Current Clinical Microbiology Reports (2023) 10:85–98
https://doi.org/10.1007/s40588-023-00194-6

Therapeutic Strategies to Ameliorate Antibiotic Resistance and Host-Inflammation Response in Sepsis: an Innovative Approach

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Accepted: 24 April 2023 / Published online: 12 May 2023

Abstract

Purpose of Review Sepsis is a clinical condition with a dysregulated immune system majorly attributed to bacteremia. The contrivances underlying this disorder are essential to understand for an early and precise diagnosis. To tackle the burden of challenges like antibiotic resistance and complications of other co-existing metabolic disorders like cancer and diabetes which contribute to an ever-increasing sepsis-related mortality, innovative strategies need to be explored.

Recent Findings An accurate diagnosis, empirical antibiotic use, and supportive therapy are required for sepsis, preceding which the initial identification of the survival mechanism adopted by the causal pathogen also becomes crucial for strategizing the treatment. In-depth assessments of quinquennial studies available in literature put forth a panel of secreted host-inflammatory cytokines and immune markers that are a prerequisite, to be assessed and then targeted to regulate the host-response mechanism adopted during sepsis. New therapeutic strategies, like drug repurposing for sepsis, immunotherapy, and phytotherapy, can aid in a better management of sepsis; hence, they need to be explored in preclinical and clinical trials. A detailed analysis of lab-based studies on tacking antibiotic-resistant bacteria indicates that phytomolecules can serve as a powerful tool to ameliorate antibiotic resistance and resolve cellular inflammation.

Summary This review has led us to propose combination therapy as a novel, effective approach whereby potential phytomolecules can be clubbed with available antibiotic arsenal for use as an adjunct in sepsis treatment, for better clinical outcomes.

Keywords Antibiotic resistance · Combination therapy · Drug repurposing · Inflammation · Phytomolecules · Sepsis

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection, and it has become a global health concern due to a high incidence and associated mortality. A meta-analysis by Fleischmann et al. [1] on 27 global studies and a review by Schlapbach and group [2] concluded that approximately 30 million cases of hospital-treated sepsis in high-income countries are recorded every year with 5.3 million deaths. A comprehensive analysis published by Rudd et al. [3] revealed that there was an increase in the incidence and mortality of patients with sepsis in low- or middle-income countries (LMICs) too, which indicated that the economic status and availability of healthcare facilities are not directly linked to the incidence or mortality of this condition.

Sepsis is considered infectious when caused by bacterial, fungal, or viral species or it can be trauma-induced and therefore categorized as noninfectious. Pathogenic bacteria have been documented as the leading cause of bloodstream infections [4], and bacterial sepsis or bacteremia is one of the major causes of morbidity and mortality, worldwide [5]. Increasing fatality from bacterial sepsis is attributed to the constant development of antibiotic resistance among sepsis-causing bacteria. The most common bacteremia-causing species are a group of gram-positive and gram-negative bacteria, better known by the acronym ESKAPE [6]. In the face of increasing resistance and the emergence of multidrug resistant (MDR) bacteria, new strategies to combat sepsis need to be explored to avoid a clinical crisis.

This review aims to present a compendious overview of the mechanistics of the host–pathogen interactions during sepsis to better analyze the challenges in the diagnosis

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and treatment of sepsis. It also explores the problem arising due to antibiotic resistance, the approaches adopted by the pathogens to block antibiotic attack, and the haze created by certain comorbid conditions of sepsis. Finally, there is a focus on treatment strategies that can aid in better management of sepsis, especially on the emerging green approach, which involves the use of dietary active compounds from natural sources as an adjuvant with antibiotics to enhance their efficacy (Fig. 1), that can improve the clinical outcomes and lower the death figures.

Utility of a Panel of Markers of Host–Pathogen Interaction for Diagnosis

The blood cell counts used to establish the diagnosis of sepsis can often be misleading as their deranged values are not sepsis specific. Therefore, understanding the molecular cascade behind the host–pathogen interaction can lead to a highly specific diagnosis and help design patient-specific treatment.

Investigation of sepsis-induced immune alterations is highly desirable, wherein these deviations are diagnosed with the help of established clinical biomarkers like procalcitonin (PCT), C-reactive protein (CRP), and interleukin-6 (IL-6) that are indicative of underlying infection and inflammation. These biomarkers are in clinical use. However, due to the complexity of multiple physiological pathways involved in sepsis, no single marker is considered reliable in totality.

At the onset of bacterial infection, the activation of the intracellular signal transduction cascade in the host causes the release of proinflammatory cytokines like TNF-α, IL-1, and IL-6 [7]. A study conducted by Feng et al. [8] on serum interleukin levels in sepsis patients concludes that between interleukins IL-6 and IL-18, the levels of IL-6 in serum were high in sepsis patients. This proinflammatory cytokine, in turn, regulates various pathways, for example; activation of the complement system, proliferation of leukocytes, and upregulation of chemokine expression. This host response against any pathogen is amplified in the case of sepsis, resulting in collateral damage and death of host cells and tissues (Fig. 2A). The initial proinflammatory state of sepsis is superseded by a prolonged state of immunosuppression that leads to a drop in the number of CD4 + helper and CD8 + cytotoxic T cells due to apoptosis, and there is a decreased response to inflammatory cytokine secretion as evidenced by the postmortem studies of ICU patients who died of sepsis [9]. In addition to the state

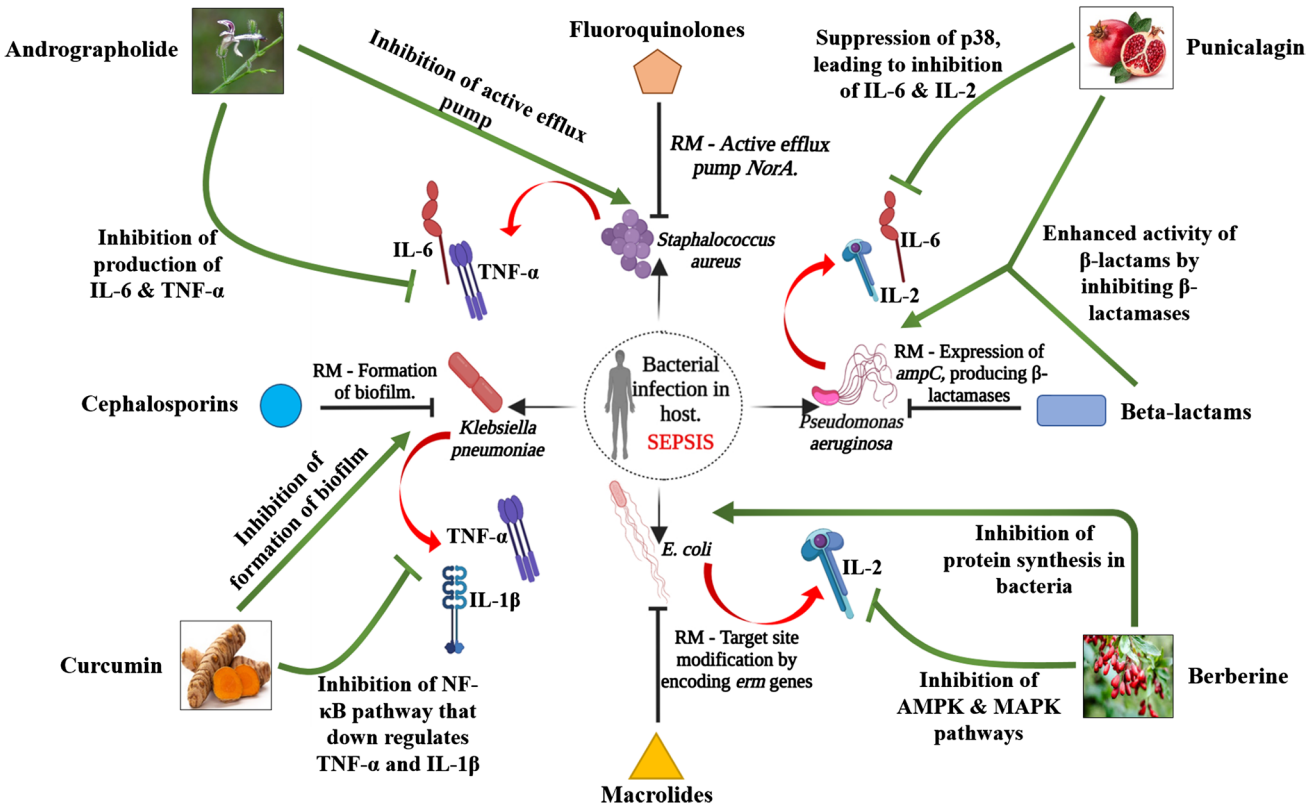

Fig. 1 A detailed illustration of the resistance mechanisms (RM) of sepsis-causing bacteria against specific classes of antibiotic and the mechanisms targeted by the phytomolecules in multi-drug resistant (MDR) bacteria

