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REVIEW

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Metal-organic frameworks (MOFs) in cancer therapeutics: exploring their potential and safety profile

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ABSTRACT

Metal-organic frameworks (MOFs) are crystalline materials known for their distinctive properties like high porosity, an extensive surface area, and ability to encase molecules, making them attractive candidates for cancer therapy drug delivery. Metal ions or clusters connected with organic ligands form these frameworks, creating an ideal structure for transporting and selectively releasing drugs to target sites (particularly cancer cells) while sparing healthy tissues. Recent research has investigated MOFs as potential aids for improving cancer therapies such as chemotherapy, photodynamic therapy, and early cancer detection. However, before transitioning MOFs into clinical settings, assessing their *in vivo* toxicity and biocompatibility is essential. Studies conducted on living organisms provide important insight into how MOFs behave within biological systems, offering valuable data regarding their safety and efficacy as drug carriers. Although MOFs offer tremendous promise, their use requires careful evaluation due to potential toxicity issues, targeting cancer cells directly, and physiological conditions stability issues that must be overcome through extensive research and clinical trials. Research being undertaken today seeks to address these challenges and optimize MOFs for clinical application - creating more effective and precise cancer therapies. As we continue to understand MOFs' capabilities and address their limitations, these unique structures represent hope in cancer therapeutics, potentially revolutionizing treatment methodologies and improving patient outcomes in this fight against cancer.

KEYWORDS

Drug deliver; Cancer therapy; Biocompatibility; Nanomedicine

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Introduction

Metal-organic frameworks (MOFs) have proven themselves an indispensable class of materials with many diverse applications; their potential in cancer therapy has received particular consideration [1]. MOFs stand out due to their unique crystalline structure composed of organic ligands and metal ions or clusters connected by coordinative bonds; this allows MOFs to boast exceptional properties like tunable porosity, extensive surface area coverage, and the capacity for encapsulating various molecules, making them prime candidates as drug delivery systems [2]. Researchers have recently explored using MOFs in cancer therapy efforts to increase effectiveness and specificity [2].

With research efforts dedicated to finding novel cancer therapies, early diagnoses, and detection methods fuelling interest in advanced materials like MOFs [1], their unique properties and tailorable nature have become attractive candidates in cancer therapy [2]. MOFs offer several advantages over their competitors for treating cancer, such as encasing and delivering multiple medications, targeting specific cancer cells with controlled drug release, and protecting healthy tissues [1]. MOFs have recently come under scrutiny as potential biomarkers of cancer diagnosis, providing non-invasive and quantitative ways of evaluating biological microenvironments [1]. This approach allows researchers to gain deeper insights into disease risk relationships and therapeutic interventions [1]. MOFs have also proven effective at treating cancer through various modalities, including photodynamic therapy (PDT), photothermal therapy (PTT), chemotherapy, radiography, and immunotherapy [1]. Their versatility in providing monomodal or multimodal treatments makes them an attractive option in combatting this disease [2].

Assessing *in vivo* toxicity and biocompatibility is paramount when considering Metal-Organic Frameworks (MOFs) as drug delivery systems in clinical environments. Studies conducted in living organisms provide crucial insights into how MOFs interact with living systems, providing critical knowledge regarding safety and efficacy. Likewise, understanding MOF biopharmaceutics helps optimize design decisions and administration routes, further expanding their potential as efficient drug carriers [3,4]. In this narrative review, we explore the potential of MOFs as future agents for cancer therapeutics with a special focus on biocompatibility and safety profiles that may act as a limitation. As MOF research (synthesis and application) is evolving rapidly and constantly, it is imperative to update with the current status of MOF as a cancer therapeutic agent, its limitations, and future research prospects. This review aims to explore challenges in developing and applying MOFs as cancer therapeutics and assess their safety profiles.

Methodology

The review considered "PubMed," "EMBASE," and "Scopus" databases for searching the literature. The publication period ranges from 2019-2023. The keywords considered for the current review include Metal-organic frameworks," "MOFs," "cancer therapy," "drug delivery," "biocompatibility," "toxicity," "safety profile," "clinical translation," and "research challenges." Both *in vivo* and *in vitro* studies were considered for the current review.

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Metal-Organic Frameworks

Metal-organic frameworks (MOFs) have gained much interest over time due to their impressive properties and wide applications - particularly drug delivery and cancer therapy.

MOFs (also referred to as porous coordination polymers) are crystalline materials made up of inorganic metal clusters connected by organic ligands that form extended network structures through self-assembly, creating highly porous materials with exceptional properties. Some critical characteristics of MOFs are high Surface Area and Porosity, tunable pore size, open architecture, diversity in organic ligands, and high crystallinity [5].

