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REVIEW

Role of Radioiodine in Cancer Therapy: A Review of the Design and Challenges in Selecting Radioligands from Natural Sources

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Abstract: The use of radioactive isotopes in cancer treatment has marked a pivotal shift in modern medicine, where precise diagnosis and targeted therapy now blend to offer patients more effective care with minimized side effects. Despite significant advancements, the exploration of iodine-labeled radioligands from natural sources remains underdeveloped, and comprehensive evaluations of their design, pharmacokinetics, and clinical relevance are still lacking. This gap has created a pressing need for systematic studies that bridge natural product chemistry with radiopharmaceutical applications. Since the initial application of iodine-131 in thyroid treatments, radioisotopes such as iodine-125 and iodine-131 have gained prominence in oncology due to their dual functionality: they enable accurate imaging while delivering therapeutic radiation directly to tumor cells, reducing harm to surrounding healthy tissues. Recent advancements in radiopharmaceuticals, particularly iodine-labeled compounds, aim to further improve this balance by enhancing cancer treatment efficacy and safety. This review synthesizes findings from clinical and experimental studies that explore a range of iodine-labeled compounds, including natural agents like hypericin, curcumin, and piperine, as well as various synthetic analogs. Key methodologies for incorporating iodine, such as the Iodogen method and other stable-labeling techniques, are evaluated for their impact on the compounds' pharmacokinetics, stability, and therapeutic performance. Furthermore, in silico methods are highlighted for their contribution to optimize the molecular structures, binding affinities, and specificity, streamlining the selection of high-potential candidates for radiopharmaceutical applications. Findings reveal that iodine-labeled compounds effectively concentrate in tumor cells, enhancing selectivity and reducing radiation exposure to non-cancerous tissues. Notably, these compounds demonstrate stability in biological environments, making them viable options for integrated diagnostic and therapeutic purposes. Moving forward, the ongoing refinement of compound stability and targeted biodistribution is crucial in ensuring these therapies can meet the demands of precision oncology and improve clinical outcomes across various cancer types.

Keywords: radioiodine isotopes, natural radiopharmaceuticals, cancer treatment, diagnostic imaging, future radioactive design

Introduction

The application of radioactive isotopes in medicine, particularly in cancer treatment, has evolved remarkably since its inception in the mid-20th century.[1,2] There are several types of ionizing radiation emitted by radioisotopes, primarily alpha (α), beta (β), and gamma (γ) radiation, each with distinct characteristics and clinical applications.[3] Alpha particles are highly cytotoxic due to their high linear energy transfer (LET), making them ideal for destroying cancer cells in targeted alpha therapy, although their short penetration range limits systemic use.[4] Beta particles, with moderate LET and

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deeper tissue penetration, are commonly used in targeted radiotherapy, such as with iodine-131 or lutetium-177.[5] Gamma rays and positron emissions are mainly employed for diagnostic imaging because of their ability to penetrate tissues and be detected externally using gamma cameras or positron emission tomography (PET) scanners.[6] Radioisotopes function by emitting ionizing radiation, which can be harnessed either to visualize biological processes (diagnostic imaging) or to destroy malignant tissues (therapy). Diagnostic applications typically rely on gamma or positron emitters that allow for non-invasive imaging using devices such as single photon emission computed tomography (SPECT) or PET scanners.[7] Therapeutic applications utilize alpha or beta emitters to deliver cytotoxic doses of radiation directly to tumors, minimizing damage to surrounding healthy tissue. Despite their targeted approach, radioisotope therapies may still induce side effects such as fatigue, nausea, inflammation of surrounding tissues, bone marrow suppression, or salivary gland dysfunction, depending on the type and location of the cancer being treated.[8,9] These adverse effects are typically dose-dependent and influenced by the biodistribution of the radiopharmaceutical. To mitigate these issues, several strategies are employed, including pre- and post-treatment hydration, administration of radioprotective agents (eg, amifostine), and patient-specific dosimetry planning to tailor the radiation dose precisely.[10] In addition, the use of ligands with higher tumor specificity and optimized pharmacokinetic properties helps to reduce off-target accumulation, thereby enhancing therapeutic efficacy while minimizing toxicity.

Radioactive isotopes have been widely used in medicine for both diagnostic and therapeutic purposes. While iodine isotopes, particularly iodine-123, iodine-125, and iodine-131, are pivotal in nuclear medicine, they are not the only radioisotopes utilized in the field. A variety of other isotopes, such as Yttrium-90 (Y-90),[11] Lutetium-177 (Lu-177),[12] Tritium (H-3),[13] Indium-111 (In-111),[14] Technetium-99m (Tc-99m),[15] Radium-223 (Ra-223),[16] Gallium-68 (Ga-68),[17] and Fluorine-18 (F-18),[18] have unique properties that make them suitable for specific medical applications. For instance, Y-90 and Lu-177 are widely used in targeted radiotherapy, such as peptide receptor radionuclide therapy (PRRT) for neuroendocrine tumors.[19] Tc-99m is predominantly used for diagnostic imaging in a variety of conditions, including cardiovascular and skeletal imaging, due to its ideal gamma emission and short half-life.[20] Ra-223 is utilized for treating bone metastases in advanced prostate cancer due to its alpha emission properties,[21] whilst Ga-68 and F-18 are frequently employed in PET imaging, providing high-resolution images for cancer detection and staging.[22] Despite this diversity, iodine isotopes remain at the forefront of nuclear medicine due to their dual functionality, offering capabilities for both imaging and therapeutic applications in oncology.[23]

The pioneering use of iodine-131 for thyroid conditions marked the beginning of nuclear medicine, establishing a new approach where radioactive substances are used to diagnose and treat disease with unprecedented precision.[24] As the knowledge on radiochemistry and pharmacology advances, iodine-125 and iodine-131 have become crucial radioisotopes in oncology, valued for their ability to simultaneously facilitate diagnostic imaging and targeted radiotherapy. These isotopes emit radiation that can be externally detected for imaging or precisely directed at tumor cells for treatment, minimizing harm to surrounding healthy tissues.[25,26] Such dual functionality has catalyzed the development of radiopharmaceuticals that target cancer cells selectively, reducing the adverse effects often associated with conventional therapies. This approach aligns with the goals of personalized medicine, which prioritizes tailored treatments to optimize therapeutic outcomes while minimizing side effects.[27] Today, the use of iodine-labeled compounds represents a significant leap forward in achieving these goals, offering precision-targeted solutions that improve patient care. The integration of radiolabeled therapies into cancer treatment protocols underscores a shift towards more patient-centered, efficient, and effective cancer management strategies.[28]

The selection of iodine-125 and iodine-131 as radioisotopes in cancer therapy is guided by their unique physical properties, making them suitable for precision targeting of tumours.[29,30] However, to maximize their effectiveness, these isotopes must be paired with an appropriate ligand, a bioactive molecule that specifically targets cancer cells. The ligand is essential because it ensures that the radioactive isotope is delivered directly to the tumor, minimizing radiation exposure to surrounding healthy tissue. Iodine-131, with its half-life of 8 days and strong beta emission, is typically paired with ligands that have high affinity for tumor-specific receptors, such as monoclonal antibodies or peptides, which can selectively bind to cancer cells.[31,32] The combination of iodine-131 and a suitable ligand not only facilitates the targeted delivery of therapeutic radiation but also allows for the simultaneous imaging of tumor cells using the gamma emissions, providing valuable diagnostic feedback. Iodine-131 emits gamma radiation with an energy of approximately

364 keV, which falls within the optimal range for imaging (100–400 keV), making it suitable for use with standard gamma cameras.[33] This diagnostic capability complements its beta emissions (606 keV) that deliver therapeutic effects, enabling a theranostic approach where treatment and imaging are integrated in a single platform.[34,35] This dual functionality makes iodine-131 an invaluable isotope in precision oncology, supporting both effective tumor targeting and real-time monitoring of therapeutic outcomes. In contrast, iodine-125, with its longer half-life (around 60 days) and softer radiation, is used in therapies requiring prolonged exposure to low-dose radiation.[36] Iodine-125 emits low-energy gamma photons (approximately 27–35 keV) with limited tissue penetration.[37] This characteristic improves penetration and minimizes damage to surrounding healthy tissues, making iodine-125 particularly suitable for localized applications such as brachytherapy and prolonged low-dose treatments. It is often paired with ligands like antibodies or small molecules designed for localized delivery, such as in brachytherapy, where the radioligand is placed near or within the tumor for sustained, precise treatment. The careful selection of a ligand is crucial because its affinity and specificity determine the effectiveness of the radiotherapy.[38] Without an appropriate ligand, the radioactive isotope would not effectively target the tumor, diminishing the overall therapeutic benefit and increasing the risk of unwanted side effects. Therefore, choosing both the right isotope and the right ligand is a key aspect of ensuring the success of radioisotope-based cancer treatments.[39]

The increasing interest in using natural compounds as ligands has introduced a new dimension to the field, offering a complementary approach to synthetic agents rather than a definitive alternative.[40,41] Natural compounds with bioactive properties are being explored as carriers for radioactive isotopes, given their favorable properties, such as low toxicity and inherent anticancer properties. However, their structural variability and purity may pose challenges in reproducibility, which synthetic compounds can address with more reliable consistency. The concept of using natural compounds as ligands leverage their natural affinity for malignant cells, enabling them to serve as effective delivery vehicles that facilitate tumor-specific accumulation of radioisotopes. When these natural ligands are radiolabeled with iodine-125 or iodine-131, for example, the resulting radiopharmaceutical exhibits dual functionality: the ligand directs the compound selectively to tumor sites, while the radioisotope provides diagnostic (gamma) or therapeutic (beta or alpha) radiation.[42] These ligands achieve tumor targeting through several mechanisms: (1) recognition of tumor-specific biomarkers or antigens via molecular interactions, such as those seen with monoclonal antibodies; (2) selective binding to over-expressed receptors on cancer cells (eg, folate, transferrin, or integrin receptors); and (3) exploitation of the enhanced permeability and retention (EPR) effect, a passive targeting mechanism wherein macromolecules preferentially accumulate in tumor tissue due to leaky vasculature and poor lymphatic drainage.[43,44] The integration of natural bioactive molecules with radiopharmaceuticals aims to maximize therapeutic impact while reducing the risk of side effects which is a primary concern in cancer treatment. It is important to note, however, that the concentration of radiopharmaceuticals is often too low to exert significant pharmacological effects, making the molecule's origin less critical in certain contexts. Radiolabeling of natural compounds aligns well with the goals of personalized and targeted therapy,[45,46] besides simplifying the pharmacokinetic profile of radiopharmaceuticals and making them more adaptable to clinical settings.[47] This integration also acknowledges the complementary roles of natural and synthetic compounds in advancing radiopharmaceutical science. Indeed, the development of natural radioligands represents a promising area in cancer research, bridging the gap between traditional therapies and innovative targeted approaches.

The dual capability of iodine-labeled compounds to function as both diagnostic tools and therapeutic agents is a key advantage in cancer treatment, allowing for a comprehensive approach that spans diagnosis, treatment, and monitoring.[48] The process begins with the administration of an iodine-labeled compound, which is designed to selectively accumulate in cancerous tissues due to its specific targeting properties. Once localized in the tumor, the compound emits beta particles that induce cellular damage, effectively killing cancer cells, while gamma emissions facilitate real-time imaging, enabling clinicians to monitor treatment response and distribution.[49,50] This dual functionality provides a full spectrum of cancer care, from initial diagnosis through treatment and follow-up, enhancing treatment accuracy and patient outcomes. By using these compounds, clinicians can achieve a level of precision that traditional therapies lack, ultimately improving the quality of life for cancer patients.[51,52] The ability to both visualize and therapeutically target malignancies with a single compound exemplifies a modern approach in oncology, providing a more holistic treatment option for patients. As shown in Figure 1, this process begins with the radiolabeling of a targeting molecule with a radioisotope,

