



A review of *Robinia pseudoacacia* on the multidrug resistance of *pseudomonas aeruginosa* strains

Hamza z Jalal¹, Faisal Al-Sarraj^{1*}, Ibrahim Alotibi²

¹ Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

² Department of Health Information Technology, Applied College, King Abdulaziz University, Jeddah, Saudi Arabia

Abstract

This study aims to evaluate the influence of regional honey. Aside from discovering an infection with honey at a cost lower than the price of antibiotics, and extracting a herbal alternative from honey to battle bacteria in addition to reducing the use of different antibiotics for patients, *Robinia pseudoacacia* on antibiotic-resistant *Pseudomonas aeruginosa* bacteria may be inhibited with honey without resorting to antibiotics. Investigate the genetic properties of bacteria. In previous studies, antibiotics such as imipenem-cilastatin-relebactam, a combination of carbapenem and relebactam, a beta-lactamase inhibitor that inhibits class A carbapenemases and class C cephalosporinases, in addition to aloe vera, were used to inhibit bacteria. Undiluted *A. vera* gel has been shown to affect all MDR isolates.

Keywords: pseudomonas, honey, DNA, treatment, and herbal

Introduction

The most extensively produced and eaten bee product on the earth is honey, a natural cure. Honey is a rich source of enzymes, proteins, organic acids, minerals, and vitamins. It also contains a concentrated mixture of the monosaccharides glucose and fructose. These compounds possess hepatoprotective, immunomodulatory, antibacterial, anti-inflammatory, and antioxidant properties. The chemical composition of honey is determined by plants, which give it a variety of flavours. The most common honey types are acacia, chestnut, manuka, pine, and oak honey. The script of honey determines its purity and quality (TSE, CEU, IHC, etc.). Moisture, conductivity, acidity, pH, colour, saccharides, sugar ratios (C4/C13), proline, diastase activity, hydroxymethylfurfural (HMF) contents, and insoluble substances are all important factors in determining honey quality (Keskin *et al.*, 2021).

Pseudomonas aeruginosa infection has grown to be a significant issue in hospital-acquired infections, especially in patients who are severely ill and immunocompromised. The increased death rate is mostly due to the introduction of drug-resistant pathogens. As a result, several strategies are now being explored to produce novel anti-infectives. Different approaches have been devised, varying from eliminating the infection (new medicines) to neutralizing it (antivirals). This review will concentrate on particular facets of *P. aeruginosa* infection control and antibiotic resistance. Numerous researches have been carried out to assess the risk variables for resistance and their possible effects on mortality and attributable mortality. *P. aeruginosa* is a bacterium with a vast genome that can create a significant number of agents linked with antibiotic resistance, spanning practically all antibiotic classes. The review also explores the mechanisms of resistance. Discussed is the clinical treatment of patients with bacteraemia, pneumonia brought on by a ventilator, uTIs, and cutaneous soft tissue infections. Antibiotic compositions and pharmacokinetic and pharmacodynamic factors are studied to enhance *P. aeruginosa* treatment. Along with the potential for new

therapies and other medications, the constraints of current therapies were also covered (Bassetti *et al.*, 2018).

It is generally understood that manuka honey has antibacterial qualities and inhibits *Pseudomonas aeruginosa* biofilm development. Additionally, *P. aeruginosa* that has embedded itself in a biofilm is successfully eradicated by manuka honey. There is no proof that honey is resistant to plankton or the *P. aeruginosa* biofilm over the long term (Camplin & Maddocks, 2014).

Chronic wound care is becoming more difficult and expensive, and these issues worsen in the case of an infected injury. Bacterial biofilms, which are antibiotic-resistant, are the main cause of chronic wound infections. A re-evaluation of honey as a treatment approach has been prompted by its wide-ranging antimicrobial action and low antibacterial tendency, as well as the demand for new tactics to combat the chronic wounds in polymicrobial biofilms. In order to test five popular New Zealand honeys for their potential to inhibit and remove biofilms produced by the common pathogen *Pseudomonas aeruginosa*, we used essential antibacterial components such as methylglyoxal, hydrogen peroxide, and sugar. We discovered that cells recovered from biofilms treated with semi-inhibited concentrations of honey have a slightly increased honey tolerance; honey used in clinically available concentrations completely eradicates *P. aeruginosa*; and honey's anti-biofilm effect was largely caused by its sugar element. These findings demonstrate the efficacy and broad spectrum of the antibacterial properties of manuka honey-based wound dressings. Dressings are a viable therapy for infected wounds, particularly those with *P. aeruginosa* biofilms (Roberts *et al.*, n.d.).

