Review Article

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Research Progress of Microwave Hyperthermia and Microwave Dynamic Therapy in the Treatment of Solid Tumors

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1. Abstract

Microwaves (MW), utilized in both microwave thermal therapy (MWTT) and microwave dynamic therapy (MWDT), exhibit superior penetrative capabilities compared to traditional inducers such as near-infrared light or ultrasound. They are characterized by an absence of bone-air reflection, minimal bone-air interference, and enhanced clinical safety. [1-3] Studies have established that microwaves possess intrinsic properties that promote osteogenesis4, exhibit anti-inflammatory and anti-infective effects [5, 6] and have antitumor activity [7-10], while allowing for repeated application. Collectively termed microwave therapy, these modalities have demonstrated remarkable therapeutic potential, particularly for the treatment of deep-seated solid tumors [11]. This review systematically categorizes and summarizes current research on microwave sensitizers, evaluates the application of microwave therapy in various solid tumors, and elucidates the therapeutic mechanisms of microwave therapy. It serves as a comprehensive synthesis of advancements in microwave therapy, offering a foundation and inspiration for future research endeavors.

2. Introduction

Microwave therapy, encompassing both hyperthermia and dynamic therapy, has emerged as a promising clinical approach for the management of solid tumors. The superior penetration depth of microwaves, in contrast to near-infrared light or ultrasound, allows for effective treatment of deep-seated tumors without the impediment of bone-air reflection. The unique ability of microwaves to traverse biological tissues with minimal interference presents a significant advantage in cancer therapy. Moreover, microwaves have been shown to possess osteogenic, anti-inflammatory, and anti-infective properties, in addition to their antitumor capabilities. The repeatability of microwave therapy further enhances its clinical applicability.

This manuscript aims to provide a detailed classification and summary of the current research on microwave sensitizers, which are crucial for enhancing the efficacy of microwave therapy. We will review the literature on the application of microwave therapy in the treatment of various solid tumors and discuss the underlying mechanisms that contribute to its therapeutic success. The synthesis of this research progress not only serves as a reference for existing knowledge but also aims to inspire innovative directions for future investigations in the field of microwave therapy.

3. Research of Microwave Sensitizers

Microwave sensitizers play a pivotal role in enhancing the therapeutic effects of microwave therapy. Commonly utilized sensitizers include:

3.1. Porphyrin Compounds:

These compounds, such as hematoporphyrin derivatives, generate reactive oxygen species (ROS) like singlet oxygen under specific microwave wavelengths, exerting a cytotoxic effect on tumor cells [12-14]. In some clinical studies of tumor treatment, using hematoporphyrin derivatives as sensitizers for microwave dynamic therapy has achieved certain therapeutic effects. For example, 5,10,15,20-tetrakis (4-trimethylamino) phenylporphyrinte tratoluene sulfonate, which is a derivative of porphyrin and has certain photosensitive properties, and may exhibit good sensitivity under the action of microwaves. Porphyrin compounds have unique structures and properties and have potential application value in microwave dynamic therapy [15-18]. However, the specific application and effect of porphyrin microwave sensitizers may be affected by various factors, such as the structure of the compound, microwave parameters, and treatment environment. Researchers usually optimize the microwave sensitive performance by modifying the porphyrin structure or

compounding it with other materials to improve the effect in microwave dynamic therapy [15, 16, 19]. In addition, different porphyrin derivatives may have different characteristics and application scopes, and the specific application requires in-depth research and screening based on the actual situation. As in this article [20], the researchers designed covalent organic framework-coated metal-organic framework nanocapsules (MOF@COF), in which the MOF of Bi-Mn-porphyrin (BM) is designed as a microwave sensitizer to generate cytotoxic reactive oxygen species and heat for microwave dynamic therapy (MWDT) in coordination with MWTT.

3.2. Phthalocyanine Compounds:

such as zinc phthalocyanine. These compounds possess excellent optical and microwave absorption characteristics. Among phthalocyanine compounds, zinc phthalocyanine has a structure that enables it to efficiently absorb energy in a microwave field and convert it into active substances required for treatment [21, 22]. It has shown potential application value in some experimental studies.

3.3. Metal ions:

For the development and use of many reported sensitizers for microwave tumor thermal therapy (MWTT) and microwave tumor dynamic therapy (MWDT), research mainly focuses on metal ions or metal-organic frameworks. Some are evolved and developed from photosensitizers and sonosensitizers. For example, as reported by Wang Yuxin et al[23], the organic metal framework COF-covered and packaged TiMOF can generate high-intensity and high-concentration reactive oxygen species (ROS) under microwave action for anti-tumor treatment. Ma Xiaoyan et al. [24] confirmed that Fe metal-organic framework nanoparticles (MIL-101(Fe) NPS) can be used to prepare nanoenzymes to generate reactive oxygen species (ROS) and induce cancer cell death by catalyzing endogenous substances in the tumor microenvironment. A large number of stimulus-responsive hydroxyl radicals (•OH) are accelerated to generate under microwave irradiation, thereby realizing microwave-enhanced dynamic therapy (MEDT). Zhou Hui et al [25] confirmed that microwave dynamic therapy mediated by copper cysteamine nanoparticles can improve cancer treatment by inducing ferroptosis. In addition, there are also nanoenzymes based on liquid metals [26]. Manganese-doped Ti-based MOFs cooperate with MWTT and MWDT for the treatment of liver cancer [27].

In In a study [28], a novel flexible Mn-doped zirconium metal-organic framework (Mn-ZrMOF) nanocube (NCs) with an average size of approximately 60 nm is easily prepared by a one-pot hydrothermal method. Due to the strong inelastic collisions of ions confined in a large number of micropores, Mn-ZrMOF NCs are proven to be an effective microwave sensitizer with a thermal conversion efficiency as high as 28.7%, which is one of the highest among the recently reported microwave sensitizers. This kind of Mn-ZrMOF NCs generates abundant hydroxyl radical reactive oxygen species (ROS) under microwave irradiation. Therefore, Mn-ZrMOF NCs effectively inhibit the growth of tumor cells in vivo and in vitro under mild microwave irradiation, thus exerting a synergistic effect of MTT and MDT. This work paves the way for the development of nanoformulations that respond to microwave irradiation, generate ROS and improve the thermal effect to achieve non-invasive MTT and MDT treatments in clinical practice. This is the first report to determine the microwave thermal conversion efficiency, which can be used to evaluate, compare and predict the microwave sensitivity of different microwave sensitizers.

