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Enhancing Defense against Bacterial Meningitis Unveiling the Power of Bioactive Components: A Review

Ayushi Chaudhary[1], Kanchan Lata Tripathi[1], Nitika Verma[2], Himani Badoni[1*], Devendra Kumar[3], Nishesh Sharma[1]

[1]School of Applied and Life sciences, Department of Biotechnology, Uttaranchal University, Arcadia Grant, India
[2]Department of Biotechnology, Meerut Institute of Engineering & Technology, India
[3]Department of Microbiology, Chaudhary Charan Singh University, India
Email: himani318@gmail.com

Bacterial meningitis poses a significant threat to public health, especially among children under five, and can lead to life-threatening complications if untreated. It is characterized by inflammation of the meninges, the protective membranes surrounding the brain and spinal cord, potentially causing severe neurological damage. While the incidence is relatively low in developed countries, it remains a substantial burden in developing regions, with an annual occurrence rate of 5-10% per 100,000 individuals. The primary causative agents vary by age but commonly include Haemophilus influenzae, Streptococcus pneumoniae, and Neisseria meningitidis. Prompt recognition of symptoms such as headaches, high fever, and neck stiffness is crucial for timely diagnosis and treatment. The pathogenesis of bacterial meningitis involves a complex interplay of mechanisms, including blood-brain barrier disruption, oxidative stress, and dysregulated immune responses within the central nervous system. Research has identified key pathways in disease progression, enabling the development of targeted therapeutic interventions. Intravenous antibiotics are the cornerstone of treatment, aiming to eliminate the pathogens and reduce inflammation. By investigating the antimicrobial properties of these natural compounds, researchers can identify promising candidates for further study. Techniques such as extraction, purification, and formulation are essential for incorporating these bioactive chemicals into therapeutic agents for clinical use. Ongoing research into the inhibitory effects of plant-derived compounds against meningitis-causing bacteria holds promise for novel treatment strategies. Utilizing the therapeutic potential of natural compounds may enhance antibiotic efficacy and address antimicrobial resistance.

Keywords: Blood Brain Barrier, Bacterial Meningitis, CSF, Oxidative Stress, Inhibitory Factors, Bioactive Compounds.

1. Introduction

Bacterial-induced inflammation of the meninges mainly impacts the arachnoid and pia mater due to subarachnoid space bacterial invasion. These fundamentals have been recognized since the beginning of the century. The pathogens use the characteristics of the immune system of the CNS to multiply followed by initiating the inflammation. The key characteristic of bacterial meningitis is the entry of extremely active white blood cells into the cerebrospinal fluid.

Subarachnoid space is mostly filled with cerebrospinal fluid (CSF), and bacterial meningitis is an acute illness that may affect it. Symptoms include pleocytosis in the cerebrospinal fluid (CSF), headaches, fever, and dystonia brought on by inflammation of the meninges and submucosa 1. Infection with S. suis causes meningitis in 84.6% of Europeans and 75.2% of Asians 2. Brain cortex and parenchyma involvement may lead to changes in lifestyle, specific neuropathies, and memory problems, as opposed to major inflammation or vascular problems 1.

Typically, the inflammation spreads beyond the meninges to involve the brain parenchyma (leading to meningoencephalitis), and the ventricles (resulting in ventriculitis), and can even extend along the spinal cord (Fig. 1). Timely evaluation and treatment are crucial when dealing with potential cases of bacterial meningitis due to its severe nature 3.

In developing countries nowadays, Neisseria meningitidis is the major agent of meningitis. It remains a significant health issue in the USA & Europe. In addition to classical meningitis, it is probable to induce systemic disorders such as severe gram -ve sepsis or disseminated intravascular coagulopathy. The main line of thought is that meningococci bacteria start high-grade bacteremia through the bloodstream before infiltrating the CNS in blood flow. Nevertheless, there are also talks about immediate brain access through dural defects or localized infections, radiating the brain through CCT or MRI scans.

The precise location where the bloodstream enters the brain anatomically remains unknown, even though research continues. There is a hypothesis that the choroid plexus may be a pathway of infection with the presence of meningococci in this area. Different species of pneumococci on the other hand infiltrate the leptomeningeal blood vessels when they cause meningitis. This points to the fact that a multitude of highly vascularized sites are the targeted entry points. Successful passage through tight junctions by meningeal pathogens requires the meninges to use molecular mechanisms that are effective. The involvement of endothelial cells, as well as leukocytes, particularly granulocytes in cerebrospinal fluid (CSF), appear to be a major reason for the bacterial invasion, with leukocytes. Particularly, granulocytes in cerebrospinal fluid are a key diagnostic factor for meningitis.

The early phase of the inflammation and bacteria attack can be seen to progress at the same speed, and the products from the activated leukocytes, for example, MMPs and NO, are responsible for the damage in the blood-brain barriers. When the bacteria arrive within subarachnoid space, they multiply, autolyze, and cause inflammation.