Five imported and domestic honeys were examined for bactericidal/bacteriostatic action against imipenem-resistant and susceptible *Pseudomonas aeruginosa* in heart-brain infusion broth and Mueller-Hinton agar. The outcomes demonstrated that the allowed kind and concentration of honey had an impact. All honey examined totally prevented bacterial growth at the maximum measured

concentration of 50% with contact for 24 hours. At 20% and 10% concentrations, honey reduced the development of bacteria, and manuka honey had a stronger effect than nigella honey and Sidr honey. Sidr and *N. sativa* honey only displayed antibacterial activity, but Manuka honey UMF +20 had bactericidal activity against both imipenem-resistant and imipenem-sensitive *P. aeruginosa*. The strongest impact on antimicrobial resistance was provided by manuka honey UMF + 10. Imipenem resistance in *P. aeruginosa* was altered by manuka honey UMF +10. Overall, the findings indicated that the examined organisms responded differently to various varieties of honey. In the instance of UMF +10 manuka honey, antimicrobial resistance was changed (Al-Nahari *et al.*, 2015) [3].

Body

1. Robinia pseudoacacia

It is a moderately sized hardwood deciduous tree. To its native region it is labelled black locust. It is a member of the Robinieae tribe of the legume family. Despite being widely farmed and naturalised in temperate North America, Europe, South Africa, and Asia, where it is sometimes regarded as an invasive plant, it is only found in limited locations of the United States. False acacia is how the given name is translated literally (pseudo [Greek o-] means fake or false, and acacia denotes to the genus of plants with an identical name) (USDA Plants Database, n.d.).

The tree was recognised in 1607 by British colonists who utilised its wood to construct homes at Jamestown. The "Old World locust," also known as *Ceratonia siliqua*, inspired the tree's name. It's possible that the Jesuit missionaries thought this was the tree that kept Saint John alive in the desert, yet it can only be found in North America (Keeler, 1902) [18].

Although the genus *Robinia* is indigenous to North America, fragments of it have been found in rocks from the Eocene and Miocene periods in Europe.

The plant's reintroduction to Europe in 1601 by the royal French gardener Jean Robin and his son Vespasian Robin earned the genus its namesake. In Paris, Place René Viviani is still home to Vespasian Robin's black locusts.

2. Acacia honey

The honey is made by bees from Acacia flowers, which provides the origins for its name. Chronic diseases like diabetes, hypertension, atherosclerosis, cancer, and Alzheimer's disease are becoming more commonplace on a global scale. Antioxidant qualities have drawn a lot of interest since oxidative processes contribute to the onset and development of degenerative illnesses. Polyphenol-rich foods and other biologically important metabolites. Polyphenol-rich foods and other biologically important metabolites. On the diverse biological properties of acacia honey, there are several experimental reports accessible today. However, a thorough examination. All this factual information is meticulously collected. Look at the accomplishments that have been noted thus far in order to identify prospective areas for further study into the potential medicinal properties of acacia honey as a functional food. Acacia honey has a very light colour that resembles liquid glass. It is one of the most well-liked varieties of honey due to its delicate and sweet floral flavour. This is really good as it sweetens beverages without affecting their flavour (Mohammed, 2016).

It is a great option for cooking due to its mild flavour.

It also mixes well in liquids and mixtures. He is. She is.

It has a vanilla flavour and aroma. Acacia honey crystallizes slowly because it can remain in it. It keeps its liquid consistency for a prolonged period of time because of its high fructose content. However, there are some experimental factors, as already mentioned. Currently, the selection of commercial honey purity and quality is being studied (Table 1).

