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Review Article

The use of radiopharmaceuticals in targeted cancer therapy: a narrative review

Amirreza Khalaji[1], Maryam Rostampour[2], Farshad Riahi[3], Diana Rafieezadeh[4], Seyed Amirhossein Dormiani Tabatabaei[5], Shahin Fesharaki[3], Seyed Hamed Tooyserkani[5]

[1]Department of Medicine, Division of Rheumatology, Lowance Center for Human Immunology, Emory University, Atlanta, GA, USA; [2]Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran; [3]Department of Radiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran; [4]Department of Cellular and Molecular Biology, Razi University, Kermanshah, Iran; [5]School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

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Abstract: Radiopharmaceutical therapy (RPT) is an advanced targeted cancer treatment that delivers radiation through specialized radiolabeled compounds to selectively destroy cancer cells while minimizing damage to healthy tissues. This theranostic approach integrates diagnosis and therapy, enhancing treatment precision and improving the therapeutic index compared to conventional chemotherapy. RPT agents consist of a radioactive isotope conjugated to a targeting molecule, enabling specific binding to cancer-associated antigens or receptors. Upon binding, these agents induce cell death through DNA damage caused by ionizing radiation. The choice of radionuclide, including beta and alpha emitters, plays a crucial role in determining therapeutic efficacy and potential side effects. This study aims to provide a comprehensive analysis of RPT, focusing on its mechanisms of action, clinical applications, and emerging challenges. We discuss the therapeutic potential of various radionuclides and highlight key clinical trials demonstrating efficacy across different malignancies. Additionally, we address critical issues such as optimizing delivery systems, managing radiotoxicity, and refining the dose-response relationship. Future directions include the development of novel radiopharmaceuticals and personalized treatment approaches. Further investigation is essential to overcome existing limitations and maximize the clinical benefits of RPT for patients with advanced cancers. Our findings contribute to a deeper understanding of RPT and offer insights into strategies for improving therapeutic outcomes and patient care.

Keywords: Radiopharmaceuticals, radionuclide therapy, theranostics, cancer

Introduction

Cancer continues to be a primary cause of mortality and morbidity globally, necessitating ongoing improvements in diagnostic and treatment approaches [1]. Radiopharmaceuticals have emerged as a potent instrument in targeted cancer therapy among these advancements. Radiopharmaceuticals are specialized chemicals that integrate a radioactive isotope with a biologically active molecule, facilitating accurate targeting of cancer cells while reducing injury to adjacent healthy tissues [2].

Radiopharmaceuticals in cancer utilize the precision of molecular targeting agents alongside the therapeutic capabilities of ionizing radiation. This dual strategy not only improves the effectiveness of cancer therapy but also paves the way for personalized medicine, wherein medicines are customized to the unique attributes of each patient's tumor. Recent advancements in radiopharmaceuticals have shown considerable potential in the treatment of many malignancies, including prostate cancer, neuroendocrine tumors, and specific forms of lymphoma [3].

Notwithstanding its promise, the utilization of radiopharmaceuticals in targeted cancer therapy encounters several hurdles, such as improving delivery systems, minimizing radiotoxicity, and assuring patient safety [4]. This narrative review is to examine the present state of radio-

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pharmaceuticals in cancer treatment, emphasizing significant developments, clinical uses, and continuing research initiatives. Through an analysis of the accomplishments and shortcomings of existing radiopharmaceutical therapy, we aim to offer insights that will guide future advancements and enhance outcomes for cancer patients.

Radiopharmaceutical therapy (RPT) is indicated for a range of malignancies, including metastatic prostate cancer, neuroendocrine tumors, thyroid cancer, and certain hematologic cancers. It is particularly beneficial for patients with advanced or refractory disease who may not respond to conventional treatments. The main therapeutic advantages of RPT include precise tumor targeting, minimized systemic toxicity, and the ability to treat micro-metastases that are often undetectable by standard imaging techniques [5]. Additionally, RPT allows for a personalized treatment approach by tailoring the therapy to the biological characteristics of the tumor, thereby improving therapeutic efficacy while reducing adverse effects.

