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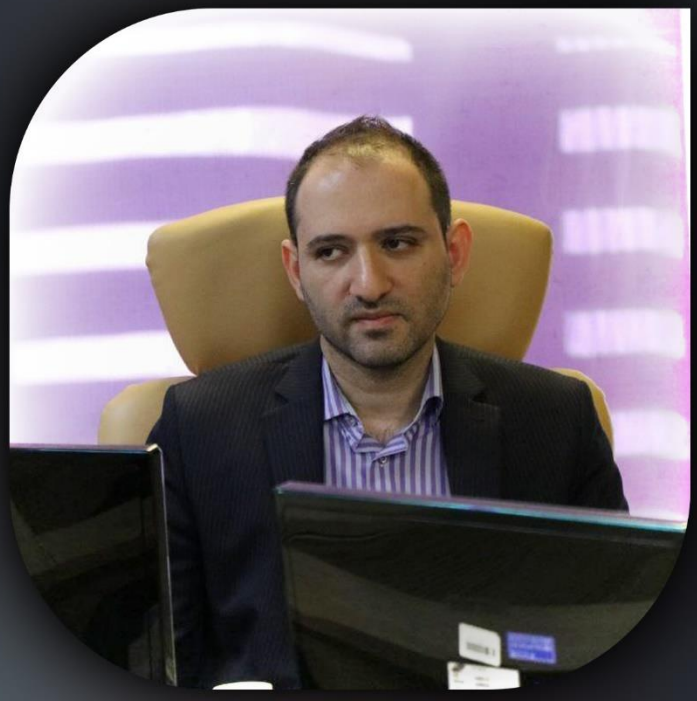

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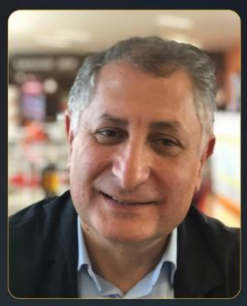

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1. **A review of MT-RNR1 gene mutations associated with nonsyndromic hearing impairment due to aminoglycoside antibiotic usage (Review)**

Nastaran Bozorgi,[1,*]

1. Department of Biology, Faculty of Science, Shahid Chamran University of Ahvaz, Iran

Introduction: Aminoglycosides are a class of antibiotics produced by soil actinomycetes. They treat infections caused by Gram-negative bacteria such as E.coli, Salmonella, and Klebsiella. These antibiotics are effective for individuals infected with bacterial strains that are resistant to multiple drugs, as well as for AIDS patients co-infected with tuberculosis and those with kidney (fibrocystic) patients. Types of aminoglycoside antibiotics include neomycin, streptomycin, gentamicin, and netilmicin. This class of antibiotics works by binding to the 16S rRNA of the bacterial small ribosomal subunit at the A site of mRNA, disrupting protein synthesis. According to the "endosymbiotic theory," the ribosome and 16S rRNA in bacteria are analogous to eukaryotic mitochondria and 12S rRNA in humans. These organelles are responsible for oxidative mechanisms. Despite some differences, such as the resistance of human mitochondria to antibiotics due to a double membrane and an allelic substitution in the aminoglycoside binding site of rRNA compared to bacterial ribosomes, research has shown that mutations in the MT-RNR1 gene can lead to the "nonsyndromic deafness" phenotype in individuals using this class of drugs. Hearing loss can significantly impact a person's life at any age. however, if it occurs in infancy before speech development, it can cause irreversible damage. Therefore, it is essential to implement personalized medicine and select appropriate treatment methods at the molecular level with high precision. This study aims to investigate genetic changes in the MT-RNR1 gene that result in aminoglycoside toxicity and subsequent hearing impairment.

Methods: Keywords like MT-RNR1, nonsyndromic hearing impairment, and aminoglycoside antibiotics were used to search scientific databases such as Google Scholar and PubMed. This led to the selection and review of relevant articles.

Results: Research in pharmacogenetics has shown that people's responses to drugs can vary significantly based on their genotype and specific genomic changes. Pharmacogenetics studies the effects of these genetic variations on drug responses. Research has shown that certain mutations in the MT-RNR1 gene are associated with the harmful effects of aminoglycoside antibiotics. This mutation is often inherited maternally, as indicated by family tree analysis. Hearing loss caused by the use of aminoglycoside

antibiotics has been observed in diverse populations around the world. The severity of hearing loss is categorized as follows: mild (26-40 dB HL), moderate (41-55 dB HL), moderately severe (56-70 dB HL), severe (71-90 dB HL), and profound (greater than 91 dB HL). In individuals with normal hearing, the softest perceivable sound is 0 dB. The 1555A>G mutation (rs267606617) in the MT-RNR1 gene is prevalent in 33-5% of patients who experience aminoglycoside-induced deafness. It is associated with the development of bilateral hearing loss, which can range from severe to profound or mild to moderate. Another significant mutation is the 1494C>T (rs267606619) variant, which occurs in approximately 5% of affected individuals and also leads to bilateral hearing loss, which can vary in severity from mild to profound. There is a less common variant, 1095T>C (rs267606618), associated with moderate to profound hearing loss. Less common variations are 827A>G (rs28358569) and a deletion at position 961 (T deletion with various C insertions). People with these genetic differences may experience problems in cellular respiration because bacterial ribosomes and human mitochondrial ribosomes have similar structures. This can affect mitochondrial protein production, lower energy levels, and ultimately result in apoptosis, leading to deafness.

Conclusion: Genetic testing and screening can help doctors identify the genetic makeup of individuals, which can prevent negative reactions to antibiotics and ensure the right medications are prescribed. While pharmacogenetic testing is needed for antibiotic treatment, There are challenges such as limited healthcare resources, high costs, time-consuming processes, complex interpretation of test results, and ethical concerns about how genetic information is used (such as its impact on insurance coverage). Also, because different people respond differently to the same drug doses, ongoing research across diverse populations and a wider range of antibiotics is necessary. The interpretation of pharmacogenetic test results can lead to the development of personalized medical strategies, which can improve antibiotic treatment by choosing the right antimicrobial agent, adjusting the dosage for each individual, and minimizing side effects.

Keywords: MT-RNR1, nonsyndromic hearing impairment, aminoglycoside antibiotics

2.

Applications of LLMs in BioInformatics (Review)

sina alemohammad,[1,*]

1. Ahvaz Jundi Shapoor university of medical sciences

Introduction: Artificial intelligence has been rapidly expanding into diverse sectors in recent years, fundamentally altering our approach to these domains. The accelerated development of NLP-powered AI and the proliferation of LLM models like Gyma, LLAMA, and ChatGPT have placed AI at the forefront of technological advancements, offering unprecedented opportunities to enhance knowledge across multiple disciplines. Bioinformatics is no exception; LLMs hold immense potential to revolutionize this field. By integrating LLMs into bioinformatics, we anticipate significant advancements, including accelerated processes and novel insights.

Methods: The following prompt has been searched in google scholar:‘large language models in bioinformatics genomic OR proteomic OR metabolomic OR Multiomic source:"Bioinformatics" OR source:"PLOS Computational Biology" OR source:"Nature" OR source:"Briefings in Bioinformatics" OR source:"Wiley -ethics -social -future’ . Time range has been narrowed between 2022 and 2024, because first release of one of the most powerful LLM models “OpenAI chat-GPT” was 2022. and the The result was About 926 articles. The articles with unrelated subjects removed. The remining articles categorized based on subject and title then these articles analyzed.

Results: There is a significant acceleration in growing LLMs with diverse tasks and applications. These models are revolutionizing the field of bioinformatics and way we analyze biologic data. these are articles can be categories in following topics. 1)Text Mining and Knowledge Extraction: LLMs excel at processing vast amounts of scientific literature, extracting valuable insights, relationships, and knowledge. Tools like PEDL+ leverage LLMs for relation extraction, while projects like PlantConnectome use LLMs to uncover nearly 400,000 functional relationships from over 100,000 plant biology abstracts. 2)Multi-Omics Integration: LLMs can integrate data from multiple omics layers, including genomics, transcriptomics, proteomics, and metabolomics. This allows for gaining comprehensive insights, elucidating disease mechanisms, and identifying pathways involved in biological processes. 3)Genomics Applications: In genomics, LLMs can assist in tasks like identifying

potential coding regions, extracting named entities for genes and proteins, and detecting antimicrobial and anti-cancer peptides. GeneGPT, a method that teaches LLMs to use NCBI Web APIs, achieves state-of-the-art performance on genomics tasks by leveraging database utilities. 4)Protein Structure Prediction and Drug Discovery: LLMs have shown promise in predicting protein structures and designing novel drugs. By processing and learning from vast amounts of protein sequence and structure data, LLMs can make accurate predictions and generate novel molecules with desired properties. 5)Bioinformatics Education and Problem-Solving: LLMs can help solve educational bioinformatics problems and assist researchers in tackling complex tasks. By understanding the context and leveraging their broad knowledge, LLMs can provide guidance and insights to bioinformatics students and professionals. 6) Engineering biomolecules and synthetic biology integration: Recently molecule programming model like MPM4 has been released and it can make entirely new proteins. Models like MPM4 are text to molecule models and the prompt for them is describing the function of the molecule and its structure.

Conclusion: It seems with growing LLMs , bioinformatics is entering new phase and it can have more impact than ever. There is a great opportunity for bioinformatics researcher to use the different LLM models and improve their researches.

Keywords: AI, LLMs, bioinformatics

3.

Applications, challenges, and perspectives of artificial intelligence & neural networks in toxicology: Narrative review (Review)

elham saber,[1,*] Sara Karimi Zeverdegani ,[2] Samira Barakat,[3]

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2. 1. Associate Professor, Department of Occupational Health and Safety Engineering, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran
3. 3. PhD Student, Student Research Committee AND Department of Occupational Health and Safety Engineering, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran

Introduction: Artificial neural networks (ANN), as a significant subset of artificial intelligence, exhibit substantial potential within the domain of toxicology research. These networks possess the capability to anticipate elevated levels of substance toxicity. Furthermore, these networks are adept at discerning intricate chemical-biological interactions that are often beyond the reach of conventional toxicology investigations.

Methods: In this study, the databases utilized include ISI Web of Science, Scopus, PubMed Central (via PubMed), Science Direct, and Google Scholar. The article's search terms encompassed: "artificial intelligence," "artificial neural networks," and "toxicology."

Results: In light of the accelerating advancements in artificial intelligence and its associated fields, it is anticipated that artificial neural networks will assume a pivotal role in the classification of various toxins and the examination of their biochemical properties

Conclusion: In light of the accelerating advancements in artificial intelligence and its associated fields, it is anticipated that artificial neural networks will assume a pivotal role in the classification of various toxins and the examination of their biochemical properties. This research underscores the significance and contribution of artificial neural networks in the exploration of toxic substances.

Keywords: Artificial intelligence (AI), Artificial Neural Networks (ANN), toxicology

4.

Assessment of melanoma metagenome and phenotypic analysis of native mutations in Iran (Research Paper)

Majid Mesgartehrani,[1,*] Samereh Khademee,[2] Mohammad Mahdi Eslami,[3] Karimi,[4]

1. Iran Genomics Scientific Pole, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2.
3. Tehran University of Medical Sciences, Tehran, Iran
4. Tehran University of Medical Sciences, Tehran, Iran

Introduction: Melanoma is a type of disease in which melanocytes, which produce skin pigments, are involved. Melanoma is one of the most common skin cancers, and there are different causes of it. Genetically, melanoma is one of the polymorphismic diseases in which mutations in some organic bases increase the likelihood of a person suffering from this disease.

Methods: We used the NCBI database to collect and research the genes involved in melanoma and MegaGene pharmacogenetic software to analyze polymorphism information and to detect adverse effects of drugs of genetic origin.

Results: after examining the genes, we came up with ten important genes (ASIP, BRAF, CDK4, EGF, MC1R, MDM2, NRAS, RB1, TYR and TYRP1). Of these 10 genes, nine (ASIP, BRAF, CDK4, EGF, MC1R, NRAS, RB1, TYR and TYRP1) are involved in about a 90% chance of developing melanoma. Four drugs (Dacacedal, Dacabarzine MEDAC, DTI and Pembrolizumab) had side effects base on genetic origin. The analysis showed that Dacacedal, Dacabarzine MEDAC, and DTI caused nausea by influencing MLH1 gene and Pembrolizumab by influencing ABCC2 gene.

Conclusion: Therefore, before prescribing therapeutic drugs for melanoma, it is necessary to first perform gene tests to investigate the presence of polymorphisms in common genes such as BRAF, ASIP, CDK4 in order to perform drugs with fewer side effects for the patient in case of polymorphism.

Keywords: Gene, Melanoma, Pharmacogenetics, Skin cancer, Phenotype

5.

Cancer treatment with the help of exosomes (Research Paper)

Hossein ameri shahrabi,[1,*]

1. Azad University

Introduction: The role of exosomes in tumor growth and development has been proven; So that it has been reported as one of the factors in the growth and spread of cancers. Breast cancer is one of the most common types of cancer and one of the causes of cancer-related deaths worldwide. Texosomes can be used as a drug carrier to inhibit cancer.

Methods: In this study, after separating the exosomes from the patient's serum and determining their nature and size by scanning electron microscopy and transferring Cytolysin A into the exosomes, the effect of Cytolysin A on cancer cells was investigated using flow cytometry. The expression of Bax and Bcl-2 genes in fibroblast cells after treatment with exosome, toxin and exotoxin was investigated using real-time PCR method.

Results: Effects of Bacterial Toxin Treatment on Induction of Apoptosis or Programmed Cell Death in Cancer Cells Cells were treated with bacterial toxin loaded in exosomes and killed.

Conclusion: With the help of exosomes, drug or toxin can be carried in it and attack the target cell and destroy it.

Keywords: Cancer, exosome, extracellular vesicles

6.

Changes in The Microbiota in Colon Cancer Detection - in Personalized (Review)

Neda Zahmatkesh,[1,*]

1. Msc of Molecular Genetic Department of Genetics, Zanjan Branch, Islamic Azad University, Zanjan, Iran.

Introduction: Since microbiota are influential in many physiological systems of the body, including the immune system, it can be an effective tool for individual-oriented medical use. Microbiota refers to all the microorganisms present in the organs and different parts of a person's body, but the meaning of microbiome is the genetic content and the set of functions and benefits of microorganisms for the host body. The development of 165 ribosomal RNA gene sequencing methods has led to our better understanding of the diversity of microbial species present in the microbiota. The difference between the microbiota composition of healthy people and cancer patients can be used in personalized medicine to identify the pattern of microbiota change that indicates a certain type of cancer. Recently, evidence has revealed the role of disturbance in the composition of host microbiota in the development of cancers. Intestinal microbiota plays an important role in causing cancer by causing inflammation or growth factor induction, which makes it a suitable target for Personalized Medicine interventions. According to the statistics of the World Health Organization in 2018, colon cancer is the third most common cancer in Iran with 9% of all cases and 4.7% of deaths. The aim of this study was to investigate Changes in the microbiota of people in colon cancer detection - in Personalized Medicine.

Methods: The present study is titled Changes in the microbiota of people in colon cancer detection which was done by searching scientific databases such as Science Direct, Springer, Google Scholar, and PubMed.

