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REVIEW

Green Dentistry in Oral Cancer Treatment Using Biosynthesis Superparamagnetic Iron Oxide Nanoparticles: A Systematic Review

Faris Hernando Reviansyah[1,*], Daffa Rahmad Dwiyana Putra[1,*], Juan Alexander Supriatna[1], Veni Takarini[2,3], Maria Komariah[4]

[1]Faculty of Dentistry, Padjadjaran University, Bandung, Indonesia; [2]Department of Dental Materials and Technology, Faculty of Dentistry, Padjadjaran University, Bandung, 40132, Indonesia; [3]Oral Biomaterials Research Centre, Faculty of Dentistry, Padjadjaran University, Bandung, 40132, Indonesia; [4]Department of Fundamental Nursing, Faculty of Nursing, Padjadjaran University, Bandung, 40132, Indonesia

*These authors contributed equally to this work

Correspondence: Faris Hernando Reviansyah, Email faris21001@mail.unpad.ac.id

Abstract: Oral cancer is a worldwide health issue with high incidence and mortality, demands an effective treatment to improve patient prognosis. Superparamagnetic iron oxide nanoparticles (SPIONs) emerged as a candidate for oral cancer treatment due to their unique attributes, enabling a synergistic combination with its drug-delivery capabilities and hyperthermia when exposed to magnetic fields. SPIONs can be synthesized using biopolymers from agricultural waste like lignin from paddy, which produce biogenic nano iron oxide with superparamagnetic and antioxidant effects. In addition, lignin also acts as a stabilizing agent in creating SPIONs. This study aimed to explore how agricultural waste could be used to prepare SPIONs using the green synthesis method and to evaluate its potential for oral cancer specifically focusing on its effectiveness, side effects, biocompatibility, and toxicity. A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol. PubMed, EBSCO, and Scopus databases were exploited in the selection of articles published within the last decade. This study quality assessment uses OHAT for critical appraisal tools. Only 10 studies met the inclusion criteria. The findings suggest that the use of agricultural waste in the preparation of SPIONs not only holds potency for oral cancer treatment through drug delivery and hyperthermia but also aligns with the concept of green dentistry. SPIONs as a treatment modality for oral cancer have demonstrated notable effectiveness and versatility. This study provides robust evidence supporting green dentistry by using agricultural waste in the preparation and formulation of SPIONs for managing oral cancer. Its multifunctional nature and ability to enhance treatment efficacy while minimizing adverse effects on healthy tissues highlights the potency of SPION-based oral cancer treatments.

Keywords: SPIONs, oral cancer, treatment, biosynthesis, green dentistry

Introduction

Oral cancer, with its high incidence and mortality rates, is a global health concern. A new effective treatment option is required to increase the patient's prognosis related to their Quality of Life (QoL). The estimated number of new cases of oral cancer worldwide increased from 354,864 cases reported by the Global Cancer Observatory (GLOBOCAN) in 2018 to 377,173 cases according to GLOBOCAN data in 2020. Meanwhile, the number of new deaths remained stable at about 177,000 cases.[1] Oral cancer has a poor prognosis as the severity phase increases, hence the need for treatment at an early stage is required.[2] Treatment for oral cancer might involve several techniques, such as immunotherapy, targeted medications, radiotherapy, chemotherapy, and surgery. However, because it requires intrusive procedures and has lower efficacy, this approach is thought to be less effective in treating oral cancer, It is because of the lack of tumor selectivity in the delivery of anticancer medicines, systemic toxicity frequently compromises conventional cancer chemotherapy therapies. The drug's dose is restricted due to adverse effects, which makes it challenging to treat cancer effectively.

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Superparamagnetic iron oxide (SPIONs) nanoparticles are one of the interesting biomedicine nanoparticles because of their advanced properties and cytotoxicity features.[3] SPIONs can be obtained through coprecipitation methods, which involve the simultaneous precipitation of iron salts in the presence of suitable reactants.[4] Different coprecipitation techniques have been introduced in the literature. One method involves the use of glycine as a reactant, allowing for the creation of SPIONs with size and decoration that can be adjusted. Another method utilizes a reaction involving dextran, ferric trichloride, and ferrous chloride, followed by ultrafiltration to obtain purified SPIONs. Targeted theranostic nanosystems can also be created by engineering SPIONs with an organic covering made of bovine serum albumin and low molecular weight heparin.[5] The coprecipitation process of SPIONs involves the aggregation of initially formed primary particles, which then accrete to form the final nanoparticles.[6] Still, using the coprecipitation method makes it hard to achieve the proper size and shape for the nanomaterial. Additionally, it will lead to the formation of aggregated structures rather than monodisperse particles.[7,8]

Due to its affordability and potential uses in a variety of industries, the environmentally friendly synthesis of superparamagnetic iron oxide nanoparticles, or SPIONs, has drawn a lot of interest.[9–11] By utilizing plant materials and agro-wastes as reducing agents and stabilizers in the synthesis process, researchers have explored a biocompatible and non-toxic alternative to traditional physical and chemical methods.[12] The optimization of synthesis parameters, including temperature, pH, iron salt concentration, and coating materials, has resulted in SPIONs with exceptional properties such as superparamagnetism, stability, and biocompatibility. These synthesized SPIONs hold promise for various applications in medicine and sustainable agro-environments.[1] Additionally, the green synthesis approach demonstrates various advantages such as low catalyst loading, short reaction time, stability, and recyclability, positioning it as a promising method for the fabrication of magnetic organic-inorganic hybrid catalysts. In summary, the green synthesis of SPIONs provides a sustainable and environmentally conscious approach to producing nanoparticles with wide-ranging applications in different fields.

In 2023, the rice harvest area in Indonesia is estimated to be 10.20 million hectares with rice production of around 53.63 million tons.[13] The waste produced from paddy plants is straw, bran, and husks. Straw is produced as much as 55.6% of the total rice yield, grain is around 44.4%, and only around 65% becomes rice, while the rest is in the form of husks and bran.[14] With the high amount of waste produced, we need a way to utilize it to develop the potential of the waste. SPIONs can be synthesized using biopolymers from agricultural waste, like lignin from paddy straw, which produces biogenic nanoiron oxide with superparamagnetic and antioxidant effects. Antioxidants protect cells and organelles from oxidative damage, thereby preventing chronic diseases. It also eliminates the use of dangerous chemicals as capping and reducing agents in an economical, non-toxic, and environmentally friendly manner.