This article [29] also discovered and confirmed the microwave response characteristics of metal ions. This research developed a composite metal ion hydrogel of calcium ions (Ca^{2+}), manganese ions (Mn^{2+}), and sodium alginate. It can enhance the heating effect of microwaves and confine the heating range through the ion confinement effect. A higher concentration of extracellular Ca^{2+} can significantly enhance the cell killing effect of mild hyperthermia treatment (~45°C) and improve the therapeutic effect of microwave ablation on primary tumors. At the same time, it can also induce immunogenic cell death of tumor cells by interfering with intracellular Ca^{2+} homeostasis. When combined with Mn^{2+} with STING activation function, it can induce the body to produce a specific anti-tumor immune response and effectively inhibit tumor metastasis and recurrence. The above research results all suggest that metal-organic frameworks and certain metal ions may have microwave response properties and induce microwave hyperthermia and microwave dynamic therapy for tumors, which provides new ideas and solutions for the treatment of deep-seated solid tumors in the body.

In the realm of microwave therapy, the development of metal ion sensitizers has been extensively documented within patent disclosures and scholarly articles. Notably, a patent delineates a core-shell nanoparticle, MCOF-3@ZIF-67, which represents a sophisticated construct of the zeolitic imidazolate framework ZIF-67 enveloping the metal chalcogenide open framework MCOF-3. This intricate architecture facilitates the generation of reactive oxygen species (ROS) and Co^{3+} ions upon exposure to microwave irradiation. Concurrently, the Co^{3+} ions catalyze the production of O_2, which in turn, augments ROS proliferation, thereby enhancing the responsiveness to microwave stimuli and bolstering the oxidative stress inflicted upon tumor cells. Furthermore, the Cu^{+} ions embedded within the MCOF-3 framework are induced to transfer electrons under microwave irradiation, leading to the formation of hydroxyl radicals and an ensuing surge of ROS. This process is pivotal in instigating tumor cell apoptosis, underscoring the dynamic sensitizing role of the construct. The internal porous structure of ZIF-67 plays a crucial role in confining the movement of MCOF-3 particles, thereby localizing the thermal effect. When subjected to microwave irradiation, these particles vibrate within the ZIF-67 matrix, intensifying heat generation and endowing the core-shell nanoparticles with superior microwave thermal and dynamic sensitization properties.

The synthesis protocol of this microwave sensitizer entails the initial blending of a cobalt salt ethanol solution with an aqueous solution of the metal chalcogenide open framework MCOF-3, yielding a mixed solution of MCOF-3/cobalt salt. Subsequently, an ethanol solution of 2-methylimidazole and polyvinylpyrrolidone is incorporated into the mixture, culminating in the formation of the microwave sensitizer. This

sensitizer holds significant promise in oncological applications, where it can be integrated with microwave radiation to target tumors. Beyond oncology, the technology also exhibits potential in applications pertaining to antibacterial and anti-inflammatory therapies, thus broadening its scope of therapeutic utility.In addition, the development of some metal nanozyme microwave sensitizers can also solve the limitation of the tumor hypoxic microenvironment on microwave dynamic therapy. Research team [26] designed a liquid metal-based nanozyme LM@ZIF@HA (LZH), which takes eutectic gallium-indium (EGaIn) as the core and is coated with CoNi bimetallic zeolitic imidazolate framework (ZIF) and hyaluronic acid (HA). The flexibility of liquid metal and the targeting property of HA enable the nanozyme to be effectively endocytosed by tumor cells, solving the problem of poor delivery of microwave sensitizers. Due to its catalase-like activity, the nanozyme catalyzes the excessive H_2O_2 in the tumor microenvironment to produce O_2, alleviating the limitation of the tumor hypoxic microenvironment and promoting the production of reactive oxygen species (ROS) under microwave irradiation. In in vitro cell experiments, the nanozyme has significant targeting effect, oxygen production capacity and microwave dynamic effect, effectively solving the defects of MDT. In the constructed patient-derived xenograft (PDX) model, the nanozyme still achieves excellent MDT effect. The tumor volume in the LZH+MW group is only about 1/20 of that in the control group, and the tumor inhibition rate is as high as 95%. Based on TiMOF (TM) [23], this paper designs an efficient microwave sensitizer for microwave thermo-dynamic therapy. TM can generate heat and cytotoxic reactive oxygen species (ROS) under microwave irradiation and may be used as a microwave sensitizer. However, the poor microwave dynamic sensitization effect of TM limits its application. In order to improve the molecular weight dynamic sensitization performance, a covalent organic framework (COF) with good stability and a large conjugated system are used to cover TM. TM helps electron and energy transfer, thereby increasing the ROS production rate and prolonging the ROS lifetime. In addition, loading nickel nanoparticles endows nanomaterials with magnetic resonance imaging ability. Therefore, this study developed a TM-based microwave sensitizer for the first time and preliminarily explored the mechanism of COF coating to enhance the microwave dynamic sensitization of TM, providing a new idea for further developing microwave sensitizers with great potential.

