Acinetobacter baumannii: An overview of emerging multidrug-resistant pathogen

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ABSTRACT

The emergence of infections caused by *Acinetobacter baumannii*, a multidrug-resistant bacterium, has been a concern worldwide. This bacterium is an important hospital-acquired pathogen that causes several diseases, including ventilator-associated pneumonia, bloodstream infections, and meningitis. This study aimed to determine antibiotic-resistant mechanisms in the pathogenesis of *A. baumannii* and the alternative treatment strategies against it. The combined actions of the outer membrane protein A, formation of a biofilm on biotic and abiotic surfaces, phospholipases C and D, metal homeostatic system, lipopolysaccharides, and verotoxins are relevant for virulence and pathogenesis. *A. baumannii* resists to a broad-spectrum antibiotics by its mechanisms of resistance, such as β-lactamases, efflux pump, aminoglycoside modifying enzymes, permeability changes, and alternation of targets. In an attempt to overcome the resistance mechanisms, plant-derived compounds and a combination of the antibiotics and the plant phytocompounds have been focused. Nanoparticles synthesised with the plant extract have been studied extensively. Furthermore, we projected modern methods, including multi-omics analysis, to study insight into mechanisms of actions of antibiotics. The information suggested that the potential antibiotic mechanisms of *A. baumannii* could lead to an alternative treatment against *A. baumannii* infections.

KEYWORDS:
Acinetobacter baumannii, Multidrug resistance, Hospital-acquired infection, Advance diagnostic, Nanoparticles, and Plant-derived compounds

1. Introduction

Acinetobacter baumannii has been a human pathogen with increasing importance, since it causes a high number of infections and the occurrence of multidrug-resistant (MDR) strains. *Acinetobacter spp.* are characterised by being aerobic, non-fermentative, non-mobile, non-fastidious, catalase-positive, oxidative-negative, and Gram-negative coccobacilli.[1] This bacterium was first described in 1911, and having been isolated from the soil, it has been given several designations such as *Micrococcus calcoaceticus, Achromobacter, Alcaligenes, Bacterium anitratum, Moraxella glucidolytica, Neisseria winogradsky, Alcaligenes haemolysans, Mima polymorpha, and Moraxella lwoffii*.[2] Over the past few decades, the nomenclature of the genus Acinetobacter has been changed, and then, in 1974, it was described in Bergey's Manual of Systematic Bacteriology, with one species only: *Acinetobacter calcoaceticus*.[3] The complex *A. calcoaceticus-baumannii* includes four genospecies: genospecies 1, *A. calcoaceticus*; genospecies 2, *A. baumannii*; genospecies 3, *A. pittii*; and genospecies 13TU, *A. nosocomialis*. *A. baumannii* is the most important species in clinical settings due to nosocomial infections that are associated with the highest mortality rate.[4-5] Habitat-wise, since they are ubiquitous, they are found everywhere, especially in wet/moist environments like ponds, waste water, water treatment plants, and soil/mud.[6] The environmental reservoirs like food and various types of livestock have served as an important source for resistance elements making their way from multiple environmental sources into the human population and changing into clinically relevant strains, often harbouring antibiotic resistance mechanisms, namely extended-spectrum-lactamases (ESBLs) and metallo-beta lactamases (MBL).[6-7] Usually, it is resistant to complete decolourisation and can deceive as Gram-positive cocci. It does not produce urease, indole, cytochrome oxidase, and citrate; however, it produces catalase enzyme. *A. baumannii* is able to grow at 44°C, as the only bacterium of this genus to grow on the commonly used media in the laboratory.[8]

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Once considered of low virulent activity, it has literally taken over most of the commonly used drugs and has made them impotent, and there has been a significant interest in this organism over the past few decades.[4,9-10] It have been called 'Iraqibacter' as they have been isolated from individuals serving in the war in Iraq and Afghanistan.[10] The bacteria have rapidly spread across the globe in many hospital settings, especially the intensive care units (ICUs), where it account for 20% of infections worldwide.[11] Today, Acinetobacter infections have spread rapidly across the globe in the community. It can survive and thrive in diverse conditions of pH and temperature, in dry and moist conditions, and on surgical tools, ventilators, catheters, and respirometers.[12-13] As a result, they cause hospital- and community-acquired infections like meningitis, bloodstream infections, endocarditis, and wound and soft tissue infections.[1,11,14] The WHO stated that one of the most resistant ESKAPE organisms *(Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, A. baumannii, Pseudomonas aeruginosa, and Enterobacter species)* escaping the action of antibacterial drugs was *A. baumannii* and classified it as a top priority critical pathogen for antibiotic research and development.[15-16] They can form biofilms on several abiotic surfaces that may account for their perseverance in the hospital environment, increasing the possibility of causing healthcare-associated infections and outbreaks.[17-18] There are unknown virulence and resistance mechanisms developed by *A. baumannii* against the drugs counting with β-lactamase, low-porin expressions, lipopolysaccharides (LPS), alteration of target cells by mutations, iron-chelating systems, and capsular polysaccharides.[1,19,20] Another significant factor that contributed to its spread was the failure to accurately diagnose this organism due to the similarities between species. Misidentification on several occasions by phenotypic and chemotaxonomic methods underrated the role of *A. baumannii* as a cause of nosocomial infection. In addition, the presence of a hospital environment fully supported a selective pressure for cloning of resistant properties of some antibiotics. The ability of *A. baumannii* to incorporate exogenous DNA, through horizontal genetic transfer (HGT), is one of the factors responsible for the multidrug resistance phenotype observed in severalty of clinical strains worldwide.[21-22] With the advent of molecular techniques, such as mass spectrometry, ribotyping, multilocus sequence typing (MLST), RNA spacer fingerprinting, amplified fragment length polymorphism analysis, pulsed-field gel electrophoresis (PFGE), and matrix-assisted laser desorption ionisation time-of-flight (MALDI-TOF), identification of several virulence factors have been made easier.[23-24]

This review article aims to focus on the virulence factors of *A. baumannii*, its pathogenesis, antimicrobial resistance, advanced technology for identification, and alternative treatment strategies, which provide information for the development and discovery of new antibiotics and for the determination of essential effective combination treatment to combat multidrug resistant infections.

2. Search Strategy

We searched full-text research and review articles on *Acinetobacter baumannii* through PubMed (Medline) databases and Google Scholar, published in English in the last 20 years, using the following keywords: *'Acinetobacter baumannii'*, 'epidemiology', 'pathogenesis', 'antibiotic resistance', 'multi-omic study', '*in vitro* studies' 'virulence', and 'treatment'. Exclusion criteria included irrelevant studies on *A. baumannii* (Figure 1).

3. Epidemiology

The epidemiology of *A. baumannii* infection is broad, which includes infections associated with hospital outbreaks, wars, natural disasters, and the community in tropical climates. Several previous research studies focused on the mechanisms of occurrence of MDR *A. baumannii* infection all around the globe, including Europe, North America, South America, China, Taiwan, Hongkong, Japan, Korea, and other parts of Asia and the Middle East.[25]

The outbreaks are commonly seen in critical care and burn units, with mechanically ventilated patients.[25] An international report in ICUs showed that *Acinetobacter* infection rate was 19.2% in Asia, 17.1% in Eastern Europe, 14.8% in Africa, 13.8% in Central and South America, 5.6% in Western Europe, 4.4% in Oceania, and 3.7% in North America.[11] It was found to be 15% in HIV-positive patients in South Africa and 13% in critical burn care units in Canada.[26,27] Community-acquired pneumonia has been reported in the tropical climatic regions, mainly in Asia and Australia, during warm and humid months.[25] *A. baumannii* was once also coined as 'Iraqbacter' because of its outbreak within military treatment facilities in Iraq war.[28] UK and US military also detected an abundant number of multidrug-resistant *A. baumannii calcoaceticus* complex in military individuals injured during Iraq and Afghanistan war.[4] *A. baumannii* was the most frequent isolated organism (32.5%) from the combat casualties in Iraq and Afghanistan battle victims with open tibia fractures.[29] *A. baumannii* can cause outbreaks since it is highly resistant to antimicrobials and can overcome desiccation.[30] It is noted that the ability of *A. baumannii* to form a biofilm is one of the major virulence factors to a large number of its clinical isolates.[31]

The outbreaks of *Acinetobacter* have been attributed to source contamination, particularly contaminated respiratory and mechanical ventilators, and the cross-infection by the contaminated hands of healthcare workers caring for colonised or infected patients.[32-33] The several risk factors associated with colonisation or infection by multidrug-resistant (MDR) *A. baumannii* are prior exposure to long-term antimicrobial therapy, mechanical ventilation, duration of hospital stay, the severity of disease, current surgery, and other invasive processes.[34]

During 2016, the National Healthcare Safety Network (NHSN) of the United States reviewed the commonest drug-resistant organism involved in healthcare-associated infections where the *Acinetobacter* accounted for the following proportions among the most common Gram-negative isolates: ventilator-associated pneumonia (12.8%), central line-associated bloodstream infection (8.8%), catheter-associated UTIs (1.3%), and surgical site infection (1.3).[35] According to the prevalence study of infections in 2009, EPIC II (Extended Prevalence of Infection in Intensive Care) classified *A. baumannii* as the fifth most common pathogen in

ICU in 75 countries.[11] Furthermore, as reported by the international surveillance program (2009–2011), *A. baumannii* was the seventh most common pathogen isolated from ICU patients in the USA and European hospitals and ranked the eighth and seventh from non-ICU patients in the USA and European hospitals, respectively.[36] The report of drug resistance in the USA (2011) showed that 63% of *Acinetobacter* spp. infections were caused by multi-drug resistance strains.[37] The global rate of MDR *A. baumannii* was increased from 23% in 2004 to 63% in 2014.[38] In the USA and Europe, from 2009–2011, the colistin-resistant *A. baumannii* was around 5% and 3%, respectively, whereas the worldwide prevalence of *A. baumannii* resistant to colistin and polymyxins B was only 0.9% and 0.8%, respectively.[36,39]

4. Pathogenesis

4.1. Virulence factors

The single virulence factors of *A. baumannii* are not clearly defined, and the joint action of multiple factors leads to the pathogenesis by adherence, biofilm formation, invasion, serum resistance, *in vivo* survival, and killing of host cells.[40] Biofilm formation is one of the important factors that enhance its adherence to biotic and abiotic surfaces, including those of host tissues and medical devices.[41] The production of biofilm-associated protein (BAP) gene is correlated to the formation and maturation of biofilms.[42] The BAP enhances adherence to epithelial cells, and the inhibition of its production can control *A. baumannii* infection.[43] The metallic homeostatic system, which is required for colonisation in different tissues is well defined in *A. baumannii*; among these, iron uptake system and zinc acquisition system play an important role in virulence.[44-45] Another factor is that the K1 capsular polysaccharide prevents *A. baumannii* from phagocytosis by macrophages and facilitates its multiplication in fluid from human ascites and serum.[46] Several other proteins, such as Omp38, RecA protein, phospholipases C, and phospholipases D, are estimated as probable virulence factors in *A. baumannii* as they lead to apoptosis of host cells, increase survival as a response to heat shock and desiccation, and enhance survival in human serum and epithelial cells invasion.[47-48] Significantly, the other factors related to epithelial cells apoptosis caused by targeting the bacterial mitochondria is the outer membrane protein 'A', which is most abundantly present in *A. baumannii*.[49] Once the *A. baumannii* enters the bloodstream, the lipopolysaccharides, an important component of cell envelop, may cause septic shock. *A. baumannii* also produces two antigenic types of verotoxins, vtx-1 and vtx-2, which enhance virulence by targeting the cell ribosome machinery and inhibiting protein synthesis.[25,50]

