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RESEARCH ARTICLE

SCOPE OF VARIOUS PHYTOCONSTITUENTS IN THE TREATMENT OF MULTIDRUG RESISTANT BACTERIA - A REVIEW

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Abstract

The major problem in drug manufacture nowadays is that many bacteria have evolved and became resistant to some particular drugs, these bacteria are referred to as multidrug resistant bacteria (MDR). The major reason for this being the overuse of antibiotics for the healthcare of people in the recent past. These multidrug resistant bacteria have reduced the efficiency of already existing drugs and also increased the expenditure of newer drugs and healthcare facilities. Therefore, novel and effective new drugs and innovative new therapies are urgently needed to treat MDR infections. From ancient times people have always tried to find cure for their health-related problems from the nature and the same has been the case in finding a solution to these multidrug resistant bacteria. So, in recent times studies have been conducted on different phytoconstituents like flavonoids, alkaloids, tannins, phytosterol etc. of plant origin to check their antimicrobial property against multidrug resistant bacteria. The Middle East comprises of a wide spectrum of plant diversity with over 20,000 different species in habitats ranging from deserts to snow-capped mountains. This review will help in considering certain phytoconstituents for preparation of drugs against multidrug resistant bacteria and solving this increasing problem which is to make drugs against multidrug resistant bacteria.

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Introduction:-

On Earth, there are an estimated 500,000 species of plants, both known and unknown, only 1–10 percent of them are consumed as food by animals and humans (Borris 1996; Cowan 1999). Antibiotic or antimicrobial resistance is a condition in which microbes develop resistance to a spectrum of antibiotics, also known as multidrug resistance and these microbes are commonly known as drug or antibiotic resistant pathogens (Yu et al., 2020). MDR bacteria are responsible for over half of all hospital-acquired infections globally (Leen Othman¹, Ahmad Sleiman² and Roula M. Abdel-Massih² et al. 2019). Infections caused by antibiotic-resistant bacteria are frequently associated with high morbidity and death, as well as a significant financial burden on global healthcare (Centers for Disease Control and Prevention, 2019). Pathogens are classified as multidrug resistant (MDR), extensively drug – resistant (XDR), or pandrug – resistant (PDR) based on their drug resistance profile, according to the European Centre for Disease Prevention and Control (CDC) (Magiorakos et al., 2012). Given the rapid growth of medication resistance microbes and the substantial threat it poses to global health, the World Health

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Organization has made developing new treatments to treat such infections as primary priority (WHO) (The Lancet Infectious Diseases, 2017). Plant derivatives are being studied to discover a solution to these multidrug resistant bacteria. The number of bioactive chemicals derived from plants is believed to be at least 200,000 yet this is still a small percentage of the compounds compared by number of plant species on Earth (Efferth and Koch 2011).

List of antibiotic resistant bacteria published by WHO-

The WHO list is divided into three categories which are as follows:

Critical - It is the most critical group of all which includes multidrug resistant bacteria that causes hazard in hospitals, nursing homes, and among patients whose treatment needs devices such as ventilators and blood catheters, making this the most critical category of all.

Acinetobacter, *Pseudomonas*, and several *Enterobacteriaceae* (including *Klebsiella*, *E. coli*, *Serratia*, and *Proteus*) are among them. They can cause infections that are serious and often fatal, such as bloodstream infections and pneumonia.

High and medium priority – Other more drug-resistant bacteria that cause more prevalent disorders like gonorrhoea and salmonella-related food poisoning are found in the second and third tiers of the list.

Table 1-

Critical group -	
i) <i>Acinetobacter baumannii</i>	carbapenem-resistant
ii) <i>Pseudomonas aeruginosa</i>	Carbapenem –resistant
iii) <i>Enterobacteriaceae</i>	carbapenem-resistant, ESBL-producing
High group-	
i) <i>Enterococcus faecium</i>	Vancomycin-resistant
ii) <i>Staphylococcus aureus</i>	methicillin-resistant, vancomycin-intermediate and resistant
iii) <i>Helicobacter pylori</i>	Clarithromycin-resistant
iv) <i>Campylobacter</i> spp.	Fluoroquinolone – resistant
v) <i>Salmonella</i> sp.	Fluoroquinolone – resistant
vi) <i>Neisseria gonorrhoeae</i>	cephalosporin-resistant, fluoroquinolone-resistant
Medium group	
i) <i>Streptococcus pneumoniae</i>	penicillin-non-susceptible
ii) <i>Hemophilus influenzae</i>	ampicillin-resistant
iii) <i>Shigella</i> spp.	Fluoroquinolone-resistant