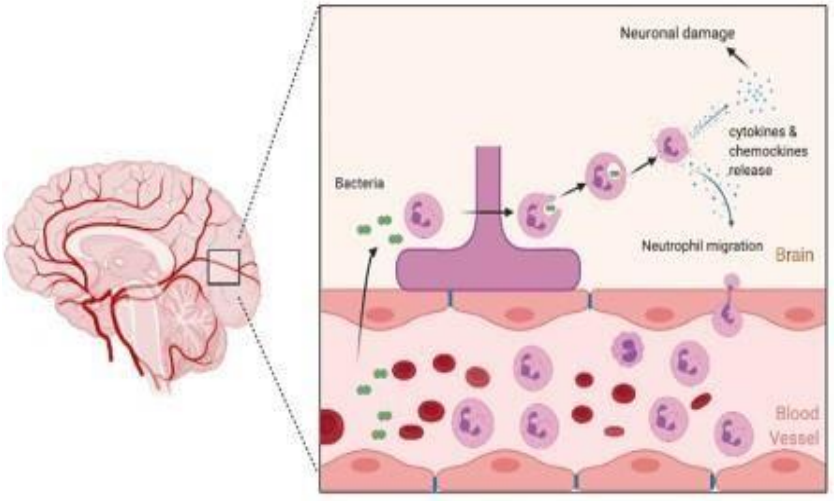

Figure 1: Bacterial meningitis 3

1.1 Cause of Bacterial meningitis

Worldwide, 75% of cases of bacterial meningitis are known to originate in wealthy nations, where S.pneumoniae is one of the most common causative agents [4-5]. When humans are healthy, the commensal bacteria Streptococcus pneumoniae resides in their throats and lungs. However invasive pneumococcal disease (IPD) may develop when it spreads and establishes itself in normally sterile settings including blood, cerebrospinal fluid (CSF), and the pleural space [6]. 7, 8]. Prompt amoxicillin treatment is crucial in improving the terrible outcome of meningitis caused by L. monocytogenes [VIII]. Pneumococcal meningitis is more frequent in children less than five and in those over the age of 65, while meningococcal meningitis predominates among adults, teenagers, and young adults [9].

In developed countries, the occurrence of pneumococcal meningitis has decreased thanks to the utilization of pneumococcal polysaccharide vaccines, which lower the transmission of harmful strains. This impact is observed in both age groups, whether vaccinated or unvaccinated (herd immunity) [5, 10]. A wide variety of microbes may induce severe encephalopathy, or it might be an indicator of a non-communicable disease. Although respiratory infections are the most common, bacterial meningitis may also enter the body via the intestines (as in listerial infection) and cause the most fatal form of the illness [11].

1.2 Mechanism

Potential entry points for bacteria into the brain include the circulatory system the nasal passages or the inner ear's coronoid bone. The most common way for bacteria to get into the subarachnoid space is by a process called blood-borne pathogen invasion. This starts with the bacteria penetrating the epithelium, then moving on to the incursion, diligence, and reproduction stages of the transmission process, and finally breaking through the blood-brain barrier (BBB) [3].

Fig 2 [3] illustrates the sequential process of bacterial meningitis development, starting from the presence of meningitis bacteria and influenced by factors such as environmental

conditions, age, and immunocompromise. The bacteria initially colonize and invade the host's mucosal barriers, usually in the respiratory tract, then survive and replicate in the bloodstream. Following this, the bacteria adhere to and disrupt the blood-brain barrier (BBB), allowing them to invade the central nervous system (CNS). This invasion leads to neuronal apoptosis and death, causing significant brain damage. The process culminates in the clinical symptoms of bacterial meningitis, including fever, headache, neck stiffness, and altered mental status.

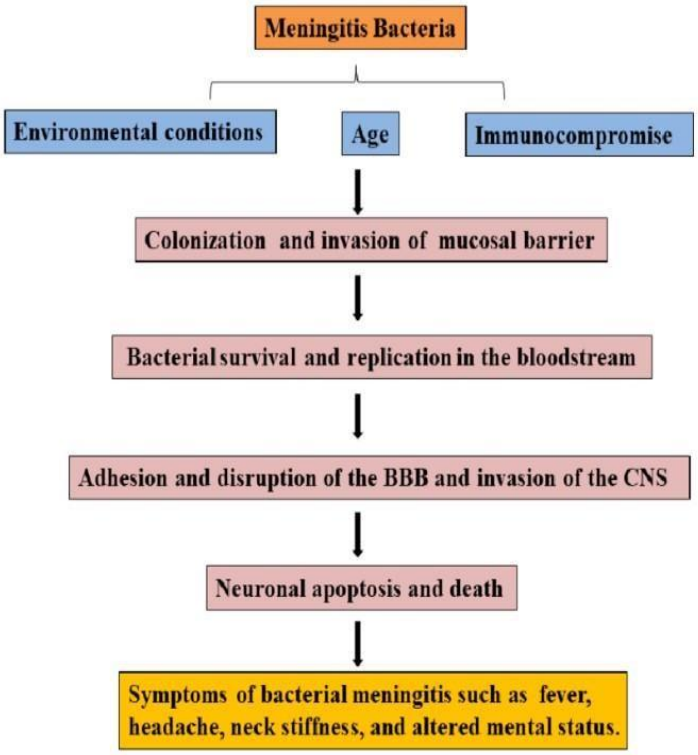

Figure 2: Bacterial meningitis process [3]

1.3 Pathogen invading the host through immigration

Mucosa surfaces in the respiratory tract, urogenital tract, and stomach tract are infected by numerous pathogens before they reach the stream [12-13]. Host variables that increase the risk of meningeal pathogens producing invasive infection include fetal asplenia, component shortage, cytotoxic treatment, and antibody insufficiency [14].

