Scholars Academic Journal of Pharmacy
Abbreviated Key Title: Sch Acad J Pharm
ISSN 2347-9531 (Print) | ISSN 2320-4206 (Online)
Journal homepage: http://saspublishers.com

OPEN ACCESS
Urology

Application of Triterpenes and Omega-3 Fatty Acids in Cases bith Resistance to Antibacterial and Anticancer Drugs

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DOI: https://doi.org/10.36347/sajp.2025.v14i05.003 | **Received:** 16.04.2025 | **Accepted:** 22.05.2025 | **Published:** 14.06.2025

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Abstract | **Review Article**

A major factor in the emergence of resistance to pathogens is the misuse and overuse of antimicrobials. The spread of microorganisms, often resistant to antimicrobial therapy is also facilitated by the lack of quality water and sanitation and infection prevention and control measures. In recent days it has been observed the emergence of resistance in several pathogenic Gram-positive and Gram-negative bacteria against the drugs applied. To control this global problem, there is an urgent need for the development of new antibacterial agents that can reduce treatment period, affect resistant strains and increase the effect of the applied treatment. It has been described that riboswitches regulate the expression of a number of genes which are responsible for synthesizing important metabolites which are need for finction of bacterial cells. An important strategy for overcoming bacterial resistance can be the development of drugs which can inhibit different bacterial riboswitches, which are essential for bacterial life and which are known to be suitable targets for creating of new antibacterial drugs. Cancer is one of the world's most common diseases, causing millions of deaths a year. Malignant diseases are the second (after heartvascular diseases) in terms of public health importance in Europe. This highlights the need for searching for new therapeutic agents for treatment of malignant diseases. One important trend can be application of plant extracts, containing compounds such as triterpenes: Oleanolic acid and Ursolic acid and omega-3 fatty acids such as Eicosapentaenoic acid and Docosahexaenoic acid, which advantages are that possess simultaneously both antimicrobial and anticancer activities and that are less toxic than synthetic produsedd drugs and this is of great importance for healt prevention.

Keywords: Microbial; Cancer; Resistance; Riboswitches; Triterpenes; Omega-3 fatty acids.

I. INTRODUCTION

I. Antimicrobial resistance.

Antimicrobial resistance cannot be defined as a new phenomenon, but it represents a serious threat to public health. It affects infectious diseases that are acquired in the community, but also nosocomial infections or, as the new term is now coming to mean, healthcare-associated infections [1].

As a result of the ineffectiveness of antibiotic therapies and treatment in home, the antibiotic resistance can increase. Antibiotic resistance and the inability of traditional medicines to affect infections caused by bacteria lead to a huge number of deaths and are a serious problem [2]. Antibiotic resistance is cause for reemergence of infections [3], especially in developing countries [4]. It has been reported a global increased antimicrobial resistance in 2029 [5]. The analysis of the possibility of future resistant to therapeutic drugs with bacteriostatic or bactericidal effects is important. Increased spread of antimicrobial resistance need preventive measures for healthcare [6].

It has been reported that about 70% of infections caused by antibiotic-resistant bacteria are hospital-acquired infections. This is a results from longer patient stays, higher hospital charges, and the need for larger hospital budgets. If resistance continues to grow, it will reduce global gross domestic product by 2% to

3.5%, and by 2050, the global economy could face treatment costs of up to US$100 trillion.

Our country, Bulgaria, is defined as a country with a very high mortality rate from bacterial infections that do not respond to antibiotic treatment in the EU. This means that at the local level, antibiotic resistance is very widespread, and the population in our country is unprotected from serious infectious diseases. Due to their effectiveness on pathogenic bacteria that affectvarious organisms, antibiotics are also used on animals. Thus, more and more types of bacteria are subjected to antibiotic therapy, which puts pressure on them, causing even more widespread antibiotic resistance [7]. The most dangerous bacteria are Gram-negative multi-resistant bacteria, which can adapt and show resistance to many drugs. At the same time, they can transfer their genetic material to other bacteria, thus making them resistant to specific antibiotics [8].

The major examples for resistant bacteria include [7]:

1) Staphylococcus aureus to Penicillin, Methicillin [9], Tetracycline and Erythromycin
2) Streptococcus pneumoniae to Penicillin [10]
3) Streptococcus pyogenes to Penicillin [10]
4) Enterococcus faecium to. Penicillin and Vancomycin [11]
5) Escherichia coli to fluoroquinolones [12]
6) Pseudomonas aerogunosa [13].