Research [30] studies a theranostic agent based on ZIF-67. It loads MCOF 3 and HSP 70 as internal components and combines TCM as a biomimetic shell. The metal ions in MCOF 3 give the composite agent peroxidase-like activity to generate •OH and destroy cancer cells. The MW thermosensitive agent of ZIF-67 converts MW energy into heat and selectively heats tumors through cell targeting. Continuous microwave hyperthermia promotes HSP 70 expression and activates effector cells like CD4 T and CD8α T cells. Due to the synergy of MTDT and immune cell activation, the reagent effectively inhibits tumor cell growth under MW irradiation in vitro and in vivo, providing an emerging strategy for effective cancer ablation. This paper [31] constructs a heterojunction of Fe_2O_3/Fe_3S_4 magnetic composite for the short-term effective treatment of osteomyelitis caused by MRSA. The composite shows strong MW absorption, converting electromagnetic energy into heat. Finite element analysis reveals greater electromagnetic field enhancement and more hot spots than Fe_2O_3 alone. These hot spots facilitate charge differential movement at the interface, increasing free electron release which combines with adsorbed oxygen to generate ROS and heat. The study achieves remarkable bacterial eradication through the synergy of MWTT and MDT, providing a new strategy for treating deep tissue bacterial infections. Although this article is not targeted at tumor treatment, it proposes and verifies the microwave response and absorption function of iron ions and their composite materials. Meanwhile, it confirms their potential for microwave dynamic therapy.

The above results indicate that metal nanozyme-based microwave sensitizers can be fused and improved with different types of material systems due to their plasticity, further solving various problems in microwave hyperthermia and microwave dynamic therapy. 3.4.New Materials Category:In addition, some studies have synthesized and invented new microwave-sensitive molecules. For instance, “Aggregation-induced emission luminogens for highly effective microwave dynamic therapy” [32] was published in Bioactive Materials. The article presents the activation of a special type of photosensitive molecule—aggregation-induced emitters (AIEgens) using microwave technology, which can effectively generate reactive oxygen species and thus kill cancer cells effectively. They discovered that two AIEgens (TPEPy-I and TPEPy-PF6) serve as a new type of microwave (MW) sensitizer to produce reactive oxygen species including singlet oxygen (1O2), thereby destroying cancer cells effectively. The results of MTT assays and live/dead assays indicate that these two AIEgens can effectively kill cancer cells when activated by microwave radiation, with average IC-50 values of 2.73 and 3.22 μM respectively. Generally speaking, the ability of these two AIEgens to be activated by microwaves not only overcomes the limitations of traditional PDT but also helps improve existing microwave ablation therapy by reducing the microwave dose required to achieve the same therapeutic effect, thereby reducing the occurrence of side effects of microwave radiation.

In a recent study [33], authors designed and prepared a nonionic microwave sensitizer by encapsulating ethyl formate (EF) and doxorubicin (DOX) in liposomes (EF-DOX-Lips) to enhance microwave ablation (MWA) for antitumor therapy. The comprehensive effects of EF-DOX-Lips include the enhanced microwave heat conversion efficiency by EF, chemical ablation triggered by EF metabolism, enhanced cavitation effect by EF vaporization, and DOX release. Multiple antitumor mechanisms synergistically and powerfully induce tumor cell death, inhibit tumor proliferation and angiogenesis, thereby improving the survival prognosis of mice with primary liver cancer (HCC). In a study [34], a nanomedicine delivery system named ATSL was developed for effective sequential cancer therapy by using thermosensitive liposomes (TSL) and an oxygen-independent free radical generator (2,2’-azobis[2-(2-imidazolin-2-yl) propane] dihydrochloride [AIPH]). Under the action of a microwave field, the temperature rise of local tissues can not only cause damage to tumor cells but also induce the release of AIPH encapsulated by ATSL to generate free radicals, leading to the death of tumor cells.

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In general, microwave sensitizers can improve the effect of microwave ablation. The mechanisms of action include:

1. Enhanced thermal effect: Microwave sensitizers can absorb microwave energy more effectively and convert it into heat energy, thereby enabling tumor tissues to reach a higher temperature and completely kill cancer cells.
2. Expanded ablation range: Ensure that tumor tissues are more comprehensively covered, reduce residual cancer cells, and lower the risk of recurrence.
3. Synergistic therapeutic effect. Combination with chemotherapeutic drugs: For example, combining drugs such as doxorubicin with microwave sensitizers can simultaneously exert the synergistic effect of chemotherapy and hyperthermia under microwave action and enhance the lethality to tumor cells. Inducing immune response: Some microwave sensitizers can induce immunogenic cell death in tumor cells, activate the body's immune system, enhance the anti-tumor immune response, and inhibit tumor metastasis and recurrence.
4. Precise treatment and targeted delivery: By modifying microwave sensitizers, they can specifically target tumor tissues and reduce damage to normal tissues.

In general, microwave-sensitive materials and nanoparticles include porphyrins and their derivatives, metal ions and their metal-organic frameworks, and some new material types such as polymers and liposomes. These materials have their own advantages and disadvantages, but they can all respond to microwaves and exert microwave thermal effects or the generation effects of reactive oxygen species molecules, thereby exerting antitumor or antibacterial functions. Their classification is shown in Figure 1.

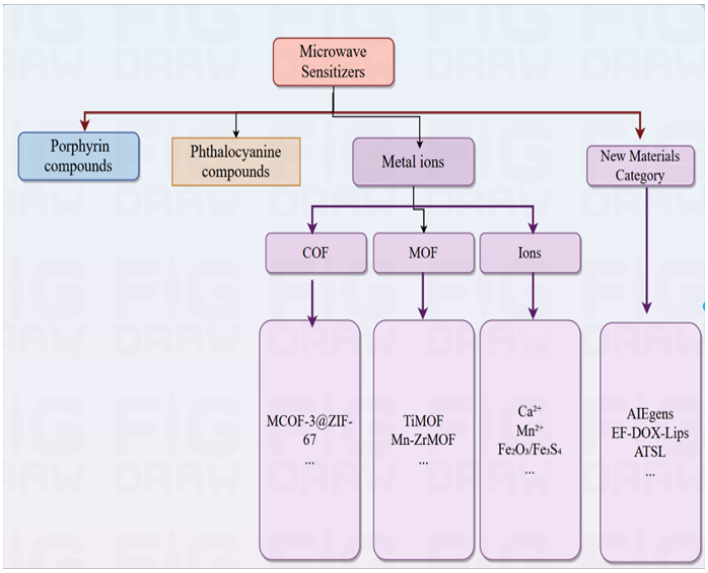

Figure 1: Schematic diagram of the classification of microwave-responsive materials.