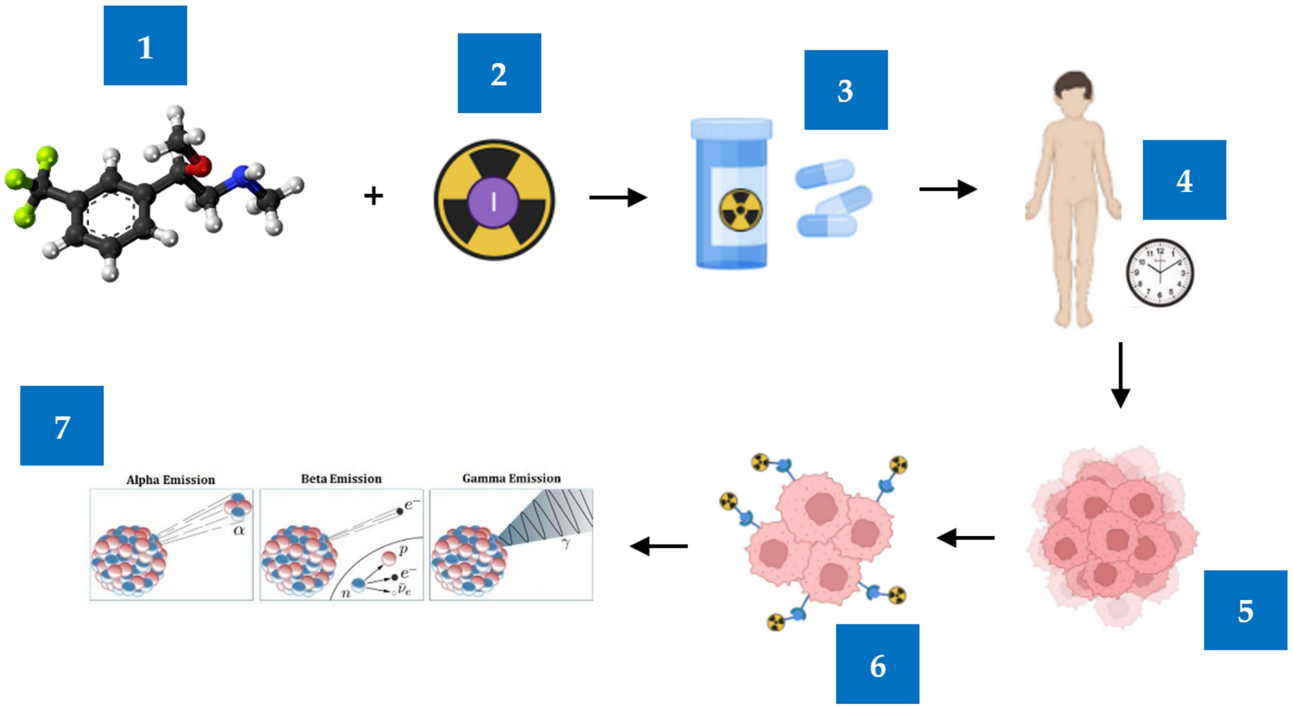

Figure 1 The use of radiopharmaceuticals in cancer therapy begins with the synthesis of a ligand (1), radiolabeling a compound and a radioactive isotope (2). This compound is then formulated (3) and administered to the patient (4). After a biodistribution time, it accumulates in targeted cancer cells (5), where it emits radiation (6) that disrupts cancer cell DNA. The type of radiation (7) determines its purpose: gamma and beta+ for diagnostics, and alpha, beta-, or Auger for therapeutic effects. Adapted from Faivre-Chauvet A, Bourdeau C, Bourgeois M. Radiopharmaceutical good practices: regulation between hospital and industry. *Front Nuclear Med*. 2022;2:990330. Creative Commons.[56] and Calcaterra V, Mameli C, Rossi V, et al. The iodine rush: over- or under-iodination risk in the prophylactic use of iodine for thyroid blocking in the event of a nuclear disaster. *Front Endocrinol*. 2022;13:901620. Creative Commons.[57]

creating a compound that is administered to the patient. Once in the body, the compound binds specifically to cancer cells, enabling precise visualization and destruction of malignant cells through radiation emissions, including alpha, beta, and gamma rays.[53–55] This dual functionality enhances treatment accuracy and reduces off-target effects, offering an integrated diagnostic and therapeutic solution.

Recent developments in radiopharmaceutical science have highlighted the untapped potential of natural compounds as targeting ligands, particularly in the field of personalized cancer therapy. Unlike their synthetic counterparts, these compounds, derived from peptides, alkaloids, flavonoids, and other plant-based bioactives, are increasingly recognized for their biocompatibility and inherent bioactivity.[58,59] Their selective affinity for tumor cells makes them suitable candidates for radiolabeling, enabling precise delivery of therapeutic isotopes. Importantly, their low systemic toxicity provides a favorable safety profile, which is critical in minimizing off-target radiation effects.[60] When labeled with isotopes such as iodine-125 or iodine-131, these ligands can function both as tumor-homing agents and as carriers of cytotoxic radiation, thus fulfilling theranostic roles.[61] This dual utility is particularly beneficial in clinical settings that demand both effective treatment and real-time monitoring of therapeutic responses. Natural radioligands may also facilitate improved pharmacokinetics, contributing to enhanced biodistribution and target selectivity.[62] By integrating these compounds into nuclear medicine protocols, clinicians can leverage their advantages to develop safer, more effective, and patient-specific interventions. Continued exploration of these bioactive ligands could therefore expand the radiopharmaceutical toolbox and contribute to the next generation of targeted cancer therapies.

As research continues to explore the therapeutic potential of these natural radioligands, it is becoming increasingly clear that they could bridge the gap between traditional cancer therapies and the more innovative, targeted approaches of modern oncology. Their versatility and efficacy offer a promising direction for future cancer treatments, providing more holistic, patient-centered care. However, despite the growing interest and individual reports on various iodine-labeled natural compounds, there remains a lack of comprehensive synthesis that evaluates their design strategies,

pharmacological behavior, and translational readiness. This knowledge gap has limited our ability to draw generalizable conclusions and to standardize development pathways for these agents in clinical oncology. In this context, this review aims to provide a comprehensive exploration of the therapeutic potential of natural radioligands in modern oncology. To ensure the rigor and reliability of this review, a systematic approach was employed in the design and execution of the study. Data sources included peer-reviewed journals indexed in databases such as PubMed, Scopus, and Web of Science. Keywords and search terms such as "radioiodine", "radioisotopes in oncology", "iodine therapy", "diagnostic radioiodine imaging", and "theranostics" were used to identify relevant studies. The search was limited to articles published in English from 2000 to 2023 to ensure the inclusion of up-to-date and high-quality research. Studies were selected based on predefined inclusion and exclusion criteria, in which only articles that provided substantial experimental or clinical evidence on the application of natural radioligands in cancer treatment were included. The selection process involved an initial screening of titles and abstracts, followed by a full-text review of eligible studies to ensure relevance and validity. By adopting this systematic approach, the review aims to present an accurate and comprehensive understanding of the current landscape and future directions for the use of natural radioligands in oncology.

Application of Radioiodine in Various Cancer Treatments

Radioiodine therapy has long been established as a cornerstone in the management of various malignancies, owing to its unique capability to deliver targeted cytotoxic radiation to iodine-avid tissues[63] (Table 1). With the development of both iodine-125 (^{125}I) and iodine-131 (^{131}I) isotopes, the therapeutic landscape has expanded to encompass multiple cancer types, from localized tumors to advanced metastatic disease. The versatility of radioiodine lies in its dual capacity for both brachytherapy and systemic radiotherapy, which enables clinicians to tailor treatment strategies according to tumor location, type, and iodine uptake characteristics. Advancements in nuclear medicine have further improved the precision and safety of radioiodine-based treatments through the integration of imaging-guided implantation, nanocarrier delivery systems, and gene-enhanced uptake modulation.[64] These strategies have allowed radioiodine to be effectively applied in treating cervical, prostate, and differentiated thyroid cancers, among others. Notably, the incorporation of technologies such as three-dimensional (3D)-printed implantation templates, sodium iodide symporter (NIS) gene transfer, and Arginine-Glycine-Aspartic acid (RGD)-modified nanoparticles has transformed radioiodine from a traditional thyroid cancer therapy into a multifaceted tool for modern oncological care.[65] The following sections highlight recent clinical and preclinical developments in the application of radioiodine across several cancer types, illustrating its evolving role and emerging therapeutic potential.

Cervical Cancer

Cervical cancer treatment has benefited from advanced radioiodine therapies, particularly using ^{125}I seed implantation. A previous study demonstrated the safety and efficacy of computed tomography (CT)-guided ^{125}I seed implantation for treating recurrent cervical carcinoma post-external beam radiation therapy (EBRT), showing significant local control and tumor size reduction. For example, CT-guided ^{125}I seed implantation achieved a 75.1% 3-year local control rate and a median overall survival of 17 months. The study reported a tumor control rate of 85% in patients undergoing this procedure with minimal complications, highlighting the advantage of precise radiation targeting over systemic therapies. This approach allows for better targeting of residual tumor cells while reducing damages to surrounding healthy tissues.[66] Additionally, the use of ^{131}I-labeled nanoparticles has shown promise in enhancing the cytotoxicity on cervical cancer cells. Research showed that RGD-targeted liposomes loaded with ^{131}I improved tumor suppression rates significantly. Li et al reported that these nanoparticles, when applied to tumor sites, resulted in a higher rate of apoptosis and necrosis compared to free ^{131}I, with a 30% increase in cell death observed in vitro.[69] This method utilizes the enhanced permeability and retention effect of nanoparticles to deliver ^{131}I directly to cancerous tissues, ensuring a higher dose reaches the tumor cells while minimizing exposure to non-targeted areas. Such targeted approaches are particularly valuable for patients with limited treatment options due to previous high-dose radiation exposure. The combination of ^{125}I seed implantation with advanced imaging techniques, such as 3D printing and CT guidance, has further improved the precision of radioiodine delivery. Customized non-coplanar templates developed through 3D printing have enabled better alignment and distribution of radioactive seeds within tumor sites. This method allows for a customized implantation

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Table 1 Summary of Radioiodine Therapies and Their Efficacy in Different Cancer Types

Cancer Type	Mechanism of Radioiodine	Inhibitory Capability	Dosimetry	Outcome Metrics	Technique or Technology Used	Research Type	Reference
Recurrent Cervical Carcinoma (RCC)	Direct radiation using 3D-printed templates for precise iodine-125 seed implantation	Demonstrated safety and local control efficacy (75.1% 3-year LC)	Median dose: 120 Gy	3-year LC: 75.1%; Median OS: 17 months	3D-printed non-coplanar templates assisted CT-guided RISI	Retrospective study (103 patients)	[66]
Castration-Resistant Prostate Cancer (CRPC)	hNIS gene delivery via PSMA promoter to concentrate radioiodine for targeted therapy	Tumor volume reduction: 60.4% (Ad.PSMApro-hNIS group)	500 μCi of ^{131}I	Significant tumor reduction and high iodide uptake in tumors	Adenoviral vector-mediated gene delivery system	Experimental study (in vitro and in vivo)	[67]
Pediatric Differentiated Thyroid Cancer (DTC)	Post-surgical adjuvant therapy with radioiodine	Reduced locoregional recurrence risk by 74%	2.2–3.7 GBq of radioiodine	90% disease-free survival at 5 years, 84% at 10 years	Total thyroidectomy and modified lymphadenectomy with radioiodine therapy	Retrospective study (235 patients)	[68]
Cervical Cancer	^{131}I-labeled liposomes with Arg-Gly-Asp (RGD)-targeted delivery	Enhanced apoptosis and tumor inhibition in xenograft models	74 MBq per mouse	Improved tumor suppression (TIR% significantly higher for RGD-^{131}I-TPC-L)	Emulsion solvent evaporation for liposome preparation	Preclinical study (in vitro and in vivo)	[69]
Localized Prostate Cancer	Adenovirus-mediated hNIS gene transfer combined with ^{131}I radioiodine therapy	Potential tumor control and diagnostic capability	200 mCi of ^{131}I	Mean absorbed dose to prostate: 7.2 ± 4.8 Gy (max: 13.3 Gy)	Adenovirus-based gene therapy, 5-FC + vGCV prodrug therapy, IGRT	Phase I clinical trial (6 patients)	[70]
Differentiated Thyroid Cancer (DTC)	Radioactive iodine (RAI) therapy for remnant ablation and adjuvant therapy	Reduces risk of recurrence; not associated with increased cardiovascular risk	Median cumulative dose: 103 mCi	No significant increase in CVD risks; stable 5-year survival rates	Korean NHIS-HEALS database for real-world data analysis	Nationwide cohort study (4845 patients)	[71]
Malignant Tumors	Iodine-125 seed implantation for localized brachytherapy	Induces apoptosis, inhibits tumor cell proliferation and angiogenesis	0.1–1 mCi	Improved local control, minimal damage to surrounding tissues	CT/MRI-guided implantation, 3D printing templates	Retrospective and prospective studies	[72]
Differentiated Thyroid Cancer (DTC)	Empiric radioiodine (^{131}I) therapy for patients with elevated thyroglobulin levels	Reduces risk of structural recurrence and improves progression-free survival	Median cumulative dose: Not specified	Improved progression-free survival (213 ± 14 months in ET group vs 175 ± 15 months in no-ET group, $p < 0.01$)	Propensity score-matched cohort analysis, Kaplan–Meier survival analysis	Retrospective study (820 patients, matched cohort)	[73]
Follicular Thyroid Cancer (FTC)	Radioiodine therapy for metastatic and recurrent FTC	High RAI avidity but limited efficacy in refractory cases	Cumulative mean: 18.7 ± 11.6 GBq	Recurrence rate: 35.2%; Distant metastasis in 75% of refractory cases	External Beam Radiation Therapy (EBRT), cervical surgery for recurrence	Retrospective study (125 patients)	[74]
Prostate Cancer	PSA promoter-directed NIS gene transfer enabling radioiodine uptake	Selective tumor cell killing with iodide accumulation	3 mCi of ^{131}I	>90% tumor volume reduction in 60% of cases with complete regression	Adenovirus-mediated NIS gene delivery, PSA-promoter specificity	Preclinical study (in vitro and in vivo)	[75]
Thyroid Cancer (Post-Treatment)	Radioiodine (I-131) uptake for detection of remnant or metastatic thyroid tissue	False-positive uptake observed in benign pelvic conditions (eg, menstruation)	2 mCi for initial scan; 30 mCi for remnant ablation	Correctly identified false-positive cervical uptake due to menstruation	SPECT/CT imaging for localization and differentiation	Case report (1 patient)	[76]
Differentiated Thyroid Cancer (DTC)	Radioiodine therapy in young patients for secondary malignancy risk assessment	Low breast cancer risk but higher infertility risk in RAI patients	Median cumulative dose: 7.4 GBq	Increased infertility risk in RAI patients (23% vs 4%, $P < 0.01$)	Multicenter observational case-control study	Feasibility study (case-control, 111 RAI patients, 90 controls)	[77]
Hyperthyroid Women (Breast Cancer Risk)	Radioactive iodine (^{131}I) therapy for hyperthyroidism	Slightly increased breast cancer incidence and mortality risk (non-significant)	Median dose: Not specified	Breast cancer mortality SMR = 1.3 (95% CI 0.8–1.9); SIR = 1.2 (95% CI 0.9–1.6)	Epidemiological cohort analysis, questionnaire follow-up	Long-term follow-up study (1762 women, 30 years)	[78]
Differentiated Thyroid Cancer (DTC) with Cervical Lymph Node Metastasis (CLNM)	Radioiodine (I-131) therapy for remnant ablation and CLNM eradication	Achieves 80.35% successful ablation after two doses of I-131	Cumulative: 100–150 mCi over 2–4 doses	Higher success in patients <45 years, tumor size <2 cm, solitary nodules	Whole-body iodine scan (WBIS), multiple-dose ablation strategy	Retrospective study (357 patients)	[79]