Results: The results of numerous types of research have shown that among the environmental factors in causing intestinal cancer, the role of microorganisms is more important than before so about 20% of the world's cancers are attributed to microbial microorganisms inside the intestinal tract. The large intestine contains 70% of the total microbiota of the body. Part of the microbial population protects the human body against intestinal cancer by inducing immune tolerance and neutralizing fungal pathogenic factors. However, it seems that another part of the microbiota plays a major role in the occurrence

and progression of cancer by creating carcinogenic substances and metabolites or toxins or affecting the immune system. Some bacteria such as Bacteroides fragilis and Enterococcus faecalis damage the DNA of human cells by producing enterotoxin. Sulfidogenic bacteria such as Fusobacterium and Bilophylla produce hydrogen sulfide. Hydrogen sulfide disrupts the repair process of DNA genetic material and at the same time accelerates cell division. The presence of Streptococcus gallolyticus bacteria, which is a subgroup of Streptococcus bovis bacteria, has been reported in 71% of colon cancer patients. Unlike Streptococcus gallolyticus, other subspecies of Streptococcus bovis have been observed in 17% of these patients, which suggests a link between this bacterium and colon cancer. An increase in other bacteria such as Escherichia coli, Peptostreptococcus, Campylobacter and Shigella and a decrease in Clostridium, Biora and Blasia have also been found in colon cancer patients. Due to the active role of microbiota in causing this cancer, efforts have been made to identify and create differential microbial patterns between patients and healthy people. The presence or absence or the abundance of bacteria and types of microbial species during an examination of patients' stool samples can be a practical method of using microbiota for diagnostic procedures. Metabolites produced by the microbiota in faeces are another way to diagnose. For example, the amount of short-chain fatty acids produced by microbiota, which includes acetate butyrate and other compounds, is lower in the faeces of colon cancer patients than in other people.

Conclusion: Since the composition of the microbiota is known to be an effective factor in causing disease or maintaining health, personalized medicine helps to identify patterns of microbiota change during disease development by using tools. personalized medicine aims to extract the composition of microbiota in all people and the pattern of microbial change in all diseases soon. Identifying the pattern of microbiota change in the disease first leads to the progress of diagnostic processes and then easy and efficient specific treatment. In the future, personalized medicine seeks to reveal more and more the connections between microbiota and body diseases, including cancers, and to use them in practice.

Keywords: Microbiota, Colon Cancer, Personalized Medicine, Ribosomal

7.

Chemotherapy: Evolving Strategies for Effective Cancer Treatment (Review)

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2. Cellular and Molecular Endocrine Research Center (CMERC), Research Institute for Endocrine Science, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Introduction: The advent of chemotherapy has transformed the prognosis of cancer from a uniformly fatal disease to one that can be effectively treated and, in some cases, cured when administered correctly. The objective of chemotherapy is to impede the proliferation and multiplication of cells, thereby preventing the invasion and metastasis that are hallmarks of cancer. However, this approach inevitably results in toxic effects on normal cells as well. Chemotherapy may be divided into two principal categories: traditional chemotherapy and combination chemotherapy. Traditional chemotherapy agents exert their effects on neoplastic cells by interfering with the synthesis and functioning of macromolecules, including nucleic acids (DNA and RNA) and proteins. This can either disrupt the appropriate functioning of preformed molecules or affect the synthesis of new macromolecules. Consequently, the death of the cells may be delayed, depending on the agent and the treatment regimen used. The use of combination chemotherapy is a common approach to achieving adequate responses, as well as preventing the emergence of resistant clones, by promoting cell death in both resting and dividing cells. Combination therapy, also known as multitargeted therapy, has been demonstrated to have superior efficacy compared to traditional single-agent therapies in the majority of cancer treatments. This is attributed to the diverse mechanisms of action of these combination therapies, which can lead to a more optimal therapeutic ratio compared to traditional chemotherapy. The potential for decreased resistance and reduced toxicities associated with these therapies can be further exploited through the strategic selection of agents. It is a common assumption that chemotherapeutic agents are associated with a range of side effects. The side effects of chemotherapy are typically a reflection of the mechanism of action of the agents used. For example, agents that are metabolized and excreted by the liver or kidneys can lead to increase toxic levels that can cause dysfunction of these organs and others. Therefore, dose adjustments are essential for patients with organ failure. For

instance, the dosage of capecitabine must be modified for patients with renal disease. Moreover, the majority of chemotherapy drugs demonstrate efficacy against rapidly dividing cells, resulting in rapid impact on proliferating cells, including those in the bone marrow, gastrointestinal tract, and hair follicles. The most commonly observed adverse effects associated with these agents include myelosuppression, mucositis, nausea, vomiting, diarrhea, alopecia, fatigue, sterility, infertility, and infusion reactions.

Methods: The research methodology entailed an extensive search across PubMed, Google Scholar, and NCBI databases to locate articles pertinent to Chemotherapy. A comprehensive literature review was conducted to identify studies investigating Chemotherapy: Evolving Strategies for Effective Cancer Treatment. Electronic databases were searched using relevant keywords, and studies published between 2023 and 2016 were included. The review encompassed clinical trials to provide a comprehensive understanding of the topic.

Results: While many strategies focus on modifying the native tumor microenvironment by chemotherapy, there is an alternative strategy. Injecting oncolytic viruses directly into the tumor microenvironment is an alternative technique for improving tumor antigen recognition and strengthening T cell responses. Talimogene laherparepvec (T-VEC) is a modified herpes simplex virus that is injected intra-lesionally into the melanoma tumor in individuals who have failed to get their tumor removed. It induces immediate lysis of tumor cells and the production of granulocyte-macrophage colony-stimulating factor (GM-CSF).

Conclusion: It can be concluded that clinical practice in the area of cancer chemotherapy has achieved considerable success; however, there are still opportunities for further improvement, particularly in terms of the efficacy and safety of the chemotherapeutic regimes used. A team-based approach to monitoring is essential for patients undergoing chemotherapy, given the potential for adverse events. The role of nursing and allied health professionals is to provide supportive care, prevent infections, monitor for adequate nutrition and hydration, and monitor patient safety. Handwashing and infection precautions, such as isolation protocols, require strict adherence. Given the necessity for frequent laboratory monitoring in patients, it is of the utmost importance for them to possess a comprehensive understanding of the infusion protocols and to be able to identify any abnormalities in the parameters. In such instances, it is imperative that they promptly alert the treating clinicians. The implementation of early nursing interventions has the potential to prevent adverse outcomes in patients. It is of paramount importance to

identify the most common causes of errors associated with cancer chemotherapy and to quantify their impact. Interventions aimed at enhancing communication, standardizing protocols, and implementing measures such as read back and verification of dosages can collectively contribute to reducing medical errors in a multidisciplinary setting. Collaborating with and consulting pharmacists also plays an important role in ensuring the accuracy and safety of medication administration.

Keywords: Chemotherapy, Cancer, Traditional Chemotherapy, Traditional Chemotherapy, side effects

8.

Economic effects on gut microbiome (Review)

Hossein ameri shahrabi,[1,*]

1. Azad University

Introduction: Gut microbiota is well recognized as a key determinant of health and disease. Consequently, several studies have focused on the causality and predictive/prognostic value of microbiota in a wide range of diseases. However, understanding what sparks changes in the microbiota and how these changes contribute to increased disease susceptibility is of greater importance. Few studies have shown that gut microbiota can be altered by lifestyle and thus lead to pathology. What if socio-economic factors also affect the composition of the gut microbiota and thus increase susceptibility to disease? Perhaps, this is one of the factors that may have contributed to the increase in inequality between people with higher and lower socio-economic status in terms of health. In this review, we aim to understand more about this issue and the true impact of the biological community. In addition, we proposed criteria to reduce the impact of these factors on the gut microbiota composition.

Methods: Eradication of poverty is listed as one of the main Millennium Development Goals (MDGs) that must be tackled by the World Health Organization, especially in low-income countries (1). Therefore, it shows that health is a key determinant of increasing socio-economic status and, hence, can affect a person's success throughout life. Therefore, it is important to get the best chance for health at an early age. The microbiota is intrinsically linked to health and disease, making it promising to understand part of the pathophysiology, which, in turn, can help achieve a healthier state, especially given the therapeutic potential to modulate microbiota composition.

Results: It seems that this trait has a greater impact than heritability on the composition of their microbiota. Thus, childhood interventions on the microbiota can increase an individual's chances of success throughout life, along with improving the country's productivity because the burden of disease will be reduced. In addition, biocommunity can lead to better screening of harms along with increased efficiency through appropriate health policies specifically designed for specific neighborhoods. In summary, investing in personal microbiota interventions in early life, especially in low SE neighborhoods, can

induce a win-win situation, where health inequalities are attenuated along with increased overall productivity.

Conclusion: Microbiota has a great impact on health and disease. As a result, the factors that can form its composition are among the factors affecting a person's health. Therefore, we may understand that society influences health inequalities and can reduce these inequalities. In addition, SES should be considered in microbiota research because it can be an important intervening variable that can affect the interpretation of study results.

Keywords: Microbiome - Gut - Health - Disease

9.

Engineering Bacillus anthracis Protective Antigen for Targeted Cancer Therapy via Urokinase Plasminogen Activator Modulation (Research Paper)

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Introduction: The challenge of cancer therapy is targeting malignant cells without harming normal tissues. The unique expression of uPA on cancer cells provides an opportunity to use bacterial proteins as precision therapeutic agents. Bacillus anthracis's protective antigen (PA) is crucial in anthrax pathogenesis, and its modifications could enhance selectivity towards these uPA-expressing cancer cells.

Methods: Bioinformatics tools were used to identify potential mutation sites within the PA gene to improve its affinity for uPA receptors. After introducing mutations via Overlap Extension PCR, plasmid construction included verification steps to ensure the accuracy of the insert. The TA-vector system was utilized for efficient cloning, and electroporation facilitated transformation into competent WB600 cells, optimized for protein expression.

Results: Subsequent analyses, including Sanger sequencing, confirmed the successful incorporation of mutations. Advances in protein expression were monitored through SDS-PAGE and Western blotting, demonstrating increased levels of modified PA proteins. Binding assays showed the enhanced affinity of mutated PA towards uPA receptors, a significant improvement over wild-type PA.

Conclusion: This study contributes to ongoing research in targeted cancer therapies, demonstrating the potential of bacterial proteins in clinical applications. The engineered PA proteins not only provide insight into novel treatment strategies but also pave the way for future explorations into receptor-mediated targeting mechanisms in oncology.

Keywords: Targeted cancer therapy, Bacillus anthracis, Protective antigen, Urokinase Plasminogen Activator

10.

Epigenetics and cancer signaling (Review)

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Introduction: Overview of Epigenetics in Cellular Function Epigenetics plays a crucial role in cellular function by regulating gene expression without altering the DNA sequence. This regulation is essential for maintaining cellular homeostasis and facilitating proper responses to environmental changes. For instance, epigenetic mechanisms such as DNA methylation and histone modifications can determine whether specific genes are active or silenced, influencing vital processes like cell differentiation and proliferation. In cancer, these mechanisms can become dysregulated, leading to aberrant gene expression that contributes to tumorigenesis and cancer progression. Breast cancer, in particular, exemplifies this phenomenon, as breast cancer stem cells (BCSCs) exhibit distinct epigenetic changes that impact their behavior in terms of metastasis and resistance to treatments (Hsing-Ju Wu & P. Chu, 2021). Understanding these epigenetic alterations offers potential therapeutic avenues for targeting cancer stem cells and improving treatment outcomes.

Methods: Mechanisms of Epigenetic Regulation The dysregulation of epigenetic mechanisms can lead to significant alterations in cellular behavior, particularly in cancer. In breast cancer, for example, breast cancer stem cells (BCSCs) show unique epigenetic modifications that influence their ability to metastasize and resist treatment (Hsing-Ju Wu & P. Chu, 2021). This highlights the importance of understanding the balance between epigenetic regulation and gene expression, as these changes do not involve alterations in the DNA sequence itself but can still result in profound effects on cellular functions. Moreover, the role of a-synuclein in neurodegenerative diseases underscores how epigenetic factors can impact gene transcription and contribute to disease progression (A. Surguchov, 2023). By studying these mechanisms, researchers hope to identify novel therapeutic strategies that target the underlying epigenetic changes, potentially improving patient outcomes. Role of Epigenetics in Cancer Development The dysregulation of epigenetic mechanisms can lead to significant alterations in cellular behavior, particularly

in cancer. In breast cancer, for example, breast cancer stem cells (BCSCs) show unique epigenetic modifications that influence their ability to metastasize and resist treatment (Hsing-Ju Wu & P. Chu, 2021). This highlights the importance of understanding the balance between epigenetic regulation and gene expression, as these changes do not involve alterations in the DNA sequence itself but can still result in profound effects on cellular functions. Furthermore, various epigenetic abnormalities, such as DNA methylation and histone modifications, are known to play critical roles in breast cancer development and progression (Joanna Szczepanek et al., 2023). By studying these mechanisms, researchers hope to identify novel therapeutic strategies that target the underlying epigenetic changes, potentially improving patient outcomes. Epigenetic Alterations in Tumor Suppressor Genes Understanding the intricate roles of epigenetic alterations, particularly in tumor suppressor genes, is crucial for grasping breast cancer development. These modifications, such as DNA methylation and histone changes, can lead to the silencing of genes responsible for controlling cell growth and division, contributing to uncontrolled proliferation characteristic of tumors (Joanna Szczepanek et al., 2023). Furthermore, breast cancer stem cells (BCSCs) exhibit specific epigenetic changes that not only enhance their ability to metastasize but also confer resistance to conventional treatments (Hsing-Ju Wu & P. Chu, 2021). Targeting these epigenetic mechanisms might provide a novel approach to therapy, allowing for the restoration of normal gene expression and potentially reversing cancer progression. Thus, continued research into the epigenetic landscape of breast cancer may unlock new avenues for effective treatment strategies. Therapeutic Implications of Targeting Epigenetic Modifications in Cancer Moreover, the complexity of breast cancer necessitates a multifaceted approach to therapy that integrates the understanding of epigenetic modifications. Recent studies indicate that combining epigenetic-targeting drugs with established treatments can enhance therapeutic efficacy and overcome resistance associated with BCSCs (Joanna Szczepanek et al., 2023). For instance, agents like azacitidine and vorinostat have shown promising results when used alongside chemotherapy, highlighting their potential in reversing harmful epigenetic changes (Joanna Szczepanek et al., 2023). This approach not only targets the cancer cells directly but also modifies the tumor microenvironment, potentially leading to improved patient outcomes. By harnessing the power of epigenetics in treatment strategies, researchers can aim for more personalized and effective care options for breast cancer patients, paving the way for innovative therapies

Results: Future Directions in Epigenetics and Cancer Research The integration of epigenetic understanding into cancer therapy represents a significant shift in treatment methodologies. By targeting the specific epigenetic alterations observed in breast cancer, researchers can develop more refined approaches to counteract the disease's complexity. Epigenetic changes, such as DNA methylation and histone modifications, play crucial roles in regulating gene expression and tumor behavior (Hsing-Ju Wu & P. Chu, 2021). The use of epigenetic drugs, including DNA methyltransferase inhibitors and histone deacetylase inhibitors, not only aims to reverse these alterations but also enhances the overall efficacy of traditional therapies (Joanna Szczepanek et al., 2023). This strategic combination could lead to breakthrough treatments that are more effective in managing breast cancer, ultimately improving patient outcomes and personalizing care based on individual epigenetic profiles.

