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Review article

Engineering materials for pyroptosis induction in cancer treatment

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ABSTRACT

Cancer remains a significant global health concern, necessitating the development of innovative therapeutic strategies. This research paper aims to investigate the role of pyroptosis induction in cancer treatment. Pyroptosis, a form of programmed cell death characterized by the release of pro-inflammatory cytokines and the formation of plasma membrane pores, has gained significant attention as a potential target for cancer therapy. The objective of this study is to provide a comprehensive overview of the current understanding of pyroptosis and its role in cancer treatment. The paper discusses the concept of pyroptosis and its relationship with other forms of cell death, such as apoptosis and necroptosis. It explores the role of pyroptosis in immune activation and its potential for combination therapy. The study also reviews the use of natural, biological, chemical, and multifunctional composite materials for pyroptosis induction in cancer cells. The molecular mechanisms underlying pyroptosis induction by these materials are discussed, along with their advantages and challenges in cancer treatment. The findings of this study highlight the potential of pyroptosis induction as a novel therapeutic strategy in cancer treatment and provide insights into the different materials and mechanisms involved in pyroptosis induction.

1. Introduction

Cancer remains a major global health concern, necessitating the development of innovative therapeutic strategies. In recent years, programmed cell death pathways have emerged as promising targets for cancer treatment [1–3]. Among these pathways, pyroptosis, a form of programmed cell death characterized by the release of pro-inflammatory cytokines and the formation of plasma membrane pores, has gained significant attention. Pyroptosis is primarily mediated by the caspase and gasdermin protein family, and its induction holds multiple implications in the context of cancer therapy [4–7].

Pyroptosis, as a tumor-suppressive mechanism, has been shown to share similarities with other forms of cell death, such as apoptosis and necroptosis [8–10]. Combined therapies that activate multiple cell death pathways have the potential to enhance tumor destruction [11–14]. Furthermore, the release of biological molecules during pyroptosis induction intersects with immune signaling pathways, stimulating an immune response [15–17]. This intersection presents an opportunity to combine pyroptosis-inducing agents with other immune activators to amplify tumor cell destruction and immune activation [17,18]. The application of engineering materials in pyroptosis induction offers multiple potentials, including targeted delivery, combination therapy, and immunomodulation [19–23].

Previous studies have investigated the role of natural materials, such as saponins, curcumin, and nanocarriers, in enhancing pyroptosis-mediated cancer therapy [24–27]. These studies have highlighted the potential of natural compounds in boosting the efficacy of cancer treatment and mitigating chemotherapy-induced adverse effects. Similarly, biological materials, including viruses, bacteria, and engineered cells, have shown promise in inducing pyroptosis and stimulating

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anti-tumor immune responses [28–31]. Chemical materials, such as targeted inhibitors, nanoparticles, and photosensitizers, have also been explored for their ability to induce pyroptosis in cancer cells [32–37]. However, what are the differences and similarities of materials used for pyroptosis induction in cancer therapy? What are the molecular mechanisms underlying pyroptosis induction by these materials? What are the advantages and challenges associated with the application of these materials in cancer treatment? There is a need for further research to fully understand the molecular mechanisms underlying pyroptosis induction by these materials and to optimize their therapeutic efficacy.

The objective of this review is to provide a comprehensive overview of the current understanding of pyroptosis and its role in cancer treatment. By synthesizing the existing literatures, this review aims to identify research gaps and highlight the potential of different materials in inducing pyroptosis for enhanced cancer therapy. The significance of this research lies in its potential to contribute to the development of novel therapeutic strategies that exploit the unique properties of pyroptosis and lies in its comprehensive analysis of the different materials used for pyroptosis induction and their mechanisms of action.

This review is organized into several sections (Fig. 1). Firstly, the concept of pyroptosis and its relationship with other forms of cell death, such as apoptosis and necroptosis, will be discussed. Secondly, the role of pyroptosis in immune activation and its potential for combination therapy will be explored. Thirdly, the use of natural, biological, chemical, and multifunctional composite materials for pyroptosis induction will be reviewed. The molecular mechanisms underlying pyroptosis induction by these materials will be discussed, along with their advantages and challenges in cancer treatment. Finally, the review will conclude with a summary of the key findings and future research directions in the field of pyroptosis-induced cancer therapy.

2. Understanding pyroptosis and its role in tumor treatment

2.1. Pyroptosis and engineering materials

Pyroptosis can be initiated through either inflammatory or non-inflammatory pathways. Their primary distinctions lie in the triggering mechanisms, activation of caspase/gasdermin, and the release of inflammatory mediators [1,38–41]. Specifically, inflammatory pyroptosis is predominantly activated by external stimuli, mediated by caspase-1, resulting in the cleavage of gasdermin D and the release of interleukin (IL). In contrast, non-inflammatory pyroptosis involves caspase-3 activation, leading to the cleavage of gasdermin E and the absence of pro-inflammatory cytokine release [38–41]. Additionally, pyroptosis is associated with the depletion of ATP, the release of LDH, and the extracellular release of HMGB1. These events, while relatively independent, are interconnected and are often employed as indicators of pyroptotic cell death in the study of molecular mechanisms [42,43]. In the context of cancer, pyroptosis holds multiple implications [44–46]. Firstly, it acts as a tumor-suppressive mechanism. Secondly, pyroptosis shares similarities with other forms of cell death, such as apoptosis or necroptosis, and combined therapies could enhance tumor destruction by synergistically activating various cell death pathways [13,47]. Thirdly, the release of biological molecules during pyroptosis induction intersects with immune signaling pathways, stimulating an immune response [48–51]. Combining pyroptosis-inducing agents with other immune activators can further amplify tumor cell destruction and immune activation. Engineering materials exhibit various talents, including targeted delivery, combination therapy, and immunomodulation, making them promising candidates for the application of pyroptosis induction in cancer treatment [52–55]. In conclusion, the application of engineering materials in pyroptosis induction offers multiple potentials. By leveraging their unique properties, these materials can enhance the specificity, effectiveness, and safety of pyroptosis induction (Fig. 2).

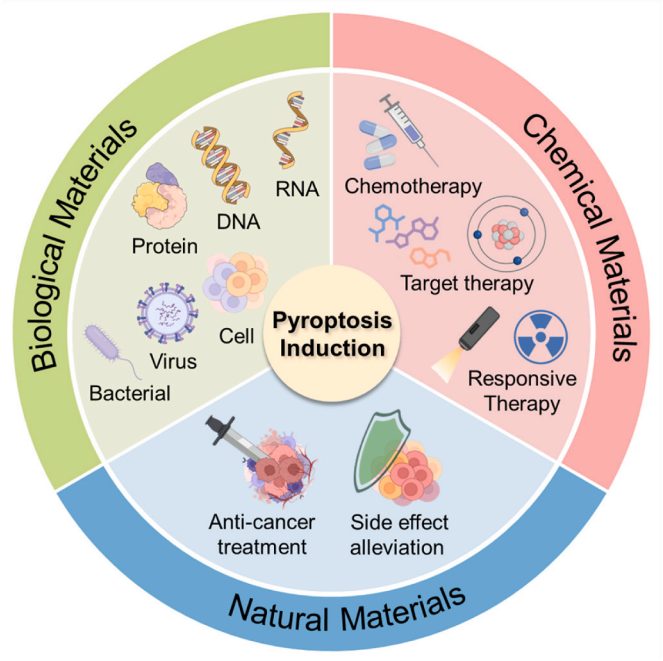

Fig. 1. Summative scheme of pyroptosis induction from natural, biological, and chemical materials. Figure created with Biorender.com.

2.2. Pyroptosis and immune system

Pyroptosis, a programmed cell death mechanism, has garnered considerable attention for its significant role in orchestrating immune activation. Within the realm of tumor biology, the induction of pyroptosis in tumor cells holds a transformative potential—it triggers a phenomenon known as immunogenic cell death (ICD) [54,56,57]. This process triggers the liberation of crucial components such as tumor antigens, damage-associated molecular patterns (DAMPs), and pro-inflammatory cytokines. Collectively, these elements form a dynamic cascade that stimulates the activation of dendritic cells (DCs), cytotoxic T lymphocytes (CTLs), natural killer cells (NKs), and macrophages, thereby markedly amplifying the body's anti-tumor immune responses [37,58,59].

Beyond its initial impact, pyroptosis wields an additional capability—the capacity to reconfigure the intricate tumor microenvironment (TME), characterized by its inherent immunosuppressive nature [37,60–62]. This transformation is achieved through precise modulation of immune cell functionality and activity. This encompasses mechanisms such as the differentiation of macrophages, targeted antigen presentation to memory T cells, secretion of immunostimulatory factors like Tumor Necrosis Factor-α (TNF-α) and Interferon-γ (IFN-γ), and the adept hindrance of PD-1 expression. These intricate adjustments collectively culminate in a landscape that promotes the infiltration of potent effector immune cells into the heart of tumors (Fig. 3) [63–66].