Magnetic iron oxide nanoparticles have gained significant interest in various fields due to their unique physicochemical properties and potential applications. Several studies have focused on the synthesis and characterization of these nanoparticles using green methods. Abdullah et al, for instance, examined the effects of adding chemical and green magnetic iron oxide nanoparticles to poly(ε-caprolactone) nanofibrous membranes and discovered that the green nanoparticles performed better than the chemical nanoparticles in terms of their physicochemical, morphological, and functional characteristics.[15] Elizondo-Villarreal et al synthesized magnetite nanoparticles using extracts of green lemon residues and demonstrated their potential application in anticorrosive coatings.[9] Moacă et al successfully synthesized biocompatible magnetic iron oxide nanoparticles using ethanolic extracts of *Camellia sinensis* and *Ocimum basilicum* leaves and evaluated their biological effects on lung cancer cell lines.[16] Kharey et al reported the green synthesis of biocompatible iron oxide-gold composite nanoparticles using a medicinal plant extract and highlighted their potential for biomedical imaging and therapeutics.[10] Amos-Tautua et al synthesized gold-coated magnetic nanoparticles using a green method and characterized their textural, thermo-gravimetric, and magnetic properties, demonstrating their potential for biomedical and analytical applications.[17]

This study aims to explore how to produce superparamagnetic iron oxide nanoparticles using lignin from agricultural waste and to evaluate its potential for oral cancer treatment, specifically focusing on their effectiveness, side effects, biocompatibility, and toxicity. This review will hopefully provide insight into the potential of SPIONs as a new modality in the treatment of oral cancer. This study has implications for future research directions and future clinical practice, which will ultimately contribute to better treatment and outcomes for patients in the management of oral cancer.

Methods

Study Design and Objective

This study's design was arranged based on guidelines from *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA). This study aimed to analyze the ability of SPIONs that can be synthesized from plants to treat oral cancer through a hyperthermia process. Through the screening process, eleven eligible articles were included in this systematic review. The selection process only used two results-oriented research studies that measured results related to SPIONs for treating oral cancer with the plant-derived SPION manufacturing process.

Search and Strategy

The literature search for this study was carried out in the PubMed, Scopus, and EBSCO databases until 6th April 2024. There are 2 search strategies conducted for the literature search, the primary objective search strategy is to find the efficacy of SPIONs in treating oral cancer, and the secondary objective is to explore how to synthesize SPIONs using bioagricultural material from various plants. For the primary objective, the search using keyword is adjusted to Medical Subject Headings (MeSH) with boolean operator keywords as follows "(Superparamagnetic Iron Oxide Nanoparticles OR Superparamagnetic Iron Nanoparticles OR Iron Nanoparticle Superparamagnetic OR Nanoparticle Superparamagnetic Iron OR Nanoparticles Superparamagnetic Iron OR Superparamagnetic Iron Nanoparticle OR SPIONs) AND (Treatment OR Therapeutic OR Therapy OR Therapies OR Treatment) AND. (Mouth Neoplasm OR Mouth Neoplasms OR Oral Cancer OR Oral Cancers OR Mouth Cancers OR Mouth Cancer OR Cancer of the Mouth OR Cancer of Mouth)". The same intervene was done for the secondary search, with the following keywords (Superparamagnetic Iron Oxide Nanoparticles OR Superparamagnetic Iron Nanoparticles OR Iron Nanoparticle Superparamagnetic OR Nanoparticle Superparamagnetic Iron OR Nanoparticles Superparamagnetic Iron OR Superparamagnetic Iron Nanoparticle OR SPIONs) AND (Green Synthesis OR Biosynthesis OR Green Dentistry) AND (Agricultural OR Plant OR Plants) AND (Waste). In detail the literature search strategy can be seen in (File Attachment 1).

Eligibility Criteria

The inclusion criteria in this study followed the PICOS framework (Population, Intervention, Comparison, Outcome, and Study), as follows:

P: Patient (Human/Animal) with oral cancer

I: SPIONs application to oral cancer treatment; Biosynthesis application to SPIONs

C: Comparison with other existing method to produce SPIONs

O: Cancer cell suppression and clinical outcome

S: In vivo and in vitro

In addition, other inclusion criteria include: research published in peer-reviewed journals in English and accessible in its entirety; samples of humans/animals; tests carried out in vitro/in vivo; biosynthesis of superparamagnetic nanoparticles; and the research was conducted over the period 2013–2023. Meanwhile, exclusion criteria include full paper restriction, not suitable with PICOS, and limit of access to data.

Data Extraction

Two examiners (FH and DR) carried out the data extraction process independently to ensure the consistency and accuracy of the information extracted from each study. Any discrepancies between examiners are resolved through mutual discussion and agreement. In addition, the accuracy of the extracted data was also checked by other examiners (JA and VT) to ensure the quality and accuracy of the information extracted from each study included in this study.

The data extraction from this study was carried out manually using an extraction table The following were extracted: (1) author name and year of publication; (2) study characteristics, such as study location and research design; (3) study population, including study sample and clinical condition; (4) intervention, including the production of SPIONs using the biosynthesis method and the use of SPIONs in the treatment of oral cancer; and (5) study results, which included the usefulness, toxicity, side effects, and biocompatibility of SPIONs on the treatment of oral cancer using the biosynthesis method.

Data Analysis and Risk of Bias Assessment

This study was analyzed using descriptive analysis. The risk of bias was assessed using the OHAT appraisal tool. Information about the study design, the methodology used, qualitative results, and statistical analysis related to the objectives are included in the data extracted from the included articles. The data is a complete set of information regarding the ability of SPIONs to treat oral cancer. It also includes a list of the plants that can be used to synthesize SPIONs.

Results

Study Selection

As for the study selection, this literature review is based on search results from three databases, The systematic search retrieved 136 articles, and duplicates were found in as many as six articles using Mendeley. After screening based on the title and abstract, 12 articles were obtained. Among the initial pool of 136 articles, 12 studies met the inclusion criteria for full-text. Among 12 studies, two were excluded because of the full-text restriction. Finally, 10 studies were included for this study. In detail, the article search flow can be seen in (Figure 1).