Bacterial Resistance

Bacterial resistance to traditional antimicrobial treatments has been linked to about 20,000 resistant genes, and numerous mechanisms have been proposed to explain it (Aslam et al, 2018). Some bacteria are naturally antibiotic-resistant, whereas others develop resistance primarily as a result of antibiotic abuse and the introduction of new resistant strains (Vargiu et al., 2016).

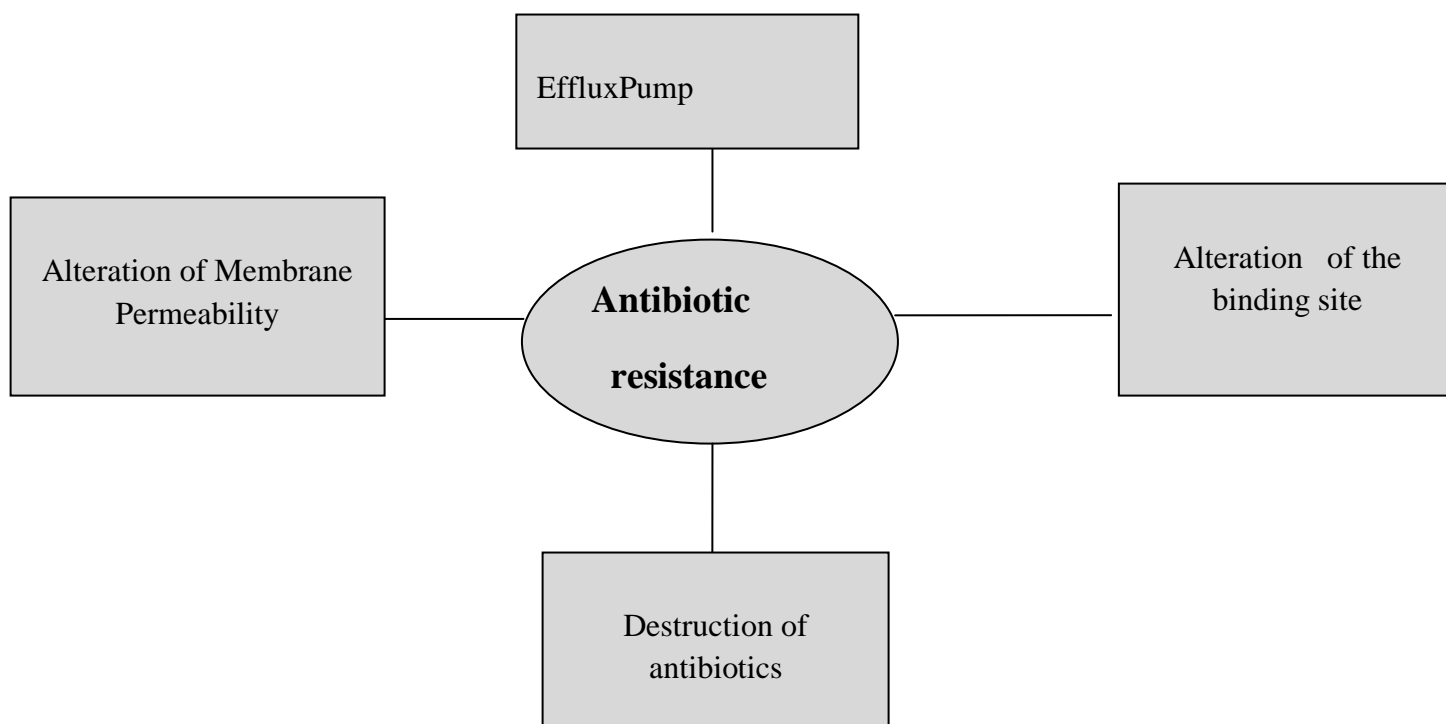


Fig 1:- Different mechanisms acquired by microorganisms for antibiotic resistance.