Conclusion: Future Directions in Epigenetics and Cancer Research The integration of epigenetic understanding into cancer therapy represents a significant shift in treatment methodologies. By targeting the specific epigenetic alterations observed in breast cancer, researchers can develop more refined approaches to counteract the disease's complexity. Epigenetic changes, such as DNA methylation and histone modifications, play crucial roles in regulating gene expression and tumor behavior (Hsing-Ju Wu & P. Chu, 2021). The use of epigenetic drugs, including DNA methyltransferase inhibitors and histone deacetylase inhibitors, not only aims to reverse these alterations but also enhances the overall efficacy of traditional therapies (Joanna Szczepanek et al., 2023). This strategic combination could lead to breakthrough treatments that are more effective in managing breast cancer, ultimately improving patient outcomes and personalizing care based on individual epigenetic profiles.

Keywords: Cancer signaling Epigenetics Tumor Genes

11.

Evaluation and bioinformatic analysis of the genetic origin of acute lymphoblastic leukemia cancer patients and their response to novel chemotherapy drugs (Research Paper)

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Introduction: Acute lymphoblastic leukemia (ALL) is a relatively rare heterogeneous blood malignancy in adults, but it is one of the most common types of cancer in children, which is characterized by the uncontrolled proliferation of lymphoid progenitor cells in the bone marrow and peripheral blood. ALL is characterized by the rapid development of white blood cell precursors called lymphoblasts, which divide inappropriately and disrupt the production of healthy blood cells, resulting in the production of very low amounts of red blood cells, white blood cells and platelets, which cause anemia, neutropenia and thrombocytopenia respectively. The two main subtypes of ALL, which are classified according to immunophenotype, are B cell ALL (in 85 to 90% of cases) and T cell ALL (in 10 to 15% of cases) are ALL. This disease is very common in children but also occurs in adults, but the probability of treatment in adults is very low, but in children, treatments are a good opportunity for their recovery. Chemotherapy and radiation exposure may increase the risk of developing ALL. Leukemia treatment means that the cancer is gone, does not recur and no further treatment is needed.

Methods: To conduct this research, prominent sources in the field of bioinformatics and molecular biology were used, including the NCBI database and using Mega-gene pharmacogenetic software. With the help of this program, we categorized and analyzed the data related to the data management of each gene, the data related to the polymorphism of a gene, and the drug information related to the disease, In order to be able to analyze the polymorphism information of the genes involved in this disease and to diagnose the side effects of medicinal uses with genetic origin of people.

Results: With the investigations entered in Mega-gene, we have reached the processing of common polymorphisms in the occurrence of this disease, which includes, among the 47 genes that are involved in the occurrence of the disease, three genes have the highest percentage. the Effect of a gene is based on its occurrence rate in the statistical population and also the highest number of reports of that gene. Polymorphism refers to the presence of two or more different forms of a particular DNA sequence that can occur in different individuals or populations. The most common type of polymorphism involves changes in SNPs, so each SNP represents a difference in a DNA building block called a nucleotide. As mentioned, among all the genes that are effective in the occurrence of this disease, despite the presence of polymorphism in each of them, these three genes have the highest polymorphism statistics, which include: 1-JAK2 with 48 SNPs and 6.04% influence in the community. 2-RUNX1 with 25 SNPs and 3.14% influence in society. 3-RB1 with 23 SNPs and 2.89% influence in society. Also, by examining the effects of drug treatment in affected people, despite the existence of polymorphisms in the genes involved in this disease, by examining 24 different drugs in the treatment of ALL, affected patients should not use a number of drugs to treat their symptoms. These six items include: 1-People with MLH1 genetic background, taking the drugs Adriamycin, Thioguanine, Erwinase, Dasatinib and Azacitidine causes side effect of nausea in patients. 2-People with JAK2 genetic background by using Methotrexate, L-Asparaginase and Azacitidine drugs cause side effect of Crohn, Inflammation, Platelet Hyperaggregability and Psoriasis in patients. 3-People with RB1 genetic background by using Etoposide drugs causes side effect of Mucositis in patients. 4-People with TP53 genetic background by using Nelarabine drugs causes side effect of Anorexia in patients. 5-People with BCR genetic background by using Dasatinib drugs causes side effect of Tinnitus in patients. 6-People with IKZF1 genetic background by using Thioguanine drugs causes side effect of Decreased cell growth in patients.

Conclusion: To use drugs to treat the ALL disease Before prescribing medicine and therapy, it is necessary to carry out genetic tests to check the presence of polymorphisms in common genes, including MLH1, JAK2 and RB1 then It should be done on patients so that in case of polymorphism, drugs with less side effects can be prescribed for the patient.

Keywords: acute lymphoblastic leukemia, Bioinformatic database, chemotherapy drugs, Cell lines, polymorphisms

12.

Evaluation and bioinformatic analysis of the genetic origin of colorectal cancer patients and their response to new chemotherapy drugs (Research Paper)

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Introduction: CRC is the third most common cancer and the fourth leading cause of cancer-related deaths, with a higher incidence in Western countries. The probability of developing CRC is about 4%-5%. Risk factors include age, chronic disease history, lifestyle, and gut microbiota imbalances. CRC is caused by mutations in oncogenes, tumor suppressor genes, and DNA repair genes. It can be classified as sporadic (70%), inherited (5%), or familial (25%). Common symptoms include rectal bleeding, abdominal pain, changes in bowel habits (constipation or diarrhea), unexplained weight loss, and anemia. Rectal bleeding is the most frequently reported symptom. Pathogenic mechanisms include chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP). Key mutations affect pathways like WNT, MAPK/PI3K, TGF-β, and TP53. Treatment typically involves surgical resection followed by chemotherapy and targeted therapies (e.g., monoclonal antibodies against VEGF and EGFR). Alternative therapies are also being explored to enhance effectiveness and reduce side effects.

Methods: One of the most reliable sources in this research is the NCBI database. The National Center for Biotechnology Information (NCBI) is part of the United States National Library of Medicine (NLM), a branch of the National Institutes of Health (NIH). First, we found genes related to colorectal cancer through the NCBI site, and then entered the abbreviations of genes related to colorectal cancer from the SNP section of the same site in the search section. Then we analyzed the data related to polymorphisms and after preparing this information, we entered the MagaGene software. In the meta-analysis stage, we first entered the names of genes involved in colorectal cancer, phenotypes, alleles, and the number of population and citations of each gene. In the next step, the names of the drugs and the side effects of taking the drugs in colorectal cancer were investigated.

Results: With the investigations carried out on the MegaGene site, we found out that among the 96 genes that play a role in the occurrence of colorectal cancer, three genes account for the highest percentage, which means that they have the highest polymorphism statistics. These 3 genes are: 1)CRP with 6 SNPs and 3.87% influence 2)TNF with 5 SNPs and 3.22% influence 3)IL10 with 4 SNPs and 2.58% influence

Conclusion: By examining the effects and side effects of drugs in people with colorectal cancer despite the presence of polymorphisms in the genes involved in this disease, while examining 8 different drugs for the treatment of CRC, we found that patients should not use multiple drugs to treat their symptoms. These drugs include: 1) The side effect of Eloxatin for people with ABCC2 genetic background is diarrhea. 2) The side effect of A.S.A for people with MLH1 genetic background is nausea. 3) The side effect of Celebrex for people with MLH1 genetic background is nausea. 4) The side effect of Adrucil for people with MLH1 genetic background is nausea.

Keywords: Key words:Colorectal cancer ,CRC symptoms, Polymorphism, Bioinformatics analysis, chemotherapy drug

13.

Exploring Cytarabine's Affinity for SMO receptor in Hedgehog pathway in AML via Molecular Docking (Research Paper)

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Introduction: Acute myeloid leukemia (AML) is a type of cancer that affects the blood and bone marrow, leading to an overproduction of abnormal white blood cells. The Hedgehog signaling pathway is pivotal for normal cell proliferation and development. Still, when it becomes dysregulated, it can lead to the unbridled growth of cancer cells. The Smoothened (SMO) receptor is a key component of this pathway, and its activation is related to the progression of leukemia. One of the most constantly employed treatments for leukemia is Cytarabine, a chemotherapeutic agent that effectively disrupts DNA synthesis. This interference serves to target cancer cells, eventually leading to their destruction. The impact of Cytarabine on the hedgehog pathway remains to be determined. Nonetheless there are promising indications of its potential as an adjunct therapy to hedgehog pathway inhibitors. The ideal of this study is to estimate the affinity of Cytarabine to SMO protein and to hypothecate the probable association of Cytarabine through the hedgehog pathway in leukemia.

Methods: In this research, initially, the SMO protein structure was obtained from the Uniprot website, then necessary preparations, such as adding charge and hydrogen ions, were done using Chimera software. The three-dimensional structure of the Cytarabine was downloaded from the PubChem website. The binding site of the SMO protein was determined using Deepsite. [Center; X: -13.926, Y: -29.800, Z: -12.1197 and Dimensions (Angstrom); X, Y, Z: 25.00] Finally, the molecular docking process was conducted using AutoDock Vina in PyRx 0.8 to test the binding status of Cytarabine to SMO protein.

Results: Following the completion of the docking process of Cytarabine with SMO protein, using PyRx software, the obtained results are as followed. For each model, the data belongs to their binding affinity, RMSD lower bond and RMSD upper bound, respectively: Model #1: [-6.9, 0.0, 0.0] Model #2: [-6.5, 2.576, 5.38] Model #3: [-6.5, 1.757, 3.215] Model #4: [-6.4, 2.563, 5.154] Model #5: [-6.1, 1.67, 2.537]

Conclusion: Based on the findings from the molecular docking analysis of Cytarabine with SMO protein, it was determined that in accordance with the negative binding energy, Cytarabine can bind well to SMO protein. According to the data presented in this research, it is likely that Cytarabine is involved in regulating the SMO protein, potentially offering a novel pathway of this drug for AML treatment. Nevertheless, further investigation is still needed to determine if cytarabine has got a role in inhibiting SMO protein.

Keywords: Cytarabine, Hedgehog pathway, SMO, Chemotherapy, AML

14.

Exploring the Anticancer Mechanisms of Ibuprofen in Gastric Cancer: From Molecular Pathways to Clinical Potential (Review)

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Introduction: Gastric cancer is a significant public health concern, ranking as the fifth most common cancer and the third most common cause of cancer death globally. The relationship between stomach cancer and preventive measures, including the use of certain medications, is therefore a crucial area of study. One such medication is ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID) renowned for its analgesic, antipyretic, and anti-inflammatory properties. Ibuprofen's mechanism of action involves non-selective inhibition of cyclooxygenase (COX) enzymes, specifically COX-1 and COX-2, which play a pivotal role in the synthesis of prostaglandins that mediate inflammation and pain.

Methods: A comprehensive literature search was conducted across two databases: PubMed and the Scientific Information Database (SID). The search spanned from 1988 to 2024 and utilized the keywords "ibuprofen" and "gastric cancer." In the SID database, one relevant study was identified. The search in PubMed initially yielded 39 articles. After applying the inclusion criteria and removing duplicates, a total of 7 articles were selected for further review. These articles were subsequently analyzed to evaluate the relationship between ibuprofen and gastric cancer.

Results: Research indicates that ibuprofen may have a protective effect against various types of cancer, including stomach cancer. The mechanisms through which ibuprofen exerts its anticancer effects include: 1. Inhibition of Cell Proliferation: Ibuprofen has been shown to reduce cell proliferation in gastric cancer stem cells by inhibiting the Wnt/β-catenin signaling pathway and altering the expression of stemness markers such as CD44, OCT3/4, SOX2, Nanog, and KLF4 [Akrami, 2018]. 2. Modulation of MicroRNAs: Ibuprofen affects the expression of microRNAs that target COX-1/2 mRNA in gastric cancer stem-like cells. This modulation impacts several signaling pathways, including PI3K-Akt, P53, and TGF-beta, which are crucial in cancer development and progression [Akrami, 2019]. 3. Enhancement of Detoxification Enzymes: Ibuprofen increases the activity of glutathione S-transferases (GSTs) in the stomach, which are detoxification enzymes that help in reducing

cancer risk by enhancing the detoxification of carcinogens [Lieshout, 1997]. 4. Reduction in Cancer Risk: Epidemiological studies have shown that regular intake of NSAIDs, including ibuprofen, is associated with a significant reduction in the risk of stomach cancer. This protective effect is more pronounced with long-term use [Harris, 2005]. Overall, ibuprofen's anticancer effects are attributed to its ability to inhibit COX enzymes, modulate signaling pathways, and enhance detoxification processes, making it a potential chemopreventive agent against stomach cancer.

Conclusion: In the discussion section, we summarize the theories and talk about their strengths and weaknesses Theory 1: Inhibition of Cell Proliferation via Wnt/β-Catenin Pathway Ibuprofen has been shown to reduce cell proliferation in gastric cancer stem cells by inhibiting the Wnt/β-catenin signaling pathway and altering the expression of stemness markers. While this theory provides a clear molecular mechanism, it is primarily supported by in vitro studies and requires further validation in clinical settings. Theory 2: Modulation of MicroRNAs Ibuprofen has been found to affect the expression of microRNAs that target COX-1/2 mRNA in gastric cancer stem-like cells, impacting several signaling pathways. This theory highlights the role of microRNAs in cancer therapy and provides a broader understanding of ibuprofen's molecular effects, but is primarily based on cellular models and requires further investigation in clinical settings. Theory 3: Enhancement of Detoxification Enzymes Ibuprofen has been shown to increase the activity of glutathione S-transferases (GSTs) in the stomach, enhancing detoxification processes and reducing cancer risk. While this theory demonstrates a protective mechanism through detoxification, it is based on animal model studies and requires human trials to confirm its findings. Theory 4: Epidemiological Evidence of Risk Reduction Regular intake of NSAIDs, including ibuprofen, has been associated with a significant reduction in the risk of stomach cancer. This theory is supported by large-scale epidemiological studies, but is based on observational data and may be influenced by confounding factors. Theory 5: Phospho-Ibuprofen as a Novel Agent Phospho-ibuprofen, a modified derivative, has been shown to exhibit enhanced anticancer efficacy and reduced toxicity compared to conventional ibuprofen. While this theory demonstrates improved safety and efficacy in preclinical models, it is currently in the preclinical stage and requires clinical trials to validate its potential therapeutic benefits. Each of these theories offers valuable insights into the potential anticancer effects of ibuprofen. However, there remains a critical need for more clinical studies to substantiate these findings and fully elucidate ibuprofen’s role in cancer prevention and therapy.

Keywords: Ibuprofen Gastric Cancer

15.

From Stem Cells to Tumors: The Epigenetic Control of Cancer Signaling Pathways

(Review)

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Introduction: It takes a lot of changes in genetic and epigenetic processes that control cell fate, proliferation, and differentiation for normal stem cells to turn into cancerous cells. One of the most important is epigenetic regulation, which controls which cancer signaling pathways are turned on and off without changing the DNA code underneath. Cancer research is now mainly focused on figuring out how epigenetic changes affect the growth of tumors. This has led to discoveries about how DNA methylation, histone modification, and non-coding RNAs affect the functions of cells that cause cancer to spread. This review discusses how epigenetic control affects cancer signaling pathways, focusing on how stem cells are controlled, how they turn into cancerous cells, and possible cancer therapies targeting epigenetic changes.

