femur, kidneys, pancreas, and testis through the generation of active metabolites.
Abreu et al. (23)	*Psidium guajava*	Experimental (*in vitro*)	Aqueous extract	Decreasing the radiolabeling of BC via antioxidant action and alters the membrane structures involved in ion transport into cells.
Farias et al. (45)	*Nectandra membranacea*	Experimental (*in vitro*)	Aqueous extract	Increase in the percentage of ATI of ^{99}mTc by muscle, thyroid, heart, kidney and thyroid (%ATI/gram of tissue). So the extract could generate active metabolites able to influence the bioavailability of ^{99}mTc.
Moreno et al. (35)	*Ginkgo biloba*	Experimental (*in vivo* and *in vitro*)	Solution	Decreasing the uptake of the $Na^{99m}TcO_4$ in the duodenum. This may be due to scavengers of free radicals and chelating agents in the extract.
Moreno et al. (46)	*Ginkgo biloba*	Experimental (*in vivo* and *in vitro*)	Extract	Decrease uptake of the $Na^{99m}TcO_4$ in the duodenum. It is possible that *in vivo* treatment with extract may generate active metabolites that could alter the ultrastructure of cells and the biodistribution of the $Na^{99m}TcO_4$.
Moreno et al. (28)	*Uncaria tomentosa*	Experimental (*in vitro*)	Solution	Decreasing in the uptake of this $Na^{99m}TcO_4$ %ATI/organ was observed in the heart. But the extract can increasing uptake radiobiocomplex %ATI/g in the Pancreas and muscles.
Santos et al. (47)	*Hypericum perforatum*	Experimental (*in vitro*)	Extract	Decreasing in radioactivity distribution and interfering with the fixation on the IF-P and IF-BC in young rats (not in elderly one).
Santos et al. (48)	*Mentha crispa*	Experimental (*in vitro*)	Aqueous extract	Increasing fixation observed in kidney, spleen, and thyroid the %ATI/g values by the generation of active metabolites.
Cekic et al. (49)	*Brassica oleraceaItalica*	Experimental (*in vivo* and *in vitro*)	Methanolic extract	Decreasing in the percentage of injected dose per gram of tissue weight (% ID/g) particular in the kidney. The extract was not effected labeling blood components with ^{99}mTc.
Rebello et al. (50)	*Passiflora edulis*	Experimental (*in vivo* and *in vitro*)	Solution	Decreasing in the percentage of ATI/g of tissues from duodenum, spleen, pancreas, and blood and increasing in stomach tissue. The extract does not alter the labeling of blood constituents.
Souza et al. (51)	*Cassia angustifolia*	Experimental (*in vivo* and *in vitro*)	Aqueous extract	Reducing %ATI/g of the $Na^{99m}TcO_4$ in the thyroid, liver, pancreas, lungs and blood. The extract did not modify the radiolabeling of the blood constituents.

Table 1: Contd.

Zora et al. (52)	*Passiflora incarnata*	Experimental (*in vivo* and *in vitro*)	Syrup	Reducing biodistribution uptake of ^{99m}Tc-DTPA in the kidney and reducing %ID/g of in particular kidney. In addition percentage of radioactivity on serum and BC decreased.
Benarroz et al. (36)	*Cinnamomum zeylanicum*	Experimental (*in vitro*)	Solution	Decreased significantly the percentage of ATI on BC, IF-P and IF-BC.
Garcia-Pinto et al. (53)	*Matricaria recutita*	Experimental (*in vivo* and *in vitro*)	Aqueous extract	Reducing radioactivity on blood cells compartment and on insoluble fractions of plasma and increasing of the percentage of radioactivity in the stomach.
Ucar et al. (54)	*Rosmarinus officinalis*	Experimental (*in vitro*)	Methanolic extract	Increasing in the uptake of ^{99}mTc-SC in the liver.
Holanda et al. (24)	*Annona muricata*	Experimental (*in vivo* and *in vitro*)	Solution	Decreasing in the uptake of ATI/g percent in bladder, kidney, and blood.
Holanda et al. (37)	*Aloe vera*	Experimental (*in vivo* and *in vitro*)	Aqueous extract	Increasing of %ATI/g in blood, kidneys, stomach, liver, testis femur and thyroid, so increasing uptake of $Na^{99m}TcO_4$.
Capriles et al. (55)	*Solanum melongena*	Experimental (*in vitro*)	Extract	Decreasing the labeling of RBC, IF-P, reducing %ATI, and IF-RBC due to the extract oxidation potential.
de Oliveira et al. (56)	*Fucus vesiculosus*	Experimental (*in vitro*)	Extract	Decreasing the %ATI, IF-P and IF-BC via increase the valence of these ions to stannic (+4).
de Paoli et al. (57)	*Caryophyllu saromaticus*	Experimental (*in vitro*)	Aqueous extract	Decreasing in the percentage of ATI of blood constituents and theradioactivity fixation.
Neves et al. (58)	*Arctium lappa*	Experimental (*in vitro*)	Aqueous extract	Decreasing in the percentage of ATI and the RBC labeling through alter the transport of ions (stannous and pertechnetate ions).
Rebello et al. (59)	*Passiflora edulis*	Experimental (*in vitro*)	Solution	Decreasing the fixation of ^{99}mTc on plasma proteins and BC but it can't interfere with blood cells labeling.
Terra et al. (60)	*Artemisia vulgaris*	Experimental (*in vitro*)	Solution	Decreasing in the percentage of ATI on the blood compartments and on the blood cells proteins (IF-BC and IF-P) via erythrocyte membrane alternating.
Sabuncu et al. (61)	*Camellia sinensis*	Experimental (*in vivo*)	Ethanolic and aqueous extract	Radiolabeling was not changed in blood component but decreasing the uptake of $Na^{99}mTcO_4$ by stomach, liver and prostate.

