REVIEW PAPER

TREATING THE CHALLENGE OF PNEUMOCOCCAL MENINGITIS USING NOVEL DRUG DELIVERY SYSTEMS

Ms. Vaishnavi A. Ghormade[1*], Dr. Harsha Sonaye[2], Dr. Jignesh M. Doshi[3]
[1*]Research Scholar, School of Pharmacy, G. H. Raisoni University, Saikheda (M.P.)
Email: vaishnavighormade1998@gmail.com
[2]Professor, School of Pharmacy, G. H. Raisoni University, Saikheda (M.P.)
Email: harshasonaye12@gmail.com
[3]Research Head, Mapni Healthcare Products, 33, 34 B, MPIDC, Borgaon, Pandhurna (M.P.) Email: jigneshmdoshi@gmail.com
***Corresponding author:**
Ms. Vaishnavi A. Ghormade,
Research Scholar,
School of Pharmacy,
G. H. Raisoni University, Saikheda (MP).
Email: vaishnavighormade1998@gmail.com

ABSTRACT:
Even though vaccinations and effective treatments are accessible, pneumococcal meningitis caused by Streptococcus pneumonia is still one of the major determinants of morbidity and mortality worldwide. As a result of the rapid progression of disease, increased resistance to antibiotics, and low medication permeation through the blood-brain barrier (BBB), conventional methodologies to treatment are often limited. Treatment methodologies for CNS infections were totally revolutionized by the recent developments in innovative drug delivery systems (NDDS). Delivery approaches like intranasal administration, liposomes, niosomes, dendrimers, micelles, nanoparticles, and polymer-based drug delivery are known to offer better drug bioavailability, extended drug-release profile, and better drug permeability via the BBB. The pathology behind pneumococcal meningitis, existing problems with treatment, and the new advances in NDDS have been elaborated on in this review to facilitate effective management of the condition. The combination of effective antibiotics and advanced delivery systems can bring considerable improvements in the treatment of the disease, reducing its mortality rates and combating antibiotic resistance.

Keywords: Pneumococcal meningitis; Blood–brain barrier; Nanoparticles; Liposomes; Intranasal delivery; Antibiotic resistance; Targeted therapy; Novel drug delivery systems.
How to cite this article: Ms Vaishnavi A. Ghormade*, Dr Harsha Sonaye, Dr Jignesh M. Doshi. TREATING THE CHALLENGE OF PNEUMOCOCCAL MENINGITIS USING NOVEL DRUG DELIVERY SYSTEMS. Int J Drug Deliv Technol. 2026;16(88s):855-870. DOI: 10.25258/ijddt.16.88s.87.

INTRODUCTION:
The bacteria that cause infections are facultative anaerobic, lancet-shaped, and Gram-positive. Antigenic capsular polysaccharides, which serve as the foundation for pneumococci serotype classification, are the source of pathogenicity. The nasopharyngeal region of symptom-free individuals is recognized as a major reservoir for pneumococcal colonization, which can be detected in 5% to 90% of healthy individuals. SP is spread by direct contact between people, by respiratory droplets in those who have the bacterium in their upper respiratory system. [1]. The first essential step for the disease's development is colonisation. The polysaccharide capsule does this by protecting SP from opsonophagocytic and host receptor recognition while also allowing SP to avoid becoming trapped by mucus in the respiratory system. Because of these traits, SP is able to withstand the respiratory tract's early inherent defences. Then, toxins such as hyaluronidase, pneumolysin, and hydrogen peroxide (H_2O_2) generation continue the ciliary slowing and epithelium destruction. Simultaneously, the non-protein virulence component phosphorylcholine first forms the binding of bacteria to the epithelium, which then strengthened by protein adhesins and by pilus-like structures for some serotypes as well. Pneumococcal surface protein expression and tissue invasion are also influenced by capsular serotypes. In the course of pathogenesis, the bacterium circumvents host immune responses and antibacterial therapy by forming a biofilm, which facilitates persistence and allows re-emergence under conditions of impaired host defense.
The subsequent activities primerily rely on the pathogen's interactions with the host's defenses as well as the increased production of certain proteins. The connection between the PspA/PspC and the epithelial polymeric immunoglobulin (Ig) receptor, which typically carries secretory IgA, E-caderin, permits pathogen to enter the circulation and

eventually infect the central nervous system. In fact, pneumolysin's cytotoxic and proinflammatory effects in severe pneumococcal pneumonia cause lung damage and epithelial destruction, which causes SP to move from the alveoli to the interstitium and ultimately the bloodstream [2]. The tussive reflex, mucus, mucociliary clearance, and humoral components are the first lane defenses that might fail on several levels. The crucial element is the cellular immune response, which is first initiated by macrophages and, if they are unable to do so, is carried out by neutrophils stimulated by chemokines. Although the neutrophilic activity is crucial for limiting the infection, it may also be the cause of lung damage.[3]. Meningitis is a condition characterized by inflammation that affects the nervous system and is concomitant with high rates of morbidity and mortality. About 318,000 individuals worldwide pass away from this illness every year, and the majority of survivors experience profound neurological aftereffects for example epilepsy, deafness, cognitive dysfunction, and localized neurological damage. [4,5] SP is the most prominent cause of bacterial meningitis globally. The incidence of S. pneumoniae meningitis is still high, despite the fact that certain industrialized nations in the US and Europe have implemented vaccine and drug policies to avoid invasive infections brought on by the bacteria. The blood-brain barrier (BBB) consist of the basement membrane, cellular layer comprising endothelial cells, pericytes, and astrocytes, and glycocalyx. It controls the transport of various chemicals across the brain and the external environment, ensuring that only necessary materials such as glucose and amino acids pass through while preventing harmful agents like infections and neurotoxicants from crossing over. [6]. Selective permeability is important for maintaining the equilibrium of the central nervous system. In addition, there is another barrier found in the central nervous system called the blood-cerebrospinal fluid barrier (BCSFB), composed of arachnoid barrier cells, meningeal microvasculature, and the choroid. Together with the BBB, the BCSFB protects the brain tissue and cerebrospinal fluid against toxins present in the bloodstream. Though most bacteria causing infections cannot cross both barriers, there are some that can breach the BBB, leading to meningitis. The TLR signaling pathway is necessary for S. pneumoniae to translocate across the BCSFB. [7]. But according to other scientists, S. pneumoniae preferentially attaches itself to subarachnoid blood vessels in mice before invading the veins, indicating that it may not enter the brain by the BCSFB route. [8,9]. The issue regarding S. pneumoniae truly traverses the blood-cerebrospinal fluid barrier in humans is still up for contention because these results are based on animal models. Thus, the processes by which S. pneumoniae pass the blood-brain barrier are the main focus of our review. S. pneumoniae uses its own receptors to bind to host cells to penetrate the barrier and enter the nervous system. Once inside, it sets off a chain of inflammatory events and produces virulence factors that interact with host cells to compromise the BBB's integrity.[10]. Meningitis has more than just bacterial characteristics as its causes; the host's vulnerability and immune system are important factors. S. pneumoniae-caused meningitis can afflict individuals of all ages, although it is more common in children under five and in those over 65. [11]. All antibacterial medicines now undergoing phase I to phase III clinical trials against Gram-positive bacteria are thoroughly described in a recent review by Koulenti et al. [12]. In this way, structure-activity relationship (SAR) of existing antibiotics is better understood, which might govern to the discovery of a new antibiotic-equivalent. Although their mode of action is comparable to that of an antibiotic that is currently on the market, resistance mechanisms often change, and/or there is greater effectiveness against resistant bacteria. Clinical studies are now being conducted on a number of these analogues. Analyzing novel antibacterial targets may also aid in overcoming resistance mechanisms, even though examining derivatives of well-known antibiotics might be helpful. Therefore, focusing on bacterial pathogenicity rather than bacterial physiology should be taken into consideration. [13]. Computational screening is a common method for finding these new targets. It involves screening the genome sequences of bacteria and humans to find critical bacterial proteins without harming the human carrier or its [14]

Modification of the host's immune system

Enhancing host immune responses following infection is the focus of numerous recently investigated anti-pneumococcal drug targets. Interfering with these processes is challenging because doing so may result in either excessive immune system suppression that permits infections to proliferate and spread uncontrolled or an unexpected immunological cascade that enhances inflammatory damage [15].

Epidemiology

There are notable regional variations in the prevalence of pneumococcal meningitis (PM). Africa and other regions had a verified PM share of 57%, which is almost twice as high as Europe's (29.8%). [16,17]. Approximately 83,900 PM cases were reported in China in 2015, according to earlier data [18]. The incidence of PM decreased globally due to extensive use of pneumococcal conjugate vaccines (PCVs). For instance, the US had a 63% decrease in

the incidence rate of PM between 1997 and 2014 when PCVs were introduced, while low-income nations saw comparable significant improvements. [19,20], even while the PM rate stayed high. With a mortality rate of 12.2%, S. pneumoniae led the globe in pediatric bacterial meningitis deaths from 2014 to 2019, according to the globe Health Organization's disease monitoring report. [17]. PM lethality, which has a far surpassing fatality rate in poor nations with limited medical facilities than in rich countries, is greatly influenced by economic variables. For instance, the median time to death for PM in South Africa is only three days, and the in-hospital mortality rate can reach 41%.[21], In the United States, the median survival time with PM is 9.3 days, and the death rate is 9.7%.[22]. It is crucial to remember that the South African statistics contained people with HIV, which may have affected the reported death rate. In S. pneumoniae, capsular polysaccharides (CPSs) are crucial virulence agents. On the basis of genetic variations in capsule content, more than 100 serotypes have been established. Sero types 1 and 14 are the most common PM serotypes in Africa, and they are both linked to higher mortality and meningitis epidemics. [23,24] In Europe, the primary serotypes responsible for PM are widely distributed. The spread of drug-resistant clones, variations in antibiotic selection pressures brought on by various antimicrobial drug use strategies, variations in vaccine introduction times and vaccination rates, and serotype replacement are the main causes of the variations in serotype distribution among nations. [17,25].

