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Alternatives to Antibiotics GOAL: ELEVATING Antibiotic Resistance During the Post-COVID Period

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Abstract:

The COVID-19 outbreak offers an unmatched chance to take advantage of personalized medicine's benefits for the protection, detection, medication, monitoring, and administration of a fresh public health crisis. Antibiotics, which were formerly regarded as miracle cures and among the most difficult life-saving discoveries of the twentieth century, are now posing a hazard to society as a result of overuse and abuse. Antimicrobial resistance (AMR) is a widespread issue that is becoming worse, and the current COVID-19 pandemic might make things even worse. It has been shown that a significant portion of Covid-19 patients gets secondary microbiological infections. The medical industry is now facing difficulties because of this. As a result, several non-antibiotic techniques have been sought, and their processes have been examined, to slow the spread of AMR.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) was classified as a pandemic by the World Health Organization in March 2020 (1). The majority of Coronavirus (COVID-19) individuals globally are most susceptible to secondary infections. Antimicrobial resistance (AMR) has increased as a result of the introduction of COVID-19 due to an increase in microbial pathogens as secondary infections (2,3). The World Health Organization has stated that by 2050, the number of human fatalities brought on by drug-resistant bacteria might increase from around 700,000 to 10 million (4). The biggest contributor to AMR has been the increasing use of antibiotics during covid outbreaks. However, high rates of incorrect antimicrobial prescription, improper use of biocides, and discontinuation of therapy for other disorders may be to blame for the establishment of antimicrobial resistance. Antibiotic use has increased, which has contributed to the creation and spread of antimicrobial

resistance (AMR), a significant worldwide health issue. Antimicrobial stewardship programs include minimizing the use of antibiotics as one of their key suggestions for combating AMR (5). A concerning biological issue is the inability of some illnesses to be treated by currently available antibiotics (6,7). The need of integrating antimicrobial stewardship practices with the healthcare system's COVID-19 response has been emphasized by the World Health Organization. Researchers and doctors are scrambling to identify a medicine that may exert antiviral efficacy with minimal side effects and should be inexpensive in the wake of the COVID-19 epidemic (8). Since SARS-CoV-2 is a recently discovered virus, repurposed medications are the only effective treatments available outside vaccinations. Based on our prior experiences with these antiviral medications against extremely pathogenic RNA viruses including HIV, Ebola, influenza, etc., clinical studies are now being done.

In addition to antiviral medications, several clinical investigations have found that COVID-19 causes an increase in cytokine and chemokine production (9), and as a result, immuno-modulatory US FDA-approved medications may also be able to help reduce the abnormal inflammatory immune response. Overall, it is recommended that antiviral and anti-inflammatory medicine combination treatment may be able to mitigate the current COVID-19 pandemic (10).

Antibiotic Resistant Emergence Favouring Factors

- enhancing environmental use of bactericidal agents
- A halt to research into other infectious illnesses
- A halt to research into other pathogens
- Shortages of medications, particularly narrow spectrum antimicrobials, and personal protective equipment (e.g., hydroxychloroquine);
- Scarcity of medications, particularly limited spectrum antimicrobials, and personal protective (e.g., hydroxychloroquine);
- Overpopulation and overburden of medical systems (11).

Most antibiotic medications are used as prophylaxis to shield hospitalized patients from further bacterial infections. The widespread issue of antibiotic resistance is not the only one. Changes in the gut flora may be another unfavourable impact of antibiotic therapy in patients. Furthermore, individuals with COVID-19 may experience poorer outcomes as a result of gut microbiome abnormalities. It's interesting to note that COVID-19 patients with GI issues have been reported

to have more respiratory discomfort than COVID-19 patients without GI symptoms (12).

Anti-Microbial Resistance (AMR)

using cleaning products and washing hands

While suffering from a covid-19 infection, using hand sanitizers and disinfectants commonly exposes the user to both pharmacological and non-pharmaceutical substances in various amounts (13). Phenol and hydrogen peroxides, which cause bacterial DNA damage, are included in the majority of commercial sanitizers (11–13).

Antimicrobial resistance gene transmission mechanisms

Inhibiting or restricting drug absorption, bypassing the pathway (compensatory tack) impeded by a drug, demeaning and inactivating a drug by modification/ degradation enzymes, and pumping a drug out of the body by different types of active efflux pumps are the primary mechanism of resistance to antibiotics. Modifications in cellular membranes that reduce the permeability of the membrane and alteration in cell wall proteins are the prevalent antibiotic targets (14).