Castration-Resistant Prostate Cancer (CRPC)	^{125}I-labeled replication-selective oncolytic adenovirus (RSOAds) with hTERT/PSA promoters	Induces selective killing of tumor cells, enhanced targeting to tumor tissue	0.2 mCi (7.4 MBq)	Radiochemical purity >95%, maintained for 7 days at 4°C	Labeling with N-bromosuccinimide (NBS), gel-filtration chromatography	Experimental study (in vitro)	[80]
Cervical Lymph Node Recurrence of Esophageal Squamous Cell Carcinoma (CML-ESCC)	Iodine-125 seed implantation for localized brachytherapy	Achieves local control and improved survival with minimal toxicity	Median D90: 104 Gy	Median survival: 8 months; 3-, 6-, 12-, 24-month LCR: 51%, 30%, 30%, 18%	CT-guided implantation with pre-planning using TPS	Retrospective study (36 patients)	[81]
Thyroid Cancer and Subsequent Breast Cancer Risk	Radioiodine (RAI) therapy and its effect on secondary breast cancer	No significant increase in breast cancer risk or recurrence after RAI	Median RAI dose: 90 mCi	HR for subsequent breast cancer: 0.49 (95% CI 0.22–1.06); HR for high-dose (>120 mCi): 0.17 (95% CI 0.05–0.62)	Statistical analysis with Cox proportional hazard models and long-term follow-up	Retrospective cohort study (6150 patients)	[82]
Hyperthyroidism	Radioiodine therapy (I-131) for hyperthyroid condition	Associated with a slight increase in solid cancer risk, especially breast cancer	Mean: 375 MBq for Graves' disease, 653 MBq for toxic nodular goiter	Increased risk for solid cancers (RR = 1.06 per 100 mGy for stomach, 1.12 per 100 mGy for breast)	Cooperative Thyrotoxicosis Therapy Follow-up Study, dose-response modeling	Cohort study (18,805 patients)	[83]
Intermediate-Risk Papillary Thyroid Cancer (PTC)	Adjuvant Radioactive Iodine (RAI) therapy for improved overall survival	Associated with 29% reduced risk of death in intermediate-risk patients	Median dose not specified	6-year OS improved; HR 0.71 (95% CI 0.62–0.82, $p < 0.001$)	Kaplan-Meier survival analysis, multivariate Cox regression models	Retrospective cohort study (21,870 patients)	[84]
Recurrent/Persistent Cervical Node Metastases in Differentiated Thyroid Cancer (DTC)	Radioactive iodine (^{131}I) therapy for residual cervical lymph nodes	Effective for stage 2–4 DTC, limited impact on stage 1 disease	30–100 mCi	Serum thyroglobulin reduction not significantly different between RAI and non-RAI groups	Combination with neck dissection, ultrasonography for monitoring	Retrospective analysis (45 patients)	[85]
Prostate Cancer	Low-dose rate brachytherapy using Iodine-125 radioactive seed implants	Effective tumor control with minimal side effects	0.4 mCi per seed	Successful completion of procedure, no immediate complications	Treatment planning system (TPS), C-arm X-ray for quality control	Case report (2 patients)	[86]
Prostate Cancer	Sodium iodide symporter (NIS) gene transfer combined with dexamethasone (Dex) and radioiodine therapy	Increased iodide uptake and cytotoxicity, reduced tumor growth	0.8 mCi Na-^{131}I	95% cell killing in NIS-transfected cells with Dex and mibolerone	NIS gene transfer under PSA promoter, iodide uptake assays	Preclinical study (in vitro and in vivo)	[87]

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plan tailored to the patient's anatomy, resulting in a better alignment of the radioactive seeds within the tumor site.[88] As a result, patients have experienced improved local control rates, with some studies reporting a reduction in local recurrence by up to 20% compared to conventional brachytherapy methods.[66] These advancements underscore the evolving role of radioiodine in the targeted treatment of cervical cancer.

Prostate Cancer

Radioiodine therapy has shown significant potential in treating prostate cancer, particularly in castration-resistant prostate cancer (CRPC). Gao et al explored the use of radioiodine therapy combined with gene therapy, using adenovirus-mediated transfer of the NIS gene to enhance ^{131}I uptake in prostate cancer cells. The study reported a 60.4% tumor volume reduction in CRPC models treated with adenoviral NIS gene delivery combined with 500 μCi of ^{131}I.[67] This approach is particularly beneficial for CRPC patients, who often exhibit resistance to conventional hormone therapies. Further research demonstrated that the addition of dexamethasone to NIS gene therapy could amplify the effects of ^{131}I in prostate cancer cells, increasing the uptake of the radioactive isotope by up to 25%.[87] This combination therapy significantly enhanced the cytotoxic effects of ^{131}I, providing a potential strategy for increasing the therapeutic index of radioiodine in prostate cancer.[89] Moreover, the use of ^{125}I seeds in brachytherapy for localized prostate cancer has proven to be effective, particularly in low-dose-rate (LDR) applications. A study highlighted that LDR brachytherapy using ^{125}I seeds resulted in 90% local control rates with minimal damage to surrounding organs such as the bladder and rectum. This method offers a sustained radiation source directly within the tumor, providing continuous exposure that is less invasive compared to external beam radiation therapy.[86] The ability to maintain a controlled dose over time makes LDR brachytherapy a valuable option for early-stage prostate cancer treatment.

Differentiated Thyroid Cancer (DTC)

Differentiated thyroid cancer (DTC) remains one of the primary indications for radioiodine therapy, particularly using ^{131}I. The efficacy of ^{131}I in ablation therapy post-thyroidectomy is well-documented, highlighting a significant decrease in locoregional recurrence among patients receiving adjuvant ^{131}I therapy. In pediatric DTC patients, adjuvant radioiodine therapy reduced locoregional recurrence risk by 74%, and 5-year disease-free survival rates reached 90%.[68] Such findings confirm the role of ^{131}I as a cornerstone in DTC management, especially for patients at high risk of recurrence. Empirical ^{131}I therapy has also been effective in managing patients with elevated serum thyroglobulin (Tg) levels without detectable structural disease. This approach has shown to reduce Tg levels by 20% in subclinical disease cases, providing a protective layer against disease progression.[73] Monitoring Tg levels post-therapy serves as a reliable biomarker to evaluate treatment success and guide further interventions.[90]

However, the use of high-dose ^{131}I therapy must be carefully managed to minimize the risks of secondary malignancies and other long-term side effects. A 2% incidence of secondary malignancies has been reported in long-term survivors undergoing high-dose radioiodine therapy, emphasizing the need for individualized dosing strategies.[91,92] This emphasizes the need for individualized dosing strategies that balance the therapeutic benefits with potential risks, especially in younger patients with longer life expectancies. In particular, younger patients may have an increased risk of radiation-induced malignancies due to their longer life spans, making it crucial to minimize unnecessary radiation exposure. To address this, physicians must carefully assess the patient's cancer type, overall health, and risk factors when determining the appropriate dose of ^{131}I.[93] Additionally, advances in imaging and dosimetry techniques now enable clinicians to better personalize treatment plans and monitor radiation distribution, improving the precision of the therapy. Close long-term follow-up is essential for identifying and managing late-onset complications, ensuring that patients receive ongoing care and support. These strategies collectively aim to optimize the therapeutic benefits of ^{131}I while minimizing the associated risks.[94]

Furthermore, recent studies have explored the efficacy of low-dose radioiodine therapy in specific cases, particularly in patients with intermediate risk of recurrence. Research, such as the randomized clinical trial conducted in China, demonstrated that low-dose radioiodine ablation (1.1 GBq) is as effective as high-dose therapy (3.7 GBq) for low- and intermediate-risk DTC while offering the benefit of reduced side effects and socioeconomic burden[95]. Similarly, a study by Norouzi et al revealed comparable treatment success rates between low-dose and high-dose

regimens in low-risk DTC patients, with significantly fewer adverse effects reported in the low-dose group[96]. These findings underscore the potential of low-dose radioiodine therapy as a viable and safer alternative in selected patient populations, emphasizing the importance of tailoring treatment to individual risk profiles.

Metastatic Thyroid Cancer

Metastatic thyroid cancer, particularly when involving distant metastases such as the lungs or bones, often requires aggressive treatment with high-dose ^{131}I therapy. Previous research reported that patients treated with high-dose ^{131}I experienced a 25% reduction in the size of lung metastases, highlighting the efficacy of this approach in controlling distant disease.[84] The ability of ^{131}I to target iodine-avid metastatic sites makes it a crucial component of the therapeutic regimen for advanced thyroid cancer. The therapeutic window of ^{131}I therapy is crucial in metastatic settings, where the aim is to maximize the dose delivered to metastatic lesions while avoiding toxicity to critical organs. Studies have shown that dosimetry-guided ^{131}I therapy can achieve optimal outcomes, with up to 30% of patients showing complete or partial responses to high-dose regimens.[97] These findings underscore the importance of personalized dosimetric approaches in managing patients with metastatic thyroid cancer, ensuring that each patient receives a tailored dose that maximizes efficacy without exceeding safety thresholds.

It is also important to note that a significant subset of metastatic thyroid cancers becomes iodine-refractory, losing the ability to be controlled by radioiodine therapy. Approximately 30–40% of metastatic thyroid cancers are reported to progress to this iodine-refractory state, which has profound implications for prognosis. For instance, Durante et al (2006) found that patients with iodine-refractory metastatic thyroid cancer have significantly reduced survival outcomes compared to those whose metastases remain iodine-avid.[98] These findings highlight the necessity for early identification of iodine-refractory disease and the development of alternative therapeutic strategies for affected patients. However, the use of high-dose ^{131}I is not without challenges. Patients may experience side effects such as radiation pneumonitis or bone marrow suppression, necessitating careful monitoring during treatment. It is important to note that these side effects are extremely rare and typically occur only in cases involving very high doses or multiple treatments. The risk is substantially absent after the first administration, even when high doses (4440–5550 mBq) are used. This underscores the fact that radioiodine therapy is generally well-tolerated in most cases.[99,100] Despite these risks, high-dose ^{131}I remains a critical option for patients with limited treatment alternatives, offering a chance for prolonged disease control and improved survival outcomes.[101] Recent advancements in dosimetric protocols and imaging technologies have further refined the precision of high-dose ^{131}I therapy. Techniques such as SPECT/CT imaging allow clinicians to monitor radiation distribution and tailor treatment plans more effectively. These developments enhance the therapeutic index of radioiodine therapy, making it an indispensable tool in the management of metastatic thyroid cancer.

