Journal of Population Therapeutics & Clinical Pharmacology

REVIEW ARTICLE
DOI: 10.53555/jptcp.v31i8.7392

NATURAL ANTI-BACTERIAL COMPOUNDS AGAINST MDR (MULTIDRUG RESISTANCE) BACTERIA

Javeria Arshad[1*], Sara Naqvi[2], Aisha Sethi[3], Muhammad Hassan Butt[1], Anfas Muneeb[4], Maira Tahir[3], Nayab Zehra[5], Mahrukh[5], Ijaz Ali[6*], Muhammad Hashir Naeem[7], Amir Jalal[8]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, Government College University, Faisalabad-38000, Punjab, Pakistan.
[2]Faculty of Pharmacy, Iqra University North Campus, Karachi, Sindh, Pakistan.
[3]Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Government College University, Faisalabad-38000, Punjab, Pakistan.
[4]Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Government College University, Faisalabad-38000, Punjab, Pakistan.
[5]Department of Botany, Government College Women University, Faisalabad-38000, Punjab, Pakistan.
[6]Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, Government College University, Faisalabad-38000, Punjab, Pakistan.
[7]Department of Pharmacy, Faculty of Pharmaceutical Sciences Government College University, Faisalabad-38000, Punjab, Pakistan.
[8]Sahara Medical College, Narowal, Sialkot. 0542, Punjab, Pakistan

***Corresponding author(s):** Javeria Arshad, Dr. Ijaz Ali
*Email: pharmacistj.arshad@yahoo.com
*Email: drijazali@gcuf.edu.pk

Abstract
Antibiotic resistance is one of the major concerns in healthcare department these days, because now resistance is not limited to hospitals only. Resistance due to multidrug-resistant bacteria is responsible for high mortality rate. Infections due to these type of bacteria is increasing day by day, while the production of antibiotics is very slow as compared to the pace of production of the antibiotics. Usage of antibiotics causes the elimination of normal flora that produces multi drug resistant bacteria (MDR). Due to increase in antibiotic resistance, now the world is moving toward using natural compounds to overcome all these issues. Because these methods are cost effective, eco-friendly and have no side effects as observed in case of conventional antibiotics.

Keywords: Multi drug Resistance, Conventional antibiotics, Bacterial infections, Normal flora

1. Introduction

Multi drug resistant (MDR) bacteria are well recognized to be one of the most important current public health problems (Van Duin & Paterson, 2016). Antibiotic resistance is one of the greatest challenges in health system nowadays. Initially, antibiotic resistant strains were restricted to the hospital environment but now they can be found everywhere (Vivas et al., 2019). Infections due to multidrug resistant, gram-negative pathogens are responsible for high mortality rates and may leave few effective antimicrobial options (Bassetti & Righi, 2013). Drug resistance in bacteria is increasing and the pace at which new antibiotics are being produced is slowing. It is now almost common place to hear about methicillin resistant Staphylococcus aureus (MRSA), vancomycin resistant enterococci(VRE), multi drug resistance in Mycobacterium tuberculosis (MDRTB) strains and multi drug resistant gram negative bacteria (Russell, 2002) . The most common antibiotic resistant, clinically relevant gram negative species are extended-spectrum beta-lactamase (ESBL) and carbapenemase-producing *Enterobacteriaceae* such as *Klebsiella pneumoniae* and *Escherichia coli* as well as non-fermenters such as *Pseudo monas aeruginosa* and *Acinetobacter baumannii*. Infection with these agents often affects susceptible patient populations (immunocompromised patients, neonates etc) in oncology and intensive care units.

Microbial resistance has progressed rapidly and is becoming the leading cause of death. The spread of antibiotic resistant microorganism has been a significant threat to the successful therapy against microbial infections. Scientists have become more concerned about the possibility of return to pre antibiotic era. Thus, searching for alternatives. To fight microorganisms has become necessity. Some bacteria are resistant to antibiotics, while others acquire resistance mainly by the misuse of antibiotics and emergence of new resistant variants through mutation. Some ancient times, plants represent the leasing source of drugs and alternative medicine for fighting against disease. Some natural antibacterial compounds that we use in our daily life i.e. cinnamon ginger garlic possess antimicrobial action against resistant bacteria either alone or in combination with other antibiotic.