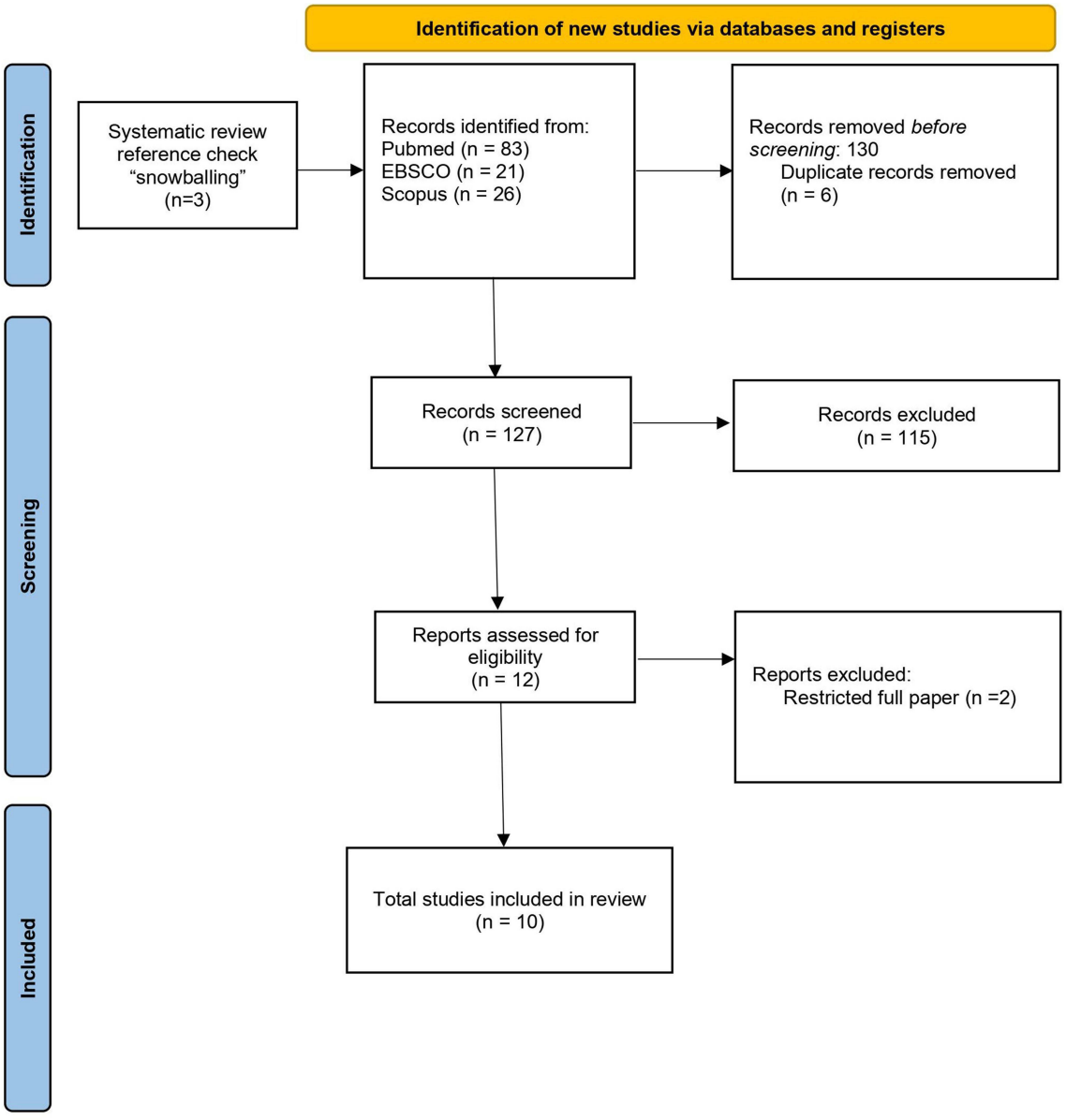

Figure 1 PRISMA Flowchart of Study Selection.

Study Characteristics

The characteristic of the study consists of a total of 9 included studies using experimental design studies in vitro and in vivo. The samples were divided into several categories including oral squamous cells, human tongue squamous cell carcinoma cell line, Mouse Embryo Fibroblast (MEF), tumor-bearing mouse, and rabbit tongue cancer, for the biosynthesis were also divided into several categories including, lignin, Garcinia mangostana fruit peel extract, Persicaria bistorta root extract, pomegranate rind extract, and Musa acuminata peel ash extract. A detailed study of the characteristics can be seen in the following table.

Study Found

Studies found that there are several plant extracts used in the production of SPIONs using the biosynthesis method, such as lignin that can be obtained from paddy straw and wheat straw. The plant extract combined with $FeSO_4$. There are several ways to use SPIONs to inhibit or destroy cancer cells. Some of the ways that SPIONs work, it can be modified by PEI (branch Fe_3O_4) by binding into Tca83 cell DNA (Tongue carcinoma cell). In addition, SPION can target cancer cells specifically through anticancer imaging and potentially has anti-cancer activity in tongue cancer by targeting the mitochondria. Furthermore, the use of SPION with the combination of magnetic exposure could kill carcinoma cells with hyperthermia. Studies found that the most effective and good way to destroy and kill cancer cells is the use of SPION to destroy cancers through hyperthermia. The table extraction can be accessed in the (Tables 1 and 2).[18–29]