Nanomaterials: Implementations in Meningitis and Bacterial Infection of Brain

Numerous chances to improve medicine transport across the BBB have been made possible by the development of nanotechnology. Utilizing nano-dimensional vehicles with a large surface area can aid overcome the difficulties in penetrating the sophisticated physiology of the blood-brain barrier under pathological situations. The increased stability following chemical and physical changes opens up countless options for treating inflammatory diseases with drugs that could cross the BBB. Many medication delivery techniques utilizing nanotechnology are Numerous chances to improve medicine transport across the BBB have been made possible by the development of nanotechnology. Using nanoscale vectors with a large surface area can help overcome the challenges of penetrating the complex physiology of the blood-brain barrier in diseased conditions.[26]. Their increased stability following chemical and physical changes opens up countless options for treating inflammatory diseases with medications that pass the blood-brain barrier. There are now numerous medication delivery methods based on nanotechnology in use. Improved bioavailability, high solubility and non-toxicity, extended circulation time, biodegradability, and continuous drug release are all features of the nanocarriers.[27]. Nano pharmaceuticals can induce receptor-mediated transport across the choroid plexus or the brain's endothelial cells and passive diffusion. Nonetheless, the hydrophobic nanostructures could be able to traverse the BBB by active diffusion.[28]. A basic illustration of medication distribution using nanocarriers in meningitis is presented in Figure 1. Here is a list of several nanocarriers that are used to treat bacterial infections and meningitis. currently in use. Improved bioavailability, high solubility and non-toxicity, extended circulation time, biodegradability, and continuous drug release are all features of the nanocarriers.[27]. Nano pharmaceuticals can induce transport mediated by receptors across the choroid plexus or the brain's endothelial cells in addition to passive diffusion via a transcellular pathway. Nonetheless, the hydrophobic nanostructures could be able to traverse the BBB by active diffusion. A basic illustration of medication distribution using nanocarriers in meningitis is presented in Figure 1. Here is a list of several nanocarriers that are used to treat bacterial infections and meningitis. [28].

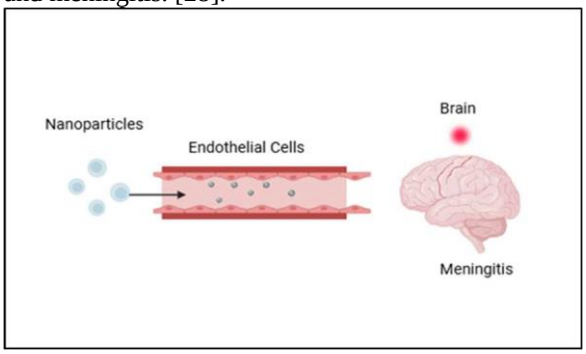


Fig. 1 An illustration showing how nanoparticles affect the brain's endothelial cells to transport drugs in meningitis.

Pathophysiology of Pneumococcal Meningitis:

Blood vessel strike, proliferation and mucosal colonization to attain a large bacteremia load and breach the three main stages of bacterial meningitis pathophysiology are the BBB and BCSFB. For PM sufferers, intranasal colonisation is a significant issue. Upon circumventing the host’s intrinsic immune response, comprising complement-mediated lysis and neutrophilic phagocytosis, the bacteria penetrate the nasopharyngeal mucosal epithelium, access the bloodstream, and ultimately transverse the blood-brain barrier to infiltrate the brain. Virulence elements are crucial to this procedure. Bacteria must live and multiply in the blood to invade the central

nervous system (CNS) after colonising the mucosal surface. Additionally, a certain degree of bacteremia is conducive to the formation of inflammatory reactions and subsequent interactions between bacteria and host cells. When the host immune system detects germs entering the circulation, defensive mechanisms are triggered. The immunological escape of S. pneumoniae is then facilitated by pathogenic determinants. When S. pneumoniae enters the bloodstream, CPS is a major virulence factor. It stops the bacteria from attaching to IgG and C- reactive proteins, which stops the classical complement system from being activated. [29]. Additionally, CPS prevents non-receptor-driven phagocytosis, which is beneficial for S. pneumoniae persistence. [30] Second, in order to avoid complement assaults and boost bacterial survival in the serum, S. pneumoniae surface proteins A and C can attach to the host serum's C4b binding protein and restrict complement C4b accumulation on the surface of bacteria.[31]

Attachment and Invasion

Through the interaction of several adhesion factors with receptors, S. pneumoniae may adhere to brain endothelial cells or epithelial cells of the choroid plexus and translocate to the central nervous system (CNS) after evading the host immune system in blood. S. pneumoniae's surface phosphorylcholine is essential for the interactions among the bacterium and host organisms. It forms a complex with the host's platelet-activating factor receptor (PAFR) to improve bacterial adherence. S. pneumoniae adhesion and invasion were greatly decreased when PAFR was inhibited. [32,33]. Choline-binding proteins (CBPs), a broad family of proteins docked to phosphorylcholine, are involved in bacterial invasion and adhesion. A well-known member of this family, choline-binding protein A (CbpA, also known as PspC), increases the bacterium's adherence to the brain endothelium by binding to brain endothelial cells polymeric immunoglobulin receptor (pIgR) and laminin receptors. [34,35]. In S. pneumoniae, RrgA is a key adhesin that serves a function in the bacterial adhesion and invasion processes. Notably it is a type 1 heterotrimeric pilus subunit. RrgA has the same ability to bind to pIgR as CbpA. Additionally, it helps S. pneumoniae transgress the blood-brain barrier by interacting containing the adhesion molecule of platelet endothelial cells (PECAM-1). Additionally, high RrgA expression levels increased bacterial adherence to the host and encouraged the development of individual spherical bacteria, which increased the potential of the bacteria to infiltrate the BBB.[35]. Antibodies that hindered RrgA dramatically decreased S. pneumoniae's ability to infiltrate the mouse brain.[36]. Pneumococcal adherence and penetration of brain microvascular endothelial cells are facilitated by the N-terminal lectin-like structural category of Neuraminidase A (NanA), sometimes referred to as sialidase, a surface-attached exonuclease that cleaves sialic acid from host cells and proteins. [37]. Remarkably, it has been shown that some S. pneumoniae strains without a functioning LPXTG anchor motif excrete NanA instead of expressing it on their surface. According to Gratz et al.'s research, clinical isolates derived from blood and cerebrospinal fluid are more likely to contain strains that secrete NanA. Additionally, it has been noted that secreted NanA may promote meningitis development more successfully than the surface-anchored version.[38]. Although both the secreted and cell-bound forms of NanA are important for S. pneumoniae's BBB invasion, additional research is needed to determine which form is more important for this process.

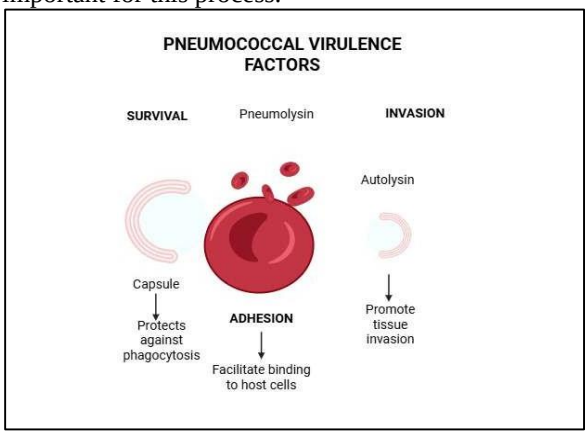


Fig. 2: Pneumococcal virulence factors encourage blood bacterial invasion, adhesion, and survival.

Endocytosis

S. pneumoniae adheres to the surface of the cellular host, then uses the cellular host to communicate with it through endocytosis and pass the blood-brain barrier. We covered by what means phosphorylcholine attaches to the PAFR to promote cellular invasion and adhesion in the preceding sections. Once S. pneumoniae binds to PAFR, β-arrestin helps the bacterium be internalised inside the cell by endocytosis, and clathrin is then recruited.[32]. Similarly, caveolin and clathrin, which are crucial elements of the dynamin-dependent endocytic pathway, must also be involved for PspC to bind to pIgR [39]. S. pneumoniae combines with early endosomes and then lysosomes after internalization. One of S. pneumoniae's main host pro- endocytic factors, pneumolysin (Ply), is essential to the pathogenicity of the bacterium's brain infections.

It attaches itself to cholesterol in the recipient's membrane cell, creating holes that cause cell lysis.

Experimental results from Ply's incubation with microglia and astrocytes demonstrate its ability to promote endocytosis in particular brain cells. Interestingly, the endocytosis inhibitor chlorpromazine was successfully injected intraperitoneally to reduce neuroinflammatory symptoms in rats.[40]. While S. pneumoniae with elevated Ply levels show reduced intracellular survival of the host following infection, and the bacteria and more readily cleared via cellular host cell ubiquitination, S. pneumoniae with low levels of Ply show improved endocytosis and intracellular survival enabling the pathogen to enter the brain through BBB. [41]. Bacterial survival is negatively impacted by excessively high Ply levels. Additionally, Ply may induce neuronal death by endocytosis and RrgA. Pneumococcal infection of neurones is promoted by the increased exposure of β-actin following Ply's action on the neuronal plasma membrane, which permits more RrgA to join with it.[42].