Methods: This review utilized trustworthy articles published in databases such as Scopus, ScienceDirect, Google Scholar, ResearchGate, and PubMed. Library researches were also conducted. English keywords such as "epigenetic control," "stem cell," "tumors," and "cancer signaling" and chose the articles whose descriptions and full texts had similar words. No limitation of date and year of publications was included.

Results: Cancer stem cells (CSCs) are cancerous cells that cause tumors to grow, become resistant to treatment, and return. Epigenetic changes, like DNA methylation, histone modifications, and non-coding RNA expression, are the significant ways they are made and

kept up. These pathways manage critical signaling networks needed for CSCs to live and grow. They include Wnt/β-catenin, Hedgehog, Notch, and TGFβ/BMP. When these pathways are changed, they can set off feedback loops that help keep CSC stable but also cause cancer. The epigenome of cancer is unstable, and it changes even more with age, the surroundings, and mutations in epigenetic regulators. This instability changes the structure of chromatin and the links between enhancers and promoters. This changes how signaling pathways that keep CSC alive are controlled. Recent improvements in single-cell sequencing methods have made it possible for researchers to look into these epigenetic changes at a level of detail that has never been seen before. This has shown how complicated tumor heterogeneity is and helped them find the epigenetic changes that support pathways that are driven by CSCs. How things are done now suggests that finding new biomarkers and making specific medicines that mess up epigenetic regulation in cancer might be possible. These methods might help treatments work better by focusing on epigenetic changes that support the survival of CSCs and the growth of tumors. Cells and stem cells share the same functions, like the ability to divide and make new cells. But cancer cells take over these control systems, which lets them multiply out of control and form tumors. Epigenetic processes, like DNA methylation and histone change, are essential for keeping the balance between dividing and growing stem cells. In cancer, these epigenetic factors are often changed, which sets off signaling pathways that help tumors grow. Epigenetic mechanisms tightly control several essential signaling pathways that play a role in cancer development. These include the Wnt, Notch, Hedgehog, and PI3K/AKT/mTOR pathways. Changes in epigenetics that affect the activity or production of parts in these pathways can cause cells to grow out of control, become resistant to apoptosis, and spread to other body parts. Since epigenetic changes play a big part in controlling cancer signaling pathways, more and more people are interested in making epigenetic treatments that target these changes.

Conclusion: Epigenetic mechanisms are essential for both standard and abnormal development. Chemical changes in the epigenome, like histone modifications and DNA methylation, are significant for stem cells to differentiate and become different tissue types. The best way to treat various types of cancer is to use non-responsive, inactive cancer stem cells. These cells stay dormant for long periods and become active again when the cancer has spread. Figuring out how these changes affect the growth of cancer has led to new ways of creating epigenetic treatments that target the molecular processes that cause cancer. As the studies go further, focusing on the epigenetic regulators of

cancer signaling pathways could lead to new ways to treat and control cancer and improve patients' clinical situation.

Keywords: Epigenetic Control, Stem Cell, Tumors and Cancer Signaling

16.

Harnessing AI for Nanomedicine: Innovations in Drug Delivery and Therapeutics in Cancer Management (Review)

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Introduction: Many researchers are interested in nanomedicine because it can send drugs directly to tumors while minimizing lousy side effects. Nanotechnology has come a long way in the last thirty years, which has sparked new interest in cancer care. Large amounts of new information have been learned about cancer nanomedicine. It has been possible to make lipid-based, polymeric, and inorganic nanoparticles that can carry therapeutic nucleic acids, chemotherapeutic drugs, or immunotherapeutic agents to tumors. Nanotechnology and Artificial Intelligence (AI) are used to make better, more focused, and more personalized medicines for various illnesses, such as cancer and non-infectious and infectious diseases. Thanks to progress in nanotechnology, it is now easy to make different kinds of nanocarriers. Anticancer drugs work better in cancerous tissue, cells, or structures. This keeps the drugs from hurting other parts of the body. AI can make nanopharmaceuticals, which include jobs like designing and finding new materials, improving the synthesis process, characterizing them, checking their quality, and creating personalized medicines. The focus of this study is on how AI has changed nanomedicine, especially when it comes to cancer treatment and drug delivery. The aim is to improve patient results and significantly change how healthcare is provided today.

Methods: A thorough study of the scientific background of using AI for nanomedicine has been performed, focusing on new ways of delivering medications and managing cancer through therapy. In this review article, we searched Google Scholar, PubMed, and Scopus

using keywords that are often linked to each other, such as "artificial intelligence," "nanomedicine," "drug delivery," "therapeutics," and "cancer management." From the different studies already done in this area, we chose and evaluated papers mainly about designing nanoparticles, delivering drugs to specific regions, and customizing cancer treatment.

Results: Nanomedicine, which uses nanotechnology in health care, has gotten a lot of interest because it could help doctors deliver medicines more precisely, especially in cancer treatment. Different nanoparticles, like liposomes, dendrimers, and gold nanoparticles, have been used to carry chemotherapy drugs straight to tumors. However, problems with nanoparticles' stability, toxicity, and distribution still make it hard for nanomedicine to be widely used in cancer treatment. AI plays a more significant role in improving the design of nanoparticles, predicting how medicines will combine, and making nanomedicine therapies work better. Modern Machine Learning (ML) algorithms can look at vast amounts of data to find patterns and expect the best nanoparticle designs, considering how well medications dissolve and release and are poisonous. Because of this, it is possible to make drug delivery systems tailored to each patient's needs. This makes the treatment work better and decreases the harmful effects. It is also possible for AI to make models of how nanoparticles interact with cancer cells. These models can help doctors determine the best ways to treat different types of tumors. Nanomedicine, which AI enhances, has a lot of promise for creating and using new ways to treat cancer. Making smart nanoparticles that react to the tumor's environment is an exciting study area. Scientists could make these nanoparticles release their medicine when certain conditions are met. This would ensure the medicine reaches the tumor at the right time and place. AI can also improve combination therapies by examining substantial drug interactions and patient outcomes databases. This helps make multi-modal treatment plans that attack cancer from different directions.

Conclusion: Using AI and nanomedicine together is a revolutionary way to treat cancer. It creates new opportunities for targeted therapies, personalized drug delivery, and early detection. AI-powered nanomedicine could make a big difference in how well patients do and change the future of cancer treatment, according to more studies being done in this area. But, even though it has a lot of potential, combining AI and nanomedicine in cancer care is still very hard. Some problems that need to be fixed are the difficulty of AI algorithms, the need for big datasets to train these systems, and worries about data privacy

and security. Also, we still need to fully understand the long-term effects of treatments based on nanoparticles, which is why more research is required. AI and nanotechnology will likely make cancer treatments more personalized and accurate. With the creation of more competent AI models and new nanoparticle designs, AI-enhanced nanomedicine has the vast potential to change how cancer is treated completely.

Keywords: Artificial Intelligence, Nanomedicine, Drug Delivery, Therapeutics, Cancer Management

17.

Harnessing Artificial Intelligence for Innovative Drug Discovery (Review)

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Introduction: The process of drug development is complex and lengthy, as the main aim is to create treatments for various diseases. The introduction of Artificial Intelligence (AI) in this industry has played a significant role by accelerating the rate of discovery and minimizing costs. The goal of this review is to present some key AI applications in drug discovery, such as Machine Learning (ML) for drug property prediction and molecular optimization, Deep Learning (DL) for searching biological databases and drug retrieval, Natural Language Processing (NLP) for analyzing bioliterature, Generative Models (GM) for molecule design, and networks aimed at drug targeting. The history of AI application in medicine began with expert systems and image recognition and has evolved to include the management of personalized medicine and drug discovery. Despite AI being conceptualized in the 1920s and its first practical realization in mechanical robots, its application in pharmaceutical research and development has grown significantly. Deep learning algorithms, such as artificial neural networks (ANN), are also employed for predicting drug properties and managing information, including potential large datasets and understanding progress in macromolecule drug development. However, there is still room for improvement in these areas.

Methods: This review explores the application of artificial intelligence (AI) in various stages of drug discovery and development (DDD). The DDD process encompasses target discovery, target validation, lead generation and refinement, and preclinical development. AI techniques, including machine learning (ML) and deep learning (DL), play a crucial role throughout these stages. Key methods highlighted include virtual screening, where AI tools analyze protein structures to predict drug interactions; toxicological profiling, which uses AI for predicting adverse effects; and scoring protein-ligand interactions. Specific AI approaches, such as Kronecker regularized least squares (KronRLS) and SimBoost, are employed to estimate drug-target binding affinities. Additionally, generative models and neural networks contribute to the design of novel drug molecules and the prediction of physicochemical properties. Network-based analyses and natural language processing

(NLP) are also discussed for their roles in identifying potential drug targets and repurposing opportunities. The review emphasizes the transformative impact of AI on drug discovery, enhancing efficiency, accuracy, and the ability to navigate complex biological systems. The integration of AI-driven methodologies is positioned as crucial for advancing pharmaceutical research and optimizing drug development processes.

Results: AI-assisted drug discovery faces several challenges despite its transformative potential. A primary issue is the quality and volume of data; AI models need large, high-quality datasets to avoid biased or inaccurate predictions. In materials science, obtaining comprehensive data is difficult due to the vast variety of materials and properties. Additionally, ensuring accurate data representation and selecting appropriate algorithms for material discovery are critical, as is integrating domain-specific knowledge to interpret AI predictions. Other challenges include the need for diverse and representative training data to prevent model biases and the requirement for substantial computational resources for high-throughput simulations. Validation of AI predictions through experimental testing is time-consuming and costly. Ethical considerations, such as data security and compliance with regulations, also play a crucial role in the implementation of AI. For successful AI integration in drug discovery, interdisciplinary collaboration, improved data management, and ethical practices are essential. Addressing these issues will enhance AI's ability to drive innovation and efficiency in drug discovery processes.

Conclusion: The future of AI in the field of drug discovery is on the brink of improving automation, which could shift the process from human-assisted to self-sufficient. This transition aims to simplify the drug discovery process by empowering AI to manage the creation, testing, and analysis of new compounds independently. The goal is to establish fully automated laboratories capable of efficiently progressing through the drug discovery cycle. While this offers the potential for faster and more effective drug development, challenges like ensuring the trustworthiness and consistency of AI results persist. Moreover, the success of AI in drug discovery hinges on the availability of top-notch datasets and ongoing investments in AI technology. Despite these obstacles, AI has already demonstrated significant promise in enhancing drug discovery by pinpointing new drug combinations, refining formulations, improving target identification, and enhancing virtual screening procedures. Looking forward, advancements in AI-driven automation are anticipated to bring about a significant transformation in the field, promising a brighter future for more efficient and cost-effective drug discovery.

Keywords: drug discovery, machine learning, deep learning, artificial intelligence, pharmaceutical AI

18.

HSP27: A missing element in drug resistance in cancers (Review)

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Introduction: HSP27, a member of the small heat shock protein family, holds a vital role in personalized medicine, particularly in cancer therapy. Its versatile properties have elevated it as a promising target for enhancing treatment effectiveness and reducing side effects. Despite advancements in treatment modalities like chemotherapy, radiotherapy, surgery, and the latest immunotherapy, cancer continues to stand as a primary global mortality cause. In the year 2020 alone, an estimated 19.3 million new cancer cases and 10 million cancer-related deaths were recorded. Although chemotherapy remains the prevailing cancer treatment, it fails to yield desired responses in some patients, primarily due to the emergence of drug resistance within tumors. Hence, investigating and unraveling the impactful mechanisms of drug resistance and formulating therapeutic strategies to combat it become imperative. Drug resistance can stem from various mechanisms, including alterations in drug absorption and expulsion, DNA damage repair, cellular apoptosis, tumor microenvironment influences, and genetic modifications. HSP27 emerges as a pivotal player influencing pharmacogenetic responses, particularly in cancer therapy, where its expression levels can dictate cellular susceptibility or resistance to diverse chemotherapeutic agents and targeted treatments.

Methods: Data were collected by conducting to outline comprehensive studies published in PubMed, Web of science, Scopus and Google scholar databases from 2015 to 2024 by using keywords such as “HSP27”, “drug resistance”, “cancer”, “pharmacogenetic” and related combinations.

Results: The review of findings highlights the significance of the HSP27 molecule in drug resistance and sensitivity mechanisms. HSP27 is associated with drug resistance in various cancers, inhibition of apoptosis, and promotion of cell survival. It is often overexpressed in tumors and provides protection against drugs like Doxorubicin by inhibiting senescence through p53 mediation, thus enabling cancer cells to evade

treatment. In oncogene-addicted cancer cells, suppression of HSP27 can shift target factors from cytostatic to cytotoxic, enhancing apoptosis and drug efficacy. Additionally, significant increases in sensitivity to 5-Fluorouracil and Vincristine, and promotion of apoptosis and tumor growth inhibition, are observed upon reducing HSP27 in colon cancer cells. Inhibiting HSP27, especially through its phosphorylation, has shown potential in enhancing radiotherapy efficacy, as evident by decreased cell survival in cancer cell lines. Besides HSP27 acts as a negative regulator of apoptosis in glioblastoma, suggesting that its modulation could improve treatment outcomes.

Conclusion: In summary, HSP27 plays a significant role in the development of drug resistance; however, its modulation can enhance drug sensitivity. While HSP27 presents opportunities for strengthening cancer therapies and safeguarding against treatment-related toxicity, its overexpression can also complicate treatment strategies, hence needs for precise examination in personalized medical approaches.

Keywords: HSP27, Pharmacogenetic, Cancer, Drug resistance

19.

Investigating the anticancer effect of antibiotics in ITM and microbiome (Review)

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Introduction: The essay investigates the complex relationship between antibiotics, the microbiome, and cancer treatment, highlighting the potential benefits and risks of antibiotic use in oncology. Central to the discussion is how the human microbiome, particularly gut microbiota, influences cancer progression and treatment outcomes. The study emphasizes the dual role of antibiotics, which can both support and hinder cancer therapies depending on their effects on microbial communities. The Role of the Microbiome in Cancer Progression and Treatment The human microbiome plays a pivotal role in regulating immune responses, metabolism, and cellular functions, all of which are essential in cancer development and treatment responses. Microbial communities within the gastrointestinal tract are particularly influential in modulating inflammation, immune activity, and the efficacy of cancer therapies. For instance, specific bacterial species can enhance the effects of immunotherapies by boosting T-cell activity, while others may interfere with treatment by inducing immunosuppression (1). The essay explains that variations in microbial composition within the gut or other epithelial barriers can affect both local and systemic immune responses, altering cancer progression and therapy effectiveness. This influence of microbiota on anticancer therapies is becoming increasingly recognized, with studies showing that a healthy, balanced microbiome can improve treatment outcomes in chemotherapy and immunotherapy by regulating immune responses (2). The Dual Nature of Antibiotics in Cancer Treatment Antibiotics are

frequently used in cancer patients to manage infections due to compromised immune systems. However, while antibiotics have been shown to exhibit antitumor properties by inducing apoptosis and inhibiting cancer cell proliferation, they can also disrupt the microbiome, leading to a condition known as dysbiosis (3). Dysbiosis negatively affects the body's immune responses, potentially diminishing the effectiveness of cancer treatments, especially immune checkpoint inhibitors (ICI). This can result in suboptimal treatment outcomes for cancer patients undergoing immunotherapy (3). The essay elaborates on how antibiotics, while beneficial in preventing infections, must be used with caution in cancer patients. By disrupting gut microbiota, antibiotics can impair the immune system's ability to fight cancer, leading to decreased effectiveness of therapies like chemotherapy and immunotherapy. This is particularly concerning in the context of ICIs, where a balanced microbiome is critical for optimal immune function (4). Intratumoral Microbiome and Its Impact on Treatment In addition to the gut microbiome, the essay explores the role of the intratumoral microbiome, which refers to the bacterial communities found within tumors. Although research in this area is still emerging, there is growing evidence that intratumoral bacteria can influence cancer progression and response to treatment. Some bacteria found in tumors can metabolize chemotherapeutic agents, reducing their effectiveness. For instance, intratumoral bacteria have been shown to inactivate gemcitabine, a common chemotherapy drug, thereby leading to drug resistance (5). The presence of intratumoral microbiota also affects immune regulation and gene expression within the tumor microenvironment. These bacteria can either enhance or suppress immune responses, impacting the effectiveness of anticancer therapies (6). Thus, understanding the role of intratumoral microbiota offers new opportunities to optimize cancer treatments by potentially targeting these bacteria to improve therapeutic outcomes.