II. Riboswitches in bacteria

It has been investigated that RNA is an effective antibiotic target in the bacterial cell. Over 36 classes of riboswitches have been identified in bacteria. Their structure is well-studied, and with the help of fundamental bioinformatics studies, specific regions of riboswitches can be found in the Priority Bacteria Resistance genome of one or more bacteria - pathogenic or non-pathogenic for humans, to which a specificagent with a precise structural design can be targeted [14]. Due to their large number and widespread distribution in bacteria, they represent a vast new set of targets under investigation and development. A single riboswitch can be found in many different bacteria and repeated multiple times in a particular genome [15]. About 215 bacterial riboswitches from 16 different types found in 50 human pathogenic bacteria have been described. The riboswitch classes include those sensing essential flavin mononucleotide, GlmS, Cobalamin, Lysine, Glycine, Purine TPP and SAM-I [14].

FMN riboswitches is found in 3098 different organism species, of which 30 are human bacterial pathogens, including Gram-positive and Gram-negative. GlmS riboswitches has been found in 800 species, of which 11 are Gram-negative bacteria pathogenic to humans. The two riboswitches mentioned are among the most abundant in human pathogenic bacteria [14].

It has been described that riboswitches regulate the expression of a limited number of genes. However, most of these genes are responsible for synthesizing important metabolites, without which the cell cannot function [16]. It has been observed that riboswitches are antibacterial drug targets, Therefore, the dissemination of riboswitches is important for the discovery of new antibacterial drugs [17]. Bioinformatic and genomic studies – for example, the riboswitches Flavin mononucleotide and GlmS are among the first, that can be categorized as suitable and highly suitable targets for creating new antisense oligonucleotides (ASOs) [18]. For example of possible opportunity for drug development for overcoming bacterial resistance is observed fact that Gram-negative antibiotic are active by suppressing of an essential flavin mononucleotide (FMN) riboswitch [19].

III. Mechanisms of antibiotic resistance.

Mechanisms of antibiotic resistance are connected with the fact that bacterial cells are characterized by variability of their genetic material through mutations. The important mechanisms by which microorganisms exhibit resistance to antimicrobials include:

1) alteration on target place – the structure that an antibiotic targets is changed
2) reduction of drug accumulationby increasing drug elimination by efflux pumps – special pumps, which are created in the membranes of bacteria to eject the antibiotic from the cell;
3) modification of drug activation – enzymes are produced that disrupt the activation of the antibiotic or those that inactivate it.
4) alteration of metabolic pathways.

Bacteria, in addition to being able to build their own resistance mechanisms, can also pass them on to other bacteria, which is a serious problem. The distinction between resistance and persistence is important because of several facts, one of which is that for resistant bacteria, the development of new antibacterial agents is necessary, whereas a completely different approach is needed to overcome persisters [20].

IV. Resistance of tuberculosis species to antibiotics.

The disease is caused by a group of mycobacteria designated as the Mycobacterium tuberculosis complex (MTBC), which comprises species and subspecies sharing 99.9% of the DNA sequence but differ in their hosts. Mycobacterium tuberculosis is resistant to Isoniazid and Rifampin. The MTBC includes both the species causing the most common disease in humans (M. tuberculosis sensustricto, M. africanum, M. canettii), as well as the species primarily adapted to animal hosts (M. bovis, M. caprae, M. pinnipedii, M. microti, M. mungi, M. orygis, M. suricattae). Although prone to invasion, establishment and spread among certain animal species, there is evidence that each of these mycobacteria is capable of cause disease in other

mammalian species, including humans. From adapted to animal species, the most common causative agents of tuberculosis in humans are M. bovis and M. caprae, which have serious zoonotic and anthropozoonotic potential [21].

Intra-species referral for identification of the causative agent in MTCV in ill people is undertaken when the patient's association with cattle farming is established. For such identification in the NRL TB, NCIPB, for the last 14 years no patient has been referred or clinical isolate. Thus, diseases caused by M. bovis or M. caprae, although significantly less frequent, are not differentiated from cases of M. tuberculosis sensustricto, and patients are treated according to standard TB treatment regimens, which could lead to treatment failure or the emergence and transmission of antibiotic resistance. Species identification in the MTBC complex is important both for early establishing the epidemiological links of transmission [21].

Resistance in MTBC is particularly problematic as the range of agents that can successfully treat it is extremely small. Inappropriate use of antibiotics is a prerequisite for the emergence and spread of mutations in bacteria that are found in humans, animals, water, soil, plants, food products and can spread from one source to another. For this reason, the proposed project on "Determinants of antibiotic resistance in M. bovis and M. caprae and tracking of interspecies transmission" is important and relevant [22].