In the quest to harness the immune therapeutic potential of pyroptosis, an array of strategies has been meticulously explored—each aimed at instigating pyroptosis within tumor cells. These stratagems encompass innovative approaches, including the judicious deployment of nanoparticles, photosensitizers, DNA sensors, and immunomodulatory agents [47,58,67–70] These endeavors serve as an embodiment of the growing realization of pyroptosis as an intriguing therapeutic target within the realm of cancer immunotherapy. The insights gleaned from these investigative pursuits illuminate a tantalizing prospect—the prospect of leveraging pyroptosis as a transformative tool in the arsenal of cancer treatments. Its potential to activate and engage the immune system, both by driving immunogenic cell death and by reshaping the tumor microenvironment, offers a novel avenue for enhancing

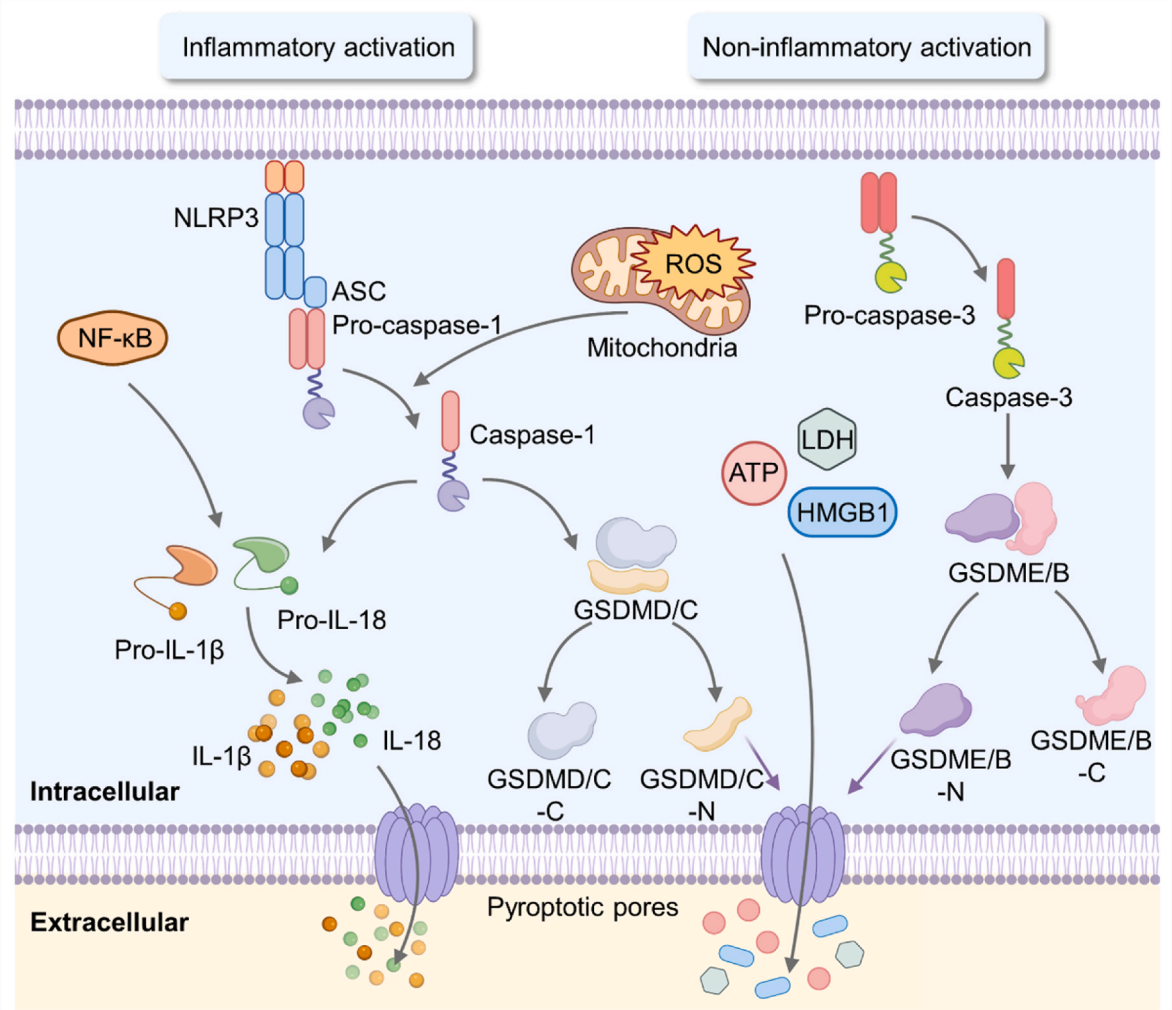

Fig. 2. Schematic illustration of the molecular mechanism of engineering materials-induced pyroptosis in intracellular environments. The authors provide mechanistic insights, uncovering the roles of inflammatory and non-inflammatory activation during pyroptosis induction. Abbreviations: ROS, Reactive Oxygen Species; NLRP3, NOD-like receptor thermal protein domain associated protein 3; NF-κβ, nuclear factor kappa-Beta; ATP, adenosine 5′-triphosphate; LDH, lactate dehydrogenase; HMGB1, High mobility group box-1 protein; IL-1β/18, Interleukin-1β/18; GSDMB/C/E/D, gasdermin B/C/E/D; Figure created with Biorender.com.

anti-tumor immune responses.

2.3. Pyroptosis, apoptosis, and necroptosis

Pyroptosis, apoptosis, and necroptosis stand as three distinct paradigms of programmed cell death, each governed by unique molecular underpinnings [8–10]. While sharing the commonality of being orchestrated forms of cellular demise, they diverge significantly in terms of their initiating triggers, signaling cascades, and ultimate consequences. A comprehensive exploration of these mechanisms unveils their intricacies and highlights potential intersections that could shape novel therapeutic avenues [71–74].

Pyroptosis, typified by the involvement of gasdermin proteins, represents a fiery demise. This phenomenon unfolds through the assembly of pores within the cell membrane, culminating in cell swelling, nuclear distension, and DNA impairment [75,76]. In contrast, apoptosis, a well-recognized mode of programmed cell death, emerges as an orchestrator of development and tissue equilibrium. The activation of caspases, chromatin fragmentation, and cellular contraction characterize this intricate dance of self-destruction [77–80]. Nestled within this spectrum is necroptosis, a programmed variant of necrosis. Here, the spotlight shifts to receptor-interacting protein kinases (RIPKs) and the integral role played by mixed lineage kinase domain-like protein (MLKL) in orchestrating the rupture of the cell membrane (Fig. 4) [81–84].

While these processes epitomize distinct trajectories, recent research accentuates the interconnectedness that often underpins cellular fate. The concept of PANoptosis, a provocative amalgamation of pyroptosis, apoptosis, and necroptosis, illustrates the extent of the interplay between these seemingly disparate routes to cell demise [85–87]. This inflammatory variant of cell death mirrors the intricate choreography of the immune response, reflecting the intricate synergy between cell death and the ensuing immune reactions [42,55,88].

The scientific horizon expands even more with the unveiling that natural, biological, and chemical agents, through their adept manipulation of these mechanisms, hold a substantial allure for pioneering innovative anti-cancer strategies. In the pursuit of precision medicine, unraveling the intricate tapestry of these cell death pathways takes on paramount significance. By deeply comprehending the subtleties that differentiate and intertwine pyroptosis, apoptosis, and necroptosis, researchers and clinicians find themselves in a poised position to craft precisely targeted therapeutic interventions. Amid the intricate choreography between the vitality and cessation of cellular life, harnessing the harmonious symphony of these processes could indeed hold the pivotal key to unlocking transformative treatments, transcending the boundaries of cancer, and reaching into the realms of medical progress.

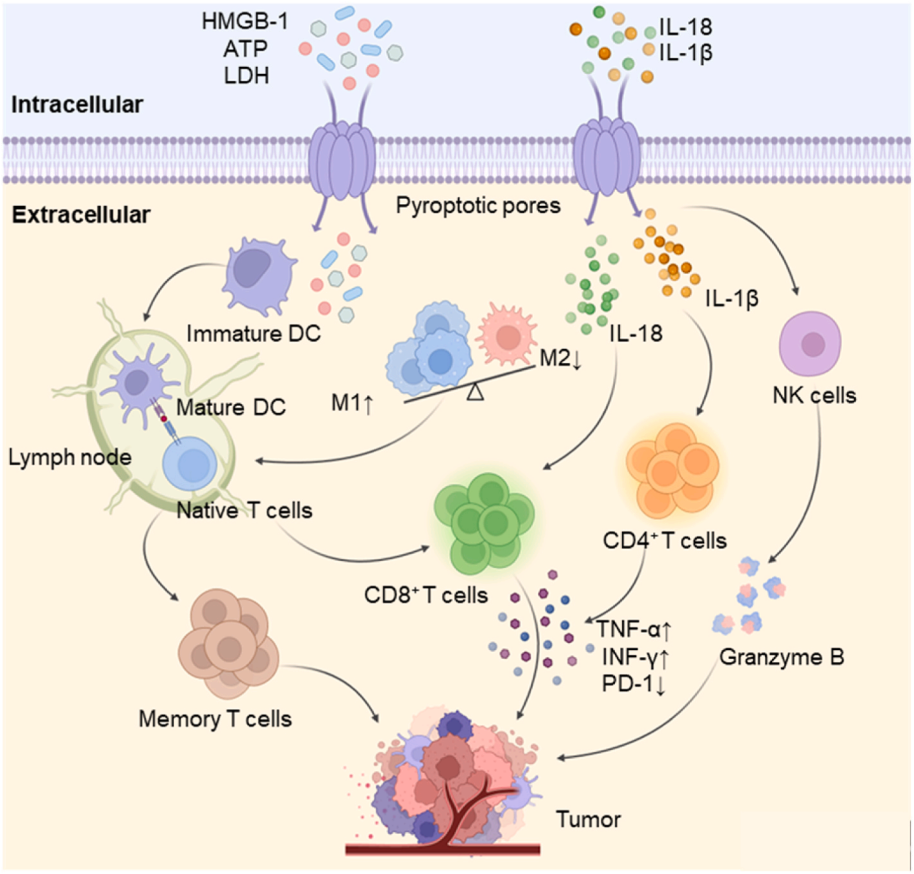

Fig. 3. Schematic illustration of engineering materials-induced pyroptosis for cancer immunotherapy in extracellular environments. Authors provide mechanistic insights into immune response activation after pyroptosis induction. Abbreviations: ATP, adenosine 5′-triphosphate; LDH, lactate dehydrogenase; HMGB1, High mobility group box-1 protein; IL-1β/18, Interleukin-1β/18; NK, natural killer; M1/M2, macrophages M1/M2; TNF-α, tumor necrosis factor-α; IFN-γ, Interferon-γ; PD-1, programmed cell death protein 1. Figure created with Biorender.com.