2. The need for new antibacterial compounds

Resistance to antibiotics and other antimicrobial compounds continues to increase. There are several possibilities for protection against pathogenic organism, for instance, preparation of new vaccines against bacterial strains, use of specific bacteriophages, and searching for new antibiotics (Jackson et al., 2018). The antibiotic search includes:

i. Looking for new antibiotics from non-traditional or less traditional sources
ii. Sequencing microbial genomes with the aim of finding genes specifying biosynthesis of antibiotics
iii. Analyzing DNA from the environment
iv. Re-examining natural compounds and products of their transformation
v. Investigating new antibiotic targets in pathogenic bacteria

Antibacterial drug discovery and development has slowed considerably in recent years, with novel classes discovered decades ago and regulatory approvals tougher to get. Traditional approaches and newer genomic mining approaches have not yielded novel classes of antibacterial compounds. Instead, improved analogues of existing classes of antibacterial drugs have been developed by improving potency, improving resistance and alleviating toxicity (Devasahayam et al., 2010). After the introduction of streptogramins and quinolones in 1962, no novel class of antibiotics was identified and approved for clinical use until linezolid was launched in 2000 (O'Shea & Moser, 2008). New molecules are vital to overcoming the resistances that have developed as well as the need to empower the use of existing antibiotics and to promote the study of increasingly valid diagnostic tests for identification of resistant bacteria and for determining antibiotic sensitivity (Marco Terreni, 2021).

3. Exploring natural sources for antibacterial compounds

Over the last few decades, many of the existing drugs used to treat infectious diseases have become increasingly ineffective due to global emergence of antimicrobial resistance (Caruso et al., 2022). Natural products have historically been of crucial importance in the identification and development of antibacterial agents (Moloney, 2016). Current research trends emphasize the strategic utilization of natural and renewable resources, specifically within food and medicine focusing on naturally occurring antimicrobial compound (Karnwal & Malik, 2024).

4. Identifying the Natural compound

Some of the natural sources for antibacterial compounds are listed below

4.1 Garlic

Garlic is one of the most useful aromatic spices. It is made up of portions known as cloves, which may be separated for cooking and eating. Garlic can be provided in the form of capsules and powder, as dietary supplement and thus differ from the conventional food or food ingredients. It is also effective against antibiotic resistant organisms. Garlic extract has antimicrobial activity against oral bacterial species particularly gram negative species. The organosulfur compounds of garlic exhibit a range of antibacterial properties such as bactericidal, antibiofilm, antitoxin against multi drug resistant strains (Bhatwalkar et al., 2021). Garlic exhibit a broad spectrum of antimicrobial activity against the gram positive and gram negative bacteria (Moghadam et al., 2014). The antibacterial potency of aqueous and methanol extracts of garlic was determined in vitro against three bacterial isolates *Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa* (Garba et al., 2013).

4.2 Cranberry

Antibacterial effects of cranberry concentrate on foodborne pathogens, *Escherichia coli, Listeria monocytogenes, Salmonella typhimurium and Staphylococcus aureus* in vitro were investigated (Wu et al., 2008). Antibacterial activity of the cranberry extract in the formed biofilm was evaluated by assessing the reduction in in bacteria viability using the quantitative polymerase reaction(qPCR) (Sánchez et al., 2020). The aqueous extract of cranberry produced inhibition zone ranging from (10.8-23.8) mm against the tested bacteria. While the methanol extract produces larger zone of inhibition (12.1-24.2)mm against the bacteria (Ibrahim et al., 2015). The dried fruit extract of cranberry was also determined. The most sensitive bacteria was *A. hydrophilia* whereas the most resistant bacterium was the *Y. enterocolitica (Sagdic et al., 2006).*