4. Application Of Microwave Hyper thermia And Microwave Dynamic Therapy In Solid Tumors.

4.1. Breast Cancer:

Microwave hyperthermia can increase the sensitivity of tumor cells to radiotherapy and chemotherapy and improve the treatment effect. For example, in some clinical trials, breast cancer patients received microwave hyperthermia while undergoing radiotherapy, and the tumor control rate was significantly improved. As mentioned [35], the combined treatment of microwave hyperthermia and lobaplatin can reduce the viability, colony formation, cell invasion and metastasis of breast cancer cells. In addition, drugs induce apoptosis and autophagy in breast cancer cells, activate the c-Jun N-terminal kinase (JNK) signaling pathway, inhibit the protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway, and down-regulate the expression of IAP and Bcl-2 family proteins. These results indicate that lobaplatin is an effective anti-tumor drug for breast cancer, and microwave hyperthermia is an effective preventive treatment method. A research36 designs an ultra-wideband phased array applicator for breast cancer hyperthermia therapy. It is a three-ring phased array applicator composed of ultra-wideband (UWB) microstrip antennas and can be used for cancer treatment. The working frequencies are 0.915 GHz and 2.45 GHz respectively. The proposed antenna has an ultra-wide bandwidth from 0.7 GHz to 5.5 GHz, with resonant frequencies of 0.915 GHz and 2.45 GHz, and a size of $15\times43.5\times1.575$ mm^3. According to the performance indicators of the SAR distribution and tumor eccentric focusing results of four different numbers of single-ring arrays, the number of each ring is selected to be 12. The uniform breast model is applied to the three-ring phased array composed of 36 elements for focusing simulation, and tumors of 1 cm^3 and 2 cm^3 are placed in three different positions of the breast. The simulation results show that after selecting the appropriate working frequency, the proposed phased array has good performance and can increase the temperature of cancers of different volumes to above 42.5 °C. The proposed applicator allows precise treatment of tumors by selecting an appropriate operating frequency based on the size of the malignancy.

Zhang H. et [37] uses microwave hyperthermia to enhance drug permeability. The researchers designed a smart drug delivery system (SDDS) to change the resistance of triple-negative breast cancer and improve the drug delivery and therapeutic efficacy of TNBC. This system uses microwave radiation to generate mild hyperthermia. The SDDS is formulated with thermosensitive polymer-lipid nanoparticles (HA-BNP@Ptx), which are composed of polymer PLGA, phospholipid DPPC, hyaluronic acid, 1-butyl-3-methylimidazolium-L-lactate (BML, a MW sensitizer), and paclitaxel (Ptx, a chemotherapy drug). Before injecting nanoparticles, tumors in mice are pretreated with the first MW irradiation to modify and promote the tumor microenvironment (TME) and promote nanoparticle uptake and retention. The tumor is subjected to a second MW irradiation 24 hours after injecting HA-BNPs@Ptx to generate a synergistic cascade effect by activating BML, thereby enhancing the hyperthermia effect and immediately releasing Ptx at the tumor site. After the first MW irradiation of mouse tumors, the intratumoral perfusion increased

by 2 times and the nanoparticle uptake increased by 7 times. After the second microwave irradiation, the tumor inhibition rate can reach 88%. In addition, immunohistochemical analysis shows that SCS treatment can not only promote tumor cell apoptosis but also significantly reduce lung metastasis. A paper [38] conducted research on microwave thermokinetic therapy of breast cancer using magnetic bimetallic heterogeneous interface nanoparticles. In this study, by introducing magnetic loss and dielectric loss, a Ni-based multilayer heterogeneous interface MOFs-Ni-Ru@COFs (MNRC) nano-ceramic was developed. The heterogeneous interface formed in MNRC through nanoengineering induces significant interface polarization, increases dielectric loss, and then enhances the generated MA performance. In addition, MNRC with strong MA performance in the required frequency range not only enhances the MW thermal effect of MWT but also promotes electron and energy transfer, generating reactive oxygen species (ROS) at the tumor site to mediate microwave dynamic therapy (MDT). The strategy of improving MWT-MDT by enhancing the MA performance of sensitizers in the medical frequency band provides a direction for expanding the clinical application of MWT in tumor treatment. Wu Q et. [39] designed nano-activators enhance micro wave the rmodynamic chemotherapy to effectively kill primary tumors, while improving the immunosuppressive microenvironment, activating tumor infiltration of T lymphocytes, and enhancing the accumulation and penetration of PD-1/PD-L1 immuno therapeutic agents, ultimately enhancing the efficacy of immune checkpoint blockade therapy to achieve effective inhibition of distal tumors and metastases. Thus, it can be seen that microwave hyperthermia and microwave dynamic therapy in triple-negative breast cancer are mainly carried out through the combination with other treatment methods, which can achieve a lasting tumor suppression effect. The treatment mechanism of microwave therapy for breast cancer is shown in Figure 2. It includes enhancing drug penetration, improving the tumor immune microenvironment, enhancing T cell infiltration, and reducing the viability of tumor cells.

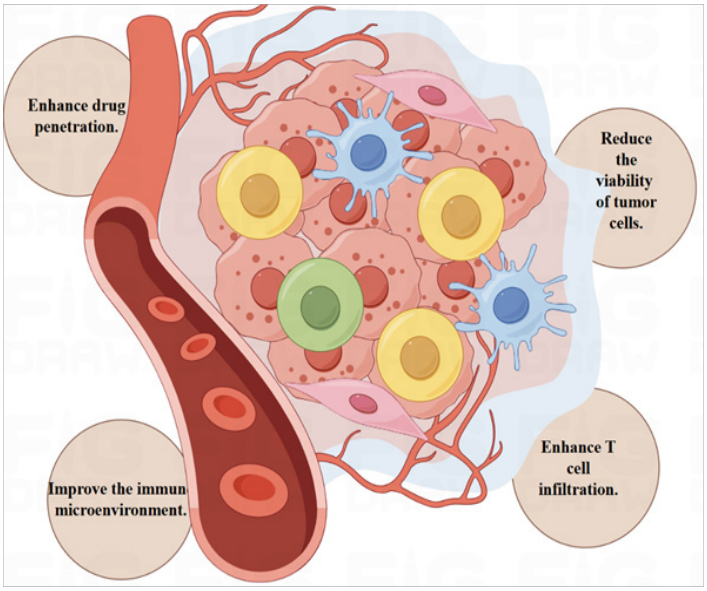

Figure 2: The effect of microwave therapy on breast cancer cells.