Role of genes in multidrug resistance

Some bacteria become multidrug resistant due to accumulation of many resistant genes on mobile genetic elements (MGE) by using the process of Human Gene Transfer (HGT). The main reservoirs and hotspots for the propagation of antibiotic resistance genes have been demonstrated to be human and animal guts, as well as naturally occurring and artificial habitats such wastewater treatment plants and manured soils (ARGs) (Kim et al.,2021).

Different plant constituents

Flavonoids are powerful antioxidants that also work as antibacterial agents in vitro against a wide range of pathogens by inhibiting membrane – bound enzymes. Because of their antioxidant and anti-inflammatory qualities, they also showed significant anticarcinogenic and antimutagenic activity.

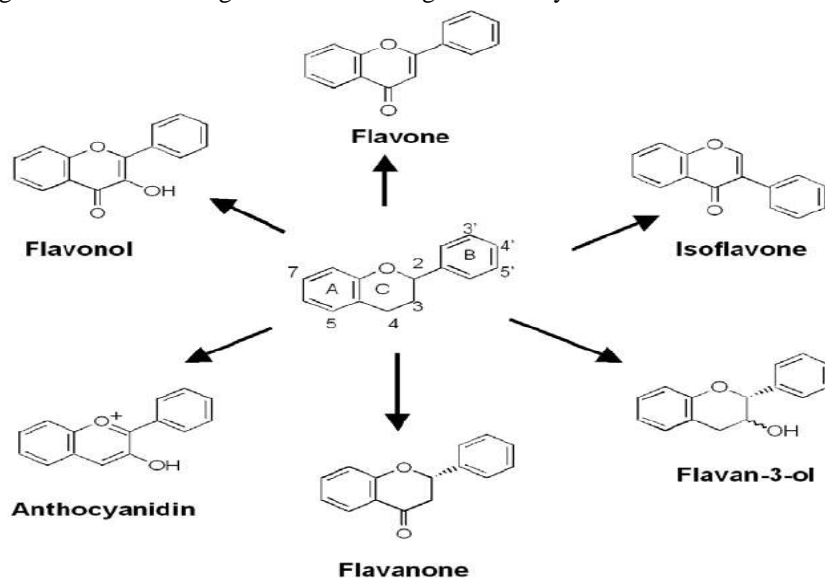


Fig 2:- Structure of flavonoids.

(Nishiumi et al., 2011)

Alkaloids are a class of chemical compounds found in nature that are largely made up of basic nitrogen atoms. Some similar chemicals with neutral or even slightly acidic characteristics are also included in this group. Along with hydrogen, nitrogen and carbon, alkaloids may also contain oxygen, sulfur and more rarely other elements such as chlorine, bromine and phosphorus.

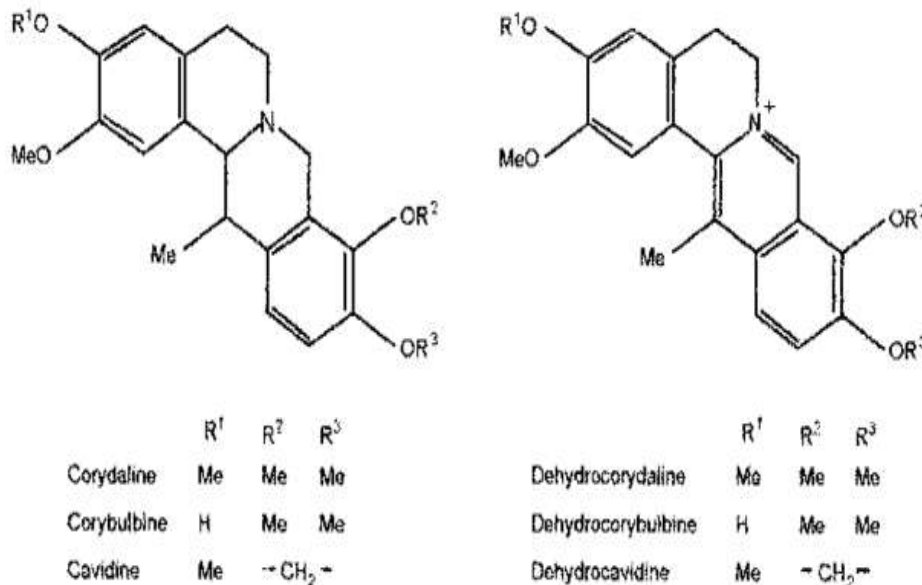


Fig 3:- Structure of flavonoids(Hiraoka et al., 2004).