This study will examine the fundamental concepts of radiopharmaceuticals, the processes that drive their therapeutic benefits, and the most recent advancements in their design and implementation. Furthermore, we will examine the clinical experiences and results associated with different radiopharmaceutical agents, offering a thorough review of their significance in contemporary oncology. This research highlights the significant role of radiopharmaceuticals in the fight against cancer and outlines potential developments and ways to incorporate them into clinical practice.

Methods

Study design

A comprehensive literature review was conducted to analyze the mechanisms, clinical applications, and challenges of RPT in cancer treatment. This review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure transparency and methodological rigor. The study aimed to provide an in-depth evaluation of RPT, including therapeutic mechanisms, clinical outcomes, and emerging research directions.

Search strategy

A systematic search was performed across six electronic databases: PubMed, Embase, Google Scholar, Scopus, Web of Science, and the Cochrane Library. The search included articles published up to August 2024. The search terms combined Medical Subject Headings (MeSH) and free-text keywords related to RPT and cancer, including 'radiopharmaceutical therapy', 'targeted radionuclide therapy', 'cancer treatment', 'radionuclides', and 'theranostics'. **Table 1** details the specific search strategies employed for each database. Only peer-reviewed articles written in English were included to maintain scientific validity.

Incusion and exclusion criteria

Two independent reviewers screened the titles and abstracts of all retrieved articles to determine their relevance. Full-text articles were assessed based on predefined eligibility criteria. Inclusion criteria were: (1) original research studies, (2) publication in English, and (3) studies investigating RPT mechanisms, clinical efficacy, or safety. Exclusion criteria included: (1) review articles, case reports, and letters to the editor, (2) studies unrelated to RPT in cancer, and (3) non-English publications. Any discrepancies were resolved through discussion and consensus.

Data extraction

Data extraction was performed using a standardized data collection form, recording details such as author, publication year, study design, sample size, intervention or exposure, outcome measures, and main findings. The quality of randomized controlled trials (RCTs) was assessed using the Cochrane Risk of Bias tool, while the ROBINS-I tool was used for non-randomized studies.

A narrative synthesis approach was used to analyze the extracted data, summarizing key findings with supporting evidence. The analysis emphasized the therapeutic potential of RPT, its clinical applications, and the challenges

Table 1. Search strategies used for databases

Database	Search strategy
PubMed	((radiopharmaceuticals OR target* radionuclide therap* OR theranostics OR radioisotopes OR radionuclide therap* OR radioimmunotherap*) AND (cancer* OR tumor target* OR neoplasm* OR target* cancer therap* OR oncolog* OR cancer treatment OR metasta* cancer))
Google scholar	((radiopharmaceuticals OR target* radionuclide therap* OR theranostics OR radioisotopes OR radionuclide therap* OR radioimmunotherap*) AND (cancer* OR tumor target* OR neoplasm* OR target* cancer therap* OR oncolog* OR cancer treatment OR metasta* cancer))
Web of science	((radiopharmaceuticals OR target* radionuclide therap* OR theranostics OR radioisotopes OR radionuclide therap* OR radioimmunotherap*) AND (cancer* OR tumor target* OR neoplasm* OR target* cancer therap* OR oncolog* OR cancer treatment OR metasta* cancer))
Scopus	((radiopharmaceuticals OR target* AND radionuclide AND therap* OR theranostics OR radioisotopes OR radionuclide AND therap* OR radioimmunotherap*) AND (cancer* OR tumor AND target* OR neoplasm* OR target* AND cancer AND therap* OR oncolog* OR cancer AND treatment OR metasta* AND cancer)) AND (LIMIT-TO (OA, "all")) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (LANGUAGE, "English"))
Cochrane Library	((radiopharmaceuticals OR target* radionuclide therap* OR theranostics OR radioisotopes OR radionuclide therap* OR radioimmunotherap*) AND (cancer* OR tumor target* OR neoplasm* OR target* cancer therap* OR oncolog* OR cancer treatment OR metasta* cancer)) in All Text
Embase	(((‘radiopharmaceuticals’/exp OR radiopharmaceuticals OR target*) AND (‘radionuclide’/exp OR radionuclide) AND therap* OR ‘theranostics’/exp OR theranostics OR ‘radioisotopes’/exp OR radioisotopes OR ‘radionuclide’/exp OR radionuclide) AND therap* OR radioimmunotherap*) AND ((((cancer* OR ‘tumor’/exp OR tumor) AND target* OR neoplasm* OR target*) AND (‘cancer’/exp OR cancer) AND therap* OR oncolog* OR ‘cancer’/exp OR cancer) AND (‘treatment’/exp OR treatment) OR metasta*) AND (‘cancer’/exp OR cancer) AND [article]/lim AND [english]/lim

associated with optimizing treatment delivery and minimizing radiotoxicity.