Methods: Research suggests that the human microbiome plays a crucial role in the initiation and progression of cancer by influencing the balance between cellular proliferation and apoptosis, regulating immune responses, and affecting metabolic processes within cells. Comprehensive studies have highlighted that manipulating the microbiota could potentially enhance cancer therapies. One strategy for modulating the microbiota is the administration of antibiotics, though the effects of antibiotic use can range from beneficial to detrimental. Antibiotics may directly impact cancer cells by promoting apoptosis, targeting cancer stem cells to prevent recurrence, inhibiting cancer cell proliferation, and blocking metastasis. Alternatively, antibiotics may indirectly affect cancer cells by altering the microbiota in ways that inhibit cancer growth. Due to these

effects, antibiotics are increasingly used to support cancer treatment. We identified 35 relevant articles through searches on PubMed and Google Scholar using conventional keyword strategies. These studies examined the microbiome of various human anatomical sites before and after antibiotic therapy using 16S rRNA gene sequencing. The primary goal of this study is to explore the anticancer effects of antibiotics on the microbiome and intra-tumoral microbiota.

Results: Research suggests that the human microbiome plays a crucial role in the initiation and progression of cancer by influencing the balance between cellular proliferation and apoptosis, regulating immune responses, and affecting metabolic processes within cells. Comprehensive studies have highlighted that manipulating the microbiota could potentially enhance cancer therapies. One strategy for modulating the microbiota is the administration of antibiotics, though the effects of antibiotic use can range from beneficial to detrimental. Antibiotics may directly impact cancer cells by promoting apoptosis, targeting cancer stem cells to prevent recurrence, inhibiting cancer cell proliferation, and blocking metastasis. Alternatively, antibiotics may indirectly affect cancer cells by altering the microbiota in ways that inhibit cancer growth. Due to these effects, antibiotics are increasingly used to support cancer treatment. We identified 35 relevant articles through searches on PubMed and Google Scholar using conventional keyword strategies. These studies examined the microbiome of various human anatomical sites before and after antibiotic therapy using 16S rRNA gene sequencing. The primary goal of this study is to explore the anticancer effects of antibiotics on the microbiome and intra-tumoral microbiota.

Conclusion: Conclusion In summary, while antibiotics remain an essential tool in managing infections in cancer patients, their impact on the microbiome demands careful consideration. The disruption of gut and intratumoral microbiota can have significant consequences for cancer progression, treatment effectiveness, and overall patient survival. The essay emphasizes the importance of personalized approaches to antibiotic use in cancer therapy and the potential of microbiome-targeted interventions to improve treatment outcomes. Through further research and a better understanding of the microbiome's role in cancer therapy, clinicians can optimize antibiotic use, ensuring that these treatments support rather than hinder cancer therapies.

Keywords: cancer, antibiotic, microbiome, anticancer, intra-tumoral microbiome

20.

Investigating the effect of the extracted polysaccharide from Brittle star (Ophiocoma erinaceus) on biochemical parameters in the experimental model of liver cirrhosis

(Review)

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Introduction: Brittle star possess bioactive compounds which confer the wound healing capacity and regenerative potency of damaged arms and organisms to this creature. The purpose of this study was to investigate the protective effect of extracted polysaccharide from Brittle star on biochemical parameters in the experimental model of liver damage caused by carbon tetrachloride in adult male Wistar rats.

Methods: To extract polysaccharide, dried brittle stars were ground and extracted mechanically. We analyzed the levels of GSH, TBARS, H2O2, SOD, CAT, GPx, GST, LOX markers. The rats were fed with 0.1%CCl4 (0.2 mL/10 g) mixed with soybean oil for 7 days. The rats in the BSP treatment groups administered intragastrically with Brittle Star Extracted Polysaccharide at the level of 12.5, 25, 37.5 mg/kg body weight (b.w.)/day for7days after CCl4 induction.

Results: Carbon tetrachloride significantly decreased the rats' body weight, but it increased their livers weight. Histopathological evaluations showed .extensive liver damage. On the other hand, treatment with extracted polysaccharide from Brittle star increased liver weight, reduced body weight and significantly altered other induced changes by carbon tetrachloride on liver structure such as hepatocytes number, Kupffer cells, and arteritis, which indicated the improvement of damaged liver tissue. Brittle Star

Extracted Polysaccharide treated rats significantly increased SOD, CAT, GPx, GST activities and GSH level.

Conclusion: It was found that extracted polysaccharide from Brittle star can exert protective effects on liver damages induced by carbon tetrachloride on male Wistar rat.

Keywords: Carbon tetrachloride, Brittle star, Polysaccharides, Antioxidants, Stress oxidative

21.

Investigating the effect of the extracted polysaccharide from Brittle star (Ophiocoma erinaceus) on Immunological parameters in the experimental model of liver cirrhosis (Review)

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Introduction: Hepatoprotective potential of marine natural products such as polysaccharides represented therapeutic potential in hepatological researches. In this study, total polysaccharide from brittle star [Ophiocoma erinaceus (O.erinaceus)] was extracted, immunotherapy efficacy of Persian Gulf brittle star polysaccharide was investigated in carbon tetrachloride-induced acute liver injury in rats

Methods: To extract polysaccharide, dried brittle stars were ground and extracted mechanically. Western blot analysis was conducted to assess the expressions of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and adenosine A2A receptor. The rats were fed with 0.1%CCl4 (0.2 mL/10 g) mixed with soybean oil for 7 days. The rats in the BSP treatment groups administered intragastrically with Brittle Star Extracted Polysaccharide at the level of 12.5, 25, 37.5 mg/kg body weight (b.w.)/day for7days after CCl4 induction.

Results: Carbon tetrachloride significantly decreased the rats' body weight, but it increased their livers weight. The polysaccharide detection methods demonstrated isolation of crude polysaccharide from Persian Gulf brittle star. TNF-α, IL-1β, and IL-6 expressions were decreased by Brittle Star Extracted Polysaccharide treatment in CCl4-intoxicated rats. Also BSP administration overexpressed adenosine A2A receptor in CCl4-intoxicated rats. Histopathological evaluations showed extensive liver damage. On the

other hand, treatment with extracted polysaccharide from Brittle star increased liver weight, reduced body weight and significantly altered other induced changes by carbon tetrachloride on liver structure such as hepatocytes number, Kupffer cells, and arteritis, which indicated the improvement of damaged liver tissue.

Conclusion: The therapeutic efficacy of Brittle Star Extracted Polysaccharide also can be expected for CCl4-intoxicated rats. The current research suggests that Brittle Star Extracted Polysaccharide may be used for the therapeutic agent of CCl4-intoxicated rats. Therefore, these findings proposed new insight into Hepatoprotective potential of brittle star polysaccharide as a promising agent in hepatic treatment.

Keywords: Carbon tetrachloride, Brittle star, Proinflammatory cytokines, Polysaccharides

22.

Investigation of Common Mutations related to Pharmacotherapy (pharmacogenetics) in Chronic Kidney Disease (CKD) patients using Next-Generation Sequencing (NGS) Technique **(Research Paper)**

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Introduction: Chronic kidney disease (CKD) patients frequently show diverse responses to medications,which can be attributed to underlying genetic mutations affecting drug metabolism and efficacy. Pharmacogenetic profiling is essential for tailoring treatments to individual genetic profiles, thus enhancing therapeutic outcomes. This study employs next generation sequencing (NGS) to identify and analyze common mutations in CKD patients, providing insights fir more personalized and effective pharmacotherapy.

Methods: This cross-sectional study was conducted in 2022 at the Department of Nephrology of Hashemi Nezhad in Tehran,Iran,and included 60 participants, Comprising 20 patients with CKD and 40 controls selected from marriage screening . Eligible CKD patients underwent clinical tests confirming their diagnosis,after which blood samples were collected for genetic analysis using NGS. DNA extraction was performed via the salting out method,Ultimately comparing clinical data between the patients and control groups.

Results: Patients,Matching the initial findings with the patient's clinical and preparing the final reports of each patient and extracting and analyzing data related to the design variables and statistical analysis based on the pharmacogenetics of the patients.The molecular diagnosis and genetic confirmation of the disease was done with aim of classification and then by analyzing the genetic finding related to drug metabolism, We achieved interesting results in terms of the extent and variety of mutations and the heterogeneity of the changes. The must mutations were detected for the genes of Atorvastatin ,Losartan ,Mycophenolate and Tacrolimus, which can be expected to disrupt the response process to the above drugs.For Belatacept,Zidovudine,Sirolimus, Hydrochlorothiazide,Sandimmone,Carvedilol and Allopurinol, The patagenic effect of mutation and drug resistance was not observed in patients with CKD. The clinical data were compatible with the genotype.

Conclusion: This study demonstrates that investigating common mutations related to drug treatment in patients with CKD using next generation sequencing can serve as a valuable public health approach to prevent CKD development , Progression and complications. Further research is essential to address key issues and validate these findings, While urgent action is needed to collect data on the efficacy, Effectiveness , and costs associated with CKD management.

Keywords: Chronic Kidney Disease , CKD, Next generation sequencing (NGS) technique , Pharmacogenetics

23.

Lipid nanomaterials-based RNA therapy and Lung cancer treatment (Review)

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Introduction: The launch of several RNA-based treatments Targeted nucleic acid sequence delivery can be made possible via RNA treatments to correct particular genetic abnormalities or defects. RNA has emerged as a promising therapeutic agent for several disorders due to its purportedly exceptional therapeutic properties. The following are some benefits of RNA therapies: (i) The potential for very safe, comparatively inexpensive patient-specific medicines. (ii) therapies may require various types of encoded RNA to accomplish different cell-regulating tasks. (iii) The synthesis and design of the RNA sequence are rather straightforward. Most notably, RNA therapies preserve the host genome in contrast to DNA therapies since they do not require nuclear membrane entry to start cytoplasmic protein translation. The traits above have prompted the development of more precise and individualized treatments for various ailments. There are two types of common RNA therapeutic approaches: coding and noncoding. The coding RNA technique primarily involves gene activation, which initiates the creation of coded-protein antigens. It influences the generation of cytotoxic lymphocytes and antibodies, which in turn causes associated immunity. On the other hand, other trace amounts of coding RNA regulate constitutive and functional protein synthesis and activation, which can be applied in protein supplementation treatment. The noncoding RNA (ncRNA) method suppresses one or more related genes to prevent the synthesis of proteins with encoded sequences. With an annual growth rate of 11.4% for new cases, lung cancer is the most deadly cancer type and the leading cause of cancer-related deaths globally. There are two types of lung cancer: small-cell lung carcinoma (SCLC) and nonsmall-cell lung carcinoma (NSCLC). This study looked into RNA therapy based on lipid nanoparticles and their application to lung cancer treatment.

Methods: Lipid nanomaterials-based RNA therapy and Lung cancer treatment is the title of the current study. It was conducted by scanning academic databases, including Science Direct, Springer, Google Scholar, and PubMed.

Results: The efficacy of existing medicines is limited by the heterogeneity and adaptability of lung cancer. As a result, RNA-based therapies with the potential to combat cancer are of tremendous interest. The high surface area of nanoparticles and their easy synthesis into therapeutic RNA nanoparticles make them beneficial. Zhao et al. created lipid-polycation-hyaluronic acid nanoparticles for VEGF siRNA delivery in a human lung cancer mouse model as part of early-phase liposomal DDS research. By inhibiting rapamycin and activating adenosine monophosphate-activated protein kinase, these nanoparticles demonstrated effective antitumor effects that were comparable to those of the anticancer medication metformin. Additionally, mesoporous silica nanoparticles, or MSNPs, are thought to be another potent DDS. Dilnawaz et al. created DDSs for the treatment of lung cancer, which used the MSNPs to deliver anticancer medications (such as docetaxel or etoposide) with survivin siRNA. They proposed that the use of high-dose co-deliver medicines in vitro had a notable apoptotic effect on this system. Polyethylenimine (PEI) functionalized siRNA/MSNPs fixed on electrospun nanofibers were reported by Nascimento et al. Disrupting the proliferation of cancer cells is an additional method of cancer treatment. Even if scientists have found several siRNA that can inhibit the growth of cancer cells in recent years, the majority of them are frequently linked to unfavourable side effects. Thus, more study is needed in the area of creating siRNA DDSs with less systemic side effects.

Conclusion: Using novel nanocarriers as drug delivery vehicles offers special benefits for RNA-based technologies utilizing nanoplatforms. Bioactive compounds can be efficiently prevented from degrading during administration by maintaining the structural stability of nanoplatforms. Most notably, therapeutic RNA combined with nanocarrier delivery offers high biocompatibility, enabling medications to target particular cells and tissues and effectively cross biological barriers. Additionally, patients undergoing treatment can reduce unwanted inflammation in tissue or organs, improving the therapeutic effect, due to its biocompatibility and stability. These distinct benefits have shown that treatments aided by nanotechnology have a promising future. Many disciplines (such as chemistry, material science, biology, and medicine) have invested a great deal of time and energy into designing, developing, and testing RNA-targeting nanoplatforms with unique properties. While miRNA-based therapies have great promise for wound healing, we think mRNA therapeutics will continue to be investigated for the creation of novel vaccines.

Keywords: Nanomaterials, RNA, Lung Cancer, Sirna/Msnps

24.

Meta-analysis of breast cancer and association with phenotypes of common polymorphisms in Iran (Research Paper)

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Introduction: Breast cancer is a critical global public health issue and the most frequently diagnosed cancer worldwide. From January to June 2023, the World Health Organization (WHO) recorded 577 new cancer cases, including 33 breast cancer cases.

Methods: Common polymorphisms were selected based on citation and population data from the National Center for Biotechnology Information (NCBI). In addition, we evaluated related drug treatments in Iran and analyzed their related side effects. Data were then processed using MagaGene software, a specialized pharmacogenetic tool.