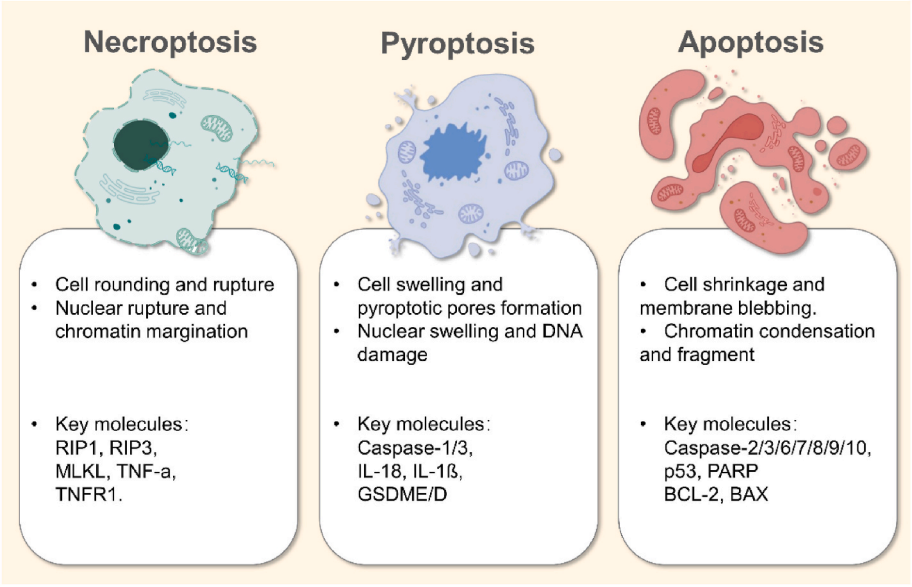

Fig. 4. Morphological and molecular mechanical differences among pyroptosis, necroptosis, and apoptosis. Abbreviations: RIP, receptor-interacting protein; MLKL, mixed lineage kinase domain-like protein; TNF-α, tumor necrosis factor-alpha; IL-1β/18, interleukin-1β/18; GSDME/D, gasdermin E/D; PARP, poly ADP-ribose polymerase; Bcl-2, B-cell lymphoma-2; BAX, BCL2-Associated X. Figure created with Biorender.com.

3. Natural materials for pyroptosis induction

3.1. Natural materials for boosting cancer therapy

Various natural products have been successfully used to treat cancers, including glioblastoma, lung cancer, and oral squamous cell carcinoma [89–91]. Several natural compounds, such as Bacteriochlorin, Saponins, Aloe-emodin, Curcumin, and Galangin, have been investigated for their ability to induce pyroptosis and enhance the efficacy of cancer therapy [24,26,89,92,93]. These compounds have shown the potential to enhance radiosensitizing potency and enhanced chemical sensitivity [90,94,95]. Additionally, Betulinic acid and Ophiopogonin B suggest its potential as a target for overcoming drug resistance in cancer therapy [90,95]. Furthermore, the use of nanocarriers, such as AE@ZIF-8 NPs and transferrin-modified nanocarriers, has been explored to improve the delivery and targeting of these compounds to tumor cells [89]. Overall, these studies (as shown in Table 1) highlight the applications of natural compounds in enhancing pyroptosis-mediated cancer therapy.

3.2. Natural materials for alleviating adverse effects via regulating pyroptosis

The demand for exploring strategies to alleviate adverse effects using natural compounds is increasing. Sinensetin has been found to inhibit cisplatin-induced pyroptosis and attenuate intestinal injury [96]. Another study investigated the potential cardioprotective effects of Carnosic Acid in response to doxorubicin-induced cardiotoxicity [97]. Additionally, coffee consumption has been associated with a reduced risk of hepatocellular carcinoma, possibly through the inhibition of inflammasome activation by caffeine [98]. Geranylgeranoic Acid has been developed as a preventive agent against second primary hepatoma. It was found to induce cell death in human hepatoma cells via pyroptosis. Supplementation of Geranylgeranoic Acid in mice showed a decrease in hepatocarcinogenesis [99]. Ligustrazine was found to alleviate cyclophosphamide-induced hepatotoxicity by inhibiting pyroptosis [100]. Mitochonic acid can mitigate DOX-induced cardiac complications by regulating pyroptosis through TNF mediation [101]. These studies (as shown in Table 1) highlight the potential of natural compounds in mitigating chemotherapy-induced adverse effects, protecting against cardiotoxicity, and reducing the risk of hepatocellular carcinoma. Thus, in the realm of pyroptosis-induced anti-cancer treatments, the mitigation of side effects is exclusively discernible in natural materials.

3.3. The key molecular mechanism of natural materials induced pyroptosis

Several natural compounds (as shown in Table 1) have been investigated for their specific mechanism. Most natural compounds, Sinensetin, Aloe-Emodin, Garcoblone F, and Triptolide, were investigated for induced pyroptosis via the activation of gasdermin E (GSDME) [89,96,102,107,110]. Caspase-1/-3, and NOD-like receptor protein 3 (NLRP3) are also common molecules in the process of pyroptosis induction, their upregulated or downregulated have a strong relationship with activating or mitigating pyroptosis [24,97,103,105]. Moreover, several studies showed ROS often acts as the initiating mechanism of molecular action [26,27]. Thus, the activation of key molecules of natural material induced Pyroptosis, such as GSDME, caspases, NLRP3, and ROS, plays a crucial role in natural materials induced Pyroptosis.

Table 1
Summary of natural materials enhancing anti-tumor therapy or reducing drug-related adverse effects via regulating pyroptosis.

Natural materials	Derivation	Molecular Mechanism	Type of cancer	Functions	Ref.
Bacteriochlorin	Natural plants	Caspase-1, GSDMD, HMGB1	Liver and breast cancer	Activate pyroptosis	[93]
Saponins	P. Polyphylla Var. Yunnanensis	Caspase-1/3/7	Liver and pancreas cancer	Activate pyroptosis and apoptosis	[24]
Aloe-Emodin	Plants	Caspase-3, GSDME	Glioblastoma	Pyroptosis Induction	[89]
Garcoblone F	G. oblongifolia	Caspase-9, GSDME	Nasopharyngeal carcinoma	Activate mitophagy to promote pyroptosis	[102]
Curcumin	Ginger Plants	GSDME, LDH, ROS	Liver cancer	Activate pyroptosis and apoptosis	[27]
Curcumin Analogues	Curcuma Longa	Caspase-3, BCL-2, ROS	Lung cancer	Activate pyroptosis and apoptosis	[26]
Neobractatin	Garcinia Bracteata	Caspase-3, GSDME, ROS	Esophageal cancer	Activate pyroptosis	[103]
Myricetin	Fruits And Plants	Caspase-3/12, GSDME, ROS	Lung cancer	Activate pyroptosis	[104]
Ophiopogonin B	Radix Ophiopogon Japonicus	Caspase-1, GSDMD	Lung cancer	Activate pyroptosis	[90]
Nobiletin	Citrus Fruits	Caspase-1	Breast cancer	Activate pyroptosis and apoptosis	[105]
Moscatilin	Dendrobium	Unknown	Liver cancer and neuroblastoma	Activate pyroptosis and Necroptosis	[94]
Ardisianone	Ardisia Virens/Ardisia Compressa	Caspase-1/5, HMGB1	Acute myeloid leukemia	Activate pyroptosis and apoptosis	[106]
Triptolide	Herb Tripterygium Wilfordii Hook F	Caspase-3, GSDME, ROS	Head and neck cancer	Activate pyroptosis	[107]
Camptothecin	Camptotheca	Caspase-1, IL-1β, NLRP3	Colorectal cancer	Activate pyroptosis	[108]
Betulinic Acid	Mulberry Tree	Caspase-1	Esophageal cancer	Activate pyroptosis	[95]
Anthocyanin	Plants	Caspase-1, IL-1β, NLRP3	Oral squamous cell carcinoma	Activate pyroptosis	[91]
Galangin	Galangal	GSDME	Glioblastoma multiforme	Activate pyroptosis, apoptosis, and autophagy	[92]
Andrographolide	Andrographis Paniculata	Caspase-8	Breast and ovarian cancers	Activate pyroptosis	[109]
Sinensetin	Citrus Fruits	GSDME, ROS	Melanoma and breast cancers	Inhibit cisplatin-induced pyroptosis	[96]
Carnosic acid	Rosemary	BCL-2, Caspase-3, NLRP3, ROS	Solid cancers	Mitigate pyroptosis to reduce cardiotoxicity	[97]
Caffeine	Tea or Coffee	NLRP3	Liver cancer	Inhibit pyroptosis to reduce cancer risk	[98]
Geranylgeranoic acid	Medicinal Herbs	TLR4	Liver cancer	Activate pyroptosis	[99]
Ligustrazine	Rhizoma Chuanxiong	NLRP3, NF-κB, ROS	Liver cancer	Inhibit pyroptosis to reduce hepatotoxicity	[100]
Mitochonic acid	dietary tryptophan	TNF, IL-6, and caspase-3	Glioblastoma and breast cancers	Inhibit pyroptosis to reduce cardiotoxicity	[101]

GSDME/D, gasdermin E/D; LDH, lactate dehydrogenase; ROS, Reactive Oxygen Species; HMGB1, High mobility group box-1 protein; IL-1β/6, Interleukin-1β/6; NLRP3, NOD-like receptor thermal protein domain associated protein 3; TLR4, Toll-like receptor 4; NF-κβ, nuclear factor kappa-Beta; RIG-I, retinoic acid-inducible gene I; TNF, Tumor Necrosis Factor.