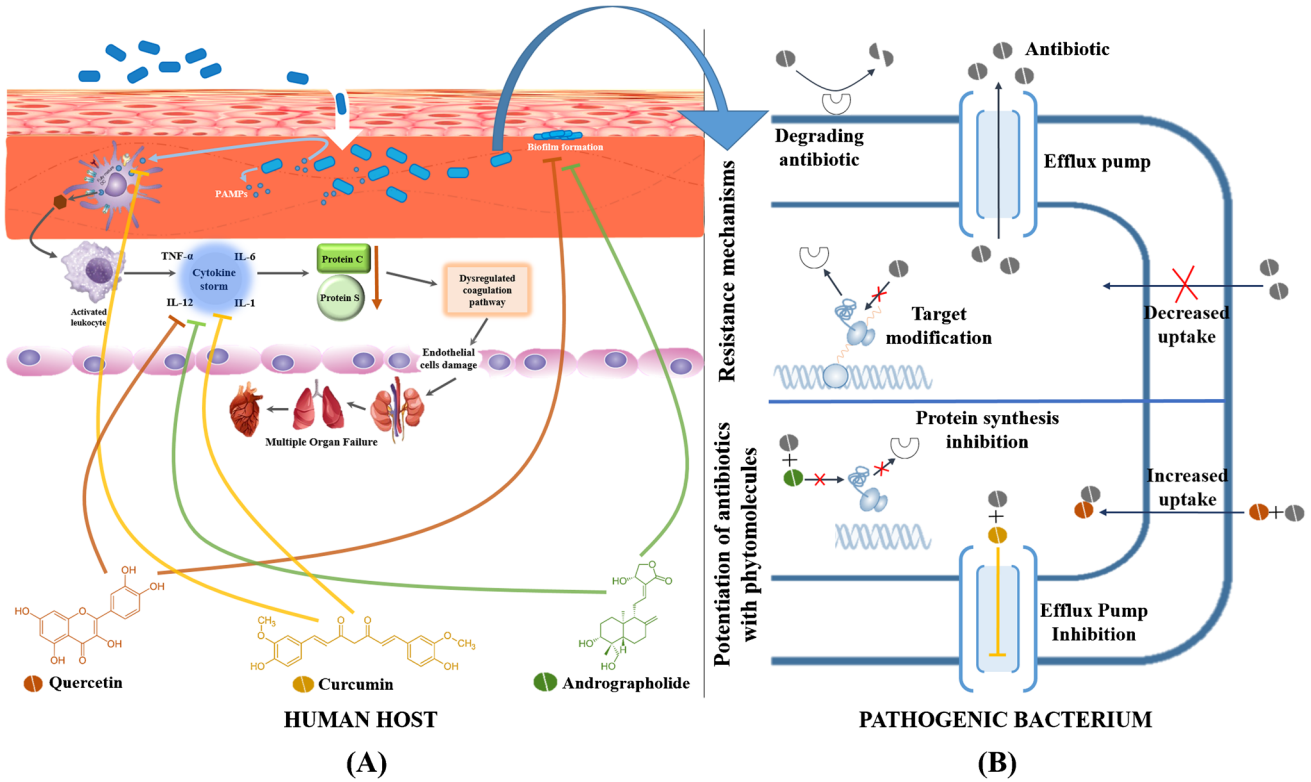

Fig. 2 **A** The mechanism of bacterial sepsis initiated by deregulation of the host immune system, leading to multiple organ dysfunctions in the host and the process by which pleiotropic molecules like quercetin, curcumin, and andrographolide can help in regulating the sepsis pathogenesis. **B** The different mechanisms of resistance to antibiotics adopted by bacteria and how the action of antibiotics can be potentiated with the chosen phytomolecules

of immunosuppression, persistent inflammation sustained by the release of damage-associated molecular patterns (DAMPs) can present in sepsis patients [10]. Therefore, a more sensitive panel of proinflammatory markers TNF-α, IL-1, IL-6, serum lactate, and presepsin, along with CD4/CD8 counts, needs to be monitored for the status of systemic chronic inflammation and immunosuppression, to design an effective support therapy in sepsis patients.

In addition to the host–pathogen response, the challenge of antibiotic resistance needs to be understood and resolved for the effective treatment of sepsis. Therefore, next in the route to successful treatment is alleviating antibiotic resistance.

The Problem of Antibiotic Resistance in Sepsis

The management of sepsis requires a comprehensive and systemic approach that includes accurate and prompt diagnosis, empirical antibiotic use, and supportive therapy. The appropriate and timely administration of antibiotics plays a crucial role in the achievement of a favorable outcome for patients with sepsis by avoiding septic shock. However, the abuse and misuse of antibiotics have led to the problem of antibiotic resistance in causal organisms (Table 1), which is more pronounced in the case of sepsis. The lack of effective therapy due to the rising phenomenon of antibiotic resistance among the causative pathogens [20] is leading to the emergence of numerous sepsis-causing antibiotic-resistant bacteria that present a most serious challenge in medicine for future years if new antimicrobials are not discovered [21]. To overcome the generation of more antibiotic-resistant bacterial species, the mechanism adopted by sepsis-causing bacteria needs to be defined for each patient.

Mechanisms Adopted by Bacteria to Survive Host Immune Surveillance

The increasing rate of antibiotic resistance in sepsis-causing bacteria is leading to a decrease in the efficacy of the current arsenal of antibiotics. Two approaches are adopted by bacteria to survive in the host. The first approach is developing self-defense mechanisms against the host response. Bacteria can enter the bloodstream through various sites, but the

Table 1 List of antibiotics generally used for treatment of sepsis and their resistance pattern to sepsis-causing bacteria

Sr. no	Antibiotics	Class of antibiotic	Resistant against organism	References
1	Azithromycin	Macrolide	*S. aureus*	[11]
2	Ceftriaxone	β-Lactam	MRSA, *Streptococci*, *Enterococcus* spp., *Clostridium* spp.	[12]
3	Ceftazidime	β-Lactam	*Pseudomonas* spp.	[13]
4	Cefotaxime	β-Lactam	*Pseudomonas* spp., *E. coli*, *Enterobacter* spp.	[14]
5	Ciprofloxacin	Fluoroquinolone	*K. pneumoniae*	[15]
6	Clindamycin	Lincomycin	MRSA	[16]
7	Meropenem	β-Lactam	*Enterobacter* spp., *K. pneumoniae*	[17]
8	Levofloxacin	Quinolone	*E. coli*	[18]
9	Vancomycin	Glycopeptide	*Enterococcus* spp.	[19]

majority of bacterial species are sensitive to oxidation by the reactive oxygen species (ROS) released from the surface of the host erythrocytes and therefore get killed instantly. This is the initial host response to eradicate the pathogens on entry. However, the sepsis-causing bacteria have evolved multiple evasion systems that facilitate their survival in the bloodstream. One mechanism that is common to all sepsis-causing bacteria is the secretion of hemolysin (α-hemolysin, β-hemolysin, or γ-hemolysin) while they are latched onto the erythrocytes, leading to cell lysis via the formation of pores in the phospholipid bilayer [22]. This aids in the survival and further proliferation of bacteria using host hemoglobin as a source of nutrition and the formation of a bacterial pool that can then spread through the bloodstream.

Another survival strategy of sepsis-causing bacteria is to evolve themselves to escape the host immune system and survive and replicate inside the host cells. Many of the sepsis-causing bacteria adapt to the intracellular existence for protection and survival by adhering on to the immune cells like macrophages and nonimmune cells like epithelial cells and osteocytes cells [23]. The sepsis-causing bacteria form biofilms on the epithelial tissue surface surrounding the site of the wound in the skin created due to injury or the insertion of medical devices (Fig. 2A). The bacteria that enter the bloodstream and are not caught by the innate immune cells then adhere to the lining of the blood vessel and form clusters of bacteria, embedded in a self-created matrix made up of protein, lipid, nucleic acid, and/or polysaccharide. This matrix provides a protective layer that helps in the growth of pathogenic bacteria and also aids in resisting the action of treatment modalities like antibiotics [24]. After growth within the colony and maturation, the bacteria start spreading in the surrounding tissues, and this dispersal catches the attention of macrophages and NK cells which then initiates an enhanced immune response in the host [25]. Biofilms are mostly reported to form on indwelling medical devices and are generally contaminated with sepsis-causing ESKAPE organisms. They are most often composed of a single bacterial species; however, many biofilms associated with sepsis are composed of multiple bacterial species making treatment more difficult [26].

A similar protective layer is also formed by the commensal bacteria present on the mucosal surfaces of the host to prevent themselves from the host sentinels due to which they are able to replicate and exist without detection. Such bacteria can opportunistically become rogue and travel to the breached endothelial lining caused by dysregulated coagulation pathway during sepsis [27]. There are studies to document the adaptation of certain sepsis-causing bacteria by internalizing in host cells. Wright et al. [28] studied the intracellular association ability of uropathogenic *E. coli* invading bladder epithelial cells causing UTI. Similarly, Edwards et al. [29] reported a sepsis model in which *S. aureus* could invade endothelial cells and later on cause infection by entering the blood stream. Horsley et al. [30] experimentally showed that *E. faecalis* could internalize in the urothelium of patients and cause urinary tract infections. Another study on *S. pyrogens* invading macrophages to escape immune clearance and degrading epithelial intercellular junctions has also been presented [31].