5. Clinical Relevance

A. baumannii can lead to several human infections, including ventilator-associated pneumonia, bacteraemia, septicaemia, urinary tract infection, surgical site wound infection, and meningitis.[30] The mortality rate ranging from 7.8% to 43 % was seen in *A. baumannii* infections with higher levels in ICUs patients. Studies on morbidity reported that *Acinetobacter pneumonia* increases patients' stay in ICU for several days.[51]

5.1. Hospital-associated pneumonia

Acinetobacter pneumonia is observed predominantly in ICU patients who are under mechanical ventilation, and however, sometimes it is not easy to distinguish between airway colonisation from true pneumonia. *A. baumannii* is the second commonest pathogen among Gram-negative bacteria causing hospital-associated pneumonia.[52] The hospital-associated pneumonia caused by *A. baumannii* was around 3–5%, with a death rate of 30–75% being reported.[53]

5.2. Community-associated pneumonia

Community-associated *Acinetobacter* pneumonia shows sudden onset, which progresses rapidly, causing respiratory failure and hemodynamic instability, though the infection is rare.[54-55] It has been reported in people who consume alcohol or in patients with chronic obstructive pulmonary disease from tropical areas of Asia and Australia during monsoon.[4,56]

5.3. Bloodstream infections

The vascular catheters and respiratory tract are the commonest sources for *A. baumannii* bacteraemia, and the origin remains unknown in about 21–70% cases.[57,58] About 1.5–2.4 % of the patients acquired infections nosocomially.[57,59] The mortality rate of *A. baumannii* septicemia ranged 34–43.4% in critical care units and 16.3% in other units of the hospital.[7,60] *A. baumannii* bloodstream infections are associated with various risk factors, including prolonged hospital and ICU stay, mechanical ventilation, surgery and other invasive procedures, wounds, burns, use of broad-spectrum antibiotics, and immunosuppression.[57-58,61-62]

5.4. Urinary tract infection

A. baumannii urinary tract infection is infrequent and accounts for only 1.6% cases.[4] The setting of indwelling urinary catheters usually causes the colonisation of the urinary tract, leading to nosocomial urinary tract infections.[57]

5.5. Meningitis

Meningitis followed by neurosurgery induced by multidrug-resistant *A. baumannii* is a relevant issue.[63] One study showed that about 2.1% of cases of meningitis post-craniotomy were caused by *Acinetobacter*.[64] The certain risk factor associated with it includes surgery involving the brain and spinal cord, cerebrospinal fluid leakage, prior antibiotic treatment, and intracranial hemorrhage.[65] Studies have shown that the mortality rate was about 20–30% and the survivors being left with severe neurologic deficits.[4,66]

5.6. Skin, soft tissue, and bone infection

The soft tissue infection progressing to osteomyelitis caused by contaminated surgical and traumatic wounds is seen in the case of *A. baumannii* infections.[67] It rarely causes other skin infections such as cellulitis, folliculitis, skin abscesses, and necrotising fasciitis.[68-71] The wound and soft tissue infections caused by multidrug-resistant *A. baumannii* are mainly recognised after war injuries. Among different isolated organisms, *A. baumannii* accounted for 32% of the war victims of combat casualties in Iraq and Afghanistan war.[72]

5.7. Other infections

Acinetobacter eye infection is mainly seen in contact lens wearers, which may lead to corneal ulcers, endophthalmitis, periorbital cellulitis, and traumatic infection.[73-77] Some rarely

reported cases of *A. baumannii* infection are endocarditis, nosocomial sinusitis, and peritonitis.[78-80]

6. Laboratory Identification of *A. baumannii*

6.1. Conventional and molecular methods

A. baumannii is a pleomorphic coccobacillus bacterium that is 0.9–1.6 × 1.5–2.5 µm in size, which becomes spherical in the stationary phase of growth.[81] It is a strict aerobe, Gram-negative, non-lactose fermenter, glucose oxidiser, catalase-positive, and oxidase-negative, which grows at 44^{0}C, but practically these properties cannot confidently specify *A. baumannii* and could be easily misinterpreted with the other clinically relevant *Acinetobacter* species. The overnight colony morphology of *A. baumannii* on sheep blood agar at 37℃ is light grey, circular, convex, entire, translucent, shiny, mucoid, and non-pigmented.

Automated methods like analytical profile index (API) kits, VITEK 2 system, and matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI TOF MS) are currently used for the identification of different species.[82] The 16S ribosomal DNA sequence comparison, amplified fragment length polymorphism (AFLP), and amplified 16S ribosomal DNA restriction analysis (ARDRA) are also used to identify *Acinetobacter* species in comparison with restriction enzyme-digested DNA fragment pattern on a gel.[83] Amplification of *recA* and *bla*$_{OXA-51}$-like gene using Real-time PCR is also used for identification of *A. baumannii*. At present, phylogenetic trees of *rpoB* gene or 7 housekeeping genes from multilocus sequence typing (MLST) are an indeed more reliable way to discriminate between species within *Acb*-complex that includes six species: *A. calcoaceticus, A. baumannii, A. pittii, A. nosocomialis, A. seifertii,* and *A. dijkshoorniae*, as well as NIPH 542 and NIPH 817 that have no scientific names.[83-84]

6.2. Advance technology

6.2.1. Detection of *Acinetobacter baumannii* by nanoparticles

A. baumannii infections can cause serious damage to patients if not treated in a timely manner. Therefore, it is relevant to implement rapid analytical methods to detect *A. baumannii* to control its spread. DNA-based techniques as conventional methods have been employed for the identification of *A. baumannii*.[85-86] However, these methods are complicated and require well-trained personnel. Currently, nanoparticle-based diagnostic procedures, such as fluorescence technique, colorimetric assays along with gold nanoparticles, and fluorescence nanoprobes, are used for detection of *A. baumannii*.[87-90] As a result of the attraction and ease-of-functionalisation of magnetic nanoparticles, they are used very often to trap bacteria from complex clinical specimens, and those bacteria trapped by functional magnetic nanoparticles may be readily identified using MALDI-TOF mass spectrometry.[91-93]

Yi-Ling et al. reported on Fe_3O_4 and Al_2O_3 magnetic nanoparticles against *A. baumannii*, with values of M3237 and 54149, respectively.[94] The bacteria trapped by functional nanoparticles were characterised using MALDI-TOF mass spectrometry, and the specificity and sensitivity of these nanoprobes against particular *A. baumannii* strains were evaluated.[95] Similarly, Khalil et al. developed a nano-gold assay, which can colorimetrically identify and differentiate *A. baumannii* from other Gram-negative bacteria.[88] Chan et al. reported that the gold nanoclusters encapsulated with lysozyme in the presence of red photo-luminescence act as affinity probes to attract and accumulate infectious bacteria such as *A. baumannii, Enterococcus faecalis,* and *Staphylococcus aureus*.[94] Chan et al. reported that MALDI-MS coupled with principal component analysis could identify bacteria in the conjugates. A fluorometric assay is used to demonstrate *A. baumannii* in the blood specimen using Zr-MOFs with methods such as functional coating for magnetic Fe_3O_4 nanoparticles to offer surface modification and as a carrier to fluorescein to create fluorescence indicators.[89,95]

6.2.2. Multi-omics analysis of *A. baumannii*

Infections caused by *A. baumannii* are a crucial cause of morbidity and mortality in hospital settings, and *A. baumannii* resists a wide spectrum of antibiotics used to treat the infections. Therefore, many researchers have focused on studying insight into the mechanisms of actions of the drugs against the pathogen.[96-97] Multi-omics analysis, including proteomic, genomic, and transcriptomic analyses, is a powerful tool to shed light on the key expression of genes, metabolites, and proteins in the different metabolic pathways, as shown in Table I. The method has been used to study the expression of genes and metabolites in exposure to antibiotics and nutrient-limited conditions.

In a study on proteomic analysis, Tiwari and team reported that the excess production of membrane proteins like ferric-acinetobactin, ferrienterochelin, ferric siderophore, and FhuE receptors were detected under iron-limited conditions.[98] Besides, the interaction between FhuE receptor and siderophores was synthesised by *A. baumannii* as well as other bacteria in iron acquirement. Depending upon the immune status established by the host, the interaction between the siderophores and the corresponding receptors favours iron sequestration and bacterial survival. It has been concluded that the target-FhuE receptor inhibits siderophore-mediated iron acquirement in *A. baumannii*.[98] It has been reported that a total of 65 unique periplasmic proteins of the pathogen were identified underexposure and un-exposure to imipenem; among these, the eight types of proteins were associated with protein fate in relation to antibiotic resistance, energy metabolism, and oxidative stress (Figure 2).[99] In antibiotic resistance, four proteins were detected, which include GES-11, the carbapenemases OXA-23, the cephalosporinase AmpC, and the RND-type efflux pump AdeT. In protection against oxidative stress, ABUW_2868 encoding a heat shock protein was possibly found to be associated under upregulated imipenem-exposed bacteria.[99]

A combination of drugs is a powerful treatment to cure the infection caused by *A. baumannii*. A synergistic effect of colistin in combination with sulbactam against the organism has been reported. The combination was carried out by colistin through agitation of the levels of fatty acid and phospholipid at 1 hour. The biosynthesis of the bacterial cell wall was perturbed when *A. baumannii* was treated with sulbactam alone and the combination over 24 hours. Using metabolic analysis, expression of uridine diphosphate-N-