Table 1 Search Strategy

Database	Term	Keyword	Retrieved
PubMed	#1	Superparamagnetic Iron Oxide Nanoparticles OR Superparamagnetic Iron Nanoparticles OR Iron Nanoparticle Superparamagnetic OR Nanoparticle Superparamagnetic Iron OR Nanoparticles Superparamagnetic Iron OR Superparamagnetic Iron Nanoparticle OR SPIONs	16,912
	#2	Treatment OR Therapeutic OR Therapy OR Therapies OR Treatments	14,114,610
	#3	Mouth Neoplasm OR Mouth Neoplasms OR Oral Cancer OR Oral Cancers OR Mouth Cancers OR Mouth Cancer OR Cancer of the Mouth OR Cancer of Mouth	179,509
	Query	(Superparamagnetic Iron Oxide Nanoparticles OR Superparamagnetic Iron Nanoparticles OR Iron Nanoparticle Superparamagnetic OR Nanoparticle Superparamagnetic Iron OR Nanoparticles Superparamagnetic Iron OR Superparamagnetic Iron Nanoparticle OR SPIONs) AND (Treatment OR Therapeutic OR Therapy OR Therapies OR Treatment) AND (Mouth Neoplasm OR Mouth Neoplasms OR Oral Cancer OR Oral Cancers OR Mouth Cancers OR Mouth Cancer OR Cancer of the Mouth OR Cancer of Mouth)	63
Scopus	#1	Superparamagnetic Iron Oxide Nanoparticles OR Superparamagnetic Iron Nanoparticles OR Iron Nanoparticle Superparamagnetic OR Nanoparticle Superparamagnetic Iron OR Nanoparticles Superparamagnetic Iron OR Superparamagnetic Iron Nanoparticle OR SPIONs	13,642
	#2	Treatment OR Therapeutic OR Therapy OR Therapies OR Treatments	13,550,293
	#3	Mouth Neoplasm OR Mouth Neoplasms OR Oral Cancer OR Oral Cancers OR Mouth Cancers OR Mouth Cancer OR Cancer of the Mouth OR Cancer of Mouth	59,140
	Query	"Superparamagnetic Iron Oxide Nanoparticles" OR "Superparamagnetic Iron Nanoparticles" OR "Iron Nanoparticle Superparamagnetic" OR "Nanoparticle Superparamagnetic Iron" OR "Nanoparticles Superparamagnetic Iron" OR "Superparamagnetic Iron Nanoparticle" AND "Treatment" OR "Therapeutic" OR "Therapy" OR "Therapies" OR "Treatments" AND "Mouth Neoplasm" OR "Mouth Neoplasms" OR "Oral Cancer" OR "Oral Cancers" OR "Mouth Cancers" OR "Mouth Cancer" OR "cancer off the mouth" OR "cancer off mouth"	9

(*Continued*)

Table 1 (Continued).

Database	Term	Keyword	Retrieved
Ebsco	#1	Superparamagnetic Iron Oxide Nanoparticles OR Superparamagnetic Iron Nanoparticles OR Iron Nanoparticle Superparamagnetic OR Nanoparticle Superparamagnetic Iron OR Nanoparticles Superparamagnetic Iron OR Superparamagnetic Iron Nanoparticle OR SPIONs	3,818
	#2	Treatment OR Therapeutic OR Therapy OR Therapies OR Treatments	10,836,116
	#3	Mouth Neoplasm OR Mouth Neoplasms OR Oral Cancer OR Oral Cancers OR Mouth Cancers OR Mouth Cancer OR Cancer of the Mouth OR Cancer of Mouth	61,273
	Query	(Superparamagnetic Iron Oxide Nanoparticles OR Superparamagnetic Iron Nanoparticles OR Iron Nanoparticle Superparamagnetic OR Nanoparticle Superparamagnetic Iron OR Nanoparticles Superparamagnetic Iron OR Superparamagnetic Iron Nanoparticle OR SPIONs) AND (Treatment OR Therapeutic OR Therapy OR Therapies OR Treatment) AND (Mouth Neoplasm OR Mouth Neoplasms OR Oral Cancer OR Oral Cancers OR Mouth Cancers OR Mouth Cancer OR Cancer of the Mouth OR Cancer of Mouth)	5

Risk of Bias

The results of the risk of bias assessment in experimental in vitro and in vivo studies showed variations in the methodological quality of the studies (Figures 2 and 3). Overall, most studies had a low risk of bias and therefore high article reliability.

Discussion

The findings suggest that SPIONs can be produced from biosynthesis methods, which is an effective and inexpensive process. Lignin, which is derived from natural resources like wheat, lumber, and paddy straw, is one instance of a plant component that can be regarded as agricultural waste. It is derived from the waste products produced by paper mills and the paper industry. In order to create nanomaterials, lignin was extracted from agricultural waste and utilized as a capping and reducing agent. The plant list can be viewed in (Table 3). The extract's lignin was layered on superparamagnetic nanomaterials and served as a reducing and capping agent during the synthesis of SPIONs. The process can be seen in (Figure 4).[1]

The straw of wheat and paddy was used to extract lignin. As per the earlier research conducted by R. Periakaruppan et al,[35] toluene-ethanol was added to the powdered lignin extract to dewax it. Using an alkali extraction method, lignin was extracted from the dewaxed straw of wheat and paddy and then submerged in a sodium hydroxide solution. The soluble hemicelluloses were eliminated by mixing 95% ethanol with 2.5 N HCl. Finally, the soluble alkali lignin was separated using repeated precipitation of lignin by retaining the pH 1.5–2.0. De-ionized water was used to create a 100 mL solution of 0.1 M ferrous sulfate, which was then combined with lignin. Furthermore, 0.3 M sodium hydroxide was added to the reaction mixture. In the end, brownish-black precipitation was obtained.

SPIONs can be made using a variety of methods, such as co-precipitation, thermal decomposition, and microemulsion.[36] While the co-precipitation is one of the most simple and efficient methods, but This approach often produces nanoparticles with a high degree of polydispersity and low crystallinity which unsuitable for producing a highly pure, accurate stoichiometric phase The thermal decomposition method provides monodisperse and high quality nanoparticles. However, because harmful chemicals including hexane, iron pentacarbonyl, and chloroform are used in the synthesis, this method is not very environmentally friendly. The primary benefit of using microemulsion methods for the preparation of SPION is the ability to regulate the size of the nanoparticles by adjustment of the micelle size. Furthermore, a better particle polydispersity is seen as a result of the micelles' generally uniform size. The low yield and low crystallinity of SPION produced by the usually achievable reaction temperature is one of the drawbacks of microemulsion synthesis.[37–39] Compared to the other existing methods, SPIONs using a biosynthesis method from agricultural waste are affordable, more environmentally friendly, more sustainable, and more effective. This is because SPIONs produced by biosynthesis are recognized for their biocompatibility

Table 2 Superparamagnetic Iron Oxide Nanoparticles (SPIONs) for Treating Oral Cancer