The second approach undertaken by pathogens is to resist the antibiotic action via three different mechanisms (Fig. 2B): (1) modification or degradation of antibiotic molecules and the presence of resistant genes in the genetic material of the causal microbe; (2) use of efflux pump(s) in the bacterial cell wall; (3) modification of the bacterial target site where the antibiotic molecule was supposed to act [32]. Taking cognizance of these survival mechanisms propounds that the immunocompromised state of the host suffering from sepsis needs to be diagnosed timely and accurately along with the contrivances adopted by sepsis-causing bacteria so that the antibiotic treatment or supportive therapy is strategized accordingly.

Exploratory Therapies for Effective Treatment of Sepsis

Antibiotic combinations exhibiting synergistic action in preclinical studies and trials are already out for clinical use. An exploration study conducted by Abdul-Jabar and group [33] on the combinations of piperacillin with tazobactam, ceftazidime, and/or amikacin showed effective results against sepsis-causing MDR *Klebsiella pneumonia* and *E. coli* strains. Although there are clinical trials that have assessed the effect of antibiotic combination therapy in sepsis [34–36], and some are already in clinical use for the treatment, bacteria have already started to develop resistance against them too (Table 2). Therefore, nonantibiotic drugs present a greater potential for being used against resistant pathogenic bacteria. The strategies that can be adopted for achieving this endpoint are discussed herein.

Drug Repurposing

Drug repurposing is a process of identifying new therapeutic use(s) for existing and available drugs. It can create a novel effective regimen out of the ineffective drugs, thus reducing the time taken in the discovery, preclinical studies, and clinical trials of a new drug [42]. In a study by Miró-Canturri et al. [43], tamoxifen, an anticancerous, selective estrogen receptor modulator drug, was shown to inhibit the growth of gram-negative MDR bacteria, making it a candidate for drug repurposing. Another promising candidate that emerged in a study was gallium nitrate, a non-redox iron (III) analog used for treating hypercalcemia in malignancy, which exhibited broad antimicrobial activity against the ESKAPE bacteria *P. aeruginosa* and *A. baumannii* [44]. Hegazy and group [45] conducted a screening of antidiabetic drugs metformin, sitagliptin, and vildagliptin as antibacterial agents against MDR *Pseudomonas aeruginosa* and found that they inhibited bacterial pathogenesis in vitro.

Immunotherapy

In addition to antibiotics, immune-stimulation therapies to restore and reorganize the immune system of the host can be another strategy that may serve as a powerful tool in developing future treatments for sepsis. Immuno-modulators like thymosin α1 are being investigated to reduce long-term sepsis-related mortality [46]. Another immune-modulator, interleukin-7 (IL-7) essential for lymphocyte survival, can induce the proliferation of CD4 + and CD8 + T cells. A randomized, double-blind, placebo-controlled study conducted by Francois and group on the immunomodulation by IL-7 in patients with septic shock and severe lymphopenia found that IL-7 reversed the distinct loss of CD4 + and CD8 + immune cells, and it also increased the T cell activation that in turn was beneficial for host immunity [47] Similarly, IL-6 inhibitors and anti-IL-6 receptor antagonists that are clinically used in various diseases to control inflammation [48] should be evaluated for their effect in sepsis and septic shock [49]. Although there are effective adjuvants that can serve as immune modulators to manage the dysregulated immune system, most of them are still under different phases of clinical trials with no sufficient evidence of use in sepsis. Therefore, more studies and trials are needed for immunotherapies to be established as a treatment for sepsis.

Phytotherapy

Apart from the chemical modalities, the therapeutic properties of several natural phytomolecules have been traditionally used for treating infections. Most of these are dietary ingredients and have been used in Chinese traditional medicine, Ayurveda, and alternative herbal treatment regimens for therapeutic purposes since ancient times [50]. Phytomolecules like alkaloids, flavonoids, and polyphenols that exhibit anti-inflammatory, antioxidant, and antibacterial

Table 2 Resistance mechanisms adopted by sepsis-causing bacteria against clinically used antibiotic combinations

Sr. no	Antibiotic–antibiotic combination	Resistance against organism	Resistance mechanism adopted	Geographical region	References
1	Ampicillin + sulbactam	*E. coli*	Hyperproduction of TEM-1	Pittsburgh, PA, USA	[37]
2	Amoxicillin + clavulanic acid	*Enterobacter* spp., *E. coli*	Hyperproduction of OXA-1 β-lactamase, and penicillinases	Barcelona, Spain	[38]
3	Cefoperazone + sulbactam	*K. pneumoniae*	Gene amplification of bla_{OXA-23} gene	Shanghai, China	[39]
4	Piperacillin + tazobactam	*E. coli*, *K. pneumoniae*	Gene amplification of bla_{TEM-1B} gene	Liverpool, UK	[40]
5	Trimethoprim + sulfamethoxazole	*E. coli*	Development of permeability barriers	Manila, Philippines	[41]

properties can be explored for use in the treatment regimen of sepsis patients as complementary therapeutic agents [51].

Phytomolecules as Potentiators of Antibiotics

Individually, phytomolecules like berberine, rutin, sanguinarine, piperine, and punicalagin have been reported to have strong antibacterial activity [52]. Their combination with the current antimicrobials that have become ineffective toward certain sepsis-causing bacteria can be an effective strategy to tackle bacterial defense mechanisms and thereby augment antibiotic action (Table 3). The activity of some important bioactive groups such as alkaloids, polyphenols, terpenoids, and tannins is discussed below.

Alkaloids

Alkaloids are a class of nitrogen-containing compounds found mainly in plants and also in animals. The well-known alkaloids used in clinical settings are morphine, quinine, ephedrine, etc. They are known for their anesthetic, cardioprotective, anti-inflammatory, and antibacterial properties [75]. The synergistic potential of some known alkaloids is shown in Table 3, 3. A. Berberine, a common alkaloid, has been reported to exhibit antibacterial activity by inhibiting the DNA and protein synthesis in *Streptococcus* spp. [76]. The alkaloid sanguinarine was checked for its synergistic potential with kanamycin, an aminoglycoside antibiotic, and it was found that this combination was able to inhibit the growth of antibiotic-resistant *E. coli* strain due to increased uptake of the alkaloid followed by an increased ROS production that eventually damaged the cell wall of the bacteria [59]. Another alkaloid, piperine, also showed a synergistic effect against resistant *K. pneumonia* when combined with amikacin by inhibiting the biofilm formation [57].

Polyphenols

Polyphenols are secondary metabolites that are ubiquitously distributed in higher plants and protect the plants from pathogens and various abiotic and biotic conditions like salinity, temperature, drought, and stress. The polyphenols are divided into two major groups, namely, flavonoids and non-flavonoids. Flavonoids are a subclass of polyphenols and further comprise different subdivisions, namely flavones, flavonols, anthocyanidins, etc. The non-flavonoid group of polyphenols comprises of benzoic acid, cinnamic acid, etc. All polyphenols have been widely investigated for their antimicrobial property and have been reported to show activities like inhibiting biofilm formation, reduction of host tissue

Table 3 Various classes of bioactive phytomolecules and their synergistic antibacterial action with antibiotics

Section	Class of bioactives	Phytomolecule	Antibiotic combination	Mechanism of action	References
1.A	**Alkaloids**	Berberine	Linezolid	Efflux pump inhibitor	[53]
			Rifampicin	Damage cell wall and cell membrane	[54]
		Conessine	Levofloxacin	Efflux pump inhibitor	[55]
		Piperine	Rifampicin	Not reported	[56]
			Amikacin	Biofilm inhibition	[57]
		Sanguinarine	Streptomycin	Not reported	[58]
			Kanamycin	Increased ROS production	[59]
1.B	**Polyphenols**	Morin	Ampicillin	Inhibition of cell wall synthesis	[60]
			Imipenem	Cell wall damage	[61]
		Rutin	Gentamycin	Adhesion inhibitor	[62]
			Ceftriaxone	Inhibiting the entry in the cell wall	[63]
		Quercetin	Amoxicillin	Inhibition of β-lactamase activity	[64]
			Meropenem	Downregulation of gene expression	[65]
		Baicalein	Cefotaxime	Inhibition of gene expression	[66]
			Ceftazidime	Increase cell membrane permeability	[67]
1.C	**Terpenoids**	Andrographolide	Erythromycin	Not reported	[68]
			Imipenem	Not reported	[69]
		Thymol	Neomycin	Destabilizing the permeability of cell membrane	[70]
			Tetracycline	Inhibition of biofilm formation	[71]
		Carsonic acid	Gentamycin	Efflux pump inhibitor	[72]
1.D	**Tannins**	Punicalagin	Oxacillin	Suppression of the *mec* operon	[73]
		Epigallocatechin	Ciprofloxacin	Inhibition of biofilm formation	[74]

adhesion, and neutralizing bacterial toxins [77]. A literature search yielded studies on the synergistic potential of 4 different polyphenols in combination with various antibiotics in overcoming the defense mechanism of bacteria (Table 3, 3. B). The flavonoid quercetin was shown to exhibit antibacterial activity against some gram-positive and gram-negative bacteria by damaging the cell membrane and by inhibiting the biofilm formation [78]. Baicalein, when combined with cefotaxime and probed against antibiotic-resistant *K. pneumonia* strains, was observed to exhibit synergistic activity by inhibiting the expression of the CTX-M-1 gene of *K. pneumonia* [66].