High Surface Area and Porosity: MOFs exhibit an extraordinarily high surface area per gram, typically from 1000 to 10,000 square meters per gram, making them the perfect medium to store biomolecules and pharmaceuticals for efficient drug delivery [6].

Tunable Pore Sizes: MOFs have microporous structures with pores of typically less than 2 nanometers in diameter, providing for tuning of their pore sizes to enable selective encapsulation of molecules based on size and shape. This feature makes MOFs ideal for selective encapsulators for molecules of various shapes and sizes [6].

Open Architectures: MOFs provide open frameworks that facilitate interactions between biomolecules incorporated within them and their surroundings, allowing the controlled release of substances [6].

Variety of Inorganic Clusters and Organic Ligands: MOFs offer an expansive selection of inorganic metal clusters and organic ligands, precisely customizing MOF properties according to specific applications [6].

Biodegradability: MOFs feature weak coordination bonds that facilitate controlled drug release, making them biodegradable and thus limiting potential toxicity risks [6].

High Crystallinity: MOFs have high crystallinity levels that provide specific morphological information and transparent networks - essential tools for studying host-guest interactions [6].

Owing to their distinctive properties, potential structural modifications, and post-synthesis modifications, they have been extrapolated to biomedical use. In the subsequent section, we will evaluate how MOFs have been used in cancer therapy and drug delivery system that augments cancer therapeutics.

Application in Cancer Therapy and Drug Delivery

Drug delivery

MOFs have emerged as promising drug delivery vehicles thanks to their unique properties. Their encapsulating capabilities efficiently store pharmaceuticals, while their controlled release capabilities allow targeted drug delivery [7]. An interesting example include anticancer drug doxorubicin, which was released directly at tumor sites due to pH-responsive behavior of certain MOFs, which releases doses when exposed to acidic environments such as tumors, thereby improving efficacy while minimizing side effects [8].

Cancer therapy

MOFs are currently being researched to explore their use in cancer diagnosis and therapy, both for early detection and therapy purposes. They could serve both roles effectively [9,10]. MOFs can also help to detect cancer biomarkers more precisely; for instance, MOFs have been successfully utilized to detect tumor markers in breast cancer cells for early diagnosis with high precision [11]. MOFs have proven effective as targeted drug delivery vehicles for cancer therapy, encapsulating anticancer medications before dispensing them selectively to tumor sites without harming healthy tissues [7]. Furthermore, using MOFs alongside photothermal treatment (PTT) or photodynamic therapy (PDT) has shown promising results in eliminating cancer cells while sparing healthy tissue [12].

Some MOFs have been developed for multimodal imaging, providing simultaneous cancer diagnosis and therapy. These materials serve as contrast agents in magnetic resonance imaging (MRI) or positron emission tomography (PET), delivering anticancer drugs directly into cancerous cells [13,14]. MOFs are highly flexible materials with unique properties that make them invaluable in drug delivery and cancer therapy. Their large surface area, tunable pore sizes, and biodegradability make them suitable for targeted therapy, controlled drug release, and cancer diagnosis [3]. With research in this field continuing apace, MOFs promise to improve treatment outcomes while decreasing side effects associated with traditional therapies.

In vivo-toxicity assessment

Assessment of *in vivo* toxicity of Metal-Organic Frameworks (MOFs) is critical to understanding their suitability for clinical application, with recent studies offering multiple approaches to evaluate MOF toxicity in animal models and pinpoint potential sources of harm while emphasizing the necessity of creating safety profiles before clinical translation [4,15-20]. Multiple methods are employed as part of a comprehensive assessment of MOF *in vivo* toxicity. Pharmacokinetic studies provide valuable insight into how MOFs are distributed, metabolized, and excreted from the body [3,15]. Biodistribution studies can monitor MOF dispersion across various organs and tissues to pinpoint potential accumulation sites [3,15].

To explore deeper, histopathological examinations scrutinize tissue samples for any pathological changes or damage attributed to MOFs [3]. Simultaneously, blood chemistry analyses explore assessing blood parameters and unearthing any systemic effects of MOFs on organ function [3]. Additionally, cellular uptake studies aid in elucidating the processes by which cells absorb MOFs, thus unraveling their intracellular behavior and potential toxicity [4]. Furthermore, analyzing metabolites generated from MOF degradation furnishes valuable insights into their potential toxicity [4]. Recent investigations have unveiled the intricate landscape of MOF toxicity, revealing that MOFs can exhibit varying degrees of toxicity contingent on factors like composition, size, and surface properties. MOFs containing toxic metals such as lead, arsenic, chromium, or cadmium can pose health hazards due to the inherent toxicity of these metals [4].