Therapies without antibiotics to target AMR

To solve the AMR issue, suitable antimicrobial alternatives must be taken into consideration. Probiotics, phages, and phytomedicines are a few non-antibiotic methods for treating and preventing different illnesses (15).

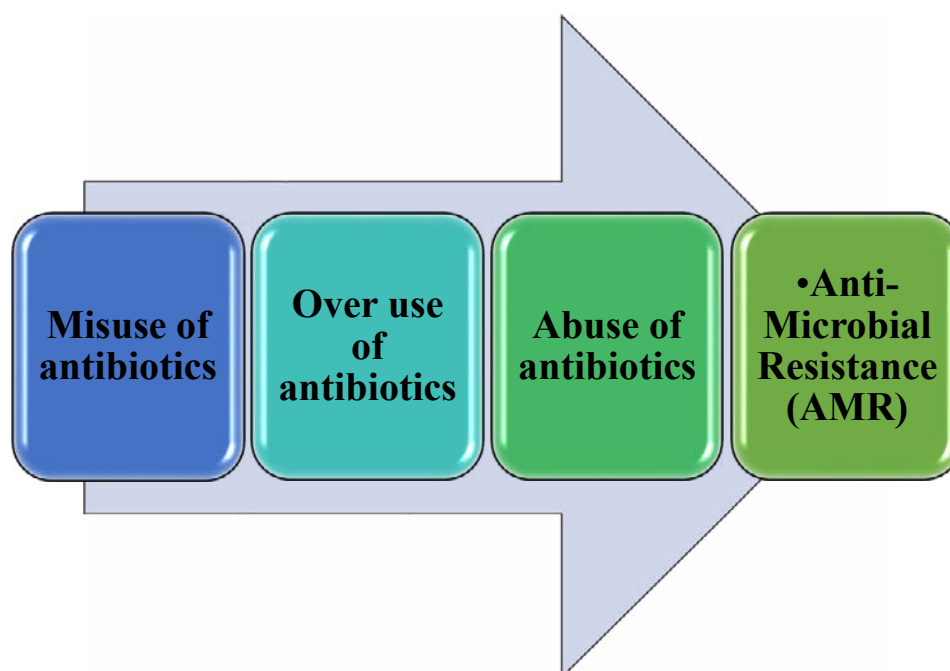


Fig1. Development of Antibiotic Resistance.

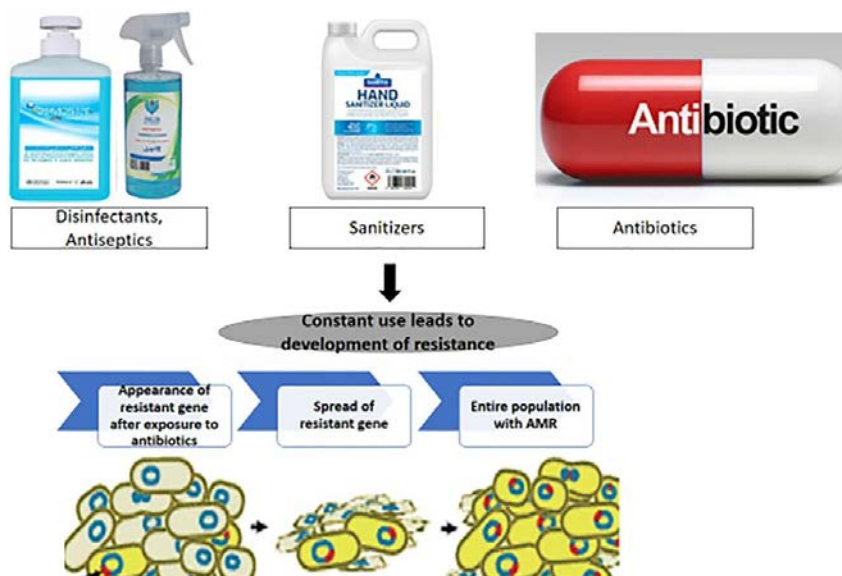


Fig2. Antimicrobial resistance gene transmission mechanisms.