Results: Our analysis revealed prevalent phenotypes associated with breast cancer. We also identified which specific phenotypes are likely to appear when cancer develops. Furthermore, we identified which side effects of drugs available in Iran might have a genetic basis.

Conclusion: We recommend that oncologists conduct Sanger sequencing to ascertain the genetic profiles of breast cancer patients. This approach enables the selection of alternative therapies with potentially reduced side effects based on the patient's genetic makeup.

Keywords: Breast cancer, pharmacogenetics, polymorphisms, drug side effects, Sanger sequencing.

25.

New Biomarkers Based on Smoking-Related Phenotypes for Smoking Cessation Outcomes of Nicotine Replacement Therapy: A Prospective Study (Research Paper)

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Introduction: Identifying a potent biomarker for smoking cessation can play a key role in predicting prognosis and improving treatment outcomes. This study aimed to evaluate the contribution of new biomarkers based on the levels of Cotinine (Cot) and carbon monoxide (CO) to the short- and long-term quit rates of nicotine replacement therapies (Nicotine Patch [NP] and Nicotine Lozenge [NL]).

Methods: In this prospective interventional study, 124 smokers under treatment with the 5A's method were selected from an outpatient smoking cessation center in district 18 of Tehran City, Iran. The study was conducted from April 2016 to December 2018. They were divided into NP (n=56) and NL (n=61) intervention groups. The levels of Cot and CO were measured using ELISA and breath analysis at the beginning of the study. Three markers were calculated: Cot/CO, Cot to cigarette per day ratio (Cot/CPD), and CO/CPD. Binary logistic regression models and generalized estimating equations models were analyzed by SPSS software, version 21 to determine the chances of quitting smoking.

Results: Of the NP participants, 30.4% and 19.6% were abstinent after 2 and 6 months, respectively, while NL was found less effective with 19.7% for 2-month follow-up and 13.1% for 6-month follow-up. The 6-month success of quitting attempts was significantly different for the NP participants at the second half of Cot/CO (P=0.029). Of the NL participants, CO/CPD would be a superior predictor for smoking cessation success (P>0.05).

Conclusion: The findings of this study suggested two markers of Cot/CO and CO/CPD in this order for the optimum treatment outcomes of NP and NL.

Keywords: Cotinine, Carbon monoxide, Nicotine replacement therapy, Smoking cessation

26.

Notch Signaling Pathway in Breast Cancer (Review)

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Introduction: Breast cancer is the most common cancer and also the primary cause of mortality due to cancer in female around the World. The Notch signaling system is the critical fundamental pathway, a unique cellular program that is encountered in cell type specification and organ development. It is the main regulator of cell destination and differentiation. Notch signaling is dysregulated in multiple cancer types. Canonical notch signaling is initiated by the interaction between a notch ligand and notch transmembrane receptor on the surface of a neighboring cell. In mammals, the notch pathway consists of four equivalent receptors (NOTCH1-NOTCH4) and five ligands, including three Delta-like proteins (DLL-1, 2 and 4) and two Jagged proteins (Jagged-1 and Jagged-2).

Methods: In the current study, keywords including Notch Signaling, Breast Cancer, and Progression were reviewed from the list of Mesh and other credible websites including PubMed, Science Direct and Google Scholar and the data was organized. The searches comprised all published paper from 2010 to 2022. All of full text was considered and the papers manifested as only abstract was excluded. The full papers selected that specific prognostic role of notch signaling pathway in breast cancer only. Totally 50 papers were selected and studied in this review.

Results: Articles have been shown that notch is an oncogene in the breast, as overexpression of Notch1IC, Notch3IC, or Notch4IC is sufficient for transformation of normal breast epithelial cells into cancer cells. Also, notch signaling contributes significantly to cell survival, proliferation, differentiation, apoptosis, tissue patterning, cell-fate decision, and morphogenesis. However, its dysregulation and role in promoting cellular transformation has led to further investigations of the role of notch in a variety of

cancers. Moreover, in one clinical study expression of the notch receptors and their ligands was found to be highly elevated in breast cancer tissues and correlated with poor survival of human breast cancer patients. Several studies have established that notch signaling exhibits its oncogenic properties through its interactions with other signaling pathways, such as Ras, TGFβ, and Wnt in the mammary gland tumorigenesis. Also, upregulated notch expression was found in breast cancer stem cell and initiating cell populations characterized by phenotypic markers CD44+/CD24−, and was linked to tumor-initiating properties and cancer stem cells-like invasive features. Numerous articles concluded notch signaling promotes proliferation in breast cancer cell lines by upregulating cyclin A, cyclin B, and cyclin D1 expression. Moreover, Notch protects breast epithelial cells from apoptosis by activating Akt. In breast cancer cells, Notch1 or Notch4 can promote the expression of Slug by activating the Slug promoter. In several recent studies NOTCH3 signaling was shown to promote the growth of basal breast cancers in functional studies.

Conclusion: In mammals, there is clinical and laboratory evidence that the notch family is clearly implicated in human breast cancer in different combinations. The Notch pathway masters and maintains a balance between cell multiplication, differentiation, and programmed cell death, but the mis- regulated notch ligand-receptor interaction in breast cancer gives the spark for tumor growth initiation, progression, and maintenance by inducing aberrant tumorigenesis.

Keywords: Notch Signaling, Breast Cancer, Progression

27.

Overview of Bioinformatics in Drug Design (Review)

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Introduction: The integration of bioinformatics into drug design emerged from the need to process and analyze vast amounts of biological data generated through genomic research. By unraveling human genome sequences, scientists have been able to identify new potential drugs and understand their mechanisms of action more clearly. This interdisciplinary approach, combining genomics, proteomics, and bioinformatics, has led to innovative strategies for addressing complex biochemical problems in drug discovery (Ataya Fs). Modern techniques such as molecular docking and mass spectrometry play crucial roles in these efforts, allowing researchers to predict protein structures and identify drug resistance factors efficiently. Consequently, this evolution in pharmaceutical research is not only enhancing our understanding of diseases but also streamlining the development of novel therapeutics.

Methods: Key Bioinformatics Tools and Techniques The historical development of bioinformatics in drug design reflects an essential shift towards leveraging computational methods to tackle intricate biological questions. By utilizing vast datasets derived from genomic studies, researchers can better predict how drugs interact with their targets at a molecular level. This capability is further enhanced by various bioinformatics tools that facilitate the analysis of biomolecular sequences and expression profiles, leading to more effective drug formulations. Moreover, the rising integration of high-throughput technologies, such as automated microscopy and bioimaging, allows for real-time monitoring of drug efficacy and safety during clinical trials (V. Kuznetsov et al.). As these technological advancements continue to evolve, they promise to not only improve drug discovery processes but also contribute significantly to personalized medicine approaches, tailoring therapies to individual patient profiles. Molecular Modeling and Simulation in Drug Discovery The integration of computational methods in drug discovery has revolutionized the field, enabling researchers to design and optimize drugs with unprecedented efficiency. Machine learning algorithms and artificial intelligence play a

crucial role in predicting interactions between drugs and their targets, thus facilitating the identification of promising drug candidates (Yakubu Magaji Yuguda et al.). Additionally, molecular modeling techniques allow for detailed visualization of molecular structures and interactions, which are essential for understanding how drugs exert their effects. These advancements not only enhance the accuracy of predictions but also streamline the drug development process, reducing time and costs associated with traditional methodologies. By harnessing big data and omics approaches, researchers can further tailor drug formulations to meet the specific needs of patients, marking a significant step toward personalized medicine (Rajat Saini et al.). Genomic and Proteomic Approaches in Drug Development Moreover, the unraveling of human genome sequences has significantly contributed to drug discovery by enabling researchers to identify new drug targets and understand the mechanisms of drug action. This integration of genomics, proteomics, and bioinformatics allows for the development of powerful strategies that address complex biochemical challenges in drug design (Ataya Fs). By examining the genetic underpinnings of diseases, scientists can predict drug resistance and identify potential biomarkers, which are essential for the effective treatment of various conditions. As a result, the combinatorial approaches employed in modern drug design not only improve the understanding of protein structures and functions but also enhance the overall efficiency of identifying and developing new therapeutic agents. This evolution towards more targeted and personalized treatments represents a significant advancement in the field of pharmacology. Case Studies of Successful Drug Design Using Bioinformatics The integration of bioinformatics into drug design not only streamlines the identification of drug candidates but also enhances the understanding of their interactions at a molecular level. By employing advanced computational techniques, researchers can simulate how potential drugs interact with biological targets, significantly reducing the time and cost associated with traditional trial-and-error methods in drug development. Furthermore, bioinformatics facilitates the analysis of large datasets generated from genomic and proteomic studies, enabling scientists to uncover patterns that link genetic variations to drug responses (Ataya Fs). This data-driven approach leads to more precise therapeutic strategies tailored to individual patient profiles, improving efficacy and minimizing adverse effects. Consequently, the collaboration between bioinformatics and drug design marks a transformative shift towards more personalized medicine.

Results: The collaboration between bioinformatics and drug design also paves the way for innovative computational approaches that can further refine the drug discovery process.

Recent advancements in artificial intelligence and machine learning techniques enable researchers to analyze vast amounts of biological data more efficiently, enhancing the precision of drug-target interaction predictions (Yakubu Magaji Yuguda et al.). These technologies not only streamline the identification of potential drug candidates but also facilitate the exploration of chemical spaces to discover novel compounds. By integrating diverse datasets from genomics, proteomics, and clinical studies, scientists can develop personalized medication strategies that are tailored to individual genetic profiles, thus improving therapeutic outcomes (Ataya Fs). As computational methods continue to evolve, they hold the promise of transforming traditional drug discovery paradigms into more efficient and effective frameworks aimed at addressing complex diseases.

Conclusion: The collaboration between bioinformatics and drug design also paves the way for innovative computational approaches that can further refine the drug discovery process. Recent advancements in artificial intelligence and machine learning techniques enable researchers to analyze vast amounts of biological data more efficiently, enhancing the precision of drug-target interaction predictions.

Keywords: Drug Bioinformatics

28.

Personalized medicine and cancer (Review)

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Introduction: BACKGROUND: Cancer is a complex and heterogeneous disease that affects many people worldwide every year. The development and progress of this disease is the result of accumulated mutations in cells and various functional disorders in cancer cells; which gives them the advantage of survival, further reproduction and the ability to escape from the host's immune system. Over the past few decades, major advances in disease identification and treatment methods have been made. Treatment methods and many problems have high costs, lack of proper functioning and sufficient accuracy, etc., they do not show the heterogeneity of the tumor completely, and different types of cancer respond differently to different treatments. Personalized medicine, as a novel and new field but with an old background based on this promising biological approach that can create a unique treatment path by identifying the genomic profile of each patient, has attracted a lot of attention. OBJECTIVE: The purpose of this study is to review and explain personalized medicine for cancer treatment and general explanations about this treatment method.

Methods: METHODS: In the present review article, we studied both original and review studies published in Science Direct, Scopus, PubMed and Google Scholar database using the key words Personalized medicine; Cancer; Biomarkers and Genetic.

Results: RESULTS: Recent studies have shown that the basis of this type of treatment is that it uses the individual's genome, molecular and clinical characteristics, the patient's personality, habits and lifestyle, as well as environmental factors such as age, environment and family to design a specific treatment path and prevent diagnose and predict the response to drugs and in general adjust the entire course of the patient's treatment in the best possible way. This method uses various sciences such as bioinformatics, biomathematics, statistics and systems biology to integrate, analyze and interpret genomic

(DNA), transcriptome (RNA), proteomics, nutrition, epigenomics, microbiome and metabolomic data to achieve Personalization makes better use of it.

Conclusion: Conclusion: In conclusion, personalized medicine in cancer treatment offers great promise and has many benefits for healthcare organizations, care providers such as physicians and treatment staff, and patients, including: improved quality of treatment and greater likelihood of outcomes desirable, reducing costs, increasing patient participation as well as increasing adherence to treatment, increasing the probability of choosing the best treatment and accurately predicting the disease, finding the right drug with the correct dose, reducing risky invasive test methods, improving the therapist's ability to understand the underlying mechanisms of the disease, finding strategies Disease prevention and community health promotion. However, there are still limitations and problems that prevent the full expression of the potential of this therapeutic method in prediction and treatment. But it is very important that PM shows promise in improving treatment outcomes and reducing toxicity associated with conventional chemotherapy. As personalized medicine continues to evolve, more effective and targeted treatments are likely to emerge in the near future, offering hope to patients with previously incurable cancers.

Keywords: KEYWORDS: Personalized medicine, Cancer, Genome, Biomarkers.

29.

Pharmacogenetics and Personalized Medicine: A Paradigm Shift in Drug Development and Clinical Practice **(Review)**

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Introduction: Pharmacogenetics, the study of how genetic variations affect drug response, is revolutionizing the field of medicine. By uncovering the genetic factors that dictate individual variability in drug efficacy and safety, pharmacogenetics allows for a more personalized approach to treatment. This has significant implications for both drug development and clinical practice. Personalized medicine leverages genetic information to tailor therapies that maximize therapeutic efficacy while minimizing adverse drug reactions (ADRs). This review explores the current landscape of pharmacogenetics, highlighting key genetic biomarkers and their role in transforming drug development, with a focus on regulatory frameworks, case studies of successful personalized treatments, and challenges in clinical integration.

Methods: This review was conducted by surveying literature from PubMed and Google Scholar using keywords such as "pharmacogenetics," "personalized medicine," "genetic biomarkers," "drug response," and "adverse drug reactions." The search covered articles from 2000 to 2024, focusing on peer-reviewed studies, clinical trials, and meta-analyses. Articles addressing regulatory considerations in the implementation of pharmacogenetic testing were also included. Data were synthesized to identify trends in pharmacogenetics research and its applications in personalized treatment.

Results: The review found that the identification of genetic biomarkers, such as CYP450 enzyme polymorphisms, plays a critical role in determining drug metabolism and response. Drugs like warfarin, clopidogrel, and statins were among the most cited examples where pharmacogenetic testing has enabled more precise dosing and reduced adverse effects. Case studies show significant improvements in patient outcomes when treatments are personalized based on genetic profiles. The clinical relevance of genes such as *CYP2C9*, *VKORC1*, *TPMT*, and *HLA-B* has been extensively documented in conditions ranging from cardiovascular disease to oncology. Moreover, regulatory bodies such as the FDA (Food and Drug Administration) have started incorporating

pharmacogenetic information into drug labels, reflecting the growing recognition of its value. However, challenges remain in widespread clinical implementation due to costs, accessibility, and the need for further education among healthcare providers.

Conclusion: Pharmacogenetics is rapidly reshaping both drug development and clinical practice, heralding a shift towards more individualized treatment paradigms. Genetic biomarkers provide invaluable insights that help tailor therapies to the unique genetic makeup of patients, reducing the risk of ADRs (adverse drug reactions) and improving therapeutic outcomes. While the clinical integration of pharmacogenetics faces hurdles, ongoing advancements in the field, coupled with evolving regulatory frameworks, hold promise for more widespread adoption of personalized medicine. Future research must focus on expanding genetic databases, increasing accessibility of testing, and further refining clinical guidelines to ensure the successful implementation of pharmacogenetics in routine healthcare.