Berberine (isoquinoline alkaloid) discovered in Berberi's species (roots/stems) has antibacterial activity, which can be linked to berberine's actions against DNA intercalation, RNA polymerase, gyrase/topoisomerase, and cellular division. (Iwasa et al., 2001; Yi et al., 2007; Domadia et al., 2008)

Reserpine (an indole alkaloid) from the plant *Rauwolfia serpentina* has similarly been shown to block efflux pumps (Sridevi et al., 2017). When co-administrated with antibiotics like ciprofloxacin or gentamicin, piperine (an alkaloid) from *Piper nigrum* and *Piper longum* has shown to inhibit methicillin-resistant *S. aureus* (Kumar et al., 2008; Khameneh et al., 2015).

Quinoline alkaloids isolated from the stem bark of *Tecleaafzelii* (such as masculine, kokusagine and dictamine) have demonstrated considerable antibacterial activity (Kuetee et al., 2008).

Tannins - Local tumors are brought on by a class of polymeric phenolic chemicals known as tannins. They are able to inactivate and kill microorganisms. They used in the treatment of varicose ulcers, hemorrhoids, minor burns, frostbite as well as inflammation of gums, in recent years, these compounds have demonstrated their antiviral diseases including AIDS.

Quinine, is a natural white crystalline alkaloid having antipyretic (fever reducing), analgesic (painkilling), and anti-inflammatory properties and a bitter taste used in treating malaria, can cause dizziness if taken in large doses.

Polyphenols are a class of secondary plant metabolites that have a phenolic pharmacophore (Leen Othman et al., 2019). Apart from their antioxidant properties, polyphenols have been shown to have anti-inflammatory, antiallergic, anticancer, antihypertensive, and antibacterial properties (Lin D et al., 2016). Although the precise mechanism for polyphenols' antimicrobial effect is unknown, multiple studies have suggested that polyphenols link to bacterial enzymes via a hydrogen bond at the cellular level, causing significant changes in cell membrane permeability and cell wall integrity (Ganesan et al., 2017).

Plant	Compound	Target	References
Piper nigrum and Piper longum	Piperine (alkaloid)	methicillin-resistant <i>S. aureus</i>	Umar et al., 2008; Khameneh et al., 2015
<i>Chelidonium majus</i> L. (roots)	Sanguinarine	<i>S. aureus</i>	H. S. Cho, S. H. Chang, Y. S. Chung et al., 2009
Solanaceous plants (tomato, potato, eggplant etc.)	tomatidine (steroidal alkaloid)	drug-resistant <i>S. aureus</i>	Mitchell et al., 2012
Plants from the family Alliaceae , especially fin garlic (<i>Allium sativum</i>)	Allicin (diallyl thiosulfinate, organosulfur compound)	methicillin-resistant <i>S. aureus</i> , <i>S. epidermidis</i> , <i>P. aeruginosa</i> and the periodontitis	Cai et al., 2008; Reiter et al., 2017
<i>Armoracia rusticana</i>	isothiocyanates (volatile organosulfur compounds)	<i>H. pylori</i>	Fahey et al., 2013; Park et al., 2013
<i>Persea lingue</i>	Kaempferol (flavonoid)	<i>S. aureus</i>	Holler et al., 2012

Conclusion and Future Perspectives: -

Antibiotic-resistant bacteria are a key source of concern in today's world healthcare system. So, the development of new/alternative and effective treatments for drug-resistant diseases is becoming a global priority. Phytochemicals, or active principles derived from plants, have developed as an alternative to traditional antibiotics for treating infections caused by antibiotic resistant pathogens. Many phytochemicals have shown promise as bactericidal or antimicrobial agents that enhance the effectiveness of current antibiotics. In response to the diminishing stock of conventional antibiotics, phytochemicals are proving to be potential alternatives. These phytochemicals have shown promise as future medications, and more scientific information is needed in this area. Despite multiple effective examples of phytochemicals treating antibiotic-resistant diseases, their translational success or commercial application is quite poor and requires significant improvement. So, there is a critical need for expedited study, regulatory approval, and implementation of these phytochemicals to combat MDR-related clinical consequences.