Terpenoids

Terpenoids are the largest and structurally most diverse natural bioactive. These are derived from mevalonic acid, which is composed of isoprene structural units [79]. The essential oil citronellol is a natural monoterpenoid and is known for its antimicrobial properties. In a study by Lopez-Romero et al. [80], the antimicrobial efficacy of essential oils carveol and carvone was assessed on antibiotic-resistant *E. coli* and *S. aureus*. It was found that the essential oils formed a monolayer around the cell and modified the electrostatic potential and hydrophobicity of the bacterial cell wall, thereby destabilizing the membrane integrity, and resulting in the release of internal cellular components. Thymol was reported to show antibacterial activity by permeabilization of the cytoplasmic membrane of bacteria. Its synergistic effect was assessed by combining it with tetracycline, and it was found to be an effective combination against *S. aureus* [71]. Studies on the synergistic action of terpenoids with antibiotics are presented in Table 3, 3. C.

Tannins

Another important class of secondary metabolites are tannins. Tannins are classified into two groups on the basis of chemical structure and stability, hydrolysable tannins, and condensed tannins [81]. These compounds are useful in the external treatment of skin inflammation and injuries, and it is also reported that the intake of tannins may prevent the onset of chronic diseases [82]. Tannins are not majorly reported for their antibacterial activity; however, their potential to act in synergy with antibiotics has been reported (Table 2, 2.D.). Punicalagin, a tannin obtained from the pomegranate, exhibited great potential in combination with oxacillin when assessed against β-lactam methicillin-resistant *S. aureus*, and it was observed that this combination was able to reverse the resistance by suppressing the resistance genes [73].

The use of phytochemicals of plant origin in the clinical regimen along with the standard antibiotic therapy has already begun. Cai et al. [83] observed the synergistic effect of cefoperazone with Xuebijing injection, a Chinese herbal–based medicine, on severe sepsis patients and reported a significant difference in the effectiveness of the combined treatment. Similarly, septimeb (a herbal formulation of several plant extracts fortified with selenium and flavonoids) was used as an adjunct to the standard treatment in sepsis management, and it was found to decrease mortality rate due to sepsis [84]. Similar trials designed in bigger cohorts are the need of the hour. It is important to highlight here that the major advantage of using these phytomolecules in clinical regimens is that bacteria are unable to develop resistance as phytomolecules are effective against the multiple molecular determinants responsible for bestowing drug resistance to pathogens [85]. Hence, they can be classified as antibiotic resistance breakers (ARBs). They also enhance the bioavailability of the antibiotic molecule, thereby increasing the overall efficacy [86] which makes phytomolecules a better option as an adjunct for designing therapy against antibiotic-resistant bacteria.

Tackling Complications Arising due to Overlap of Other Immunosuppressive Conditions with Sepsis

Although the major hindrance of antibiotic resistance in sepsis may be dealt with the strategies discussed above, the challenges in sepsis are not limited only to the treatment. The proinflammatory and immuno-suppression phases in sepsis might occur simultaneously, and the intensity of immune response depends on multiple factors associated with both the host and the infection-causing pathogen. The most common immuno-suppressive conditions that can contribute to increasing the risk of developing sepsis are increasing age and metabolic disorders like cancer and diabetes [87].

Cancer

Cancer and sepsis as comorbidity have become a major public health concern in most parts of the world [88]. Sepsis is common in cancer patients as both the conditions are immunosuppressive and cancer causes neutropenia and monocytopenia that are reported to promote the development of sepsis [89]. The conventional cancer therapy regimens alter the phagocytic activity of neutrophils and monocytes by decreasing their count in the circulation [90]. Sepsis may or may not be caused due to cancer but the immunosenescence triggered in both conditions may contribute to this combination [91], which ensues mostly in patients undergoing onco-therapies [92]. A retrospective analysis by Subburaj et al. [93] on acute myeloid leukemia (AML) in children undergoing chemotherapy indicated that 19% of cases of

bloodstream infections were majorly caused by gram-negative bacteria and in this time there was a significant rise in multidrug resistant infections in India in the last 5 years. Another research done by Jacob et al. [94], on clinical profiles of adult patients with AML for 2 consecutive years, reported the death of 63 AML patients undergoing different phases of chemotherapy in a total of 80 of which 46% died due to sepsis. The mechanism involved here is that chemotherapeutics can rupture the gut-epithelial layer which can lead to mucositis and make it prone to ulceration and infection. The pathogenic bacteria colonizing the gut-endothelial cells start infecting the exposed areas and move into the circulation eventually leading to bloodstream infection and sepsis [95].

Diabetes

Diabetes is a complex clinical syndrome with associated chronic inflammation and immune suppression that affects an individual's overall immune homeostasis. Chronic hyperglycemia is a physiological state of increased production of reactive oxygen species that induce the secretion of proinflammatory cytokines like TNF-α, IL-6, and IL-1 [96], a mechanism similar to sepsis. There is clinical evidence that diabetes worsens the prognosis of infections and is linked to increased mortality when present as a comorbidity in sepsis [97]. Studies have shown that hyperglycemia in a patient increases susceptibility toward infection, which is related to impaired chemotaxis, phagocytic abilities, and low antimicrobial activities, and leads to disturbances in the adaptive immune response [98].

The comorbid conditions discussed herein contribute majorly to sepsis-related mortality; therefore, it is important to identify the mechanism of sepsis of the causal pathogen and monitor the inflammatory and immune status of the patient. Although there are targeted antibiotic regimens that are used for the treatment of sepsis, regulating the immune system using natural phytomolecules with anti-inflammatory and antioxidant properties, and attacking the bacterial safety mechanism have the potential to improve the overall morbidity and mortality due to sepsis [99].

Selecting Pluripotent Phytomolecules for Adjunct Therapy in Sepsis

In an exhaustive survey of 10 years of available literature [100], it was found that numerous phytomolecules are being investigated for their biological activities in vitro. The phytomolecules that are discussed in this review are reported for their noncytotoxicity in Ayurveda and are potential candidates with lab evidence to prove that they suppress the effects of diabetes and cancer on host's immune system as seen in in vitro and in vivo studies (Table 4). They also simultaneously act on lowering the risk of the development of sepsis.

Andrographolide

Andrographolide is a diterpenoid phytomolecule, from the *Andrographis paniculata* plant that is known for its broad range of therapeutic applications. Andrographolide is a strong antiviral, antithrombotic, anticancer, and anti-inflammatory agent [115]. Inflammation plays a major role in sepsis physiology; thus, the use of andrographolide can aid in downregulating inflammation by regulating the protein synthesis of bacteria. It can also inhibit the lipopolysaccharide-induced inflammation induced by sepsis-causing antibiotic-resistant bacteria via a decrease in the expression of proinflammatory cytokines like TNF-α and IL-6 at mRNA and protein levels through the nuclear factor kappa B (NF-kB) signaling pathway [101]. Andrographolide can inhibit biofilm formation by blocking the adhesion of sepsis-causing bacteria to the host tissue surface [116].

Berberine

Berberine is a natural alkaloid that has been isolated as the principal component of the popular medicinal plant *Berberis vulgaris*. The multifunctional nature of berberine as a therapeutic agent is an attribute of its diverse effects on enzymes, receptors, and cell signaling pathways. Its pharmacology has been extensively studied including its anti-inflammatory, anticancer, and antibacterial activity [117]. In a study by Xia et al. [54], the antidiabetic property of berberine was assessed on diabetic rats, and it was found that berberine was able to improve glucose metabolism and reduce fasting blood glucose levels. The anti-inflammatory property of berberine was studied in an animal model, and it was observed that in 2,4,6-trinitrobenzene sulfonic acid (TNBS)–induced colitis, berberine inhibited the levels of proinflammatory cytokines IFN-γ, IL-17, IL-6, IL-1β, and TNF-α [106]. Other than the above properties, berberine was shown to also exhibit antibacterial activity in a study by Peng et al. [76], wherein this alkaloid inhibited the growth of *Streptococcus agalactiae* by affecting the activity of its DNA topoisomerase enzyme, leading to the inhibition of DNA synthesis.

