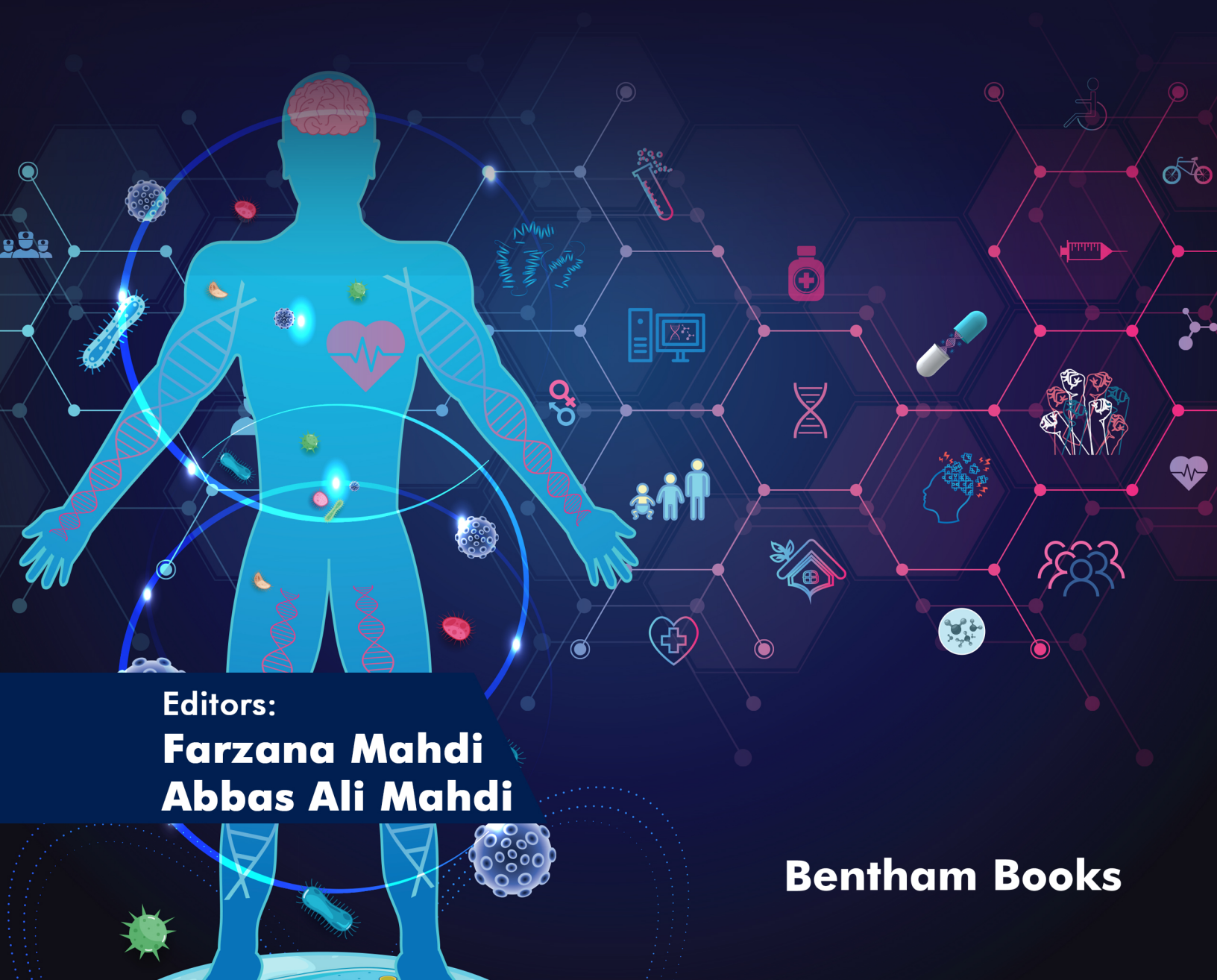
PRECISION MEDICINE AND HUMAN HEALTH



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Precision Medicine and Human Health

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FOREWORD

Precision Medicine seems to be a new adage in the world of Medical Science. However, a careful analysis of human civilization from across the globe suggests that almost every civilization has been health-conscious and requires medical attention. Historically, the most reliable and single source of all the medicines were plants, which were carefully selected, propagated and used in different forms. American Indians in the USA used plant-based medicines for relieving pain. Approximately, 40% of all modern drugs are plant-based. Among the 252 essential chemicals designated by the World Health Organization, 11.1% are sourced from plants, while 8.7% originate from animals. Currently, the United States employs approximately 19,000 FDA-approved prescription drugs, with several of them having their origins rooted in the animal kingdom. This suggests that almost 50% of all the drugs are either from plants or animals and perhaps many more may be discovered in due course of time.