Table I: Multi-omics analysis of *Acinetobacter baumannii*

Type of Omics	Result	Reference
Proteomic	- It was found that the outer membrane vesicles of antibiotic-sensitive strain consisted of 8 antibiotic resistance-conferring proteins. In contrarily, the vesicles of multidrug-resistant stain comprised 24 proteins of antibiotic resistance.	96
Proteomic	- It was shown that Type II secretion system secretome provides an advantage of the colonization to the pathogen multi-drug resistant strain rather than the reference strain used for biofilm formation.	97
Proteomic	- The over-expression of four membrane proteins including ferric-acinetobactin, ferrienterochelin, ferric siderophore, and Fhu-E receptors were detected under iron-limited conditions. - The interaction between FhuE receptor and siderophores was produced by *A. baumannii* as well as other bacteria in iron acquirement. - Under nutritional immunity established by the host, The interaction between the receptor and siderophores helps in iron sequestration and survival of *A. baumannii*. - FhuE receptor, as a target, was shown to inhibiting siderophore-mediated iron acquirement in *A. baumannii*.	98
Proteomic	- A total of 65 unique periplasmic proteins were identified underexposure and un-exposure to imipenem. - There are eight proteins involved in protein fate and response to antibiotic-resistance, energy metabolism, and oxidative stress. - In antibiotic-resistance, four proteins were detected which include GES-11, the carbapenemases OXA-23, the cephalosporinaseAmpC, and the RND-type efflux pump AdeT. - In protection against oxidative stress, ABUW_2868 encoding a heat shock protein was likely found to be involved under upregulated in imipenem-exposed bacteria.	99
Metabolomic	- A synergistic effect of colistin in combination with sulbactam against *A. baumannii* has been reported. - The combination was carried out by colistin through agitation of the levels of fatty acid and phospholipid at 1 h. - The biosynthesis of the bacterial cell wall was perturbed when *A. baumannii* was treated with sulbactam alone and the combination over 24 hrs. - Expression of uridine diphosphate-N-acetylglucosamine and uridine diphosphate-N-acetylmuramate involved in amino sugar metabolism were decreased when the pathogen was treated with the drug combination.	100
Metabolomic	- A synergistic effect of colistin in combination with doripenem against *A. baumannii* has been reported. - Perturbation of glycerophospholipids and fatty acids by colistin resulted in the disruption of A. baumannii outer membrane and cell wall. - Doripenem alone suppressed the expression of peptidoglycan biosynthesis metabolites at 4 h. - The combination of the drugs suppressed the expression of D-sedoheptulose 7-phosphate (nucleotid metabolism) and D-ribose 5-phosphate (pentose phosphate pathway).	101
Transcriptomic	- The upregulation of genes associated with transposable elements was detected when the bacteria were treated with antibiotic including amikacin, imipenem, and meropenem. - In pan-drug resistant *z*strains, overexpression of amino acid metabolism and membrane transporters has been reported. - Antibiotic resistance genes were up-regulated in both antibiotic-resistant and -sensitive strains of *A. baumannii*.	102
Transcriptomic	- Under tigecycline pressure, upregulation of efflux pumps including RND transporter permease subunit, EmrAB, MacB, and Tet resistance operon was detected in antibiotic-resistant *A. baumannii*, when compared with the sensitive strain. - Genes related to benzene-containing compound metabolic process, translation, ribosomal structure, and biogenesis were found to be overexpress in the resistant strain treated with tigecycline.	103
Transcriptomic and proteomic	- Upregulation of ribosomal proteins and resistance pumps including MFS, RND, MATE, and ABC transporters were observed in *A. baumannii* treated with eravacycline. - In outer membrane vesicle, overexpression of ribosomal proteins, toluene tolerance protein, siderophore receptor, and peptidases was detected in multidrug-resistant *A. baumannii*.	104 \

Table II: Antimicrobial activity of plant-derived compounds against *Acinetobacter baumannii*

Product/Plant species	Examination procedure	Antibacterial activity	Reference
Norwogonin/*Scutellaria baicalensis*	MIC_{90} determination	MIC_{90} = 128 µg/mL	129
Terchebulin/*Terminalia chebula*	MIC_{90} determination	MIC_{90} = 500 µg/mL	129
Ellagic acid/*Terminalia chebula*	MIC_{90} determination	67% inhibition at 250 µg/mL	129
Chebulagic acid/*Terminalia chebula*	MIC_{90} determination	60.39% inhibition at 62.5 µg/mL and 88% inhibition at 1,000 µg/mL	129
Chebulinic acid/*Terminalia chebula*	MIC_{90} determination	65% inhibition at 62.5 µg/mL	129
Corilagin/*Terminalia chebula*	MIC_{90} determination	56% inhibition at 15.625 µg/ml and 83% inhibition at 1,000 µg/mL	129
Norwogonin/ *Scutellaria baicalensis*	Time-kill analysis	Complete growth inhibition at 2 ×MIC (256 µg/mL) after 24 h	129
Ellagic acid	Inhibition zone measurement	Increased inhibition zone of aminocoumarins (novobiocin, chlorobiocin, and coumermycin), tetracycline, rifampicin, andfusidic acid by 4 to >8 mm	130
Tannic acid	Inhibition zone measurement	Increased inhibition zone of aminocoumarins (novobiocin, chlorobiocin, and coumermycin), tetracycline, rifampicin, and fusidic acid by 4 to >8 mm	130
Ellagic acid	MIC determination	2- to 4-fold reduction in MICs of novobiocin, chlorobiocin, coumermycin, fusidic acid, and rifampicin	130
Tannic acid	MIC determination	2- to 4-fold reduction in MICs of novobiocin, chlorobiocin, coumermycin, rifampicin, and tetracycline	130
(–)-epigallocatechin-3-gallate/ *Camellia sinesis*	Inhibition zone measurement	IZ = up to 7 mm	131
(–)-epigallocatechin-3-gallate/ *Camellia sinesis*	MIC determination	MIC_{50} = 0.312 µg/mL MIC_{90} = 0.625 µg/mL	131
(–)-epigallocatechin-3-gallate/ *Camellia sinesis*	Chequerboard assay	The synergistic effect at a concentration of 0.039 µg/µL in combination with 0.625% µg/µL concentration of mafenide acetate (Sulfamylon)	131
(–)-epigallocatechin-3-gallate/ *Camellia sinesis*	Time-kill analysis	3-log reduction in CFU/ml at 2 ×MIC after 5 h	131
Oleanolic acid	MIC determination	MIC = 512 µg/mL A 4-fold reduction in MICs of both aminoglycosides gentamicin and kanamycin	132
Oleanolic acid	Chequerboard assay	Synergistic effect in combination with both gentamicin and kanamycin, with FICI values of 0.375 and 0.313, respectively	132
Oleanolic acid	Time-kill analysis	Bactericidal effect at < 1/16 MIC (64 µg/mL) in combination with gentamicin at 1/16 MIC (0.13 µg/mL) concentration	132
Cinnamon natural oil	MIC determination	MIC = 0.125-1 mg/mL	133
Clove natural oil	MIC determination	MIC = 0.125-1 mg/mL	133
Thyme natural oil		MIC determination MIC = 0.25-1 mg/mL	133
Tea tree natural oil	MIC determination	MIC = 0.25-2 mg/mL	133
Lavander natural oil	MIC determination	MIC = 0.25-3 mg/mL	133
(-) Terpinen-4-ol	MID determination	MID = 130.61 mg/L	134
Carvacrol	MID determination	MID = 4.88 mg/L	134
Carvacrol	MID determination	MID = 3.89-48.8 mg/L	134
Tea tree oil (NanoTTO)/ *Melaleuca alternifolia*	MIC determination	MIC = 3.52 mg TTO/mL	141
Oregano essential oil/ *Origanum vulgare*	MIC and MBC determination	MIC = 0.298 mg/Ml MBC = 0.298 mg/mL	142
Oregano essential oil/ *Origanum vulgare*	Chequerboard assay	Additive antibacterial effect at concentration of 0.149 mg/mL in combination with 15.62 µM concentration of Bio-AgNP, with FICI values of 0.62	142

Bio-AgNP: Biological silver nanoparticles, FICI: Fractional inhibitory concentration index, IZ: Inhibition zone, MBC: MIC: Minimum bactericidal concentration, Minimum inhibitory concentration, MID: Minimum inhibitory dose

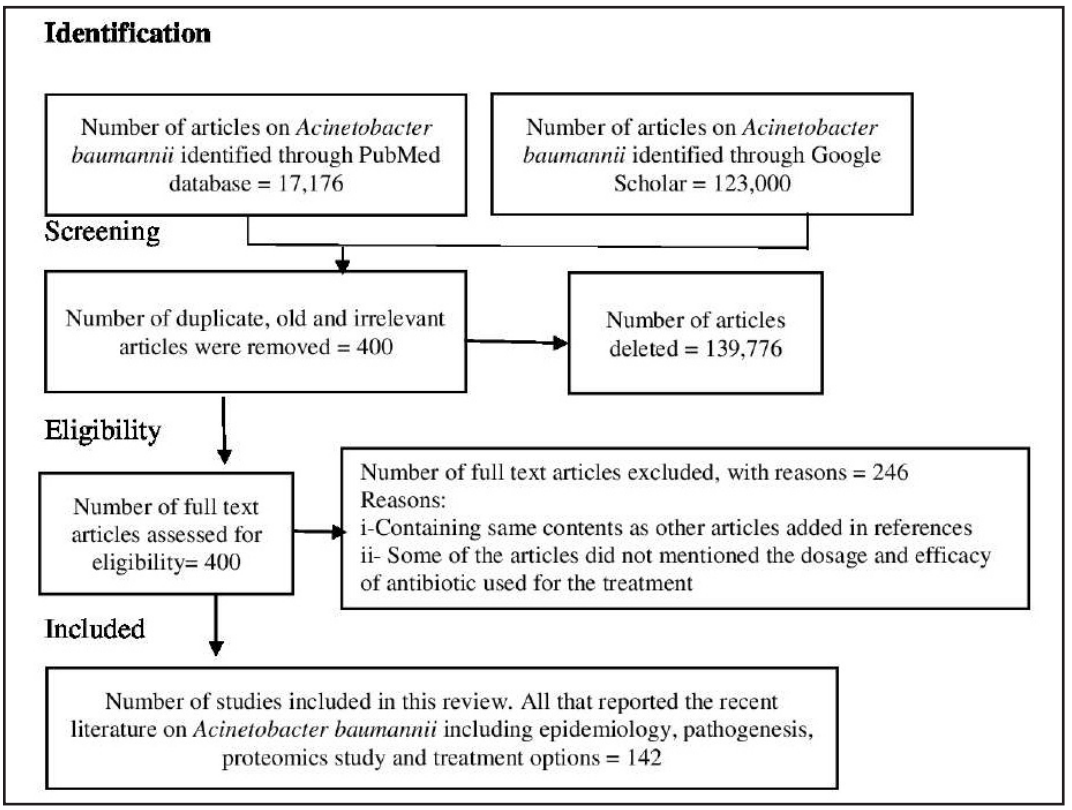

Fig. 1: The overall flowchart of phases used to identify published articles included in this review.

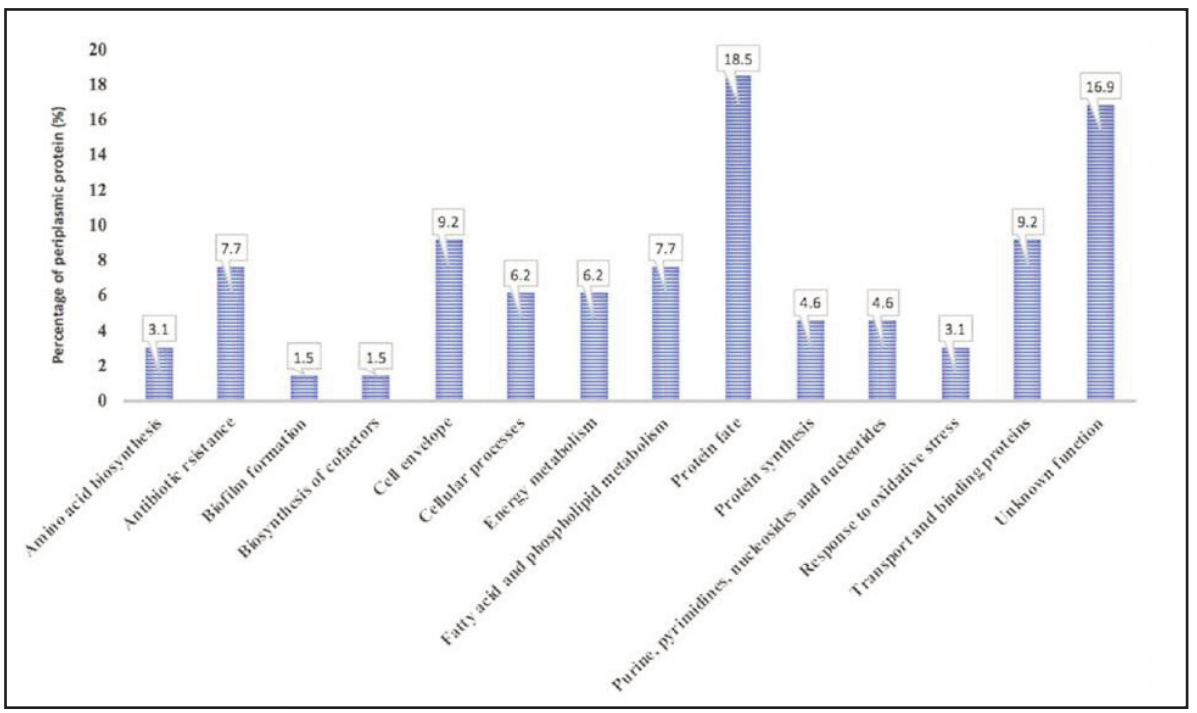

Fig. 2: Periplasmic proteins identified in MDR *A. baumannii* strain AB7075 cultured in the presence and absence of imipenem.

