Chapter 35

Harnessing Nanomedicine for Targeted Sepsis Therapy

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ABSTRACT

Sepsis is an extreme host response to microbial invasion that is characterized by excessive release of cytokines, reactive oxygen species, and coagulopathies, leading to multiple organ failure and mortality. Sepsis remained the most common cause of mortalities throughout the world for centuries. Conventional sepsis management includes antibiotic therapy, anti-inflammatory drugs, and fluid therapy. However, due to the extensive application of antibiotics, most microorganisms are resistant to commercially available antimicrobial drugs, demanding new methods to control sepsis. Nanomedicines and other nanoparticles hold a promising potential in sepsis theragnostic due to their drug carrying, site targeting, and sustained release of the drugs. Scientists have successfully applied these nanomedicines to overcome tissue damage due to the excessive release of cytokines and reactive oxygen species and eliminate the microbes from the body. Nanomedicines have also shown their action against antibiotic resistance by targeting microbial biofilms. Similarly, several nanoplatforms have been discovered to detect and quantify sepsis-associated biomarkers, such as pro-inflammatory cytokines, PCT, and CRP. Although nanotechnology offers several opportunities to reduce sepsis-associated mortalities, toxicity and other complications associated with nanomedicines and nanoparticles can be a major hurdle in their clinical applications. Thus, scientists should explore the natural sources for the preparation of nanomedicines and prepare guidelines for their safe applications.

KEYWORDS
Nanomedicine, Cytokines, Sepsis, Immunosuppression, Antimicrobials

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INTRODUCTION

Sepsis is defined as a life-threatening extreme host response to infectious agents, leading to multiple organ failure due to the release of inflammatory mediators into the circulation. Sepsis is characterized by the disruption in a finely tuned immunological balance between the inflammatory and anti-inflammatory mediators, cytokines, and pathogen-related molecules, resulting in the activation of coagulation and complement cascades (Jarczak et al., 2021). Despite the improvement in therapeutic algorithms and an increase in research to understand the pathophysiological mechanisms, sepsis is still considered the major global health issue, responsible for 2.8 million deaths annually (Maneta et al., 2023). According to a report published by Vincent et al. (2014), mortality rates with sepsis are higher than those of myocardial infarction and stroke. Bacteria are considered the most common cause of sepsis in an intensive care unit (ICU). According to a study conducted with 7,000 sepsis patients, gram-negative bacteria are a major cause of sepsis (62.2%), followed by Gram-positive bacteria (46.8%) and fungi 19.4%) (Esparza et al., 2023). The release of microbial products, such as endotoxins from gram-negative bacteria, activates toll-like receptors (TLR) on monocytes and other antigen-presenting cells, leading to the upregulation of pro and anti-inflammatory pathways. The storm of pro-inflammatory cytokines (IL-1, IL-12, IL-18, and TNF-α) and other inflammatory mediators leads to tissue damage, an aberration in the coagulation cascade, and irreversible damage to vital organs (Hollenberg and Singer, 2021).

Early diagnosis of sepsis and timely therapeutic interventions are necessary to reduce mortality and improve clinical outcomes. Conventionally, sepsis can be managed with broad-spectrum antibiotics, fluid therapy, and end-organ support through mechanical ventilation and stabilization of hemodynamics (Gauer, 2013). However, due to the irrational use of

antibiotics in both human and veterinary medicine, most pathogens are resistant to antibiotics, demanding new therapeutical approaches to manage the severity of sepsis. Furthermore, due to the complex pathophysiology of sepsis, the targeted delivery of antibiotics and other drugs is generally not achieved. Similarly, due to non-specific signs and symptoms and a lack of guidelines, sepsis diagnosis can be challenging for clinicians. The standard methods to diagnose sepsis include microbial culture, isothermal amplification methods, and molecular techniques, such as PCR. These conventional methods for sepsis diagnosis are time-consuming, require trained personnel, and are multi-step and resource intensive, with a restricted limit of detection (LOD) and specificity. Hence the complications associated with sepsis treatment and diagnosis demands advanced platforms and therapeutic strategies for sepsis management (Claxton et al., 2020; Pant et al., 2021).