4.3 Licorice

Plants have always been an important source of medicines for humans; licorice is very significant herb in the development of human. It has strong pharmacological activities such as anti-inflammatory, antibacterial and anti-ulcer (Wang et al., 2020). The antibacterial activity of compounds obtained from licorice was measured against upper airway respiratory tract bacteria such as *Streptococcus pyogenes, Haemophilus influenza and Moraxella catarrhalis* (Tanaka et al., 2001). The effectiveness of licorice extracts have been shown by modern science to be credible, a root component (Glycyrrhizin) being regarded as major biologically active principle (Nitalikar et al., 2010). The antibiotic resistance has led to pressing need to develop new and innovative antimicrobial agents, in search for that the researchers has turned to use of herbal products (Rodino et al., 2015). The extracts of licorice represent the new candidates for antimicrobial agents against MDR (Kim et al., 2014).

4.4 Honey

It is a powerful antimicrobial agent with a wide range of effects. Various components contribute to the antibacterial efficacy of honey such as sugar content, polyphenol compounds and hydrogen peroxide. These components work synergistically allowing honey to be potent against microorganism including MDR bacteria (Almasaudi, 2021). The antimicrobial activity in most honeys is due to the enzymatic production of hydrogen peroxide (Mandal & Mandal, 2011). Honey has been found to be effective in treating bacterial gastroenteritis in infants (Molan, 1992). It is one of such product that used to be widely used to combat bacteria (Albaridi, 2019). The inhibition of growth of bacteria is principally due to the peroxide effect, which is very common in honey worldwide (Libonatti et al., 2014).

4.5 Tea tree oil

The essential oil of *Melaleuca alternifolia* (tea tree) exhibits broad spectrum antimicrobial activity. Its mode of action against *E. coli, S. aureus,* and the yeast *Candida albicans* has been investigated

(Cox et al., 2000). Tea tree oil exhibit observable zone of inhibition against all the bacteria (Mumu & Hossain, 2018).

4.6 Cinnamon

The rise in cases of antibiotic resistant pathogens has become a global phenomenon threatens human health and requires search for alternative antibiotics. Cinnamon bark is a popular spice that comes from Cinnamomum spp. Which are rich in bioactive phytochemical molecules (Mohamed et al., 2020). The cinnamon extract (Cinnamomum burmannii) shows activity against *E. coli* and *S. aureus.* These two are common causes of number of infections and are resistant to many antibiotics (Parisa et al., 2019). The minimum inhibition concentration of cinnamon was similar for both bacteria while the minimum bactericide concentration were 4.0mg/ml and 2mg/ml for *E. coli and S. aureus* (Zhang et al., 2016). Essential oil from cinnamon tree bark was extracted using steam distillation technique and gas chromatography (Abdulrasheed et al., 2019).

5. Mechanism of action of natural antimicrobial compounds

5.1. Membrane Disruption

Many natural anti-microbial compounds cause disruption of bacterial cell membrane causing leakage of cellular contents and ultimately cell death. It attacks bacterial membranes. They are good antimicrobial agent at low concentration and they are non-toxic to human erythrocytes or all eukaryotic cells. They also stop growth of antibiotic resistant bacteria. They interfere with bacterial DNA and membrane proteins that have phosphorus and Sulphur complex. They are broad spectrum and have high bactericidal and antimicrobial activity. They even act against methicillin resistant bacterial strains (Abo-Shama et al., 2020).

5.2. Enzyme Inhibition

Certain enzymes can inhibit enzymes in bacterial metabolism, making cellular processes non-functional. Enzymes, proteins, terpenoids are agents involved in the reduction step. Shape, size, surface chemistry, composition are some properties determined by the stability of natural compounds. All these properties have the greatest stimulatory impact on the anti-microbial property of natural compounds, especially size shape, and composition has the greatest impact on the property of nanoparticles of killing microorganisms. So, Natural compounds should be used wisely against microbes (Phan & Haes, 2019).