Signaling routes in pathogens

The first line of host protection mechanism against microbial incursion is the human immunological response. However, it can also cause a broad inflammatory effect that might harm the brain and cause negative neurological consequences, even while it is defending the body. The components of the bacteria or their secreted immunogenic chemicals can attach to cells of the host immune cells, including astrocytes, macrophages, microglia, once they have crossed the blood-brain barrier. Pattern recognition receptors (PRRs) present on the host are stimulated by this binding, and this sets off a variety of signaling pathways that eventually result in an immunological response. Diverse infections that penetrate the blood-brain barrier activate distinct signaling pathways. S. pneumoniae-induced meningitis primarily affects NF-κB, Notch, and P75NTR signaling pathways, that may be linked to the inflammatory reaction being triggered, the BBB being damaged, and subsequent complications (Figure 3). Lipopolysaccharides, peptidoglycans, and lipoteichoic acids constitute among the elements of microorganisms' cell walls that are recognized by toll-like receptors (TLR), which are essential receptors implicated in innate immunity. Strong immunological responses are triggered when TLRs recognize these cell wall components, which in turn trigger a number of downstream signaling pathways. In PM, S. pneumoniae's lipoteichoic acid and lipoprotein bind to TLR2 on immune cells, activating them and causing a significant liberation of inflammatory molecules such TNF-α and IL-6. The synthesis of inflammatory factors is somewhat dependent on lipoprotein stimulation, and these inflammatory mediators have the potential to worsen meningitis symptoms and further disrupt the blood-brain barrier. [43,44]. Additionally, TLR stimulation improves microglia's capacity to phagocytose and kill S. pneumoniae, protecting the brain.[45]. On the other hand, PM mice that lack these TLRs have higher BBB permeability, lower survival rates, and a higher chance of neurological effects.[46]. NF-κB nuclear translocation and cytokine production are mediated by the protein's carboxy-terminus, which cooperates structural domain of the Toll/IL-1 receptor and transmits upstream information in the TLR signalling cascade. According to research by Picard C et al., mice with PM who had MyD88 were more resistant to S. pneumoniae, whereas those who lacked it were more vulnerable to bacterial meningitis.[47]. Additionally, by activating downstream signalling pathways, MyD88 causes NF-κB to increase the articulation of neural-derived neurotrophic factor, enhancing its protective impact on nerves.[48]

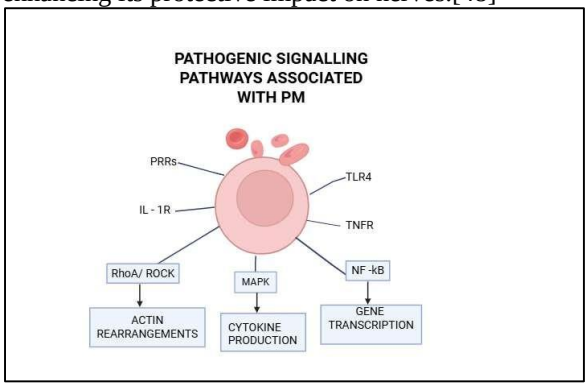


Fig. 3: PM-related pathogenic signaling pathways.

Limitations of Conventional Treatment:

Antibiotic resistance trends:

Bacteria typically become resistant to antibiotics throughout the course of anti-infection treatment. Importantly, bacterial tolerance and sensitivity are rising at an alarming rate due to the ongoing misuse and overuse of conventional antimicrobial medications globally.[49]. Data from research indicates that within five years of being put on the market, a new antibiotic may cause bacterial resistance.[50]. Antimicrobial sensitivity was one of the top 10 global health problems in 2019, according to the WHO. [51]. The failure of conventional antimicrobial medications is a worldwide public health issue that is made worse by rising antibiotic usage worldwide.[52]. In order to withstand the majority of the existing antibiotics, MDR bacteria have currently evolved a number of resistance mechanisms. Numerous viewpoints, such as genetic, metabolic, and biochemical factors, can be used to explain these resistance mechanisms. Bacteria can acquire resistance through a variety of means,

including mutations in their own genes, chromosomes moving vertically, plasmids or transposons moving horizontally, and integrons capturing external resistance genes.[53]. The physiological metabolic process primarily explains the "viable but non-culturable state" (VBNC) of bacteria, which represents a special viability used by bacteria in stressful situations. As the majority of antibacterial agents exclusively eliminate biochemically active bacteria, these microorganisms can circumvent antibiotic actions and transition into a dormant phase. In this stage, bacterial growth and metabolism are extremely sluggish, if not completely stopped. [54,55]. The biochemical mechanism at the protein level, wherein bacteria either synthesize and secrete active proteins or alter their structural proteins, predominantly indicates their antibiotic resistance. An illustration of the four distinct mechanisms of drug resistance at the protein level.

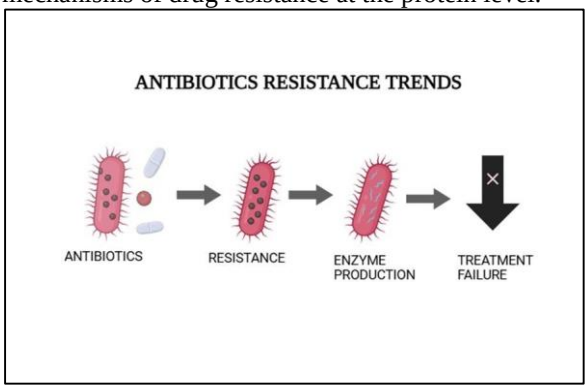


Fig. 4: Antibiotic resistance trends

High mortality and neurological sequelae

In high-income nations (HICs) with access to necessary antibiotic treatment and vaccines, acute bacterial meningitis can cause serious complications with long-term neurological aftereffects that lead to disability.[56]. For instance, a recent study on pediatric bacterial meningitis in the US showed that the most common short-term neurological complications of community-acquired bacterial meningitis were hydrocephalus (20.8%), intracranial abscess (8.8%), and cerebral edema (8.1%), with a 45.9% complication rate at 30 days.[57]. Edmond et al. conducted a comprehensive systematic review and meta- analysis that calculated worldwide risks of neural effects by socioeconomic status and geographic location between 1980 and 2008. They found that 20% of people will experience various complications subsequent to bacterial meningitis. In Africa and Asia, the danger was nearly three times greater than in Europe.[58]. Action interruption [59,60], the amount of time spent travelling for care, weakened immune systems due to long-term hunger, and hospital expenses [61], each of which has been shown to raise the risk in low-income nations. Merely two studies from Asia and Africa explicitly assessed cognitive areas; it is evident that cognitive dysfunction affects a significant number of individuals and is undoubtedly underreported in LMICs, even though hearing impairment and seizures were the most significant aftereffects among the 132 studies in the Edmond et al. meta-analysis. Because standardized evaluation instruments and comprehensive neurological tests are rarely used in many LMIC investigations, potential subtle indications like neurocognitive impairment or behavioural alterations are missed.[58]. In addition, comparing the rates of aftereffects in children with and without a history of meningitis is mostly absent in most studies. This approach accounts for baseline rates of neurological problems in a community, perhaps giving a more realistic picture of the likelihood of sequelae following bacterial meningitis. This approach was employed in prospective cohort research in Senegal, which improved the reliability of comparison and categorization by using uniform evaluation instruments on both the control and afflicted groups. In Senegal, the children who contracted bacterial meningitis had three times the chance of experiencing a serious handicap (e.g., hearing loss, seizures, or cognitive/motor abnormalities) compared to a community control group. Seizures and cognitive and motor impairments were the most common domains to be affected.[62].

Challenges with systemic delivery

Because of their special advantages, including substrate specificity and excellent selectivity under moderate settings, enzymes have been employed as stimuli in the design of smart DDSs in recent years. [63, 64, 65,66] Bacterial enzymes can be prevented from breaking down nanocarriers at their source by sending out a visual signal. Employing fluorescently labeled hyaluronan nanocapsules that incorporate polyhexanide biguanide and poly-L-lactic acid nanoparticles, octenidine has also been utilized to investigate its effects on primary human dermal microvascular endothelial cells, which are crucial for the healing of cutaneous wounds Interestingly, cytokines and adhesion molecules of endothelial cells are unaffected by enzyme immunoassays. Additionally, the capacity of cutaneous fibroblasts to produce capillary-like structures remained unchanged when co-cultured with angiogenic inducers. According to the study's findings, antimicrobial nanocomposites may therefore be a secure and efficient way to stop wound infections. [67]. The capacity of MRSA to survive intraphagocytically shields them from the bactericidal effect of drugs, which results in recurrent infections, according to additional studies. [68]. Therefore, creating delivery