Table 2: Effects of phytochemicals and herbal combinations on radiolabeling and biodistribution of radiopharmaceuticals

References	Herbal compounds/derivatives	Study Design	Type of administra-tion	Type of radiopharma-ceutical	Main outcomes or mechanisms
Giani et al. (62)	Buzhong Yi Qi Wan composed of *Radix Astragalus, Radix codonopsis, Radix glycyrrhizae, Rhizoma atractylodis macrocephalae, Radix angelicaesinensis, Rhizoma cimicifugae, Radix bupleuri, Pericarpium citri reticulatae, Rhizoma zingiberis recens* and *Fructus jujubae*	Experimental (*in vitro*)	Aqueous extract	^{99}mTc	Decreasing in radioactivity distribution by the BC was reported. Besides decreasing in radioactivity fixation by the IF-BC and IF-P via free radicals generation causing oxidation of the stannous ions and the fixation of ^{99}mTc would be decreased.
Mattos et al. (26)	Vincristine derived from *Vincarosea* Linn	Experimental (*in vivo*)	Extract	^{99}mTc	Percentage of radioactivity decreased in the ovary, uterus, lymph nodes (inguinal and mesentheric), thymus, spleen, kidney, pancreas, liver, stomach, brain, heart and bone of the animals.
Dervis et al. (63)	Eugenol derived from *Syzygium aromaticum, Pimenta racemosa* and *Cinnamomum verum*	Experimental (*in vitro*)	Extract	Iodine-131 (^{131}I)	The extract causes radioiodinated with ^{131}I, which is a convenient radioisotope for therapy and potential for therapy and imaging due to its notable uptake.
Kamal et al. (27)	Resveratrol derived from herbs	Experimental (*in vitro*)	Extract	Technetium-^{99}m labelled resveratrol loaded gold nanoparticles (Res-AuNP)	administration of (^{99}m)Tc-Res-AuNP to colon tumor, demonstrating better *in vivo* targeting of colon adenocarcinoma with (^{99}m)Tc-Res-AuNP when compared to (^{99}m)Tc-resveratrol
Toksoz et al. (64)	Epigallocatechin gallate (EGCG) derived from *Camellia sinensis* Theaceae	Experimental (*in vitro*)	Solution	^{131}I	EGCG increasing radiolabeling in lung, liver, pancreas, and kidney. Besides max biodistribution was seen in lung and pancreas.

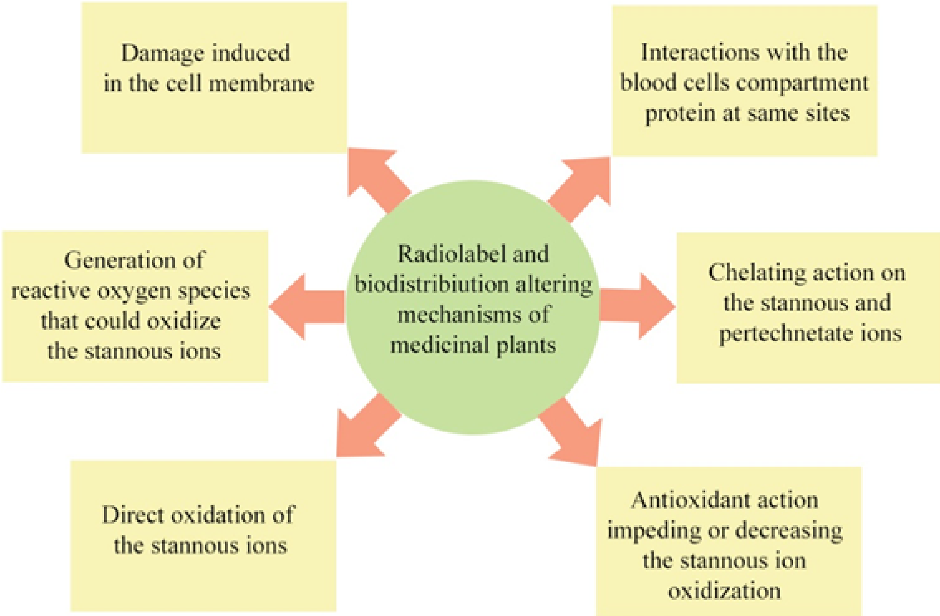

Fig. 2. Altering mechanisms of medicinal plants, derivatives and compounds on radiolabeling and bioavailability of radiopharmaceuticals

Acknowledgements

The authors would like to acknowledge Research and Technology Deputy of Shahrekord University of Medical Sciences for supporting this study.

Conflicts of interest

The authors declare no conflict of interest.

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