Antibiotic resistance levels in bovine tuberculosis in Bulgaria are expected to be established. The results would assess the risk of antibiotic resistance transmission. An important contribution would be the result related to establishing or rejecting the presence of transmission between humans and animals, which is an important prerequisite for assessing the outcome of TB control programmes. By whole-genome sequencing of isolated strains, the M. bovis / M. caprae resistome would be characterized.

V. Mechanisms of anticancer resistance.

In Bulgaria, every yearmore than 35,000 cases are diagnosed and more than 18,000 deaths, which together withthe trend of increasing mortality and lower survival rates compared to Europe, highlights the need for well-organised and consistent control activities and treatment of malignant diseases.

It has been reported that mechanisms of drug resistance in cancer are different and inlcide: drug inactivation, modification of drug target [23], decreasing of cell content of drug by redused influx and increased drug efflux and cell death inhibition [24]. Glutatione is known as a drug-detoxifying mechanism which leads to drug inactivation. Other mechanism which contribute to enhance the resistance to drugs of cancer cells is connected with the DNA damage response, which can reverse the damages in DNA from drugs [25]. Other factors include individual variations in patients and genetic differences in tumors [26].

An important factor for insensitivity of cancer cells to drugs is explaned with the occurred mutations in the cell transporters for drugs, by which is minimized drug up-take in cancer cell. The reasons that caused the resistance of chemotherapeutics include the genetic defects in intrinsic and extrinsic pathways. Defects in intrinsic path are connected with decrease of activity of Bax apoptotic protein, of permeability of mitochondrial membrane and of inhibition of cytochrome C release, which can block the further formation of proapoptotic caspases 9, 3, 7 and will contribute to death escape [27].

Genetic defects in extrinsic pathways include decreasing of possibility of binding of specific receptor massagers to their respective receptors, which leads to desactivation of death domain in cancer cells and as a result this blocks the activation of caspases [8, 10, 3, 7] and to suppresion of Bax apoptotic protein [28].

The drug resistance can occur due to:

1) the overexpression of anti-apoptosis proteins Bcl-2, Bcl-XL
2) activation of pro-survival pathways such as the PI3K-Akt [29].
3) Drugresistance can be overcome by simultaneous multi-target therapy [30].

V. Natural plants and compounds with potential antibacterial and antitumor activity.

Nature is a limitless source of new therapeutic candidates. The vastvariety of compounds in millions of species of plants, animals, marine organisms andmicroorganisms is an endless library of structures available for study and applicationin medicine.A successful approach to finding new pharmacological agents to useas antibacterial or antitumour agents is the use of natural products and their synthetic derivatives. Analysis of the number of chemotherapeutic agents and their sources shows that more than 60% of approved drugs are isolated orderived from natural compounds. On the other hand, in recent years a number of new anticancer agents derived from natural products are in late preclinical and earlyclinical trials [31].

It has been reported that various medicinal plant extracts possess antibacterial, antitumor and antioxidant activities [31]. These effects are result of mechanism of action of compounds, which present in plant extracts such as phenolic derivatives, flavonoids, triterpens. It has been reported that flavonoids exhibit antimicrobial and antioxidant properties.[32]. Phenolic derivatives have been known to exert antioxidant and anticancer potential. [33]. For example antibacterial, antifungal and antioxidant effect possess polyphenols of *Withania frutescens L.* [34] has been observed that blueberry

flavonoids, quercetin, kaempferol, and gentisic acid decrease proliferation of cancer HCT-116 cell line [35].

It has been reported that the following plants exhibit both antibacterial and anticancer activity:

1) *Anacardium occidentale L.* [36]
2) *Brassica rapa L*. [37]
3) *Clinopodium vulgare L.* [38,39]
4) *Colocasia esculenta* [40]
5) *Cucumis sativum* [41]
6) *Ficus drupacea* [42]
7) *Origanum vulgare L.* [43]
8) *Phoenix dactylifera L.* [44].

1. Triterpenes

An example of such structures of natural origin are triterpenes, which exhibit significant, broad-spectrum biological activity. Triterpenes also provide scientists with a good basis for the synthesis of their derivatives containing in their structure suitable active groups that can modulate various regulatory pathways in the cell and therefore enhance the pharmacological action both against infectious and oncological diseases [45].