Exploring potential mechanisms of toxicity, it is

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discernible that MOFs containing toxic metals may release these elements into the body, potentially resulting in harmful effects and accumulation in organs and tissues [4]. Additionally, the degradation of MOFs into their constituent materials, including organic linkers, can give rise to adverse health effects contingent on the nature of these constituents [4]. The solvents employed in MOF synthesis may also wield toxic effects if entrapped within MOFs and subsequently released, causing potential health issues [4]. Moreover, the stability of MOFs emerges as a critical factor, with unstable MOFs potentially releasing their components into cellular compartments, thereby yielding toxic effects dependent on the nature and concentration of these components [4]. The pivotal role of establishing safety profiles for MOFs becomes evident in the context of clinical translation. Understanding MOFs' toxicity is paramount for their secure integration into clinical applications, drug delivery, cancer therapy, or other biomedical endeavors. This understanding empowers researchers to fashion MOFs that prove safe for human usage and minimize potential side effects, ensuring the realization of the full potential of MOFs in medical practice [15].

In summation, an array of comprehensive methods underpin the assessment of MOF *in vivo* toxicity. Recent research has shed light on the importance of this assessment, elucidated potential mechanisms of toxicity, and underscored the significance of safety profiles for MOFs' successful translation into clinical applications. Continued research and development efforts are essential to craft MOFs with heightened biocompatibility and minimal toxicity, ensuring seamless integration into medical practice.

Biocompatibility

Biocompatibility, an essential aspect of medical applications, refers to a material's ability to interact safely and effectively with biological systems, such as living tissues and cells, without inducing harm, adverse reactions, or immune reactions [21]. Biocompatibility plays a pivotal role in assuring patient well-being and functionality, mitigating rejection risks, and prolonging its viability in human bodies - thus, its evaluation is vital in medical applications [22]. Prioritizing biocompatibility in medical applications is one of the key reasons it should be prioritized. Biocompatible materials significantly decrease risks of adverse reactions, infections, or inflammation when in contact with patient tissue - essential in protecting patient well-being during and after post-medical procedures [22].

Biocompatible materials contribute to the efficient functioning of medical devices and drug delivery systems inside the body without interfering with their intended function. They ensure effective diagnosis, treatment, or alleviation of medical conditions [23]. They play an essential role in helping reduce the likelihood of the immune system rejecting them as foreign objects, especially for implants and tissue engineering applications, where rejection could cause complications or treatment failure. This factor should be especially considered in medical device applications where refusal could have severe repercussions for complications or treatment failure [23]. Biocompatible materials offer numerous advantages, one being long-term viability in the body. Biocompatible materials tend to last longer without needing replacement or intervention - creating savings for patients and healthcare systems. Metal-organic frameworks (MOFs) must be evaluated carefully in biological systems to assess their biocompatibility, using rigorous approaches and assays that provide insights into their safety and feasibility for medical applications. These tests give a complete picture of MOF safety [24].

Cell viability assays such as MTT and Alamar Blue provide invaluable insight by measuring MOFs' effect on cell viability and proliferation. These assays also measure mitochondrial and metabolic activities to provide a comprehensive view of how MOFs affect cells. Hemolysis assays help determine if MOFs contain ingredients that can rupture red blood cells and thus pose potential threats to blood components and their components [25]. Cytotoxicity studies seek to investigate any harmful effects MOFs may have on cells by studying cell membrane integrity, cell morphology, and apoptosis, providing insights into their safety profile. Researchers assess MOFs' inflammatory response by monitoring their effects on pro-inflammatory cytokines like IL-6 and TNF-a production; these markers provide vital insight into their impact on our immune systems [26]. Hemocompatibility assays evaluate MOFs to ensure their compatibility with blood components, such as platelets and plasma proteins, to prevent them from triggering unwanted clotting reactions when exposed to blood [27]. Researchers use *in vivo* studies, typically on rodent models, to test MOFs' biocompatibility in living organisms by monitoring factors like tissue response, inflammation, and organ function [27].

Biodistribution studies examine how MOFs move throughout a body over time, providing essential insights into their processing and elimination processes and a picture of their fate in biological systems. Biodegradable MOFs are promising as multimodal imaging and therapy agents, particularly given their biocompatibility and potential as cancer nanocarriers. Nejadshafiee et al. (2010) provided evidence supporting this assertion by showing their use in multimodal cancer imaging/therapy procedures with optimal efficacy, including multimodal PET scans of lung tumors and potential use as nanocarriers in treating cancer [28]. Orellana-Tavra et al. (2020) demonstrated iron-based MOFs' biocompatibility and controlled drug release capabilities, positioning them as viable candidates for cancer therapy drug delivery [29]. Biocompatibility is of utmost importance in medical applications, ensuring the safety, functionality, and lifespan of materials within the human body. Rigorous evaluation of Metal-Organic Frameworks (MOFs) plays an essential role in establishing their suitability for various biomedical uses; recent studies demonstrate their immense potential in revolutionizing cancer treatments and drug deliveries - further underscoring biocompatibility's significance as part of advances in medicine and patient care.