3.4. Advantages of natural materials: safe, diverse, and effective

Natural materials-induced pyroptosis has shown several advantages in tumor therapy. Firstly, most of the reported natural materials are derived from plants or other natural sources that may be safe and well-tolerated for the human body, compared to synthetic compounds that may have more adverse effects [96,98,100]. Secondly, natural materials often simultaneously induce several biological phenotypes. Besides, they can regulate various signaling pathways involved in inflammation, cell death, and immune response, which are crucial in tumor development and progression [89–91,108].

3.5. Challenges of natural materials: compound identification, synergies, and mechanistic understanding

There are also challenges associated with the application of natural materials-induced pyroptosis in tumor therapy. One challenge is the isolation and characterization of single compounds from natural sources. Natural materials are often complex mixtures of various compounds, and it can be difficult to determine which components are responsible for the observed effects. Another challenge is that although studies showed the active effects of highly purified specific compounds, the corresponding mechanisms underlying natural materials-induced pyroptosis are not fully exhibited. More studies are required to elucidate the precise molecular pathways. Moreover, few studies focus on the synergistic effects of combining natural materials with conventional cancer therapies. This suggests that they can enhance the efficacy of existing treatments and maximally alleviate the side effects of tumor therapy. In brief, natural materials-induced pyroptosis holds great promise in tumor therapy due to their safety, multi-target effects, and potential synergistic effects with conventional treatments. However, further research is needed to overcome challenges related to compound identification, and mechanistic understanding to fully exploit the therapeutic potential of natural materials in cancer treatment.

4. Biological materials for pyroptosis induction

4.1. Virus, bacterium, and cell for pyroptosis induction

Several studies provided investigate the oncolytic activity of various viruses, including coxsackievirus A11/B3, Parapoxvirus ovis, herpes simplex virus type 1, and adeno-associated virus, in different types of cancer cells, such as malignant pleural mesothelioma, colon cancer, and glioblastoma, by inducing pyroptosis, which not only leads to the inhibition of tumor growth but also partially stimulates an antitumor immune response [28,111–114]. Similarly, some articles related to bacterium-induced pyroptosis also show the same trends, in regulating pyroptosis in the context of cancer development and immunotherapy [29,31,65,115,116]. Notably, as of now, only one study reported engineer-modified cells for inducing pyroptosis in tumor therapy [30]. Overall, these studies (as shown in Table 2) highlight the potential of oncolytic viruses, bacteria, and cells to induce pyroptosis and stimulate anti-tumor immune responses. Viruses, bacteria, and cells emerge as promising biological materials for cancer therapy, offering new opportunities for the development of effective treatments.

4.2. DNA, RNA, and protein for pyroptosis induction

DNA, RNA, and protein representing the biomolecules involved in biological activities, are not like Viruses, bacteria, and cells, representing the independent units. While exhibiting the capacity to modulate biological activities as biological agents, their effective delivery to

Table 2
Summary of biological materials inducing pyroptosis.

Biological Material	Definition	Molecular Mechanism	Type of cancer	Biological phenotypes except for pyroptosis	Ref.
Oxsackievirus A11	Virus	Calreticulin, HSP70, ICAM-1, IL-1β,	Malignant pleural mesothelioma	Activate apoptosis and necroptosis	[111]
Coxsackievirus B3	Virus	Caspase-3, GSDME	Colon Cancer	NA	[28]
Parapoxvirus ovis	Virus	Caspase-3, GSDME	Colon Cancer	Activates antitumor immunity	[112]
Herpes simplex virus 1	Virus	ATP, GSDME, HMGB1, LDH	Various cancers	Activates antitumor immunity	[113]
Adeno-associated virus	Virus	GSDMNT	Glioblastoma	Evoke a robust immune-response	[114]
E. coli Nissle	Bacterium	Caspase-1, GSDMD	Breast cancer	Enhance Immunotherapy	[116]
Neisseria sicca and Corynebacterium matruchotii	Bacterium	Caspase-1, GSDMD, NLRP3	Oral squamous cell carcinomas	NA	[115]
Salmonella	Bacterium	Calreticulin, Caspase-1/11, GSDMD, IL-1β,	Melanoma	Induce macrophage recruitment	[65]
Listeria monocytogenes	Bacterium	ATP, Caspase-8, GSDMC, IL-1β, IL-18, LDH, NLRP3, ROS	Various cancers	Activates antitumor immunity	[29]
Pseudoalteromonas haloplanktis TAC125	Bacterium	Caspase-1, IL-1β, IL-18	Lung cancer	NA	[31]
NK-tailored CCCR	Cell	GSDME	Lung cancer	Reverse the immune suppressive effects	[30]
DNA aptamers	DNA	GSDMD, Caspase-11	Breast cancer	Improve Immunotherapy	[123]
ASC plasmid	DNA	Caspase-1, Glucose, GSDMD, IL-1β	Breast cancer	NA	[125]
Caspase-1 plasmid	DNA	Caspase-1	Melanoma	Amplify CD8 T cell responses	[69]
Long dsDNA building blocks	DNA	ATP, Caspase-1, GSDMD	Breast cancer	Boost antitumor immunity.	[118]
mRNA lipid nanoparticle	RNA	GSDMB, LDH	Various cancers	Mediate checkpoint immunotherapy	[124]
GSDMD-N mRNA	RNA	ROS, GSDMD	Various cancers	Enhance immunotherapy	[119]
stem-loop RNA 20	RNA	NF-κB, RIG-I, STAT1	Breast Cancer	Induce apoptosis	[126]
sgRNA	RNA	Caspase-3, GDSME, HMGB1, IL-1β	Melanoma	Modulate immunological processes	[49]
Peptide T22	Peptide	Caspase-3, GSDME	Melanoma	NA	[117]
Anti-HER2 antibody	Protein	Caspase-1, GSDMB	Lung cancer	NA	[127]
GSDMD and MLKL protein	Protein	GSDMD	Cervical cancer	Promote lymphocyte infiltration	[120]
DeFer-2 chimera	Protein	Caspase-3, GSDME, iron overload stress	Melanoma	NA	[121]
RNase A and granzyme B	Protein	Caspase-3, GSDME,	Breast cancer	Potentiate the immunotherapy	[122]
Glucose oxidase	Protein	Caspase-1, Glucose, GSDMD, HMGB1, IL-1β	Breast cancer	Robust antitumor immunotherapy	[12]

HSP70, heat shock protein; ICAM-1, intercellular adhesion molecule-1; IL-1β/18, interleukin-1β/18; GSDMB/C/D/E, gasdermin B/C/D/E; ATP, adenosine 5′-triphosphate; HMGB1, high mobility group box-1 protein; LDH, lactate dehydrogenase; GSDMNT, N-terminal gasdermin domain; NLRP3, NOD-like receptor thermal protein domain associated protein 3; NF-κβ, nuclear factor kappa-B; RIG-I, retinoic acid-inducible gene I; STAT1, signal transducer and activator of transcription 1.

specific regions necessitates the utilization of distinct carriers. We reviewed these literatures (as shown in Table 2), which not only showed their explicit effects of pyroptosis Induction, but also exhibited their various delivery carriers, including targeted nanotoxins, virus-like particles, engineered extracellular vesicles, cooperative nano-CRISPR scaffolds, self-assembling nanoparticles, small-molecule ferritin degraders, pore-forming-mediated intracellular protein delivery, and biomineralized two-enzyme nanoparticles, highlighting the diverse strategies and approaches for inducing pyroptosis and enhancing antitumor immune responses [12,49,69,117–124].

4.3. The key molecular mechanism of biological materials-induced pyroptosis

GSDME plays a pivotal role as an initial molecular component in most virus-induced reactions, including pyroptosis, proinflammatory cytokine release, and damage-associated molecular patterns [28,112,113]. In contrast, GSDMD assumes a crucial role as an initiator in bacterium-induced pyroptosis [65,115]. However, the involvement of GSDME/GSDMD and caspase-1/-3 in small molecule-regulated pyroptosis remains a topic of controversy, ultimately leading to tumor regression [69,117,119–122]. Typically, caspase-1 is associated with GSDMD [12,118,125], while caspase-3 is associated with GSDME [117,121,122]. Moreover, combining pyroptosis-inducing agents with immunotherapies such as immune checkpoint blockade, chimeric antigen receptor (CAR) T cell therapy, and engineered extracellular carrier has shown synergistic effects in promoting antitumor immune responses and enhancing therapeutic outcomes [12,30,119].

4.4. Advantages of biological materials: specificity, efficient payload delivery

The use of biological materials to induce pyroptosis offers advantages in the application of tumor therapy. One such advantage is the specificity of biological molecular materials, such as DNA, RNA, and protein, compared with viruses, bacteria, and cells, because they can directly modulate the mechanism, instead of the indirect mechanism, such as ROS or inflammation activation [29,115]. The other advantage is that bacterium and cell-based materials can provide their specific excretions, which can be harnessed for the pyroptosis-inducing agents. This advantage allows for releasing efficient or enough therapeutic payloads within target cells, enhancing the effectiveness of pyroptosis induction [29,114].