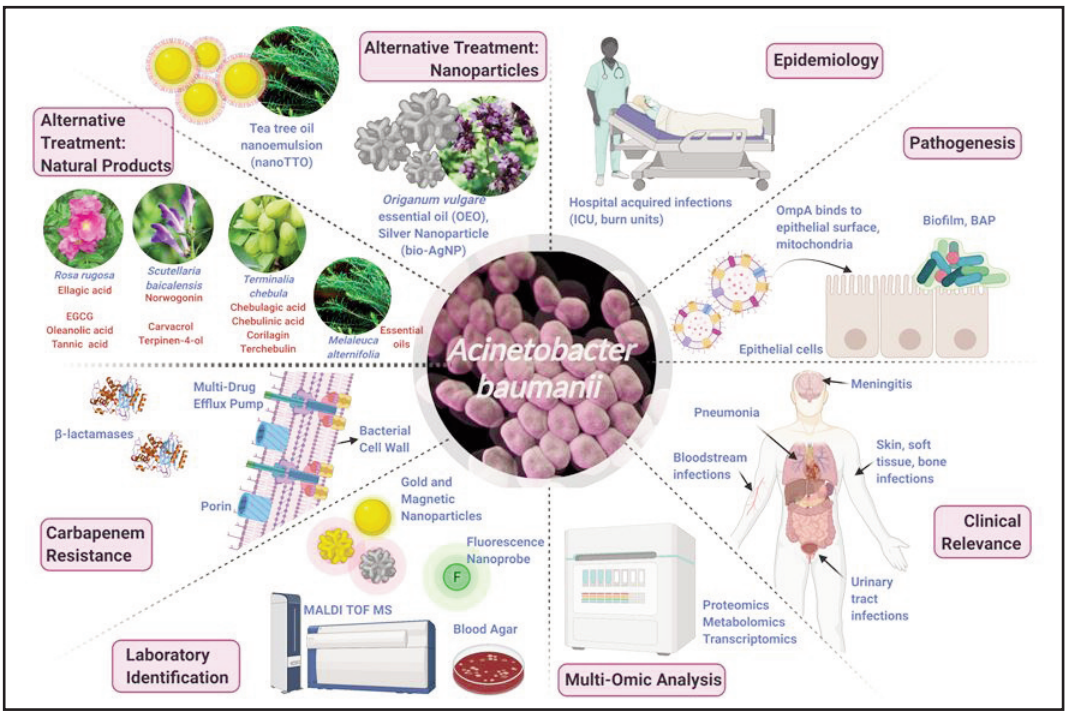

Fig. 3: Overview of *A. baumannii*.

acetylglucosamine and uridine diphosphate-N-acetylmuramate involved in amino sugar metabolism was decreased when the pathogen was treated with the drug combination.[100] Maifiah and the team reported the synergistic effects of colistin in combination with doripenem against *A. baumannii*.[101] The perturbation of glycerophospholipids and fatty acids by colistin resulted in the disruption of *A. baumannii* outer membrane and cell wall. Doripenem alone suppressed the expression of peptidoglycan biosynthesis metabolites at 4 hours. The combination of the drugs suppressed the expression of D-sedoheptulose 7-phosphate (nucleotid metabolism) and D-ribose 5-phosphate (pentose phosphate pathway).[101]

Study on transcriptomic analysis, Qin and team reported that upregulation of genes associated with transposable elements was detected when the bacteria were treated with antibiotics, including amikacin, imipenem, and meropenem.[102] In pan-drug resistant *A. baumannii* strains, overexpression of amino acid metabolism and membrane transporters has been reported. Antibiotic resistance genes were upregulated in both antibiotic-resistant and sensitive strains of *A. baumannii*.[102] Under tigecycline pressure, upregulation of efflux pumps, including RND transporter permease subunit, EmrAB, MacB, and Tet resistance operon, was detected in antibiotic-resistant *A. baumannii*, compared with the sensitive strain. Genes linked to the metabolism of benzene-containing compounds, translation, ribosomal structure, and biogenesis were found to be overexpressed in the resistant strain treated with tigecycline.[103] Integration of transcriptomic and proteomic analysis is a powerful tool to clarify the key expression of genes and proteins in the organism. Kesavan and team reported that the upregulation of ribosomal proteins and resistance pumps, including MFS, RND, MATE, and ABC transporters, was observed in *A. baumannii* treated with eravacycline. In the outer membrane vesicle, overexpression of ribosomal proteins, toluene tolerance proteins, siderophore receptors, and peptidases was detected in multidrug-resistant *A. baumannii*.[104]

In summary, multi-omics analysis, including proteomic, genomic, and transcriptomic analyses, is a powerful tool to shed light on the key expression of genes, metabolites, and proteins in the different metabolic pathways. The analysis can be used to identify the antibacterial mode of action and the expression of the resistance mechanism of the drug against *A. baumannii*.

7. Treatment

It is well known that carbapenems are the drug of choice against the infection caused by multidrug-resistant *A. baumannii*. For *A. baumannii* resistant to carbapenem, tigecycline and colistin are used.[30] The global emergence of MDR, XDR, and PDR *A. baumannii* and the paucity of newer antimicrobial compounds are a major challenge for the healthcare industries.[105] For PDR *A. baumannii*, combination therapies like carbapenem+ampicillin/sulbactam, carbapenem+colistin, colistin+rifampicin+sulbactam, and tigecycline+rifampicin+ampicillin have been used worldwide. The combination therapies are costly, and their toxicity and adverse effects are strong.[106]

7.1. Carbapenem resistance in *A. baumannii*

Currently, most strains of *A. baumannii* are highly resistant to broad-spectrum antibiotics used clinically. Several resistance mechanisms targeting different antibiotic classes are observed in *A. baumannii*, such as production of β-lactamases, efflux pumps, aminoglycoside-modifying enzymes, permeability defects, and target sites alteration.[107] Mostly these mechanisms target the different antibiotic classes; however, various mechanisms can also support the resistance to a single antibiotic class. The chief β-lactamases resistance

mechanism involving carbapenem-hydrolysing property is due to the presence of class Docxcillinase and class B metallo-β-lactamases (MBLs). In addition, the loss or mutation of CarO porins and alteration of penicillin-binding proteins also favour carbapenem resistance.[108-109] The dissemination of multidrug resistance determinants in *A. baumannii* is strongly due to plasmid conjugation and acquisition of transposons, which leads to mobilisation of a bunch of drug resistance genes to several antibiotic class.[110] Furthermore, the presence of insertion sequences also multiplies the antibiotic-resistant strains.[111]

The leading source of carbapenem resistance in *A. baumannii* is due to the presence of class D (OXA) oxacillinase, a type of beta lactamase, which occurs naturally in *A. baumannii* (OXA51/66 group). In most strains, the oxacillinase, OXA-51-like genes are expressed poorly, having less influence on susceptibility pattern to all beta-lactam antibiotics, including carbapenems. The expression and influence of these genes are also facilitated by the presence of insertion sequence ISAba1, when present upstream to the structural gene, further leading to the development of carbapenem resistance in *A. baumannii*.[112] Based on sequence homology, OXA carbapenemases are further grouped into the various clusters: OXA-23-like (includes OXA-27 and OXA-49), OXA-(24)-40-like (includes OXA-25, OXA-26, and OXA-40), and OXA-58.[113] The OXA-23-like genes, which are most commonly seen in *A. baumannii*, are mediated through both chromosome and plasmid. The OXA-23-like genes in *A. baumannii* have been frequently observed since 1985, including the strains obtained from outbreaks in the UK, Asia, and South America. This strain exists in one multi-resistant clone, which is prevalent in the UK and identified as OXA 23 clone-1.[114] Another oxacillinase group of resistance genes, OXA-24-like, which are also chromosomal or plasmid mediated, are less prevalent compared to OXA-23-like genes, with data mainly restricted to European countries and the United States.[115] The expression of other genes like ambler class B metallo-beta lactamases (MBLs), such as IMP, VIM, and SIM-1, was also observed in *A. baumannii*. The expression of these genes also confers a high level of resistance to most of the beta lactams, including carbapenems, but excluding aztreonam.[116]

7.2. Drug metabolism

Carbapenem-resistant *A. baumannii* strains are considered as a pathogen for causing life-threatening infections since no alternative therapy is available. Though the mechanisms leading to antibiotic resistance in *A. baumannii* have been studied extensively, the general response to keep the viability of bacteria under antimicrobial exposure needs more investigation.[117] A study based on periplasmic protein of MDR *A. baumannii* strain AB7075 cultured in the presence and absence of imipenem reported that besides carbapenems, the periplasmic space also displays various other proteins with essential functions of the cell. In both types of culture conditions, a total of 65 periplasmic proteins were detected by proteomic approach, and out of this, eight proteins were associated with protein fate, resistance to antibiotics, energy breakdown, and reaction to oxidative stress. Among these proteins, some gene products like ABUW_1746 and ABUW_2363 presented the tetratricopeptide repeat motif, which mediates the protein–protein interactions. These proteins expressed by the genes can regulate definite proteins and help to adapt well in altered environmental situations. The heat shock proteins coded by ABUW_2868 genes are possibly associated with defence against oxidative damage, which is seen upregulated in bacteria exposed to imipenem. Scribano et al. evidenced the first report on the content of the periplasmic proteins of a multidrug-resistant *A. baumannii* strain and its susceptibility to imipenem, pointing towards the probable new targets to develop substitute antibiotics.[99] The new antibacterial molecules can be designed with the knowledge of IMP upregulated proteins and their molecular functions, and it has been concluded that MDR *A. baumannii* on stressful exposure to IMP adapts various strategies to successfully cope with it.