Challenges and Future Research

Metal-organic frameworks (MOFs) hold immense promise as an anticancer therapy and drug delivery option. However, several challenges and limitations must be overcome before clinical implementation to facilitate successful clinical translation. A primary concern revolves around the potential toxicity associated with specific MOFs. Some MOFs may contain toxic metal ions or unstable organic linkers, raising concerns about their safety in medical applications [4]. To mitigate these concerns, future research should prioritize the development of MOFs with inherently safer compositions,

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exploring alternative metal ions and ligands with proven safety records.

While many MOFs are biodegradable, questions linger regarding the long-term safety of their degradation products. Understanding the pathways of MOF biodegradation and their potential impact on the body is crucial for addressing this limitation [4]. Furthermore, the journey from laboratory research to clinical applications presents a substantial challenge. It necessitates rigorous testing, comprehensive safety profiles, and regulatory approvals, demanding significant resources and collaboration between researchers, clinicians, and regulatory authorities [4]. Achieving precise targeting of cancer cells while sparing healthy tissues remains formidable. Innovations in ligand design and integrating MOFs with other targeting technologies are avenues for future research to enhance selectivity [2]. Lastly, ensuring the stability of MOFs in physiological conditions is essential for their efficacy. MOFs may degrade or lose structural integrity over time, affecting drug release kinetics. Future investigations should focus on Stability-enhancing modifications and formulations to address this challenge [2]. To overcome these challenges and limitations, several targeted research avenues emerge. Firstly, researchers should prioritize the development of MOFs with inherently safe compositions, reducing the presence of toxic elements and ensuring biocompatibility. This involves exploring alternative metal ions and ligands with established safety records, allowing MOFs to be used more confidently in medical applications [4].

Another crucial research target is fine-tuning the controlled drug release capabilities of MOFs. By designing MOFs that respond to specific stimuli such as pH or temperature, researchers can enable precise drug release at tumor sites while minimizing systemic side effects [2]. Conducting comprehensive, long-term safety studies in animal models is imperative to address concerns about MOF accumulation, potential toxicity, and overall biocompatibility. These studies provide crucial data for assessing the suitability of MOFs for clinical use and mitigating safety concerns [4]. To bridge the gap between research and clinical practice, well-designed clinical trials are essential. These trials should evaluate the safety and efficacy of MOF-based cancer therapies, collaborating with healthcare institutions and pharmaceutical companies to advance MOF-based treatments to benefit patients [2]. Developing "smart" MOFs that actively respond to changes in the tumor microenvironment or deliver payloads in a highly controlled manner represents an exciting research avenue. These adaptive MOFs could optimize treatment efficacy by adapting to evolving conditions within the body [2]. Expanding the use of MOFs in cancer diagnosis by developing MOFs capable of detecting a broader range of cancer biomarkers can revolutionize early detection methods, potentially leading to earlier intervention and improved patient outcomes [1].

Conclusions

Metal-organic frameworks (MOFs) stand at the forefront of innovation in cancer therapy and drug delivery. Their unique properties, such as high surface area, tunable porosity, and controlled drug release capabilities, position them as promising candidates for revolutionizing medical practice. MOFs have shown immense potential in enhancing cancer therapy through tailored drug delivery, multimodal treatments, and precise targeting while minimizing harm to healthy tissues. Additionally, their utility extends to cancer diagnosis, offering non-invasive, quantitative assessments of biological microenvironments. However, the journey to clinical translation is challenging. Assessing *in vivo* toxicity and biocompatibility is critical to ensure patient safety and optimize MOF design. Addressing toxicity, stability, and specific targeting concerns necessitates ongoing research and collaboration among scientists, clinicians, and regulatory authorities. Moreover, conducting well-designed clinical trials and developing "smart" MOFs that respond dynamically to the tumor microenvironment are vital steps toward realizing MOFs' full potential. As research advances and safety concerns are addressed, MOFs promise to improve cancer treatment outcomes, reduce side effects, and usher in a new era of precision medicine. These versatile materials can potentially transform the landscape of cancer therapy and drug delivery, offering hope to patients and healthcare practitioners alike.

Disclosure statement

No potential conflict of interest was reported by the author.

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