Authors & Year	Study Design	Intervention	Methodology	Sample				Outcomes
				Clinical	Cancer Types	Stages	Characteristic	
Tsai et al, 2021[30]	In-vitro study	Iron-gold bimetallic nanoparticles (FeAu NPs) with Superparamagnetic properties	FeAu bimetallic NPs were prepared via thermal pyrolysis method with conjugated MMP-1 antibody	Human oral squamous cell carcinoma (HSC-3)	Malignant	Not mentioned	Cultured HSC-3 cells	The growth of HSC-3 Cells was inhibited by magnetic hyperthermia therapy. Injected FeAU NPs elongated with antiMMP1 antibody penetrate the tumor tissue via phagocytosis
Afrasiabi et al, 2021[31]	In-vitro study	Superparamagnetic Iron Oxide Nanoparticles (SPIONs)	The mitochondria isolated from OSCC and normal groups were suspended in the MMP assay buffer and then the OSCC and normal mitochondria supsension were incubated with different concentrations of SPIONs	Animals oral squamous cells carcinoma induced from rats	Malignant	Not mentioned	The sample was cut into smaller pieces for homogenization using a glass hand-held homogenizer, then the mitochondria were suspended from isolated OSCC.	SPIONs decrease the SDH activity which lead to inability for cell to metabolism also the level of reactive oxygen species (ROS) in OSCC was increased. Overall, SPIONs induce the OSCC leading to death.
Jahanbani et al, 2020[27]	In-vitro study	SPION nano-powder	Isolated mitochondria were removed from the separated cancer and control tissues from the squamous cells of tango in male Wistar rats and exposed to the different concentrations of SPIONs	Animals oral tongue squamous cell carcinoma (OTSCC). (6–8 weeks old)	Malignant	Not mentioned	The mitochondria isolated from OTSCC, the samples were divided into small fragments for homogenizing.	SPIONs could induce the mitochondrial toxicity and reduced the SDH activity also the injected SPIONs can induced ROS production lead to death of cancer cells.
Jin et al, 2019[21]	In-vitro study	Magnetic Nanoparticles PEI- Fe3O4	A series of experiments to evaluate the cellular uptake, gene silencing efficiencies, and biological effects of the nanoparticle-delivered siRNAs.	B-cell lymphoma-2 (BCL2) and Baculoviral IAP repeat-containing 5 (BIRC5) into Ca9-22 oral cancer cells	Malignant	Not mentioned	The Human Oral Cancer Cell Ca9-22 and CAL 27 were cultured in Dulbecco's Modified Eagle Medium (DMEM)	The development of a simple and universal siRNA delivery system for oral cancer treatment, as well as the successful delivery of siRNAs targeting BCL2 and BIRC5, which remarkably inhibit the viability and migration of oral cancer cells.

(*Continued*)

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Table 2 (Continued).

Authors & Year	Study Design	Intervention	Methodology	Sample				Outcomes
				Clinical	Cancer Types	Stages	Characteristic	
Su et al, 2019[20]	In-vivo study	The researchers used CD44-targeted magnetic nanoparticles combined with an alternating magnetic field (AMF) to target and kill cancer stem cells within the tumors.	A CCK-8 assay for biocompatibility evaluation, a 3D cell culture technique for obtaining CSCs, Prussian blue staining and laser scanning flow cytometry for targeting efficiency, and AMF treatment for inducing apoptosis in CSCs.	Mice with grafted head and neck squamous cell carcinoma tumors, cell line Cal-27 tumors. (4–5 weeks old)	Malignant	Not mentioned	Cells were cultured using DMEM	CD44-SPIONPs exhibit good biocompatibility, penetrate the cell membrane, and induce CSC apoptosis after AMF treatment, resulting in a 33.43% inhibitory ratio and necrotic areas in the tumor tissue. The study also shows that magnetic fluid hyperthermia can significantly inhibit grafted tumor growth in the Cal-27 mouse model, offering a promising strategy for using targeted magnetic nanoparticles to treat cancers and reduce side effects.
Shanavas et al, 2017[23]	In-vitro study	The intervention in this study is the use of magnetic core-shell hybrid nanoparticles, which are designed to target specific receptors on cancer cells and deliver therapeutic agents which is docetaxel, an anti-cancer drug, encapsulated in the core for targeted therapy while also enhancing magnetic resonance imaging capabilities.	Synthesis of the nanoparticles, their characterization for structural and magnetic properties, and in vitro and in vivo testing for their efficacy in anti-cancer therapy and imaging.	Cultured human cancer cells that express the targeted receptor on their surface, cancer cell lines viz KB (Folate Receptor overexpressing) and PC3 (Folate receptor negative)	Malignant	Not mentioned	Not mentioned	The efficacy of the nanoparticles in targeting and treating cancer cells using encapsulated docetaxel, as well as their ability to enhance magnetic resonance imaging capabilities. Enhancement in nanoparticle uptake by folate receptor positive oral cancer cells caused significant increase in docetaxel mediated cytotoxicity
Cheng et al, 2016[32]	In-vitro study	The development and characterization of a multifunctional nanocomplex consisting of SPIONs conjugated with alginate, which is designed to deliver DOX to oral cancer cells.	Synthesis of SPIONs functionalized with the-NH3+ group, followed by conjugation with alginate through a carbodiimide reaction. The resulting nanocomplex is then used to encapsulate DOX, which is released in a controlled manner in response to changes in pH. The release profile of DOX from the nanocomplex is evaluated in vitro using various pH conditions and evaluated the in vitro cytotoxicity of the doxorubicin-loaded nanoparticles on cancer cells.	Cultured human oral cancer cells	Malignant	Not mentioned	Not mentioned	The characterization of the nanocomplex and its ability to deliver DOX in a controlled manner. The results show that the nanocomplex successfully releases DOX in a pH-dependent manner, with the highest release percentage observed at pH 5.5. This suggests that the nanocomplex could potentially be used to target oral cancer cells, which typically have a lower pH environment than normal tissues.