ß-Lactamases, coded chromosomally, plays an important role in finding alternative and efficient therapy for treatment against multidrug-resistant *Acinetobacter* spp. The occurrence of chromosome-mediated ß-lactamases, like class C *Acinetobacter*-derived cephalosporinases and class D oxacillinases, and also the existence of plasmid-encoded class A ß-lactamases represent a therapeutic challenge in *Acinetobacter* spp. The newly permitted ß-lactamase inhibitors such as avibactam and vaborbactam represent a range of gap in inhibition against OXA like ß-lactamase. The new, sensibly designed, diazabicyclooctenone inhibitor ETX2514 adequately targets against all, class A, C, and D ß-lactamases.[118] Barnes et al. showed that the sulbactam-ETX2514 combination has an extensive inhibitory range to target class D, A, and C ß-lactamases and also promising treatment options against infections induced by MDR *Acinetobacter* spp.[119] For instance, curcumin in combination with blue light is an effective photodynamic treatment (PDT), exerting antimicrobial operation. In one of the studies, Chang et al. explored the probable underlying mechanism to examine the protein carbonylation in response to the bactericidal action in the presence of oxidative stress when *A. baumannii* resistant to imipenem was subjected to blue light assisted curcumin a shotgun proteomics approach has been implemented and afterwards, the bacterial proteins were extracted, 2,4-dinitrophenylhydrazine (DNPH) derivatised, and trypsin were digested.[118] On searching the customised database, the carbonylated proteins were documented, and the analysis of the peptides was conducted using LC-nano ESI ion trap mass spectrometry. After utilising the investigation of gene ontology, annotation and the STRING protein association network for the 70 identified proteins, the commonest was the protein related to the membrane, translation, and oxidative stress response. Various proteins, which are associated in interpretation of *A. baumannii*, were described to be carbonylated targets. These proteins incorporate the lengthening factor Tu and P, two ribosomal proteins, and ribosome discharging factor. A maximum number of these interpretation-associated proteins in bacteria has been documented in past studies based on the exploration of the target macromolecules in microorganisms under oxidative pressure.[118]

Several micronutrients are required for the survival of *A. baumannii* inside the host. Among these micronutrients, the bio-availability of iron is limited by the nutritional immunity

created by the host, and because of this, *A. baumannii* needs to develop a mechanism to uptake iron while causing infections. Research by Tiwari et al.[98] attempted to recognise membrane proteins associated with the iron sequestration process of *A. baumannii* with the use of two-dimensional electrophoresis and liquid chromatography with tandem mass. The distinguished iron-directed layer protein (IRMP) of *A. baumannii* was utilised during communication studies with various siderophores, and inhibitor against *A. baumannii* was also designed focusing on this IRMP212. The four membrane proteins were overexpressed in the membrane proteomic results, which include FhuE receptor, ferric-acinetobactin receptor, ferrienterochelin receptor, and ferric siderophore receptor, under iron-constrained condition. Iron-managed layer proteins like FhuE receptor cause the bacteria to oblige during difficult situations inside the host. A great association has been observed between the siderophores produced by *A. baumannii* and the FhuE receptor. Similar results also demonstrated that FhuE receptor has an association with siderophores delivered by bacteria other than *A. baumannii*. This connection between the FhuE receptor and siderophores supports iron sequestration and bacterial survival under a nutritionally invulnerable environment. Therefore, it gets basic to locate a possible FhuE receptor–inhibitor through which the survival of *A. baumannii* within the host is suppressed. In-silico screening and molecular mechanics studies recognised ZINC03794794 and ZINC01530652 as major structure inhibitors against the FhuE receptor of *A. baumannii*. The structured inhibitors are tentatively approved for their bactericidal action against *A. baumannii*. Thus, a structured inhibitor affects the iron uptake mechanism of *Acinetobacter*, and therefore, it might be favourable in the prevention of infections caused by *A. baumannii* by constraining nutrient accessibility. Additionally, a study involving an animal model is to be performed further to explore the utilisation of FhuE receptor inhibitor and to validate its function.[98]

8. Alternative strategies for MDR *A. baumannii*

With rising antibiotic resistance and treatment difficulties, many studies have focused on alternative drugs and phytomedicine.[120] Combined actions of antibiotics and active components of plant extracts have been studied mostly as an alternative strategy.[121] Many studies stated that the synergistic action of plant active components and the antibiotics could play a role to combat drug resistance and increase bacterial susceptibility.[122] Along with the screening of herbal compounds, a nanomaterial-based approach has been tried to find susceptible alternative agents to MDR *A. baumannii*.[123] The nanoparticles having low molecular weight were potentially effective against most bacteria causing human infections.[124] Silver nanoparticles have shown antimicrobial activity against a wide array of microbes, including *A. baumannii*, probably caused by their several bactericidal mechanisms.[125] The effectiveness of synergistic action of nanoparticles and plant active components against bacterial inhibition was seen high compared to its independent action.[126] The study also demonstrated a synergistic effect of imipenem and silver nanoparticles against *A. baumannii* planktonic cells as well as biofilms.[127]

8.1. Use of natural products and nanoparticles

Many plant active compounds (Table II) are being used worldwide as traditional remedies against several antibiotic-resistant bacteria, including carbapenem-resistant *A. baumannii*.[128] For example, flavones, tannins, and phenolic compounds are demonstrated to have inhibitory activity against *Acinetobacter*. Miyasaki et al. reported that six compounds, including ellagic acid extracted from *Rosa* sp., norwogonin extracted from *Scutellaria baicalensis*, and chebulagic acid, chebulinic acid, corilagin, and terchebulin extracted from *Terminalia chebula*, had the maximum antimicrobial effect against *A. baumannii in vitro*.[129] Norwogonin (5,6,7-trihydroxyflavone) from *Scutellaria baicalensis* was identified as the most potent compound with a minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values of 128 µg/mL and 256 µg/mL, respectively, against clinical isolates of *A. baumannii*. Other herbal compounds, including ellagic acid (67% inhibition at 250 µg/mL), chebulinic acid (65% inhibition at 62.5 µg/mL), chebulagic acid (60.39% and 88% inhibition at 62.5 µg/mL and 1,000 µg/mL, respectively), and corilagin (56% and 83% inhibition at 15.625 µg/mL and 1,000 µg/mL, respectively) exhibited lower antimicrobial activity. Furthermore, several plant-derived phenolic compounds are reported in the medical literature to increase the strength of synthetic antibiotics against *A. baumannii*. For instance, the *in vitro* activity of several antibiotics, including novobiocin, coumermycin, chlorobiocin, rifampicin, and fusidic acid, has been increased against MDR *A. baumannii* in the presence of ellagic and tannic acids.[130] Synergy was also observed between the epigallocatechin-3-gallate (EGCG), a purified polyphenol from green tea leaves, and topical mafenide acetate (Sulfamylon) against a clinical isolate of MDR *A. baumannii in vitro*.[131] Another study showed that the MIC of aminoglycosides (e.g., gentamicin and kanamycin) in combination with oleanolic acid (a pentacyclic triterpenoid compound) decreased to one-fourth of the MIC alone in *A. baumannii*. Moreover, the fractional inhibitory concentration index (FICI) values of both aminoglycosides in combination with oleanolic acid were indicative of synergism.[132] In contrast, Miyasaki et al. observed no synergy effect between anti-Gram-negative antibiotics and norwogonin.[129]

Interest in the inspection of antimicrobial properties of aromatic plant extracts has grown, particularly essential oils (also known as volatile oils).[132] One study found that cinnamon, thyme, lavender, clove, and tea tree essential oils had very powerful activity against *A. baumannii* with MIC values from 0.125 to 1 mg/mL, followed by lemon and orange oils with MIC value > 2 mg/mL.[133] The antibacterial activities of 15 essential oil compounds against hospital-associated pathogens, including clinical isolates of multidrug-resistant *A. baumannii* were reported, and among carvacrol and terpinen-4-ol, the latter had broad antimicrobial spectrum affecting all five pathogenic species, ESBL-*Klebsiella pneumoniae*, ESBL-*Escherichia coli*, MDR *A. baumannii*, ATCC Methicillin-resistant *Staphylococcus aureus* (MRSA), and *Pseudomonas aeruginosa*. In particular, carvacrol showed strong activity, such as very low MIDs for MDR *A. baumannii* (4.88 mg/L) and MRSA (24.4 mg/L) compared to other bacterial species tested, representing an important molecule against infection, especially for *A. baumannii* resistant to carbapenem.[134]

Nanoparticles have received great attention in recent years to combat antimicrobial resistance in microbial pathogens.[135] Several types of nanoparticles, such as silver, gold, zinc, chitosan, platinum, iron, copper, and carbon nanotubes, have been evaluated for their antimicrobial activity in combination with essential oils.[136-140] One study assessed the antimicrobial activity of tree tea oil nanoemulsion (nanoTTO) against different microbial pathogens associated with pneumonia, including *A. baumannii*.[141] The nanoTTOs showed strong antibacterial effects in *A. baumannii* ATCC19606 with the MIC of 3.52 mg TTO/mL. Furthermore, this nanoemulsion notably decreased the lung injury of pneumonia induced by *A. baumannii* in the rat model, indicating its relatively high in vivo anti-*A. baumannii* effect, which is vital for the treatment of bacterial pneumonia. In another study, *Origanum vulgare* essential oil (OEO) and the biologically synthesised silver nanoparticle (bio-AgNP) showed a bactericidal effect in low concentration against all bacterial strains resistant to multi-drugs tested, with MBC values of 0.298 mg/mL and 125 µM, respectively, for multidrug-resistant to carbapenem-resistant *A. baumannii* isolate.[142]

Besides, the combination of OEO and bio-AgNP resulted in significantly lower MICs compared to individual treatment, where the two compounds together led to additive antibacterial activity against *A. baumannii*. Taken together, the promising results of synergistic and additive interactions are a milestone that facilitates the combination of nanoparticles and antimicrobial compounds derived from plants as antimicrobial agents to be applied in certain industries (e.g., cosmetics, food, and pharmaceuticals) and healthcare facilities for the control and treatment of various infections or disinfection of hospitals to combat pathogens resistant to several multi-drugs, particularly *A. baumannii*.

The synergistic action of nanoparticles and antibiotics could be a promising treatment option to combat bacterial resistance in future. Moreover, nanoparticles have the property to deliver antibiotics to the infected cells and also decrease the dose and toxicity of antibiotics.[143] The synergistic bactericidal action of antibiotics and silver nanoparticles at low concentrations against different bacteria including *A. baumannii* has been reported.[144] Though the plant extract and metal-based nanoparticles, alone or in synergy with antibiotics, have shown their bactericidal activity against *A. baumannii* and other bacteria *in vitro*, to confirm this as a novel treatment against various bacterial infections, without causing severe damage to the human cells, there should be a randomised control study. The nanomaterial causes huge cell damage *in vitro*, which is not suitable for direct application to human cells without proper dosage recommendation based on clinical trials. The appropriate and effective dosage that is suitable for use in human infections needs to be studied thoroughly, and more clinical trials are needed before the application of nanoparticle-based treatment in patients.

9. Conclusion

The clinical significance of *A. baumannii* in the past one and half decades has been increased by its isolation in ICU patients causing several infections, high morbidity, and mortality, its resistant-acquiring mechanisms, and its emergence as a prominent nosocomial pathogen challenging the current antibiotic era. To combat dissemination of this MDR bug, strict hospital aseptic procedures and appropriate antimicrobial stewardship policies are highly recommended. The prompt diagnosis of *A. baumannii* infections to overcome serious damage to the patients is a sole priority. The MALDI-TOF mass spectrometry and nanoparticle-based diagnostic procedures involving fluorescence technique, colorimetric assays, and fluorescence nanoprobes are used as advanced diagnostic tools. The antibiotics and phytochemicals in combination or synergy with silver or gold nanoparticles showed a promising result to overcome this MDR challenge in future with further intensive research (Figure 3).