The advancement in the field of nanotechnology and drug delivery system has revolutionized the diagnostic and treatment of life-threatening diseases. Nanotechnology and nanomedicines have now enabled clinicians to diagnose and treat sepsis more easily, providing an innovative solution to longstanding challenges. Nanoparticles, with their unique properties, enable more sensitive and specific detection of sepsis biomarkers, improving early diagnosis and timely intervention. Furthermore, nano-based drug delivery systems enhance the targeted delivery of therapeutics, optimizing treatment and efficacy while minimizing side effects. These advancements hold promising potential to transform sepsis management, offering hope for improved patient outcomes and reduced mortality rates (Claxton, Papafilippou, Hadjidemetriou, Kostarelos, and Dark, 2020).

Pathophysiology of Sepsis

Sepsis is an overwhelming hyperinflammatory and immunosuppressive stage characterized by a "cytokine storm" resulting in fever, refractory shock followed by multiple organ failure and death. The triggering event of sepsis starts with the recognition of pathogen-associated molecular patterns (PAMPs) or Danger-associated molecular patterns, such as LPS in the case of gram-negative bacteria and Polysaccharides in the case of gram-positive bacteria. The recognition of these microbial products by the body's innate immune system leads to the activation of complex intracellular signaling pathways, leading to the release of inflammatory mediators. The signaling molecules pathways and microbially derived molecules determined the intensity of inflammatory response. For example, recognition of LPS by Toll-like receptors (TLR-4) of macrophages activates nuclear factor-κB (NF-κB) pathways, resulting in the release of inflammation-active mediators (such as IL-1, IL-6, IL-18, TNF-α to clear microbial invasion. However, excessive activation of macrophages causes a "cytokine storm" that impairs the host immune system, leading to tissue damage. This hyperinflammatory stage also causes the activation of the complement system and the release of vasoactive molecules from endothelial cells and chemoattractant, thus switching from an anticoagulant to a procoagulant state. The activation of the complement system also causes the generation of Reactive Oxygen Species (ROS) and the release of granular enzymes, leading to more tissue damage (Hotchkiss et al., 2016; Luo et al., 2021).

Along with the hyper-inflammatory stage, sepsis also causes long-term immunosuppression in surviving patients, leading to persistent catabolism syndrome. This clinical syndrome is characterized by markedly increased C-reactive protein (CRP) concentrations, neutrophilia, and the release of immature myeloid cells. The release of immature myeloid cells into the circulation has defective antimicrobial activity and releases anti-inflammatory cytokines. The exact etiology of immature myeloid cells is still unknown. However, it is likely driven by DAMPs produced by injured tissues and organs (Gentile et al., 2012; Hawkins et al., 2018).