4.2. Liver Cancer:

For patients with liver cancer, especially those with unresectable or advanced liver cancer, microwave hyperthermia and microwave dynamic therapy can be used as a local treatment method. Through thermal effects or other mechanisms, it induces tumor cell apoptosis and inhibits tumor growth. The article [40] prepared Mn-doped Ti MOFs (Mn-Ti MOFs) nanosheets by an in situ doping method and applied them to microwave therapy. Infrared thermal imaging results show that the porous structure of Mn-Ti MOFs increases the frequency of microwave-induced ion collisions, thereby rapidly increasing the temperature of physiological saline. The results on HepG2 tumor-bearing mice prove that microwave-triggered Mn-Ti MOFs almost eradicated liver cancer tumors after 14 days of treatment. This study provides a promising sensitizer for microwave thermodynamic synergistic treatment of liver cancer. In research [41], a novel microwave-activated copper-doped zirconium metal-organic framework (MOF) (CuZr-MOF) for enhancing percutaneous microwave ablation (PMA) is proposed, with significantly improved microwave sensitization effect. CuZr-MOF can inhibit the production of heat shock proteins (HSPs) by generating a large amount of ROS, thereby enhancing tumor destruction. Mechanistically, we found that CuZr-MOF + MW treatment regulates ferroptosis-mediated tumor cell death by targeting the HMOX1/GPX4 axis. This study has developed a novel CuZr-MOF microwave sensitizer with great potential for synergistic treatment of cancer by MTT and MDT. The [42] paper mentions that nanozymes have good enzyme-mimicking catalytic properties. In this paper, iron-metal organic framework nanoparticles (MIL-101(Fe) NPs) are prepared as nanozymes, which generate reactive oxygen species (ROS) by catalyzing endogenous substances in the tumor microenvironment and induce cancer cell death. Microwave radiation can accelerate the generation of a large amount of stimulus-responsive hydroxyl radicals (•OH), realizing microwave-enhanced dynamic therapy (MEDT).

In addition, MIL-101(Fe) NPs have biodegradability and biological responsiveness, and compared with inorganic nanozymes, they show good metabolic and non-toxic accumulation characteristics. Fluorescent gold nanoclusters (BSA-Au NC) are rapidly coupled to the surface of MIL-101(Fe) NPs to obtain MIL-101 (Fe) @ BSA-Au NC NPs. The magnetic resonance imaging (MRI) and fluorescence imaging (FI) of MIL-101 (Fe) @ BSA-AuNCs nanoparticles can not only accurately image the tumor site, but also monitor the dynamic distribution process of MIL-101(Fe) in vivo. The liver FI and MRI signals reach the maximum value at 1 hour, and the tumor reaches the maximum value at 5 hours. Ionic liquid (IL) is also loaded into MIL-101 (Fe) @ BSA-Au NCs NPs as a microwave-sensitive reagent for microwave thermal therapy (MTT). In this work, a nanozyme with degradability, microwave sensitivity and dual-mode imaging is synthesized, realizing the combined anti-tumor effect of MTT and MEDT. The results of in vivo experiments confirm that the killing rate of tumors is as high as 96.65%, showing a significant anti-tumor effect.

4.3. Lung Cancer:

Microwave therapy can assist traditional lung cancer treatment methods such as surgery, chemotherapy, and radiotherapy. It plays a certain role in

the comprehensive treatment of lung cancer. Researchs43 proposes that a targeted nanoplatform is developed for the construction method of a microwave-responsive nanoplatform (MgFe2O4@ZOL). MgFe2O4@ ZOL nanoparticles release Fe3+, Mg2+ and the cargo of zoledronic acid (ZOL) in the acidic tumor microenvironment (TME). Fe3+ can deplete intracellular glutathione (GSH) and catalyze the generation of •OH from H2O2, thereby producing chemodynamic therapy (CDT). In addition, microwaves can significantly enhance the generation of reactive oxygen species (ROS), so that microwave dynamic therapy (MDT) can be effectively implemented. Moreover, Mg2+ and ZOL promote the differentiation of osteoblasts. In addition, MgFe2O4@ZOL nanoparticles can target and selectively heat tumor tissues and enhance the effect of microwave thermal therapy (MTT). In vitro and in vivo experiments show that synergistic targeting, GSH depletion-enhanced CDT, MDT and selective MTT show significant antitumor efficacy and bone repair. This multimodal combination therapy provides a promising strategy for the treatment of bone metastasis in lung cancer patients.

4.4. Pancreatic Cancer:

Due to the deep location of pancreatic cancer and the complex surrounding tissues, microwave therapy is somewhat challenging in the treatment of pancreatic cancer, but there are still relevant studies exploring its feasibility and effectiveness.