Table 1: The physico-chemical properties of Acacia honey

Parameters	Amount	Standard amount (imposed limit)	References
Water content (g/100g)	18.3.9	NA	(6)
Electrical conductivity (mS/cm)	0.1.8	0.0.6-2.1.7	(6)
pH	4.0.7	3.5.0-5.5.0	(6), (9)
Total acidity (meq/kg)	16.6.5	Up to 50.0.0	(6), (8)
Fructose (g/100g)	43.5.1	NA	(6)
Glucose (g/100g)	29.6.8	NA	(6)
F/G ratio	1.5.7	Up to 1.6.4	(6)
F+G content (g/100g)	72.5.7	Up to 92	(9)
Maltose (g/100g)	3.0.8	NA	(6)
Sucrose (g/100g)	2.5.0	≤5.0.0	(6), (8)
Diatase activity (units/g of honey)	2.7.0	>8.0.0	(7), (8)
Hydroxymethylfurfural (mg/100g)	0.4.4	>15.0.0	(7), (8)

NA: Not available in the literature, F: Fructose, G: Glucose

Many different honey types are developed in Area A as a result of various sources of nectar. It is situated in the District. microscopic examination and other cutting-edge technologies currently (Adekanmbi & Ogundipe, 2009;

Gomes *et al.*, 2010; Lutier & Vaissière, 1993; Bibi *et al.*, n.d.) [1, 14, 20].

It's used to look for pollen grains in honey. It might eventually figure out where it came from. The biological

activity of honey as a potential asset in terms of its preventative and therapeutic potential may also be shown by pollen analysis. The local plant may contain certain phytochemicals. These techniques were used to gather acacia pollen.

Acacia honey has primarily been used to identify the flower (Aliyu *et al.*, 2013; Odunola *et al.*, 2013) [2, 22].

Therefore, terms are commonly used, but other techniques, aside from microscopic ones, are being studied (Melissopalynology). The identification of flower origins (monofloral or polyfloral) uses near-infrared spectroscopy, gas chromatography-mass spectrometry, amino acids, and mineral analytics (Muhammad, 2016; Adekanmbi & Ogundipe, 2009; Muhammad, 2016) [21]. In most cases, the plural form. Such methods will be of marked use.

Honey's quality is commercially relevant but is also necessary to achieve accurate results for both *in vitro* and *in vivo* experiments.

3. *Pseudomonas aeruginosa* multidrug resistant

For a number of reasons, the rise and spread of *Pseudomonas aeruginosa* strains that are multi-drug resistant have become a public health concern. Firstly, *P. aeruginosa* can lead to serious infections, especially in hospitals and among patients who are immunocompromised. It also has a remarkable capacity to choose and disseminate antimicrobial resistance *in vivo* (Horcajada *et al.*, 2019; Breidenstein *et al.*, 2011) [16, 8]. Further, the widespread emergence of so-called *P. aeruginosa* clones are a risk to public health and must be closely investigated.

Antibiotic-resistant bacteria infections represent a high morbidity and death risk globally as there are no therapeutic options. Ineffective therapy has a substantial effect on these infections. In fact, the World Health Organization identified carbapenem-resistant *P. aeruginosa* as a "critical" infection in need of new antibiotics immediately (Tacconelli *et al.*, 2018) [26].

P. aeruginosa, MDR, and XDR strains have grown in prevalence recently. In some locales, the growth is between 15% to 30% (Peña *et al.*, 2015; Sader *et al.*, 2018; Horcajada *et al.*, 2019) [23, 25, 16]. For controlled antimicrobial groups, resistance rates are above 10%, as reported by the majority of countries within Europe (Horcajada *et al.*, 2019) [16]. Resistance can be seen in *P. aeruginosa*. As per the European Centers for Disease Prevention and Control, in 2015, resistance from *P. aeruginosa* isolates to, at minimum, three antimicrobial groups was seen in 13.7% of cases. Resistance to all controlled antimicrobials was seen in 5.5% of cases (EARS-Net) (Horcajada *et al.*, 2019) [16]. MDR *P. aeruginosa* is the reason behind 13% of acute healthcare related infections, data from the United States reveals. (Antibiotic Resistance Threats in the United States: Stepping Back from the Brink, n.d.). Basic clinical research, infection control, antimicrobial stewardship, the creation of antimicrobials, and the improved use of those already on the market should all receive more funding.