methods that may specifically target macrophages and eliminate intracellular MRSA is essential. Mannose receptors (MRs) are present in monocytes or macrophages, alveolar macrophages, brain astrocytes, and hepatocytes in the liver. [69,70]. Hydrogels containing ferrocene (Fc) and redox. The use of responsive ferrocene (Fr) in catalysis, medicine, and material science was growing in popularity. A dendritic tetrablock terpolymer with a triethylene glycol chain derived from polynorbornene was synthesized with a third-generation Grubbs catalyst, in conjunction with an aldehyde and ferrocene (Fc). Silver nanoparticles (AgNPs) can be reduced and stabilized due to the inclusion of Fc and triazole moieties. This copolymer enables the crosslinking of gelatin hydrogels by the Schiff's base reaction involving aldehyde groups and side-chain amino groups. Fc-containing gelatin hydrogels were reduced in situ using AgI to Ag0 by either dipping the gels in the AgNO3 solution or combining this copolymer with gelatin and AgNO3. Interestingly, inhibition zone testing with the composites verified antibacterial efficacy against S. aureus and E. coli. [71]. Furthermore, it was reported that RBC-nanogels for MRSA infection have both antiviral and antibacterial qualities. In order to coat the RBC membrane onto the nanogel, membrane vesicles template-assisted in situ gelation were employed. The reactive crosslinker was L-cystine, and the disulphide bond-based crosslinker was cystine dimethacrylate (CDA). VAN was also detected in the RBC-nanogels. MRSA-associated toxins were effectively neutralized by RBC-nanogels in the extracellular environment, which promoted macrophage uptake. In an intracellular-reducing environment, faster medication release from RBC-nanogels also resulted in higher bacterial inhibition. The RBC-nanogels also significantly inhibited the development of intracellular MRSA germs in macrophage cells. Therefore, as these research findings indicate, the RBC-nanogel system may include a new antibacterial agent for MRSA. [72]. New, effective, and transportable approaches are needed for targeted, specific antimicrobial delivery. Temperature sensitive liposomes and high intensity targeted ultrasonic heating guided by magnetic resonance are utilized to administer antibiotics. This research evaluates the efficacy of delivering ciprofloxacin locally alongside MR-HIFU hyperthermia in a rodent model, utilizing a low-temperature-sensitive liposome (LTSL) designed for the release of the antimicrobial agent (ciprofloxacin) at mild hyperthermia levels (~42 ^{0}C). Subsequently, the in vitro analysis of release and its effectiveness against Staphylococcus aureus in both planktonic form and biofilms is conducted. Disc diffusion, the MBEC biofilm appratus, and scanning electron microscopy (SEM) were used to examine LTSLs that were actively loaded with ciprofloxacin. The release of LTSL ciprofloxacin in physiological buffers and in rats was quantified using fluorescence spectroscopy and MR-HIFU. At 42 °C, the LTSL released >95% ciprofloxacin, but just 5% at 37 °C. In comparison to controls (free ciprofloxacin + MR-HIFU or LTSL alone), targeted hyperthermia applications within the thigh of rats employing MR-HIFU with intravenous (I.V.) administration. The LTSL administration culminated in a fourfold increase in the localized concentration of ciprofloxacin. The biodistribution of ciprofloxacin in passively active tissues was consistent across all groups. The initiated discharge at 42 °C eradicated more S. aureus bacteria, compromised membranes, and altered the biofilm matrix with free ciprofloxacin or LTSL at 37 °C. This technique could deliver high-concentration antibiotics to chronic wounds.

Novel Drug Delivery Systems for Pneumococcal Meningitis

Drug targeting specificity, decreased adverse effects related to nanoparticle absorption, biocompatibility, and creative ways to creating novel therapeutics are all crucial factors to take into account when building nanocarriers for medical purposes. NP-based carrier systems are superior to conventional treatment approaches in several ways. Properties like solubility, medication stability, and bioavailability can be improved by engineering them. Furthermore, it is possible to customize the gradual and regulated delivery of medications to reduce adverse effects. Targeting cells precisely is essential to reducing harm to surrounding tissues, particularly in the management of illnesses such as cancer. Improving the effectiveness of NP-based treatments requires overcoming this obstacle. [73]. The immunological response caused by NP is another strategy. By altering their surface, NPs can better enter the central nervous system.[74].

Classification of Nanoparticles

Surface charge, size, shape, and composition may all be used to classify nanoparticles. Nanoparticle categorization according to composition includes inorganic and organic nanoparticles. Inorganic nanoparticles are carbon nanotubes, metal nanoparticles, and quantum dots; organic nanoparticles include polymeric, lipid-based, dendrimer, and micelle nanoparticles. [75]. NPs can be categorized into disk-like, spherical, or rod-shaped structures based on their form. They might be tiny (10–100 nm), big (>100 nm), or ultra-small (<10 nm). Every kind of NP has unique characteristics and restrictions. Liposomes are biocompatible and capable of carrying both hydrophilic and hydrophobic drugs due to their phospholipid composition and

cholesterol-filled vesicles. [76]

Because of their greater stability and ability to bind drugs, polymers are employed. [77]. A lipid core encased in a layer of surfactant makes up solid lipid nanoparticles (SLNs), an organic nanoparticle form that is well-known for its durability and biodegradability.[78]

Nanoparticles Based on Polymers (PBNPs)

Polymeric nanoparticles (PBNPs), typically ranging from 60 to 200 nanometers in size, are considered promising carriers for drug delivery applications. These nanoparticles' hydrophilic corona helps maintain their steric stability and stops them from clumping together in bodily fluids. [79]. For medication delivery, nanoparticle-incorporated polymers, including chitosan, polyglycolide (PGA), and polylactides (PLA), are frequently utilized. [78,80]. The drug delivery efficiency of PBNPs can be improved using hydrophilic polymers that could be immobilized on the nanoparticle surface through either chemical bonding or physical adsorption, thereby extending their retention time within the blood circulation system. Specific target delivery can be attained by conjugation of ligands specific to particular tissue either on functionalized polymers or on the surface of nanoparticles. Studies have shown that incorporating more amounts of polymer nanocarriers to drugs would increase their ability to permeate membranes and improve their overall efficacy [81]. The PBNPs, as delivery agents, hold great promise and potential in developing innovative strategies in the management of neurological disorders. Hyperbranched generations are branched structures found in dendrimers, whose main characteristics include high molecular specificity, uniformity of size, and regularity of shape. By providing sites where functional groups could be conjugated, the branches make ligand activity more effective. Dendrimers are ideal candidates in designing safe biomedical therapies owing to their good solubility, degradability, and biocompatibility [82].

The specificity of targeted medication delivery can be increased by altering the surface of dendrimers to form bonds with targeting ligands like peptides and antibodies. [83]. Additionally, dendrimers' multivalency makes it possible to administer several medications or diagnostic agents at once, which makes them useful for imaging or combination treatment. Furthermore, because polymeric micelles may encapsulate hydrophobic medicines, improving their solubility and bioavailability, they have demonstrated encouraging outcomes as drug delivery vehicles. [84]. The hydrophilic shell shields the hydrophobic core of polymeric micelles, enhancing their stability and preventing recognition by the immune system through opsonization. To make these polymeric micelles more selective for cancer cells or other targeted tissues, they can also be functionalized with targeting ligands. Polymeric micelles have been extensively investigated as carriers for a wide range of therapeutic agents, including proteins, nucleic acids, and small-molecule drugs.[85]. These micelles can transport several medications in a single formulation. [86]. Because of their distinct physicochemical characteristics, ease of functionalization, and ability to incorporate a diverse range of therapeutic agents, dendrimers and polymeric micelles both exhibit significant promise for drug delivery. They are appealing choices for biomedical applications because of their biocompatibility and biodegradability, especially in targeted drug administration.

Targeting efficiency in medication delivery could be improved further by modifying the outer surface of dendrimers to create bonds with the targeting ligands such as peptides and antibodies. [83] Besides, the multivalency property exhibited by dendrimers makes it possible to simultaneously deliver several medications or agents used for diagnostic purposes. Moreover, since the polymeric micelles are capable of loading hydrophobic drugs within the structure, making them more soluble, they have shown promising results as drug-delivery systems [84]. The hydrophilic coaring protects the hydrophobic center of the polymeric micelles, thus promoting their stability and preventing immune system recognition by means of opsonization. In addition, for the purpose of increasing selectivity towards cancer cells or any other targeted tissues, the micelles could also be functionalized with the help of ligands for targeting. The application of polymeric micelle as carriers for abroad range of drugs has received considerable attention from researchers. This includes proteins, nucleic acids, and small molecules [86]. The physicochemical properties, ability to easily modify these polymers, and incorporating different kinds of therapeutic agents make dendrimers and polymeric micelles promising candidates for use as drug carriers.

Lipid-Based Nanoparticles (LBNPs)

Nanoparticles derived from lipids (LBNPs) have attracted considerable attention as nanocarriers for drug delivery owing to their distinctive properties Liposomes—nanocarriers composed of one or more vesicular lipid bilayers (lamellae) and made from biodegradable, biocompatible amphiphilic lipids have been widely utilized for drug delivery to the brain. Liposomes are capable of encapsulating both hydrophilic and hydrophobic drugs. [81]. Positive charged lipids found in cationic liposomes are utilized as delivery systems and to carry genetic

material. Among the most often positively charged liposomes used for drug delivery is DOTAP in combination with DOPE.

Studies have demonstrated that cationic liposomes loaded with photosensitive drugs can enhance the delivery of paclitaxel—a mitotic inhibitor used in cancer therapy—and induce laser-activated cytotoxic effects in glioblastoma cells.

Solid Lipid Nanoparticles (SLNs)

Typically, spherical and between 50 and 100 nm in size, solid lipid nanoparticles (SLNs) are a subtype of liposomes that exhibit lesser toxicity and greater biological stability. [80,87,88]. Lipid molecules known as SLNs are solid at normal temperatures. Triglycerides, fatty acids, or waxes are commonly used in the composition of SLNs, with their hydrophobic solid lipid core serving as a matrix for drug incorporation or dispersion.