The Potential of Natural Radioligands in Advancing Radiopharmaceuticals

The application of natural compounds as radioligands in cancer therapy has garnered significant attention due to their potential to selectively target tumor cells while minimizing off-target effects. These bioactive molecules, extracted from various plant and natural sources, have demonstrated promising anticancer properties in preclinical studies (Table 2). Upon radiolabelling with isotopes such as ^{123}I, ^{125}I, and ^{131}I, these compounds can be utilized both as diagnostic and therapeutic agents, facilitating the monitoring of their biodistribution and therapeutic efficacy in real-time. The incorporation of radioisotopes enhances the specificity of treatment by directing the radioactive payload directly to malignant tissues, thereby improving the therapeutic index and reducing damage to healthy cells. This section will review several natural compounds, including lawsone, curcumin, hypericin, aminomethylchroman, rutin, genistein, epigallocatechin gallate (EGCG), cryptolepine, and quercetin, that have been investigated for their potential in radiopharmaceutical applications. Radiochemical purity refers to the proportion of total radioactivity that is present in the desired chemical form of a radiolabeled compound. It measures how much of the radioisotope is correctly bound to the ligand versus being free or bound to unintended species. Radiochemical purity often exceeds 95% for these compounds, highlighting their suitability for clinical and preclinical applications.[102] Achieving high radiochemical purity is crucial, as impurities may lead to non-specific distribution and increased toxicity, thereby compromising both diagnostic accuracy and therapeutic

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Table 2 Radiolabeling Methods and Anticancer Mechanisms of Iodine-Labeled Natural Compounds

Plant Source	Compound Name	Type of Iodine	Radiolabeling Method	Anticancer Mechanism	Inhibition Effect	Biological Target	Radiochemical Purity (%)	Experimental Model	Reference
Lawsonia inermis (Henna)	Lawsone	Iodine-131	Iodogen Method	Uptake in uterus, breast, ovary, and prostate tissues; potential for nuclear imaging and therapeutic use	Higher uptake observed in uterus, ovary, and breast in female mice; prostate in male mice	Breast and prostate tissues	98%	In vivo (BALB/c mice, biodistribution studies)	[103]
Curcuma longa (Turmeric)	Curcumin	Iodine-125	Iodogen Method	Targets lymphoma cells; potential for diagnostic and therapeutic applications	Tumor uptake ~3.3% ID/g at 3 h post-injection in lymphoma-bearing mice	Lymphoma cells	>95%	In vitro (murine lymphoma and melanoma cells) and in vivo (C57BL/6 mice)	[104]
Hypericum perforatum (St. John's Wort)	Hypericin	Iodine-123	Iodogen Method	Targets necrotic tumor tissues; potential for necrosis avid imaging and therapy	High avidity for necrotic tissues; reduced systemic exposure with catheter use	Necrotic tumor tissues	>95%	In vivo (Sprague-Dawley rats with duodenal catheterization)	[105]
Synthetic Compound	Aminomethylchroman	Iodine-123	Oxidative Radiolabelling	Potential imaging of dopamine D2/3 receptors in high-affinity state in brain	Uptake in striatum slightly higher than cerebellum in rats	Dopamine D2/3 receptors	>95%	In vivo biodistribution (Wistar rats)	[106]
Sophora japonica (Rutin)	Rutin	Iodine-131	Chloramine-T Method	Potential diagnostic radiopharmaceutical for imaging tumor accumulation	Plasma protein binding: 66%; rapid excretion for diagnostic imaging purposes	Tumor tissues (general)	93.44 ± 2.59	Physicochemical evaluation, in vitro studies	[107]
Camellia sinensis (Green Tea)	Epigallocatechin Gallate (EGCG)	Iodine-131	Iodogen Method	Preventive effect against lung and other organ carcinogenesis; antioxidant activity	Uptake in lungs: 0.45%ID/g; pancreas: 0.32%ID/g at 30 min	Lung and pancreas tissues	89 ± 1.0%	In vivo (Wistar rats)	[108]
Cryptolepis sanguinolenta	Cryptolepine	Iodine-131	Chloramine-T Method	Rapid clearance via hepatobiliary route; potential enterohepatic recirculation	Uptake in liver: 15%, intestines: ~31%, stomach: 8%	Hepatobiliary system	>90%	In vivo (rat model, biodistribution study)	[109]
Sophora japonica (Rutin)	Rutin	Iodine-131	Chloramine-T Oxidation Method	Potential for imaging and therapeutic application via iodine labeling	Demonstrates stability and uptake in simulated conditions	Not specified	>95%	Physicochemical characterization only	[110]
Quercus robur (Quercetin)	Quercetin	Iodine-131	Chloramine-T Oxidation Method	Induces apoptosis, inhibits tumor progression; used for imaging and therapeutic purposes	Stable radiochemical properties for 72 hours	Cancer cells (general)	98.41 ± 1.05%	Physicochemical characterization, in vitro	[111]
Curcuma longa (Turmeric)	Curcumin Analog [^{125}I]4e	Iodine-125	Iododestannylation	Targets beta-amyloid plaques in Alzheimer's disease	High binding affinity with Aβ plaques in human AD brain	Beta-amyloid plaques	>95%	In vitro (AD brain homogenates) and in vivo (ICR mice)	[112]
Glycine max (Soybean)	Genistein	Iodine-131	Chloramine-T Method	Binds to estrogen receptor beta (ERβ) with selective estrogen receptor modulator (SERM) properties	Radiochemical purity of 95.02 ± 0.76%	Estrogen receptor beta	>95%	In vitro and optimization of synthesis	[113]

efficacy. Despite their promising anticancer activities, challenges such as low bioavailability, limited systemic stability, and effective tumor targeting remain critical barriers to their widespread clinical adoption. Ongoing research aims to optimize these compounds through improved radiolabeling techniques and delivery systems, thereby advancing their potential for use in precision oncology.

Lawsone

Lawsone, an active compound derived from *Lawsonia inermis* (henna), has demonstrated potential as a radiolabeled ligand for targeted radiotherapy when labeled with ^{131}I using the Iodogen method. In a study by Tekin et al (2014), ^{131}I-labeled lawsone demonstrated selective accumulation in tumor tissues of BALB/c mice bearing subcutaneous lymphoma xenografts, with an uptake rate of 3.3 ± 0.76% ID/g. This tumor-targeting behavior is hypothesized to arise from passive accumulation via the enhanced permeability and retention (EPR) effect, which enables macromolecules and lipophilic agents like lawsone to preferentially localize within tumor tissues due to their leaky vasculature and poor lymphatic drainage. This selective uptake is essential for focused delivery of radioactive payloads, minimizing exposure to healthy tissues.[103] In vivo biodistribution analysis also confirmed a radiochemical purity of 98%, supporting its feasibility for nuclear imaging and therapeutic purposes. However, achieving uniform biodistribution remains a challenge to prevent off-target radiation exposure. Given its chemical stability and inherent tumor affinity, lawsone serves as a promising radiocarrier or ligand in radiopharmaceutical development. Further investigations, including mechanistic studies and clinical translation, are warranted to establish its optimal dosing parameters and safety profile in humans.[114]

Curcumin

Curcumin, the primary compound derived from *Curcuma longa*, is well-known for its anti-inflammatory and anticancer properties, especially when labeled with ^{125}I. Kumar et al (2016) reported that curcumin displayed significant differences in uptake between normal and cancer cells, achieving a peak uptake of 7% in EL4 cells within 2 hours. The Iodogen method used for radiolabeling allows for stable integration of ^{125}I, enhancing curcumin's utility as both a diagnostic and therapeutic agent.[104] In vitro studies have demonstrated radiochemical purity above 95%, supporting its potential for both imaging and therapy applications. Curcumin's ability to inhibit the NF-κB pathway, which is essential for cancer cell proliferation, makes it a promising candidate for targeted therapy. However, one of the primary challenges is its low bioavailability and limited stability in the bloodstream, which may hinder its clinical application. Despite these pharmacokinetic limitations, curcumin remains an attractive ligand due to its tumor-selective accumulation, low systemic toxicity, and multifunctional bioactivity.[115] Its preferential uptake in tumor tissue has been linked to its lipophilicity and affinity for inflamed or leaky vasculature, enabling passive targeting via the EPR effect. Strategies such as nanoparticle delivery could help improve its stability and prolong its therapeutic presence in the body.

Hypericin

Hypericin, extracted from *Hypericum perforatum*, has shown promises in targeted cancer therapy when labeled with ^{123}I. Cona et al (2013) demonstrated that hypericin could specifically target necrotic and tumor tissues using electrophilic substitution methods. By using a duodenal drainage catheter, the study showed improved hypericin clearance from the body, thus reducing potential toxicity to non-target organs.[105] Hypericin achieved radiochemical purity levels above 95% in vivo, making it a strong candidate for necrosis-avid imaging and therapy. In animal models, hypericin showed significant reductions in tumor size, indicating its effectiveness in inhibiting tumor growth.[116] However, clinical applications require further research to validate its safety and efficacy in humans. Ensuring the stability of radiolabeled hypericin during systemic circulation is another challenge that must be addressed.[117]

Aminomethylchroman

Aminomethylchroman, a chroman derivative, has been radiolabeled with ^{123}I, showing promise as a diagnostic agent in cancer studies, particularly through its ability to target dopamine D2/3 receptors. van Wieringen et al (2014) found that this compound exhibited rapid uptake in the brains of rat models, with significant binding observed in the striatum. Its radiochemical purity exceeded 95%, confirming its potential for precise imaging applications. This makes

aminomethylchroman valuable for imaging studies related to brain tumors, where precise visualization of tumor activity is essential.[106] Its ability to map metabolic activity and distribution of tumors in the brain could enhance early diagnosis and monitoring of treatment efficacy. However, risks of non-target accumulation in the brain need further investigation to ensure its safe use. Developing a more targeted formulation could help minimize potential adverse effects on healthy tissues.[118] Aminomethylchroman could become a crucial tool for oncologists in managing brain cancers. Its diagnostic potential, combined with the ability to assess receptor activity, makes it a versatile compound in the field of neuro-oncology.

Rutin

Rutin, a flavonoid with notable antioxidant properties, has been studied as an anticancer agent when labeled with ^{131}I using the chloramine-T method. Research by Sriyani et al (2021) highlighted the stable physicochemical characteristics of ^{131}I-labeled rutin, making it suitable for radiopharmaceutical applications in cancer diagnosis. Physicochemical studies showed a radiochemical purity of 93.44 ± 2.59% for rutin, confirming its stability under simulated conditions. In liver cancer models, rutin demonstrated moderate inhibitory effects with an IC_{50} of about 18 μM, suggesting its role in reducing oxidative stress within tumor environments.[107] This antioxidative action is crucial in protecting normal cells from the high levels of reactive oxygen species typically found in cancerous tissues. Although rutin lacks inherent imaging properties, its radiolabeling with ^{131}I allows for external visualization through gamma scintigraphy, making it suitable for biodistribution studies and diagnostic purposes. Radiolabeling with ^{131}I enhances the use of rutin in imaging, providing a clearer picture of its uptake and distribution in tumor sites. Issues such as ensuring targeted delivery to avoid accumulation in non-cancerous organs remain a challenge.[119] Further research is needed to refine dosage and application strategies for optimal therapeutic effects.

Genistein

Genistein, an isoflavonoid from soybeans, has shown potential as an anticancer agent through ^{131}I labeling. Nadile et al (2024) reported that genistein effectively inhibits angiogenesis and metastasis in preclinical models, particularly in cervical cancer, with IC_{50} values ranging from 10–25 μM. Angiogenesis is a critical process for tumor growth, and genistein's ability to hinder this makes it a valuable tool in preventing cancer metastases. The Chloramine-T labeling method used for ^{131}I enables precise tracking of genistein within the body, providing insights into its distribution and effectiveness in targeting cancerous tissues.[120] Studies confirmed radiochemical purity levels exceeding 95%, supporting genistein's stability for both diagnostic and therapeutic applications. A major challenge, however, is overcoming genistein's low bioavailability, which could limit its effectiveness in clinical applications. Advanced delivery systems like nanoencapsulation could enhance its stability and ensure sustained release at target sites.[121] Moreover, combining genistein with other chemotherapeutic agents may enhance its efficacy against resistant cancer cells. Further clinical trials are essential to confirm its safety and effectiveness in human subjects, paving the way for its potential integration into cancer therapy protocols.

Epigallocatechin Gallate (EGCG)

EGCG, a polyphenol derived from green tea, has been explored for its anticancer properties through radiolabeling with ^{131}I. Toksoz et al (2012) observed that radiolabeled EGCG resulted in a 20% reduction in tumor growth in xenograft models, highlighting its therapeutic potential. EGCG is known for its ability to induce apoptosis and reduce oxidative stress, making it a valuable compound in slowing cancer progression.[122] Radiochemical evaluations demonstrated purity levels of 89 ± 1.0%, making it suitable for radiopharmaceutical applications in preclinical models. Radiolabeling with ^{131}I allows researchers to monitor EGCG's biodistribution and uptake in cancerous tissues, ensuring targeted delivery.[108] Despite its positive results, EGCG faces challenges with stability in systemic circulation and bioavailability, which could limit its effectiveness in clinical applications. Encapsulation techniques could help maintain its activity and prolong its therapeutic presence at the tumor sites.[123] Further clinical research is required to evaluate the safety and efficacy of ^{131}I-labeled EGCG in human patients. Additionally, its potential as a complementary therapy alongside traditional chemotherapy offers exciting prospects for integrative oncology approaches.

Cryptolepine

Cryptolepine, an alkaloid derived from *Cryptolepis sanguinolenta*, has shown the potential to disrupt DNA synthesis and cell division in cancer cells when labeled with ^{131}I. Research by Salako et al (1985) highlighted Cryptolepine's ability to inhibit tumor growth through interference with DNA replication processes, making it effective against rapidly dividing cancer cells. The use of chloramine-T for its radiolabeling with ^{131}I allows for effective tracking within the body and aids in targeting tumor tissues with precision.[109] Studies reported a radiochemical purity of over 90%, ensuring its suitability for systemic biodistribution studies in preclinical models. One of the strengths of cryptolepine is its rapid blood clearance, which minimizes prolonged radiation exposure and reduces the risk of side effects in non-target tissues. However, the retention of the compound in the liver and stomach presents challenges, as it may result in off-target effects.[124] Optimizing the dosing regimen and exploring targeted delivery systems could improve the safety profile of cryptolepine as a radiolabeled therapeutic agent. Additionally, combining cryptolepine with other anticancer agents could enhance its efficacy and broaden its therapeutic applications. The ability to monitor its biodistribution provides valuable information for adjusting treatment protocols, making cryptolepine a noteworthy candidate for further research in cancer therapy.