Results

Included studies

A total of 27 articles were found to meet our inclusion criteria (**Figure 1**). These articles encompass a broad spectrum of study trends, methodologies, and cancer types, reflecting the diverse applications and outcomes associated with the use of radiopharmaceuticals in targeted cancer therapy.

Article filtering

The studies varied significantly in their design, including randomized controlled trials, observational studies, and retrospective analyses. The patient populations differed in terms of cancer types, stages, and previous treatment histories. This diversity highlights the wide-ranging potential and adaptability of radiopharmaceuticals in oncology.

Despite the variability, several common themes and findings emerged. Many studies reported significant improvements in progression-free survival and overall survival rates among patients treated with radiopharmaceuticals. For instance, Lutetium-177 Dotatate was frequently highlighted for its effectiveness in treating neuroendocrine tumors, with several studies demonstrating substantial reductions in tumor size and prolonged survival.

Conversely, some studies indicated mixed results regarding the side effect profiles of these treatments. While radiopharmaceuticals generally exhibited favorable safety profiles, certain adverse effects, such as myelosuppression and renal toxicity, were noted. These findings underscore the importance of patient selection and monitoring to mitigate potential risks.

Additionally, the integration of imaging functionalities within radiopharmaceuticals was consistently noted to enhance treatment precision. Many studies emphasized the theranos-