Due to their diminutive dimensions, SLNs can evade the reticuloendothelial system (RES) and traverse the tight endothelial cells of the blood-brain barrier (BBB) making them effective carriers for drug delivery to the brain. Stearic acid, trimyristin, and glyceryl behenate are among the lipid types that have been successfully used for SLNs in medicinal applications. The simplicity of surface modification for drug targeting, prolonged drug release over weeks, and decreased RES absorption are some benefits of using SLNs as nanocarriers. [86]. Oral medication administration, especially for neurological illnesses, has been accomplished with success using SLNs. Because SLNs may pass through the intestinal and stomach mucosal layers, they have made it easier to provide drug carriers orally to patients with neurological diseases. When curcumincoated microemulsions are administered orally to individuals suffering from illnesses like depression, stroke, or Alzheimer's disease, they have demonstrated efficacy. The lipid components of solid lipid nanoparticles (SLNs) play a significant role in influencing neuronal excitability, as the brain contains structures predominantly composed of phospholipid bilayers. [89,90].

Nanoliposomes (NLPs)

Nanoliposomes (NLPs) are nanoscale carrier systems characterized by a unique lipid bilayer structure capable of encapsulating both hydrophilic and hydrophobic drugs, thereby enabling effective delivery of therapeutic agents to the brain. It is possible to deliver these biodegradable compounds intravenously and they are less harmful [91]. Doxil, the first nanoliposomal formulation approved by the U.S. Food and Drug Administration, has been widely utilized in the treatment of various malignancies. Additionally, Nanotherm is currently undergoing clinical evaluation for its potential application in the treatment of prostate cancer. [92]. Notably, cationic liposomes have showed promise for drug delivery that targets the brain, and adding sulphur nanoparticles has been proven to improve their capacity to cross the blood-brain barrier.[93]. Liposome surface alterations address the issues related to BBB permeability. In order to enhance brain delivery, a research showed how to create a brain-targeted medication formulation using glycosylated and pegylated liposomes coated with the antidepressant sertraline [94]. In addition to its use in brain problems, liposomes have been used to treat bacterial and fungal infections of the liver and spleen. [95]. All things considered, liposomes show great promise for targeted medication delivery in a number of neurological conditions, including meningitis. However, to lessen issues with toxicity and immunogenicity, liposome characteristics and drug delivery must be improved. [96].

Nanoemulsions (NEs)

Emulsions with diameters between 20 and 200 nm that have improved stability and transparency are called nanoemulsions (NEs). These droplets consist of two immiscible liquids such as water and oil and stabilized using co-surfactants or surfactants. Due to their increased surface area and thermodynamics stability, Nes are suitable for use in various industries, including food, cosmetics, and pharmaceutical products [97]. In contrast to traditional emulsions, Nes show higher stability, drug release properties, and bioavailability because of their minute size. By overcoming the blood-brain barrier, they are able to target specific regions, including the brain, and encapsulate both hydrophobic and hydrophilic molecules [98]. Through various delivery systems including oral, intranasal, intravenous, and topical, Nes have proven successful in the treatment of fungal infections, cancer, Alzheimer’s disease, and other neurological disorders [99]. In addition to these uses, they can be produced in different forms, including liquids, gels, creams, and sprays, allowing the targeted delivery of medications in neurological the targeted delivery of medications in neurological disorders such as meningitis [91]. Based on the type of ingredients used, NEs may either be multiphase or biphasic, consisting of oil-in-water and water-in-oil NEs. As NEs possess the ability to penetrate the blood-brain barrier, saquinavir-loaded and risperidone-loaded biphasic NEs have been recommended as effective carriers for brain-targeted drug delivery [100]. With future improvements in stability and biocompatibility, the potential of NEs as therapeutic agents is expected to increase significantly [101].

Metallic Nanoparticles (MNPs)

Metallic nanoparticles (MNPs) are considered to be

nanomaterials having particle sizes of around 10-100 nm. MNPs consist of metals like copper, silver, and gold, which have been used in medical treatments since ages. Out of all these, AgNPs have multiple physiochemical properties that make them highly promising for the treatment of neurological diseases. Moreover, in ancient Indian medicine, AuNPs have been used as Ayurvedic treatments to cure various disorders of the nervous system [102]. The AuNPs with an average size of 56 nm colloidal gold called Swarna bhasmal (gold ash) was mixed with honey and cow ghee and ingested in order to cure a wide range of diseases, including neurological disorders [103]. Nowadays, the use of MNPs has become extensive in theranostics, antimicrobial therapy, and anticancer treatment. Some of the advantages of MNPs include their large surface-to-volume ratio, which enhances their cellular uptake and allows them to be used in targeted drug delivery [104]. MNPs are relatively affordable; therefore, they can be considered a reasonable alternative for pharmaceutical applications [105]. Concerns about toxicity are still present despite promising results of the technology, especially regarding brain targeting [103]. MNPs have shown promise regarding targeted medication delivery to the brain in neurological disorders like meningitis and gliomas [106]. There are several directions for improving the safety and biocompatibility of MNPs in neurotherapeutics that could help solve the toxicity problem. Surface modification that would minimize oxidative stress and inflammatory reactions caused by MNPs is one of the main directions in improving MNPs safety. MNPs covered with biocompatible polymers including polyethylene glycol (PEG) to reduce contact between the particles and immune system cells. AuNPs and AgNPs have shown improved biocompatibility due to their surface modification, which also increases their duration of circulation in blood [107,108]. Another alternative would be alter the structure and size of MNP nanoparticles to ensure that they do not accumulate in tissues but rather aid in exertion. It has been reported from previous studies that MNPs with sizes less than 20nm could easily be exerted by renal clearance, minimizing the chances of accumulation within important organs. It was found that due to controlled surface interactions, spherical and rod-shaped MNPs were safer compared to the ones with irregular shapes [109]. The toxicity of the MNPs can be significantly decreased by coating them with biocompatible agents as well as antioxidant molecules. The oxidative damages caused by the MNPs can be minimized by binding them with molecules such as glutathione or curcumin, thereby rendering reactive oxygen species inactive [110]. For avoiding the problem of neurotoxicity, optimization of dosage and mode of administration becomes necessary. This can be accomplished through proper targeting via ligands to specific receptors [111]. Safe and effective utilization of MNPs for therapy purposes in neurological diseases within clinical practice requires not only the above strategies but also further studies related to the long-term effects of MNPs [112]. There were other interesting strategies in relation to brain-targeted drug delivery systems by means of MNPs that were considered recently in other investigations. For instance, there was an investigation of ultrasmall gold nanoparticles (2 nm) capable of passing through the in vitro BBB in six cells of human brain three-dimensional (3D) spheroids [113]. It is shown that iron oxide NPs delivered through the nasal cavity may migrate into the brain along with olfactory nerve; therefore, bypassing the BBB becomes possible [114]. These advancements will be necessary in order to achieve safe and efficient use of MNPs in clinical practice, as well as further research regarding the long-term effects of MNPs.

CONCLUSIONS:

Multidrug resistance of the organism, poor absorption of medicines across the blood-brain barrier, and rapid disease progression make pneumococcal meningitis a potentially deadly condition with high levels of morbidity and mortality. The creation of innovative drug delivery systems presents a possible substitute for traditional treatment methods, which only partially succeed in improving therapeutic results. In preclinical and clinical investigations, formulations such as nanoparticles, liposomes, niosomes, and intranasal drug delivery platforms have demonstrated great promise by increasing drug availability in the central nervous system and boosting antibacterial activity.

CONFLICT OF INTEREST:

The authors declare that there is no conflict of interest.

REFERENCES:

1. Patil-Bhole, T., Wele, A., Gudi, R., Thakur, K., Nadkarni, S., Panmand, R., & Kale, B. (2021). Nanostructured gold in ancient Ayurvedic calcined drug „swarnabhasma“. Journal of Ayurveda and Integrative Medicine, 12(4), 640-648.
2. Feldman, C., & Anderson, R. (2011). Bacteraemic pneumococcal pneumonia: current therapeutic options. Drugs, 71(2), 131-153.
3. Dockrell, D. H., Whyte, M. K., & Mitchell, T. J. (2012). Pneumococcal pneumonia: mechanisms of infection and resolution. Chest, 142(2), 482-491.
4. Naghavi, M., Abajobir, A. A., Abbafati, C.,