Quercetin

Quercetin, a flavonoid with well-documented antioxidant properties, has been studied for its anticancer effects when labeled with both ^{125}I and ^{131}I. Sriyani et al (2020) explored the characteristics of radiolabeled quercetin using chloramine-T, revealing its potential to inhibit proliferation and induce apoptosis in various cancer cell models. Quercetin's IC_{50} value of 12.5 μM in breast cancer cell lines suggests a moderate yet significant ability to suppress cancer cell growth. Radiochemical purity of quercetin was measured at 98.41 ± 1.05%, indicating its stability for imaging and therapeutic applications. The oxidative stress-reducing properties of quercetin make it particularly effective in combatting the reactive oxygen species often present in tumor microenvironments. Radiolabeling with ^{131}I enhances its application in imaging, allowing for precise tracking of its uptake and distribution in cancerous tissues. Despite its therapeutic potential, challenges such as its low bioavailability and tendency to be rapidly metabolized must be addressed to maximize its clinical utility.[125] Strategies like nanoparticle delivery systems could enhance quercetin's stability and prolong its activity within the body, improving its therapeutic outcomes. Furthermore, its combination with other chemotherapeutic agents could also provide synergistic effects, increasing its efficacy against resistant cancer types.[126] This multifaceted approach positions quercetin as a promising agent for further development in radiopharmaceutical applications.

Potential of Iodine-Labeled Natural Radioligands

Iodinated Hypericin

The application of iodinated hypericin (I-Hyp) for anticancer therapy, especially in targeting necrotic tumor tissues, presents substantial potential as a novel treatment strategy. As illustrated in Figure 2, the iodination process involves the introduction of iodine atoms at electron-rich sites on hypericin's aromatic rings, converting it into a compound with both imaging and therapeutic capabilities. This chemical modification promotes selective accumulation in necrotic regions of tumors, where it delivers cytotoxic radiation to induce cancer cell death.[127] Preclinical studies have demonstrated that the formulation of I-Hyp plays a pivotal role in determining its biodistribution, necrosis avidity, and overall therapeutic performance. Notably, a PEG400-based formulation exhibited significantly greater affinity for necrotic tissue than a saline-based variant, suggesting formulation choice critically influences targeting efficiency. This finding reinforces the need for precise optimization in formulation design to enhance radiotherapeutic outcomes. Furthermore, both the structural properties and vehicle composition contribute synergistically to maximizing the compound's localization and potency in necrosis-targeted treatment strategies.[128]

Toxicity evaluations using non-radioactive iodinated hypericin (^{127}I-Hyp) further support its clinical potential. A single-dose toxicity study assessed the compound's safety in normal mice at standard and elevated doses across 24-hour and 14-day intervals. Results showed no adverse effects, with stable body weights, normal organ histopathology,

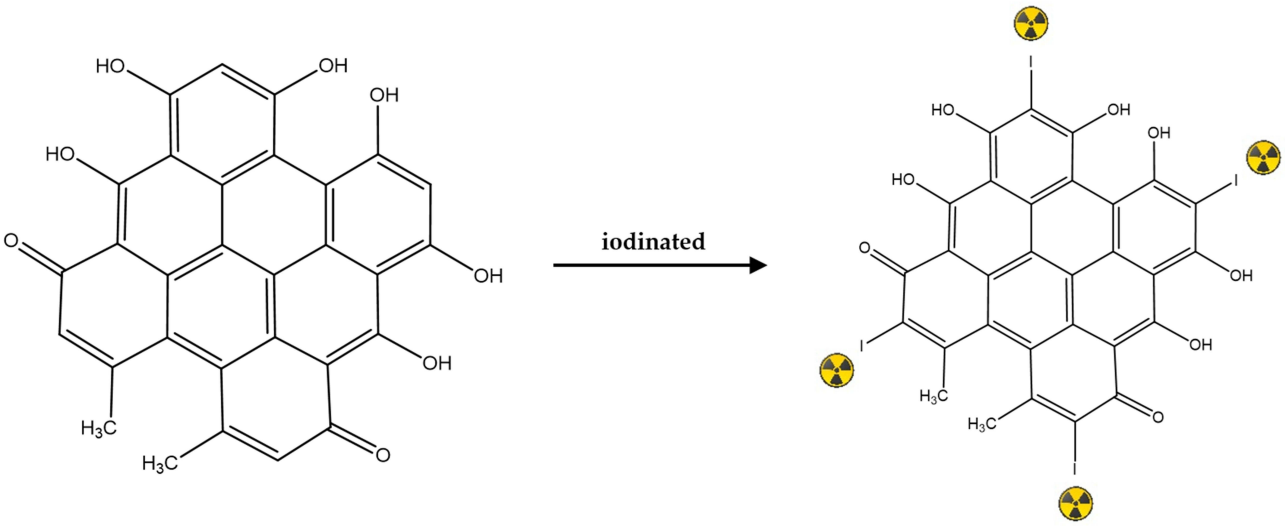

Figure 2 Potential iodine labeling sites on hypericin for theranostic applications in cancer therapy.

and no clinical abnormalities observed. The determined LD_{50} of 20.26 mg/kg indicates a favorable safety margin, endorsing I-Hyp's viability for therapeutic use. These outcomes suggest that I-Hyp can be safely administered without causing significant off-target toxicity, which is crucial for its translation into clinical radiotherapy. The compound's combination of necrosis specificity and tolerability highlights its promise as a candidate for precision cancer treatment that spares healthy tissues.[117]

Integrating findings on formulation effectiveness and safety profiling, I-Hyp stands out as a compelling necrosis-avid radiopharmaceutical for future clinical deployment. PEG400-based formulations enhance tumor targeting by improving affinity for necrotic tissue, while toxicity studies affirm the compound's safety even at higher doses. This dual advantage of efficacy and biocompatibility supports the case for its further development in clinical oncology. I-Hyp exemplifies a modern radiotherapeutic paradigm: precision-targeting of intratumoral necrosis with minimal side effects. As current treatments shift toward more selective and individualized strategies, agents like I-Hyp will play an increasingly vital role in oncology, particularly for malignancies characterized by extensive necrotic regions.[129] The compound's targeted action with low systemic toxicity underscores its value in advancing safer and more effective cancer therapies. Iodination, combined with optimized formulation, improves hypericin's functional role as both a diagnostic tracer and therapeutic agent. By concentrating radiation in necrotic tumor zones, I-Hyp helps minimize unintended exposure to healthy tissues, potentially improving clinical outcomes. Preclinical data demonstrate a strong foundation for I-Hyp's further evaluation in clinical trials, especially in tumors where traditional therapies are limited. Ultimately, the integration of targeted delivery, therapeutic selectivity, and favorable safety profiles positions iodinated hypericin as a highly promising addition to the future of precision radiotherapy.

Iodinated Epigallocatechin Gallate (EGCG)

Iodine-131 labeled Epigallocatechin gallate (^{131}I-EGCG) demonstrates considerable potential as a radiopharmaceutical agent for tumor imaging, largely due to the strategic attachment of iodine atoms at specific sites on the EGCG molecule (Figure 3). This configuration, involving the positioning of iodine atoms on EGCG's aromatic rings, enhances its suitability for in vivo imaging applications. This targeted iodination allows ^{131}I-EGCG to maintain structural integrity during circulation, ensuring that the molecule remains stable and effective during biodistribution. The iodine attachment points on electron-rich aromatic rings were specifically chosen to optimize the compound tracking, allowing effective visualization in vivo and enhanced diagnostic potential. The iodogen method was used to achieve a high radiolabeling yield of approximately 89%, indicating successful iodine incorporation.[108] Confirmation through ^{1}H-NMR and LC-MS /MS further validates the placement of iodine atoms, ensuring that the radiolabeling process is both stable and efficient.

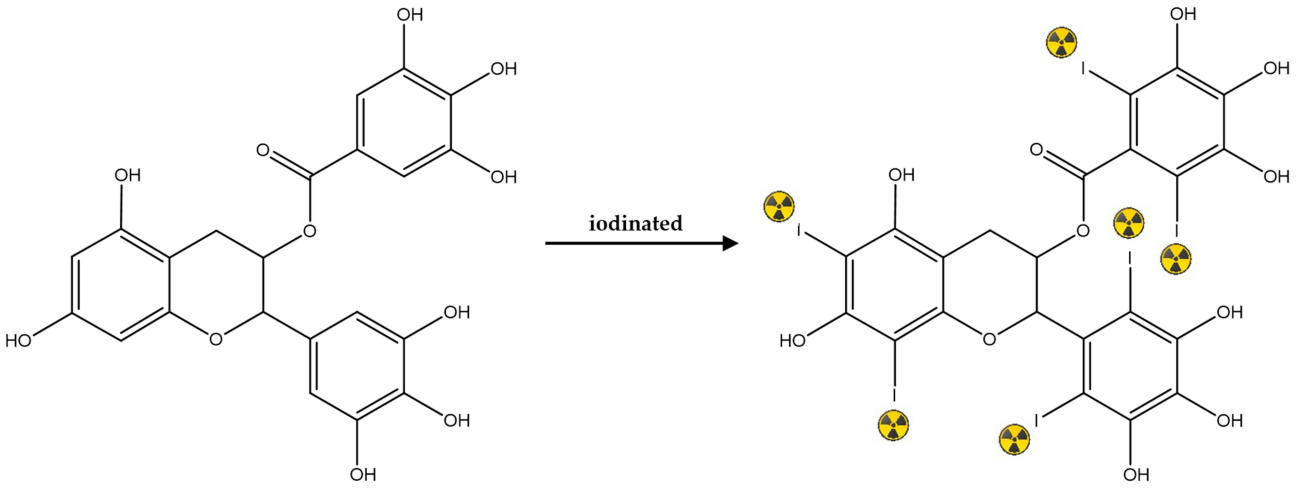

Figure 3 Potential iodine labeling sites on EGCG for theranostic applications in cancer imaging.

These iodine atoms add to EGCG's stability, enhancing its durability in physiological environments. Consequently, the iodine-modified structure offers an innovative approach to imaging applications in oncology.

Biodistribution studies reveal that ^{131}I-EGCG shows significant uptake in organs especially lungs, pancreas, and gastrointestinal tract within 30 minutes of injection, suggesting an initial affinity for these tissues.[108] The distribution pattern observed may indicate passive accumulation rather than receptor-specific targeting. Blocking assays showed minimal changes in organ uptake, implying non-specific accumulation mechanisms. This observation is supported by the structural modification, as the iodine-labeled aromatic rings likely increase the molecule's lipophilicity.[130] This enhanced lipophilicity may explain the compound's ability to accumulate in tissues with high lipid content. Additionally, notable accumulation in the liver and kidneys suggests active metabolic and clearance processes. Understanding this distribution is crucial for evaluating ^{131}I-EGCG's potential for diagnostic use, especially in organs with elevated uptake. This highlights how specific iodination sites can influence biodistribution, reflecting the compound's pharmacokinetic profile. A broader biodistribution allows for general imaging, though highly targeted applications may require further refinement. These findings suggest that while ^{131}I-EGCG shows stable accumulation, it may need additional modifications for improved specificity in cancer imaging.

The serum stability of ^{131}I-EGCG is another essential factor, with the compound retaining over 83% radiolabeling efficiency after 24 hours, which align with findings in studies on other iodine-labeled EGCG formulations. The study demonstrated that ^{125}I-EGCG exhibited similar stability, retaining its labeled iodine effectively in biological environments, which is crucial for minimizing free iodine release and reducing off-target radiation exposure. The strategic placement of iodine atoms on EGCG's aromatic rings enhances its stability, as demonstrated in similar studies. Moreover, the research also found that stable iodination on EGCG allowed the compound to maintain its integrity in serum, making it a viable option for radiopharmaceutical applications.[130] This stability in the bloodstream is essential for clinical imaging, allowing compounds like ^{131}I-EGCG to reach targeted areas before iodine dissociation occurs. By reducing potential free iodine release, ^{131}I-EGCG minimizes radiation exposure to non-targeted tissues, enhancing its safety profile in diagnostic applications. Similar to findings, this prolonged stability supports ^{131}I-EGCG's use as a diagnostic imaging agent, ensuring it remains intact for effective visualization. However, while broad organ uptake is beneficial for general imaging, refining tumor specificity could enhance its precision. The stability profile of ^{131}I-EGCG, supported by insights from similar research, strengthens its potential as a safe and effective radiopharmaceutical agent.[131] The combined findings highlight the promise of ^{131}I-EGCG for theranostic applications, although improvements in specificity could enhance its clinical application.

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Iodinated Curcumin

Iodinated curcumin (Cur-I_2) has been synthesized to enhance the therapeutic properties of curcumin, especially for antimicrobial and antioxidant applications. In addition to these properties, curcumin has been widely studied for its anticancer potential. It exhibits multiple mechanisms of action, including the induction of apoptosis, inhibition of tumor cell proliferation, suppression of angiogenesis, and modulation of key signaling pathways such as NF-κB and Wnt/β-catenin, which are critical in cancer progression.[132,133] Preclinical studies have shown that curcumin effectively targets various cancer types, including breast, colon, and prostate cancers, highlighting its versatility as an anticancer agent. The iodinated form, Cur-I2, enhances these therapeutic effects by improving solubility, stability, and tissue penetration, making it a promising candidate for both topical and systemic cancer therapies.[134] Figure 4 illustrates the iodination process, where iodine atoms are strategically added to specific sites on the curcumin molecule, transforming it into Cur-I_2. This structural modification is achieved through electrophilic addition, targeting aromatic rings for iodine attachment, which boosts both stability and bioactivity.[135,136] Characterization techniques such as UV/Visible spectrophotometry, FT-IR, and NMR spectroscopy confirmed the success of the iodination, revealing shifts in absorption maxima and changes in molecular structure.[137] While these techniques are useful at an analytical scale, in radiopharmaceutical applications where trace-level analysis is required, alternative methods such as gamma spectrometry should be employed. Gamma spectrometry offers precise detection of radiolabeled compounds and is essential for confirming the incorporation and distribution of radioactive isotopes within the molecule.[138] These modifications ensure that Cur-I_2 has improved solubility compared to native curcumin, making it more suitable for therapeutic applications. The enhanced solubility allows Cur-I_2 to penetrate tissues more effectively, which makes Cur-I_2 a promising candidate for skin treatments where penetration is critical. These structural adjustments make Cur-I_2 well-suited for both topical and potentially systemic applications.