Curcumin

Curcumin is a dietary polyphenol, which is present in the rhizome of the *Curcuma longa* plant. The bioactive curcumin is known to possess several therapeutic properties like anti-inflammatory, anticancer, antibacterial, and antioxidant [118]. Curcumin can inhibit the expression of

Table 4 Biological activity of phytomolecules and their mechanism of action studied in preclinical models

Sr. no	Phytomolecules	Plant source	Biological activity	Mechanism of action	Study model	References
1	Andrographolide	*Andrographis paniculata*	Anti-inflammatory	Inhibition of lipopolysaccharide induced inflammation by decreasing the expression of proinflammatory cytokines at mRNA and protein level	In vitro cell line	[101]
			Anticancerous	Inhibition of proliferation and invasion via inhibiting NF-κB target gene expression	In vitro cells	[76]
2	Baicalein	*Scutellaria baicalensis*	Antidiabetic	Inhibition of gluconeogenesis by regulating AKT/IRS-1 pathway	In vitro cells	[102]
3	Curcumin	*Curcuma longa*	Strong anti-inflammatory	Inhibition of NF-κB pathway and P38 MAPK activation	In vivo cells	[103]
			Immunomodulatory	Promotes differentiation of naïve CD4 + T cells	In vivo mice model	[104]
4	Berberine	*Berberis vulgaris*	Anti-inflammatory	Inhibiting the activation of TLR4/NF-κB signaling pathway	In vivo mouse model	[105]
			Immunomodulatory	Inhibits the function and differentiation of Th-1 and Th-17 cells	In vivo mice model	[106]
			Anticancerous	Induction of apoptotic cell death via activation of caspases 3 and 8	In vitro cells	[107]
5	Carsonic acid	*Rosmarinus officinalis*	Anticancerous	Derangement of the endocytic pathway in breast cancer	In vitro cell line	[108]
7	Piperine	*Piper longum*	Anticancerous	Regression in breast cancer by angiogenesis inhibition and apoptosis induction	In vitro cell line	[109]
8	Punicalagin	*Punica granatum*	Anti-cancerous	Stimulation of apoptosis via activation of caspases 3 and 9	In vitro cells	[110]
			Anti-inflammatory	Inhibition of neuro-inflammatory by NF-κB pathway	In vivo rat model	[111]
			Antidiabetic	Insulin stimulation	In vivo mice model	[112]
9	Quercetin	*Amaranthus tricolor*	Anti-inflammatory	Decreases transcriptional activity of NF-κB	Case–control study	[113]
			Anti-diabetic	Promotes insulin secretion, increases glucose uptake	In vivo rat model	[114]

proinflammatory cytokines like TNF-α, IL-6, and IL-12 secreted from innate immune cells like dendritic cells or macrophages after the entrapment of bacteria, and thereby lower the inflammation induced by these secretions [119]. In a study performed by Sundaramoorthy et al. [120], curcumin acted as an efflux pump inhibitor against colistin-resistant *E. coli*. In another study conducted on the mechanisms of antibacterial activity of curcumin, it was found that irrespective of significantly different cell walls of *S. aureus* and *E. coli*, curcumin was able to damage both types of cell walls and promote increased uptake of propidium iodide (intercalates in DNA) inside the cells, leading to the death of the bacteria [121]. These observations indicate that curcumin is a potential phytomolecule for overcoming antibiotic resistance against sepsis-causing bacteria.

Punicalagin

Punicalagin is a hydrolyzable ellagitannin found in alpha and beta forms in the *Punica granatum* plant. This natural bioactive is reported to exhibit multiple therapeutic properties including anti-inflammatory and anti-cancer [122]. The anti-inflammatory property of punicalagin was assessed by Cao et al. [123] in lipopolysaccharide-induced RAW264.7 macrophages and it was observed that punicalagin inhibited NF-κB activation and initiated autophagy inhibition. In another study conducted by Xu et al. [124], the effect of punicalagin on resistant *S. aureus* was investigated and from the results, it was inferred that punicalagin induced morphological damage to the cell membrane of the bacteria, and it also inhibited the biofilm formation.

Quercetin

Quercetin is a natural polyphenolic flavonoid that is present in various foods including onion, tomatoes, red amaranthus leaves, and apples. It is a potent antioxidant possessing anti-inflammatory, anticancer, antidiabetic, and antimicrobial properties [125]. The high levels of secreted inflammatory cytokines that add to the suppression of the host's immune system during sepsis can be managed with this phytomolecule. A study assessed the anti-inflammatory potential of quercetin in vitro, in which it was observed that quercetin reversed the upregulation of ICAM-1 and VCAM-1 via inhibiting the activation of NF-κB and AP-1 [126]. Therefore, the use of quercetin can decrease the transcriptional activity of NF-κB that in turn may prevent the development of sepsis [113]. Quercetin is capable of reducing bacterial attachment to the surface of host cells and blocking the expression of genes involved in bacterial adhesion. It can also degrade the extracellular matrix formed by bacterial biofilm [127], thus making it a key molecule for adjunct therapy.

Conclusion

Sepsis is associated with extremely high mortality and long-term morbidity in patients who survive. Cognizance of the pathophysiology, specifically host immune response and adaptations of sepsis-causing bacteria, is essential for precise and effective clinical intervention. In this context, based on the available lab evidence, a panel of inflammatory and immune status markers of the host has been delineated in this study that can be investigated and targeted to manage the organ dysfunction cascade. The problem of antibiotic resistance and the mechanisms that sepsis-causing bacteria adopt puts forth in three unconventional approaches of treatment, viz. drug repurposing, immunotherapy, and phytotherapy that will aid in alleviating the resistance in sepsis-causing bacteria and in stabilizing the deranged immune system of the host. The common etiopathology of sepsis with other immune-compromised conditions like diabetes and cancer adds-on to the state of organ dysfunction and contributes to sepsis-related mortality. Such comorbid conditions can be dealt with the phytomolecules that have anti-inflammatory and antioxidant properties as an adjuvant. The phytomolecules have been screened for their therapeutic efficacy, safety, and multiple molecular targeting in preclinical studies which makes them suitable candidates for combination therapy. Further studies and clinical trials are needed in this direction to evaluate the efficacy of these innovative therapies on sepsis outcomes.

Abbreviations *ARBs*: Antibiotic resistance breakers; *LMICs*: Low-middle-income countries; *NK cells*: Natural killer cells; *PAMPs*: Pathogen-associated molecular patterns; *DAMPs*: Damage-associated molecular patterns; *ROS*: Reactive oxygen species; *CRP*: C-reactive protein; *PCT*: Procalcitonin; *AML*: Acute myeloid leukemia; *TNF-α*: Tumor necrosis factor; *IL*: Interleukins; *MDR*: Multidrug resistant; *CD*: Cluster of differentiation; *NF-κB*: Nuclear factor kappa B

Author Contribution Acquisition and analysis of data, writing the original draft, and the artwork were done by Parkhi Shrivastava. Reviewing the manuscript and preparing the final draft were done by Ragini Gothalwal. Conceptualization of idea and creation of model, analysis/interpretation of data, writing and editing the manuscript, and supervision of the work were done by Puneet Gandhi. All authors read and approved the final manuscript.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, et al. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. Am J Respir Crit Care Med. 2016;193:259–72.
2. Schlapbach LJ, Kissoon N, Alhawsawi A, Aljuaid MH, Daniels R, Gorordo-Delsol LA, et al. World Sepsis Day: a global agenda to target a leading cause of morbidity and mortality. Am J Physiol Lung Cell Mol Physiol. 2020;319:518–22.
3. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. Lancet. 2020;395:200–11.
4. Santella B, Folliero V, Pirofalo GM, Serretiello E, Zannella C, Moccia G, Santoro E, Sanna G, Motta O, De Caro F, Pagliano P. Sepsis—a retrospective cohort study of bloodstream infections. Antibiotics. 2020;9(12):851.