Abbas, K. M., Abd-Allah, F., Abera, S. F., ... & Fischer,

5. F. (2017). Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–
6. 2016: a systematic analysis for the Global Burden of Disease Study 2016. The lancet, 390(10100), 1151-1210.
7. Lucas, M. J., Brouwer, M. C., & van de Beek, D. (2016). Neurological sequelae of bacterial meningitis. Journal of Infection, 73(1), 18-27.
8. Galea, I. (2021). The blood–brain barrier in systemic infection and inflammation. Cellular & molecular immunology, 18(11), 2489-2501.
9. Ampie L, McGavern DB. Immunological defense of CNS barriers against infections. Immunity. 2022;55 (5):781–799.
10. Coureuil, M., Lécuyer, H., Bourdoulous, S., & Nassif, X. (2017). A journey into the brain: insight into how bacterial pathogens cross blood–brain barriers. Nature Reviews Microbiology, 15(3), 149- 159.
11. Iovino, F., Orihuela, C. J., Moorlag, H. E., Molema, G., & Bijlsma, J. J. (2013). Interactions between blood-borne Streptococcus pneumoniae and the blood-brain barrier preceding meningitis. PloS one, 8(7), e68408.
12. Doran, K. S., Fulde, M., Gratz, N., Kim, B. J., Nau, R., Prasadarao, N., ... & Valentin-Weigand, P. (2016). Host–pathogen interactions in bacterial meningitis. Acta neuropathologica, 131(2), 185- 209.
13. Block, N., Naucler, P., Wagner, P., Morfeldt, E., & Henriques-Normark, B. (2022). Bacterial meningitis: aetiology, risk factors, disease trends and severe sequelae during 50 years in Sweden. Journal of Internal Medicine, 292(2), 350-364.
14. Koulenti, D., Xu, E., Song, A., Sum Mok, I. Y., Karageorgopoulos, D. E., Armaganidis, A., ... & Lipman, J. (2020). Emerging treatment options for infections by multidrug-resistant gram-positive microorganisms. Microorganisms, 8(2), 191.
15. Rasko, D. A., & Sperandio, V. (2010). Anti-virulence strategies to combat bacteria-mediated disease. Nature reviews Drug discovery, 9(2), 117-128.
16. Sheoran, S., Arora, S., Singh, P., Velingkar, A., & Mohamed, A. K. (2022). Subtractive genome analysis for identification and characterization of novel drug targets in the streptococcus pneumoniae by using in-silico approach.
17. Hernansanz-Agustín, P., Izquierdo-Alvarez, A., García-Ortiz, A., Ibiza, S., Serrador, J. M., & Martínez-Ruiz, A. (2013). Nitrosothiols in the immune system: signaling and protection. Antioxidants & redox signaling, 18(3), 288-308.
18. Oordt-Speets, A. M., Bolijn, R., van Hoorn, R. C., Bhavsar, A., & Kyaw, M. H. (2018). Global etiology of bacterial meningitis: a systematic review and meta-analysis. PloS one, 13(6), e0198772.
19. Nakamura, T., Cohen, A. L., Schwartz, S., Mwenda, J. M., Weldegebriel, G., Biey, J. N., ... & Serhan, F. (2021). The global landscape of pediatric bacterial meningitis data reported to the World Health Organization–coordinated Invasive Bacterial Vaccine-Preventable Disease Surveillance Network, 2014–2019. The Journal of infectious diseases, 224(Supplement_3), S161-S173.
20. Wahl, B., O'Brien, K. L., Greenbaum, A., Majumder, A., Liu, L., Chu, Y., ... & Knoll, M. D. (2018). Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000–15. The Lancet Global Health, 6(7), e744-e757.
21. Wahl, B., Sharan, A., Knoll, M. D., Kumar, R., Liu, L., Chu, Y., ... & Arora, N. K. (2019). National, regional, and state-level burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in India: modelled estimates for 2000–15. The Lancet Global Health, 7(6), e735- e747.
22. Castelblanco, R. L., Lee, M., & Hasbun, R. (2014). Epidemiology of bacterial meningitis in the USA from 1997 to 2010: a population-based observational study. The Lancet Infectious Diseases, 14(9), 813-819.
23. Meiring, S., Cohen, C., De Gouveia, L., Du Plessis, M., Quan, V., Kleynhans, J., ... & Von Gottberg, A. (2022). Case-fatality and sequelae following acute bacterial meningitis in South Africa, 2016 through 2020. International Journal of Infectious Diseases, 122, 1056-1066.
24. Jacobs, D. M., Yung, F., Hart, E., Nguyen, M. N., & Shaver, A. (2017). Trends in pneumococcal meningitis hospitalizations following the introduction of the 13-valent pneumococcal conjugate vaccine in the United States. Vaccine, 35(45), 6160-6165.
25. Sanneh, B., Okoi, C., Grey-Johnson, M., Bah-

Camara, H., Kunta Fofana, B., Baldeh, I., ... & Antonio, M. (2019). Declining trends of pneumococcal meningitis in Gambian children after the introduction of pneumococcal conjugate vaccines. Clinical Infectious Diseases, 69(Supplement_2), S126-S132.

26. Kourna Hama, M., Khan, D., Laouali, B., Okoi, C., Yam, A., Haladou, M., ... & Antonio, M. (2019). Pediatric bacterial meningitis surveillance in Niger: increased importance of Neisseria meningitidis serogroup C, and a decrease in Streptococcus pneumoniae following 13-valent pneumococcal conjugate vaccine introduction. Clinical Infectious Diseases, 69(Supplement_2), S133-S139.
27. Lo, S. W., Mellor, K., Cohen, R., Alonso, A. R., Belman, S., Kumar, N., ... & Urban, Y. (2022). Emergence of a multidrug-resistant and virulent Streptococcus pneumoniae lineage mediates serotype replacement after PCV13: an international whole-genome sequencing study. The Lancet Microbe, 3(10), e735-e743.
28. Nair, K. G., Ramaiyan, V., & Sukumaran, S. K. (2018). Enhancement of drug permeability across blood brain barrier using nanoparticles in meningitis. Inflammopharmacology, 26(3), 675-684.
29. Nair, M., Jayant, R. D., Kaushik, A., & Sagar, V. (2016). Getting into the brain: Potential of nanotechnology in the management of NeuroAIDS. Advanced drug delivery reviews, 103, 202-217.
30. Zeeshan, M., Mukhtar, M., Ain, Q. U., Khan, S., & Ali, H. (2019). Nanopharmaceuticals: A boon to the brain-targeted drug delivery. Pharmaceutical Formulation Design-Recent Practices, 1-15.
31. Hyams, C., Camberlein, E., Cohen, J. M., Bax, K., & Brown, J. S. (2010). The Streptococcus pneumoniae capsule inhibits complement activity and neutrophil phagocytosis by multiple mechanisms. Infection and immunity, 78(2), 704-715.
32. Abeyta, M., Hardy, G. G., & Yother, J. (2003). Genetic alteration of capsule type but not PspA type affects accessibility of surface-bound complement and surface antigens of Streptococcus pneumoniae. Infection and immunity, 71(1), 218-225.
33. Haleem, K. S., Ali, Y. M., Yesilkaya, H., Kohler, T., Hammerschmidt, S., Andrew, P. W., & Lynch, N. J. (2019). The pneumococcal surface proteins PspA and PspC sequester host C4-binding protein to inactivate complement C4b on the bacterial surface. Infection and immunity, 87(1), 10- 1128.
34. Radin, J. N., Orihuela, C. J., Murti, G., Guglielmo, C., Murray, P. J., & Tuomanen, E. I. (2005). β- Arrestin 1 Participates in Platelet-Activating Factor Receptor-Mediated Endocytosis of Streptococcus pneumoniae. Infection and Immunity, 74(5), 3078-3078.
35. Cundell, D. R., Gerard, N. P., Gerard, C., Idanpaan-Heikkila, I., & Tuomanen, E. I. (1995). Streptococcus pneumoniae anchor to activated human cells by the receptor for platelet-activating factor. Nature, 377(6548), 435-438.
36. Orihuela, C. J., Mahdavi, J., Thornton, J., Mann, B., Wooldridge, K. G., Abouseada, N., ... & Tuomanen, E. I. (2009). Laminin receptor initiates bacterial contact with the blood brain barrier in experimental meningitis models. The Journal of clinical investigation, 119(6), 1638-1646.
37. Iovino, F., Engelen-Lee, J. Y., Brouwer, M., van de Beek, D., van der Ende, A., Valls Seron, M., ... & Henriques-Normark, B. (2017). pIgR and PECAM-1 bind to pneumococcal adhesins RrgA and PspC mediating bacterial brain invasion. Journal of Experimental Medicine, 214(6), 1619-1630.
38. Iovino, F., Hammarlöf, D. L., Garriss, G., Brovall, S., Nannapaneni, P., & Henriques-Normark, B. (2016). Pneumococcal meningitis is promoted by single cocci expressing pilus adhesin RrgA. The Journal of clinical investigation, 126(8), 2821-2826.
39. Uchiyama, S., Carlin, A. F., Khosravi, A., Weiman, S., Banerjee, A., Quach, D., ... & Nizet, V. (2009). The surface-anchored NanA protein promotes pneumococcal brain endothelial cell invasion. Journal of Experimental Medicine, 206(9), 1845-1852.
40. Gratz, N., Loh, L. N., Mann, B., Gao, G., Carter, R., Rosch, J., & Tuomanen, E. I. (2017). Pneumococcal neuraminidase activates TGF-β signalling. Microbiology, 163(8), 1198-1207.
41. Asmat, T. M., Agarwal, V., Saleh, M., & Hammerschmidt, S. (2014). Endocytosis of Streptococcus pneumoniae via the polymeric immunoglobulin receptor of epithelial cells relies on clathrin and caveolin dependent mechanisms. International Journal of Medical Microbiology, 304(8), 1233- 1246.
42. Hupp, S., Förtsch, C., Graber, F., Mitchell, T. J., & Iliev, A. I. (2022). Pneumolysin boosts the neuroinflammatory response to

Streptococcus pneumoniae through enhanced endocytosis. Nature communications, 13(1), 5032.