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REFERENCES

1. Lin MF, Lan CY. Antimicrobial resistance in *Acinetobacter baumannii*: From bench to bedside. World J Clin Cases 2014; 2(12): 787-814.
2. Henriksen SD. Moraxella, Acinetobacter, and the mimeae. Bacteriol Rev 1973; 37(4): 522-61.
3. Rossau R, Van LA, Gillis M, De-Ley J. Taxonomy of Moraxellaceae fam. Nov., a new bacterial family to accommodate the genera Moraxella, Acinetobacter, and Psychrobacter and related organisms. Int J System Bacteriol 1991; 41(2): 310-19.
4. Peleg AY, SeifertH, Paterson DL. *Acinetobacter baumannii*: Emergence of a successful pathogen. Clin Microbiol Rev 2008; 21(3): 538-82.
5. Chuang YC, Sheng WH, Li SY, Lin YC, Wang JT, Chen YC, et al. Influence of genospecies of *Acinetobacter baumannii* complex on clinical outcomes of patients with *Acinetobacter bacteremia*. Clin Infect Dis 2011; 52(3): 352-60.
6. Al Atrouni A, Joly-Guillou ML, Hamze M, Kempf M. Reservoirs of non-*Acinetobacter baumannii* species. Front Microbiol 2016; 7: 49.
7. Zhang WJ, Lu Z, Schwarz S, Zhang RM, Wang XM, Si W, et al. Complete sequence of the bla(NDM-1)-carrying plasmid pNDM-AB from *Acinetobacter baumannii* of food animal origin. J Antimicrob Chemother 2013; 68(7): 1681-2.
8. Bouvet PJ, Grimont PA. Identification and biotyping of clinical isolates of Acinetobacter. Annales de l'Institut Pasteur/Microbiologie 1987; 138(5): 569-78.
9. Spellberg B, Bonomo RA. The deadly impact of extreme drug resistance in *Acinetobacter baumannii*. Crit Care Med 2014; 42(5): 1289-91.

10. Scott P, Deye G, Srinivasan A, Murray C, Moran K, Hulten E, et al. An outbreak of multidrug-resistant *Acinetobacter baumannii*-calcoaceticus complex infection in the US military health care system associated with military operations in Iraq. Clin Infect Dis 2007; 44(12): 1577-84.
11. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009; 302(21): 2323-9.
12. Tiwari V, Moganty RR. Conformational stability of OXA-51 beta-lactamase explains its role in carbapenem resistance of *Acinetobacter baumannii*. J Biomol Struct Dyn 2014; 32(9): 1406-20.
13. Bravo Z, Orruno M, Parada C, Kaberdin VR, Barcina I, Arana I. The long-term survival of *Acinetobacter baumannii* ATCC 19606(T) under nutrient-deprived conditions does not require the entry into the viable but non-culturable state. Arch Microbiol 2016; 198(5): 399-407.
14. Su CH, Wang JT, Hsiung CA, Chien LJ, Chi CL, Yu HT, et al. Increase of carbapenem-resistant *Acinetobacter baumannii* infection in acute care hospitals in Taiwan: Association with hospital antimicrobial usage. PloS One 2012; 7: e37788.
15. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. Bad bugs, no drugs: No ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis.2009; 48(1): 1-12.
16. World Health Organization, Geneva. 2017. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. News release by the WHO.
17. Tomaras AP, Dorsey CW, Edelmann RE, Actis LA. Attachment to and biofilm formation on abiotic surfaces by *Acinetobacter baumannii*: Involvement of a novel chaperone–usher pili assembly system. Microbiol 2003; 149(pt 12): 3473–84.
18. Jawad A, Seifert H, Snelling AM, Heritage J, Hawkey PM. Survival of *Acinetobacter baumannii* on dry surfaces: Comparison of outbreak and sporadic isolates. J Clin Microbiol 1998; 36(7): 1938–41.
19. Santella G, Docquier JD, Gutkind G, Rossolini GM, Radice M. Purification and biochemical characterization of IMP-13 metallo-beta-lactamase. Antimicrob Agents Chemother2011; 55(1), 399-401.
20. McConnell MJ, Actis L, Pachon J. *Acinetobacter baumannii*: Human infections, factors contributing to pathogenesis and animal models. FEMS Microbiol Rev 2013; 37(2): 130-55.
21. Roca I, Espinal P, Vila-Farres X, Vila J. The *Acinetobacter baumannii* oxymoron: Commensal hospital dweller turned pan-drug-resistant menace. Front Microbiol 2012; 3: 148.
22. Ramirez MS, Merkier AK, Quiroga MP, Centron D. *Acinetobacter baumannii* is able to gain and maintain a plasmid harbouring In35 found in Enterobacteriaceae isolates from Argentina. Curr Microbiol 2012; 64(3): 211-3.
23. Higgins PG, Perez-Llarena FJ, Zander E, Fernandez A, Bou G, Seifert H. OXA-235, a novel class D β-lactamase involved in resistance to carbapenems in *Acinetobacter baumannii*. Antimicrob Agents Chemother 2013; 57(5): 2121-6.
24. Li XM, Choi JA, Choi IS, Kook JK, Chang YH, Park G, et al. Development and evaluation of species-specific PCR for detection of nine Acinetobacter species. Ann Clin Lab Sci 2016; 46(3): 270-8.
25. Kanafani AZ, Kanj SS, 2014. Ministry of Health, Kingdome of Saudi Arabia. http://www.updates.com/contents/ XXXcinetobacter-infection-treatment-and –prevention.
26. Ntusi NB, Badri M, Khalfey H, Whitelaw A, Oliver S, Piercy J, et al. ICU-associated *Acinetobacter baumannii* colonisation/infection in a high HIV prevalence resource-poor setting. PloS One2012; 7(12): e52452.
27. Simor AE, Lee M, Vearncombe M, Paul LJ, Barry C, Gomez M, et al. An outbreak due to multirésistant *Acinetobacter baumannii* in burn unit: Risk factors for acquisition and management. Infect Control Hosp Epidemiol 2002; 23(5): 261-67.
28. Centers for Disease Control and Prevention. *Acinetobacter baumannii* infections among patients at military medical facilities treating injured U.S. service members, 2002-2004. MMWR Morb Mortal Wkly Rep 2004; 53(45): 1063-6.
29. Falagas ME, Vardakas KZ, Kapaskelis A, Triarides NA, Roussos NS. Tetracyclines for multidrug-resistant *Acinetobacter baumannii* infections. Int J Microb Agents 2015; 45(5): 455-60.
30. Fournier PE, Richet H, Weinstein RA. The epidemiology and control of *Acinetobacter baumanniiin* health care facilities. Clin Infect Dis 2006; 42(5): 692-9.
31. Longo F, Vuotto C, Donelli G. Biofilm formation in *Acinetobacter baumannii*. New Microbiol 2014; 37(2): 119-27.
32. Huang YC, Su LH, Wu TL, Leu HS, Hsieh WS, Chang TM, et al. Outbreak of *Acinetobacter baumannii* bacteremia in a neonatal intensive care unit: Clinical implications and genotyping analysis. Pediatr Infect Dis J 2002; 21(12): 1105-9.
33. Hartstein AI, Rashad AL, Liebler JM, Actis LA, Freeman J, Rourke JW, et al. Multiple intensive care unit outbreak of *Acinetobacter calcoaceticus* subspecies anitratus respiratory infection and colonization associated with contaminated, reusable ventilator circuits and resuscitation bags. Am J Med 1988; 85(5): 624-31.
34. Shamsizadeh Z, Nikaeen M, Esfahani BN, Mirhoseini SH, Hatamzadeh M, Hassanzadeh A. Detection of antibiotic resistant *Acinetobacter baumannii* in various hospital environments: Potential sources for transmission of Acinetobacter infections. Environ Health Prev Med 2017; 22(1): 44.
35. Weiner LM, Webb AK, Limbago B, Dudeck MA, Patel J, Kallen AJ, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: Summary of data reported to the national healthcare safety network at the Centers for Disease Control and Prevention, 2011-2014. Infect Control Hosp Epidemiol 2016; 37(11): 1288-301.
36. Sader HS, Farrell DJ, Flamm RK, Jones RN. Antimicrobial susceptibility of gram negative organism isolated from patients hospitalized in intensive care units in United States and European hospitals (2009-2011). Diagn Microbial Infect Dis 2014; 78(4): 443-8.
37. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2013. [Report] Atlanta, Georgia: U.S. Department of Health and Human Services, CDC; 2013 [cited 31 May 2018]. Accessed from: https://www.cdc.gov/drugresistance/ threat-report-2013/pdf/ar-threats-2013-508.pdf.
38. Giammanco A, Cala C, Fasciana T, Dowzicky MJ. Global assessment of the activity of tigecycline against multidrug-resistant Gram-negative pathogens between 2004 and 2014 as part of the Tigecycline Evaluation and Surveillance Trial. M Sphere 2017; 2(1): e00310-16.
39. Gales AC, Jones RN, Sader HS. Contemporary activity of colistin and polymyxins B against a worldwide collection of Gram-negative pathogens: Results from the SENTRY Antimircobial Surveillance Program (2006-2009). J Antimicrob Chemother 2011; 66(9): 2070-4.
40. Lee CR, Lee JH, Park KS, Park KS, Bae IK, Kim YB, et al. Biology of *Acinetobacter baumannii*: Pathogenesis, antibiotic resistance mechanisms, and prospective treatment options. Front Cell Infect Microbiol 2017; 7: 55.
41. Gaddy JA, Actis LA. Regulation of *Acinetobacter baumannii* biofilm formation. Future Microbiol 2009; 4(3): 273-8.
42. Tomaras AP, Flagler MJ, Dorsey CW, Gaddy JA, Actis LA. Characterization of a two-component regulatory system from *Acinetobacter baumannii* that controls biofilm formation and cellular morphology. Microbiol 2008; 154(pt 11): 3398-409.
43. Fattahian Y, Rasooli I, Mousavi-Gargari SL, Rahbar MR, Astaneh SDA, Amani J, et al. Protection against *Acinetobacter baumannii* infection via its functional deprivation of biofilm associated protein (Bap). Microb Pathog 2011; 51(6): 402-6.
44. Eijkelkamp BA, Hassan KA, Paulsen IT, Brown MH. Investigation of the human pathogen *Acinetobacter baumannii* under iron limiting conditions. BMC Genom 2011; 12: 126.