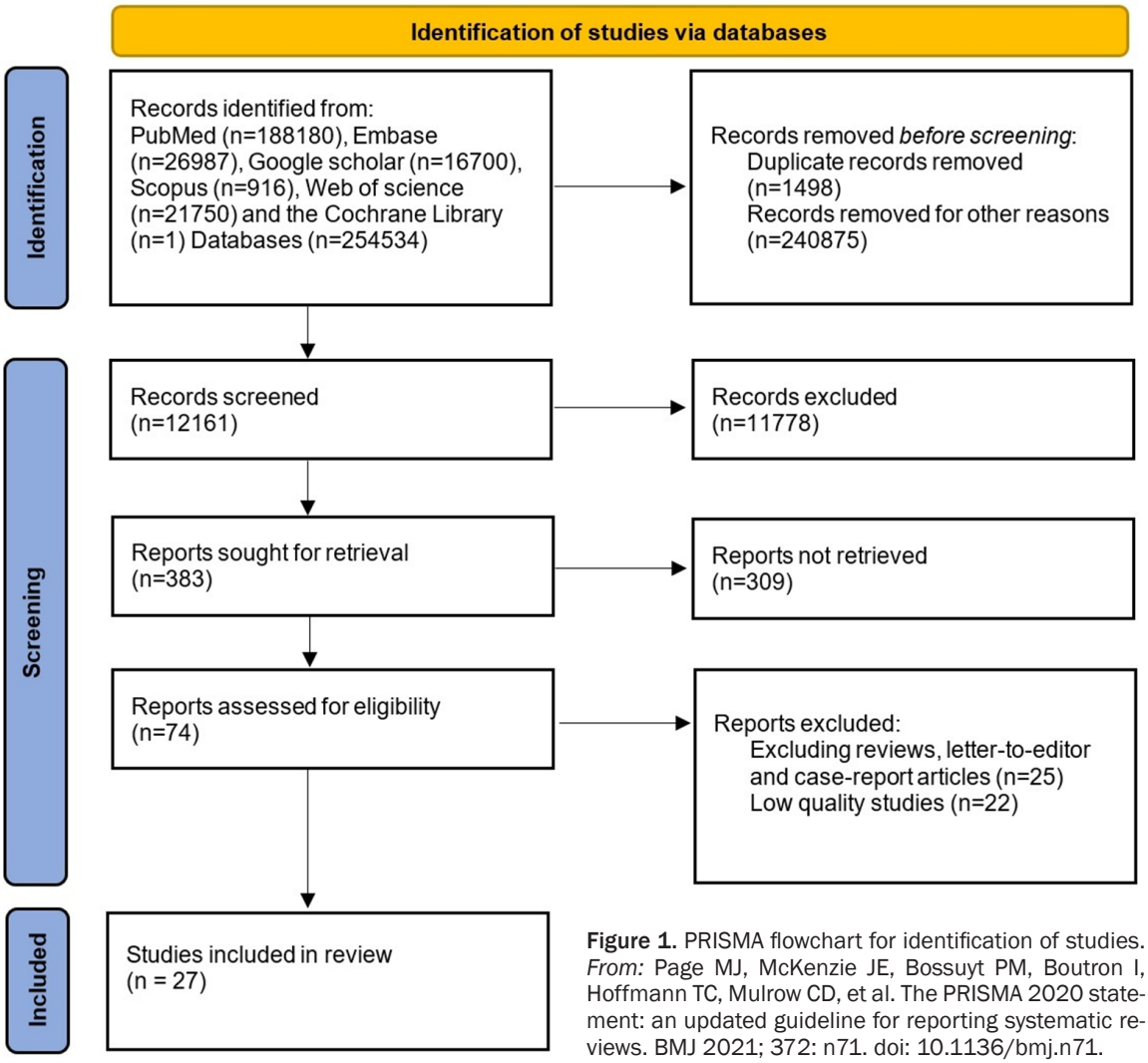

Figure 1. PRISMA flowchart for identification of studies. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71. doi: 10.1136/bmj.n71.

tic approach, where diagnostic imaging guides therapeutic interventions, allowing for individualized treatment planning and real-time monitoring of treatment efficacy.

Data points

The synthesis of these articles provides a comprehensive overview of the current landscape of radiopharmaceuticals in targeted cancer therapy. It underscores their efficacy in improving patient outcomes, while also highlighting the need for further research to optimize treatment protocols and manage side effects effectively. The mixed results observed across studies point to the necessity for standardized guidelines and more extensive clinical trials to validate these findings and expand the therapeutic utility of radiopharmaceuticals.

Discussion

RPT utilizes radiation administered either systemically or locally through pharmaceuticals designed to target cancer cells or concentrate in particular tissues. This targeted approach distinguishes RPT from conventional external beam radiotherapy, providing an effective yet minimally toxic treatment option [6]. RPT employs radioactive atoms directed at tumor-associated targets, resulting in cell death via ionizing radiation. It provides integrated imaging functionalities that facilitate individualized treatment planning, delivery verification, and response assessment. This theranostic approach facilitates accurate dose delivery and may enhance the therapeutic index relative to traditional chemotherapy [5].

Table 2. Types of RPT

Type	Description
Targeted tumor therapy	Utilizing radiopharmaceuticals that selectively bind to tumor cells, delivering a lethal dose of radiation while minimizing damage to healthy tissue [11].
Peptide receptor radionuclide therapy (PRRT)	Systemic delivery of therapeutic peptides labeled with radionuclides specifically targeting neuroendocrine tumors (NETs) [12].
Targeted alpha therapy (TAT)	Uses alpha-emitting radionuclides, offering high precision for targeting micrometastases and disseminated malignancies with minimal off-target effects [13].
Palliative care	RPT effectively alleviates metastatic bone pain by targeting and destroying cancerous cells within the bone [14].

RPT provides a focused method for cancer treatment, potentially enhancing efficacy and minimizing toxicity relative to standard chemotherapy. Comprehending the dose-response relationship is essential for enhancing treatment efficacy and maximizing patient outcomes. Current RPT practices frequently depend on conventional toxicity management frameworks, failing to fully utilize the distinct characteristics of RPT [7]. **Table 2** shows the types of RPT.