1.4 Endurance within the bloodstream

Bacteria and viruses that get into the bloodstream must fight against a bactericidal and hostile environment. The carbohydrate-based antiphagocytic capsules in many bacteria, such as Staphylococcus pneumoniae, Neisseria meningitidis, group B streptococci, Haemophilus influenzae, and Escherichia coli, are the key to overcoming the host defenses through the hindrance of the attachment of another consequence of the capsular polysaccharides in meningococci is the decreased complement system bacterial killing activity [15, 16].

This is likely caused by a decrease in the amount of C4 binding protein (C4bp) being deposited on the surface of the bacteria. On the other hand, positive bacteria have different surface molecules that allow them to detect the specific complement components outside the capsule. This property may help them to evade the clearance mechanisms [17]. Porin B, neisserial surface protein A (NspA), and fH-binding protein (fHbp) all work together to keep N. meningitidis attached to fH, the important player in two distinct but overlapping routes [18]. Prominent façade proteins in E. coli, outer membrane protein A (OmpA) binds to C4bp, a substance found in nature that blocks the classical and lectin pathways, ultimately improving the bactericidal function of serum [19].

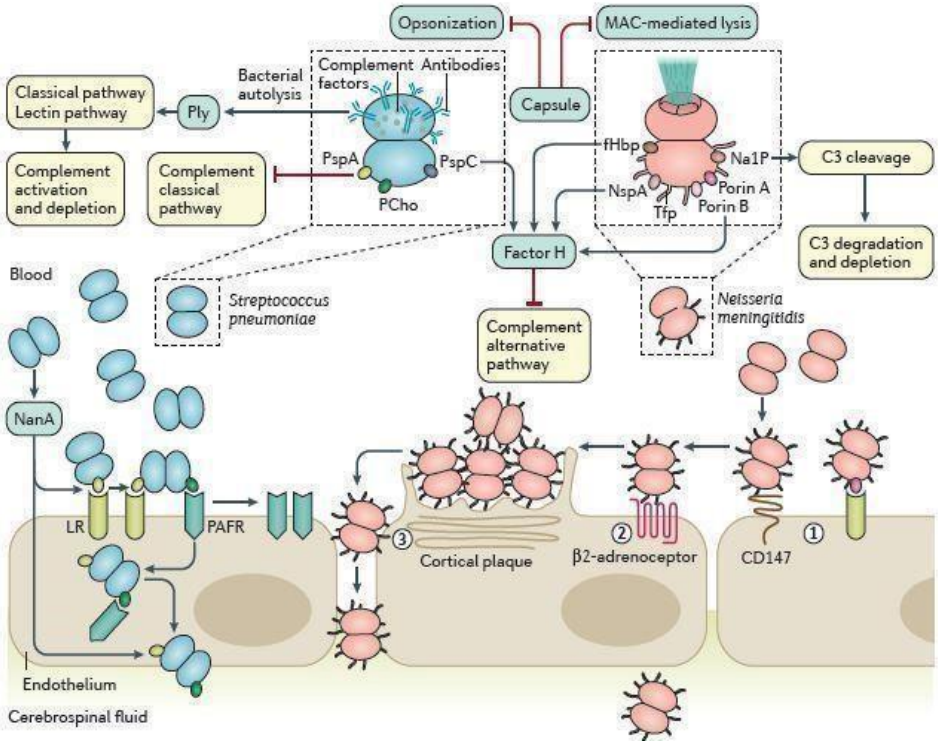

Figure 3: Microbial involvement in the spread and invasion of the CNS [11]

Fig 3 [11] illustrates the mechanisms by which microbes, specifically Streptococcus pneumoniae and Neisseria meningitidis, invade and spread within the central nervous system (CNS). Streptococcus pneumoniae utilizes various pathways, including classical and lectin pathways, to activate and deplete complement factors, leading to bacterial autolysis and evasion of immune responses. It binds to endothelial receptors like LR and PAFR via specific proteins to breach the blood-brain barrier. Neisseria meningitidis evades the immune system by using its capsule to resist opsonization and MAC-mediated lysis, and it binds to endothelial cells through interactions involving the β2-adrenoceptor and CD147. Both pathogens manipulate complement factors to enhance their invasion and spread, ultimately reaching the cerebrospinal fluid and causing infection.

1.5 Invasion of the CNS

It has been shown that many invading pathogens can invade the subarachnoid space when persistently high bacteremia levels are established in both people and animals. The analysis of the probability of pathogens connecting with the blood-CSF barrier's innermost cells is probably to blame for this [14]. Veins and post-capillary venules may serve as entry sites for bacteria in the perivascular and subarachnoid areas. On top of that, the brain's vascular tree includes the 'leaky' post-capillary venules and veins, which are situated near the CSF [20-21].