5. Zlatian O, Balasoiu AT, Balasoiu M, Cristea O, Docea AO, Mitrut R, et al. Antimicrobial resistance in bacterial pathogens among hospitalized patients with severe invasive infections. Exp Ther Med. 2018;16:4499–510.
6. Zhen X, Lundborg CS, Sun X, Hu X, Dong H. Economic burden of antibiotic resistance in ESKAPE organisms: a systematic review. Antimicrob Resist Infect Control. 2019;8:137.
7. Akin A, Alp E, Altindiş MU, Azak E, Batirel A, Çağ Y et al. Current diagnosis and treatment approach to sepsis. Mediterr J Infect Microbes Antimicrob. 2018;7:1–19.
8. Feng M, Sun T, Zhao Y, Zhang H. Detection of serum interleukin-6/10/18 levels in sepsis and its clinical significance. J Clin Lab Anal. 2016;6:1037–43.
9. Gyawali B, Ramakrishna K, Dhamoon AS. Sepsis: the evolution in definition, pathophysiology, and management. SAGE Open Med. 2019;2050312119835043. https://doi.org/10.1177/2050312119835043.
10. Mira JC, Cuschieri J, Ozrazgat-Baslanti T, Wang Z, Ghita GL, Loftus TJ, et al. The epidemiology of chronic critical illness after severe traumatic injury at two level one trauma centers. Crit Care Med. 2017;45:1989–96.
11. McMullan BJ, Mostaghim M. Prescribing azithromycin Aust Prescr. 2015;38:87–9.
12. FDA. Rocephin (Ceftriaxone injection). Genentech, USA. 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/050585s068lbl.pdf. Accessed 17 Nov 2021.
13. Atkin SD, Abid S, Foster M, Bose M, Keller A, Hollaway R, et al. Multidrug-resistant Pseudomonas aeruginosa from sputum of patients with cystic fibrosis demonstrates a high rate of susceptibility to ceftazidime–avibactam. Infect Drug Resist. 2018;11:1499–510.
14. Bonomo RA, Donskey CJ, Blumer JL, Hujer AM, Hoyenm CK, Jacobs MR, et al. Cefotaxime-resistant bacteria colonizing older people admitted to an acute care hospital. J Am Geriat Soc. 2003;51:519–22.
15. Afriyie DK, Adu LB, Dzradosi M, Amponsah SK, Ohene-Manu P, Manu-Ofei F. Comparative in vitro activity of ciprofloxacin and levofloxacin against isolated uropathogens in Ghana: a pilot study. Pan Afr Med J. 2018;30. https://doi.org/10.11604/pamj.2018.30.194.15457
16. Stein M, Komerska J, Prizade M, Sheinberg B, Tasher D, Somekh E. Clindamycin resistance among Staphylococcus aureus strains in Israel: implications for empirical treatment of skin and soft tissue infections. Int J Infect Dis. 2016;46:18–21.
17. CDC. Carbapenem resistant Enterobacterals. 2019. https://www.cdc.gov/hai/organisms/cre/index.html. Accessed 17 Nov 2021.
18. Jang WH, Yoo DH, Park SW. Prevalence of and risk factors for levofloxacin-resistant E. coli isolated from outpatients with urinary tract infection. Korean J Urol. 2011;52:554–9.
19. Levitus M, Rewane A, Perera TB. Vancomycin-resistant enterococci. [Updated 2022 May 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513233/
20. Banin E, Hughes D, Kuipers OP. Bacterial pathogens, antibiotics and antibiotic resistance. FEMS microbial Rev. 2017;41:450–2.
21. Esposito S, De Simone G, Boccia G, De Caro F, Pagliano P. Sepsis and septic shock: new definitions, new diagnostic and therapeutic approaches. J Glob Antimicrob Resist. 2017;10:204–12.
22. Minasyan H. Sepsis: mechanisms of bacterial injury to the patient. Scand J Trauma Resusc Emerg Med. 2019;27:1–22.
23. Subramaniam S, Joyce P, Thomas N, Prestidge CA. Bioinspired drug delivery strategies for repurposing conventional antibiotics against intracellular infections. Adv Drug Deliv Rev. 2021;177:113948.
24. Yin W, Wang Y, Liu L, He J. Biofilms: the microbial "protective clothing" in extreme environments. Int J Mol Sci. 2019;20:3423.
25. Vestby LK, Grønseth T, Simm R, Nesse LL. Bacterial biofilm and its role in the pathogenesis of disease. Antibiotics. 2020;9:59.
26. Kvich L, Burmølle M, Bjarnsholt T, Lichtenberg M. Do mixed-species biofilms dominate in chronic infections?–need for in situ visualization of bacterial organization. Front Cell Infect Microbiol. 2020;10:396.
27. Thakur A, Mikkelsen H, Jungersen G. Intracellular pathogens: host immunity and microbial persistence strategies. J Immunol Res. 2019;2019:1356540. https://doi.org/10.1155/2019/1356540
28. Wright KJ, Seed PC, Hultgren SJ. Development of intracellular bacterial communities of uropathogenic Escherichia coli depends on type 1 pili. Cell Microbiol. 2007;9:2230–41.
29. Edwards AM, Potts JR, Josefsson E, Massey RC. Staphylococcus aureus host cell invasion and virulence in sepsis is facilitated by the multiple repeats within FnBPA. PLoS pathog. 2010;6:e1000964.
30. Horsley H, Malone-Lee J, Holland D, Tuz M, Hibbert A, Kelsey M, Kupelian A, Rohn JL. Enterococcus faecalis subverts and invades the host urothelium in patients with chronic urinary tract infection. PLoS ONE. 2013;8:e83637.
31. Bergmann R, Gulotta G, Andreoni F, Sumitomo T, Kawabata S, Zinkernagel AS, Chhatwal GS, Nizet V, Rohde M, Uchiyama S. The group A Streptococcus interleukin-8 protease SpyCEP promotes bacterial intracellular survival by evasion of autophagy. Infect Microbe Dis. 2022;4(3):116–23.
32. Peterson E, Kaur P. Antibiotic resistance mechanisms in bacteria: relationships between resistance determinants of antibiotic producers, environmental bacteria, and clinical pathogens. Front Microbiol. 2018;9:2928.
33. Abdul-Jabar HH, Abd AH, Abdulamir AS. Efficacy of combinations of piperacilline/tazobactam, ceftazidime, amikacin and bacteriophage against Enterobacteriaceae sepsis in neonates: in vitro study. SRP. 2020;11:165–70.
34. Brunkhorst FM, Oppert M, Marx G, Bloos F, Ludewig K, Putensen C, et al. Effect of empirical treatment with moxifloxacin and meropenem vs meropenem on sepsis-related organ dysfunction in patients with severe sepsis: a randomized trial. JAMA. 2012;307:2390–9.
35. Martínez ML, Plata-Menchaca EP, Ruiz-Rodríguez JC, Ferrer R. An approach to antibiotic treatment in patients with sepsis. J Thorac Dis. 2020;12:1007–21.
36. Thomson KM, Dyer C, Liu F, Sands K, Portal E, Carvalho MJ, et al. Effects of antibiotic resistance, drug target attainment, bacterial pathogenicity and virulence, and antibiotic access and affordability on outcomes in neonatal sepsis: an international microbiology and drug evaluation prospective substudy. Lancet Infect Dis. 2021;21:1677–88.
37. Waltner-Toews RI, Paterson DL, Qureshi ZA, Sidjabat HE, Adams-Haduch JM, Shutt KA, et al. Clinical characteristics of bloodstream infections due to ampicillin-sulbactam-resistant, non-extended-spectrum-β-lactamase-producing Escherichia coli and the role of TEM-1 hyperproduction. Antimicrob Agents Chemother. 2011;55:495–501.
38. Martínez-Casanova J, Gómez-Zorrilla S, Prim N, Dal Molin A, Echeverría-Esnal D, Gracia-Arnillas MP, et al. Risk factors for amoxicillin-clavulanate resistance in community-onset urinary tract infections caused by Escherichia coli or Klebsiella pneumoniae: the role of prior exposure to fluoroquinolones. Antibiotics. 2021;10:582.
39. Liu X, Zheng H, Zhang W, Shen Z, Zhao M, Chen Y, Sun L, Shi J, Zhang J. Tracking cefoperazone/sulbactam resistance development in vivo in A. baumannii isolated from a patient with hospital-acquired pneumonia by whole-genome sequencing. Front Microbiol. 2016;7:1268.
40. Hubbard A, Mason J, Roberts P, Parry CM, Corless C, van Aartsen J, Howard A, Bulgasim I, Fraser AJ, Adams ER,