Radiopharmaceuticals are composed of a radioactive isotope linked to a targeting molecule that specifically binds to cancer cells. Ionizing radiation, including alpha, beta, and gamma particles, induces DNA damage, resulting in cell death [8]. Radiopharmaceuticals demonstrate anticancer effects by inducing cytotoxic DNA damage via several mechanisms, such as the generation of reactive oxygen species, the induction of single and double-strand breaks, and the inhibition of DNA repair processes (**Table 3**).

Radiation types utilized in RPT comprise photons (mainly for imaging purposes rather than localized cytotoxicity), electrons (which encompass Auger electrons (very short-range), β-particles (longer-range and frequently employed), and monoenergetic electrons), and α-particles (which are highly effective with a short range, resulting in intricate DNA damage and limited off-target effects).

The evolution of RPT has been characterized by the introduction and adoption of multiple radionuclides. The initial applications concentrated on β-emitters such as Iodine-131 for thyroid cancer, Yttrium-90 for various cancers including hepatic metastases, and Samarium-153 for bone pain palliation. There is an increasing interest in α-emitters, such as Astatine-211, Bismuth-212, Lead-212, Bismuth-213, Actinium-225, Radium-223, and Thorium-227. The transition is influenced by the high potency and limited range of α-particles, resulting in enhanced efficacy and decreased toxicity [5, 6].

RPT offers several significant advantages. RPT agents are engineered to selectively bind to cancer cells, thereby reducing harm to healthy tissues. This is accomplished through the use of specific molecules such as antibodies, peptides, or small molecules that identify distinct receptors or features of cancer cells. RPT provides flexibility in administration, accommodating different cancer types and sites. This can be accomplished via intravenous injection for systemic distribution or direct injection into specific body cavities or targeted tissues. Most RPT agents emit photons that can be detected using imaging techniques like SPECT or PET. This facilitates real-time observation of the agent's biodistribution, permitting patient-specific dosimetry and treatment optimization [6]. RPT agents employ different forms of radiation, such as α-particles and β-particles, which are recognized for their significant cytotoxic capabilities. This facilitates efficient tumor cell destruction at reduced doses, resulting in notable clinical advantages. Recent studies support the superior efficacy of α-particle emitters in treating metastatic cancers compared to β-emitters, particularly in cases of bone metastases and hematological malignancies. For example, trials involving Radium-223 demonstrated prolonged overall survival in patients with castration-resistant prostate cancer and symptomatic bone metastases [17]. This aligns with findings from a multicenter trial where Actinium-225 labeled PSMA ligands showed promising

Table 3. Commonly used radiopharmaceuticals in targeted cancer therapy

Radiopharmaceutical	Target	Mechanism	Clinical impact
Lutetium-177 (Lu-177) Dotatate [15]	Neuroendocrine tumors	Beta radiation targets and destroys cancer cells	Improves progression-free survival and quality of life
Radium-223 Dichloride (Ra-223) [16]	Bone metastases from prostate cancer	Alpha radiation selectively targets bone lesions	Reduces pain and improves survival
Iodine-131 (I-131) [16]	Thyroid cancer	Beta radiation destroys residual thyroid tissue and metastatic cancer	Gold standard for treating differentiated thyroid cancers
Lutetium-177 (Lu-177) vipivotide tetraxetan (PLUVICTO®) [17]	Prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer (PSMA-positive mCRPC)	Beta radiation targets and destroys cancer cells	FDA-approved for treatment
Yttrium-90 (Y-90) Microspheres [18]	Liver tumors	Beta radiation targets and destroys liver tumors	Used in radioembolization for unresectable liver cancer
Strontium-89 (Sr-89) Chloride	Bone metastases	Beta radiation targets and destroys bone metastases	Reduces pain in patients with bone metastases
Iodine-131 MIBG (Metaiodobenzylguanidine)	Neuroblastoma and pheochromocytoma	Beta radiation targets and destroys cancer cells	Used in treating neuroendocrine tumors

results in prostate cancer patients who were refractory to conventional therapies [18].

Technical and biological factors influence the dose-response relationship. Technical factors encompass quantitative imaging accuracy, theranostic imaging, and tumor segmentation. Accurate and repeatable assessments of biological target expression through methods such as PET and SPECT are crucial for personalized dosimetry [9]. The application of a radiotracer to evaluate target expression prior to therapy can inform patient selection and facilitate dosimetry-driven treatment planning [10]. Accurate tumor delineation for dosimetry calculations presents a challenge due to the small size of lesions and dependence on manual or semi-automatic methods.