Numerous chromosomal determinants, intricate regulatory pathways, and autonomic and adaptive resistance are among *Pseudomonas aeruginosa*'s variety of mechanisms resistant to antibiotics (Horcajada *et al.*, 2019; Breidenstein *et al.*, 2011) [26, 8]; Antibiotic Resistance Threats in the United States: Stepping Back from the Brink, n.d.; Diversity and Regulation of Intrinsic β -Lactamases from Non-Fermenting

and Other Gram-Negative Opportunistic Pathogens; n.d.). The analysis of mutagenesis libraries produced by whole-genome screening identified a broad group of genes known as auto resistant genes. These genes impact antibiotic sensitivity (Fajardo *et al.*, 2014; Alvarez-Ortega *et al.*, 2010; Dötsch *et al.*, 2009) [13, 4, 12].

In addition to having a wide range of inherent resistance, *P. aeruginosa* is remarkably capable of acquiring antibiotic resistance to all current drugs through chromosomal changes. An increasing worry related to *P. aeruginosa* is transferable resistance, which is different from the frequently seen mutational resistance. There have been many definitions of MDR profiles for *P. aeruginosa*, but the definition from Magiorakos *et al.* is arguably that which is currently most frequently employed.

Treatment

1. Antibiotic

Ipenem-cilastatin-relebactam, a carbapenem combination with relebactam, a beta-lactamase inhibitor that inhibits class A carbapenemases and class C cephalosporinases, is an antibacterial used in MDR *P. aeruginosa* (Titov *et al.*, 2021; Zhanel *et al.*, 2018; Doi, 2019). In a random trial conducted recently, imipenem-cilastatin-relebactam was shown to be superior to piperacillin-tazobactam-1 in adults with HAP or VAP. (Titov *et al.*, 2021). Meropenem-vaborbactam is a carbapenem-beta-lactamase inhibitor combination that conducts activity against MDR *P. aeruginosa* (Zhanel *et al.*, 2018; Doi, 2019). There is currently no information on the use of meropenem-vaborbactam in pneumonia, however a randomised investigation of elaborate urological illnesses and acute pyelonephritis indicated that it had no further ill effects than piperacillin-tazobactam (Kaye *et al.*, 2018).

2. Herbal

There are antibacterial abilities in aloe vera gel. Results Antibacterial properties can be found in aloe vera gel. Aloe vera gel inhibited five MDR strains of *P. aeruginosa* at MIC 400 mcg/mL. Aloe vera gel values for the remaining five isolates (10.6%).

It weighed 800 g/ml. All MDR isolates are inhibited by undiluted aloe vera gel. No MDR. isolates were isolated.

Sensitive to A. vera gel dilutions of less than 25 mcg/mL. The *in vitro* susceptibility of MDR *P. aeruginosa* strains to aloe vera gel, as well as three antibiotics, was determined to the extent of MIC50 and MIC90 (Goudarzi *et al.*, 2015) [15]

Conclusion

Antibiotics, various infection methods, and *Pseudomonas aeruginosa* multidrug resistance bacteria have all been found to be extremely resistant in different areas of the human body and at various ages. Acacia honey was found to have a high concentration of antioxidants, and other forms of honey can be searched for and tested to determine the antioxidants that they contain. This aids in the creation of a remedy or can help utilise the honey as a nutritional addition to antibiotics in order to speed up the healing process. Further study is required since different plants, such as aloe vera or antioxidant fruits, may suppress the antibiotic resistant bacteria *Pseudomonas aeruginosa* in different ways. In favour of less expensive, more efficient natural forms of therapy, various types of honey or fruits are used to reduce the need for antibiotics and the negative effects that drugs

can have on some individuals. Going forward, identifying the gene types in *Pseudomonas aeruginosa* will be useful to explore why it is resistant to some drugs.

Acknowledgment

The Authors would like to thank the department of Biology and King Abdulaziz University Library for collecting data and information's.