4.5. Challenges of biological materials: tumor heterogeneity, cytotoxicity, and regulations

There are several challenges as follows. Firstly, tumor heterogeneity poses a challenge in achieving uniform and effective pyroptosis induction in all tumor cells, as different cells may have varying susceptibility to pyroptosis [65,111,112]. Secondly, Some virus materials, such as Adeno-associated viruses, and oncolytic viruses, can exhibit high cytotoxicity. The balance between efficacy and safety must be carefully optimized [28,111,114]. Thirdly, viruses, bacteria, and cell-based biological materials for pyroptosis induction may face regulatory challenges. Potential risks from their specific cultivation environment and potential damage to humans should be taken into account during the development and application of these technologies. Finally, batch-to-batch variation must also be acknowledged. The variation issue can complicate treatment consistencies, making it hard to standardize treatment and compare findings. To put it briefly, challenges related to tumor heterogeneity, cytotoxicity, regulatory consideration, and batch-to-batch variation, need to be addressed for the successful translation of these approaches into clinical applications.

5. Chemical materials for pyroptosis induction

5.1. Biomarker inhibitor and ion-regulation materials

The literatures (as shown in Table 3) involving monomeric chemical targeting materials demonstrate the potential to target cancer cells and induce pyroptosis. The targeting materials reported include molecular inhibitors, nano micelles, nano modulators, nanocarriers, oncolytic bioreactors, and compounds [33,34,128]. They used different targeting strategies to get closer to their objectives in cancer cells [51,67,129–131]. For example, Li et al. discover a VEGFR inhibitor [132]; Yang et al. induce pyroptosis by co-delivering PI3K/mTOR and CDK inhibitors [33]. While Li et al. develop biodegradable Ca(2+) nano modulators that trigger pyroptosis through mitochondrial Ca(2+) overload [133]. Huang et al. prepare Na2S2O8 nanoparticles to induce pyroptosis through a surge of Na(+) in tumor osmolarity [134]. Except for inducing pyroptosis, they could simultaneously lead to enhanced immunotherapy, DNA damage, apoptosis, ferroptosis, and osmotic change [34,61,73,134]. Overall, these chemical targeting materials include the two main technological lines, ion regulation, and biomarker inhibition, which get along with their unique biological phenotypes.

5.2. Non-targeting materials

The collected literatures (as shown in Table 3) comprehensively discuss monomeric non-targeting drugs and their diverse approaches to induce anti-tumor effects by activating pyroptosis. These non-targeting drugs comprise nanoparticles, commonly used biological oxidase, radiological elements, chemotherapeutic agents, covalent organic frameworks, isomers of paclitaxel, nano trigger platforms, benzimidazoles, metabolites like α-KG, cellulose nanofiber-based hydrogels, tetraarsenic hexoxide, chalcones, and omega-3 fatty acids [35,135–141]. Instead of focusing on specific molecular biomarkers or targeted objectives, these drugs act on various levels, including the tumor microenvironment, biological chemical reactions, epigenetic modifications, cytoplasmic organelle damage, and DNA damage [32,141–145]. For instance, covalent organic frameworks (COFs) have been ingeniously engineered as pyroptosis inducers to remodel the tumor microenvironment [36]. Additionally, Decitabine, a commonly used clinical drug, triggers pyroptosis by regulating hypermethylation [146]. Moreover, beyond their pyroptotic effects, these non-targeting drugs exhibit a broader biological impact, encompassing the inhibition of tumor metastasis and recurrence, distinguishing them from conventional targeting materials [147–149].

5.3. Physical stimuli-responsive materials

The provided literatures (as shown in Table 3) predominantly focus on inducing pyroptosis using monomeric drugs, specifically through photodynamic therapy (PDT), photothermal therapy (PTT), sonodynamic therapy (SDT), and the development of photosensitizers with pyroptotic-inducing capabilities [60,150–152]. These studies explore diverse approaches to enhance the efficacy of PDT, PTT, and SDT, employing techniques like aggregation-induced emission effect, organelle-targeting photosensitizers, membrane-tethered activation designs, and nanocarriers, all aimed at achieving precise localization of reactive oxygen species (ROS) [37,56,58,153–155]. Additionally, the literatures highlight the remarkable potential of pyroptosis in reshaping the tumor microenvironment, triggering cascade catalytic reactions, promoting immunogenic cell death, and effectively inhibiting tumor growth, both at the local and systemic levels [156,157]. Overall, photo-responsive pyroptosis remains the main responsive method, while innovative efforts are focusing on optimizing photosensitizer treatment efficacy and biological targeting.

Table 3
Summary of chemical materials inducing pyroptosis.

Targeting Material	Targeting marker	Molecular Mechanism	Type of cancer	Biological phenotypes except for pyroptosis	Ref.
CC-115	mTOR/Bax	Caspase-3, GSDME	Lung cancer	NA	[129]
Pt3	Zn(2+)	GSDMD	Breast cancer	Activate antitumor immunity	[51]
ZLF-095	VEGF receptor	Caspase-3, GSDME	Various cancers	Activate apoptosis	[132]
Ca(2+) nano modulators	Ca(2+)	Caspase-3, GSDME	Breast cancer	Robust immune responses and suppress lung metastasis	[67]
VNP-GD	Ca(2+)/ESCRT	Caspase-1, GSDMD	Various cancers	Augment the anti-tumor immune response	[133]
Prodrug nanomicelle, PNM	mTOR/CDK	Caspase-3, GSDME	Breast cancer	boost the antitumor effect	[33]
POM1/metformin	CD39/AMPK	ATP, Caspase-1, NLRP3	Melanoma	Overcome anti-PD1 resistance	[42]
SEOB	Ag(+)	ROS	Various cancers	Induce apoptosis and DNA damage	[34]
Quisinostat	Histone deacetylase	Caspase-1/-3	Tongue cancer	Induce apoptosis and ferroptosis	[73]
K(3)ZrF(7):Yb/Er	K(+)	Caspase-1, GSDMD, IL-1β	Breast cancer	Increase intracellular osmolarity	[158]
Benzoxazepine derivatives	HER2	Caspase-1/-3	Various cancers	NA	[130]
Bromodomain inhibitor JQ1	BRD4	Caspase-1, NF-κB, NLRP3	Renal cell carcinoma	NA	[131]
Na(2)S(2)O(8)	Na(+)	Caspase-1	Various cancers	Activate immune response	[134]
Ssss-VHMS	Na(+)	Caspase-1, GSDMD, IL-1β	Liver cancer	Induce apoptosis and ferroptosis	[61]
Na–Al-DMSN	Na(+)	Caspase-1, NLRP4	colon cancer	Enhance cellular immunity	[128]
Non-targeting Material	**Anti-tumor action**				
Copper-quinone-GOx nanoparticles	Disrupt redox equilibria	Caspase-1, GSDMD, NLRP3	Breast cancer	Induce cuproptosis	[139]
Cholesterol oxidase	Mechanoregulation of membranes	Caspase-1, GSDMD, IL-1β, Ca(2+)	Various cancers	Improves anti-tumor immune response	[140]
Radium-223	DNA damage	HMGB1, HSP70	Lung cancer	Enhances immunogenicity	[141]
BEM nanoparticles	Disrupt redox equilibria	ATP, HMGB1	Various cancers	Simulate immunological responses	[135]
TPA-2TIN	Mitochondria	Caspase-3, GSDME	Breast cancer	Enhance immunotherapy and imaging	[32]
Paclitaxel isomer	Induce pyroptosis	Caspase-3, GSDME	Lung cancer	NA	[136]
LaCoO3 nanocrystals	Exhibit GPx-like activity	Caspase-1, GSDMD, LDH, ROS	Lung cancer	Restrain metastasis	[35]
Diselenide nanoprodrug	Exhibit GPx- and SOD-like activities	Caspase-3, GSDME	Breast cancer	Trigger durable immunity	[36]
Flubendazole	Induce pyroptosis	Caspase-1, GSDMD, NF-κB, NLRP3	Glioblastoma	Induce mitochondria-dependent apoptosis	[137]
BI 2536	Small-molecules inhibitor	Caspase-3, GSDME, LDH, HMGB1	Ovarian cancer	Induce cell cycle arrest	[142]
NSBSO	Biosynthesis inhibition	Caspase-3, GSDME, ROS	Breast cancer	Induce ferroptosis	[143]
Liproxstatin-1	Induce pyroptosis	Caspase-3, GSDME	Leukemia	Induce cell cycle arrest and apoptosis	[144]
α-ketoglutarate	Regulate tumor microenvironment	Caspase-8, GSDMC	Various cancers	NA	[145]
Hydrogels Embedding 5-FU	Antimetabolite	Caspase-1, IL-1, IL-18	Breast cancer	NA	[149]
Tetraarsenic hexoxide	Activation of mitochondrial activity	Caspase-3, GSDME, ROS, LDH	Breast cancer	Suppress tumor metastasis	[148]
3′,5′-diprenylated chalcone	Induce pyroptosis	Caspase-3, GSDME, IL-6, IL-8	Prostate cancer	Induce cell cycle arrest and apoptosis	[147]
Decitabine	Activate hypermethylation	Caspase-3, GSDME	Various cancers	Inhibit tumor metastasis and recurrence	[146]
Omega-3 fatty acid	Induce pyroptosis	Caspase-1, GSDMD, IL-1β	Breast cancer	NA	[138]
Responsive Material	**Responsive method**				
Terpyridine-based AIE monomer	PDT	ATP, GSDME	Breast cancer	Inhibit tumor metastasis	[154]
Planar/twisted AIE-based motifs	PDT	ATP, Caspase-3, GSDME, HMGB1, LDH	Breast cancer	Induce ferroptosis	[155]
1,3-Diphenylisobenzofuran	PDT	GSDMD, LDH, ROS	Breast cancer	Urge ICD	[56]
Photosensitive dimer D1	PDT	Caspase-1, GSDMD, IL-1β, IL-18	Various cancers	Enhance ICD	[47]
PYCI	PDT	Caspase-1, GSDMD, IL-1β, IL-18	Various cancers	Enhance systemic immunity	[150]
Porphyrin nanofiber	PDT	Caspase-3	Oral cancer	Induce apoptosis	[151]
Mn-gallate nanoformulation	PTT	ATP, Caspase-3, GSDME, ROS	Osteosarcoma	Result in ATP deprivation	[152]
LPM	SDT	Caspase-3, GSDME	Breast cancer	Robust immune efficacy	[60]
LaFeO(3) perovskite nanocrystals	SDT	Caspase-1, GSDMD, NLRP3, ROS	Breast cancer	Activate cascade catalytic reactions	[156]
NI-TA	PDT	Caspase-3, GSDME	Breast cancer	Inhibit stemness	[157]
TBD-3C	PDT	Caspase-1, GSDMD, LDH, ROS	Pancreatic cancer	Attack the distant tumor	[37]
LDH@ZnPc	PDT	Caspase-1, GSDMD, CRT, HMGB1	Cervical cancer	Robust ICD ability	[58]
CA-Re	PDT	Caspase-1, GSDMD, IL-1β, IL-18	Breast cancer	Enhance systemic immunity	[153]
Acid-activatable photosensitizers	PDT	Caspase-3, Ca(2+), GSDME	Lung cancer	Minimize systemic side effects	[159]