Roberts AP. Piperacillin/tazobactam resistance in a clinical isolate of Escherichia coli due to IS26-mediated amplification of blaTEM-1B. Nat Commun. 2020;11:1–9.
41. Gangcuangco LM, Alejandria M, Henson KE, Alfaraz L, Ata RM, Lopez M, et al. Prevalence and risk factors for trimethoprim–sulfamethoxazole-resistant Escherichia coli among women with acute uncomplicated urinary tract infection in a developing country. Int J Infect Dis. 2015;34:55–60.
42. Farha MA, Brown ED. Drug repurposing for antimicrobial discovery. Nat Microbiol. 2019;4:565–77.
43. Miró-Canturri A, Ayerbe-Algaba R, Smani Y. Drug repurposing for the treatment of bacterial and fungal infections. Front Microbiol. 2019;10:41. https://doi.org/10.3389/fmicb.2019.00041
44. Quezada H, Martínez-Vázquez M, López-Jácome E, González-Pedrajo B, Andrade Á, Fernández-Presas AM, et al. Repurposed anti-cancer drugs: the future for anti-infective therapy? Expert Rev Anti Infect Therapy. 2020;18:609–12.
45. Hegazy WA, Khayat MT, Ibrahim TS, Nassar MS, Bakhrebah MA, Abdulaal WH, Alhakamy NA, Bendary MM. Repurposing anti-diabetic drugs to cripple quorum sensing in Pseudomonas aeruginosa. Microorganisms. 2020;8(9):1285.
46. US National Library of Medicine. The efficacy and safety of Ta1 for sepsis (TESTS). 2021. https://clinicaltrials.gov/ct2/show/NCT02867267. Accessed 17 Nov 2021.
47. Francois B, Jeannet R, Daix T, Walton AH, Shotwell MS, Unsinger J, Monneret G, Rimmelé T, Blood T, Morre M, Gregoire A. Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial. JCI Insight. 2018;3(5):e98960. https://doi.org/10.1172/jci.insight.98960.
48. Choy EH, De Benedetti F, Takeuchi T, Hashizume M, John MR, Kishimoto T. Translating IL-6 biology into effective treatments. Nat Rev Rheumatol. 2020;16:335–45.
49. Honore PM, Hoste E, Molnár Z, Jacobs R, Joannes-Boyau O, Malbrain ML, et al. Cytokine removal in human septic shock: where are we and where are we going? Ann Intensive Care. 2019;9:56.
50. Yuan H, Ma Q, Ye L, Piao G. The traditional medicine and modern medicine from natural products. Molecules. 2016;21(5):559. https://doi.org/10.3390/molecules21050559.
51. Alikiaii B, Bagherniya M, Askari G, Johnston TP, Sahebkar A. The role of phytochemicals in sepsis: a mechanistic and therapeutic perspective. BioFactors. 2021;47:19–40.
52. Jhanji R, Singh A, Kumar A. Antibacterial potential of selected phytomolecules: an experimental study. Microbiol Immunol. 2021;65:325–32.
53. Wojtyczka RD, Dziedzic A, Kępa M, Kubina R, Kabała-Dzik A, Mularz T, et al. Berberine enhances the antibacterial activity of selected antibiotics against coagulase-negative Staphylococcus strains in vitro. Molecules. 2014;19:6583–96.
54. Xia X, Yan J, Shen Y, Tang K, Yin J, Zhang Y, Yang D, Liang H, Ye J, Weng J. Berberine improves glucose metabolism in diabetic rats by inhibition of hepatic gluconeogenesis. PLoS one. 2011;6(2):e16556. https://doi.org/10.1371/journal.pone.0016556
55. Siriyong T, Srimanote P, Chusri S, Yingyongnarongkul BE, Suaisom C, Tipmanee V, et al. Conessine as a novel inhibitor of multidrug efflux pump systems in Pseudomonas aeruginosa. BMC Complement Altern Med. 2017;17:1–7.
56. Mgbeahuruike EE, Stålnacke M, Vuorela H, Holm Y. Antimicrobial and synergistic effects of commercial piperine and piperlongumine in combination with conventional antimicrobials. Antibiotics. 2019;8:55.
57. Ndezo B, Tokam Kuaté CR, Dzoyem JP. Synergistic antibiofilm efficacy of thymol and piperine in combination with three aminoglycoside antibiotics against Klebsiella pneumoniae biofilms. Can J Infect Dis Med Microbiol. 2021;2021:1–8. https://doi.org/10.1155/2021/7029944.
58. Hamoud R, Reichling J, Wink M. Synergistic antibacterial activity of the combination of the alkaloid sanguinarine with EDTA and the antibiotic streptomycin against multidrug resistant bacteria. J Pharm Pharmacol. 2015;67:264–73.
59. Lu C, Zhang N, Kou S, Gao L, Peng B, Dai Y, et al. Sanguinarine synergistically potentiates aminoglycoside-mediated bacterial killing. Microb Biotechnol. 2022;15:2055–70.
60. Mun SH, Lee YS, Han SH, Lee SW, Cha SW, Kim SB, et al. In vitro potential effect of morin in the combination with β-lactam antibiotics against methicillin-resistant Staphylococcus aureus. Foodborne Pathog Dis. 2015;12:545–50.
61. Amin MU, Khurram M, Khattak B, Khan J. Antibiotic additive and synergistic action of rutin, morin and quercetin against methicillin resistant Staphylococcus aureus. BMC Complement Altern Med. 2015;15:1–2.
62. Deepika MS, Thangam R, Sakthidhasan P, Arun S, Sivasubramanian S, Thirumurugan R. Combined effect of a natural flavonoid rutin from Citrus sinensis and conventional antibiotic gentamicin on Pseudomonas aeruginosa biofilm formation. Food Control. 2018;90:282–94.
63 Alnour TM, Ahmed-Abakur EH, Elssaig EH, Abuduhier FM, Ullah MF. Antimicrobial synergistic effects of dietary flavonoids rutin and quercetin in combination with antibiotics gentamicin and ceftriaxone against E. coli (MDR) and P. mirabilis (XDR) strains isolated from human infections: implications for food–medicine interactions. Ital J Food Sci. 2022;34:34–42.
64. Siriwong S, Teethaisong Y, Thumanu K, Dunkhunthod B, Eumkeb G. The synergy and mode of action of quercetin plus amoxicillin against amoxicillin-resistant Staphylococcus epidermidis. BMC Pharmacol Toxicol. 2016;17:1–4.
65. Pal A, Tripathi A. Demonstration of bactericidal and synergistic activity of quercetin with meropenem among pathogenic carbapenem resistant Escherichia coli and Klebsiella pneumoniae. Microb Pathog. 2020;143:104120.
66. Cai W, Fu Y, Zhang W, Chen X, Zhao J, Song W, et al. Synergistic effects of baicalein with cefotaxime against Klebsiella pneumoniae through inhibiting CTX-M-1 gene expression. BMC Microbiol. 2016;16:1–9.
67. Siriwong S, Pimchan T, Naknarong W, Eumkeb G. Mode of action and synergy of ceftazidime and baicalein against Streptococcus pyogenes. Trop J Pharm Res. 2015;14:641–8.
68. Sivananthan M, Imanina CW. Synergistic activity of chloroform and methanol extract of Andrographis paniculata with erythromycin against Streptococcus agalactiae. Int J Pharmtech Res. 2013;5:1393–8.
69. Zhang G, Jiang C, Xie N, Xu Y, Liu L, Liu N. Treatment with andrographolide sulfonate provides additional benefits to imipenem in a mouse model of Klebsiella pneumoniae pneumonia. Biomed Pharmacother. 2019;117:109065.
70 Veras HN, Rodrigues FF, Botelho MA, Menezes IR, Coutinho HD, Costa JG. Enhancement of aminoglycosides and β-lactams antibiotic activity by essential oil of Lippia sidoides Cham. and the thymol. Arab J Chem. 2017;10:2790–5.
71. Miladi H, Zmantar T, Kouidhi B, Al Qurashi YM, Bakhrouf A, Chaabouni Y, et al. Synergistic effect of eugenol, carvacrol, thymol, p-cymene and γ-terpinene on inhibition of drug resistance and biofilm formation of oral bacteria. Microb Pathog. 2017;112:156–63.
72. Vázquez NM, Fiorilli G, Guido PA, Moreno S. Carnosic acid acts synergistically with gentamicin in killing methicillin-resistant Staphylococcus aureus clinical isolates. Phytomedicine. 2016;23:1337–43.
73. Mun SH, Kang OH, Kong R, Zhou T, Kim SA, Shin DW, et al. Punicalagin suppresses methicillin resistance of Staphylococcus aureus to oxacillin. J Pharmacol Sci. 2018;137:317–23.