Keywords: Pharmacogenetics, Personalized Medicine, Genetic Biomarkers, Adverse Drug Reactions, Drug Response

30.

pharmacogenetics in veterinary medicine (Review)

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Introduction: Pharmacogenetics focuses on how an individual's genotype or genetic makeup affects the pharmacokinetics and pharmacodynamics of therapeutic agents, whose knowledge can positively impact the drug development process. Pharmacogenetics studies specific genes that remarkably influence the response to a drug. Like humans, animal patients respond to drugs very differently. Changes in drug response often cause problems in treatment. One of the key factors contributing to variability in drug responses is genetic factors. Variety in drug response often causes problems in the treatment because it can lead to efficacy and sometimes serious adverse drug reactions. One of the important factors contributing to variability in drug responses is genetic factors. Therefore; pharmacogenetics can be helpful and effective. This article aims to review veterinary pharmacogenetic research.

Methods: To review studies focused on this topic, Google Scholar, PubMed, and Scopus databases with keywords "pharmacogenetics " and " veterinary medicine " were searched between 2010 and 2024 for related articles.

Results: polymorphisms in animal cause differences in response to drug therapy. For example, in some dogs (especially collies) ABCB1 gene polymorphism causes fatal reactions to many p-glycoprotein (p-gp) substrates. In dogs and cats with ABCB1 mutation p-gp substrates are at considerably higher concentrations. In cattle, there have been data on ABCG2 polymorphism that affects the treatment of mastitis and the residues of drugs in dairy milk. Genetic variation causes variation in drug absorption, distribution, metabolism, and excretion in each individual. these pharmacokinetic processes are effective in drug efficacy and toxicity. Investigations in this field have been conducted on antiparasitic drugs, anti-inflammatory drugs, opioids, and anesthetic agents. Most of these drugs' lethal toxicosis is associated with their administration. mutations in the genes regulating the drug metabolism.

Conclusion: pharmacogenetic research can help identify drug target polymorphisms and also discover new drug targets. using pharmacogenetics approaches to optimal drug selection and cause a significant increase in drug efficacy. however, more research and investigations are needed in pharmacogenetics in veterinary medicine.

Keywords: pharmacogenetics- veterinary- medicine

31.

Pharmacogenomic Predictors of Toxicity and Efficacy in Combined Targeted Therapy and Radiochemotherapy: A Systematic Review (Review)

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Introduction: Both combined targeted therapy and radiochemotherapy, as two advanced methods, are used to combat cancer. These methods that can be employed simultaneously or separately, have some toxic effects that can deter patients from completing the treatment. Moreover, the efficacy of these methods depends on various factors such as the type of cancer, genetic characteristics of the tumor and tumor drug resistance. Some genomic variants are considered as potential determinants in the radiochemotherapy response and the severity of side effects. Several pharmacogenomic studies were conducted in order to explore these variants, as potential biomarkers, for predicting developing adverse effects and the effectiveness of these methods. We, in this review, aimed to provide and discuss the important findings of pharmacogenomic research projects of both toxicity and effectiveness of radiochemotherapy and combined targeted therapy during cancer management.

Methods: This systematic review was performed by searching multiple databases, including PubMed, Web of Science, Google Scholar and Scopus up to August 2024. While several keywords, such as “Combined Targeted Therapy”, “Radiochemotherapy” and “Pharmacogenomics”, were used to find related articles. In the present review, the authors reassess and summarize recent studies including clinical data, clinical trials, basic research, meta-analyses and systematic reviews evaluating the predictive values of pharmacogenomic biomarkers of drug toxicity or efficacy in combined targeted therapy or

radiochemotherapy. Exclusion criteria comprised non-English studies, case reports, case series, and studies not focused on cancer or lacking relevant outcome data.

Results: This systematic review identified several important pharmacogenomic biomarkers that play a crucial role in toxicity and efficacy of cancer treatments involving combined targeted therapy and radiochemotherapy. Genetic variations in genes like TP53, EGFR, and CYP2D6 were often linked to common toxicities such as mucositis, hematologic toxicity, and radiation-induced dermatitis. Additionally, certain variants in ERCC1 and XRCC1 were consistently associated with better survival rates, particularly in colorectal and breast cancers, emphasizing the potential of customized treatment plans based on genetic profiles. The review also highlighted specific variants in BRCA1/2, ATM, and CHEK2, which were found to increase sensitivity to radiotherapy and the risk of severe side effects like myelosuppression and gastrointestinal damage. Moreover, mutations in the PI3K/AKT pathway contributed to drug resistance, specially mTOR inhibitors and HER2-targeted agents. Loss of function mutations in TP53 were associated with both reduced treatment effectiveness and increased late-onset side effects in lung and breast cancers, indicating that combination therapies including protective agents might offer better outcomes for these individuals.

Conclusion: Pharmacogenomic biomarkers show great promise for predicting the toxicity and efficacy of combined cancer therapies, suggesting their potential as valuable tools in personalized medicine. Incorporating genetic testing into routine clinical practice can optimize their effectiveness while minimizing side effects, guiding therapeutic decisions based on individual patient profiles. The variability in pharmacogenomic predictors across different tumor types emphasizes the need for tailored treatment approaches. Future research should focus on validating these biomarkers through prospective studies and expanding the understanding of how these genetic factors interact with specific tumors. This will enhance the precision of cancer therapies and ultimately improve patient outcomes.

Keywords: Pharmacogenomics, Combined Targeted Therapy, Radiochemotherapy, Genetic Variants, Biomarkers

32.

Pharmacogenomics and Artificial Intelligence: current application and the future integration of AI in pharmacogenomic aspect (Review)

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Introduction: The integration of artificial intelligence (AI) in healthcare, particularly in cancer treatment, is transforming the landscape of precision medicine. AI programs are designed to assist clinicians with diagnosis, treatment decisions, and outcome predictions, thereby enhancing patient care through improved data management and knowledge application. A significant aspect of this integration is pharmacogenomics, which studies how genetic variations influence drug responses, allowing for tailored treatment strategies. Pharmacogenomics plays a crucial role in identifying genetic markers that determine drug efficacy and toxicity. By incorporating genomic data into healthcare systems, AI can help predict patient responses to medications, facilitating early diagnosis and enabling pharmaceutical companies to target treatments more effectively. The identification of genomic markers, such as polymorphisms or gene expression patterns, is essential for predicting drug responses, and various methodologies, including Genome-Wide Association Studies, are employed to uncover these markers. Deep learning (DL) techniques are increasingly utilized in clinical oncology to analyze genomic, transcriptomic, and histopathological data. These tools serve as decision-support systems for healthcare professionals, enhancing their ability to diagnose and manage cancer patients. The goal is not to replace human expertise but to augment it, providing researchers and clinicians with powerful tools to improve patient outcomes. Recent research highlights the development of deep neural network models that can extract critical features from genetic mutations and gene expression, bridging the gap between preclinical findings and clinical applications. For instance, studies have shown that AI can effectively translate pharmacogenomic insights from cell line models to predict drug responses in actual tumors. Moreover, AI's potential extends to drug discovery and development, where it can analyze vast datasets to identify promising drug candidates and

optimize existing therapies. This capability not only accelerates the discovery of new treatments but also enhances the precision of existing ones, ultimately leading to better patient outcomes. In summary, the fusion of AI and pharmacogenomics is paving the way for a new era in cancer treatment, characterized by personalized medicine that considers individual genetic profiles to optimize therapeutic strategies and improve patient care.

Methods: A comprehensive database of clinical, in vivo, and in vitro studies published in English between 2004 and 2023 was identified through PubMed. Search terms included pharmacogenomics, pharmacogenetics, artificial intelligence, machine learning and deep learning.

Results: A PubMed search using specific terms yielded 515 results. Following a thorough review process, 35 publications were selected for inclusion in our research. The inclusion criteria required that the publications be relevant to the title and abstract. The exclusion process involved evaluating each publication based on predefined criteria and removing duplicates. Additionally, the inability to access the full text of some publications resulted in a final selection of 35 publications for our study.

Conclusion: The digitalization of patient records enables centralized data storage and offers opportunities for gathering additional information. This also adds complexity to education, prediction, and diagnosis of medical conditions. To manage this expansion, more advanced AI technologies such as Machine Learning and Deep Learning are necessary to help healthcare professionals extract valuable details from the data. Consequently, AI is anticipated to have a significant impact on healthcare information systems, potentially providing assistance or partially substituting for medical experts in the future. Integrating genomic data into a healthcare system based on knowledge is a method to fully leverage that information into improving patient care. As a result of multi-omics analysis becoming popular, multimodal learning techniques are anticipated to be more common in cancer diagnosis. Yet, the difficulties associated with obtaining multi-omics data from patient samples in a clinical setting, rather than from samples stored for research purposes, could hinder the practical application of these methods in clinical environments. In conclusion, the combination of pharmacogenomics and AI represents a promising frontier in cancer treatment. Continued advancements in this field will likely lead to more personalized, effective, and safer therapeutic options for cancer patients, ultimately contributing to better health outcomes and quality of life.

Keywords: pharmacogenomics, pharmacogenetics, artificial intelligence, machine learning, deep learning

33.

Potentially important pharmacogenetics findings in Myeloid Blast Crisis Chronic myeloid neoplasms (MBC-CMN), using Integrated Genomic Sequencing (Research Paper)

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Introduction: Chronic myeloid neoplasms (CMNs) are a group of disorders characterized by the overproduction of blood cells in the bone marrow, including red blood cells, white blood cells, and platelets. Chronic myeloid leukemia (CML) represents a well-studied model of leukemogenesis, though the molecular mechanisms driving progression to the blast crisis phase remain poorly understood. Primary myelofibrosis (PMF), another common CMN, can similarly progress to acute myeloid leukemia. Pharmacogenetics, the study of genetic factors influencing drug response, offers the potential to tailor treatment strategies for patients, especially those who are treatment-resistant or in advanced disease stages. This study focuses on identifying pharmacogenetically important variants in patients with myeloid blast crisis CMNs using integrated genomic sequencing approaches.

Methods: Four patients with CMNs in myeloid blast crisis were included in this study: three with CML and one with PMF. Whole exome sequencing (WES) and RNA sequencing (RNA-

seq) were performed on peripheral blood samples from the CML patients, while WES was conducted for the PMF patient and control samples. An in-house bioinformatics pipeline was used to evaluate cancer-related gene variants. The ACMG and AMP guidelines were applied to interpret potentially important findings (PIFs) and actionable pharmacogenetic findings (PAFs).

Results: In three CML patients, 16 potentially important findings (PIFs) were identified across the five known classes of leukemogenic genes, including signaling pathway components (ABL1, PIK3CB, PTPN11), transcription factors (GATA2, PHF6, WT1, IKZF1), epigenetic regulators (ASXL1), tumor suppressor and DNA repair genes (BRCA2, ATM, CHEK2), and spliceosome components (PRPF8). In patient 4, seven PIFs were found, including variants in signaling pathways (JAK2-V617F, CSF3R-S624L), transcription factors (CTCF-R339Q), epigenetic regulators (IDH1-R132C), tumor suppressor and DNA repair genes (CHEK2-DS12), and spliceosome components (SRSF2-P95H, SF3B1-A149A). Notably, the CTCF-R339Q variant, which is typically found in solid tumors, was identified for the first time in a myeloid malignancy. Pharmacogenetically, key variants included ABL1-Y272H and ABL1-F359V in patients 1 and 2, respectively, leading to resistance to imatinib. Patient 3 did not have pathogenic pharmacogenetic variants but had several diagnostic and prognostic variants. In patient 4, the JAK2-V617F and IDH1-R132C variants were actionable, with responsiveness to Ruxolitinib and Ivosidenib, respectively. No pathogenic variants related to pharmacokinetics of standard CML drugs were found in any of the patients, and no Class 1 or 2 evidence was available for pharmacokinetically significant findings.

Conclusion: Integrated genomic sequencing, particularly WES, offers significant potential to uncover pharmacogenetically important variants in myeloid blast crisis patients. These findings can be more comprehensive than custom NGS panels used in hematologic malignancies and may facilitate more personalized and targeted treatment strategies for patients with resistant or advanced disease. Additionally, these results contribute to the understanding of the molecular mechanisms driving blast phase development in CMNs, potentially improving patient outcomes through tailored therapies.

Keywords: pharmacogenetics, Myeloid Blast Crisis, Chronic myeloid neoplasms, Integrated Genomic Sequencing

34.

TaqMan Probe Real-Time PCR Assay for Quantifying BCL-2 Expression in Breast Cancer Tissues: Advancing Personalized Therapy **(Research Paper)**

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Introduction: Breast cancer (BC) represents approximately 25% of all malignancies in females, making it the most prevalent type of cancer worldwide. It is responsible for about 15% of all cancer-related deaths among women. The hallmarks of cancer, including angiogenesis, uncontrolled cell proliferation, and evasion of apoptosis, are present in all tumor cells, regardless of the underlying cause or type. Central to the regulation of apoptosis are the BCL-2 protein family members, where even minor alterations in the balance of these proteins can lead to either the inhibition or promotion of cell death. Approximately 75% of early-stage breast cancer cases display elevated BCL-2 levels, with 85% of these tumors exhibiting estrogen receptor (ER) positivity and 50% expressing HER-2. The variability in BCL-2 expression across different breast cancer subtypes underscores its potential as a biomarker for prognosis and treatment decisions. High BCL-2 expression is often associated with poor clinical outcomes in breast cancer patient, serving as a prognostic biomarker that indicating increased risk of tumor progression and lower survival rates. High levels of BCL-2 are also associated with resistance to traditional therapies, including chemotherapy. Consequently, BCL-2 inhibitors, such as BH3 mimetics, can be utilized to enhance the sensitivity of tumors to chemotherapy, thereby potentially improving treatment efficacy and overcoming resistance. Moreover, a reduction in BCL-2 levels during treatment may indicate effective therapeutic response, whereas stable or rising levels could suggest the presence of resistance. Currently, assessing BCL-2 expression levels can assist physicians in selecting optimal treatment strategies and pharmacological interventions such as BCL-2 protein inhibitors. BCL-2 protein inhibitors represent a novel therapeutic approach tailored to tumor characteristics, designed to

inhibit the anti-apoptotic functions of BCL-2 and counteract tumor cell resistance to apoptosis. BCL-2 inhibitors represent a promising avenue for enhancing therapeutic responses in breast cancer patients, especially those whose cancer cells exhibit resistance to standard therapies due to elevated BCL-2 levels. Consequently, understanding BCL-2 expression levels in various breast cancer subtypes can facilitate the development of personalized therapeutic strategies by identifying patients who may benefit from therapies targeting apoptotic pathways. In this study, we developed a robust method for quantifying BCL-2 gene expression levels in formalin-fixed paraffin-embedded (FFPE) breast cancer tissues.

Methods: This study utilized one hundred untreated early-stage invasive breast cancer samples representing various subtypes, alongside twelve marginal non-tumor breast tissue samples which were all pathologically diagnosed and preserved in formalin-fixed paraffin-embedded (FFPE) format. Specific primers and a TaqMan probe for the BCL-2 target gene, as well as for beta-actin as the internal control gene, were designed using Allel ID software, and their efficiencies were determined using standard curves. Following RNA extraction from the FFPE samples, a one-step TaqMan probe RT-qPCR assay was conducted. The relative fold change (RFC) of BCL-2 expression in each sample was calculated using the Livak formula. An RFC greater than 2 was classified as high expression, while an RFC of 2 or lower indicated normal expression. The differences in mean BCL-2 RFC between tumor and normal samples were assessed using the Mann-Whitney test.