mTOR, mammalian target of rapamycin; GSDME/D/C, gasdermin E/D/C; VEGF, vascular endothelial growth factor; ESCRT, endosomal sorting complex required for transport; AMPK, adenosine 5′-monophosphate-activated protein kinase; ATP, adenosine 5′-triphosphate; NLRP3, NOD-like receptor thermal protein domain associated protein 3; GOx, glucose oxidase; ROS, reactive Oxygen Species; IL-1β/6/8/18, interleukin-1β/6/8/18; HSP70, heat shock protein 70; NF-κβ, nuclear factor kappa-B; GPx, glutathione peroxidase; SOD, superoxide dismutase; HMGB1, high mobility group box-1 protein; AIE, aggregation-induced emission effect; LDH, lactate dehydrogenase; CRT, calreticulin; ICD, immunogenic cell death; PDT, photodynamic therapy; PTT, photothermal therapy; SDT, sonodynamic therapy.

5.4. Key molecular mechanisms of chemical materials induced pyroptosis

Numerous studies (as shown in Table 3) have extensively explored the application of biomarker-/ion-targeting, chemotherapeutic, and physical stimuli-responsive materials to induce pyroptosis in cancer cells [34–36,42,56]. These inducers effectively activate critical molecular pathways, including gasdermin family proteins (GSDMD and GSDME), caspases (caspase-1 and caspase-3), the canonical inflammatory NLRP3 pathway, and the release of pro-inflammatory cytokines (IL-1β and IL-18) [47,60,150]. Notably, in the molecular mechanism of chemical

Table 4
Summary of multifunctional composite materials inducing pyroptosis.

Composite Material	Synergistic method	Molecular Mechanism	Type of cancer	Biological phenotypes except for pyroptosis	Ref.
Au/AgBiS(2)	Radiotherapy/imaging	ATP, Caspase-3, GSDME, LDH	Breast cancer	Prevent tumor metastasis	[175]
Fe/Mn bimetal-organic framework/ resiquimod	CDT/immune therapy	Caspase-1, GSDMD	Breast cancer	Augment immunotherapy	[181]
Decitabine/Metal-organic frameworks/ macrophages	PDT/PTT/targeted delivery	GSDME, LDH, IL-1β	Breast cancer	Augment the immune response	[173]
Au/mesoporous CeO(2)/Rhodamine B/ membrane	PDT/imaging/targeted delivery	Caspase-3, GSDME	Breast cancer	Enhanced immunotherapy	[174]
Copper ions/porphyrin/membrane-based vesicles	PDT/chemotherapy /targeted delivery	Caspase-3, GSDME	Various cancers	Boost the immunogenicity	[183]
Anchoring peptide RKC/photosensitizer/ immune checkpoint inhibitor	PDT/immune therapy/ targeted delivery	ATP, Caspase-1, GSDMD, HMGB1	Prostate cancer	Stimulate immune response	[182]
Na(2)S(2)O(8)/liquid drops/tannic acid/ ferrous ions	Chemotherapy /targeted delivery	Caspase-1, GSDMD	Lung cancer	Execute ferroptosis	[184]
Decitabine/gold nanoclusters/ precise Au/Au ratios	Chemotherapy/ radiofrequency therapy	ATP, Caspase-3, GSDME, HMGB1, IL-1β	Breast cancer	Enhance the antitumor efficacy	[48]
Black phosphorus/lonidamine/ membrane	Chemotherapy/PDT/ targeted delivery	ATP, Caspase-3, GSDME, LDH, HMGB1	Glioblastoma	Boost the release of immune-activated factors	[160]
Cross-linker PSe–Se/ indocyanine green/mannose	PDT/targeted therapy	Caspase-3, GSDME, GSH, ROS, LDH, HMGB1	Breast cancer	Promote cancer immunotherapy	[88]
Chlorin e6/GSDMD-N/mRNA/HER2 antibody	PDT/targeted therapy	ROS, GSDMD	Various cancers	Enhance immunotherapy	[119]
Prodrug of paclitaxel-oxaliplatin/Chlorin e6/ diselenide cross-linking	Chemotherapy/PDT/ targeted delivery	ATP, Caspase-3, GSDME, LDH, HMGB1	Breast cancer	Remodel the tumor microenvironment	[50]
Chlorin e6/doxorubicin/ bacterial membrane vesicles	Chemotherapy/PDT/ targeted delivery	Caspase-1, GSDMD, NLRP3, ROS	Breast cancer	Minimize therapeutic side effects	[177]
Chlorin e6/cytarabine	Chemotherapy/PDT	ATP, Caspase-3, GSDME, ROS, HMGB1	Breast cancer	Improve the global anticancer immune response	[161]
Bi(2)Te(3) nanoplates/hygrogel	PDT/PTT	ROS	Melanoma	Induce apoptosis and ferroptosis	[167]
Block copolymer/dasatinib/ oxaliplatin	Chemotherapy/ targeted therapy	Caspase-3, GSDME, LDH, HMGB1	Various cancers	Enhance the immunological effects	[176]
Apatinib/MnO(2)/porphyrin/ tumor cell membrane	Chemotherapy/PDT/ targeted therapy/ imaging	GSH, ROS	Various cancers	Anti-angiogenesis	[162]
IR780-iodide/Na(2)S(2)O(8)/succinate	CDT/PDT/ targeted therapy	ROS	Various cancers	Overcome chemo-resistance	[168]
4,4′-azobisbenzoic acid/ Cu(2+)/glucose oxidase	Targeted therapy	Caspase-1, GSDMD, LDH	Cervical Cancer	NA	[185]
Chlorin e6/RGX-104 amphiphilic block polymer	PDT/targeted therapy	ATP, GSDME, HMGB1, IL-1β	Breast cancer	Augment immunotherapy	[163]
Decitabine/nigericin/ hexahistidine-metal assembly	Chemotherapy/ targeted therapy	Caspase-1, GSDMD, NLRP3	Various cancers	Induce systemic antitumor immunity	[178]
Benzoic imine and hydrazone bonds/ doxorubicin	Chemotherapy/ targeted therapy	ATP, Caspase-3, GSDME, LDH, HMGB1	Colon cancer	Enhance the immunological response	[179]
Dichloroacetate/ poly ethyl methacrylate	Chemotherapy/ targeted therapy	ATP, Caspase-1, GSDMD, HMGB1, IL-1β	Osteosarcoma	Enhance immunotherapy	[180]
IR780/sericin derivative /Vitamin B12	PDT/PTT/ targeted delivery	Caspase-1, GSDMD, NLRP3, ROS	Gastric cancer	Induced mitoDNA oxidative damage	[169]
IR820/piperlongumine /polydopamine	CDT/PTT/ targeted delivery	GSH, H(2)O(2), ROS	Breast cancer	Elicit ferroptosis	[164]
Hydralazine/mitoxantrone/zeolitic imidazolate framework-8	Chemotherapy/ targeted therapy	Caspase-3, GSDME	Breast cancer	Build a long-term immune memory response	[72]
Quinone oxidoreductase isozyme 1/ fluorogenic hemicyanine	Chemotherapy/imaging/ targeted delivery	Caspase-3, GSDME, LDH	Various cancers	Activate antitumor immunity	[170]
Doxorubicin/folic acid/ metformin	Chemotherapy/ targeted therapy	Caspase-7, GSDMD	Melanoma	Trigger apoptosis, and necroptosis	[171]
Citric acid/iron oxide core/ manganese dioxide protrusions	Chemotherapy/ targeted therapy	Caspase-1, GSDMD, LDH, NLRP3, ROS	Breast cancer	NA	[172]
NBS/1-methyltryptophan	PDT/targeted therapy	Caspase-1, GSDMD, ROS	Breast cancer	Boost the immune response	[59]
Apatinib/cinobufagin/ hybrid membrane	Chemotherapy/ targeted therapy	Caspase-1, ROS	Gastric cancer	Induce apoptosis and autophagy	[165]
Decitabine/indocyanine green/cancer cell membrane	Chemotherapy/PDT/ targeted delivery	Caspase-3, GSDME	Breast cancer	Impress systemic antitumor immunity	[166]

PDT, photodynamic therapy; PTT, photothermal therapy; CDT, chemodynamic therapy. ATP, adenosine 5′-triphosphate; GSDME/D/C, gasdermin E/D/C; LDH, lactate dehydrogenase; HMGB1, high mobility group box-1 protein; ROS, reactive Oxygen Species; GSH, glutathione; NLRP3, NOD-like receptor thermal protein domain associated protein 3; IL-1β, interleukin-1β.

material-induced pyroptosis, overexpressed caspase-1 and GSDMD consistently coincide with the activation of inflammatory pathways or pro-inflammatory cytokines, whereas overexpressed caspase-3 and GSDME rarely exhibit similar patterns [32,131,136,144]. Furthermore, pyroptosis induction has demonstrated significant potential in enhancing antitumor immune responses by overcoming anti-PD1 resistance, promoting dendritic cell maturation, and triggering the release of DAMPs such as HMGB1 [37,133,158]. In a word, these studies provide valuable insights into the molecular mechanisms of pyroptosis induction using chemical materials, shedding light on potential therapeutic strategies for cancer treatment.