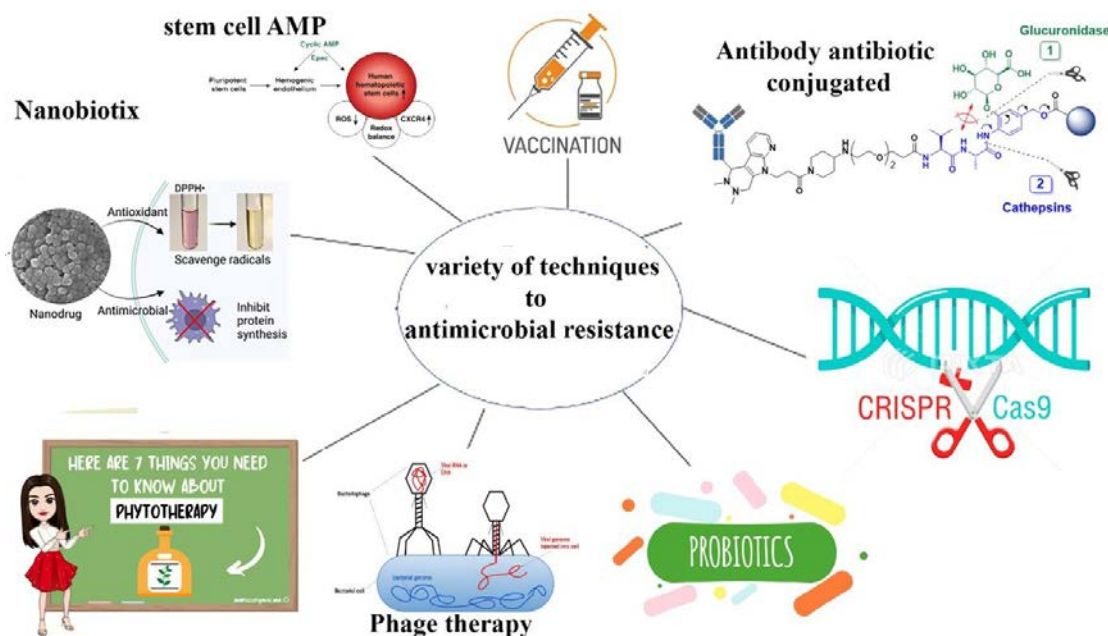


Fig3. Multiple strategies are used to address antimicrobial resistance.

The probiotic and prebiotic

Probiotics have been used as an alternative therapy for several intestinal illnesses, including gastroenteritis and diarrhea brought on by antibiotics. By granting immunity to infection or getting rid of infectious agents, probiotics have a positive impact on the digestive and other systems. As probiotics, several bacterial and yeast species have been employed (16).

Prebiotics are non-absorbable polysaccharides (like inulin and fructo-oligosaccharides) that promote the variety of the human gut microbiota and demonstrate health advantages in the host. According to studies,

giving prebiotics to individuals who suffer diarrhea brought on by antibiotics has worked well (17).

Antimicrobial agents based on Bacteriophages

Bacteriophage treatment involves lysing bacterial pathogens with phages. Bacteriophage treatment has gained increased attention as antibiotic resistance has become a significant issue in contemporary medicine (18).

Phytomedicines

Bioactive substances that are obtained from plants

are known as phytomedicines. To treat diverse illnesses, several phytochemicals are utilized as lead molecules. Approximately 25% of all prescription pharmaceuticals used in the USA contain one or more bioactive chemicals derived from vascular plants. It is estimated that more than two-thirds of the world's population now depends on plant-derived medicines (19). According to estimates, plant ingredients make up or have served as models for 50% of current Western pharmaceuticals (20). Many of the commercially successful medications used in contemporary medicine were first used in undeveloped forms in conventional or folk medicine, or for other uses that showed potential biological activity. Additionally, researcher (21) found that extracts from 15 widely used Indian medicinal herbs were effective against enteric bacteria that produce ESBLs and are multidrug resistant. 45 Iranian medicinal herbs were shown to have an action against many drug-resistant human diseases, according to researches (22). Additionally, beta-lactamase generating methicillin-resistant *Staphylococcus aureus* was observed to be affected by several bioactive plant extracts (23). Several studies have been conducted to support the claims made for alternative treatments.