Oleanolic acid (OA) [3β-hydroxyolean-12-en-28-oic acid], is a natural pentacyclic triterpenic acid that can be isolated from more than 1620 species of plants, including food and medicinal ones. In nature the compound exists either as a free acid or as an aglycone precursor of triterpene saponins, in which it may be bound to one or more carbohydrate chains [46].

Ursolic acid (3 β-hydroxy-urs-12-en-28-oic acid) is a pentacyclic triterpenoid which exert anti-carcinogenic, anti-inflammatory, antioxidant, antiviral properties. *Ocimum sanctum* (Lamiaceae) is a plant which contains Ursolic acid and possesses anticancer effect [47].

It has been demonstrated that triterpenoids Oleanolic acid and Ursolic acid exhibit antibacterial activity towards microorganisms such as Streptococcus mutans, Streptococcus mitis, Streptococcus sanguinis, Streptococcus salivarius, Streptococcus sobrinus, and Enterococcus faecalis [48].

It has been investigated that Oleanolic acid and Ursolic acid induce apoptosis in HuH7 human hepatocellular carcinoma cells [49] and antiproliferative effect against gastric, colon, pancreatic, and liver cancers [50]. The antitumor activity of these compounds is explained by their ability to block activation of the nuclear factor NF-kB by inducing apoptosis, inhibition of signaling pathways and activation of transcription, and through angiogenesis.

In addition to its excellent hepatoprotective effect (it has been in clinical use as anti-hepatitis agent in China for more than 20 years) Oleanolic acid has been found to exhibit strong antitumor, anti-HIV, anti-inflammatory activity, improves cardiovascular function and inhibits glycogen phosphorylase. In view of its widespread use in nature, its high biological activity and relatively non-toxic nature Oleanolic acid represents a suitable starting compound for many synthetic transformations.

2. Omega-3 fatty acids

Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) are a polyunsaturated omega−3 fatty acid, which arenot synthesized by the organism. The ω-3 PUFAs EPA and DHA exert antimicrobial activity against Staphylococcus aureus, Staphylococcus epidermidis, *and* Pseudomonas aeruginosa [51]. Their anticancer role is connected with the fact that these compounds can influence multiple targets and different stages of cancer formation. These fatty acids have been known to suppress cell proliferation, decrease cell survival and reduce of metastasis. It has been observed that the reduction of cancer cell proliferation from omega-3 fatty acids is a result from their properties to modify the inflammatory responses and by their role to decrease oxidative stress [52].

It has been reported that the mechanisms of anticancer action of Docosahexaenoic acid against non-small lung tumor A549 cells include:

1) suppression of tumor growth by increasing the apoptosis of A549 cells
2) decreasing of the degree of metastasis of A549 cells, by reduction of the levels of metastasis-associated proteins [52].

All of these mechanisms lead to the enchanced production of intracellular reactive oxygen species in cancer cells. These facts with combination with the redused by Docosahexaenoic acid concentration of antioxidant enzyme catalase, lead to decreased cancer viability and apoptosis [53].

All these different mechanisms of antitumor action are important for suppression of progression of cancer development [54]. The anticancer role of omega-3 polyunsaturated fatty acids olso is connected with the enhance of DNA hydroxymethylation [55].

CONCLUSION

The treatment of infections in recent years continues to be a serious challenge, regardless of the successes achieved in the field of clinical microbiology and infectious diseases. The reason is the emergence of resistance in several pathogenic bacteria against the drugs used. To control this global problem, there is an urgent need for the development of new antibacterial agents that can reduce treatment period, affect resistant strains and increase the effect of the applied treatment. One of the important possible opportunity for drug development for over coming bacterial resistance is to

obtained drugs with properties to suppress of an essential flavin mononucle riboswitch, which is a promising antibacterial drug target. Other bacterial riboswitches are olso known as an animportant targets for the discovery of new antibacterial drugs

Another global health problem is the spread of tumor diseases. All of these data show the need for development of new drugs with decreased resistanse to them. One important and beneficial strategy can be application of plant extracts, containing compounds which exhibit significant, broad-spectrum biological activity. Such kind of compounds are triterpenes: Oleanolic acid and Ursolic acid and omega-3fatty acids such as Eicosapentaenoic acid and Docosahexaenoic acid which exerts both antibacterial and anticancer effect. These findings support the idea for application of plant compounds with multiple activities against these two very deingereous human diseases such as bacterial infections and tumors. Additional advantage of plant therapy is that they are less toxic than synthetic produsedrugs and this is of great importance for healthcare.

Additional information

Conflict of interest: The authors have declared that no competing interests exist.