5.5. Advantages of chemical materials: precise design, scalable production

Chemical materials-induced pyroptosis in tumor therapy offers several advantages compared to biological and natural materials. Firstly, chemical materials can be easily synthesized and modified, allowing for precise control over their properties and functions. This enables the design of materials with enhanced therapeutic efficacy and targeted delivery to tumor cells [56,60,156]. Secondly, chemical materials can be easily scaled up for mass production with high purity, making them more suitable for clinical translation [136]. The simplicity of the chemical synthesis and the potential for large-scale production make this complex a promising candidate for future clinical applications [32,37,145,152].

5.6. Challenges of chemical materials: toxicity, stability, and biocompatibility

There are also challenges associated with the use of chemical materials in pyroptosis-based tumor therapy. One challenge is the potential toxicity of the materials. Some chemical materials used to induce pyroptosis, such as nanoparticles and small molecules, may exhibit cytotoxic effects on both tumor and normal cells. This can limit their therapeutic potential. Additionally, chemical materials may have stability and biocompatibility issues, especially when used in vivo. Some materials may degrade or undergo chemical reactions that can affect their therapeutic efficacy and safety. In summary, careful consideration of their safety, stability, and biocompatibility is necessary for their successful translation into clinical applications.

6. Multifunctional composite materials for pyroptosis induction

6.1. Multifunctional composite materials

The provided literatures (as shown in Table 4) focus on inducing pyroptosis in multifunctional composite materials through synergistic effects for tumor treatment. Various innovative approaches are proposed in these studies, with a common strategy being the utilization of nanoscale materials as carriers for pyroptosis-inducing agents. For instance, macrophage/tumor cell membranes, membrane vesicles, metal-organic frameworks, and polymers are employed to enhance tumor targeting, blood-brain barrier penetration, and drug-carrying capacity [88,119,160–166]. Apart from drug delivery, several literatures explore other therapeutic modalities utilizing pyroptosis induction. Combining phototherapy with pyroptosis induction using photosensitizers like chlorin e6, indocyanine green, and IR780/820 is one such approach [164,167–169]. The types of phototherapy include photodynamic therapy, photothermal therapy, and chemodynamic therapy [50,72,119,160,166,168,170–174]. Notably, a composite radiosensitizer (Au@AgBiS2) is designed to enhance the efficacy of radiotherapy for cancer treatment and prevent tumor metastasis [175]. Additionally, some literatures incorporate immunomodulatory agents into the composite materials to enhance the immune response [59,176–182]. For example, engineered extracellular vesicles (EVs) are utilized to deliver GSDMD-N mRNA, an essential molecule for pyroptosis, to tumor cells [119]. Some engineered vesicles/drops also contain hydrophilic sensitizers and compounds for tumor targeting, resulting in enhanced pyroptosis induction and activation of a potent tumor immune response [119,183,184]. As a collaborative technology, radiofrequency irradiation and dynamic imaging have been applied to multi-functional materials [48,168]. In conclusion, the multifunctional integration of drug delivery, therapy, imaging, and immunomodulation allows for synergistic effects and improved therapeutic outcomes via pyroptosis induction.

6.2. Key molecular mechanisms of multifunctional composite materials induced pyroptosis

The role of reactive oxygen species (ROS) is consistently emphasized in the molecular mechanisms discussed among the literatures on multifunctional composite materials (as shown in Table 4) [50,88,119,160–162,167,177,185]. One approach involves regulating the pH within cells, leading to the accumulation of damaged mitochondria and subsequent ROS release, further promoting pyroptosis in glioblastoma cells [179]. Another strategy involves splitting diselenide bonds within the prodrug due to high glutathione levels in the tumor microenvironment, resulting in ROS generation and subsequent pyroptosis induction [50]. Furthermore, alternative strategies focus on photo-activated thermoelectric catalysts based on bismuth telluride nanoplates. When exposed to near-infrared light, these nanoplates induce a significant temperature elevation, disrupting the redox balance in tumor cells and generating ROS. This ROS-induced oxidative stress triggers tumor cell pyroptosis, enhancing the efficacy of tumor nanotherapy [167]. In summary, ROS generation can be triggered by various stimuli, such as light, pH changes, or redox imbalances, leading to the activation of pyroptotic pathways and subsequent anti-tumor responses. Alongside ROS, the molecular mechanisms involved in pyroptosis induction encompass the activation of specific pathways, such as the caspase/GSDM pathway, the NLRP3 inflammasome pathway, and the release of high-mobility group box 1 (HMGB1), adenosine triphosphate (ATP), and cytokines, which can trigger apoptosis, necroptosis, or promote immune response activation and contribute to tumor cell elimination [59,72,165,166,170,171].

6.3. Advantages of composite materials: enhancing tumor therapy synergistically

Multifunctional composite materials (as shown in Table 4) have been developed to induce pyroptosis in tumor cells, offering two advantages in tumor therapy. Firstly, multifunctional composite materials can combine different therapeutic modalities to achieve synergistic effects. For instance, in paper [88], a dual-stimulus phototherapeutic nanogel combined photothermal therapy (PTT) and photodynamic therapy (PDT) was developed for triggering pyroptosis and promoting cancer immunotherapy. Similarly, in paper [167], bismuth telluride nanoparticles were engineered to achieve photothermal, photodynamic, and electrocatalytic effects, leading to tumor-synergistic treatment through ferroptosis and pyroptosis. Secondly, multifunctional composite materials can overcome the limitations of single-agent therapy and enhance therapeutic efficacy. In paper [50], a diselenide-based dual-responsive prodrug was developed to induce pyroptosis and potentiate cancer immunotherapy. This prodrug exhibited excellent tumor microenvironment on-target effects and triggered robust immune responses, leading to effective tumor growth inhibition. Similarly, in paper [176], pH-responsive nano prodrugs combining an Src inhibitor and chemotherapy were designed to potentiate antitumor immunity via pyroptosis in head and neck cancer. This combination therapy effectively suppressed tumor growth and prolonged the survival of mice.

6.4. Challenges of composite materials: delivery, understanding, and targeting issues

Despite these advantages, there are still challenges in the application of multifunctional composite materials induced pyroptosis in tumor therapy. One challenge is the optimization of drug delivery and release kinetics to ensure efficient and controlled pyroptosis induction. For example, in paper [178], hexahistidine-metal nanocarriers were used to co-deliver nigericin and decitabine for pyroptosis-induced immunotherapeutics. The design of such nanocarriers requires careful consideration of drug loading, release mechanisms, and stability. Another challenge is Incomplete understanding of mechanisms: The mechanisms underlying pyroptosis induction by multifunctional composite materials are not fully understood. Further studies are needed to elucidate the molecular pathways and signaling cascades involved in pyroptosis induction, which will help optimize the design of composite materials for tumor therapy. Furthermore, some of the composite materials used in the studies lack tumor-specific targeting capabilities, which may result in off-target effects and potential damage to healthy tissues. For example, on paper [177], bacterial outer membrane vesicles (OMVs) were used as a therapeutic platform, but their therapeutic window was narrow due to toxicity.

Overall, multifunctional composite materials induced pyroptosis offers great potential in tumor therapy. They provide synergistic effects, enhanced therapeutic efficacy, and targeted delivery. However, further research is needed to minimize potential off-target effects and maximize their therapeutic specificity, paving the way for the clinical translation of these innovative approaches.

7. Outlooks for engineering materials in cancer pyroptosis induction

7.1. Minimizing drug side effects

Natural engineering materials play a crucial role in inhibiting the pyroptosis pathway in cancer treatment. This characteristic stands out as one of the most remarkable features of these materials, as they effectively alleviate side effects by disrupting the molecular pathways of pyroptosis. Natural materials are highly valuable for researchers exploring cell and tissue protection through pyroptosis [96–98,100]. Additionally, natural sources provide a wide array of compounds with diverse properties. Scientists can selectively choose and modify these compounds to cater to specific types of cancers. Similar outcomes can be attained through alternative technologies such as surface modifications, controlled release systems, and biocompatibility testing [24,89,103]. Consequently, the use of natural extractive materials to minimize drug side effects holds immense promise in the realm of cancer treatment (Fig. 5).

7.2. Precision drug delivery

Biological engineering materials-induced pyroptosis offers immense potential for tumor therapy, providing precise modification and higher payload capacity for enhanced antitumor efficacy. Materials like DNA, RNA, and proteins directly modulate the mechanism, setting them apart from other materials that act indirectly [49,69,70,119]. Personalized medicine approaches facilitated by engineering materials are becoming more commonplace, leading to treatments tailored to individual genetic profiles [3,12,117]. Future goals include innovative drug delivery systems that are highly efficient and precise for cancer treatment(Fig. 5).

7.3. Enhance the immunotherapy

Engineering materials-induced pyroptosis not only triggers immunogenic tumor cell death but also reconfigures the intricate tumor microenvironment [29,112,113,118]. Immunotherapy has proven effective against various cancers due to its adaptability for different malignancies and personalization based on patients' immunological profiles [186–188]. Integrating engineering materials into immunotherapy has transformative potential, revolutionizing cancer treatment and other immunological disorders [48,50,88,176]. Ongoing research and technological advancements are expected to yield more effective, personalized, and targeted immunotherapies, offering new hope for patients and significantly improving outcomes(Fig. 5).