References

1. Adekanmbi O, Ogundipe O. Nectar Sources for the Honey Bee (*Apis mellifera adansonii*) Revealed by Pollen Content. *Notulae Botanicae Horti Agrobotanici Cluj-Napoca*, 2009, 37. <https://doi.org/10.15835/nbha3723245>
2. Aliyu M, Odunola OA, Farooq AD, Rasheed H, Mesaik AM, Choudhary MI *et al.* Molecular Mechanism of Antiproliferation Potential of Acacia Honey on NCI-H460 Cell Line. *Nutrition and Cancer*,2013;65(2):296-304. <https://doi.org/10.1080/01635581.2013.756920>
3. Al-Nahari AAM, Almasaudi SB, Abd El-Ghany ESM, Barbour E, Al Jaouni SK, Harakeh S. Antimicrobial activities of Saudi honey against *Pseudomonas aeruginosa*. *Saudi Journal of Biological Sciences*,2015;22(5):521-525. <https://doi.org/10.1016/j.sjbs.2015.04.006>
4. Alvarez-Ortega C, Wiegand I, Olivares J, Hancock REW, Martínez JL. Genetic Determinants Involved in the Susceptibility of *Pseudomonas aeruginosa* to β -Lactam Antibiotics. *Antimicrobial Agents and Chemotherapy*,2010;54(10):4159-4167. <https://doi.org/10.1128/AAC.00257-10>
5. *Antibiotic Resistance Threats in the United States: Stepping Back from the Brink.* (n.d.). Retrieved, 2022. from <https://www.aafp.org/pubs/afp/issues/2014/0615/p938.html>
6. Bassetti M, Vena A, Croxatto A, Righi E, Guery B. How to manage *Pseudomonas aeruginosa* infections. *Drugs in Context*,2018;7:212527. <https://doi.org/10.7573/dic.212527>
7. Bibi S, Husain SZ, Malik RN. (n.d.). Pollen Analysis And Heavy Metals Detection In Honey Samples From Seven Selected Countries. 10.
8. Breidenstein EBM, de la Fuente-Núñez C, Hancock REW. *Pseudomonas aeruginosa*: All roads lead to resistance. *Trends in Microbiology*,2011;19(8):419-426. <https://doi.org/10.1016/j.tim.2011.04.005>
9. Camplin AL, Maddocks SE. Manuka honey treatment of biofilms of *Pseudomonas aeruginosa* results in the emergence of isolates with increased honey resistance. *Annals of Clinical Microbiology and Antimicrobials*,2014;13(1):19. <https://doi.org/10.1186/1476-0711-13-19>
10. Diversity and regulation of intrinsic β -lactamases from non-fermenting and other Gram-negative opportunistic pathogens | FEMS Microbiology Reviews | Oxford Academic. (n.d.). Retrieved, 2022. from <https://academic.oup.com/femsre/article/41/6/781/4209640>
11. Doi Y. Treatment Options for Carbapenem-resistant Gram-negative Bacterial Infections. *Clinical Infectious Diseases*,2019;69(7):S565-S575. <https://doi.org/10.1093/cid/ciz830>
12. Dötsch A, Becker T, Pommerenke C, Magnowska Z, Jänsch L, Häussler S. Genomewide Identification of Genetic Determinants of Antimicrobial Drug Resistance in *Pseudomonas aeruginosa*. *Antimicrobial Agents and Chemotherapy*,2009;53(6):2522-2531. <https://doi.org/10.1128/AAC.00035-09>
13. Fajardo A, Hernando-Amado S, Oliver A, Ball G, Filloux A, Martinez JL. Characterization of a novel Zn²⁺-dependent intrinsic imipenemase from *Pseudomonas aeruginosa*. *Journal of Antimicrobial Chemotherapy*,2014;69(11):2972–2978. <https://doi.org/10.1093/jac/dku267>
14. Gomes MTR, Ribeiro HA, Lopes MTP, Guzman F, Salas CE. Biochemical comparison of two proteolytic enzymes from *Carica candamarcensis*: Structural motifs underlying resistance to cystatin inhibition. *Phytochemistry*,2010;71(5):524-530. <https://doi.org/10.1016/j.phytochem.2009.12.018>
15. Goudarzi M, Fazeli M, Azad M, Seyedjavadi SS, Mousavi R. *Aloe vera* Gel: Effective Therapeutic Agent against Multidrug-Resistant *Pseudomonas aeruginosa* Isolates Recovered from Burn Wound Infections. *Chemotherapy Research and Practice*, 2015, 1-5. <https://doi.org/10.1155/2015/639806>
16. Horcajada JP, Montero M, Oliver A, Sorlí L, Luque S, Gómez-Zorrilla S *et al.* Epidemiology and Treatment of Multidrug-Resistant and Extensively Drug-Resistant *Pseudomonas aeruginosa* Infections. *Clinical Microbiology Reviews*,2019;32(4):e00031-19. <https://doi.org/10.1128/CMR.00031-19>
17. Kaye KS, Bhowmick T, Metallidis S, Bleasdale SC, Sagan OS, Stus V *et al.* Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection: The TANGO I Randomized Clinical Trial. *JAMA*,2018;319(8):788-799. <https://doi.org/10.1001/jama.2018.0438>
18. Keeler HL, Harriet L. Our native trees and how to identify them: A popular study of their habits and their peculiarities. New York: Charles Scribner's Sons. 1902. <http://archive.org/details/ournativetreesa02keelgoog>
19. Keskin M, Keskin Ş, Kolaylı S. Chapter 17—Health-promoting benefits of honey. In C. Egbuna, A. P. Mishra, & M. R. Goyal (Eds.), *Preparation of Phytopharmaceuticals for the Management of Disorders* Academic Press, 2021, 303-306. <https://doi.org/10.1016/B978-0-12-820284-5.00024-1>
20. Lutier PM, Vaissière BE. An improved method for pollen analysis of honey. *Review of Palaeobotany and Palynology*,1993;78(1-2):129.
21. Muhammad A. Potential biological activity of acacia honey. *Frontiers in Bioscience*,2016;8:351-357. <https://doi.org/10.2741/771>
22. Odunola O, Muhammad A, Dar A, Dalvandi K, Rasheed H, Choudhary MI *et al.* Comparative assessment of redox-sensitive biomarkers due to acacia honey and sodium arsenite administration *in vivo*. *Mediterranean Journal of Nutrition and Metabolism*, 2013, 6. <https://doi.org/10.1007/s12349-013-0127-1>
23. Peña C, Cabot G, Gómez-Zorrilla S, Zamorano L, Ocampo-Sosa A, Murillas J *et al.* & for the Spanish Network for Research in Infectious Diseases (REIPI). Influence of Virulence Genotype and Resistance Profile