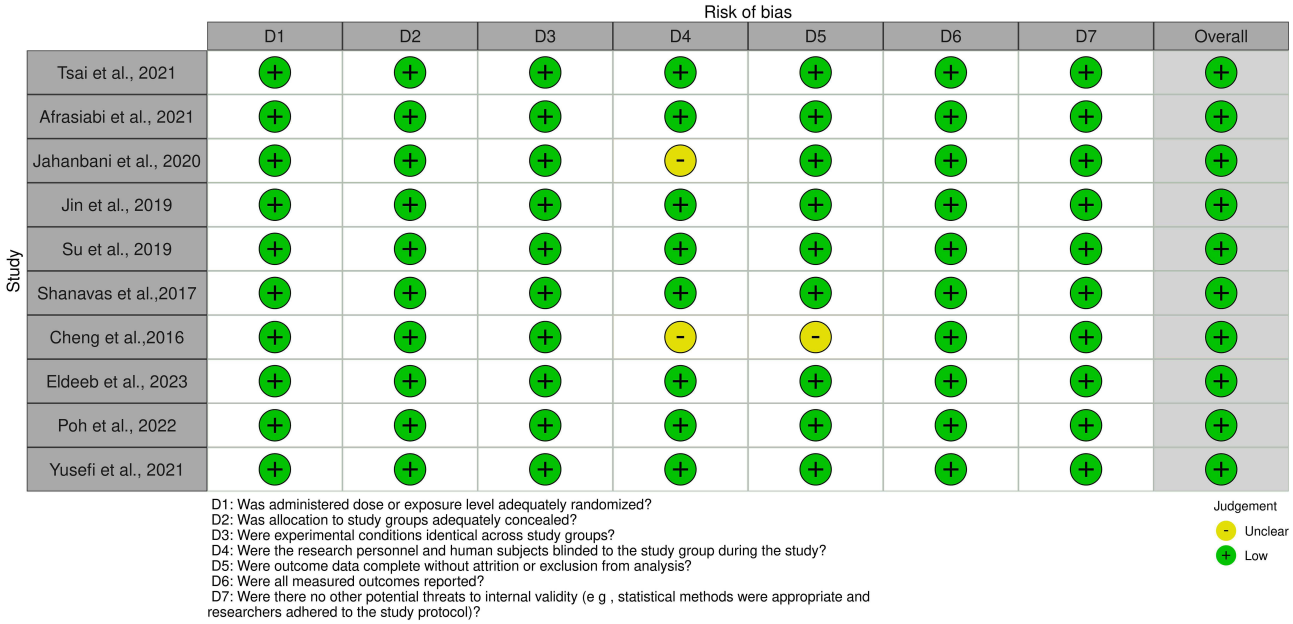

Figure 2 Risk of Bias Table.

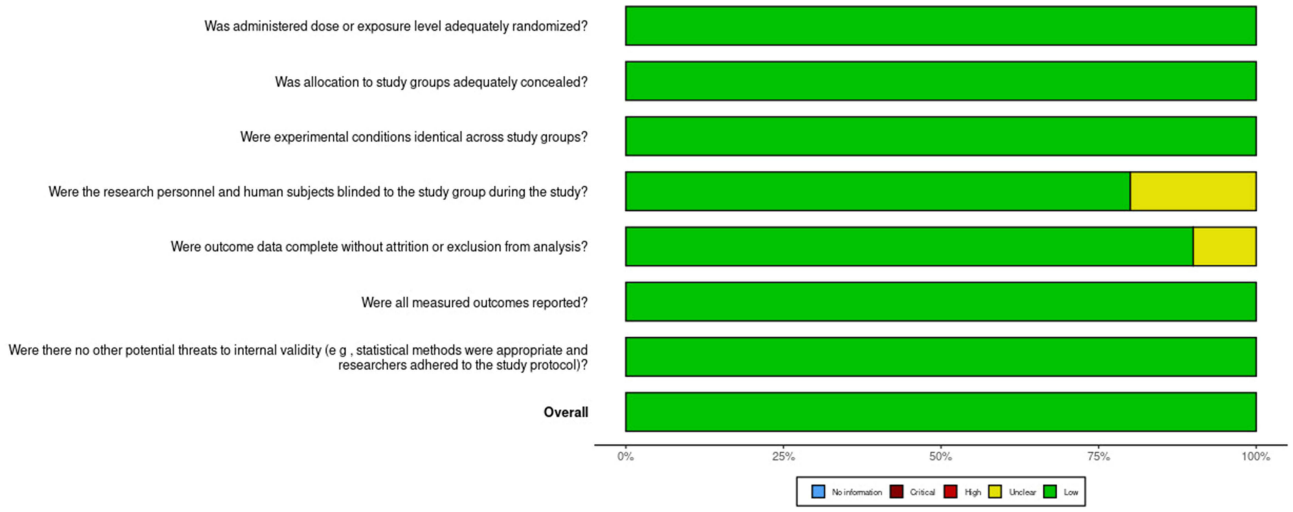

Figure 3 Risk of Bias Chart.

and versatility, rendering them appropriate for a range of medical uses. It also provides a simple and effective means of producing SPIONs, rendering it a more economical and accessible method.[40]

Mostly by inducing hyperthermia, which is noninvasive and causes little harm to the surrounding healthy tissues, SPIONs have great promise as a cutting-edge treatment for oral cancer. SPIONs hold significant potential as a novel approach to oral cancer treatment, mainly through hyperthermia, which is noninvasive and minimally disruptive to surrounding healthy tissues.[41]

Magnetic hyperthermia is used in the treatment of oral cancer with SPIONs. The Alternating Magnetic Field (AMF) is the foundation of this technique. Heat is released into the environment as iron's magnetization changes in response to certain resistance forces (also known as the Brownian and Neel relaxation process).[42] This phenomenon explained in (Figure 5) can be employed as an adjuvant treatment for radiation or chemotherapy, or it can be used directly in cancer treatments. Either drug delivery or cell damage is caused by the emitted heat. Because superparamagnetic have larger

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Table 3 Superparamagnetic Iron Oxide Nanoparticles (SPIONs) from Green Dentistry Process