Results: The developed TaqMan probe Real-Time PCR assay demonstrated acceptable efficiency for assessing BCL-2 gene expression levels. The results revealed that high expression of BCL-2 was observed in 49 out of 100 (49%) tumor samples and in 3 out of 12 (25%) normal samples. While BCL-2 expression was found to be higher in tumor tissues compared to normal tissues, the difference between the two groups was not statistically significant ($p > 0.05$).

Conclusion: As the expression levels of BCL-2 in breast cancer have several potential implications for prognosis, treatment resistance, and therapeutic strategies, highlighting the need for a quantitative method to assess its expression in breast cancer tissues. Our developed assay is capable of accurately measuring BCL-2 gene expression levels in both tumor and non-tumor samples. Consequently, this method has the potential to be implemented in clinical laboratories for the evaluation of breast cancer patients.

Keywords: Breast cancer BCL-2 TaqMan Probe Real-Time PCR BCL-2 protein inhibitor

35.

The effect of vanillic acid on the expression of osteocalcin and osteopentin genes in rat bone marrow mesenchymal stem cells (Review)

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Introduction: Bone tissue engineering is a progressive approach in bone tissue repair in medical science. Induction of osteogenic differentiation is a very important process for bone repair. The aim of this study was to investigate the effect of vanillic acid on the expression level of osteocalcin and osteopentin genes in the differentiation of rat bone marrow mesenchymal stem cells.

Methods: For this purpose, mesenchymal stem cells were isolated from the bone marrow of Wistar rats and identified with specific antibodies against surface markers CD45, CD44 and CD31. Mesenchymal stem cells of rat bone marrow were treated with different concentrations of vanillic acid. Cytotoxicity was evaluated by MTT method after 48 hours. The differentiation effects of vanillic acid on stem cells to osteoblasts were investigated by alizarin red staining methods and Real Time-PCR for specific markers of osteoblasts, osteocalcin and osteopentin.

Results: The results of the treatment of the cells showed that vanillic acid had no significant effect on the viability of these cells up to a concentration of less than 0.5 µM; The concentration that led to the death of 50% of the cells was equal to 10 µM, and higher concentrations led to the death of cells in the first hours of the treatment, therefore, the concentrations of 0.5, 1 and 2 µM were chosen to investigate the advancement of cell differentiation. Alizarin staining showed rejection. Vanillic acid led to bone differentiation

on day 21 in a dose-dependent manner. The results of Real Time-PCR showed that the gene expression of osteocalcin and osteopentin increased significantly in the treatment groups.

Conclusion: The results of this study showed that vanillic acid increases osteogenic differentiation in mesenchymal stem cells derived from the bone marrow of Wistar rats.

Keywords: vanillic acid, rat, osteopentin, mesenchymal stem cells, osteocalcin

36.

The effect of vanillic acid on the level of alkaline phosphatase in rat bone marrow mesenchymal stem cells (Review)

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Introduction: Studies on stem cells have created a new opportunity to treat some bone disorders, including defects in bone repair. The aim of the present study was to investigate the effect of vanillic acid on the level of alkaline phosphatase in the differentiation of rat bone marrow mesenchymal stem cells.

Methods: For this purpose, mesenchymal stem cells were isolated from the bone marrow of Wistar rats and identified with specific antibodies against surface markers CD45, CD44 and CD31. Mesenchymal stem cells of rat bone marrow were treated with different concentrations of vanillic acid. Cytotoxicity was evaluated by MTT method after 48 hours. Alkaline phosphatase level was measured using the corresponding commercial kit.

Results: The results of the treatment of the cells showed that vanillic acid had no significant effect on the viability of these cells up to a concentration of less than 0.5 µM; The concentration that led to the death of 50% of the cells was equal to 10 µM, and higher concentrations led to the death of cells in the first hours of the treatment, therefore, the concentrations of 0.5, 1 and 2 µM were chosen to investigate the advancement of cell differentiation. Alizarin staining showed rejection. Vanillic acid led to bone differentiation on day 21 in a dose-dependent manner, and alkaline phosphatase activity was higher in the treatment groups on day 10 than in the control group.

Conclusion: The results of this study showed that vanillic acid increases osteogenic differentiation in mesenchymal stem cells derived from the bone marrow of Wistar rats.

Keywords: vanillic acid, rat, alkaline phosphatase, mesenchymal stem cells

37.

The impact of antisense oligonucleotides in duchenne muscular dystrophy as a personal medicine approach (Review)

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Introduction: Duchenne muscular dystrophy (DMD) is a severe and progressive disease characterized by muscle degeneration. The initial manifestations of the disease typically include challenges in ascending stairs, a waddling gait, and a propensity for frequent falls, with these symptoms generally emerging between the ages of 2 and 3 years. DMD is attributed to mutations in the DMD gene, which result in the disruption of the open-reading frame, leading to a deficiency in dystrophin protein and ongoing degeneration of muscle fibers. In contrast, Becker muscular dystrophy (BMD) is generally associated with a milder clinical presentation and an extended lifespan. In BMD, mutations in the same DMD gene preserve the open-reading frame, resulting in an internally truncated dystrophin protein that retains partial to substantial functionality. A promising therapeutic approach for restoring dystrophin expression involves the conversion of a DMD transcript into a BMD transcript through the application of antisense oligonucleotides (AONs), which facilitate specific exon skipping during the splicing of pre-messenger RNA (pre-mRNA). This strategy holds the potential for delivering a personalized therapy.

Methods: In this review article, the necessary data were collected from citation and keyword databases such as PubMed, ScienceDirect, and Google Scholar. The studies reviewed focus on the effects of antisense oligonucleotides in muscular dystrophy.

Results: Numerous antisense oligonucleotide (AON) drug candidates are currently under development for Duchenne muscular dystrophy (DMD). These AONs are single-stranded oligonucleotides that have been chemically modified to enhance their resistance to nucleases, thereby protecting the target RNA from RNaseH-mediated degradation and promoting stable binding to the target RNA. The mechanism of action of an AON is characterized by its highly sequence-specific binding to partially open pre-mRNA structures within the targeted exon, which interferes with splicing regulatory factors and/or structures. This interference facilitates exon skipping, which aims to rectify the open

reading frame of the mutated DMD mRNA transcript; in approximately 70% of cases, the mutation involves the deletion of one or more exons. This process enables the production of a novel Becker muscular dystrophy (BMD)-like dystrophin protein that, despite an internal truncation, retains the essential N- and C-terminal domains necessary for its structural and signaling functions at the membranes of muscle fibers. Dystrophin is a critical component of the dystrophin-associated protein complex, with its terminal domains interacting with actin, neuronal nitric oxide synthase, β-dystroglycan, syntrophins, and dystrobrevin. In the absence of dystrophin, the integrity of this complex is compromised, resulting in increased membrane permeability, exercise-induced damage, detrimental calcium influx, and ultimately, progressive degeneration of muscle fibers and severe muscle pathology. The therapeutic objective of AON-mediated dystrophin expression is to restore the dystrophin-associated protein complex at the membrane, thereby delaying or ideally halting the progressive degeneration of muscle fibers and maintaining or enhancing muscle performance in individuals with DMD. Currently, two AON drug candidates are in clinical development for DMD: drisapersen, a 20-mer 2OMePS AON, which is undergoing phase III trials, and eteplirsen, a 30-mer PMO AON, which is in phase II trials. The target sequences within exon 51 of both candidates are highly similar, and both have demonstrated efficacy in skipping exon 51 and increasing dystrophin expression in muscle tissue from patients with relevant mutations following local and systemic administration. The primary molecular outcome measure in clinical studies involving drisapersen and eteplirsen has been the detection of novel or increased dystrophin expression in muscle biopsies, providing evidence of the targeted pharmacodynamic mechanism. Additionally, other molecular biomarkers, such as matrix metalloproteinase-9 and specific microRNAs present in serum, are currently being evaluated to assess the therapeutic effects of drug treatment in patients with DMD.

Conclusion: AON-induced exon-skipping therapy is emerging as a form of personalized medicine for Duchenne Muscular Dystrophy (DMD). Currently, two chemically distinct drug candidates, drisapersen and eteplirsen, are in clinical development. Each candidate has unique physicochemical properties that present both advantages and disadvantages regarding safety and pharmacokinetics. Both agents have demonstrated the ability to specifically induce exon 51 skipping, thereby enhancing muscle dystrophin expression in a specific mutational subgroup of DMD patients. The integration of these therapeutic strategies is expected to facilitate the advancement of personalized treatment options for an expanding patient population.

Keywords: Muscular Dystrophy Duchenne, Naturopathy, Genes.

38.

Therapeutic Role of Palbociclib as a Cyclin-Dependent Kinase Inhibitor in Triple-Negative Breast Cancer (Review)

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Introduction: Breast cancer (BC) is the most commonly diagnosed cancer among women and the second leading cause of cancer-related mortality worldwide. Based on molecular markers, including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), BC is categorized into three major subtypes: hormone receptor (HR)-positive, HER2-positive, and triple-negative breast cancer (TNBC). TNBC accounts for approximately 15% to 20% of all breast carcinomas. Dysregulation of cellular proliferation is a feature of all human cancers, and the maintenance of abnormal proliferative signals is a key marker for cancer. The main function of inhibitors is to block cell cycle and inhibit cell proliferation by inhibiting the Cyclin-dependent kinase (CDK) enzyme activity. In this pathway, cyclin D1 forms an activating complex with CDK 4 and CDK6 that go on to phosphorylate the retinoblastoma protein (Rb). Palbociclib, a selective CDK1, exerts its killing effect on tumor cells rather than on normal cells.

Methods: In the current study, keywords including Palbociclib, Cyclin-Dependent Kinase Inhibitor, and Triple-Negative Breast Cancer were reviewed from the list of Mesh and other credible websites including PubMed, Science Direct and Google Scholar and the data was organized. The searches comprised all published paper from 2010 to 2023. All of full text was considered and the papers manifested as only abstract was excluded. The full papers selected that specific role of Therapeutic Role of Palbociclib as a Cyclin-Dependent Kinase Inhibitor in Triple-Negative Breast Cancer only. Totally 50 papers were selected and studied in this review.

Results: Evidences showed inhibition of CDK4 decreased the percentage of chemotherapy-resistant cells and breast cancer stem cells in TNBC. Several preclinical studies have evaluated palbociclib, a CDK4/6 inhibitor, together with a second-generation dual mTOR kinase inhibitor MLN0128, has demonstrated a cooperative suppressed tumor growth effect in retinoblastoma protein expressing TNBC patient-derived tumor xenograft (PDX) tumors. Moreover CDK4/6 inhibitors can inhibit Rb phosphorylation to prevent the proliferation of tumor cells. One study showed palbociclib to significantly reduce the cell proliferation rate of several aggressive basal-like TNBC cell lines (SUM159, MDA-MB231, and SCP2). Other study reavelant that blocking CDK4 kinase activity using palbociclib reduced breast cancer stem cells numbers and their self-renewal capacity in TNBCs. In vivo trials, palbociclib caused a sustained suppression of tumor Rb phosphorylation, and exhibited significant antitumor efficacy that arrested Rb-positive tumors exclusively in G1, including Rb-positive breast cancer. In addition, synergistic activity between cell cycle and anti-estrogen therapies had been observed in breast cancer cell lines. In the following tumor cell lines, such as MDA-MB-231 and more significant levels in MCF-7 cells, Rb deficiency produced a very significant growth advantage in the presence of palbociclib, which had been observed to increase levels of E2F-target genes cyclins A and E.

Conclusion: Inhibition of CDKs inactivates the G1 transcription factor and E2F during. Because the CDK4/6 plays an important role in the development and progression of breast cancer, CDK4/6 inhibitors have revolutionized the treatment of metastatic breast cancer. In combination with endocrine therapies, CDK4/6 inhibitors have become a new standard of care for patients with ER-positive breast cancer.

Keywords: Palbociclib, Cyclin-Dependent Kinase Inhibitor, Triple-Negative Breast Cancer

39.

Three-Brains Supplement (Review)

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Introduction: We are all aware of the big brain above our shoulders (did you know our brain has over 80 billion neurons firing up to 17.2 trillion synapses every second?!), the “second brain”, a fascinating neural center located in our gut, and amazingly, over 500 million neurons are located in this area of our body. According to numerous studies over the past twenty years, the gut sends about 400 more messages to the brain, than the brain does to the gut and, almost 70% of our body’s immune system and 95% of serotonin is actually found in the gut. And, finally our “third brain” is heart where houses more than 39 million neurons,The heart sends as many messages to the head brain as it receives.

Methods: Through Monitoring Gut-Brain Axis (Vagus Nerve) and Heart-Brain Axis researchers found that many mental health disorders(such as:Alzheimer, ADHD, Panic, Autism, Bipolar disorders, Mood disorders, Memory loss, Sleep disorders, Depression), brain cancer and Psychophysiological problems are related to our three-brains health.

Results: Gut host more than 95% of our serotonin and 70% of our immune system of our body and through a balanced gut microbiome (avoiding dysbiosis) we can prevent all mental disorders and many cancers(by boosting our immune system) and also keeping a coherent and sinus heart rhythm pattern(bpm) we can boost our cardiac health which has critical roles in preventing cancer and generating stress hormones.

Conclusion: in order to prevent many mental disorders and cancer problems these specific otc supplements can boost three-brains public health: 1-Supplement Name: Three-Brains:Memory Boost •Enhances memory and cognitive function •Promotes mental sharpness and concentration •Supports healthy blood flow and peripheral circulation to the brain •Provides key antioxidants to protect the brain from free radical damage 2-Supplement Name: Three-Brains:Brilliant Mind •Supports brain function and cardiovascular health •Helps build and protect healthy brain cells •Boosts cognitive function •Supports mood, memory, and brain power •Enhances focus and mental stamina 3-Supplement Name: Three-Brains:The Gut-Brain Strain •Contains whole cell BB536 Bifidobacterium longum •10 billion cfu per vegetarian capsule •No refrigeration required,

ideal for daily use and for travel •Helps support gastrointestinal health 4-Supplement Name: Three-Brains:Cloud Nine •Promotes healthy mood balance •Encourages mental clarity while maintaining an overall feeling of relaxation •Helps address symptoms associated with workplace stress •Supports healthy sleep patterns •Enteric coating minimizes gastric discomfort and optimizes absorption 5-Supplement Name: Three-Brains:Brain Defence •Helps reduce the biomarkers of stress, cortisol, and C-reactive protein levels •Reduces symptoms of stress including fatigue, sleeplessness, irritability, and inability to concentrate •Helps relieve inflammatory conditions of the gastrointestinal tract •Acts as a calmative and helps ease mild digestive disturbances 6-Supplement Name: Three-Brains:Restful Sleep •Promotes healthy sleep •Helps relieve insomnia, nervousness, and restlessness caused by mental stress •Enhances cognitive health through adequate sleep •Acts as a natural, non-habit-forming mild sleep aid •Provides an analgesic action

Keywords: 1-Three-Brains public Health 2-Optimal Mental Health 3-Inner Health 4-Naturopathic medicine

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