5.3. Interfering with Protein synthesis

Antibacterial compounds target bacterial ribosome, stopping the synthesis of essential proteins required for survival (Rayner et al., 1990).

5.4. Oxidative Stress Induction

Antibacterial compounds synthesized from natural sources generate reactive oxygen species that overwhelming the bacterial antioxidant systems leading to cellular damage. Recent studies from numerous research groups claim that by suppressing free radicals in in vitro trails, they were able to demonstrate the unique capabilities of Natural compounds produced through organic manufacture (Selvan et al., 2018) .The excessive accumulation of free radicals is the basic cause of numerous serious disorders, including diabetes, Alzheimer's disease, inflammatory joint disease, cancer, senile dementia, atherosclerosis, degenerative eye disease, ageing, asthma, and senile dementia (Erdin & Wegmann, 1996). It plays important role for treating these diseased because of having antioxidant ability.

6. Evaluation of Anti-microbial Activity

In-vitro assays are performed to access the antibacterial activity of the compound. This type of experiments access the ability of compounds to inhibit the growth of various bacterial strains including gram positive and gram negative pathogens for their multi drug resistance (El-Deeb et al., 2020).

7. Challenges of Multi-Drug Resistant Bacteria

Many factors are the reason behind the resistance against the bacteria. But two important factors are

7.1. Limited Therapy Tools

As resistance to antibiotics are growing, the available treatment options are decreasing, leaving healthcare providers with fewer options of therapy against the bacterial infections (Yuan et al., 2017)

Increased Mortality

Infections caused by multidrug-resistant bacteria are the reasons of increased high mortality despite of the infections caused by susceptible strains (Teixeira et al., 2018).

REFERENCES

1. Abdulrasheed, M., Ibrahim, I., Luka, A., Maryam, A., Hafsat, L., Ibrahim, S., . . . Gidado, M. (2019). Antibacterial effect of Cinnamon (Cinnamomum zeylanicum) bark extract on different bacterial isolates. *Journal of Environmental Microbiology and Toxicology, 7*(1), 16-20.
2. Abo-Shama, U. H., El-Gendy, H., Mousa, W. S., Hamouda, R. A., Yousuf, W. E., Hetta, H. F., & Abdeen, E. E. (2020). Synergistic and antagonistic effects of metal nanoparticles in combination with antibiotics against some reference strains of pathogenic microorganisms. *Infection and Drug Resistance*, 351-362.
3. Albaridi, N. A. (2019). Antibacterial potency of honey. *International Journal of Microbiology, 2019*.
4. Almasaudi, S. (2021). The antibacterial activities of honey. *Saudi journal of biological sciences, 28*(4), 2188-2196.
5. Bassetti, M., & Righi, E. (2013). Multidrug-resistant bacteria: what is the threat? *Hematology 2013, the American Society of Hematology Education Program Book, 2013*(1), 428-432.
6. Bhatwalkar, S. B., Mondal, R., Krishna, S. B. N., Adam, J. K., Govender, P., & Anupam, R. (2021). Antibacterial properties of organosulfur compounds of garlic (Allium sativum). *Frontiers in microbiology, 12*, 613077.
7. Caruso, D. J., Palombo, E. A., Moulton, S. E., & Zaferanloo, B. (2022). Exploring the promise of endophytic fungi: A review of novel antimicrobial compounds. *Microorganisms, 10*(10), 1990.
8. Cox, S., Mann, C., Markham, J., Bell, H. C., Gustafson, J., Warmington, J., & Wyllie, S. G. (2000). The mode of antimicrobial action of the essential oil of Melaleuca alternifolia (tea tree oil). *Journal of applied microbiology, 88*(1), 170-175.
9. Devasahayam, G., Scheld, W. M., & Hoffman, P. S. (2010). Newer antibacterial drugs for a new century. *Expert opinion on investigational drugs, 19*(2), 215-234.
10. El-Deeb, N. M., Abo-Eleneen, M. A., Al-Madboly, L. A., Sharaf, M. M., Othman, S. S., Ibrahim, O. M., & Mubarak, M. S. (2020). Biogenically synthesized polysaccharides-capped silver nanoparticles: immunomodulatory and antibacterial potentialities against resistant Pseudomonas aeruginosa. *Frontiers in Bioengineering and Biotechnology, 8*, 643.
11. Erdin, D., & Wegmann, W. (1996). Lungenmetastase eines gutartigen Riesenzelltumors des Skeletts 27 Jahre nach Resektion eines Tumorrezidivs. *Der Pathologe, 17*, 219-221.
12. Garba, I., Umar, A., Abdulrahman, A., Tijjani, M., Aliyu, M., Zango, U., & Muhammad, A. (2013). Phytochemical and antibacterial properties of garlic extracts. *Bayero Journal of Pure and Applied Sciences, 6*(2), 45-48.
13. Ibrahim, O., Sarhan, S., & Hameed, A. (2015). In vivo and in vitro antibacterial activities of cranberry extract against E. coli O157: H7 in urinary tract infected rats. *Adv. Anim. Vet. Sci, 3*(4), 233-244.