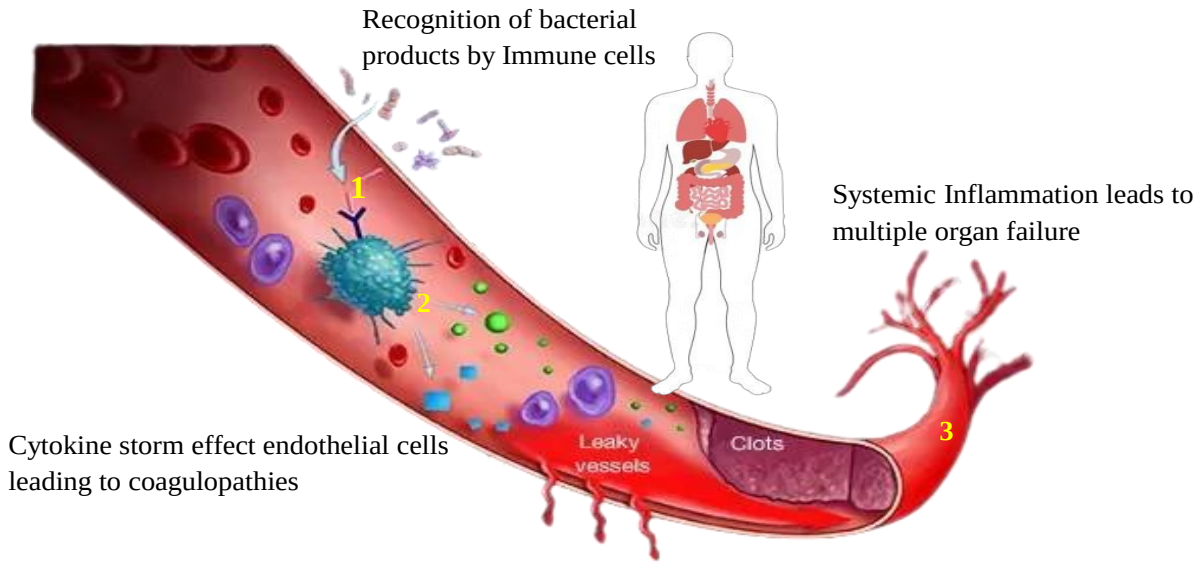

Fig. 1: Pathophysiology of sepsis from recognition of microbes to multiple organ failure

Pathway	Description	Reference
TREM	• Upregulate pro-inflammatory cytokines and chemokines, leading to amplification of inflammatory cascades. • Blocking TREM1 signaling pathways can prevent Polymicrobial and LPS induced sepsis.	(Cohen, 2001; Siskind et al., 2022)
S1PR	• S1PR2 member of this pathway prevent phagocytic activity of macrophages, triggers macrophages proptosis, and stimulates complications associated with gram negative sepsis.	Luo et al., 2021
P2X	• P2X7 riggers macrophages proptosis and activates caspase-1 when interacting with HNP1, worsening the sepsis. • Inhibition of this pathway can prevent septic renal damage and improve sepsis outcomes.	(Antonioli et al., 2019; Savio, 2022)
TRPM	• TRPM2 of this pathway causes clearance of invaded microbes and their products. • TRPM2 deletion leads to microbial load, organ damage, systemic inflammation, resulting in increased mortality.	(Liu et al., 2019)

Decoding Sepsis: Nanomedicine's Promising Frontier

The emergence and rapid progression of nanotechnology in recent eras have allowed clinicians and researchers to manage life-threatening diseases and overcome the serious adverse effects and resistance of drugs. Nanomaterials are now being used in the medical field for targeted drug delivery and diagnosis of several life-threatening conditions, including sepsis and other hyperinflammatory disorders. The smaller size of the nanoparticles enables them to cross the small capillaries and actively targeting the target site, proving a more effective option to treat sepsis compared to conventional method of sepsis management. For example, nanomedicine with the size of 0.5µm to 5µm can easily cross the pulmonary capillaries and prevent lung injury. Similarly, a nanocarrier drug-delivery system with a particle size of 70-90nm (size smaller than endothelial fenestration) can pass glomerulus membrane and endothelial fenestrations. Fabrication or encapsulation of active drugs modulates the pharmacokinetics of the drug, improving its bioavailability, efficacy, and stability. Nanomedicines have a characteristic dimension of 1 to 100 nm and are designed based on the desired biological properties and functions with specific physical (Vasconcelos and Santos, 2023). Chemical and surface properties. Generally, nanoparticles can be classified into two categories:

1. Organic Nanoparticles
2. Inorganic nanoparticles.

Organic Nanoparticles

Organic nanoparticles usually contain carbon skeletons and are classified as lipid bases or synthetic polymeric nanoparticles. Common types of organic nanomedicines include chitosan, protein-based, polysaccharides, liposomes, polymeric micelles, and poly-amidoamine. Organic nanomedicines are usually less toxic, with excellent biocompatibility, and do not elicit immune responses due to the presence of bio-elements such as carbon, oxygen, and nitrogen in their structure. Several studies have proved their effectiveness in sepsis (Abdelkader et al., 2017; Wu et al., 2021; Guo et al., 2023). Organic nanoparticles are also currently being used for vaccine development, immunotherapy, and diagnostics.