References:-

- Aslam, B., Wang, W., Arshad, M. I., Khurshid, M., Muzammil, S., Rasool, M. H., ... Baloch, Z. (2018). Antibiotic resistance: A rundown of a global crisis. **Infection and Drug Resistance**, **11**, 1645-1658. doi:10.2147/idr.s173867
- Borris RP. Natural products research: perspectives from a major pharmaceutical company. *J Ethnopharmacol.* 1996; 51:29–38. doi: 10.1016/0378–8741(95)01347-4
- Cai, Y., Wang, R., An, M.-M., Liang, B.-B., and Fang, Y. (2008). **In Vitro** bactericidal Activity of Allicin Combined with Cefoperazone, Tobramycin and Ciprofloxacin. **Int. J. Antimicrob. Agents** 31,179–180. doi: 10.1016/j.ijantimicag.2007.10.009
- Centers for Disease Control and Prevention (2019). Biggest Threats and Data | Antibiotic/Antimicrobial Resistance| CDC. Available at: <https://www.cdc.gov/drugresistance/biggest-threats.html>
- Cowan, M. M. (1999). Plant products as antimicrobial agents. **Clinical Microbiology Reviews**, **12**(4), 564-582. doi:10.1128/cmr.12.4.564
- Domadia, P. N., Bhunia, A., Sivaraman, J., Swarup, S., and Dasgupta, D. (2008). Berberine Targets Assembly of *Escherichia coli* Cell Division Protein FtsZ. **Biochemistry** 47, 3225–3234. doi:10.1021/bi7018546
- Efferth T, Koch E. Complex interactions between phytochemicals. The multi-target therapeutic concept of phytotherapy. *Curr Drug Targets.* 2011; 12:122–132. doi: 10.2174/138945011793591626
- Fahey, J. W., Stephenson, K. K., Wade, K. L., and Talalay, P. (2013). Urease from *Helicobacter pylori* Is Inactivated by Sulforaphane and Other Isothiocyanates. **Biochem. Biophys. Res. Commun.** 435, 1–7. doi: 10.1016/j.bbrc.2013.03.126
- Ganesan, K., & Xu, B. (2017). A critical review on polyphenols and health benefits of Black soybeans. *Nutrients*, **9**(5), 455. doi:10.3390/nu9050455
- Hiraoka, N., Bhatt, I. D., Sakurai, Y., & Chang, J. (2004). Alkaloid production by somatic embryo cultures of *corydalis ambigua*. *Plant Biotechnology*, **21**(5), 361-366. doi:10.5511/plantbiotechnology.21.361