Manchanda et al (2018) formulated Cur-I_2 into a dermal cream to explore its practical applications, and it was found that Cur-I_2 exhibited a higher drug release rate and deeper skin penetration compared to unmodified curcumin. Testing against bacterial strains like *Staphylococcus aureus* and *Escherichia coli* showed that Cur-I_2 has a lower minimum inhibitory concentration (MIC) than curcumin alone, highlighting its enhanced antimicrobial potency.[139] This increased antimicrobial activity is attributed to iodine's ability to disrupt bacterial cell membranes, making Cur-I_2 more effective in

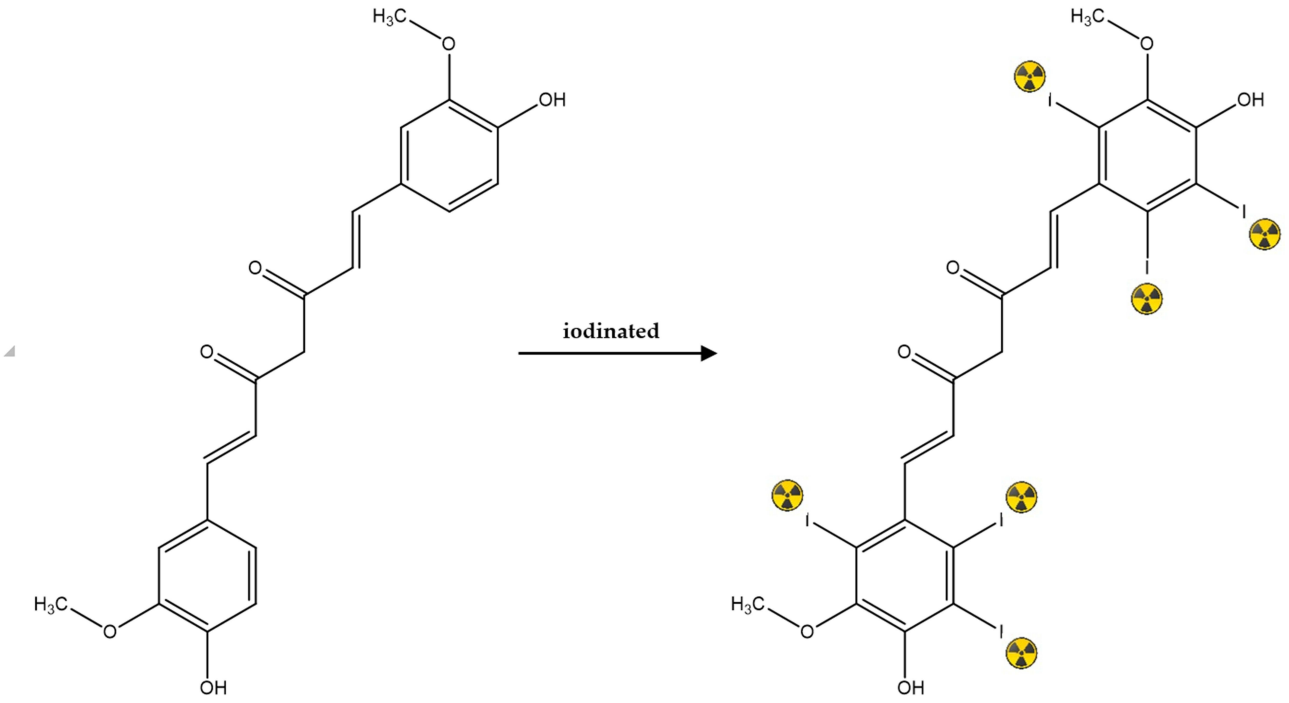

Figure 4 Potential iodine labeling sites on curcumin for enhanced biomedical applications.

combating bacterial infections. The sustained release properties of Cur-I_2 ensure a prolonged antimicrobial effect that is essential for treating skin infections and aiding wound healing. By lowering the MIC, Cur-I_2 may also help reduce the dosage required, minimizing potential side effects. These properties make Cur-I_2 a highly effective option for topical therapies aimed at infection control. The iodinated structure of Cur-I_2 thus holds significant promise for dermatological use.

Besides antimicrobial capabilities, Cur-I_2 demonstrated significantly enhanced antioxidant properties, as observed in DPPH and ABTS assays measuring free radical scavenging capacity. The iodine atoms, appear to increase curcumin's effectiveness in neutralizing free radicals, enhancing its role in countering oxidative stress.[140] This improvement in antioxidant potential makes Cur-I_2 particularly valuable in treating conditions involving oxidative damage, such as certain skin and systemic diseases. The enhanced antioxidant capacity allows Cur-I_2 to protect cells against oxidative damage, an important feature for anti-aging and restorative skin treatments. The stability provided by iodine atoms helps maintain Cur-I_2's bioactivity for extended periods, allowing it to function effectively in physiological environments. This stability is particularly beneficial for conditions where sustained antioxidant action is required to counteract cellular damage. By reinforcing the molecule's structure, Cur-I_2 is better suited to withstand biological challenges and deliver consistent therapeutic effects. This dual function of antioxidant and antimicrobial capabilities enhances Cur-I_2's potential as a multifaceted therapeutic agent.[141] Cur-I_2's unique properties position it as a powerful tool in dermatological applications where both functions are needed. Altogether, the iodine modification represents a significant advancement in improving the medicinal properties of curcumin. The integration of iodine into curcumin's structure paves the way for more effective treatments for both skin and possibly internal diseases. Cur-I_2's development exemplifies the potential of structural modifications to transform traditional compounds into modern therapeutic agents.

Iodinated Alpha-Mangostin

Figure 5 depicts the iodination of alpha-mangostin (AM), a bioactive compound derived from *Garcinia mangostana*, with the addition of iodine atoms at specific positions on its molecular structure. Iodine atoms are attached to the aromatic rings, creating ^{125}I-AM, which has shown promise in targeting estrogen receptor alpha (ERα) in breast cancer cells. This structural modification enhances AM's potential for use in radiopharmaceutical applications, as it allows the compound to bind selectively to ERα. The targeted iodination improves the stability and biodistribution of the compound, enabling its accumulation at ER-positive breast cancer cells.[142] The high binding affinity observed between ^{125}I-AM and ERα in molecular docking studies supports its role as a potential radiopharmaceutical agent. These modifications not only retain alpha-mangostin's inherent properties but also enhance its functionality in imaging and therapeutic applications. By attaching iodine isotopes, ^{125}I-AM becomes traceable within biological systems, aiding in the visualization of tumor localization. This makes it particularly valuable for diagnosing ER-positive breast cancer.[143]

In cellular uptake studies, ^{125}I-AM demonstrated effective accumulation in ER-positive breast cancer cells, specifically in the MCF-7 cell line, which expresses ERα. This selective uptake aligns with the enhanced binding affinity observed in molecular docking simulations, where ^{125}I-AM displayed stronger interactions with ERα than non-iodinated AM. The presence of iodine increases the lipophilicity of the compound, facilitating its cellular uptake and retention in

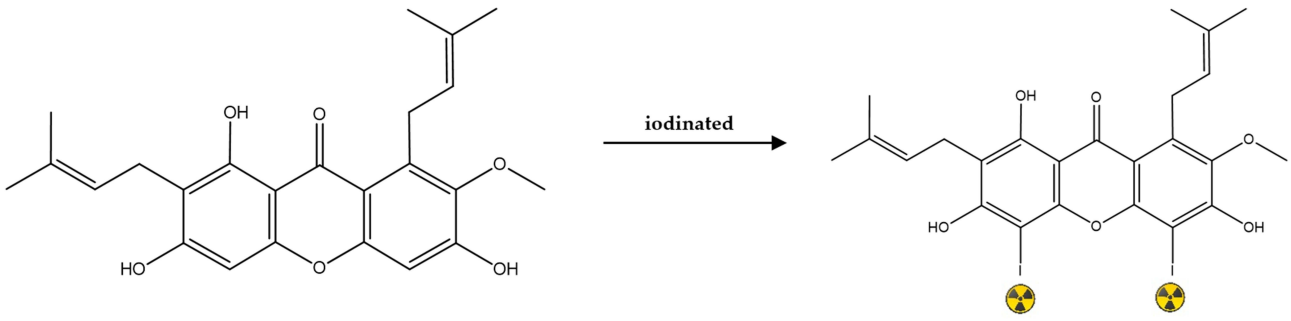

Figure 5 Potential iodination of alpha-mangostin for enhanced targeting in cancer theranostics.

https://doi.org/10.2147/DDDT.S524612

ER-positive cells.[144] The addition of iodine atoms is identified as the key factor contributing to the increased affinity and selectivity. Notably, competitive inhibition assays using tamoxifen (an ER antagonist) and non-labeled AM significantly reduced the uptake of ^{125}I-AM, affirming its ERα-mediated targeting. However, estradiol did not reduce ^{125}I-AM uptake, suggesting a distinct binding pathway.[145] The targeted uptake further underscores ^{125}I-AM's potential as a theranostic agent, combining diagnostic and therapeutic functions in breast cancer treatment. With iodine's radiolabeling capabilities, the compound offers both imaging and therapeutic benefits. This dual functionality is essential for precision oncology, as it allows for real-time monitoring of treatment efficacy. By specifically targeting ER-positive cells, ^{125}I-AM minimizes exposure to non-targeted tissues.

Biodistribution studies in animal models confirmed ^{131}I-AM's selective accumulation in tumor tissues, underscoring its potential as a necrosis-targeted agent for ER-positive breast cancer. Previous studies optimized the radiosynthesis of ^{131}I-AM by fine-tuning pH, reaction time, and oxidizing agent concentration, achieving a high radiochemical purity (RCP) of 95.17% when dissolved in ethanol. This high RCP is essential for ensuring the stability and efficacy of ^{131}I-AM in therapeutic applications. Additionally, ^{131}I-AM displayed notable stability when stored at −20°C, maintaining over 90% RCP for three days, similar to the stability findings observed in tumor-bearing mice.[146] This selective accumulation aligns with the compound's intended application in ER-positive breast cancer, focusing on cancerous cells without impacting healthy tissues. Moreover, the lipophilicity test conducted in the study revealed that ^{131}I-AM has hydrophilic characteristics, which facilitates rapid renal clearance, minimizing prolonged exposure to non-target tissues. Efficient clearance reduces off-target effects, further enhancing the safety profile of ^{131}I-AM for clinical use. The compound's selective distribution and stability confirm its suitability for radiopharmaceutical applications. Such attributes validate ^{131}I-AM's utility as a targeted imaging and therapeutic tool in cancer treatment.

The combined findings from cellular uptake studies underscore the dual-function potential of ^{131}I-AM as a theranostic agent in ER-positive breast cancer treatment. Cellular uptake experiments showed a significantly higher uptake of ^{131}I-AM in T47D breast cancer cells compared to Vero cells, illustrating the compound's affinity for ER-positive cells. This selective uptake aligns with the increased cellular retention in cancer cells making ^{131}I-AM a strong candidate for radiotherapy.[147] The ability to selectively target cancer cells reduces off-target radiation, as noted in biodistribution studies, supporting the potential of ^{131}I-AM for clinical applications. The molecular structure, characterized by strategically placed iodine atoms, enhances bioavailability and targeted effects in breast cancer cells. These insights set a foundation for further studies to optimize ^{131}I-AM's biodistribution and therapeutic efficacy in animal models.[148] With stability and selective cellular uptake established, ^{131}I-AM offers both imaging and therapeutic capabilities which address crucial needs in precision oncology. The compound's diagnostic and therapeutic dual role could enable real-time monitoring and treatment in breast cancer patients. Furthermore, this approach exemplifies advancements in radiopharmaceutical design, paving the way for safe and effective treatment options.

Iodinated Quercetin

The iodination of quercetin, a naturally occurring flavonoid, enhances its potential as a theranostic agent for cancer treatment. In this process, iodine atoms are strategically attached to specific sites on the quercetin molecule, transforming it into a radio-iodinated form (Figure 6). This structural modification is achieved using an oxidizing agent, such as chloramine-T, to facilitate the incorporation of iodine into the aromatic rings of quercetin. The presence of iodine enhances the molecule's ability to be tracked in vivo through imaging techniques, while also allowing it to deliver targeted radiation therapy to cancer cells.[149] As a result, iodinated quercetin can serve both diagnostic and therapeutic purposes, making it a promising candidate in the field of oncology. By attaching iodine isotopes, the compound becomes both visible on imaging scans and capable of emitting therapeutic radiation, offering a dual-functionality that is highly valuable in precision medicine. The specific iodine positions indicate optimal binding sites that maintain the stability of the compound in biological systems. This iodinated structure enhances quercetin's therapeutic efficacy and allows for precise targeting of cancer cells. Moreover, the iodination process expands the potential uses of quercetin in cancer diagnosis and treatment.