14. Jackson, N., Czaplewski, L., & Piddock, L. J. (2018). Discovery and development of new antibacterial drugs: learning from experience? *Journal of Antimicrobial Chemotherapy, 73*(6), 1452-1459.
15. Karnwal, A., & Malik, T. (2024). Exploring the untapped potential of naturally occurring antimicrobial compounds: novel advancements in food preservation for enhanced safety and sustainability. *Frontiers in Sustainable Food Systems, 8*, 1307210.
16. Kim, H. J., Jang, H. N., Bae, J. Y., Ha, J. H., & Park, S. N. (2014). Antimicrobial activity, quantification and bactericidal activities of licorice active ingredients. *Microbiology and Biotechnology Letters, 42*(4), 386-392.
17. Libonatti, C., Varela, S., & Basualdo, M. (2014). Antibacterial activity of honey: A review of honey around the world. *Journal of Microbiology and Antimicrobials, 6*(3), 51-56.
18. Mandal, M. D., & Mandal, S. (2011). Honey: its medicinal property and antibacterial activity. *Asian Pacific journal of tropical biomedicine, 1*(2), 154-160.
19. Marco Terreni, M. T., and Massimo Pregnolato. (2021). New antibiotics for multidrug resistant bacterial strains.
20. Moghadam, F. J., Navidifar, T., & Amin, M. (2014). Antibacterial activity of garlic (Allium sativum L.) on multi-drug resistant. *Int J Enteric Pathog, 2*(2), e16749.
21. Mohamed, A. E., Abdur, R., & MM, S. A. (2020). Cinnamon bark as antibacterial agent: A mini-review. *GSC Biological and Pharmaceutical Sciences, 10*(1), 103-108.
22. Molan, P. C. (1992). The antibacterial activity of honey: 1. The nature of the antibacterial activity. *Bee world, 73*(1), 5-28.
23. Moloney, M. G. (2016). Natural products as a source for novel antibiotics. *Trends in pharmacological sciences, 37*(8), 689-701.
24. Mumu, S. K., & Hossain, M. M. (2018). Antimicrobial activity of tea tree oil against pathogenic bacteria and comparison of its effectiveness with eucalyptus oil, lemongrass oil and conventional antibiotics. *American Journal of Microbiological Research, 6*(3), 73-78.
25. Nitalikar, M. M., Munde, K. C., Dhore, B. V., & Shikalgar, S. N. (2010). Studies of antibacterial activities of Glycyrrhiza glabra root extract. *Int J Pharm Tech Res, 2*(1), 899-901.
26. O'Shea, R., & Moser, H. E. (2008). Physicochemical properties of antibacterial compounds: implications for drug discovery. *Journal of medicinal chemistry, 51*(10), 2871-2878.
27. Parisa, N., Islami, R. N., Amalia, E., Mariana, M., & Rasyid, R. S. P. (2019). Antibacterial activity of cinnamon extract (Cinnamomum burmannii) against staphylococcus aureus and escherichia coli in vitro. *Bioscientia Medicina: Journal of Biomedicine and Translational Research, 3*(2), 19-28.
28. Phan, H. T., & Haes, A. J. (2019). What does nanoparticle stability mean? *The Journal of Physical Chemistry C, 123*(27), 16495-16507.
29. Rayner, M. H., Sadler, P. J., & Scawen, M. D. (1990). NMR studies of a bacterial cell culture medium (LB Broth): cyclic nucleosides in yeast extracts. *FEMS microbiology letters, 68*(1-2), 217-221.
30. Rodino, S., Butu, A., Butu, M., & Cornea, P. (2015). Comparative studies on antibacterial activity of licorice, elderberry and dandelion. *Digest Journal of Nanomaterials and Biostructures, 10*(3), 947-955.
31. Russell, A. (2002). Antibiotic and biocide resistance in bacteria: introduction. *Journal of applied microbiology, 92*(s1), 1S-3S.
32. Sagdic, O., Aksoy, A., & Ozkan, G. (2006). Evaluation of the antibacterial and antioxidant potentials of cranberry (gilaburu, Viburnum opulus L.) fruit extract. *Acta Alimentaria, 35*(4), 487-492.
33. Sánchez, M. C., Ribeiro-Vidal, H., Bartolomé, B., Figuero, E., Moreno-Arribas, M. V., Sanz, M., & Herrera, D. (2020). New evidences of antibacterial effects of cranberry against periodontal pathogens. *Foods, 9*(2), 246.
34. Selvan, D. A., Mahendiran, D., Kumar, R. S., & Rahiman, A. K. (2018). Garlic, green tea and turmeric extracts-mediated green synthesis of silver nanoparticles: Phytochemical, antioxidant