5. Research On The Treatment Mechanism Of Microwave Therapy For Solid Tumors

Microwave ablation (MWA) is a commonly used tumor hyperthermia in clinical practice. In patients receiving MWA treatment, the tumor-specific immune response is significantly enhanced. This is mainly because this surgery can lyse tumor cells and release cell fragments containing tumor-associated antigens, thereby triggering an anti-tumor vaccine reaction in situ. In addition, other studies have carried out enhanced improvements or corresponding mechanism explorations on MWTT and MWDT. For example, Li Shimei et[20] have confirmed that MOF@COF nanocapsules can achieve enhanced microwave thermodynamic therapy effects by inhibiting tumor angiogenesis in colorectal cancer. In this study, the researchers proposed a nanocapsule of covalent organic framework metal-organic framework (MOF@COF) and has the combined effects of microwave (MW) thermodynamic sensitization and tumor anti-angiogenesis. In vivo experiments have verified that this combination therapy significantly inhibits the growth of recurrent-free colorectal cancer. The same research team also proposed a nano-immunomodulator (BI-MOF-L-CYS @peg@ha, BMCPH) to reverse immuno suppression and improve the anti-tumor immune effect by releasing H2S in response in tumor cells to improve MWTT. BI-MOF can also scavenge reactive oxygen species (ROS), which is the main means of MDSC-mediated immuno suppression, which can further weaken the immuno suppressive effect of tumors. At the same time, the strategy of reversing immuno suppression and reactivating anti-tumor immune responses by H2S gas introduces the direction of reducing the risk of tumor recurrence and metastasis after thermal ablation [44]. The research of Zhou Wenbin et al [45]. also confirmed the T cell activity shown by blocking CTLA-4 or PD-1 in microwave ablation of peripheral blood mononuclear cells. This study provides evidence for the systemic characteristics of microwave ablation-induced systemic immune responses and paves the way for identifying potential targets to improve immune responses. In 2023, Limin Ma [46] reported a treatment scheme in which multifunctional 3D-printed scaffolds eradicate orthotopic osteosarcoma and promote osteogenesis through microwave thermo-chemotherapy combined with immunotherapy.

They believe that tumor recurrence and lack of bone tissue integration are two key issues in the surgical treatment of osteosarcoma. Therefore, an advanced multifunctional treatment platform that can simultaneously eliminate residual tumor cells and promote bone regeneration is urgently needed for the efficient treatment of osteosarcoma. To completely eliminate tumors and promote bone regeneration at the same time, the researchers designed an intelligent multifunctional treatment scaffold by integrating microwave-responsive zeolitic imidazolate framework 8 (ZIF-8) nanomaterials loaded with chemotherapeutic drugs and immune checkpoint inhibitors into a 3D-printed titanium scaffold. The constructed scaffold has obvious microwave heat sensitization and tumor microenvironment response characteristics, and can induce tumor immunogenic cell death through microwave hyperthermia and chemotherapy. The in situ implantation of the nanocomposite scaffold can enhance the immune response to osteosarcoma, thereby effectively inhibiting tumor recurrence through synergistic immunotherapy. During long-term implantation, zinc ions released by the degradation of ZIF-8 can induce osteogenic differentiation of stem cells. The porous structure and mechanical properties of the 3D-printed titanium scaffold provide a structural microenvironment for bone regeneration. This study provides a paradigm for designing multifunctional microwave-responsive composite scaffolds for the treatment of osteosarcoma, which may lead to improved treatment strategies for this disease.

6. Summary And Prospects

Microwave thermotherapy and microwave dynamic therapy, as emerging technologies for the treatment of solid tumors, hold broad prospects for future applications. The following outlines key perspectives for advancement:

6.1. Application of Nanotechnology:

With the rapid development of nanomedicine, the application of nanomaterials in tumor diagnosis and treatment has garnered increasing attention. Particularly, multifunctional nanomaterials are not only utilized as imaging contrast agents but also mediate therapies such as thermoacoustic treatment, thermotherapy, and microwave dynamic therapy to precisely eradicate tumors. These nanomaterials, triggered by microwaves, can generate thermal effects or reactive oxygen species, aiding in overcoming the limitations of traditional microwave treatments, such as tumor recurrence and metastasis, and the restricted ablation area.

6.2. Enhancing Therapeutic Efficacy:

Microwave thermotherapy and microwave dynamic therapy can enhance the effects of conventional treatment methods like radiotherapy and chemotherapy by elevating the temperature of tumor tissues. For instance, high temperatures can increase the permeability of cell membranes, facilitating drug absorption, while also activating heat shock proteins, thereby enhancing cellular responsiveness to treatment.

6.3. Precision Treatment:

Future research may focus on improving the precision of these therapeutic methods to minimize damage to surrounding healthy tissues. This could involve refining the directional energy distribution of microwave equipment, as well as developing more effective microwave-sensitive materials.

6.4. Combined Treatment Strategies:

Microwave therapy may be used in conjunction with other treatment modalities such as immunotherapy, photothermal therapy, photodynamic therapy, chemotherapy, and radiotherapy to enhance therapeutic outcomes. Such multimodal treatment strategies can target the diverse biological characteristics of tumors, achieving a more comprehensive therapeutic effect.

6.5. Expansion of Clinical Applications:

As the technology matures and clinical trials progress, microwave thermotherapy and microwave dynamic therapy are expected to become routine methods for treating various types of solid tumors. This includes cancers of the breast, nervous system, esophagus, rectum, stomach, and more.

6.6. Market and Industry Development:

It is projected that by 2030, the industry value growth rate of microwave tumor thermotherapy devices will remain steadily increasing, indicating a growing market demand for such therapeutic equipment. With technological advancements and market expansion, the industry of microwave thermotherapy devices is anticipated to encounter new opportunities for development.

6.7. In-depth Research:

Future studies will need to further elucidate the mechanisms of microwave therapy, including thermal and non-thermal effects, and how they interact with the biological characteristics of tumor cells. This will aid in optimizing treatment strategies to improve therapeutic efficacy and safety. In summary, microwave thermotherapy and microwave dynamic therapy possess significant potential in the field of solid tumor treatment. Continued research and technological development will further promote the clinical application and industrial development of these methods.