In cellular uptake studies, iodinated quercetin demonstrated a high affinity for DNA within cancer cells, particularly by localizing in the nucleus and intercalating with the DNA structure. The targeted attachment of iodine atoms in

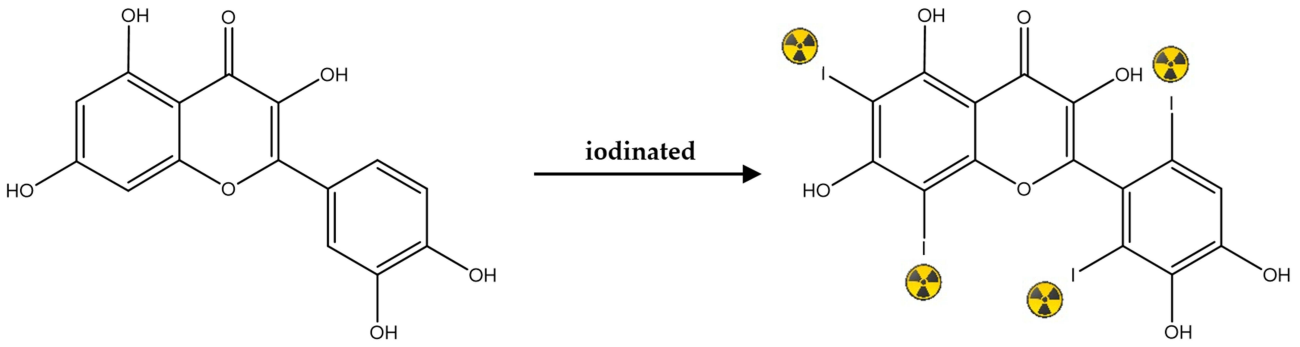

Figure 6 Potential iodination of quercetin for enhanced theranostic applications in cancer treatment.

quercetin (Figure 6), contributes to the compound's ability to penetrate cell nuclei, delivering radiation directly to cancer cell DNA and inducing apoptosis.[150] This unique property enhances quercetin's potential as a radiopharmaceutical, focusing the therapeutic radiation within tumor cells while minimizing exposure to surrounding healthy tissues. Though, further research is required to validate its selectivity and assess its effectiveness in targeting specific cancer cell types while minimizing adverse effects on normal tissues. In prostate cancer cells, iodinated quercetin exhibited significant internalization, with rapid uptake into the nucleus, causing DNA strand breaks and activating apoptosis pathways. This targeting ability can be explained by the integration of iodine atoms into specific sites of the molecule, optimizing it for nuclear localization.[151] This approach to cancer treatment aligns with precision oncology's goals of reducing off-target effects and focusing treatment on malignant cells. Additionally, the nuclear targeting observed in cellular studies provides valuable insights into the mechanisms by which iodinated quercetin exerts its therapeutic effects. By targeting the nucleus directly, iodinated quercetin delivers a higher concentration of radiation to cancer cells, increasing its effectiveness as a treatment.

The addition of iodine atoms at strategic locations in the quercetin structure ensures stability and maximizes its radiopharmaceutical properties. Optimized synthesis conditions, such as pH, reaction time, and concentration of reagents, were employed to achieve high RCP, which is essential for safe and effective use in biological systems. The labeled quercetin demonstrated over 90% RCP with sufficient, stability during transportation and administration.[152] These properties make iodine-131 labeled quercetin suitable for clinical applications, as its dual-emission capabilities facilitate both diagnostic imaging and targeted radiation therapy. This dual functionality enables clinicians to monitor the drug's distribution in real-time while simultaneously delivering therapeutic doses to tumors. Additionally, the iodinated structure supports quercetin's role as a versatile tool in cancer treatment and diagnosis.

The combined properties of stability, nuclear targeting, and dual radioactive functions underscore the potential of iodinated quercetin as a comprehensive theranostic agent. The placement of iodine atoms in quercetin's structure not only improves its stability but also enhances its ability to localize within tumor cells. This precise targeting minimizes off-target radiation, which reduces side effects and enhances patient safety during cancer treatment. Furthermore, the high affinity for DNA within cancer cells allows iodinated quercetin to function effectively as a targeted radiopharmaceutical. Future research may explore the optimization of iodinated quercetin's formulation for different cancer types, as its targeted delivery could be beneficial across a range of tumors.[153] By combining diagnostic imaging and targeted therapy, iodinated quercetin exemplifies a modern approach to precision oncology. The selective uptake and nuclear localization ensure that therapeutic radiation is concentrated within cancer cells, maximizing treatment efficacy. Ultimately, the molecular configuration of iodinated quercetin highlights its potential to revolutionize cancer treatment by providing both therapeutic and diagnostic benefits in a single compound.

Radiolabeling Techniques for Natural Compounds

Iodogen Method

The Iodogen method is one of the most commonly employed oxidative radioiodination techniques, favored for its mild conditions and ability to retain the biological activity of sensitive molecules. It utilizes 1,3,4,6-tetrachloro-3α,6α-diphenylglycoluril (Iodogen) immobilized on the reaction vessel wall, which oxidizes iodide (I^-) into electrophilic iodine (I^+) without direct contact with the ligand.[154] This makes it particularly suitable for fragile compounds such as natural phenolics. Natural ligands like curcumin, lawsone, and EGCG have been successfully labeled using this approach, achieving radiochemical purities of over 95%. The method is especially effective for compounds with activated aromatic rings, allowing for regioselective iodination. It does not require organic solvents when the compound is sufficiently soluble, making it environmentally safer. Additionally, the immobilized oxidant minimizes unwanted side reactions that could affect ligand structure. Iodogen labeling has been shown to retain the tumor-targeting capacity of the ligands, with studies reporting tumor uptake of radiolabeled lawsone in murine lymphoma models. Another key advantage is that it supports both diagnostic and therapeutic applications by facilitating the labeling of compounds with iodine-125 or iodine-131. The simplicity of the method makes it attractive for routine synthesis in radiopharmacy labs. However, a limitation lies in its lower efficiency for compounds that are poorly soluble in aqueous media, requiring co-solvents like ethanol or DMSO. Careful control of reaction time and pH is also required to prevent side reactions.[155] This method eliminates the need for toxic oxidants like chloramine-T, thus improving biocompatibility. The Iodogen method offers a balance between efficiency, selectivity, and preservation of pharmacological properties in radiolabeled natural products.

Chloramine-T Method

The chloramine-T method is another widely used oxidative labeling technique that relies on the strong oxidative power of N-chloro-p-toluenesulfonamide sodium salt (chloramine-T). This method involves mixing the ligand, iodide, and chloramine-T in an aqueous buffer, where the oxidant converts iodide into reactive iodine species.[155,156] These electrophilic species then substitute hydrogen atoms on activated aromatic rings, commonly found in polyphenolic compounds. It has been effectively applied to natural flavonoids like quercetin, rutin, genistein, and kaempferol. The labeling is usually completed within minutes, making it advantageous for time-sensitive applications. Radiochemical yields often exceed 90%, depending on the reactivity of the ligand and reaction conditions. However, because of its high reactivity, chloramine-T can also oxidize other functional groups, leading to degradation or structural modification of sensitive compounds. Optimization of pH, reaction time, and molar ratios is crucial. This method is particularly beneficial when rapid synthesis of radiotracers is required, such as in emergency diagnostics or short-lived isotope applications.[157] Its compatibility with aqueous systems also simplifies downstream purification. Despite its harshness, careful use of chloramine-T allows for successful labeling without significantly affecting the compound's bioactivity. Preclinical studies using this method have demonstrated good tumor targeting and biodistribution, especially when combined with high-affinity ligands. The technique is scalable, cost-effective, and well-documented in radiopharmaceutical literature. For natural compounds that tolerate moderate oxidative conditions, this method can be a practical choice. Caution is advised when labeling ligands with sensitive pharmacophores or metal-coordinating groups. In such cases, alternative techniques like Iodogen or iododestannylation may be preferable.

Iododestannylation Method

The iododestannylation method is a non-oxidative technique used to radiolabel compounds that have been chemically modified to include trialkylstannyl groups. These groups serve as precursors for halogen exchange reactions with radioactive iodine in the presence of a mild oxidizing agent like hydrogen peroxide or chloramine-T.[158] This method is highly regioselective, allowing for precise incorporation of iodine at predetermined positions. It is ideal for compounds that are sensitive to strong oxidation or that lack easily iodinated sites on their natural structures. The technique has been widely used in medicinal chemistry and radiopharmaceutical development, particularly for designing receptor-specific tracers. A notable example is the radioiodination of curcumin analog [^{125}I]4e, which was developed for imaging beta-amyloid plaques in Alzheimer's disease. In oncology, this method holds promise for site-specific labeling of modified

natural products, though its use is less frequent compared to Iodogen or chloramine-T due to the need for prior chemical synthesis of stannylated precursors. Radiochemical purities are typically very high (>95%), and the method supports both iodine-125 and iodine-131. It offers the advantage of avoiding over-oxidation, which is crucial for delicate natural molecules. Furthermore, iododestannylation can be performed under relatively mild conditions, preserving the structural integrity and bioactivity of the ligand.[159] The major limitation is the requirement for complex precursor synthesis, which may not be feasible for all natural products. For structure-guided radiopharmaceutical development, this method provides exceptional control over iodination sites. It also facilitates regulatory approval since the resulting compound is often structurally well-characterized. Iododestannylation is a powerful tool for precise, site-directed radioiodination of modified natural ligands.

Discussion

Iodinated radiopharmaceuticals have made a significant impact on cancer treatment, with thyroid cancer being the most commonly addressed malignancy. This preference is due to the thyroid's natural affinity for iodine, making iodine-131 particularly effective in thyroid cancer therapy, especially in cases of DTC.[77,101] Following thyroidectomy, iodine-131 is utilized in ablation therapy to prevent locoregional recurrence, effectively targeting residual cancer cells and serving a therapeutic role in cases of local persistence or distant metastases sensitive to radioiodine. Beyond thyroid cancer, iodinated compounds are increasingly applied in prostate and cervical cancers. In prostate cancer, iodine-125 seed implantation is used for brachytherapy, providing a concentrated dose of radiation that minimizes exposure to surrounding tissues.[67] Similarly, studies on recurrent cervical cancer show that iodine-125 enhances local control, offering an alternative for patients who have limited options post-surgery.[69,85] These applications underscore the versatility of iodine-labeled radiopharmaceuticals in treating different cancer types. The selective targeting capability of iodine-based agents allows for a high degree of precision, reducing the harmful effects on healthy tissue. The use of radioiodine therapy highlights the evolution of cancer treatment from broad approaches to targeted, patient-specific therapies. This development aligns with the goals of precision oncology, which prioritizes efficacy with minimized side effects.

The methods for radiolabeling natural compounds with iodine include the Iodogen method, electrophilic substitution, and direct iodination, each chosen based on the compound's structure and desired stability. The Iodogen method is a preferred choice for compounds like curcumin and lawsone, allowing for stable iodine attachment and preserving the bioactivity of the compound.[103,114,128,131,157,160] This method involves the oxidation of iodine using iodogen as a mild oxidizing agent, facilitating stable labeling with minimal damage to the compound's structure. Chloramine-T oxidation is frequently used for compounds such as quercetin and rutin, which require efficient binding of iodine-131 while maintaining high radiochemical purity.[109,110] Chloramine-T works by oxidizing iodide to reactive iodine species, enabling rapid and stable labeling of the compound. Electrophilic substitution, suitable for compounds with electron-rich sites, is commonly applied to compounds like hypericin, allowing stable labeling.[161] This method involves the introduction of iodine into the aromatic system of hypericin through an electrophilic reaction, targeting specific sites on the molecule for labeling while maintaining its structural integrity. These radiolabeling strategies are crucial because they ensure the bioactivity and stability of the labeled compound, directly influencing its therapeutic performance. These methods help maintain the structural integrity of the compound, which is crucial for effective targeting and therapy. Selecting an appropriate radiolabeling method is essential to achieve stability and bioavailability in the compound. Each method has specific advantages and limitations. For instance, the iodogen method is highly effective for sensitive compounds but may require optimization for larger-scale production. Chloramine-T is efficient for compounds with simpler structures but can sometimes affect the bioactivity of more delicate molecules. Electrophilic substitution offers precision for electron-rich compounds like hypericin but demands careful control of reaction conditions to avoid over-iodination or unwanted side reactions. The chosen method directly impacts the compound's therapeutic effectiveness and its distribution within the body. Each technique has specific benefits and limitations, but overall, these methods allow radiolabeled compounds to be formulated for the precise targeting of cancer cells. Proper radiolabeling thus enhances the therapeutic value of the compound, making it more effective for clinical applications.