43. Surve, M. V., Bhutda, S., Datey, A., Anil, A., Rawat, S., Pushpakaran, A., ... & Banerjee, A. (2018). Heterogeneity in pneumolysin expression governs the fate of Streptococcus pneumoniae during blood-brain barrier trafficking. PLoS pathogens, 14(7), e1007168.
44. Tabusi, M., Thorsdottir, S., Lysandrou, M., Narciso, A. R., Minoia, M., Srambickal, C. V., & Iovino, F. (2021). Neuronal death in pneumococcal meningitis is triggered by pneumolysin and RrgA interactions with β-actin. PLoS pathogens, 17(3), e1009432.
45. Schröder, N. W., Morath, S., Alexander, C., Hamann, L., Hartung, T., Zähringer, U., ... & Schumann, R. R. (2003). Lipoteichoic acid (LTA) of Streptococcus pneumoniaeand Staphylococcus aureus activates immune cells via Toll-like receptor (TLR)-2, lipopolysaccharide-binding protein (LBP), and CD14, whereas TLR-4 and MD-2 are not involved. Journal of biological chemistry, 278(18), 15587-15594.
46. Tomlinson, G., Chimalapati, S., Pollard, T., Lapp, T., Cohen, J., Camberlein, E., ... & Brown, J. (2014). TLR-mediated inflammatory responses to Streptococcus pneumoniae are highly dependent on surface expression of bacterial lipoproteins. The Journal of Immunology, 193(7), 3736-3745.
47. Ribes, S., Ebert, S., Regen, T., Agarwal, A., Tauber, S. C., Czesnik, D., ... & Nau, R. (2010). Toll- like receptor stimulation enhances phagocytosis and intracellular killing of nonencapsulated and encapsulated Streptococcus pneumoniae by murine microglia. Infection and immunity, 78(2), 865-871.
48. Too, L. K., Yau, B., Baxter, A. G., McGregor, I. S., & Hunt, N. H. (2019). Double deficiency of toll-like receptors 2 and 4 alters long-term neurological sequelae in mice cured of pneumococcal meningitis. Scientific reports, 9(1), 16189.
49. Picard, C., Casanova, J. L., & Puel, A. (2011). Infectious diseases in patients with IRAK-4, MyD88, NEMO, or IκBα deficiency. Clinical microbiology reviews, 24(3), 490-497.
50. Barichello, T., Fagundes, G. D., Generoso, J. S., Moreira, A. P., Costa, C. S., Zanatta, J. R., & Teixeira, A. L. (2012). Brain–blood barrier breakdown and pro-inflammatory mediators in neonate rats submitted meningitis by Streptococcus pneumoniae. Brain research, 1471, 162-168.
51. Van Boeckel, T. P., Pires, J., Silvester, R., Zhao, C., Song, J., Criscuolo, N. G., ... & Laxminarayan,
52. R. (2019). Global trends in antimicrobial resistance in animals in low-and middle-income countries. Science, 365(6459), eaaw1944.
53. Wang, Z. Q. (2020, April). A Literature Review of Bacterial Drug Resistance. In Materials Science Forum (Vol. 980, pp. 197-209). Trans Tech Publications Ltd.
54. Ferri, M., Ranucci, E., Romagnoli, P., & Giaccone, V. (2017). Antimicrobial resistance: A global emerging threat to public health systems. Critical reviews in food science and nutrition, 57(13), 2857-2876.
55. Roberts, S. C., & Zembower, T. R. (2021). Global increases in antibiotic consumption: a concerning trend for WHO targets. THE LANCET infectious diseases, 21(1), 10-11.
56. Sultan, I., Rahman, S., Jan, A. T., Siddiqui, M. T., Mondal, A. H., & Haq, Q. M. R. (2018). Antibiotics, resistome and resistance mechanisms: A bacterial perspective. Frontiers in microbiology, 9, 2066.
57. Zhu, L., Shuai, X., Xu, L., Sun, Y., Lin, Z., Zhou, Z., ... & Chen, H. (2022). Mechanisms underlying the effect of chlorination and UV disinfection on VBNC state Escherichia coli isolated from hospital wastewater. Journal of hazardous materials, 423, 127228.
58. Reading, E., Ahdash, Z., Fais, C., Ricci, V., Wang-Kan, X., Grimsey, E., ... & Politis, A. (2020). Perturbed structural dynamics underlie inhibition and altered efflux of the multidrug resistance pump AcrB. Nature communications, 11(1), 5565.
59. Jit, M. (2010). The risk of sequelae due to pneumococcal meningitis in high-income countries: a systematic review and meta-analysis. Journal of Infection, 61(2), 114-124.
60. Adil, S. M., Hodges, S. E., Charalambous, L. T., Kiyani, M., Liu, B., Lee, H. J., ... & Lad, S. P. (2021). Paediatric bacterial meningitis in the USA: outcomes and healthcare resource utilization of nosocomial versus community-acquired infection. Journal of medical microbiology, 70(1), 001276.
61. Edmond, K., Clark, A., Korczak, V. S., Sanderson, C., Griffiths, U. K., & Rudan, I. (2010). Global and regional risk of disabling sequelae from bacterial meningitis: a

systematic review and meta- analysis. The Lancet infectious diseases, 10(5), 317-328.

62. Kilpi, T., Anttila, M., Kallio, M. J., & Peltola, H. (1993). Length of prediagnostic history related to the course and sequelae of childhood bacterial meningitis. The Pediatric infectious disease journal, 12(3), 184-188.
63. Kilpi, T., Anttila, M., Kallio, M. J. T., & Peltola, H. (1991). Severity of childhood bacterial meningitis and duration of illness before diagnosis. The Lancet, 338(8764), 406-409.
64. Victora, C. G., Wagstaff, A., Schellenberg, J. A., Gwatkin, D., Claeson, M., & Habicht, J. P. (2003). Applying an equity lens to child health and mortality: more of the same is not enough. The Lancet, 362(9379), 233-241.
65. Edmond, K.; Dieye, Y.; Griffiths, U.K.; Fleming, J.; Ba, O.; Diallo, N.; Mulholland, K. Prospective Cohort Study of Disabling Sequelae and Quality of Life in Children with Bacterial Meningitis in Urban Senegal. Pediatr. Infect. Dis. J. 2010, 29, 1023–1029.
66. Nguyen, M. M., Carlini, A. S., Chien, M. P., Sonnenberg, S., Luo, C., Braden, R. L., ... & Christman, K. L. (2015). Enzyme-responsive nanoparticles for targeted accumulation and prolonged retention in heart tissue after myocardial infarction. Advanced materials (Deerfield Beach, Fla.), 27(37), 5547.
67. Callmann, C. E., Barback, C. V., Thompson, M. P., Hall, D. J., Mattrey, R. F., & Gianneschi, N. C. (2015). Therapeutic enzyme-responsive nanoparticles for targeted delivery and accumulation in tumors. Advanced materials (Deerfield Beach, Fla.), 27(31), 4611.
68. De La Rica, R., Aili, D., & Stevens, M. M. (2012). Enzyme-responsive nanoparticles for drug release and diagnostics. Advanced drug delivery reviews, 64(11), 967-978.
69. Lock, L. L., Tang, Z., Keith, D., Reyes, C., & Cui, H. (2015). Enzyme-specific doxorubicin drug beacon as drug-resistant theranostic molecular probes. ACS Macro Letters, 4(5), 552-555.
70. Grützner, V., Unger, R. E., Baier, G., Choritz, L., Freese, C., Böse, T., ... & Kirkpatrick, C. J. (2015). Enzyme-responsive nanocomposites for wound infection prophylaxis in burn management: in vitro evaluation of their compatibility with healing processes. International journal of nanomedicine, 4111-4124.
71. Garzoni, C., & Kelley, W. L. (2009). Staphylococcus aureus: new evidence for intracellular persistence. Trends in microbiology, 17(2), 59-65.
72. Irache, J. M., Salman, H. H., Gamazo, C., & Espuelas, S. (2008). Mannose-targeted systems for the delivery of therapeutics. Expert opinion on drug delivery, 5(6), 703-724.
73. Wijagkanalan, W., Kawakami, S., Higuchi, Y., Yamashita, F., & Hashida, M. (2011). Intratracheally instilled mannosylated cationic liposome/NFκB decoy complexes for effective prevention of LPS-induced lung inflammation. Journal of controlled release, 149(1), 42-50.
74. Mu, S., Liu, W., Zhao, L., Long, Y., & Gu, H. (2019). Antimicrobial AgNPs composites of gelatin hydrogels crosslinked by ferrocene-containing tetrablock terpolymer. Polymer, 169, 80-94.
75. Zhang, Y., Zhang, J., Chen, W., Angsantikul, P., Spiekermann, K. A., Fang, R. H., ... & Zhang, L. (2017). Erythrocyte membrane-coated nanogel for combinatorial antivirulence and responsive antimicrobial delivery against Staphylococcus aureus infection. Journal of Controlled Release, 263, 185-191.
76. De Jong, W. H., & Borm, P. J. (2008). Drug delivery and nanoparticles: applications and hazards. International journal of nanomedicine, 3(2), 133-149.
77. Baskin, J., Jeon, J. E., & Lewis, S. J. (2021). Nanoparticles for drug delivery in Parkinson‟s disease. Journal of Neurology, 268(5), 1981-1994.
78. Yetisgin, A. A., Cetinel, S., Zuvin, M., Kosar, A., & Kutlu, O. (2020). Therapeutic nanoparticles and their targeted delivery applications. Molecules, 25(9), 2193.
79. Lombardo, D.; Kiselev, M.A. Methods of Liposomes Preparation: Formation and Control Factors of Versatile Nanocarriers for Biomedical and Nanomedicine Application. Pharmaceutics 2022, 14, 543.
80. Begines, B., Ortiz, T., Pérez-Aranda, M., Martínez, G., Merinero, M., Argüelles-Arias, F., & Alcudia, A. (2020). Polymeric nanoparticles for drug delivery: Recent developments and future prospects. Nanomaterials, 10(7), 1403.
81. Satapathy, M. K., Yen, T. L., Jan, J. S., Tang, R. D., Wang, J. Y., Taliyan, R., & Yang, C. H. (2021). Solid lipid nanoparticles (SLNs): an advanced drug delivery system targeting brain through BBB. Pharmaceutics, 13(8), 1183.
82. Mukhtar, M.; Bilal, M.; Rahdar, A.; Barani, M.