Inorganic Nanoparticles

Inorganic nanoparticles can be prepared by using inorganic metals such as zinc, copper, gold, and aluminum and semiconductors such as cadmium selenide, zinc oxide, and carbon nanotubes. Iron oxide and Calcium phosphate can also be used to synthesize inorganic nanoparticles. Due to their tunable properties, inorganic nanoparticles have been used for the diagnosis and treatment of several infectious diseases, inflammatory disorders, cancers, and wound healing. Inorganic metal-based nanoparticles also have high drug-loading ability and long circulation and cause the sustained release of the encapsulated drug. In sepsis, metallic nanomedicines show their action according to the microenvironment, such as pH, H_2O_2, and O_2, resulting in the removal of dangerous signals and lowering the severity of sepsis (Yang et al., 2019; Luo et al., 2021).

Nanomedicines as a Potential Sepsis Treatment

The conventional methods of sepsis early diagnosis, antimicrobial therapy, and sepsis response regulation. Antimicrobial therapy with antibiotics is the standard in clinical guidelines for sepsis. However, due to increased antibiotic resistance and a lack of effective antibiotics, treatment of persistent sepsis is a significant challenge for clinicians. According to a study, E-coli, the most common cause of sepsis, is resistance to β-lactam antibiotics and aminoglycosides. Similarly, *Staphylococcus aureus* vancomycin and methicillin. This drug resistance is a significant cause of sepsis-associated mortalities, especially in neonates (Chauhan et al., 2017).

Additionally, most antibiotics are ineffective against the systemic release of various cytokines, ROS, and other biomolecules triggered by sepsis. This storm of pro-inflammatory mediators can cause death due to multiple organ damage and long-term immunosuppression in surviving patients. Therefore, new adjuvant therapies, including anti-inflammatory drugs, antioxidant agents, and immunomodulators, are being explored by the researchers. However, these therapeutical options have limitations such as low solubility, poor bioavailability, short half-life, and lack of cell-specific

targeting ability. The emergence of nanomedicine in the past few decades has opened up new pathways to overcome drug resistance, improved the pharmacokinetics of potential drugs, and improved the cell-targeting ability of medicines. Nanomedicines can actively target the sepsis microenvironment, providing a novel avenue for precision treatment and early diagnosis. The below points highlight the major applications of nanomedicines in sepsis treatment.

Nanocarriers and Targeted Drug Delivery for Sepsis Treatment

Conventional medicines have poor pharmacokinetics due to either their larger size, which makes their solubility and membrane crossing ability poor, or smaller size, which results in rapid clearance, high toxicity, and side effects. Similarly, most antimicrobial, and anti-inflammatory drugs do not actively reach the target site. Properties, such as surface charge and size of nanoparticles, can be used to overcome this challenge. For example, the short half-life of the meropenem makes the drug ineffective against sepsis. To overcome this challenge, scientists have successfully encapsulated Meropenem into chiston nanoparticles, dramatically improving these antibiotics' pharmacokinetic properties (Abdelkad et al., 2017). Furthermore, these encapsulated nanomedicines can easily cross the cell membrane, leading to their accumulation in specific tissues or organ preferentially. Similarly, many antimicrobial peptides, a promising theragnostic option to manage sepsis, have poor solubility, bioavailability and pharmacokinetic properties. Studies have shown that these antimicrobial peptides can be successfully encapsulated into a methacrylate nanocarrier. This fabrication of AMPs have successfully rescued 100% of the sublethal experimentally induced sepsis (Qian et al., 2022; Meng et al., 2023). A study published by Falciani et al. (2020) have shown the successful fabrication of these AMPs into single-chain dextran nanoparticl3es to eliminate *P. aeruginosa* in acute lung sepsis.