1.6 Immune activation in bacterial meningitis

Infestations in the CSF are expected to continue because innate responses in the cortical region are compromised, making it difficult to eliminate potential pathogens [22]. One possible cause of the immunological deficiency is the absence of soluble PRRs, like coagulation factors, which bind to pathogen surfaces and mark them for phagocytosis. In vulnerable species like Neisseria spp., bacterial lysis may be enhanced by complement deposition, which creates a membrane attack complex (MAC). The blood-brain barrier prevents blood complement proteins from entering the CSF [23]. Mainly, it restricts the admission of big macromolecules and cells that do not elicit an immunological response by functioning as a biochemical filter. In response, pathogens that successfully enter the cerebrospinal fluid (CSF) may multiply rapidly, reaching high densities in just a few hours [14].

2. BACTERIAL MENINGITIS THERAPEUTICS

The prevalence of bacterial meningitis keeps on ascending regardless of upgrades in immunization programs. This segment offers an exhaustive investigation of helpful methodologies that are planned to work on the prognosis, treatment, and diagnosis, of bacterial meningitis. These methodologies incorporate immunomodulatory targets and arising biomarkers.

2.1. Immunomodulatory Targets

2.1.1Macrophage Migration Inhibitory Factor (MIF)

MIF's ability to cause long-term cognitive issues in individuals recovering from bacterial meningitis was stressed by Kloek et al. (2021) [24]. This perception features the ramifications of MIF for neurological results and raises the likelihood that it very well may be the objective of immune-modulating additional therapy.

2.1.2Heparin-Binding Glycoprotein (HBP)

Compared to lactate and procalcitonin, intracranial hemoglobin (HBp) is a more effective additional analytical marker for differentiating meningitis illnesses in the ventriculitis and bloodstream. HBP has shown to be a more accurate diagnostic biomarker than CSF cytochemical markers, especially when it comes to differentiating between viral and bacterial meningitis. Activated neutrophils secrete HBP in the early stages of aggravation [25, 26].

2.1.3Neurofilament Light Chain (NfL)

Research has found that measuring the amount of NfL in CSF may help predict the course of

bacterial meningitis [27]. The combination of NfL with multiplex polymerase chain reaction (PCR) boosts diagnostic accuracy, especially when the results from cultures are negative [XXVIII]. More recent studies have also suggested that the CSF neutrophil-to-lymphocyte ratio (NLR) has a diagnostic value in differentiating between viral and bacterial meningitis in pediatric patients [28, 29].

The clinical manifestations of bacterial meningitis, like fever, fatigue, and headache, are not so specific at the early stage. Next, the symptoms are neck stiffness accompanied by light and sound sensitivities and vomiting that is due to the inflammation of the meninges [23]. Headaches and neck stiffness begin due to the trigeminal sensory nerve fibers in the meninges becoming inflamed. However, this process can be experimentally reversed by using certain receptor agonists. However, it is still unknown if triptan can be an effective treatment for headaches associated with bacterial meningitis. The diagnosis of bacterial meningitis is confirmed when Gram staining or positive bacterial culture from the CSF is completed, with detection rates of around 90% in CSF and approximately 50% in blood cultures.

For example, centrifugation of greater volumes of CSF samples and the application of expert microscopists can improve the diagnostic value of CSF microscopy. PCR is a widely used technique, but yet it is not a routine procedure for the identification of the pathogen. PCR offers a significant advantage in the identification of strains, especially in cases involving meningococcal disease. While rapid latex agglutination tests for major meningitis pathogens are simple to use, their limited accuracy currently prevents their implementation in clinical settings.

Elevated levels of total monocytes, neutrophils, and other white blood cells in the peripheral blood are observed in bacterial meningitis, but they lack specificity, particularly in unusual cases. Furthermore, the characteristics noted previously are not set in stone but evolve when the patient does not receive adequate antimicrobial treatment.

CT

A cranial CT scan is a valuable tool for the diagnosis of intracranial complications including brain swelling, hydrocephalus, and stroke. Also, it helps to recognize adjacent infections such as sinusitis, mastoiditis, or dental abscesses through bone window imaging. In conditions like pneumococcal meningitis, localized infections are often observed and may require surgical intervention. The debate over whether a cranial CT should precede a lumbar puncture continues because of the potential for cerebral herniation from raised intracranial pressure. Patients with focal neurological deficits, seizures, or altered consciousness should receive a cranial CT scan before undergoing a lumbar puncture. In cases where CT is unavailable, treatment should start based on clinical suspicion without the need for CSF analysis. For the patients who do not have focal signs or seizures, and also keep normal consciousness, cranial CT abnormalities are detected in less than 3% of cases. In those cases, CT scanning can be avoided as the CSF can be safely collected beforehand. Nevertheless, a normal CT scan is not specific enough to rule out increased intracranial pressure, and there is still a residual risk of herniation.