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Refrences

1. Li X, Lovell J. F, Yoon J and Chen X. Clinical development and potential of photothermal and photodynamic therapies for cancer. Nat Rev Clin Oncol 2020; 17 (11): 657-674.
2. Guo, S, Gu D, Yang, Y, Tian J, Chen X. Near-infrared photodynamic and photothermal co-therapy based on organic small molecular dyes. J Nanobiotechnology. 2023; 21(1): 348.
3. Zhi D, Yang T, O'Hagan J, Zhang S and Donnelly R. F. Photothermal therapy. J Control Release 2020, 325, 52-71.
4. Sun W. C, Wang C. F, Wan D. Y, Zheng Y F, Wu S. L, Shen J, etal. Cu-Ce-O Bimetallic Oxide Rapidly Treats -Infected Osteomyelitis through Microwave Strengthened Microwave Catalysis and Fenton-Therapy. Small Methods 2023; 7 (7).
5. Li S. M, Xu F.Y, Ren X. L, Tan L. F, Fu C. H Wu Q, etal.S-Reactivating Antitumor Immune Response after Microwave Thermal Therapy for Long-Term Tumor Suppression. Acs Nano 2023; 17(19): 19242-19253.
6. Feng Y. F, Chen Q, Jin C, Ruan Y. Y, Chen Q, Lin W. D,etal. Microwave-activated Cu-doped zirconium metal-organic framework for a highly effective combination of microwave dynamic and thermal therapy. Journal of Controlled Release 2023; 361: 102-114.
7. Wang Q. Z, Zhu X.W, Meng X.W, Zhong H. S. Lenvatinib delivery using a Gd/Fe bimetallic MOF: Enhancing antitumor immunity following microwave-based thermal therapy. Acta Biomaterialia 2023; 172: 382-394.
8. Guo R. Q, Peng J. Z, Li X. G. Microwave Ablation Combined with Anti-Pd-1/Ctla-4 Therapy Induces Anti-Tumor Immune Response to Renal Cell Carcinoma in a Murine Model. J Urology 2022; 207 (5): E1023-E1023.
9. Guo R. Q, Peng J. Z, Li X.G. Microwave ablation combined with anti-PD-1/CTLA-4 therapy induces anti-tumor immune response to renal cell carcinoma in a Murine Model. Eur Urol. 2022; 81: S602-S602.
10. Shao D, Chen Y. P, HuangH, Liu Y. T, ChenJ.J, Zhu D W, etal. LAG3 blockade coordinates with microwave ablation to promote CD8⁺ T cell-mediated anti-tumor immunity. Journal of Translational Medicine, 2022; 20 (1).
11. Dou J.P, Wu Q, FuC.H, Zhang D.Y,Yu J, MengX. W, et al. Amplified intracellular Ca²⁺ for synergistic anti-tumor therapy of microwave ablation and chemotherapy. J Nanobiotechnol. 2019; 17 (1).
12. Ando T, YoshikawaT, TanigawaT, KohnoM, YoshidaN, Kondo M. Quantification of singlet oxygen from hematoporphyrin derivative by electron spin resonance. Life Sciences 1997; 61 (19): 1953-1959.
13. Meng P. S, Sun Y, Li E. Z, Liu Y. Q, Wang C. P, Song, L.P. Hematoporphyrin monomethyl ether mediated photodynamic therapy inhibits oral squamous cell carcinoma by regulating the P53-miR-21-PDCD4 axis via singlet oxygen. Laser Med Sci 2022; 37 (6): 2629-2637.