Another common hallmark of sepsis is the excessive generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These ROS and RNS can module a series of intracellular signaling pathways and alter the function of different enzymes and ion channels. Thus, reducing the mitochondrial ROS and RNS can reduce the abnormal inflammatory response. Conventional antioxidants have poor ROS and RNS scavenging activity and structural stability. Several researchers have proved that the application of various nanoparticles (nanosheets) and nanomedicines in sepsis patients can successfully remove mitochondrial ROS and RNS (Yim et al., 2020).

In sepsis, most of the damage is caused by excessive release of pro-inflammatory cytokines. Most antibiotics are ineffective against this excessive release of inflammatory mediators and demand some alternate sources to alter the pathways that cause the release of pro-inflammatory cytokines. Scientists have successfully utilized the green nano-synthesis approach to convert the natural green agents, especially plants and fungi, to reduce the release of cytokines during sepsis (Beg et al., 2020; Elbagory, 2019; Phukan et al., 2021). Wang et al. (2015) have successfully prepared curcumin-loaded solid lipid nanoparticles to reduce and evaluate their therapeutic potential for LPS-induced sepsis. The results of an enzyme-linked immunosorbent assay showed that the curcumin-loaded solid lipid nanoparticles can successfully reduce the secretion of IL-6 and TNF-α inflammatory factors in the serum and increase the release of anti-inflammatory cytokines.

Modulating the Host Immune Response

Immunomodulation is one of the most effective strategies to treat sepsis. Studies have shown that the administration of nicotinamide adenine dinucleotide (NAD+) in sepsis patients can prevent oxidative stress and multiple organ failure. Loading the NAD and NADH into the liposomes and zeolitic imidazolate frameworks improves the cell oxygen supply, reduces inflammation-induced cell pyroptosis and apoptosis, and decreases the extent of inflammation. The application of these nanomedicine in CLP and *P. Aeruginosa* induced sepsis has shown improved therapeutic outcomes, indicating their promising ability to trat and diagnose sepsis (Grahnert et al., 2011; Ye et al., 2022).

Studies have proved that different types of nanoparticles modulate the host immune response to improve antibiotic therapy. For instance, the use of polymeric nanoparticles has shown their action against the release of pro-inflammatory cytokine, reducing the chance of tissue damage and multiple organ failure. Nanoparticles neutralize the endotoxins released by bacteria and sequestering cytokines released by host immune response dur to these endotoxins. Another innovative approach to manage sepsis is the application of a nano trap, also known as Tele-dendrimer, along with antibiotic therapy. These telodendrimer effectively absorbs septic molecules due to the different charges of pro and anti-inflammatory cytokines (Shi et al., 2020). It is also believed that nanomedicines actively target the macrophages, altering their pro-inflammatory function and reducing the release of cytokines.

Targeting the Macrophages

Macrophages or monocytes, as an important member of the host's immune response, play an important role in the pathophysiology of the sepsis, including the killing of microbes, and release of cytokines and chemokines. During sepsis, over activation of the macrophages results in the release of cytokine storm, which worsen the pathophysiological status of clinical patients, leading to poor response of the conventional sepsis therapy. Nanomedicines are important tool to alter the pro-inflammatory activity of the macrophages. Macrophages binds with the plasma protein, acquiring the new biological property, known as protein corona (PC), which changes the physiochemical properties of nanomedicines (Boraschi et al., 2017). Binding of nanoparticles with plasma protein results in the uptake of NPs by monocytes (Corbo et al., 2017). Other

mechanism to target the macrophages and preventing the release of pro-inflammatory cytokines include altering the activation of pathogen-associated molecular pattern and directly effecting the release of pro-inflammatory signals (Song et al., 2022).