74. Dey D, Ghosh S, Ray R, Hazra B. Polyphenolic secondary metabolites synergize the activity of commercial antibiotics against clinical isolates of β-lactamase-producing Klebsiella pneumoniae. Phytother Res. 2016;30:272–82.
75 Chaves SKM, Feitosa CM, da Araújo LS. Alkaloids pharmacological activities-prospects for the development of phytopharmaceuticals for neurodegenerative diseases. Curr Pharm Biotechnol. 2016;17:629–35.
76. Peng L, Kang S, Yin Z, Jia R, Song X, Li L, et al. Antibacterial activity and mechanism of berberine against Streptococcus agalactiae. Int J Clin Exp Pathl. 2015;8:5217–23.
77. Daglia M. Polyphenols as antimicrobial agents. Curr Opin Biotechnol. 2012;23:174–81.
78. Matilla-Cuenca L, Gil C, Cuesta S, Rapún-Araiz B, Žiemytė M, Mira A, et al. Antibiofilm activity of flavonoids on staphylococcal biofilms through targeting BAP amyloids. Sci Rep. 2020;10:18968.
79. Sun LC, Li SY, Wang FZ, Xin FJ. Research progresses in the synthetic biology of terpenoids. Biotechnol Bull. 2017;33:64.
80. Lopez-Romero JC, González-Ríos H, Borges A, Simões M. Antibacterial effects and mode of action of selected essential oils components against Escherichia coli and Staphylococcus aureus. Evid Based Complement Alternat Med. 2015;2015:795435. https://doi.org/10.1155/2015/795435.
81. Farha AK, Yang QQ, Kim G, Li HB, Zhu F, Liu HY, et al. Tannins as an alternative to antibiotics. Food Biosci. 2020;38:100751.
82. Serrano J, Puupponen-Pimiä R, Dauer A, Aura AM, Saura-Calixto F. Tannins: current knowledge of Ndefood sources, intake, bioavailability and biological effects. Mol Nutr Food Res. 2009;53:310–29.
83. Cai X, YU X. Synergetic effect of Xuebijing injection and cefoperazone sodium/sulbactam sodium on sepsis. China Pharmacy. 2005;20.
84. Eslami K, Mahmoodpoor A, Ahmadi A, Abdollahi M, Kamali K, Mousavi S, Najafi A, Baeeri M, Hamishehkar H, Kouti L, Javadi MR. Positive effect of septimeb™ on mortality rate in severe sepsis: a novel non antibiotic strategy. DARU J Pharmaceut Sci. 2012;20:1–7.
85. Gupta PD, Birdi TJ. Development of botanicals to combat antibiotic resistance. J Ayurveda Integr Med. 2017;8:266–75.
86. Kongkham B, Prabakaran D, Puttaswamy H. Opportunities and challenges in managing antibiotic resistance in bacteria using plant secondary metabolites. Fitoterapia. 2020;147:104762. https://doi.org/10.1016/j.fitote.2020.104762.
87. Rubio I, Osuchowski MF, Shankar-Hari M, Skirecki T, Winkler MS, Lachmann G, et al. Current gaps in sepsis immunology: new opportunities for translational research. Lancet Infect Dis. 2019;19:422–36.
88. Chinowaita F, Chaka W, Nyazika TK, Maboreke TC, Tizauone E, Mapondera P, et al. Sepsis in cancer patients residing in Zimbabwe: spectrum of bacterial and fungal aetiologies and their antimicrobial susceptibility patterns. BMC Infect Dis. 2020;20:161.
89. Ferreira JN, Correia LR, Oliveira RM, Watanabe SN, Possari JF, Lima AF. Managing febrile neutropenia in adult cancer patients: an integrative review of the literature. Rev Bras Enferm. 2017;70:1301–8.
90. Lemiale V, Pons S, Mirouse A, Tudesq JJ, Hourmant Y, Mokart D, et al. Sepsis and septic shock in patients with malignancies: a Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique study. Crit Care Med. 2020;48:822–9.
91. Liu Z, Mahale P, Engels EA. Sepsis and risk of cancer among elderly adults in the United States. Clin Infect Dis. 2019;68:717–24.
92. Gudiol C, Albasanz-Puig A, Cuervo G, Carratalà J. Understanding and managing sepsis in patients with cancer in the era of antimicrobial resistance. Front Med. 2021;8:636547. https://doi.org/10.3389/fmed.2021.636547.
93. Subburaj D, Uppuluri R, Jayaraman D, Vellaichamyswaminathan V, Kandath S, Raj R. Combating blood stream infections during induction chemotherapy in children with acute myeloid leukemia: single center results in India. Pediatr Blood Cancer. 2017;64(10):e26517.
94. Jacob S, Jacob SE, Suryanarayana BS, Dutta TK. Clinical profile and short term outcome of adult patients with acute myeloid leukemia. Indian J Hematol Blood Transfus. 2019;35:431–6.
95. Papanicolas LE, Gordon DL, Wesselingh SL, Rogers GB. Not just antibiotics: is cancer chemotherapy driving antimicrobial resistance? Trends Microbiol. 2018;26:393–400.
96. Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: a review of pathogenesis. Indian J Endocrinol Metab. 2012;16:27–36.
97. Frydrych LM, Fattahi F, He K, Ward PA, Delano MJ. Diabetes and sepsis: risk, recurrence, and ruination. Front Endocrinol. 2017;8:271. https://doi.org/10.3389/fendo.2017.00271.
98. Mor A, Dekkers OM, Nielsen JS, Beck-Nielsen H, Sørensen HT, Thomsen RW. Impact of glycemic control on risk of infections in patients with type 2 diabetes: a population-based cohort study. Am J Epidemiol. 2017;186:227–36.
99. Steinhagen F, Schmidt SV, Schewe JC, Peukert K, Klinman DM, Bode C. Immunotherapy in sepsis-brake or accelerate?. Pharmacol Ther. 2020;208:107476.
100. Liew KY, Hafiz MF, Chong YJ, Harith HH, Israf DA, Tham CL. A review of malaysian herbal plants and their active constituents with potential therapeutic applications in sepsis. Evid Based Complement Alternat Med. 2020;2020:8257817. https://doi.org/10.1155/2020/8257817.
101. Li F, Li XM, Sheng D, Chen SR, Nie X, Liu Z, et al. Discovery and preliminary SAR of 14-aryloxy-andrographolide derivatives as antibacterial agents with immunosuppressant activity. RSC Adv. 2018;8:9440–56.
102. Yang W, Chen X, Li Y, Guo S, Wang Z, Yu X. Advances in pharmacological activities of terpenoids. Nat Prod Commun. 2020;15. https://doi.org/10.1177/1934578X20903555
103. Yu Y, Shen Q, Lai Y, Park SY, Ou X, Lin D, et al. Anti-inflammatory effects of curcumin in microglial cells. Front Pharmacol. 2018;9:386.
104. Chai YS, Chen YQ, Lin SH, Xie K, Wang CJ, Yang YZ, et al. Curcumin regulates the differentiation of naïve CD4+ T cells and activates IL-10 immune modulation against acute lung injury in mice. Biomed Pharmacother. 2020;125:109946.
105. Wang X, Feng S, Ding N, He Y, Li C, Li M, et al. Anti-inflammatory effects of berberine hydrochloride in an LPS-induced murine model of mastitis. Evid Based Complement Alternat Med. 2018;2018:5164314. https://doi.org/10.1155/2018/5164314.
106. Li C, Xi Y, Li S, Zhao Q, Cheng W, Wang Z, et al. Berberine ameliorates TNBS induced colitis by inhibiting inflammatory responses and Th1/Th17 differentiation. Mol Immunol. 2015;67:444–54.
107. Okubo S, Uto T, Goto A, Tanaka H, Nishioku T, Yamada K, et al. Berberine induces apoptotic cell death via activation of caspase-3 and-8 in HL-60 human leukemia cells: nuclear localization and structure–activity relationships. Am J Chin Med. 2017;45:1497–511.
108. D'Alesio C, Bellese G, Gagliani MC, Aiello C, Grasselli E, Marcocci G, et al. Cooperative antitumor activities of carnosic acid and trastuzumab in ERBB2+ breast cancer cells. J Exp Clin Cancer Res. 2017;36:1–6.
109. Talib WH. Regressions of breast carcinoma syngraft following treatment with piperine in combination with thymoquinone. Sci Pharm. 2017;85:27.
110. Zhang L, Chinnathambi A, Alharbi SA, Veeraraghavan VP, Mohan SK, Zhang G. Punicalagin promotes the apoptosis in

human cervical cancer (ME-180) cells through mitochondrial pathway and by inhibiting the NF-kB signaling pathway. Saudi J Biol Sci. 2020;27:1100–6.
111. Olajide OA, Kumar A, Velagapudi R, Okorji UP, Fiebich BL. Punicalagin inhibits neuroinflammation in LPS-activated rat primary microglia. Mol Nutr Food Res. 2014;58:1843–51.
112. Koren-Gluzer M, Aviram M, Meilin E, Hayek T. The antioxidant HDL-associated paraoxonase-1 (PON1) attenuates diabetes development and stimulates β-cell insulin release. Atherosclerosis. 2011;219:510–8.
113. Chekalina N, Burmak Y, Petrov Y, Borisova Z, Manusha Y, Kazakov Y, et al. Quercetin reduces the transcriptional activity of NF-kb in stable coronary artery disease. Indian Heart J. 2018;70:593–7.
114. Carrasco-Pozo C, Tan KN, Reyes-Farias M, De La Jara N, Ngo ST, Garcia-Diaz DF, Llanos P, Cires MJ, Borges K. The deleterious effect of cholesterol and protection by quercetin on mitochondrial bioenergetics of pancreatic β-cells, glycemic control and inflammation: in vitro and in vivo studies. Redox Biol. 2016;9:229–43.
115. Mussard E, Cesaro A, Lespessailles E, Legrain B, Berteina-Raboin S, Toumi H. Andrographolide, a natural antioxidant: an update. Antioxidants. 2019;8(12):571. https://doi.org/10.3390/antiox8120571.
116. Zhang L, Bao M, Liu B, Zhao H, Zhang Y, Ji X, et al. Effect of andrographolide and its analogs on bacterial infection: a review. Pharmacology. 2020;105:123–34.
117. Habtemariam S. Berberine pharmacology and the gut microbiota: a hidden therapeutic link. Pharmacol Res. 2020;155:104722.
118. Zheng D, Huang C, Huang H, Zhao Y, Khan MR, Zhao H, et al. Antibacterial mechanism of curcumin: a review. Chem Biodivers. 2020;17:e2000171.
119. Karimi A, Ghodsi R, Kooshki F, Karimi M, Asghariazar V, Tarighat-Esfanjani A. Therapeutic effects of curcumin on sepsis and mechanisms of action: a systematic review of preclinical studies. Phytother Res. 2019;33:2798–820.
120. Sundaramoorthy NS, Sivasubramanian A, Nagarajan S. Simultaneous inhibition of MarR by salicylate and efflux pumps by curcumin sensitizes colistin resistant clinical isolates of Enterobacteriaceae. Microb Pathog. 2020;148:104445.
121. Tyagi P, Singh M, Kumari H, Kumari A, Mukhopadhyay K. Bactericidal activity of curcumin I is associated with damaging of bacterial membrane. PloS one. 2015;10. https://doi.org/10.1371/journal.pone.0121313
122. Gosset-Erard C, Zhao M, Lordel-Madeleine S, Ennahar S. Identification of punicalagin as the bioactive compound behind the antimicrobial activity of pomegranate (Punica granatum L.) peels. Food Chem. 2021;352:129396.
123 Cao Y, Chen J, Ren G, Zhang Y, Tan X, Yang L. Punicalagin prevents inflammation in LPS-induced RAW264. 7 macrophages by inhibiting FoxO3a/autophagy signaling pathway. Nutrients. 2019;11:2794.
124. Xu Y, Shi C, Wu Q, Zheng Z, Liu P, Li G, et al. Antimicrobial activity of punicalagin against Staphylococcus aureus and its effect on biofilm formation. Foodborne Pathog Dis. 2017;14:282–7.
125. David AV, Arulmoli R, Parasuraman S. Overviews of biological importance of quercetin: a bioactive flavonoid. Pharmacogn Rev. 2016;10:84–9.
126. Chen T, Zhang X, Zhu G, Liu H, Chen J, Wang Y, He X. Quercetin inhibits TNF-α induced HUVECs apoptosis and inflammation via downregulating NF-kB and AP-1 signaling pathway in vitro. Medicine. 2020;99(38):e22241.
127. Vipin C, Mujeeburahiman M, Ashwini P, Arun AB, Rekha PD. Anti-biofilm and cytoprotective activities of quercetin against Pseudomonas aeruginosa isolates. Lett Appl Microbiol. 2019;68:464–71.