Biological factors encompass the tumor microenvironment, tumor heterogeneity, and immune response [7]. Tumor size, location, vascularity, and hypoxia influence the delivery and efficacy of RPT agents. Variations in target expression within and between lesions can result in non-uniform absorbed dose distributions and differing responses. Radiation-induced immunogenic cell death and the role of immune checkpoint inhibitors in conjunction with radiotherapy are developing fields of study. Emerging evidence suggests that combining RPT with immune checkpoint inhibitors may amplify the therapeutic response. Preclinical models have shown that α-particles induce immunogenic cell death, which enhances anti-tumor immune responses when combined with PD-1/PD-L1 inhibitors [19]. This dual approach holds promise in overcoming tumor resistance mechanisms observed in monotherapy regimens.

Despite notable advancements, RPT encounters multiple challenges. For several decades, RPT has served as a treatment modality of last resort, accessible primarily through limited clinical trials. The absence of awareness and specialized expertise obstructs broad adoption and clinical advancement. Imaging capabilities facilitate patient-specific dosimetry; however, the accurate prediction and mitigation of toxicity is essential. This entails analyzing the micro-scale distribution of RPT agents and their effects on critical organ subregions. Tumor heterogeneity presents a challenge for attaining consistent dose distribution and therapeutic effectiveness. Ongoing research focuses on addressing mechanisms of tumor resistance. The pursuit of more effective and targeted RPT agents persists, emphasizing the refinement of delivery vehicles, optimization of pharmacokinetics, and investigation of novel therapeutic radionuclides.

Numerous domains necessitate additional investigation, encompassing: the influence of inflammation and immune-mediated effects on dose-response, the importance of negative theranostic imaging and patient outcomes, the relevance of radiobiological parameters from external beam radiotherapy (EBRT) to RPT, the contribution of genomic methodologies in evaluating individual patient radiosensitivity, the effect of hypoxia on RPT response, and the opti-

mal frameworks for correlating RPT and EBRT dose response. Comparative studies between RPT and EBRT underscore RPT's ability to deliver localized radiation with reduced systemic toxicity. For instance, head-to-head analyses reveal that RPT offers superior tumor control in cases with micro-metastatic disease, where EBRT falls short due to its broader radiation field [20]. These findings reinforce the clinical utility of RPT in scenarios requiring precision-targeted radiation.

This study had some limitations. Initially, limiting articles to English may create selection bias, disregarding exceptional research in other languages or from other periods. Narrative reviews can summarize findings but lack the rigor and reproducibility of systematic reviews and meta-analyses, potentially introducing subjectivity in data interpretation.

Conclusions

RPT constitutes a notable progression in targeted cancer treatment, utilizing radiation administered via specialized medicines to efficiently target and eradicate cancer cells while reducing injury to healthy organs. This theranostic method not only augments treatment accuracy but also increases the therapeutic index relative to conventional chemotherapy. Despite its promise, RPT encounters obstacles including the optimization of delivery systems, the management of radiotoxicity, and the comprehension of the dose-response relationship.

The utilization of several radionuclides, particularly beta and alpha emitters, has shown significant therapeutic advantages in the treatment of various malignancies. Nonetheless, the complete potential of RPT remains unfulfilled due to constraints in awareness, specialized knowledge, and the necessity for individualized dosimetry. Subsequent research must concentrate on tackling these issues, optimizing delivery methods, and investigating innovative treatment agents to augment effectiveness and patient outcomes. By surmounting these obstacles, RPT has the potential to transform cancer treatment, offering a more efficacious and less toxic alternative to traditional medicines.

Disclosure of conflict of interest

None.

Address correspondence to: Seyed Hamed Tooyserkani, School of Medicine, Isfahan University of Medical Science, Hezar Jarib Street, Isfahan 8174673461, Iran. Tel: +989103142438; Fax: +989137294009; E-mail: s.hamed.tooyserkani@gmail.com

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