Nanomedicines with Anti-microbial Properties

Biofabrication of different naturally derived metal-based nanoparticles can be effectively used as antimicrobial agents. Furthermore, studies have shown that the positive charged nanoparticles interact with microbial cell, leading to direct killing. Positive charged nanoparticles bind with negatively charged microbial cell membrane, leading to membrane disruption and desensitization, which causes loss of membrane integrity, leakage of cellular content, and cell death (Lam t al., 2016). Another mechanism responsible for the antimicrobial activity of nanomedicines is its electrostatic attraction, which causes the uptake of nanomedicine by the bacteria. Once internalized, nanomedicines disturb the normal metabolic pathway and induce cell death (Xie at al., 2019). Studies have shown that several nanoparticles result in the generation of reactive oxygen species (ROS), which facilitates the killing of invaded bacteria. Positive charged nanoparticles cause the generation of hydrogen peroxide or hydroxyl radicals, leading to oxidative stress in the bacterial cell. Along with generation of ROS, nanomedicines also interact with biofilm, a component that play a key role in antibiotic resistance in bacteria (Jiang et al., 2022). Biofilm matrix contain negative charge that interact with positively charged nanoparticles, increasing the susceptibility of the bacteria to antimicrobial agents (Koo et al., 2017). Although nanomedicines hold a promising potential to manage sepsis, some challenges need to be addressed to increase the efficacy of the drugs. These include size, surface charge, and composition of nanoparticles. Incorporating the metal-based greenly synthesized nanomedicines for antimicrobial therapy is one of the best options to lower the toxicity associated with nanoparticles (Saratale et al., 2021; Zhu et al., 2019).

Nanoparticles for Early Detection of Bacterial Sepsis

Early diagnosis of the sepsis is essential to prevent the disease progression and effective treatment. Along with their therapeutic potential, nanomedicines are also being used in sepsis diagnosis. The conventional methods of sepsis diagnosis are expensive and demand intricate procedure, altering the diagnosis of sepsis. Nanoparticles have been applied in the biomedical field to detect the specie of bacteria and guide the proper antibiotic administration. These nanoplatforms has now enabled clinicians to overcome the challenges associated with conventional methods of sepsis theragnostic.

Below few points highlight the application of nanomedicines in sepsis diagnosis:

Detection of Bacteria

Scientists have successfully used gold nanoparticles as a novel diagnostic tool for sepsis diagnosis. Biofabricated antibodies or Gold nanoparticles (AuNPs) binds with bacterial products such as LPS or peptidoglycans, resulting in color change in face plasma resonance. This technique has been successfully used for the detection of *E. coli, P. aeruginosa,* and *S. aureus*. Similarly, magnetic nanoparticles have also been investigated for the detection of bacteria (Fu et al., 2018; Rocha-Santos, 2014).

Carbon nanotubes are another important tool to detect the bacteria responsible for induction of sepsis. Binding of these nanotubes with bacterial cell membrane results in the change in electric conductivity of the CNTs, which can be detected by field effect transistor (FET). Nanomaterial-based detection of the bacteria has several advantages over conventional methods, such as PCR and ELISA, due to small amount of sample and rapid detection (Munzer at al., 2013).

Detection of Sepsis Biomarkers

Sepsis biomarkers, including ROS, Cytokine, C-reactive protein, CRP, and OCT, are commonly used in clinical setting for the early diagnosis of the sepsis. However, limitations and sensitivity associated with traditional methods demand more sensitive tool for the sepsis diagnosis. The application of nanosensors has now made the sepsis diagnosis more accurate and accessible. For examples, scientists have successfully applied nanotubes for the detection of C-reactive protein (Luo et al., 2021). Furthermore, Gold nanoparticles have also been used for the detection of pro-inflammatory cytokines (Khan and Mujahid; 2020).