- in the Mortality of *Pseudomonas aeruginosa* Bloodstream Infections. *Clinical Infectious Diseases*,2015;60(4):539-548.
<https://doi.org/10.1093/cid/ciu866>
24. Roberts AEL, Maddocks SE, Cooper RAY. (n.d.). Manuka honey is bactericidal against *Pseudomonas aeruginosa* and results in differential expression of *oprF* and *algD*. *Microbiology*,2012;158(12):3005-3013.
<https://doi.org/10.1099/mic.0.062794-0>
 25. Sader HS, Castanheira M, Duncan LR, Flamm RK. Antimicrobial Susceptibility of Enterobacteriaceae and *Pseudomonas aeruginosa* Isolates from United States Medical Centers Stratified by Infection Type: Results from the International Network for Optimal Resistance Monitoring (INFORM) Surveillance Program, 2015–2016. *Diagnostic Microbiology and Infectious Disease*,2018;92(1):69-74.
<https://doi.org/10.1016/j.diagmicrobio.2018.04.012>
 26. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL *et al.* Discovery, research, and development of new antibiotics: The WHO priority list of antibiotic-resistant bacteria and tuberculosis. *The Lancet Infectious Diseases*,2018;18(3):318-327.
[https://doi.org/10.1016/S1473-3099\(17\)30753-3](https://doi.org/10.1016/S1473-3099(17)30753-3)
 27. Titov I, Wunderink RG, Roquilly A, Rodríguez Gonzalez D, David-Wang A, Boucher HW *et al.* A Randomized, Double-blind, Multicenter Trial Comparing Efficacy and Safety of Imipenem/Cilastatin/Relebactam Versus Piperacillin/Tazobactam in Adults With Hospital-acquired or Ventilator-associated Bacterial Pneumonia (RESTORE-IMI 2 Study). *Clinical Infectious Diseases*,2021;73(11):e4539–e4548.
<https://doi.org/10.1093/cid/ciaa803>
 28. USDA Plants Database. (n.d.). Retrieved 2022. from <https://plants.sc.egov.usda.gov/home/plantProfile?symbol=ROPS>
 29. Zhanel GG, Lawrence CK, Adam H, Schweizer F, Zelenitsky S, Zhanel M *et al.* Imipenem-Relebactam and Meropenem-Vaborbactam: Two Novel Carbapenem- β -Lactamase Inhibitor Combinations. *Drugs*,2018;78(1):65-98.
<https://doi.org/10.1007/s40265-017-0851-9>