Faecal microbiota transplantation (FMT)

FMT involves transferring a healthy person's feces to a patient to repair the patient's damaged gut flora. According to research, this FMT can cure infections brought on by vancomycin-resistant enterococci or multidrug-resistant *K. pneumoniae*, two examples of drug-resistant microorganisms (24).

Stem Cell-Derived Antimicrobial Peptides

Mesenchymal stem cells (MSCs) have undergone substantial research to provide a safe and effective therapeutic solution for several chronic disorders. MSCs have remarkable potential for enhancing immunomodulation, tissue repair, and inflammation management (25). According to a recent investigation, human MSCs behave as antimicrobial peptides (AMPs) that kill bacteria in a variety of ways, including preventing the formation of bacterial cell walls (26).

Blood Filtration Variations

In some illnesses, controlling the cytokine storm is crucial to avoiding organ damage. Devices are used in hemofiltration or renal replacement therapies to bind to and remove circulating bacterial products, inflammatory mediators, and cytokines (27) as well as some pathogens. Mannose-binding lectins and bound heparin are two of the frequently used tools (28). It is believed that even in cases of multidrug resistance, the host immune system will be able to combat the remaining pathogens if a significant reduction in the pathogenic bacterial load is achieved by this hemo-filter (29).

Quorum sensing blockers

The two crucial characteristics of microbial pathogens boosting their survival chances in harsh conditions are the ability to form biofilms and quorum sensing. Numerous organic and synthetic compounds have been demonstrated to inhibit quorum sensing (30).

Role of CRISPR-Cas against AMR

In microbial species, CRISPR-cas is a particular adaptive immunological characteristic that offers defence against invasive bacteriophages (18, 31).

Significance of Nano-antibiotics to combat AMR

It is possible to use nanoparticles to deliver antimicrobial agents or for them to already contain such agents. Due to their improved antimicrobial and anticancer activity and low toxicity, metal and metal oxide-based nanomaterials and drugs are viewed as attractive therapeutic options for use in biological sciences in the future (32). Through a variety of mechanisms, including bacterial wall disruption, biofilm suppression, immune response activation in the host, production of reactive oxygen species, and damage to important DNA and protein molecules of the resistant bacteria, nanoparticles can be used as carriers for the delivery of drug candidates and also have antimicrobial effects (33).

Change in the microbial community

The entire number of microbes present in a person's body is called their microbiota, and their microbiome contains all of their genomes. More than 160 bacterial species, primarily Bacteroidetes and Genera, have been linked to the regulation of physiological processes in a healthy adult gut. Many disorders, including diabetes, cardiovascular disease, asthma, autism, inflammatory bowel disease (IBD), antibiotic-associated diarrhea, and cancer, have been linked to the dysbiosis of this ecosystem. diseases, asthma, autism, inflammatory bowel disease (IBD), antibiotics-associated diarrhoea and cancer (34).

Personalized medicine and the treatment of the corona virus

The coronavirus cannot currently be treated with a particular antiviral medication. The only medications that have only a marginal impact on the coronavirus are recombinant IFN interferons and ribavirin. This is especially true for the brand-new coronavirus COVID-19. Because of this virus's mutation, which affects a crucial enzyme as a receptor, therapy is more challenging (35). Numerous anti-coronavirus medications have been created in response to the coronavirus epidemics caused by SARS and MERS,

but none of them have yet completed clinical trials. These medications target coronavirus enzymes such as proteases, polymerases, and MTases, as well as entrance proteins. They have encountered failure (36). The major therapy up till now has been suggested to use antibodies and plasma from recovered patients. Given the intense epidemic character of COVID-19 and its low fatality rate, this plasma and antibody collection from recovered patients may be the sole treatment option available right now for people with the disease. As coronaviruses are not curable or preventable, the best strategy to handle a serious coronavirus infection is to restrict the source of infection, receive an early diagnosis, supportive therapies, and prompt information distribution, rather than spreading fear. The outbreak must be controlled with panic (37). This virus can be prevented from spreading via preventative measures including good personal cleanliness, using an appropriate N95 mask, ventilating enclosed spaces properly, and avoiding needless transportation in congested areas (38). Currently, outpatient diagnostic and treatment services and inpatient services can be used to classify therapeutic services. When personalized medicine was implemented in Covid19, activities were created to specify how genomes, evolutionary biology, metabolomics, and viral genomes interacted to create events like infection, serious infections, therapeutic response, and sensitivity to immunization (39). In order to manage specimens in the strategy to personalized medicine in COVID-19, a joint directive from the Secretary General for Research, Development, and Innovations in Health and the Executive Directorate of the Andalusian Health Service was implemented on January 2020. Additionally, medical practitioners will have electronic biochemistry request accessibility to the whole genomic research of the SARS-CoV-2 virus (MPA) (40).