Ethical statements

- The authors declared that no clinical trials were used in the present study.
- The authors declared that no experiments on humans or human tissues were performed for the present study.
- The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.
- The authors declared that no experiments on animals were performed for the present study.
- The authors declared that no commercially available immortalized human and animal cell lines were used in the present study

Funding: No funding was reported.

Author contributions: All authors have contributed equally.

Data availability: All of the data that support the findings of this study are available in the main text or Supplementary Information.

REFERENCES

1. Ahmed, S.K.; Hussein, S.; Qurbani, K.; Ibrahim, R.H.; Fareeq, A.; Mahmood, K.A.; Mohamed, M.G. 2024. Antimicrobial resistance: impacts, challenges, and future prospects. Journal of Medicine, Surgery, and Public Health, 2:100081. https://doi.org/10.1016/j.glmedi.2024.100081
2. Salam, M.A.; Al-Amin, M.Y.; Salam, M.T.; Pawar, J.S.; Akhter, N.; Rabaan, A.A.; Alqumber, M.A. 2023. Antimicrobial resistance: a growing serious threat for global public health. Healthcare, 11(13):1946. https://doi.org/10.3390/healthcare11131946
3. Subramaniam, G.; Girish, M. 2020. Antibiotic resistance – a cause for reemergence of infections. Indian Journal of Pediatrics, 87(11):937–944. https://doi.org/10.1007/s12098-019-03180-3
4. Ikhimiukor, O.O.; Odih, E.E.; Donado-Godoy, P.; Okeke, I.N. 2022. A bottom-up view of antimicrobial resistance transmission in developing countries. Nature Microbiology 7(6):757–765. https://doi.org/10.1038/s41564-022-01124-w
5. Murray, C.J.; Ikuta, K.S.; Sharara, F.; Swetschinski, L.; Aguilar, G.R.; Gray, A. et al. 2022. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet, 399(10325):629–655. https://doi.org/10.1016/S0140-6736(21)02724-0
6. Endale, H.; Mathewos, M.; Abdeta, D. 2023. Potential causes of spread of antimicrobial resistance and preventive measures in one health perspective – a review. Infection and Drug Resistance, 16:7515–7545. https://doi.org/10.2147/IDR.S428837
7. Tang, K.W.K.; Millar, B.C.; Moore, J.E. 2023. Antimicrobial resistance (AMR). British Journal of Biomedical Science, 80:11387. https://doi.org/10.3389/bjbs.2023.11387
8. Chia, P.Y.; Sengupta, S.; Kukreja, A.; S.L.; Ponnampalavanar, S.; Ng, O.T.; Marimuthu, K. 2020. The role of hospital environment in transmissions of multidrug-resistant gram-negative organisms. Antimicrobial Resistance and Infection Control, 9:1–11. https://doi.org/10.1186/s13756-020-0685-1
9. Maree, C.L.; Daum, R.S.; Boyle-Vavra, S.; Matayoshi, K.; Miller, L.G. 2007. Community-associated Methicillin-resistant Staphylococcus aureus isolates and healthcare-associated infections. Emerging Infectious Diseases, 13(2): 236–242. https://doi.org/10.3201/eid1302.060781
10. Albrich, W.C.; Monnet, D.L.; Harbarth, S. 2004. Antibiotic selection pressure and resistance in Streptococcus pneumoniae and Streptococcus pyogenes. Emerging Infectious Diseases, 10(3):514–517. https://doi.org/ 10.3201/eid1003.030252
11. Raza, T.; Ullah, S.R; Mehmood, K.; Andleeb, S. 2018. Vancomycin resistant Enterococci: a brief review. Journal of Pakistan Medical Association Form 68(5):768–772.
12. Goettsch, W.; Van Pelt, W.; Nagelkerke, N.; Hendrix, M.G.R.; Buiting, A.G.M.; Petit, P. L.; Sabbe, L.J.M.; van Griethuysen, A.J.A.; de Neeling, A.J. 2000. Increasing resistance to fluoroquinolones in Escherichia coli from urinary tract infections in the Netherlands. Journal of Antimicrobial Chemotherapy, 46(2):223–228. https://doi.org/10.1093/jac/46.2.223
13. Mladenovic-Antic, S.; Kocic, B.; Velickovic-Radovanovic, R.; Dinic, M.; Petrovic, J.; Randjelovic, G., Mitic, R. 2016. Correlation between antimicrobial consumption and antimicrobial resistance of Pseudomonas aeruginosa in a hospital setting: a 10-