The table below summarize the different types of biosensors used for sepsis diagnosis. Data is extracted from the review published by Luo et al., (2021).

Biomarker	Nanoparticles	Mechanism
E. coli	Azide fabricated AuNPs	Biomimetic strategy based on bacterial metabolic pathway
Polymicrobes	PMNs-derived microvesicles	Agglutination of bacteria due to microvesicles
S. aureus	Silica NPs	Antibody detection
CRP	Magnetic NPs	Antibody detection
CRP	Iron oxide nanocrystal	Antibody detection
CRP	Gold nanorod	Antibody detection
PCT	Ferrocene encapsulated AuNPs	Electrochemistry

PCT	Streptavidin-coated AuNPs	Immune sensing
PCT	Fluorescent microspheres	Immune sensing
IL-6	ZnS nanocrystals	Immune; optical
TNF-α	Axoplasmic AuNPs	Immune detection

Challenges and Opportunities

Nanotechnology holds promising potential for the therapy of sepsis. Several studies have shown the efficacy of nanomedicines against sepsis due to their site-targeting and antimicrobial properties. For example, liposomes loaded with vancomycin have been investigated to improve the survival rate and reduce the bacterial load in sepsis induced by methicillin-resistant Staphylococcus aureus (Nwabuife et al.,2021). Similarly, polymeric nanoparticles have shown their action against pro-inflammatory cytokines in experimentally induced sepsis.

Despite these promising results in sepsis, nanoparticles also have some limitations that must be addressed before their application in clinical practice. Formulation of the nanomedicines and nanoparticles for the theragnostic of sepsis requires diverse materials, e.g., supramolecular nanomaterials organic and inorganic nanocomposite. Safety considerations and regulatory requirements are essential for the clinical application of nanomedicines. Since most of these nanomaterials are not approved by FDA as pharmaceutically acceptable vehicles, these can be toxic for both the environment and the individual. Thus, it is essential to consider the pharmacokinetics properties, such as absorption, distribution, and elimination from the body.

Studies have shown that nanoparticles can cause oxidative stress and cause damage to tissues when applied in large quantities. Thus, researchers should consider the dose of nanomedicines before their application in living organisms. Another major challenge in the application of nanomedicines in clinical practices is their optimizing the design and formulation of NPs to maximize drug delivery and efficacy while minimizing off-target effects. The efficacy of the nanomedicines against a specific disease depends upon their size, pH, and surface charge. Thus, these conditions should be considered to maximize the results of nanomedicines.

In the recent era, nanosynthesis has gained more interest due to less toxicity and environmentally friendly properties, providing an opportunity to treat sepsis and other inflammatory conditions more effectively. The unique biomarkers in plants, fungi, and other green agents have been extensively studied due to their anti-inflammatory, anti-microbial, and antioxidant properties. Thus, researchers should focus on the application of these green agents for drug nanosynthesis. Furthermore, safety assessments of nanomedicines should include comprehensive toxicity studies to evaluate potential adverse effects on human health Zhai et al., 2022).

Conclusion

In the past few decades, the extensive use of antibiotics and the increased toxicity of conventional sepsis therapy have compelled researchers to explore alternative and novel theragnostic approaches for sepsis management. Due to targeted drug delivery and antimicrobial, antioxidant, and anti-inflammatory properties, nanomedicines provide an opportunity for clinicians to overcome the applications associated with conventional sepsis therapy.

Several types of nanomedicines have been studied to enhance the target drug delivery and lower the release of cytokines, oxidative stress, and sepsis-associated mortalities. However, due to a lack of regulatory and safety guidelines, several nanomaterials are toxic to living organisms and the environment when exposed in large quantities. Thus, researchers should design guidelines to minimize the complications and enhance the opportunities offered by these nanomedicines. Furthermore, extensive study is needed to study the factors that can affect the efficacy of nanomedicines when administered in living organisms.

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