CONCLUSIONS

The development of alternative medicines is advised to lessen reliance on chemical medications because antibiotic resistance might prove fatal. Antibiotic effectiveness is decreasing as a result of the rise of drug resistance. Therefore, it is crucial to find new approaches and therapies to address the issue and cut down on the usage of antibiotics. The epidemic has forced us into a new situation that encourages collaboration and relationships between states and research institutes. Professionals have also arisen to treat this complicated illness, and technology has been introduced to ensure home health care. Understanding the interplay between the virus and the host might be improved with the use of sequence analysis, bioinformatics, and medical professionals focusing on tailored treatment. Physicians ought to have access to these technologies and be able to use them in their regular decision-making processes. Big

data, AI systems, and the growing need for customized treatment are enabling the development of algorithms based on individual factors (genomic), the host, and the guest (pathogen and patient subject).

REFERENCES

1. Piri-Gharaghie T, Beiranvand S, Riahi A, Shirin NJ, Badmasti F, Mirzaie A, Elahianfar Y, Ghahari S, Ghahari S, Pasban K, Hajrasouliha S. Fabrication and characterization of thymol-loaded chitosan nanogels: Improved antibacterial and anti-biofilm activities with negligible cytotoxicity. *Chemistry & Biodiversity*. 2022 Mar;19(3):e202100426.
2. Piri-Gharaghie T, Jegargoshe-Shirin N, Saremi-Nouri S, Khademhosseini SH, Hoseinnezhad-Lazarjani E, Mousavi A, Kabiri H, Rajaei N, Riahi A, Farhadi-Biregani A, Fatehi-Ghahfarokhi S. Effects of Imipenem-containing Niosome nanoparticles against high prevalence methicillin-resistant *Staphylococcus Epidermidis* biofilm formed. *Scientific reports*. 2022 Mar 24;12(1):1-3.
3. Beiranvand S, Piri-Gharaghie T, Dehganad B, Khedmati F, Jalali F, AsadAlizadeh M, Momtaz H. Novel NAD-independent *Avibacterium paragallinarum*: Isolation, characterization and molecular identification in Iran. *Veterinary Medicine and Science*. 2022 May;8(3):1157-65.
4. Piri-Gharaghie T. Polycystic ovary syndrome and genetic factors influencing its development: A review article. *Personalized Medicine Journal*. 2021 Dec 1;6(23):25-9.
5. Piri-Gharaghie T, Doosti A, Mirzaei SA. Identification of Antigenic Properties of *Acinetobacter baumannii* Proteins as Novel Putative Vaccine Candidates Using Reverse Vaccinology Approach. *Applied Biochemistry and Biotechnology*. 2022 Jun 7:1-23.
6. Piri Gharaghie T, Sadat Shandiz SA, Beiranvand S. Evaluation of silver nanoparticles effects on bla-per1 gene expression for biofilm formation in isolates of antibiotic-resistant *Acinetobacter Bumanni* by real time PCR method. *Cellular and Molecular Research (Iranian Journal of Biology)*. 2020 Dec 16.
7. Piri-Gharaghie T, Doosti A, Mirzaei SA. Fabrication and Characterization of pcDNA3. 1 (+) Location within Chitosan/Nanoparticles Complexes for Enhanced Gene Delivery. *Iranian Journal of Biotechnology*. 2022 Jul 2;20(3):88-100.
8. Piri Gharaghie T, Beiranvand S, Doosti A, Ghadiri AH, Haji Mohammadi S. A review of the epidemiology and clinical signs of SARS-COV-2. *New Cellular and Molecular Biotechnology Journal*. 2020 Nov 10;11(41):103-20.
9. Piri Gharaghie T, Beiranvand S, Hajimohammadi S. Comparison of Antifungal Effects of Aquatic and Alcoholic Extract of *Mentha pulegium* L. With Fluconazole on Growth of *Candida Albicans*.