14. Tanielian C, Schweitzer C,MechinR and Wolff C. Quantum yield of singlet oxygen production by monomeric and aggregated forms of hematoporphyrin derivative. Free Radical Bio Med 2001; 30 (2): 208-212.
15. Li H, Li X. S, WangY, Zhao H. Y, Zeng J, LiuY. D, et al. Effect and Mechanism of Fluence Rate on Immunity of Photodynamic Therapy Mediated by Hematoporphyrin Derivatives in Murine Colorectal Cancer. J Biol Reg Homeos Ag 2023; 37 (5): 2601-2614.
16. Lin C. Z, Zhang Y. Y, Liao J. M, Cui S.C, Gao Z, Han W. Z. Effect of photodynamic therapy mediated by hematoporphyrin derivatives on small cell lung cancer H446 cells and bronchial epithelial BEAS-2B cells. Laser Med Sci 2024; 39 (1).
17. Long S, Zhao Y. B, Xu Y. Y, Li H, Zhao H. Y, Chen D. F,et al.Immune response induced by hematoporphyrin derivatives mediated photodynamic therapy: Immunogenic cell death and elevated costimulatory molecules. J InnovOpt Heal Sci 2022; 15:(04).
18. Wei X, Ni J. L, Yuan L, Li X. L, Hematoporphyrin derivative photodynamic therapy induces apoptosis and suppresses the migration of human esophageal squamous cell carcinoma cells by regulating the PI3K/AKT/mTOR signaling pathway. Oncology Letters 2024; 27 (1).
19. Dai H. Y, Yu D. Y, Xiao B. H, Sui A. H, Ding X.Q, Lin C. Z. Two Molecular Weights Holothurian Glycosaminoglycan and Hematoporphyrin Derivative-Photodynamic Therapy Inhibit Proliferation and Promote Apoptosis of Human Lung Adenocarcinoma Cells. Integr Cancer Ther 2023; 22.
20. Li S, Chen Z, TanL, WuQ, RenX, Fu C, et al. MOF@COF nanocapsule for the enhanced microwave thermal-dynamic therapy and anti-angiogenesis of colorectal cancer. Biomaterials 2022, 283, 121472.
21. Sari S, Durmus M, Bulut M. Microwave assisted synthesis of novel zinc (II) phthalocyanines bearing 1,3-diazido-2-propanoxy functional groups and investigation of their photochemical properties. Tetrahedron Lett 2016; 57 (10): 1124-1128.
22. VasiljevicB,Milivojevic D,BarudzijaT, BudimirM, Mijin D. Marinovic-Cincovic, M.; Marinkovic, D., Microwave-induced synthesis of zinc-phthalocyanine with improved photosensitizing potential. Mater Lett 2023; 350.
23. WangY. X, Ren X. L, Zheng Y. J, Tan L. F Li B, Y Fu C. H, Boosting Microwave Thermo-Dynamic Cancer Therapy of TiMOF via COF-Coating. Small 2023; 19 (49).
24. Ma XY, Ren XL, Guo XD, Fu CH, Wu Q, Tan LF,et al. Multifunctional iron-based Metal - Organic framework as biodegradable nanozyme for microwave enhancing dynamic therapy. Biomaterials 2019 Sep; 214: 119223.
25. Zhou H, Liu ZT, Zhang ZJ, Pandey NK, Amador E, Nguyen W,et al. Copper-cysteamine nanoparticle-mediated microwave dynamic therapy improves cancer treatment with induction of ferroptosis. Bioact Mater 2023; 24: 322-330.
26. Wu Q, Yu YN, Yu XR, Du QJ, Gou L, Tan LF,et al. Engineering liquid metal-based nanozyme for enhancing microwave dynamic therapy in breast cancer PDX model. J Nanobiotechnol 2023; 21(1): 72-81.
27. Qin QY, Yang M, Shi Y, Cui HJ, Pan CS, Ren WZ,et al. Mn-doped Ti-based MOFs for magnetic resonance imaging-guided synergistic microwave thermal and microwave dynamic therapy of liver cancer. Bioact Mater 2023; 27: 72-81.
28. Fu CH, Zhou HQ, Tan LF, Huang ZB, Wu Q, Ren XL,et al. Microwave-Activated Mn-Doped Zirconium Metal Organic Framework Nanocubes for Highly Effective Combination of Microwave Dynamic and Thermal Therapies Against Cancer. Acs Nano 2018; 12(3): 2201-2210.
29. Zhu YJ, Yang ZJ, Pan ZJ, Hao Y, Wang CJ, Dong ZL,et al. Metallo-alginate hydrogel can potentiate microwave tumor ablation for synergistic cancer treatment. Sci Adv 2022; 8(31):eabo5285.
30. Xu X, Wu Q, Tan L, Men X, Huang Y, Li H, Biomimetic Metal-Chalcogenide Agents Enable Synergistic Cancer Therapy via Microwave Thermal-Dynamic Therapy and Immune Cell Activation. ACS Appl Mater Interfaces 2023; 15(36): 42182-42195.
31. Liao SS, Wu SL, Mao CY, Wang CF, Cui ZD, Zheng YF,et al. Electron Aggregation and Oxygen Fixation Reinforced Microwave Dynamic and Thermal Therapy for Effective Treatment of MRSA-Induced Osteomyelitis. Small 2024; 20 (28).
32. Pandey NK, Xiong W, WangL, Chen W, Bui B, Yang J,et al. Aggregation-induced emission luminogens for highly effective microwave dynamic therapy. Bioact Mater 2022; 7: 112-125.
33. Hou Q, Zhang K, Chen S, Chen J, Zhang Y, Gong N,et al. Physical & Chemical Microwave Ablation (MWA) Enabled by Nonionic MWA Nanosensitizers Repress Incomplete MWA-Arised Liver Tumor Recurrence. ACS Nano 2022; 16 (4): 5704-5718.
34. Zhang WJ, Zhou H, Gong DY, Wu HT, Huang X, Miao ZH,et al. AIPH-Encapsulated Thermo-Sensitive Liposomes for Synergistic Microwave Ablation and Oxygen-Independent Dynamic Therapy. Advanced Healthcare Materials.2023 Jul; 12(17): e2202947.
35. Li X, Zhang X, Khan IU, Guo NN, Wang B, Guo Y,et al. The anti-tumor effects of the combination of microwave hyperthermia and lobaplatin against breast cancer cells in vitro and in vivo. Biosci Rep.2022 Feb 25;42(2):BSR20190878.
36. Lyu C, Li WX, Li S, Mao YL, Yang B. Design of Ultra-Wideband Phased Array Applicator for Breast Cancer Hyperthermia Therapy. Sensors-Basel.2023 Jan 17;23(3):1051.
37. Zhang H, Xu J, Gao B, WangH, Huang J, Zhou J,et al. Synergistic Cascade Strategy Based on Modifying Tumor Microenvironment for Enhanced Breast Cancer Therapy. Front Pharmacol 2021; 12: 750847.
38. Yu M, Li S, Ren X, Liu N, Guo W, Xue J,et al. Magnetic Bimetallic Heterointerface Nanomissiles with Enhanced Microwave Absorption for Microwave Thermal/Dynamics Therapy of Breast Cancer. ACS Nano 2024; 18(4): 3636-3650.
39. Wu Q, Tan L, Ren X, Fu C, Chen Z, Ren J,et al. Metal-Organic Framework-Based Nano-Activators Facilitating Microwave Combined Therapy via a Divide-and-Conquer Tactic for Triple-Negative Breast Cancer. ACS Nano 2023; 17(24): 25575-25590.
40. Qin Q, Yang M, Shi Y, Cui H, Pan C, Ren W,et al. Mn-doped Ti-

based MOFs for magnetic resonance imaging-guided synergistic microwave thermal and microwave dynamic therapy of liver cancer. Bioact Mater 2023; 27: 72-81.

41. Feng Y, Chen Q, Jin C, Ruan Y, Chen Q, Lin W,et al. Microwave-activated Cu-doped zirconium metal-organic framework for a highly effective combination of microwave dynamic and thermal therapy. J Control Release 2023; 361: 102-114.
42. Ma X, Ren X, Guo X, Fu C, Wu Q, Tan L,et al. Multifunctional iron-based Metal-Organic framework as biodegradable nanozyme for microwave enhancing dynamic therapy. Biomaterials 2019; 214: 119223.
43. Shu M, Wang J, Xu Z, Lu T, He Y, Li R,et al. Targeting nanoplatform synergistic glutathione depletion-enhanced chemodynamic, microwave dynamic, and selective-microwave thermal to treat lung cancer bone metastasis. Bioact Mater 2024; 39: 544-561.
44. Li S, Xu F, Ren X, Tan L, Fu C, Wu Q, et al.H(2)S-Reactivating Antitumor Immune Response after Microwave Thermal Therapy for Long-Term Tumor Suppression. ACS Nano. 2023; 17 (19): 19242-19253.
45. Zhou W, Yu M, Mao X, Pan H, Tang X, Wang J,et al. Landscape of the Peripheral Immune Response Induced by Local Microwave Ablation in Patients with Breast Cancer. Adv Sci (Weinh) 2022; 9 (17): e2200033.
46. Ma L, Zhou J, Wu Q, Luo G, Zhao M, Zhong G,et al. Multifunctional 3D-printed scaffolds eradiate orthotopic osteosarcoma and promote osteogenesis via microwave thermo-chemotherapy combined with immunotherapy. Biomaterials 2023; 301: 122236.