year study. Journal of Clinical Pharmacy and Therapeutics, 41(5):532-537. https://doi.org/10.1111/jcpt.12432
14. Penchovsky, R.; Pavlova, N.; Kaloudas, D. 2021. RSwitch: a novel bioinformatics database on riboswitches as antibacterial drug targets. IEEE/ACM Transactions on Computational Biology and Bioinformatics, 18(2):804–808. https://doi.org/10.1109/TCBB.2020.2983922
15. Kavita, K.; Breaker, R.R. 2023. Discovering riboswitches: the past and the future. Trends in Biochemical Sciences, 48(2):119–141. https://doi.org/10.1016/j.tibs.2022.08.009
16. Mandal, M.; Breaker, R.R. 2004. Gene regulation by riboswitches. Nature Reviews Molecular Cell Biology 5(6):451–463. https://doi.org/10.1038/nrm1403
17. Ellinger, E.; Chauvier, A.; Romero, R.A.; Liu, Y.; Ray, S.; Walter, N.G. 2023. Riboswitches as therapeutic targets: promise of a new era of antibiotics. Expert Opinion on Therapeutic Targets, 27(6):433–445. https://doi.org/10.1080/14728222.2023.2230363
18. Pavlova, N.; Traykovska, M.; Penchovsky, R. 2023. Targeting FMN, TPP, SAM-I, and glmS riboswitches with chimeric antisense oligonucleotides for completely rational antibacterial drug development. Antibiotics (Basel), 12(11):1607. https://doi.org/10.3390/antibiotics12111607
19. Motika, S.E.; Ulrich, R.J.; Geddes, E.J.; Lee, H.Y.; Lau, G.W.; Hergenrother, P.J. 2020. Gram-negative antibiotic active through inhibition of an essential riboswitch. Journal of the American Chemical Society, 142(24):10856–10862. https://doi.org/10.1021/jacs.0c04427
20. Mohanty, H.; Pachpute, S.; Yadav, R.P. 2021. Mechanism of drug resistance in bacteria: efflux pump modulation for designing of new antibiotic enhancers. Folia Microbiologica, 66(5):727–739.https://doi.org/10.1007/s12223-021-00910-z
21. van Ingen, J.; Rahim, Z.; Mulder, A.; Boeree, M.J.; Simeone, R.S.; Brosch, R.; van Soolingen, D. 2012. Characterization of Mycobacterium orygis as M. tuberculosis complex subspecies. Emerging Infectious Diseases, 18(4):653–655. https://doi.org/10.3201/eid1804.110888
22. Mishra, R.; Shukla, P.; Huang, W.; Hu, N. 2015. Gene mutations in Mycobacterium tuberculosis: Multidrug-resistant TB as an emerging global public health crisis. Tuberculosis, 95(1):1–5. https://doi.org/10.1016/j.tube.2014.08.012
23. Housman, G.; Byler, S.; Heerboth, S.; Lapinska, K.; Longacre, M.; Snyder, N.; Sarkar, S. 2014. Drug resistance in cancer: an overview. Cancers, 6(3):1769–1792. https://doi.org/10.3390/cancers6031769
24. Pan, S.T.; Li, Z.L.; He, Z.X.; Qiu, J. X.; Zhou, S.F. 2016. Molecular mechanisms for tumour resistance to chemotherapy. Clinical and Experimental Pharmacology and Physiology, 43(8):723–737. https://doi.org/10.1111/1440-1681.12581
25. Bonanno, L.; Favaretto, A.; Rosell, R. 2014. Platinum drugs and DNA repair mechanisms in lung cancer. Anticancer Research, 34(1):493–502.