2.2. Therapeutic Strategies

Accurate determination of the causative pathogen and its susceptibility to the antibiotic are

essential for successful treatment. With the increased antibiotic resistance, treatment should be personalized based on culture results to achieve high and specific effective coverage. Nevertheless, practicing penicillin G monotherapy for meningococcal or pneumococcal infections is recommended only upon confirmation of susceptibility. Most pathogens' treatment period is 10–14 days, but 5–7 days is enough for a simple meningococcal disease. Infections of L. monocytogenes and Enterobacteriaceae usually need longer treatment of 3-4 weeks. Nevertheless, data on treatment duration are scarce and experts' opinion based.

Patient isolation is advised in the initial 24 hours of treatment with chemoprophylaxis for close contacts in suspected or confirmed cases of meningococcal meningitis (refer Table 1). If there is no improvement in clinical status after 48 hours of treatment, brain imaging and a second lumbar puncture should be performed to assess for antibiotic resistance.

2.2.1. Corticosteroids

Corticosteroids, which include dexamethasone, are thought to be a supplementary treatment for bacterial infections, especially when they are acute, because they have been shown to improve patients' outcomes and reduce the risk of neurological complications [30]. In experimental models of meningitis caused by bacteria, corticosteroids are effective in reducing brain swelling, intracranial pressure, and inflammation of the meninges.

However, clinical trials have not been able to determine a conclusive result regarding the use of steroids in patients with meningitis. Available evidence indicates a decreased incidence of severe hearing loss in children with H. influenzae meningitis compared to those with other pediatric pathogens, but there is a lack of sufficient data on this subject. In a study on 301 adult patients using a double-blind randomized controlled trial, it was found that mortality rates were reduced, along with a decrease in occurrences of hearing loss and neurological complications [30, 31].

The subgroup analysis showed that dexamethasone was very successful in protecting against pneumococcal meningitis. As per experts and societal standards, it is advised to administer dexamethasone as a standard treatment for community-acquired meningitis in both children and adults. The suggested dosage for children is 15 mg/kg every 6 hours for 2-4 days, while adults should take 10 mg every 6 hours for 4 days. Nevertheless, the use of dexamethasone is terminated when it is established that the pathogen is either H. influenzae in children or S. pneumoniae in both adults and children. The remarkable thing is that the same pathogens are the reason for a decreasing number of infections in the children population due to the broad vaccination campaign. The first dose of steroids should be given at least 10-20 minutes before beginning antibiotics or it can be administered concurrently with antibiotic therapy. The late administration of dexamethasone is no good since the medicine neither can get rid of the existing brain swelling nor intracranial pressure at the later stage of meningitis. There are some worries about the possible neurotoxicity of dexamethasone treatment, but it seems to be clinically insignificant, and it may affect antibiotics penetration of CSF. Hence, the use of corticosteroids in regular practice is not feasible where there is a shortage of healthcare resources.

Other symptomatic therapy

Intense headache necessitates ample pain relief, typically involving opioids. Antiepileptic

medication should be used when there are seizures present; preventative treatment is not advised.

2.2.2. Antibiotic Therapy

Table 1: Various medications that are used to treat bacterial meningitis [32-49]

Bacteria That Cause Meningitis	Antibiotics	High Risk Age Groups	References
Streptococcus pneumoniae	Penicillin; Macrolides	Children less than 5 yrs; Adults greater than 50 yrs	32-33
Neisseria meningitidis	Ciprofloxacin; Ceftriaxone; Rifampicin; Penicillin	Children less than 5 years; Adolescents	34-35
Group B Streptococcus	Clindamycin; Erythromycin; Penicillin G; Ampicillin; Fluoroquinolones; Carbapenems; Vancomycin; Cephalosporins (First, Second, Third generations)	Less than 3 months	37-41
Streptococcus suis	Ampicillin; Penicillin G; Ceftiofur; Amoxicillin; Fluoroquinolones; Gentamicin; Florfenicol	Adults	42-44
Escherichia coli K1	Ciprofloxacin; Gentamicin; Penicillin G; Meropenem; Amoxicillin; Ampicillin	Less than 3 months	45-49

Bacterial meningitis treatment options are organized in the table below, with antibiotics listed according to the most prevalent age groups affected and the bacterium that causes the sickness. Penicillin is the treatment of choice for Streptococcus pneumoniae infections in children under five, while macrolides are preferred for adults over fifty years old people [32-33]. For Neisseria meningitidis infections in adolescents and children less than five years old, a combination of Rifampicin, Ciprofloxacin, Ceftriaxone, and Penicillin is necessary [34-36]. For Group B Streptococcus infections in babies less than three months, it is recommended to use a broad spectrum of antibiotics, including Penicillin G, Clindamycin, and Vancomycin [37-41]. Medications such as fluoroquinolones, Penicillin G, Ceftiofur, Amoxicillin, Gentamicin, and Florfenicol are used to treat infections caused by Streptococcus suis in adults [42-46]. When Escherichia coli K1 infections develop in babies less than three months of age, a combination of Gentamicin, Ceftriaxone, Penicillin G, Ampicillin, Amoxicillin, and Meropenem is recommended [45-49]. To help doctors make informed judgments regarding antibiotic selection, the references provided stress the significance of creating personalized treatment regimens that consider each patient's unique features and the specific bacteria that caused their infection.