and in vitro cytotoxicity studies. *Journal of photochemistry and photobiology b: biology, 180*, 243-252.

35. Tanaka, Y., Kikuzaki, H., Fukuda, S., & Nakatani, N. (2001). Antibacterial compounds of licorice against upper airway respiratory tract pathogens. *Journal of nutritional science and vitaminology, 47*(3), 270-273.
36. Teixeira, M., Sanchez-Lopez, E., Espina, M., Calpena, A., Silva, A. M., Veiga, F., . . . Souto, E. B. (2018). Advances in antibiotic nanotherapy: Overcoming antimicrobial resistance. *Emerging Nanotechnologies in Immunology*, 233-259.
37. Van Duin, D., & Paterson, D. L. (2016). Multidrug-resistant bacteria in the community: trends and lessons learned. *Infectious disease clinics, 30*(2), 377-390.
38. Vivas, R., Barbosa, A. A. T., Dolabela, S. S., & Jain, S. (2019). Multidrug-resistant bacteria and alternative methods to control them: an overview. *Microbial Drug Resistance, 25*(6), 890-908.
39. Wang, Z.-F., Liu, J., Yang, Y.-A., & Zhu, H.-L. (2020). A review: the anti-inflammatory, anticancer and antibacterial properties of four kinds of licorice flavonoids isolated from licorice. *Current Medicinal Chemistry, 27*(12), 1997-2011.
40. Wu, V. C.-H., Qiu, X., Bushway, A., & Harper, L. (2008). Antibacterial effects of American cranberry (Vaccinium macrocarpon) concentrate on foodborne pathogens. *LWT-Food Science and Technology, 41*(10), 1834-1841.
41. Yuan, Y.-G., Peng, Q.-L., & Gurunathan, S. (2017). Effects of silver nanoparticles on multiple drug-resistant strains of Staphylococcus aureus and Pseudomonas aeruginosa from mastitis-infected goats: an alternative approach for antimicrobial therapy. *International Journal of Molecular Sciences, 18*(3), 569.
42. Zhang, Y., Liu, X., Wang, Y., Jiang, P., & Quek, S. (2016). Antibacterial activity and mechanism of cinnamon essential oil against Escherichia coli and Staphylococcus aureus. *Food Control, 59*, 282-289.