26. Dagogo-Jack, I.; Shaw, A. 2018. Tumour heterogeneity and resistance to cancer therapies. Nature Reviews Clinical Oncology, 15(2):81–94. https://doi.org/10.1038/nrclinonc.2017.166
27. Haider, T.; Pandey, V.; Banjare, N.; Gupta, P. N.; Soni, V. 2020. Drug resistance in cancer: mechanisms and tackling strategies. Pharmacological Reports, 72(5):1125–1151. https://doi.org/10.1007/s43440-020-00138-7
28. Jeong, S.H.; Lee, H.W.; Han, J.H.; Kang, S.Y.; Choi, J.H.; Jung, Y.M.; Choi, H.; Oh, Y.T.; Park, K.J.; Hwang, S.C.; Sheen, S.S.; Oh, Y.J.; Kim, J.H.; Lim, H.-Y. 2008. Low expression of Bax predicts poor prognosis in resected non-small cell lung cancer patients with non-squamous histology. Japanese Journal of Clinical Oncology, 38(10):661–669.https://doi.org/10.1093/jjco/hyn089,
29. Bukowski, K.; Kciuk, M.; Kontek, R. 2020. Mechanisms of multidrug resistance in cancer chemotherapy. International Journal of Molecular Sciences, 21(9):3233. https://doi.org/10.3390/ijms21093233
30. Wang, X.; Zhang, H.; Chen, X. 2019. Drug resistance and combating drug resistance in cancer. Cancer Drug Resistance, 2(2):141–160. https://doi.org/10.20517/cdr.2019.10
31. Karakaş, F.P.; Yildirim, A.; Türker, A. 2012. Biological screening of various medicinal plant extracts for antibacterial and antitumor activities. Turkish Journal of Biology, 36(6):641–652. https://doi.org/10.3906/biy-1203-16
32. Cushnie, T.P.T.; Lamb, A.J. 2005. Antimicrobial activity of flavonoids. International Journal of Antimicrobial Agents, 26(5):343–356. https://doi.org/10.1016/j.ijantimicag. 2005.09.002
33. Dai, J.; Mumper, R.J. 2010. Plant phenolics: extraction, analysis and their antioxidant and anticancer properties. Molecules, 15(10):7313–7352. https://doi.org/ 10.3390/molecules15107313
34. El Moussaoui, A.; Jawhari, F.Z.; Almehdi, A.M.; Elmsellem, H.; Benbrahim, K.F.; Bousta, D.; Bari, A. 2019. Antibacterial, antifungal and antioxidant activity of total polyphenols of Withania frutescens. L. Bioorganic Chemistry, 93:103337. https://doi.org/10.1016/j.bioorg.2019.103337
35. Sezer, E.D.; Oktay, L.M.; Karadadaş, E.; Memmedov, H.; Selvi Gunel, N.; Sözmen, E. 2019. Assessing anticancer potential of blueberry flavonoids, quercetin, kaempferol, and gentisic acid, through oxidative stress and apoptosis parameters on HCT-116 cells. Journal of Medicinal Food, 22(11):1118–1126. https://doi.org/10.1089/jmf.2019.0098
36. De Araujo, J.S.C.; De Castilho, A.R.F.; Lira, A.B.,; Pereira, A.V.,; de Azevedo, T.K.B.; de Melo de Brito Costa, E.M,; Pereira, MSV; Pessôa, H.L.F.; Pereira, J.V. 2018. Antibacterial activity against cariogenic bacteria and cytotoxic and genotoxic potential of Anacardium occidentale L. and *Anadenanthera macrocarpa (Benth) Brenan* extracts. Archives of Oral Biology, 85:113–119. https://doi.org/10.1016/j.archoralbio.2017.10.008