2.3. Additional Interventions

2.3.1. Vaccination Strategies

Immunization serves as a protective mechanism for induction of the immune system against meningitis-causing organisms that are commonly found. Vaccinating those who are more vulnerable, it not only defends them from the disease but also stops it from spreading within communities and thereby benefits society at large. In this context of the persisting danger of bacterial meningitis, vaccination is an important measure in preventive healthcare. Vaccines

that cover all age groups from adults to adolescents and even children are very effective in preventing meningococcal disease. Certain at-risk groups namely travelers, students of colleges and military recruits are recommended to have polysaccharide vaccinations [50]. It is worth mentioning that no one vaccine provides immunity against the different reasons for the emergence of meningitis. Vaccines specially designed for individuals with increased risk are available. These include both bacterial and viral infections, the primary agents of the disease. There are also more than one vaccine that can protect against bacterial meningitis and septicemia of the common life-threatening type which are caused by meningococcal, pneumococcal, and Hib bacteria.

The available vaccines which offer protection against meningococcal bacteria are:

- MenACWY is for the age range between 13-15 (teenage)
- MenB vaccine is for babies between the ages of 8 to 16 weeks, with a booster given at one year (babies) This marked the first time it was included in the UK's routine vaccination schedule in 2015.
- MenC Children aged 12-13 months receive the vaccine as a combined MenC/Hib vaccine, with a booster administered to teenagers at 14 years old, using the MenC-containing vaccine Men ACWY. The UK became the global leader in this initiative when the MenC vaccine was added to the routine immunization schedule in 1999.

A vaccine intended to prevent infections caused by Haemophilus influenzae bacteria is available. The Hib vaccine was a landmark achievement, being the first conjugate vaccine with a proven record of preventing bacterial meningitis in infants. Infants are given 3 doses of Hib-containing vaccine at the age of 8, 12 and 16 weeks, with a MenC/Hib booster given at the age of 12 months to sustain the protection. The addition of that booster was aimed at addressing the phenomenon of waning immunity in the first year of life, which research found to be the reason for the resurgence of cases. Moreover, the pneumococcal bacteria have more than 90 strains, and two vaccines offer protection from the most widespread causes of severe diseases. PCV13 is given to infants at 12 weeks of age, and there is a booster given at the age of one. Since 2004, PPV23 is available for people aged 65 and above as well as for high-risk groups of 2 years and higher.

2.3.2. Nanoparticle Applications

Novel techniques, like nanoparticle technology, have demonstrated potential in the fields of diagnosis and treatment. By providing targeted medication delivery to the central nervous system (CNS), nanoparticles offer a viable treatment option for bacterial meningitis [51, 52].

2.4. Potential diagram

The potential diagram highlights the need for a comprehensive strategy that incorporates immunomodulatory targets, biomarkers, conventional therapeutics, and novel interventions to effectively manage bacterial meningitis [53]. The integration of these discoveries into medical practices could upgrade the accuracy of prognostic evaluation, general patient outcomes, and diagnosis.

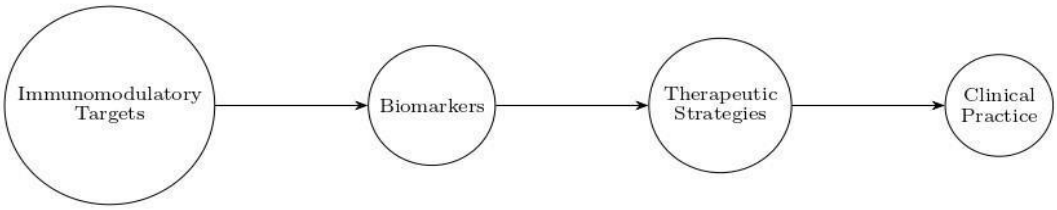

Figure 4: Potential diagram

Figure 4 gives a visual portrayal of the coordinated way to deal with treating bacterial meningitis by featuring the associations between significant components in the therapeutic landscape. Significant elements like immunomodulatory targets, biomarkers, therapeutic strategies, and clinical practice are addressed by the nodes of diagram. The dependencies and dynamic relationships between these parts are addressed by the directional arrows between these nodes. The diagram means a specific stream by which Immunomodulatory Targets influence Biomarkers, which subsequently direct therapeutic Strategies. Eventually, clinical practice is where these techniques' effects are observed. The figure emphasizes a helpful visual guide for grasping the complete structure of therapeutic interventions and their suggestions for clinical results by featuring the complex and interconnected nature of the components engaged in the battle against bacterial meningitis.

3. ROLE OF BIOACTIVE COMPONENTS

One promising direction for alternative therapeutic interventions for bacterial meningitis is the examination of bioactive elements obtained from botanical sources [55-59]. This section investigates the different phytochemical and pharmacological substances, including specific bioactive mixtures and essential oils, with an accentuation on their antibacterial efficacy. These bioactive compounds like flavonoids, polyphenols, tannins and saponins which are present in these spices can prevent the occurrence of different types of neurological disorders.