11. Holler, J. G., Christensen, S. B., Slotved, H.-C., Rasmussen, H. B., Guzman, A., Olsen, C.-E., et al. (2012). Novel Inhibitory Activity of the **Staphylococcus aureus** NorA Efflux Pump by a Kaempferol Rhamnoside Isolated from **Persea Lingue** Nees. **J. Antimicrob. Chemother.** 67, 1138–1144. doi:10.1093/jac/dks005
12. Iwasa, K., Moriyasu, M., Yamori, T., Turuo, T., Lee, D.-U., and Wiegrebe, W. (2001). **In Vitro** Cytotoxicity of the Protoberberine-type Alkaloids. **J. Nat. Prod.** 64, 896–898. doi:10.1021/np000554f
13. Jubair, N., Rajagopal, M., Chinnappan, S., Abdullah, N. B., & Fatima, A. (2021). Review on the antibacterial mechanism of plant-derived compounds against multidrug-resistant bacteria (MDR). **Evidence-Based Complementary and Alternative Medicine**, 2021, 1-30. doi:10.1155/2021/3663315
14. Kumar, A., Khan, I. A., Koul, S., Koul, J. L., Taneja, S. C., Ali, I., et al. (2008). Novel Structural Analogues of Piperine as Inhibitors of the NorA Efflux Pump of **Staphylococcus aureus**. **J. Antimicrob. Chemother.** 61, 1270–1276. doi:10.1093/jac/dkn088
15. Khameneh, B., Iransahy, M., Ghandadi, M., GhoochiAtashbeyk, D., Fazly Bazzaz, B. S., et al. (2015). Investigation of the Antibacterial Activity and Efflux Pump Inhibitory Effect of Co-loaded Piperine and Gentamicin Nanoliposomes in Methicillin-resistant **Staphylococcus Aureus**. **Drug Dev. Ind. Pharm.** 41, 989–994. doi:10.3109/03639045.2014.920025
16. Kim, M., Park, J., Kang, M., Yang, J., & Park, W. (2021). Gain and loss of antibiotic resistant genes in multidrug resistant bacteria: One health perspective. *Journal of Microbiology*, 59(6), 535-545. <https://doi.org/10.1007/s12275-021-1085-9>
17. The Lancet Infectious Diseases (2017). Antibiotic Research Priorities: Ready, Set, Now Go. **Lancet Infect. Dis.** 17, 349. doi:10.1016/S1473-3099(17)30140-8
18. Lin, D., Xiao, M., Zhao, J., Li, Z., Xing, B., Li, X., ... Chen, S. (2016). An overview of plant phenolic compounds and their importance in human nutrition and management of type 2 diabetes. *Molecules*, 21(10), 1374. doi:10.3390/molecules21101374
19. Magiorakos, A.-P., Srinivasan, A., Carey, R. B., Carmeli, Y., Falagas, M. E., Giske, C. G., et al. (2012). Multidrug-resistant, Extensively Drug-Resistant and Pandrug-Resistant Bacteria: an International Expert Proposal for Interim Standard Definitions for Acquired Resistance. **Clin. Microbiol. Infect.** 18, 268–281. doi:10.1111/j.1469-0691.2011.03570.x
20. Mitchell, G., Lafrance, M., Boulanger, S., Seguin, D. L., Guay, I., Gattuso, M., et al. (2012). Tomatidine Acts in Synergy with Aminoglycoside Antibiotics against Multiresistant **Staphylococcus aureus** and Prevents Virulence Gene Expression. **J. Antimicrob. Chemother.** 67, 559–568. doi:10.1093/jac/dkr510
21. Nishiumi, Shin & Miyamoto, Shingo & Kawabata, Kyuichi & Ohnishi, Kohta & Mukai, Rie & Murakami, Akira & Ashida, Hitoshi & Terao, Junji. (2011). Dietary flavonoids as cancer-preventive and therapeutic biofactors. *Frontiers in bioscience (Scholar edition)*. 3. 1332-62
22. Othman, L., Sleiman, A., & Abdel-Massih, R. M. (2019). Antimicrobial activity of polyphenols and alkaloids in Middle Eastern plants. **Frontiers in Microbiology**, 10. doi:10.3389/fmicb.2019.00911
23. Reiter, J., Levina, N., van der Linden, M., Gruhlke, M., Martin, C., and Slusarenko, A. (2017). Diallylthiosulfinate (Allicin), a Volatile Antimicrobial from Garlic (**Allium Sativum**), Kills Human Lung Pathogenic Bacteria, Including MDR Strains, as a Vapor. **Molecules** 22, 1711. doi:10.3390/molecules22101711
24. Sridevi, D., Shankar, C., Prakash, P., Park, J., and Thamaraiselvi, K. (2017). Inhibitory Effects of Reserpine against Efflux Pump Activity of Antibiotic Resistance Bacteria. **Chem. Biol. Lett.** 4, 69–72
25. Vargiu, A. V., Pos, K. M., Poole, K., & Nikaido, H. (2016). Editorial: Bad bugs in the XXIst century: Resistance mediated by multi-drug efflux pumps in Gram-negative bacteria. *Frontiers in Microbiology*, 7. doi:10.3389/fmicb.2016.00833
26. Yi, Z.-B., Yan Yu, Y., Liang, Y.-Z., and Bao Zeng, B. (2007). Evaluation of the Antimicrobial Mode of Berberine by LC/ESI-MS Combined with Principal Component Analysis. **J. Pharm. Biomed. Anal.** 44, 301–304. doi: 10.1016/j.jpba.2007.02.018
27. Yu, Z., Tang, J., Khare, T., and Kumar, V. (2020). The Alarming Antimicrobial Resistance in ESKAPEE Pathogens: Can Essential Oils Come to the rescue? **Fitoterapia** 140, 104433. doi: 10.1016/j.fitote.2019.104433.