45. Hood MI, Mortensen BL, Moore JL, Zhang Y, Kehl-Fie TE, Sugitani N, et al. Identification of an *Acinetobacter baumannii* zinc acquisition system that facilitates resistance to calprotectin-mediated zinc sequestration. PloS Pathog 2012; 8: e1003068.
46. Russo TA, Luke NR, Beanan JM, Olson R, Sauberan SL, MacDonald U, et al. The K1 capsular polysaccharide of *Acinetobacter baumannii* strain 307-0294 is a major virulence factor. Infect Immun 2010; 78(9): 3993-4000.
47. Choi CH, Lee EY, Lee YC, Park TI, Kim JH, Hyun SH, et al. Outer membrane protein 38 of *Acinetobacter baumannii* localizes to the mitochondria and induces apoptosis of epithelial cells. Cell Microbiol 2005; 7(8): 1127-38.
48. Jacobs AC, Hood I, Boyd KL, Olson PD, Morrison JM, Carson S, et al. Inactivation of phospholipase D diminishes *Acinetobacter baumannii* pathogenesis. Infect Immun 2010; 78(5): 1952-62.
49. Choi CH, Hyun SH, Lee JY, Lee JS, Lee YS, Kim SA, et al. *Acinetobacter baumannii* outer membrane protein A targets the nucleus and induces cytotoxicity. Cell Microbiol 2008; 10(2): 309-19.
50. Lambert T, Gerbaud G, Galimand M, Courvalin P. Characterization of *Acinetobacter haemolyticus* aac (6')-Ig geneencoding an aminoglycoside 6'-N-acetyltransferase which modifies amikacin. Antimicrob Agents Chemother 1993; 37(10): 2093-100.
51. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: A cohort study evaluating attributable mortality and hospital stay. Am J Med 1993; 94(3): 281-8.
52. Luna CM, Aruj PK. Nosocomial Acinetobacter pneumonia. Respirol 2007; 12(6): 787-91
53. Doughari HJ, Ndakidemi PA, Human IS, Benade S. Theecology, biology and pathogenesis of Acinetobacter spp.: An overview. Microbes Environ 2011; 26(2): 101-12.
54. Leung WS, Chu CM, Tsang KY, Lo FH, Lo KF, Ho PL. Fulminant community-acquired *Acinetobacter baumannii* pneumonia as a distinct clinical syndrome. Chest 2006; 129(1): 102.
55. Chen MZ, Hsueh PR, Lee LN, Yu CJ, Yang PC, Luh KT. Severe community-acquired pneumonia due to *Acinetobacter baumannii*. Chest 2001; 120(4): 1072-7.
56. Whitman TJ, Qasba SS, Timpone JG, Babel BS, Kasper MR, English JF, et al. Occupational transmission of *Acinetobacter baumannii* from a United States serviceman wounded in Iraq to a health careworker. Clin Infect Dis 2008; 47(4): 439-43.
57. Gaynes R, Edwards JR. National nosocomial infections surveillance system. Overview of nosocomial infections caused by gram-negative bacilli. Clin Infect Dis 2005; 41(6): 848-54.
58. Cisneros JM, Rodríguez-Baño J. Nosocomial bacteremia due to *Acinetobacter baumannii*: Epidemiology, clinical features and treatment. Clin Microbiol Infect 2002; 8(11): 687-93.
59. Wisplinghoff H, Edmond MB, Pfaller MA, Jones RN, Wenzel RP, Seifert H. Nosocomial bloodstream infections caused by Acinetobacter species in United States hospitals: Clinical features, molecular epidemiology, and antimicrobial susceptibility. Clin Infect Dis 2000; 31(3): 690-7.
60. Garnacho-Montero J, Amaya-Villar R, Ferra´ndiz-Millo´n C, Díaz-Martín A, López-Sánchez JM, Gutiérrez-Pizarraya A. Optimum treatment strategies for carbapenem-resistant *Acinetobacter baumannii* bacteremia. Expert Rev Anti Infect Ther 2015; 13(6): 769-77.
61. Gerner-Smidt P. The epidemiology of *Acinetobacter calcoaceticus*: Biotype and resistance-pattern of 328 strains consecutively isolated from clinical specimens. Acta Pathol Microbiol Scand Ser B Microbiol 1987; 95(1): 5-11
62. Cisneros JM, Reyes MJ, Pachón J, Becerril B, Caballero FJ, García-Garmendía JL, et al. Bacteremia due to *Acinetobacter baumannii*: Epidemiology, clinical findings, and prognostic features. Clin Infect Dis 1996; 22(6): 1026-32.
63. Basri R, Zueter AR, Mohamed Z, Alam MK, Norsa'adah B, Hasan SA, et al. Burden of bacterial meningitis: A retrospective review on laboratory parameters and factors associated with death in meningitis, Kelantan Malaysia. Nagoya J Med Sci 2015; 77(1-2): 59-68.
64. Rodríguez GA, Maradona JA, Asensi V, Cartón JA, Perez F, Blanco A, et al. Postsurgical meningitis caused by *Acinetobacter baumannii*: Study of 22 cases and review of the literature. Rev Clin Esp 2001; 201(9): 497-500.
65. Korinek AM, Baugnon T, Golmard JL, Effenterre RV, Coriat P, Puybasset L. Risk factors for adult nosocomial meningitis after craniotomy: Role of antibiotic prophylaxis. Neurosurg 2008; 62(2): 532-9.
66. Wroblewska MM, Dijkshoorn L, Marchel H, Barselaar-Van-Dan M, Swoboda-Kopec E, Broek-Van-Den PJ, et al. Outbreak of nosocomial meningitis caused by *Acinetobacter baumannii* in neurosurgical patients. J Hosp Infect 2004; 57(4): 300-7.
67. Davis KA, Moran KA, McAllister CK, Gray PJ. Multidrug-resistant Acinetobacter extremity infections in soldiers. Emerg Infect Dis 2005; 11(8): 1218.
68. Chiang WC, Su CP, Hsu CY, Chen SY, Chen YC, Chang SC, et al. Community-acquired bacteremic cellulitis caused by *Acinetobacter baumannii*. J Formos Med Assoc 2003; 102(9): 650-2.
69. Bachmeyer C, Landgraf N, Cordier F, Lemaitre P, Blum L. *Acinetobacter baumannii* folliculitis in a patient with AIDS. Clin Exp Dermatol 2005; 30(3): 256-8.
70. Ng G, Sharma BK, Fox GF. Acinetobacter skin abscess in a neonate. J Perinatol 2004; 24(8): 526-7.
71. Adler BL, Krausz A, Friedman AJ. *Acinetobacter baumannii* emerging as a multidrug-resistant skin and soft-tissue pathogen: parallels to methicillin-resistant Staphylococcus aureus. JAMA Dermatol 2014; 150(8): 905-6.
72. Sheppard FR, Keiser P, Craft DW, Gage F, Robson M, Brown TS, et al. The majority of US combat casualty soft-tissue wounds are not infected or colonized upon arrival or during treatment at a continental US military medical facility. Am J Surg 2010; 200(4): 489-95.
73. Corrigan KM, Harmis NY, Willcox MD. Association of Acinetobacter species with contact lens-induced adverse responses. Cornea 2001; 20(5): 463-6.
74. Wang AG, Wu CC, Liu JH. Bacterial corneal ulcer: A multivariate study. Ophthalmol 1998; 212(2): 126-32.
75. Gopal L, Ramaswamy AA, Madhavan HN, Saswade M, Battu RR. Postoperative endophthalmitis caused by sequestered *Acinetobacter calcoaceticus*. Am J Ophthalmol 2000; 129(3): 388-90.
76. Miller J. Acinetobacter as a causative agent in preseptal cellulitis. J Optom 2005; 76(3): 176-80.
77. Mark DB, Gaynon MW. Trauma-induced endophthalmitis caused by *Acinetobacter anitratus*. Br J Ophthalmol 1983; 67(2): 124-6.
78. Fang G, Keys TF, Gentry LO, Harris AA, Rivera N, Getz K, et al. Prosthetic valve endocarditis resulting from nosocomial bacteremia. A prospective, multicenter study. Ann Intern Med 1993; 119(7): 560-7.
79. Bert F, Lambert-Zechovsky N. Sinusitis in mechanically ventilated patients and its role in the pathogenesis of nosocomial pneumonia. Eur J Clin Microbiol Infect Dis 1996; 15(7): 533-44.
80. Dandecha P, Sangthawan P. Peritonitis in acute peritoneal dialysis in a university hospital. J Med Assoc Thai 2002; 85(4): 477-81.
81. Bouvet PJM, Grimont PAD. Taxonomy of genus Acinetobacter with recognition of Acinetobacter baumannii sp. Nov., *Acinetobacter haemolyticus* sp. Nov., *Acinetobacter johnsonii* sp. Nov., and *Acinetobacter junii* sp. Nov. and emended descriptions of *Acinetobacter calcoaceticus* and *Acinetobacter lowffii*. Int J SystEvolMicrobiol 1986; 36(2): 228-40.
82. Kim YJ, Kim SH, Park HG, Park HG, Park D, Song SA, et al. MALDI-TOF MS is more accurate than VITEK II ANC card and API Rapid ID 32: A system for the identification of Clostridium species. Anaerobe 2016; 40: 73-5.
83. Dijkshoorn L, Nemec A, Seifert H. An increasing threat in hospitals: Multidrug-resistant *Acinetobacter baumannii*. Nat Rev Microbiol 2007; 5(12): 939-51.