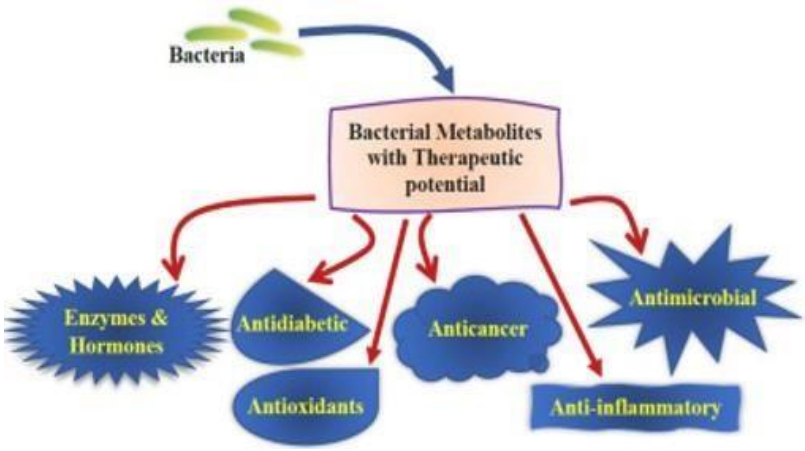

Figure 5: Interactions among various bioactive components involved in bacterial meningitis therapeutics.

The web of bioactive elements essential for bacterial meningitis medicines is displayed in Figure 5. The classification of Bioactive Parts, which incorporates essential oils from medical plants, is key to the idea. These oils have rich stores of bioactive mixtures. The antibacterial characteristics of specific bioactive substances, like lectins, alkaloids, terpenoids, and flavonoids, are assessed carefully. Extra examination centers around bioactive compounds, including ginsenosides, hyperforin, olive leaf remove, reishi mushrooms, allicin, and chlorophyll, which distinctively affect meningitis and related illnesses. The figure portrays how the overall classification utilizes explicit bioactive mixtures and essential oils, and it additionally shows how cutting-edge utilizes like silver nanoparticles are consolidated.

The connections are addressed by the directional arrows, which show that specific bioactive compounds are ingredients in essential oils and that silver nanoparticles are utilized in cutting edge applications to give an unmistakable image of the functions and interactions of these bioactive elements in meningitis medicines.

3.1 Specific Bioactive Compounds and their Sources

Essential oils are complex reservoirs of bioactive compounds that have been extensively studied. They are primarily derived from medicinal plants. These substances, which are well-known for their concentration-dependent antibacterial qualities, are carefully examined. As painstakingly detailed in Table 2, important bioactive substances like flavonoids, alkaloids, terpenoids, and lectins are carefully investigated for their effectiveness against a variety of bacterial strains. Notable examples include flavonoids from citrus fruits, green tea, apples, and Terminalia bellirica fruits; all of these have strong antibacterial properties against microbes [66].

Table 2: Various bioactive substances, their origins, and the microbes they aim to kill [60-69]

Bioactive Compounds	Targeted Microorganisms	Source	References
Flavonoids	E. coli, V. harveyi	Citrus plants	60-61
	C. albicans	Terminalia bellirica fruits	62
	P. gingivalis	Green tea	63
	E. coli	Apple	64
Alkaloids	P. aeruginosa, E. coli,S. aureus,	Terminalia chebula	65
	tumefaciens, B. subtilis		
Terpenoids and Essential Oils	S.aureus, L.monocytogenes	Nigella sativa	66
	P. vulgaris, E. coli, P. aeruginosa, S.epidermidis, B. subtilis, B. cereus	Cotton seeds	67
Lectins	P. aeruginosa	Solieriafiliformis	68
	Streptococcus spp	B. triquetrum	68
α-pinene, and γ-limonen e terpinene.	E. coli, S. Typhi, and C. koseri.	Tea tree	69

Table 2 displays a variety of bioactive chemicals together with their origins and the bacteria that they target. Fruits of the Terminalia bellirica plant, apples, green tea, and citrus trees are all sources of flavonoids. E. coli, Candida albicans, Vibrio harveyi, and Porphyromonasgingivalis are only a few of the microbes that they effectively combat. The alkaloids found in Terminalia chebula are antimicrobial and can kill Klebsiella, Escherichia coli, Staphylococcus aureus, and Acinetobacter tumefaens. The antimicrobial properties of terpenoids and essential oils derived from cotton seeds and nigella sativa are effective against a variety of bacteria, including E. coli, Pseudomonas, S. epidermidis, B. subtilis, P. vulgaris, L. monocytogenes, S. aureus, and B. cereus. Lectins from Bacillus triquetrum and Solieriafiliformis both possess antibacterial characteristics that may be used against Streptococcus species and P. aeruginosa. Moreover, research has shown that certain tea tree components including γterpinene, limonene, and α-pinene are efficient against E. coli, Typhi, and koseri. The cited sources provide a wealth of information on these bioactive components and their function in bacterial infections.