- Developmental Biology. 2021 May 22;13(2):7-18.
10. Piri Gharaghie T, Doosti A, Mirzaei SA. Detection of T6SS secretory system and membrane porins involved in antibiotic resistance in multidrug-resistant *Acinetobacter baumannii* isolates. *Journal of Microbial World*. 2021 May 22;14(1).
 11. Piri Gharaghie T, Hajimohammadi S. Comparison of anti-candida effects of aqueous, ethanolic extracts and essential oil of *E. angustifolia* with fluconazole on the growth of clinical strains of *Candida*. *New Cellular and Molecular Biotechnology Journal*. 2021 Jul 10;11(43):25-38.
 12. Zarinnezhad A, Shahhoseini MH, Piri Gharaghie T. Evaluating the Relative Frequency of Fungal Infections in the Serum of Patients with Multiple Sclerosis and Healthy Subjects Using PCR. *Biological Journal of Microorganism*. 2021 Mar 21;10(37):37-50.
 13. Piri Gharaghie T, Doosti A, Mirzaei SA. Prevalence and antibiotic resistance pattern of *Acinetobacter* spp. infections in Shahrekord medical centers. *Developmental Biology*. 2021 Nov 22;13(4):35-46.
 14. Gharaghie P, Tohid, and Seyed Ataollah Sadat Shandiz. "The Inhibitory Effects of Silver Nanoparticles on *Bap* Gene Expression in Antibiotic-Resistant *Acinetobacter baumannii* Isolates using Real-Time PCR." *scientific journal of ilam university of medical sciences*. 2018;26:175-85.
 15. Faraji H, Yazdi FT, Razmi N. The influence of ultraviolet radiation on aflatoxin producing *Aspergillus* species' isolated from Iranian rice. *Toxicology Reports*. 2022 Jul 12.
 16. Bambhroliya Z, Sandrugu J, Lowe M, Okunlola O, Raza S, Osasan S, Sethia S, Batool T, Hamid P. Diabetes, Polycystic Ovarian Syndrome, Obstructive Sleep Apnea, and Obesity: A Systematic Review and Important Emerging Themes. *Cureus*. 2022 Jun 25;14(6).
 17. Beiranvand S, Doosti A, Mirzaei SA. Putative novel B-cell vaccine candidates identified by reverse vaccinology and genomics approaches to control *Acinetobacter baumannii* serotypes. *Infection, Genetics and Evolution*. 2021 Dec 1;96:105138.
 18. Azadbakht N, Doosti A, Jami MS. CRISPR/Cas9-mediated LINC00511 knockout strategies, increased apoptosis of breast cancer cells via suppressing antiapoptotic genes. *Biological Procedures Online*. 2022 Dec;24(1):1-5.
 19. Zong TX, Silveira AP, Morais JA, Sampaio MC, Muehlmann LA, Zhang J, Jiang CS, Liu SK. Recent Advances in Antimicrobial Nano-Drug Delivery Systems. *Nanomaterials*. 2022 Jan;12(11):1855.
 20. Vallieres M, Kay-Rivest E, Perrin LJ, Liem X, Furstoss C, Aerts HJ, Khaouam N, Nguyen-Tan PF, Wang CS, Sultanem K, Seuntjens J. Radiomics strategies for risk assessment of tumour failure in head-and-neck cancer. *Scientific reports*. 2017 Aug 31;7(1):1-4.
 21. Souod N, Kargar M, Doosti A, Ranjbar R, Sarshar M. Genetic analysis of *cagA* and *vacA* genes in *Helicobacter pylori* isolates and their relationship with gastroduodenal diseases in the west of Iran. *Iranian Red Crescent Medical Journal*. 2013 May;15(5):371.
 22. Kargar M, Mohammadalipour Z, Doosti A, Lorzadeh S, Japoni-Nejad A. High prevalence of class 1 to 3 integrons among multidrug-resistant diarrheagenic *Escherichia coli* in southwest of Iran. *Osong public health and research perspectives*. 2014 Aug 1;5(4):193-8.
 23. Doosti A, Ghasemi Dehkordi P, Rahimi E. Molecular assay to fraud identification of meat products. *Journal of food science and technology*. 2014 Jan;51(1):148-52.
 24. Arshi A, Sharifi FS, Ghahfarokhi MK, Faghih Z, Doosti A, Ostovari S, Maymand EM, Seno MM. Expression analysis of MALAT1, GAS5, SRA, and NEAT1 lncRNAs in breast cancer tissues from young women and women over 45 years of age. *Molecular Therapy-Nucleic Acids*. 2018 Sep 7;12:751-7.
 25. Ghajari G, Nabiuni M, Amini E. The association between testicular toxicity induced by Li₂Co₃ and protective effect of *Ganoderma lucidum*: Alteration of *Bax* & *c-Kit* genes expression. *Tissue and Cell*. 2021 Oct 1;72:101552.
 26. Ghajari G, Heydari A, Ghorbani M. Mesenchymal stem cell-based therapy and female infertility: limitations and advances. *Current Stem Cell Research & Therapy*. 2022 May 11.
 27. Mohammed AS, Ghajar G. Epithelial-mesenchymal transition and its role in breast cancer metastasis. 2022.
 28. Jain KK. Personalized medicine. *Current opinion in molecular therapeutics*. 2002 Dec 1;4(6):548-58.
 29. Chan IS, Ginsburg GS. Personalized medicine: progress and promise. *Annual review of genomics and human genetics*. 2011 Sep 22;12:217-44.
 30. Mura S, Couvreur P. Nanotheranostics for personalized medicine. *Advanced drug delivery reviews*. 2012 Oct 1;64(13):1394-416.
 31. Safarpour-Dehkordi M, Doosti A, Jami MS. Integrative analysis of lncRNAs in kidney cancer to discover a new lncRNA (LINC00847) as a therapeutic target for staphylococcal enterotoxin *tst* gene. *Cell Journal (Yakhteh)*. 2020;22(Suppl 1):101.
 32. Safarpour-Dehkordi M, Doosti A, Jami MS. Impacts of the Staphylococcal Enterotoxin H on the Apoptosis and lncRNAs in PC3 and ACHN. *Molecular Genetics, Microbiology and Virology*. 2020 Jul;35(3):180-8.
 33. Safarpour M, Kazemi Z, Doosti E, Doosti A. Cloning tagD gene from *Helicobacter pylori* in