84. Cosgaya C, Mari-Almirall M, Van-Assche A, Fernández-OrthD, Mosqueda N, TelliM, et al. Acinetobacter dijkshoorniae sp. Nov., a member of the *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex mainly recovered from clinical samples in different countries. Int J SystEvol Microbiol 2016; 66(10): 4105-11.
85. Olive DM, Bean P. Principles and applications of methods for DNA-based typing of microbial organisms. J Clinic Microbiol 1999; 37(6): 1661-9.
86. Ma X, Song L, Zhou N, Xia Y, Wang Z. A novel aptasensor for the colorimetric detection of *S. typhimurium* based on gold nanoparticles. Int J Food Microbiol 2017; 245: 1-5.
87. Lai HZ, Wang SG, Wu CY, Chen YC. Detection of *Staphylococcus aureus* by functional gold nanoparticle-based affinity surface-assisted laser desorption/ionization mass spectrometry. Anal Chem 2015; 87(4): 2114-20.
88. Khalil MAF, Azzazy HME, Attia AS, Hashem AGM. A sensitive colorimetric assay for identification of *Acinetobacter Baumannii* using unmodified gold nanoparticles. J Appl Microbiol 2014; 117(2): 465-71.
89. Chan PH, Chen YC. Human serum albumin stabilized gold nanoclusters as selective luminescent probes for *Staphylococcus aureus* and methicillin-resistant Staphylococcus aureus. Anal Chem 2012; 84(21): 8952-56.
90. Liu JC, Tsai PJ, Lee YC, Chen YC. Affinity capture of uropathogenic *Escherichia coli* using pigeon ovalbumin-bound Fe3O4@Al2O3 magnetic nanoparticles. Anal Chem 2008; 80(14): 5425-32.
91. Kuo FY, Lin WL, Chen YC. Affinity capture using peptide-functionalized magnetic nanoparticles to target *Staphylococcus aureus*. Nanoscale 2016; 8(17): 9217-25.
92. Ho YP, Reddy PM. Advances in mass spectrometry for the identification of pathogens. Mass Spectrom Rev 2011; 30(6): 1203-24.
93. Bai YL, Mahmud MSA, Selvaprakash K, Lin NT, Chen YC. Tail fiber protein-immobilized magnetic nanoparticle-based affinity approaches for detection of *Acinetobacter baumannii*. Anal Chem 2019; 91(15): 10335-42.
94. Chan PH, Wong SY, Lin SH, Chen YC. Lysozyme-encapsulated gold nanocluster-based affinity massspectrometry for pathogenic bacteria. Rapid Commun Mass Spectrom 2013; 27(19): 2143-8.
95. Shuangshuang Y, Guo Y, Fan J, Yang Y, Zuo C, Bai S, et al. A fluorometric assay for rapid enrichment and determination of bacteria by using zirconium-metal organic frameworks as both capture surface and signal amplification tag. Mikrochim Acta 2020; 187(3): 188.
96. Agarwal B, Karthikeyan R, Gayathri P. Proteomics: Studies on the mechanism of multi-drug resistance of *Acinetobacter baumannii* by proteomic analysis of the outer membrane vesicles of the bacterium. BBA-Proteins Proteom 2019; 10(1): 1-15.
97. Elhosseiny NM, Elhezawy NB, Attia AS. Comparative proteomics analyses of *Acinetobacter baumannii* strains ATCC 17978 and AB5075 reveal the differential role of type II secretion system secretomes in lung colonization and ciprofloxacin resistance. Microb Pathog 2019; 128: 20-7.
98. Tiwari V, Rajeswari MR, Tiwari M. Proteomic analysis of iron-regulated membrane proteins identify FhuE receptor as a target to inhibit siderophore-mediated iron acquisition in *Acinetobacter baumannii*. Int J Biol Macromol 2019; 125: 1156-67.
99. Scribano D, Marzano V, Mortera SL, Sarshar M, Vernocchi P, Zagaglia C, et al. Insights into the periplasmic proteins of *Acinetobacter baumannii* AB5075 and the impact of imipenem exposure: A proteomic approach. Int J Mol Sci 2019; 20(14): 3451.
100. Han ML, Liu X, Velkov T, Lin YW, Zhu Y, Creek DJ, et al. Comparative metabolomics reveals key pathways associated with the synergistic killing of colistin and sulbactam combination against multidrug-resistant *Acinetobacter baumannii*. Front Pharmacol 2019; 10: 754.
101. Maifiah MHM, Creek DJ, Nation RL, Forrest A, Tsuji BT, Velkov T, et al. Untargeted metabolomics analysis reveals key pathways responsible for the synergistic killing of colistin and doripenem combination against *Acinetobacter baumannii*. Sci Rep 2017; 7: 45527.
102. Qin H, Lo NWS, Loo JFC, Lin X, Yim AKY, Tsui SKW, et al. Comparative transcriptomics of multidrug-resistant *Acinetobacter baumannii* in response to antibiotic treatments. Sci Rep 2018; 8(1): 3515.
103. Cheng J, Kesavan DK, Vasudevan A, Cai W, Wang H, Su Z, et al. Genome and transcriptome analysis of *A. baumannii*'s 'Transient' increase in drug resistance under tigecycline pressure. J Glob Antomicrob Re 2020; 22: 219-25.
104. Kesavan DK, Aparna V, Wu L, Chen J, Su Z, Wang S, et al. Integrative analysis of outer membrane vesicles proteomics and whole-cell transcriptome analysis of eravacycline induced *Acinetobacter baumannii* strains. BMC Microbiol 2020; 20(1): 31.
105. Giamarellou H, Antoniadou A, Kanellakopoulou K. *Acinetobacter baumannii*: A universal threat to public health? Int J Antimicrob Agents 2008; 32(2): 106-19.
106. Falagas ME, Blizniotis IA, Siempos II. Attributable mortality of *Acinetobacter baumannii* infections in critically ill patients: A systematic review of matched cohort and case-control studies. Crit Care 2006; 10(2): 48.
107. Gordon NC, Wareham DW. Multidrug-resistant *Acinetobacter baumannii*: Mechanisms of virulence and resistance. Int J Antimicrob Agents 2010; 35(3): 219-26.
108. Perez F, Hujer AM, Hujer KM, Decker BK, Rather PN, Bonomo RA. Global challenge of multidrug-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother 2007; 51(10): 3471-84.
109. Poirel L, Nordmann P. Carbapenem resistance in *Acinetobacter baumannii*: Mechanisms and epidemiology. Clin Microbiol Infect 2006; 12(9): 826-36.
110. Esterly J, Richardson CL, Eltoukhy NS, Qi C, Scheetz MH. Genetic mechanisms of antimicrobial resistance of *Acinetobacter baumannii*. Ann Pharmacother 2011; 45(2): 218-28.
111. Turton JF, Ward ME, Woodford N, Kaufmann ME, Pike R, Livermore DM, et al. The role of ISAba1 in expression of OXA carbapenemase genes in *Acinetobacter baumannii*. FEMS Microbiol Lett 2006; 258(1): 72-7.
112. Rice LB. Challenges in identifying new antimicrobial agents effective for treating infections with *Acinetobacter baumannii* and Pseudomonas aeruginosa. Clin Infect Dis 2006; 43(2): 100-5.
113. Poirel L, Pitout JD, Nordmann P. Carbapenemases: Molecular diversity and clinical consequences. Future Microbiol 2007; 2(5): 501-12.
114. Coelho JM, Turton JF, Kaufmann ME, Glover J, Woodford N, Warner M, et al. Occurrence of carbapenem-resistant *Acinetobacter baumannii* clones at multiple hospitals in London and Southeast England. J Clin Microbiol 2006; 44(10): 3623-7.
115. Suárez CJ, Lolans K, Villegas MV, Quinn JP. Mechanisms of resistance to beta-lactams in some common Gram-negative bacteria causing nosocomial infections. Expert Rev Anti Infect Ther 2005; 3(6): 915-22.
116. Maragakis LL, Perl TM. *Acinetobacter baumannii*: Epidemiology, antimicrobial resistance, and treatment options. Clin Infect Dis. 2008; 46(8): 1254-63.
117. Galata V, Laczny CC, Backes C, Hemmrich-Stanisak G, Schmolke S, Franke A, et al. Integrating culture-based antibiotic resistance profiles with whole-genome sequencing data for 11,087 clinical isolates. GPB 2019; 17(2): 169-82.
118. Chang KC, Cheng YY, Lai MJ, Hu A. Identification of carbonylated proteins in a bactericidal process induced by curcumin with blue light irradiation on imipenem-resistant *Acinetobacter baumannii*. Rapid Commun. Mass Spectrom 2020; 34(1): e8548.
119. Barnes MD, Kumar V, Bethel CR, Moussa SH, O'Donnell J, Rutter JD, et al. Targeting multidrug-resistant Acinetobacter spp.: Sulbactam and the diazabicyclooctenone β-lactamase inhibitor ETX2514 as a novel therapeutic agent. mBio 2019; 10(2): e00159-19.

120. Intorasoot A, Chornchoem P, Sookkhee S, Intorasoot S. Bactericidal activity of herbal volatile oil extracts against multidrug-resistant *Acinetobacter baumannii*. J Intercult Ethnopharmacol 20171; 6(2): 218-22.
121. Phatthalung PN, Chusri S, Voravuthikunchai SP. Thai ethnomedicinal plants as resistant modifying agents for combating *Acinetobacter baumannii* infections. BMC Complement Altern Med 2012; 56.
122. Hemaiswarya S, Kruthiventi AK, Doble M. Synergism between natural products and antibiotics against infectious diseases. Phytomed 2008; 15(8): 639-52.
123. Tiwari V, Roy R, Tiwari M. Antimicrobial active herbal compounds against Acinetobacter baumannii and other pathogens. Front Microbiol 2015; 6: 618.
124. Ito H, Ura A, Oyamada Y, Tanitame A, Yoshida H, Yamada S, et al. A4-aminofurazan derivative A 189- inhibits assembly of bacterial cell division protein FtsZ in vitro and in vivo. Microbiol Immunol 2015; 50(10): 759-64.
125. Losasso C, Belluco S, Cibin V, Zavagnin P, Micetic I, Gallocchio F, et al. Antibacterial activity of silver nanoparticles: Sensitivity of different Salmonella serovars. Front Microbiol 2014; 5: 227.
126. Ali K, Ahmed B, Dwivedi S, Saquib Q, Al-khedhairy A, Musarrat J. Microwave accelerated green synthesis of stable silver nanoparticles with *Eucalyptus globulus* leaf extract and their antibacterial and antibiofilm activity on clinical isolates. PloS One 2015; 10(7): eo131178.
127. Hendiani S, Abdi-Ali A, Mohammadi P, Kharrazi S. Synthesis of silver nanoparticles and its synergistic effects in combination with imipenem and two biocides against biofilm producing Acinetobacter baumannii. Nanomed J 2015; 2(3): 291-8.
128. Chusri S, Villanueva I, Voravuthikunchai SP, Davies J. Enhancing antibiotic activity: A strategy to control Acinetobacter infections. J Antimicrob Chemothe 2009; 64(6): 1203-11.
129. Miyasaki Y, Rabenstein JD, Rhea J, Crouch ML, Mocek UM, Kittell PE, et al. Isolation and characterization of antimicrobial compounds in plant extracts against multidrug-resistant Acinetobacter baumannii. PloS One 2013; 8(4): e61594.
130. Osterburg A, Gardner J, Hyon SH, Neely A, Babcock G. Highly antibiotic-resistant *Acinetobacter baumannii* clinical isolates are killed by the green tea polyphenol (–)-epigallocatechin-3-gallate (EGCG). Clin Microbiol Infect 2009; 15(4): 341-6.
131. Shin B, Park W. Synergistic effect of oleanolic acid on aminoglycoside antibiotics against *Acinetobacter baumannii*. PloS One 2015; 10(9): e0137751.
132. Reichling J, Schnitzler P, Suschke U, Saller R. Essential oils of aromatic plants with antibacterial, antifungal, antiviral, and cytotoxic properties–an overview. Complement Med Res 2009; 16(2): 79-90.
133. Sonbol F, El-Banna T, Abd El-Aziz A, Gouda N. Antimicrobial susceptibility of some natural oils against Acinetobacter species. J Clin Chem Lab Med 2017; 1(1): 1-9.
134. Alanís-Garza BA, Bocanegra-Ibarias P, Waksman-de-Torres N, Salazar-Aranda R, Mendoza-Olazaran S, Perez-Lopez LA, et al. Antimicrobial activity of essential oils-derived volatile compounds against several nosocomial pathogens including representative multidrug-resistant A. baumannii clinical isolates. J Essent Oil Res 2018; 30(5): 341-6.
135. Rai M, Paralikar P, Jogee P, Agarkar G, Ingle AP, Derita M, et al. Synergistic antimicrobial potential of essential oils in combination with nanoparticles: emerging trends and future perspectives. Int J Pharm 2017; 519(1-2): 67-78.
136. Merino N, Berdejo D, Bento R, Salman H, Lanz M, Maggiet F, et al. Antimicrobial efficacy of *Thymbracapitata* (L.) Cav. essential oil loaded in self-assembled zein nanoparticles in combination with heat. Ind Crops Prod 2019; 133(2): 98-104.
137. Rai M, Yadav A, Gade A. Silver nanoparticles as a new generation of antimicrobials. Biotechnol Adv 2009; 27(1): 76-83.
138. Schmitt J, Hajiw S, Lecchi A, Degrouard J, Salonen A, Imperor-Clerc M, et al. Formation of superlattices of gold nanoparticles using Ostwald ripening in emulsions: Transition from fcc to bcc structure. J Phys Chem B2016 Jun 30; 120(25): 5759-66.
139. Gortzi O, Lalas S, Chinou I, Tsaknis J. Reevaluation of antimicrobial and antioxidant activity of Thymus spp. extracts before and after encapsulation in liposomes. J Food Protect 2006; 69(12): 2998-3005.
140. Liolios CC, Gortzi O, Lalas S, Tsaknis J, Chinou I. Liposomal incorporation of carvacrol and thymol isolated from the essential oil of Origanumdictamnus L. and in vitro antimicrobial activity. Food Chem 2009; 112(1): 77-83.
141. Li M, Zhu L, Liu B, Du L, Jia X, Han L, et al. Tea tree oil nanoemulsions for inhalation therapies of bacterial and fungal pneumonia. Colloids Surf B Biointerfaces 2016; 141: 408-16.
142. Scandorieiro S, Camargo LC, Lancheros CA, Yamada-Ogatta SF, Nakamura CV, Admilton Oliveira AG, et al. Synergistic and additive effect of oregano essential oil and biological silver nanoparticles against multidrug-resistant bacterial strains. Front Microbiol 2016; 7: 760.
143. Hemeg HA. Nanomaterials for alternative antibacterial therapy. Int J Nanomed 2017; 12: 8211-25.
144. Scandorieiro S, De Camargo LC, Lancheros CA, Yamada-Ogatta SF, Nakamura CV, De Oliveira AG, et al. Synergistic and additive effect of oregano essential oil and biological silver nanoparticles against multidrug-resistant bacterial strains. Front Microbiol 2016; 7: 760.