Nanomaterials for Diagnosis and Treatment of Brain Cancer: Recent Updates. Chemosensors 2020, 8, 117.

83. Mehta, M., Bui, T. A., Yang, X., Aksoy, Y., Goldys, E. M., & Deng, W. (2023). Lipid-based nanoparticles for drug/gene delivery: an overview of the production techniques and difficulties encountered in their industrial development. ACS Materials Au, 3(6), 600-619.
84. Gregori, M., Masserini, M., & Mancini, S. (2015). Nanomedicine for the treatment of Alzheimer‟s disease. Nanomedicine, 10(7), 1203-1218.
85. Santos, A., Veiga, F., & Figueiras, A. (2019). Dendrimers as pharmaceutical excipients: synthesis, properties, toxicity and biomedical applications. Materials, 13(1), 65.
86. Madaan, K., Kumar, S., Poonia, N., Lather, V., & Pandita, D. (2014). Dendrimers in drug delivery and targeting: Drug-dendrimer interactions and toxicity issues. Journal of Pharmacy and Bioallied Sciences, 6(3), 139-150.
87. Xu, W., Ling, P., & Zhang, T. (2013). Polymeric micelles, a promising drug delivery system to enhance bioavailability of poorly water-soluble drugs. Journal of drug delivery, 2013(1), 340315.
88. Jhaveri, A. M., & Torchilin, V. P. (2014). Multifunctional polymeric micelles for delivery of drugs and siRNA. Frontiers in pharmacology, 5, 77.
89. Naqvi, S., Panghal, A., & Flora, S. J. S. (2020). Nanotechnology: a promising approach for delivery of neuroprotective drugs. Frontiers in neuroscience, 14, 494.
90. Zielińska, A.; Carreiró, F.; Oliveira, A.M.; Neves, A.; Pires, B.; Venkatesh, D.N.; Durazzo, A.; Lucarini, M.; Eder, P.; Silva, A.M.; et al. Polymeric Nanoparticles: Production, Characterization, Toxicology and Ecotoxicology. Molecules 2020, 25, 3731. [Google Scholar] [CrossRef] [PubMed]
91. Ashfaq, R., Rasul, A., Asghar, S., Kovács, A., Berkó, S., & Budai-Szűcs, M. (2023). Lipid nanoparticles: an effective tool to improve the bioavailability of nutraceuticals. International journal of molecular sciences, 24(21), 15764.
92. Singh, B., Day, C. M., Abdella, S., & Garg, S. (2024). Alzheimer's disease current therapies, novel drug delivery systems and future directions for better disease management. Journal of Controlled Release, 367, 402-424.
93. Harilal, S., Jose, J., Parambi, D. G. T., Kumar, R., Mathew, G. E., Uddin, M. S., & Mathew, B. (2019). Advancements in nanotherapeutics for Alzheimer‟s disease: current perspectives. Journal of Pharmacy and Pharmacology, 71(9), 1370-1383.
94. Sharma, N., Zahoor, I., Sachdeva, M., Subramaniyan, V., Fuloria, S., Fuloria, N. K., & Singh, S. (2021). Deciphering the role of nanoparticles for management of bacterial meningitis: an update on recent studies. Environmental Science and Pollution Research, 28(43), 60459-60476.
95. Rodriguez, F., Caruana, P., De la Fuente, N., Espanol, P., Gamez, M., Balart, J., & Céspedes, M.
96. V. (2022). Nano-based approved pharmaceuticals for cancer treatment: present and future challenges. Biomolecules, 12(6), 784.
97. Pandian, S. R. K., Vijayakumar, K. K., Murugesan, S., & Kunjiappan, S. (2022). Liposomes: An emerging carrier for targeting Alzheimer's and Parkinson's diseases. Heliyon, 8(6).
98. De Jong, W. H., & Borm, P. J. (2008). Drug delivery and nanoparticles: applications and hazards. International journal of nanomedicine, 3(2), 133-149.
99. Samad, A., Sultana, Y., & Aqil, M. (2007). Liposomal drug delivery systems: an update review. Current drug delivery, 4(4), 297-305.
100. Upadhyay, R. K. (2014). Drug delivery systems, CNS protection, and the blood brain barrier. BioMed research international, 2014(1), 869269.
101. Gupta, A., Eral, H. B., Hatton, T. A., & Doyle, P. S. (2016). Nanoemulsions: formation, properties and applications. Soft matter, 12(11), 2826-2841.
102. Jaiswal, M., Dudhe, R., & Sharma, P. K. (2015). Nanoemulsion: an advanced mode of drug delivery system. 3 Biotech, 5(2), 123-127.
103. Bonferoni, M. C., Rossi, S., Sandri, G., Ferrari, F., Gavini, E., Rassu, G., & Giunchedi, P. (2019). Nanoemulsions for “nose-to-brain” drug delivery. Pharmaceutics, 11(2), 84.
104. Singh, Y., Meher, J. G., Raval, K., Khan, F. A., Chaurasia, M., Jain, N. K., & Chourasia, M. K. (2017). Nanoemulsion: Concepts, development and applications in drug delivery. Journal of controlled release, 252, 28-49.
105. Patel, M. M., & Patel, B. M. (2017). Crossing the blood–brain barrier: recent

advances in drug delivery to the brain. CNS drugs, 31(2), 109-133.

106. Patil-Bhole, T., Wele, A., Gudi, R., Thakur, K., Nadkarni, S., Panmand, R., & Kale, B. (2021). Nanostructured gold in ancient Ayurvedic calcined drug „swarnabhasma". Journal of Ayurveda and Integrative Medicine, 12(4), 640-648.

107. Arvizo, R. R., Bhattacharyya, S., Kudgus, R. A., Giri, K., Bhattacharya, R., & Mukherjee, P. (2012). Intrinsic therapeutic applications of noble metal nanoparticles: past, present and future. Chemical Society Reviews, 41(7), 2943-2970.

108. Desai, N., Momin, M., Khan, T., Gharat, S., Ningthoujam, R. S., & Omri, A. (2021). Metallic nanoparticles as drug delivery system for the treatment of cancer. Expert opinion on drug delivery, 18(9), 1261-1290.

109. Lee, S. H., & Jun, B. H. (2019). Silver nanoparticles: synthesis and application for nanomedicine. International journal of molecular sciences, 20(4), 865.

110. Li, J., Zhao, J., Tan, T., Liu, M., Zeng, Z., Zeng, Y., ... & Xie, T. (2020). Nanoparticle drug delivery system for glioma and its efficacy improvement strategies: a comprehensive review. International Journal of Nanomedicine, 2563-2582.

111. Abdelkawi, A., Slim, A., Zinoune, Z., & Pathak, Y. (2023). Surface modification of metallic nanoparticles for targeting drugs. Coatings, 13(9), 1660

112. Yang, W., Wang, L., Fang, M., Sheth, V., Zhang, Y., Holden, A. M., & Wilhelm, S. (2022). Nanoparticle surface engineering with heparosan polysaccharide reduces serum protein adsorption and enhances cellular uptake. Nano letters, 22(5), 2103-2111.

113. Albanese, A., Tang, P. S., & Chan, W. C. (2012). The effect of nanoparticle size, shape, and surface chemistry on biological systems. Annual review of biomedical engineering, 14(1), 1-16.

114. Zhang, B., Zhao, Y., Guo, K., Tian, H., Wang, C., Wang, R., ... & Tian, W. (2023). Macromolecular nanoparticles to attenuate both reactive oxygen species and inflammatory damage for treating Alzheimer's disease. Bioengineering & Translational Medicine, 8(3), e10459.

115. Yu, M., Su, D., Yang, Y., Qin, L., Hu, C., Liu, R., ... & Gao, H. (2018). D-T7 peptide-modified PEGylated bilirubin nanoparticles loaded with cediranib and paclitaxel for antiangiogenesis and chemotherapy of glioma. ACS applied materials & interfaces, 11(1), 176-186.

116. Ekhator, C., Qureshi, M. Q., Zuberi, A. W., Hussain, M., Sangroula, N., Yerra, S., ... & Zuberi Sr, W. (2023). Advances and opportunities in nanoparticle drug delivery for central nervous system disorders: A review of current advances. Cureus, 15(8).

117. Sokolova, V., Mekky, G., van der Meer, S. B., Seeds, M. C., Atala, A. J., & Epple, M. (2020). Transport of ultrasmall gold nanoparticles (2 nm) across the blood–brain barrier in a six-cell brain spheroid model. Scientific Reports, 10(1), 18033.

118. Minigalieva, I. A., Ryabova, Y. V., Shelomencev, I. G., Amromin, L. A., Minigalieva, R. F., Sutunkova, Y. M., ... & Sutunkova, M. P. (2023). Analysis of experimental data on changes in various structures and functions of the rat brain following intranasal administration of Fe2O3 nanoparticles. International Journal of Molecular Sciences, 24(4), 3572.