One of the significant challenges in the radiolabeling of natural compounds is achieving stability and biodistribution without compromising inhibitory effectiveness against cancer cells. Many radiolabeled compounds face issues in

systemic circulation, such as premature release of free iodine, which can lead to unintended radiation exposure to non-target tissues. Stability is critical for these compounds to retain their inhibitory effects on cancer cells, as unstable compounds may distribute unevenly or degrade before reaching the tumor site.[40,46] Compounds like iodine-labeled genistein have shown high specificity but encounter issues with bioavailability, which affects their overall efficacy. Ensuring stability during the compound's journey in the bloodstream is crucial for maintaining its cancer-targeting properties.[120,121] To address these challenges, techniques like encapsulating the compound in nanoparticles are being explored, which can protect the radiolabeled compound and enhance its inhibitory capability. Stable radiolabeled compounds are more likely to deliver therapeutic doses precisely to the cancer cells, maximizing their efficacy.[162,163] The challenges in stability and biodistribution are directly linked to the compound's inhibition capability, making these aspects essential in the development of radiopharmaceuticals. By improving these factors, researchers aim to enhance the performance of radiolabeled natural compounds as effective cancer therapies.

The choice of natural compounds as radioligands has gained attention due to their inherent anticancer properties, providing a natural and often safer alternative to synthetic agents. These compounds, including various flavonoids, alkaloids, and polyphenols, have shown potential as carriers for radioactive iodine.[120,137,164] Natural compounds have been found to target cancer cells selectively, providing specificity in treatment while reducing systemic toxicity. For instance, curcumin and rutin demonstrate differential uptake in tumor cells, making them ideal candidates for targeted therapies.[104,165] The selection of natural compounds is based on their binding affinity to cancer cells, stability after radiolabeling, and intrinsic anticancer mechanisms like inducing apoptosis and inhibiting angiogenesis. These properties make natural compounds suitable for development into radiopharmaceuticals that serve both diagnostic and therapeutic purposes. Their low toxicity further enhances their applicability in clinical settings, aligning with the goals of precision medicine. By combining natural compounds with radioactive iodine, researchers can maximize therapeutic benefits while minimizing side effects. The use of natural radioligands represents a promising area in cancer treatment, offering an alternative that bridges traditional therapies with innovative targeted approaches. Compared to radionuclide administration without a targeting agent, the incorporation of natural compounds as radioligands significantly enhances tumor localization and reduces systemic toxicity.[166] Preclinical studies have demonstrated that radiolabeled natural ligands accumulate more efficiently at tumor sites than free radionuclides, which often distribute nonspecifically throughout the body. This improved targeting increases therapeutic efficacy while minimizing off-target effects, supporting the synergistic advantage of combining natural bioactives with radioisotopes. Furthermore, several comparative studies have shown that the therapeutic and imaging outcomes of radioiodinated natural compounds surpass those observed with either the unlabeled natural compound or the radioisotope alone.[167] These findings suggest that the radioligand approach yields enhanced tumor accumulation, improved visualization in diagnostic imaging, and more potent cytotoxicity in therapeutic applications, thus supporting its clinical potential.

The structure of a natural compound plays a critical role in its success as a radiolabeled agent, as certain functional groups are essential for stable iodine attachment. Functional groups like hydroxyl (–OH) and aromatic rings are critical, as they provide binding sites for iodine atoms, ensuring the stability of the radiolabeled compound. For example, compounds with rich aromatic structures, such as hypericin and quercetin, facilitate electrophilic substitution reactions that allow iodine to bind effectively.[110,168] The presence of ketone and phenolic groups also contributes to the compound's stability, enabling it to remain intact through metabolic processes. These structural features are vital for ensuring that the compound can deliver therapeutic effects without degrading prematurely. Stability is crucial as it enables the compound to reach the target site without releasing iodine too early, which would reduce its effectiveness. Understanding the significance of these structural elements is essential for selecting natural compounds with the potential to act as stable and effective radiopharmaceuticals. The ability to maintain structure and functionality after iodine attachment directly impacts the compound's effectiveness in targeting cancer cells.

One of the primary advantages of radioiodination with natural compound is its ability to enhance the tracking of biodistribution in vivo. For instance, Muchtaridi et al[167] discuss the advancements in radiopharmaceuticals derived from natural compounds, emphasizing the importance of iodine radioisotopes in improving the detection and therapeutic efficacy of these agents. The biodistribution of radiolabeled compounds can be significantly influenced by their chemical structure and formulation, which is crucial for optimizing therapeutic outcomes. Furthermore, the biodistribution patterns

of these compounds often follow expected pharmacokinetic profiles, as seen in studies involving oligonucleotides, where rapid clearance via renal pathways was observed. Moreover, the biodistribution of radiopharmaceuticals can be affected by various factors, including the physicochemical properties of the compounds and their interactions with biological systems.[169] For instance, the study by Holanda et al[170] illustrates how the presence of natural extracts can alter the biodistribution of radiopharmaceuticals, indicating that the biological activity of these compounds can significantly impact their pharmacokinetics. Similarly, Cekic et al explored the effects of broccoli extract on the biodistribution of radiolabeled compounds, further underscoring the importance of understanding these interactions in the context of natural products.[171] Thus, selecting compounds with these functional groups is critical in developing efficient and safe iodine-labeled radiopharmaceuticals for clinical applications.

Computational Approaches in Radiopharmaceutical Design

The use of in silico methods in radiopharmaceutical discovery has become essential for efficiently identifying and optimizing potential radioligands with high precision. Techniques like molecular docking, pharmacophore modeling, and molecular dynamics simulations enable the virtual screening of extensive compound libraries, narrowing down candidates based on binding affinity, stability, and specificity.[172] This approach allows researchers to assess complex molecular interactions within a controlled virtual environment, significantly reducing the need for costly and time-intensive lab experiments. The radiopharmaceutical design workflow begins with analyzing Frontier Molecular Orbitals (FMOs) to understand electronic properties crucial for stable binding. This process is especially valuable in radiopharmaceuticals, where accuracy in targeting is critical for efficacy and safety.[173] In silico modeling can predict how these compounds interact with specific cancer targets, thus enhancing therapeutic potential and minimizing off-target effects. Additionally, evaluating the compatibility of a compound with radioisotopes, such as iodine-125 or fluorine-18, helps to select the most suitable candidates for further testing.[174] Through computational simulations, potential issues like instability or rapid degradation can be identified early, preventing late-stage failures in drug development. Ultimately, in silico methods streamline the identification of high-potential compounds, saving both time and resources.

Figure 7 illustrates the comprehensive in silico workflow employed in radiopharmaceutical design. It begins with FMOs analysis to identify reactive sites suitable for iodine attachment. Subsequently, molecular docking studies are performed to simulate the interaction between radioligands and their molecular targets, predicting binding modes and affinities.[175] This is followed by molecular dynamics simulations to assess the stability of ligand-target complexes under physiological conditions. The final stage involves pharmacokinetic and biodistribution prediction, which evaluates how the compound behaves in vivo, including absorption, tissue distribution, metabolism, and clearance. Importantly, the model integrates three core selection parameters: the type of cancer targeted, the type of carrier vector (eg, small molecule, peptide, antibody), and the type of radionuclide employed.[176] These parameters guide the rational design of radiopharmaceuticals tailored to specific diagnostic or therapeutic needs.

In the context of PET radiopharmaceuticals, in silico methods significantly enhance the targeting capabilities of radiolabeled compounds. For instance, mTOR inhibitors used for PET imaging rely on high specificity and resolution, which are evaluated through binding affinity and molecular stability using fluorine-18.[177,178] Likewise, for SPECT imaging, isotopes such as technetium-99m and iodine-123 are assessed using similar computational tools.[179,180] Therapeutic radiopharmaceuticals based on iodine-131 and lutetium-177 are also optimized using molecular docking and dynamics simulations to predict their interactions with tumor targets and their expected efficacy.[181,182] These simulations enable predictions of biodistribution and systemic clearance, ensuring that radioligands reach tumor tissues efficiently while avoiding healthy ones.[183] Such data provides a strong foundation for optimizing pharmacokinetics and improving molecular selectivity before preclinical trials. This computational pipeline allows researchers to virtually modify the structure of candidate compounds, assess different iodination sites, and simulate their behavior in a biological environment.[184,185] The integration of structure-based modeling with pharmacokinetic predictions leads to a more effective and targeted radiopharmaceutical design process. In turn, this increases the likelihood of clinical success while reducing time and costs associated with empirical development.

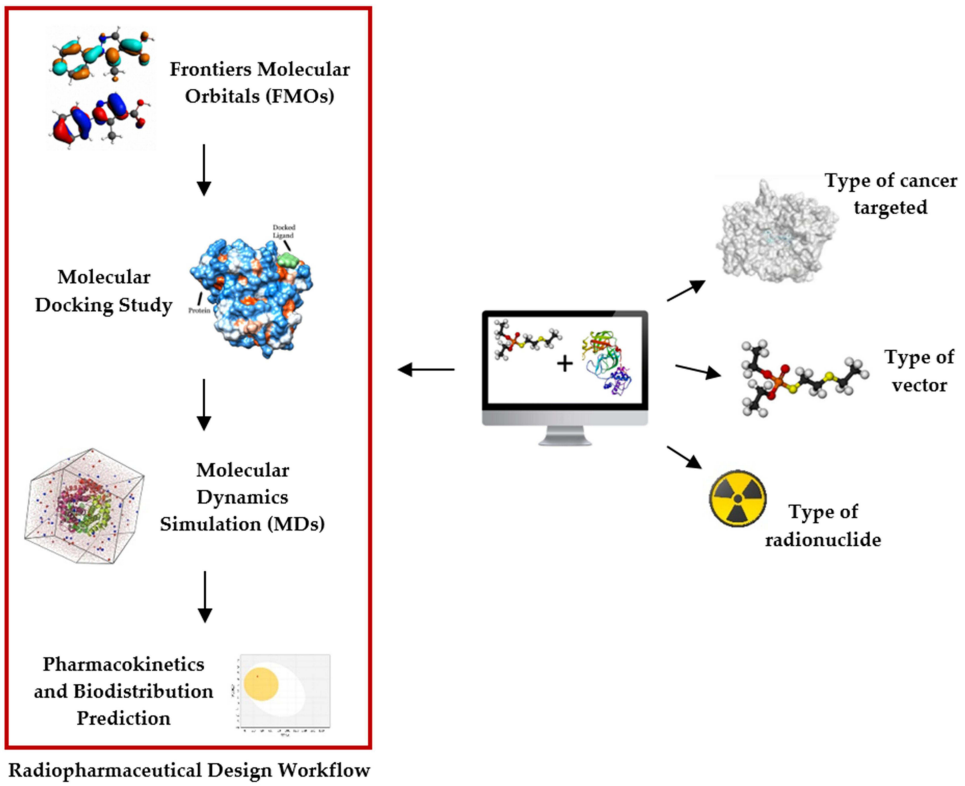

Figure 7 Radiopharmaceutical design workflow for targeted cancer therapy using computational methods.

Future Directions and Research Outlook

Looking ahead, future research should focus on addressing current limitations such as low in vivo stability, inadequate tumor selectivity, and the rapid clearance of certain natural radioligands. These challenges can hinder the clinical applicability of otherwise promising compounds. Integrating in silico predictions with high-throughput screening and in vivo validation will be crucial for translating computational insights into clinical success. Emphasis on radiopharmaceuticals derived from underexplored natural sources may unlock novel bioactive scaffolds with superior targeting properties.[186] Additionally, the optimization of isotope-pairing strategies is essential to achieve the ideal balance between imaging resolution, therapeutic potency, and patient safety. Emerging trends include the use of machine learning algorithms for pattern recognition in binding profiles, and AI-driven platforms for de novo radioligand design. These technologies can accelerate discovery by identifying new structural motifs and optimizing ligand-target interactions with unprecedented speed and accuracy. Moreover, collaborative frameworks that integrate bioinformatics, radiochemistry, pharmacology, and clinical oncology are necessary to overcome regulatory and translational barriers. Ultimately, with continued innovation, natural compound-based radiopharmaceuticals have the potential to become integral components of personalized nuclear medicine, offering safer, more effective, and patient-specific diagnostic and therapeutic solutions.

Conclusion

In conclusion, iodine-labeled radiopharmaceuticals may hold transformative potential in cancer treatment by enabling precise targeting of cancer cells and supporting both diagnostic imaging and therapeutic interventions that minimize harm to healthy tissues. Integrating natural compounds as radioligands could provide safer, biologically compatible options that align with personalized and precision medicine. The use of natural compounds introduces a dimension of bioactivity that may enhance therapeutic outcomes by leveraging the compounds' inherent anticancer properties. Structural stability and specific functional groups within these compounds are crucial for maintaining targeted delivery and minimizing off-target radiation exposure. Techniques like in silico modeling optimize the design and stability of these compounds,

predicting biodistribution and pharmacokinetics to improve therapeutic efficacy and reduce development costs. Innovations in radiolabeling methods, such as the iodogen and chloramine-T methods, help preserve the compounds' therapeutic qualities, while encapsulation techniques, like nanoparticle delivery systems, enhance bioavailability and stability, extending the reach of these radiopharmaceuticals in a biological system. With these computational and experimental advancements, iodine-labeled natural compounds might emerge as valuable tools in modern oncology, offering a comprehensive approach that spans from diagnosis to targeted therapy. However, further research is necessary to confirm the clinical utility and safety of these natural radioligands, especially in disease settings where targeted radiotherapy and imaging may offer significant benefits. This review is limited by the current lack of long-term clinical validation and direct comparative studies between natural and synthetic radioligands. These gaps make it difficult to draw definitive conclusions regarding their relative efficacy, pharmacokinetic profiles, and readiness for regulatory approval in clinical applications.

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Disclosure

The authors report no conflicts of interest in this work.

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