37. Hong, E.; Kim, G.H. 2008. Anticancer and antimicrobial activities of β-phenylethyl isothiocyanate in *Brassica rapa L*. Food Science and Technology Research, 14(4):377–377. https://doi.org/10.3136/fstr.14.377
38. Dzhambazov, B.; Daskalova, S.; Monteva, A.; Popov, N. 2002. In vitro screening for antitumour activity of *Clinopodium vulgare L.* (Lamiaceae) extracts. Biological and Pharmaceutical Bulletin, 25(4):499–504. https://doi.org/10.1248/bpb.25.499
39. Stefanovic, O,; Stankovic, M.S.; Comic, L. 2011. *In vitro* antibacterial efficacy of *Clinopodium vulgare L.* extracts and their synergistic interaction with antibiotics. Journal of Medicinal Plants Research 5(17), 4074-4079.
40. Chakraborty, P.; Deb, P.; Chakraborty, S.; Chatterjee, B.; Abraham, J. 2015. Cytotoxicity and antimicrobial activity of *Colocasia esculenta*. Journal of Chemical and Pharmaceutical Research, 7(12):627–635. http://jocpr.com/vol7-iss12-2015/JCPR-2015-7-12-627-635.pdf
41. Tuama, A.A.; Mohammed, A.A. 2019. Phytochemical screening and in vitro antibacterial and anticancer activities of the aqueous extract of *Cucumis sativus*. Saudi Journal of Biological Sciences, 26(3):600–604. https://doi.org/10.1016/j.sjbs.2018.07.012
42. Yessoufou, K.; Elansary, H.O.; Mahmoud, E.A.; Skalicka-Wozniak, K. Antifungal, antibacterial and anticancer activities of *Ficus drupacea L.* stem bark extract and biologically active isolated compounds. Industrial Crops and Products 2015, 74l:752–758 https://doi.org/10.1016/j.indcrop.2015.06.011
43. Sankar, R.; Karthik, A.; Prabu, A.; Karthik, S.; Shivashangari, K.S.; Ravikumar, V. 2013. *Origanum vulgare* mediated biosynthesis of silver nanoparticles for its antibacterial and anticancer activity. Colloids and Surfaces B: Biointerfaces, 108:80–84. https://doi.org/10.1016/j.colsurfb.2013.02.033
44. Kchaou, W.; Abbès, F.; Mansour, R.B.; Blecker, C.; Attia, H.; Besbes, S. 2016. Phenolic profile, antibacterial and cytotoxic properties of second grade date extract from Tunisian cultivars *(Phoenix dactylifera L.)*. Food Chemistry, 194:1048–1055 https://doi.org/10.1016/j.foodchem.2015.08.120
45. Mabou, F.D.; Yossa, I.B.N. 2021. Terpenes: Structural classification and biological activities. IOSR J Pharmacy Journal of Pharmacy and Biological Sciences, 16(3, Ser. I):25–40.
46. Castellano, J.M.; Ramos-Romero, S.; Perona, J.S. 2022. Oleanolic acid: extraction, characterization and biological activity. Nutrients, 14(3):623. https://doi.org/10.3390/nu14030623
47. Mlala, S.; Oyedeji, A.O.; Gondwe, M.; Oyedeji, O.O. 2019. Ursolic acid and its derivatives as bioactive agents. Molecules, 24(15):2751. https://doi.org/10.3390/ molecules24152751
48. Wolska, K.I.; Grudniak, A.M.; Fiecek, B.; Kraczkiewicz-Dowjat, A.; Kurek, A. 2010. Antibacterial activity of oleanolic and ursolic acids and their derivatives. Central European Journal of Biology, 5(5):543-53. https://doi.org/10.2478/s11535-010-0045-x
49. Shyu, M.H.; Kao, T.C.; Yen, G.C. 2010, Oleanolic acid and ursolic acid induce apoptosis in HuH7 human hepatocellular carcinoma cells through a mitochondrial-dependent pathway and downregulation of XIAPJ. Journal of Agricultural and Food Chemistry, 58(10): 6110–6118 https://doi.org/10.1021/jf100574j
50. Pięt, M.; Paduch, R. 2019. Ursolic and Oleanolic acids as potential anticancer agents acting in the gastrointestinal tract. Mini-Reviews in Organic Chemistry, 16(1):78–91. https://doi.org/10.2174/1570193X15666180612090816
51. Coraça-Huber, D.C.; Steixner, S.; Wurm, A.; Nogler, M. 2021. Antibacterial and anti-biofilm activity of omega-3 polyunsaturated fatty acids against periprosthetic joint infections-isolated multi-drug resistant strains. Biomedicines, 9(4):334. https://doi.org/10.3390/biomedicines9040334
52. Yin, Y.; Sui, C.; Meng, F.; Ma, P.; Jiang, Y. 2017. The omega-3 polyunsaturated fatty acid docosahexaenoic acid inhibits proliferation and progression of non-small cell lung cancer cells through the reactive oxygen species-mediated inactivation of the PI3K/Akt pathway. Lipids in Health and Disease, 87(16):1–9. https://doi.org/10.1186/s12944-017-0474-x
53. Fuentes, N.R.; Kim, E.; Fan, Y. Y.; Chapkin, R.S. 2018. Omega-3 fatty acids, membrane remodeling and cancer prevention. Molecular Aspects of Medicine, 64:79–91. https://doi.org/10.1016/j.mam.2018.04.001
54. Jing, K.; Wu, T.; Lim, K. 2013. Omega-3 polyunsaturated fatty acids and cancer.Anti-Cancer Agents in Medicinal Chemistry, 13(8):1162–1177. https://doi.org/10.2174/18715206113139990319
55. Huang, Q.; Mo, M.; Zhong, Y.; Yang, Q.; Zhang, J.; Ye, X.; Zhang, L; .Cai, C. 2019. The anticancer role of omega-3 polyunsaturated fatty acids was closely associated with the increase in genomic DNA hydroxymethylation. Anti-Cancer Agents in Medicinal Chemistry, 19(3):\330–336. https://doi.org/10.2174/1871520618666181018143026