Authors & Year	Study Design	Methodology	Sample				Efficacy	Outcomes
			Source	Types	Process	Characteristic		
Eldeeb et al, 2023[33]	In-vitro study	The methodology involved Citrus sinensis peel extract as a biological method in an eco-friendly approached for stabilizing, reducing, and capping agents during the synthesis of Superparamagnetic Iron Oxide Nanoparticle	*Citrus sinensis*	Superparamagnetic Iron Oxide Nanoparticles	Green synthesis using a plant extracts as a stabilizing, reducing, and capping agents for making a Fe3O4 nanoparticles.	The synthesized SPIONs are likely spherical or near-spherical nanoparticles with a size of around 20 nm. They possess a crystalline structure of magnetite (Fe3O4) and interact with biomolecules from the orange peel extract used for synthesis.	The synthesis SPIONs using Citrus successfully provide antimicrobial ability to several bacteria such as S. Aureus, S Mutans, etc. Also, SPIONs exhibited a good antioxidant activity at various concentrations.	The study demonstrate that SPIONs could be synthesize using a green approach, utilizing Citrus sinensis peel extract. The SPIONs exhibited good magnetic properties and surface functionalities, this properties could be use in hyperthermia therapy and targeted cancer treatment.
Poh et al, 2022[11]	In-vitro Study	The methodology involved of a concept green synthesis using plant extracts as a biological method for the production of Iron Oxide Nanoparticles. This study also highlights the advantages of green synthesis compared to physical and chemical methods, which can involve harmful chemicals, high energy consumption, and longer synthesis times.	Plants extracts	Iron Oxide Nanoparticles	Synthesized using a green method with plant extracts as reducing and capping agents.	Environmental friendly, simple cost effective, and tunable properties	This SPIONs can be used for drug delivery, it will reduce the side effects of specific drugs attached with SPIONs.	The main outcomes is green synthesis using plant extracts is a promising approach for producing iron oxide nanoparticles with potential applications in various fields due to their environmentally friendly nature, simplicity, and diverse functionalities.
Yusefi et al, 2021[34]	In-vitro study	The methodology involved an extraction from *Garcinia mangostana* fruit peel as a biological method for stabilizing Fe3O4 NPs for hyperthermia and anticancer activities.	*Garcinia mangostana*, Fe3O4 Nanoparticles	Fe3O4 Nanoparticles	Green synthesis using a novel stabilizer: crude extract of Garcinia mangostana fruit peel	The synthesized Fe3O4 nanoparticles have a pure cubic spinel structure as shown by the vibrating sample magnetometer (VSM) with magnetic properties, and Cytotoxicity,	This SPIONs created from *Garcinia Mangostana* fruit peel provides anticancer activity, inducing hyperthermia, and has a potential for drug delivery.	The study demonstrates that Garcinia mangostana fruit peel extract can be a cost-effective and green approach to synthesize Fe3O4 nanoparticles with potential applications in hyperthermia therapy and targeted cancer treatment.

Abbreviations: HSC, Human Oral Squamous Cell Carcinoma; MMP, Matrix Molecular Protein; SPIONs, Superparamagnetic Iron Oxide Nanoparticles; OSCC, Oral Squamous Cell Carcinoma; ROS, Reactive Oxygen Species; OTSCC, Oral Tongue Squamous Cell Carcinoma; DMEM, Dulbecco's Modified Eagle Medium; BCL, B-Cell Lymphoma; PEI, Polyethyleneimine; NPs, Nanoparticles; RNA, Ribonucleic acid; AMF, Alternatif Magnetic Field; SDH, Succinate Dehydrogenase.

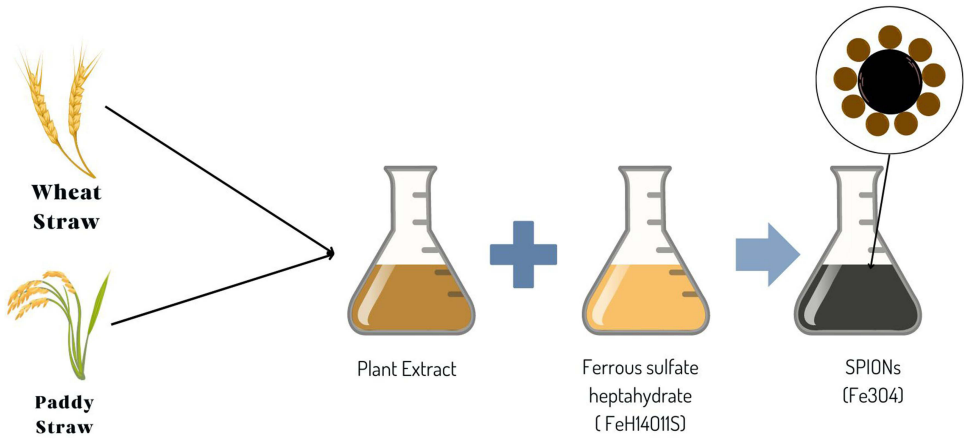

Figure 4 General Illustration for Biosynthesis Method.

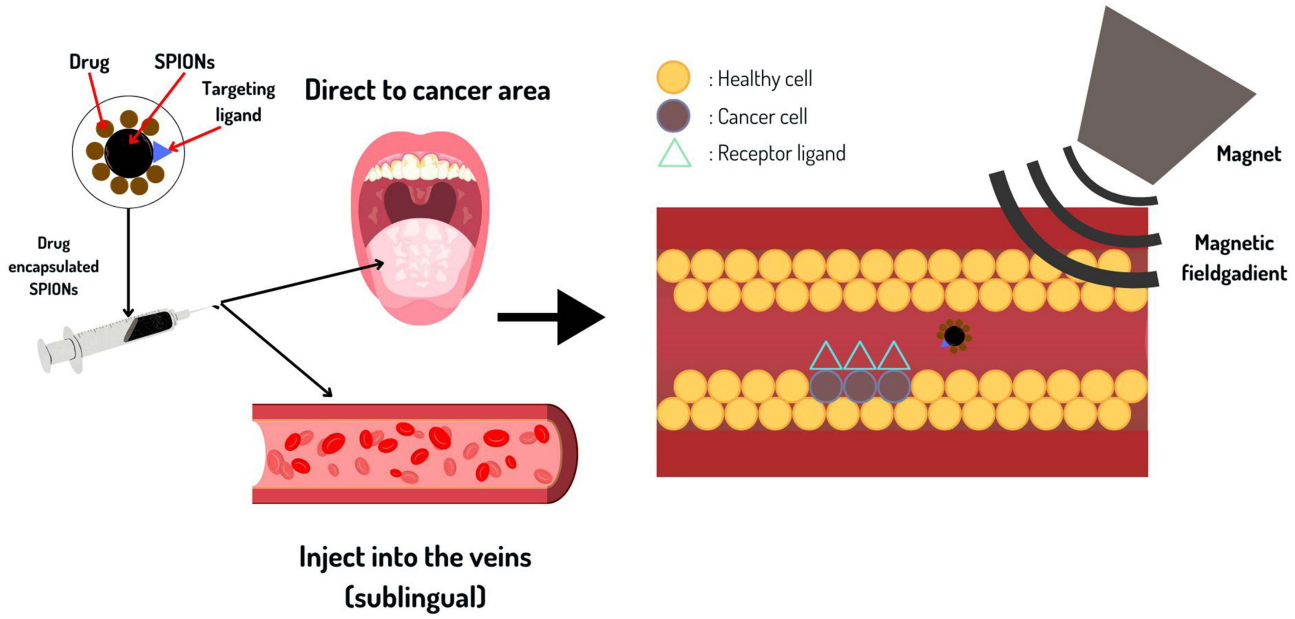

Figure 5 Schematic Illustration of SPIONs in Oral Cancer Treatment.