3.3 Advanced Applications of Bioactive Components

Research has shown that allicin, the primary component in garlic, is effective in treating various conditions, such as meningitis. Allicin and other components of garlic are powerful antioxidants and antivirus agents. They possess medicinal qualities as well. Reishi mushrooms have triterpenes and polysaccharides that enhance the immune system and lower inflammation, reducing related diseases [17, 70]. As stated by Organic Facts, chlorophyll, that is the pigment responsible for the photosynthesis of plants, has a structural similarity with hemoprotein, which in turn promotes red blood cell production, natural detoxification, and healing of the body from infection. The olive leaf extracts from olive leaves act as a natural treatment for infectious diseases and are available in dried, liquid, or capsule form. The ability of hyperforin to cross both the BBB & BTB, suggests its promise as a novel pharmaceutical remedy for combating infectious illnesses [18]. Ginsenosides, the active compounds of ginseng, are thought to straightaway hit the infection sites and eliminate it, which in turn shortens the recovery process. The ginseng root can be consumed as is or brewed as a tea to access the healing properties from centuries past [21].

Urticadiocia is a medicinal herb with a long history of use that is widely known as stinging nettle. The Urticaceae family to which this herbaceous perennial flowering plant belongs has both antibacterial and antifungal properties, as well as antiviral and antioxidant activities. Further, this static solution uses crude extracts of stinging nettle leaves to inhibit inflammatory mechanisms and control hyperglycemia. The silver nanoparticles (AgNPs) prepared from Urtica dioica were efficiently used to improve liver damage in cirrhotic rats. The nano-Ag produced from Urtica urens exhibits nematicide activity against Meloidogyne as a root-knot nematode. Several factors influence the antioxidant and antibacterial qualities of AgNP aqueous and methanol extracts, with the concentration of AgNO3 being the most significant. The synergy between AgNPs and antibiotics has been demonstrated to be effective at eradicating bacterial infections, which implies their application in the treatment of bacterial infections. Regards to the therapeutic importance of the AgNPs from Urtica dioica L. and Urtica urens, it cannot be overlooked. The joint application of AgNPs and antibiotics can generate a multiplicative effect to fight infectious diseases [72– 74]. The therapeutic potential of UD-AgNP aqueous and methanol extracts is indicated by their antioxidant and antibacterial

properties. This makes it possible to define the basic parameters for AgNO3 concentration [74– 76].

4. CONCLUSION AND FUTURE PROSPECTIVE

Despite significant advancements in diagnosing and treating bacterial meningitis, the disease remains prevalent and dangerous worldwide. Reducing mortality and morbidity rates requires prompt treatment initiation and efficient disease preventive measures. Many factors impact a patient's prognosis, including their age, number of comorbidities, the severity of their underlying illness, and the microorganism they have. Locating pertinent clinical outcomes from various vaccination and antibiotic research has been the center of attention. Bioactive compounds including tannins, flavonoids, polyphenols, and saponins have emerged as powerful weapons in the battle against bacterial meningitis and other neurological diseases, complementing more conventional medical treatments.

The impact of plant-derived components on several pathways associated with bacterial meningitis should be the subject of future investigation.

Novel, more focused therapies using a range of bioactive compounds derived from different plants should be the focus of future studies.

Researching their potential synergistic effects is crucial, especially since silver nanoparticles are already known to possess antioxidant, antiviral, antifungal, and antibacterial properties. An improved strategy for fighting emerging bacterial diseases, such as bacterial meningitis, may include combining these nanoparticles with extracts from plants. Therapeutic therapies and global efforts to combat infectious illnesses stand to benefit greatly from this approach.

Author’s Contributions

The authors of the paper on bacterial meningitis have made significant contributions to the research and writing of the document. 1Ayushi Chaudhary and 2Kanchan Lata Tripathi contributed to the overall research and writing of the paper. 3Nitika Verma focused on the mechanisms of bacterial meningitis, while 4Himani Badoni served as the corresponding author and contributed to the overall research and writing. 5Devendra kumar has contributed to the research and writing related to the diagnosis and treatment of bacterial meningitis. 6Nishesh Sharma also contributed to the overall research and writing of the paper.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Abbreviations

1. AgNP - Silver Nanoparticles
2. BBB - Blood-Brain Barrier
3. BM - Bacterial meningitis
4. BTB - Blood-Testis Barriers
5. C4bp - C4 binding protein

6. CNS - Central Nervous System
7. CSF - Cerebrospinal fluid
8. CSF NfL - Cerebrospinal fluid -Neurofilament Light Chain
9. CSF NLR - Cerebrospinal fluid- Neutrophil-to-lymphocyte Ratio
10. fH - Factor H
11. fHbp - fH-Binding Protein
12. HBP - Heparin Binding Protein
13. IPD - Invasive Pneumococcal Disease
14. MAC - Membrane Attack Complex
15. MIF - Migration Inhibitory Factor
16. NspA - Neisserial Surface Protein A
17. OmpA - Outer Membrane Protein A
18. PRRs - Pattern Recognition Receptors
19. UD-AgNP - Urtica diociaSilver Nanoparticles

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