7.4. Overcoming treatment resistance

Pyroptosis offers unique advantages by inducing a dual mechanism,

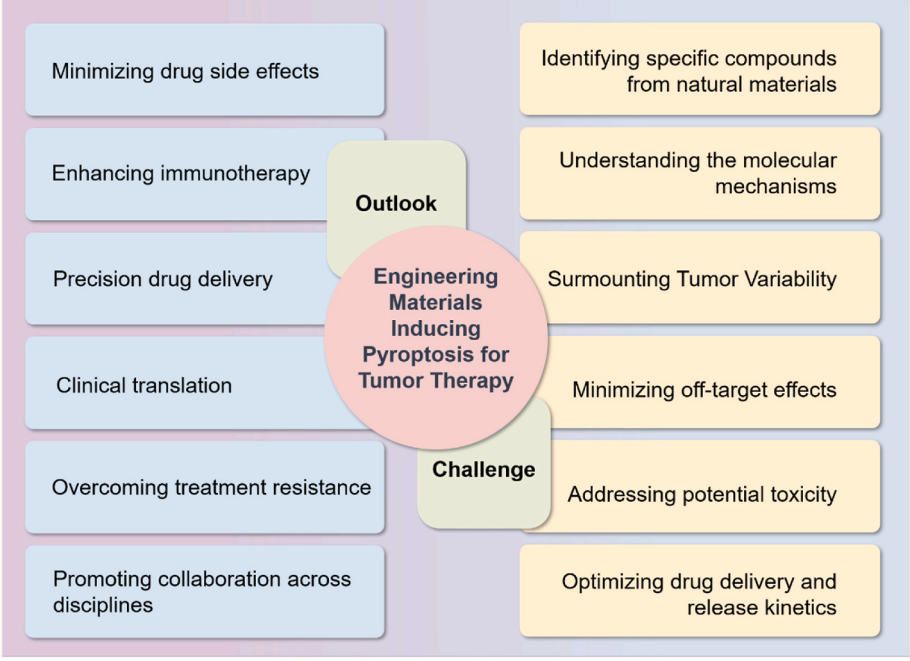

Fig. 5. Outlook and challenges in engineering materials for inducing pyroptosis in tumor therapy.

including an inflammatory response and programmed tumor cell death [189,190]. This dual mechanism can overcome certain resistance pathways, providing an alternative approach in drug-resistant scenarios [34,61,111,132]. Engineering materials-induced pyroptosis can combine multiple pyroptosis-inducing agents or drugs, enhancing overall effectiveness or activating other cell death phenotypes, especially when drug resistance mechanisms are multifaceted [167,168,171]. Integrating diagnostic capabilities into engineered materials can enable real-time monitoring of drug resistance markers, allowing timely adjustments to therapy based on evolving resistance patterns(Fig. 5).

7.5. Clinical translation

As research progresses, pyroptosis-inducing engineered materials will transition from preclinical studies to clinical trials in cancer treatment. While some mechanisms and potential safety concerns remain unclear, extensive preclinical studies are being conducted to validate efficacy, safety, and specificity. Researchers are making progress in understanding these complexities. The advantages inherent in engineering materials, including their tunability, scalability, and targeted delivery capabilities, offer substantial practical value [177,178]. These attributes are instrumental in surmounting challenges encountered during the practical application of anticancer therapies in clinical settings. By combining these engineering anti-tumor materials with cutting-edge diagnostic tools, real-time assessment of treatment responses becomes feasible. This real-time feedback empowers oncologists to dynamically adapt pyroptosis-based therapies, optimizing treatment strategies and significantly enhancing patient outcomes(Fig. 5) [191].

7.6. Collaboration across disciplines

Collaboration involving engineering materials in the application of inducing pyroptosis in tumor treatment brings together diverse expertise and perspectives, fostering innovation and addressing complex challenges. Firstly, the integration of artificial intelligence and machine learning enables researchers to predict the behavior of engineered materials, simplifying experimental processes and designing highly sophisticated and responsive drugs or their corresponding delivery systems. Secondly, oncologists, chemists, and immunologists collaborate to understand the molecular mechanisms of immune responses triggered by engineering materials-induced pyroptosis. This collaboration facilitates the design of therapies that not only induce pyroptosis in tumor cells but also enhance the immune system's molecular-level capabilities. Thirdly, clinical researchers and engineering material experts collaborate to design and conduct clinical trials. These trials rigorously assess the safety, efficacy, and long-term effects of pyroptosis-inducing tumor therapies using engineering materials. Finally, research collaborations between leading academic institutions and pharmaceutical companies are driving global innovation. Joint ventures prove beneficial in developing next-generation materials and delivery methods for pyroptosis induction in tumor therapy, propelling the industry forward into new realms of possibility.

All in all, the utilization of natural materials in inhibiting pyroptosis showcases a paradigm shift in cancer treatment. Researchers can selectively modify these compounds, tailoring treatments to specific cancer types. Simultaneously, alternative technologies such as surface modifications and controlled release systems enhance the effectiveness of these materials, broadening their applicability. The precision offered by biological engineering materials like DNA and proteins marks a significant departure from indirect approaches. Personalized medicine, guided by individual genetic profiles, is reshaping the landscape of cancer therapy, ensuring treatments are not only effective but also specific to each patient. The integration of engineered materials into immunotherapy is a transformative approach. By inducing immunogenic tumor cell death and restructuring the tumor microenvironment, these materials enhance the adaptability and personalization of immunotherapies. Moreover, the unique dual mechanism of pyroptosis overcomes resistance pathways, especially in complex drug-resistant scenarios. Combining multiple pyroptosis-inducing agents or drugs increases overall effectiveness and activates alternative cell death phenotypes, creating a multifaceted therapeutic approach. Real-time monitoring of drug resistance markers, enabled by diagnostic capabilities in engineered materials, allows timely adjustments to therapy, ensuring continuous effectiveness in the face of evolving resistance patterns.

8. Conclusion

This paper offers an extensive exploration of the potential applications of engineering materials in triggering pyroptosis as a strategy for cancer treatment. It underscores the significance of pyroptosis in suppressing tumors and its interconnectedness with other cell death pathways like apoptosis and necroptosis. The paper also examines the release of bioactive molecules during pyroptosis induction, leading to immune activation through immune signaling pathways.

The paper further delves into the use of natural materials, such as saponins, curcumin, and betulinic acid, in enhancing pyroptosis-mediated cancer therapy. These natural compounds have shown potential in enhancing radiosensitizing potency, overcoming drug resistance, and reducing chemotherapy-induced adverse effects. Besides, natural materials-induced pyroptosis holds great promise in potential synergistic effects with conventional treatments. Nonetheless, additional research is imperative to address challenges linked to compound identification and gain a comprehensive mechanistic understanding of individual components of natural materials in the context of cancer treatment.

Additionally, the paper discusses the application of biological agents, encompassing viruses, bacteria, and cells, for pyroptosis induction in cancer therapy. Notably, GSDME emerges as a critical factor in virus-induced reactions. The paper highlights the oncolytic capabilities of various viruses and the potential of engineered bacteria/cells to elicit pyroptosis and trigger anti-tumor immune responses. Challenges related to tumor heterogeneity, cytotoxicity, and regulatory considerations are acknowledged.

Furthermore, the study explores the impact of monomeric chemical materials, including biomarker- and ion-targeting compounds, non-targeting substances, and stimuli-responsive agents, inducing pyroptosis within cancer cells. The paper elaborates on their mechanisms of action, covering both inflammatory activation (via caspase-1 and GSDMD) and non-inflammatory activation (via caspase-3 and GSDME). It emphasizes the necessity of assessing their safety, stability, and biocompatibility for future applications.

Moreover, the paper delves into multifunctional composite materials that integrate drug delivery, therapy, imaging, and immunomodulation to synergistically induce pyroptosis. Reactive oxygen species (ROS) are identified as key initiators in this process. The advantages of these materials include enhanced therapeutic efficacy and targeted delivery, yet challenges such as off-target effects, therapeutic specificity, and incomplete mechanistic understanding are acknowledged.

The engineering materials for pyroptosis induction in cancer treatment represent a cutting-edge field at the intersection of oncology, nanotechnology, and materials science.

Engineering materials show significant promise in cancer treatment, particularly in inducing pyroptosis, which helps minimize drug side effects, enabling precise drug delivery, enhancing immunotherapy, and overcoming treatment resistance. The future of tumor therapy lies at the intersection of engineering materials and pyroptosis induction, with a promising trajectory toward personalized, targeted, and adaptable treatments. Clinical translation is imminent. The collaboration across diverse disciplines and the integration of cutting-edge technologies, such as AI and real-time diagnostics, are propelling this field into unexplored realms. The ongoing commitment to innovation, combined

with the tailored approaches enabled by these materials, ensures a revolution in cancer treatment, significantly enhancing patient outcomes and redefining the landscape of oncological therapies.

In conclusion, the research paper provides a comprehensive overview and outlook of the application of engineering materials and its corresponding biological molecular mechanism in pyroptosis induction for cancer treatment. It highlights the potential of natural, biological, chemical, and multifunctional composite materials in enhancing the specificity, effectiveness, and safety of pyroptosis induction.

Ethics approval and consent to participate

There are no human and animal subjects in this review and informed consent is not applicable.

CRediT authorship contribution statement

Jiayi Liu: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Taili Chen:** Writing – review & editing, Writing – original draft. **XianLing Liu:** Resources, Methodology, Conceptualization. **ZhiHong Li:** Supervision, Resources, Investigation, Conceptualization. **Yong Zhang:** Supervision, Resources, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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