- PFLAG-CMV-3 eukaryotic vector to generate a DNA vaccine. *J Jahrom Uni Med Sci.* 2016 Dec 10;14:43-50.
- 34.Safarpour-Dehkordi M, Doosti A, Jami MS, Gholipour A. Quantitative Real Time PCR study on the effects of hlaA gene deletion on the expression of pathogenicity genes in *Salmonella enterica* ssp. *Journal of BioScience and Biotechnology.* 2018;7(2-3):73-8.
- 35.Mostaghimi H, Mehdizadeh AR, Darvish L, Akbari S, Rezaei H. Mathematical formulation of 125I seed dosimetry parameters and heterogeneity correction in lung permanent implant brachytherapy. *Journal of Cancer Research and Therapeutics.* 2017 Jul 1;13(3):436.
- 36.Karimi M, Ghazikhanlou-Sani K, Mehdizadeh AR, Mostaghimi H. Lead-free transparent shields for diagnostic X-rays: Monte Carlo simulation and measurements. *Radiological Physics and Technology.* 2020 Sep;13(3):276-87.
- 37.Tahmasebi Birgani MJ, Mostaghimi H, Behrooz MA, Shahbazian H. Evaluation of the Influence of Lung Inhomogeneity on Depth Dose Distribution before and after the Lung in Electron Therapy: A Semi-Experimental Study. *Jundishapur Scientific Medical Journal.* 2014 Jul 23;13(3):315-26.
- 38.Rezaei H, Zabihzadeh M, Ghorbani M, Goli Ahmadabad F, Mostaghimi H. Evaluation of dose enhancement in presence of gold nanoparticles in eye brachytherapy by 103Pd source. *Australasian physical & engineering sciences in medicine.* 2017 Sep;40(3):545-53.
- 39.Mostaghimi H, Mehdizadeh AR, Jahanbakhsh M, Dehghanian AR, Askari R. Quantitative determination of tumor platinum concentration of patients with advanced Breast, lung, prostate, or colorectal cancers undergone platinum-based chemotherapy. *Journal of Cancer Research and Therapeutics.* 2017 Oct 1;13(6):930.
- 40.Arish M, Naz F. Personalized therapy: can it tame the COVID-19 monster?. *Personalized Medicine.* 2021 Nov;18(6):583-93.