hysteresis losses for single-domain magnetic particles, they produce more heat than ferromagnetics under the same circumstances.[43]

Litweka et al reported that SPIONs can be given in two general ways to produce hyperthermia. The first method involves directly injecting NPs into the tumor. A more uniform distribution across the entire circulatory system may be achieved by injecting them into the veins, which is the second option. When SPIONs are specifically directed towards tumor cells, as might be done using specific antibodies, the process creates a large build-up of SPIONs both outside and inside those cells.[44] Thermal energy will only be released inside the tumor and its immediate surroundings when SPIONs are placed in a magnetic field. After that, only a small number of nearby healthy cells would be impacted by collateral damage. According to a study by Szwed and Marczak. The entire process causes the tumor's temperature to rise to 43–45°C, or usually higher if it is above 42°C. This is high enough to kill the cells.[45] The treatment is successful because the high temperature triggers several processes that ultimately destroy the cells. This is especially important since cancer cells are far more sensitive to temperature increases because they have numerous somatic mutations.[46] The mechanism underlying SPIONs magnetic hyperthermia is the application of an alternate magnetic field, typically with a moderate

amplitude and frequency ranging from 100–300 kHz, to convert magnetic energy into thermal energy. The production of heat is facilitated by four distinct mechanisms, namely eddy current loss, hysteresis loss, Néel relaxation loss, and Brown relaxation loss.[42,47,48] The superparamagnetic characteristics of the SPIONs not only allow them to combine chemotherapy and hyperthermia, but they also give T2 contrast for magnetic resonance imaging (MRI) and the capacity to locally accumulate in particular tissues or organs when an external magnetic field is applied.[49]

Systemic toxicity, resulting from a lack of tumor specificity in the delivery of anticancer drugs, frequently compromises conventional cancer chemotherapy treatments. The drug's side effects restrict the dosage that can be taken, making it challenging to treat cancer effectively.[50] By specifically targeting the tumor and utilizing the naturally leaking vasculature of the tumor to enhance the accumulation of drug-loaded nanoparticles within the tumor interstitium,[51] nanoparticle-based drug delivery has the possibility of overcoming this obstacle. The more advantageous pharmacokinetics and adjustable biodistribution of nanoparticles allow for the loading of anticancer medications, which can boost the drug's effectiveness. It is also possible to shield drug molecules contained in a nanoparticle from oxidation and degradation while the particle is in circulation.[51–53]

Drugs that are delivered locally and formulated inside SPIONs have the ability to either passively or actively target cancer cells. When SPIONs are actively targeted, they are functionalized to recognize particular receptors on the cancer cell surface, which increases drug delivery inside the cancer cell while sparing most healthy cells. In passive targeting, SPIONs enter cancer cells through diffusion and enter the cytoplasm through endocytosis.[51,52] TRPV1 or the epithelial growth factor receptor (EGFR) are the type of receptors. Magnetic drug targeting (MDT) is a technique that uses an external magnetic field to guide SPIONs to the tumor region. This allows for more precise delivery of the drug to the tumor site, reducing side effects and increasing treatment efficacy.[53,54] Furthermore, SPIONs can be used as contrast agents in magnetic resonance imaging (MRI), which makes imaging-controlled therapy possible.[55]

Our study concludes the effectiveness of superparamagnetic iron oxide nanoparticles (SPIONs) in oral cancer treatment can be viewed from how SPIONs characteristics can be used for targeted drug delivery, multimodal therapy, and imaging. SPIONs can be functionalized with various cargos, such as chemotherapeutic agents, photosensitizers for photodynamic therapy, and immune modulators, allowing for targeted delivery to tumor cells. This targeted delivery can help overcome the challenges of conventional chemotherapy, such as systemic toxicity and lack of tumor specificity.

It is possible for SPIONs to identify and communicate with bloodstream-circulating immune cells. This is an example of how immune cells that have been loaded with nanomedicines function as drug carriers, greatly prolonging the half-life of nanoparticles that have broad-spectrum tumor-targeting capabilities. It is interesting to note that immune cells have homing properties that allow them to cross a variety of biological barriers and make them natural carriers. SPIONs can be made from agricultural wastes, such as lignin, using a biosynthesis method. This method involves using plant extracts or biopolymers from agricultural waste to produce biogenic nanoiron oxide with superparamagnetic power and antioxidant strength. It has been discovered that biological processes using agro-waste under green synthesis are easier, more cost-efficient, and more ecologically friendly than physical and chemical processes for creating iron oxide-based nanostructures.[11]

This study has potential limitations due to limits of access to data and limits the representativeness, validity, or reliability of the data. Only a small amount of study so far has been specifically explaining SPIONs produced with biosynthesis method in oral cancer treatment. The search result of this study relied solely on in-vitro, which may not accurately reflect the interactions that occur in vivo. This causes a gap between the research that has been carried out and the facts in the fields. The findings of this study may not be directly applicable to clinical settings. Therefore, to overcome the limitation of this study, further research could focus on incorporating in-vivo for better clinical practice. However, according to our paper, agricultural waste such as lignin can be produced into SPIONs using the biosynthesis method and holds potency for oral cancer treatment using drug delivery and hyperthermia.

Conclusion

Using SPIONs as a treatment modality for oral cancer has demonstrated notable effectiveness and versatility. This study provides robust evidence supporting the use of SPIONs in managing oral cancer and the potential of creating SPIONs through the green synthesis process. Their multifunctional nature and ability to enhance treatment efficacy while minimizing collateral damage to healthy tissues underscore the effectiveness and promise of SPION-based oral cancer

treatments. This is demonstrated by SPIONs potential ability from agricultural waste to target and destroy specific oral cancer cells. Perhaps, future research is necessary to increase the application of SPIONs in treating oral cancer.

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Disclosure

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