The concept of precision medicine has already gained momentum over the world. Simultaneously, medical science has made remarkable progress using the data from the field of Omics, cell and tissue engineering, and gene therapy. The progress and success with molecular taxonomy and tissue expressions in genetic variants have brought confidence in precision diagnosis, efficient prognosis, prevention and effective treatment. We do not have a cure for all the diseases, but are on the right track of passing on the benefits of new knowledge and technology to the patients and their families.

The book **Precision Medicine** contains well organized 20 chapters covering a wide range sub-disciplines. An overview of several important topics in addition to a critical appraisal on precision medicine has been provided. This initial attempt in the country shall pave the way for more such books on specialized sub-disciplines in future. Advances in today's medical sciences has provided a scope for new drug molecules, next generation vaccines, stem cell and gene therapy, robotic surgery and other high-end medical intervention. A careful analysis of drug molecules and finding the drug target in the body without any side effects are the areas that still warrant relentless research and innovation.

The present book on precision medicine is the brain child of Farzana Mahdi and Abbas Ali Mahdi, who have shown exemplary courage, determination and concern to provide the best possible care to the patients. Era University has a well-known and highly respected medical college. During the upsurge of Covid-19, more than 3200 patients were cured and the success rate was 98.5%. This is an achievement that has been duly acknowledged by the honourable Governor of Uttar Pradesh.

Farzana Mahdi and Abbas Ali Mahdi are hard core academicians, distinguished biochemists, capable administrators and great mentors. Both believe in quality research and transparent dealing with excellent academic records to their credit; publishing papers in high impact factor journals. They are well connected with the global body of scientists and keep an eye on the emerging advancements in the area of biomedical research. Farzana Mahdi has successfully helmed the Era University as a Vice Chancellor during the pandemic of Covid-19, and Abbas Ali Mahdi is the current Vice Chancellor of the university.

It is gratifying to mention that all the chapters in the book, one way or the other are related to Precision Medicine. I am very hopeful that this book would fuel the thoughts of academicians, clinicians and researchers alike transgressing all the sub-disciplines of biomedical research eventually culminating into a better human health care system.

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PREFACE

Writing a book on an upcoming topic like precision or personalized medicine (PM) in the context of human health is both rewarding as well as challenging. The origin of such a book is related to an International Symposium that was held on June 24, 2022, at the Department of Molecular and Personalized Medicine, Era University, Lucknow.

During the course of extensive deliberation, it became clear that we need in-depth additional information, not only regarding the diseases and their causative factors, but also about the overall background of the patients encompassing lifestyle, nutrition, age, comorbidity, previous history of the disease, demography, epidemiology, living condition, environmental, social and economic status, gender, marital status, physical and physiological attributes, mutational landscapes of the diseased gene, genetic background, upbringing, region, religion, faith, culture, tradition, familial dis/harmony, marital incompatibilities and overall awareness towards a disciplined and healthy life. Longevity has always been an enticing proposition for mankind since the dawn of civilization. The quest to live forever is still cherished in almost all the societies of the world. The dollar wellness industry thrives on this psyche and that would continue to grow because the demand for such products never seems to be ending.

As the situation stands now, much of the medical issues may be circumvented employing the approach of molecular and personalized medicine. This will require additional biomedical research, keeping in view the patient's background information and careful titration of the prescribed medicaments. Perhaps, many medicines may not be needed and only a few ones would be enough since the diagnosis will be based on the hard core molecular and "ics" data facilitating the physicians and clinicians to make the correct decision at the right time. With concerted efforts on this line, precision medicine will not only see the light of day but will provide health to all even in the fall flung areas of the country harvesting the power of digitalization, telecommunication and Artificial Intelligence. It is envisaged that the proposed health card (*made at the time of birth as proposed in the first chapter*) of the patient will carry all the relevant background data in the form of a QR code only to be accessed by authorized clinicians and physicians across the globe. This simple but reliable trick would provide past medical records instantly and do away with many social evils, false claims and impersonation augmenting much-needed transparency in the human health care system.

The present narrative embodied in this book is a biological and biomedical symphony based on research, innovation, experience, and detailed deliberation emerging from the conference, symposium and scientific meetings all culminating in the PM. This encompasses different aspects of life that we come across rather routinely not realizing that many of these events affect our health. Of course, the vicissitudes of life also prove to be blessings in disguise, making a person, careful, strong and optimistic. In conclusion, the growing consensus is that one should be aware of the wide conundrum of health issues and follow the path of a disciplined life. This may not guarantee health, happiness, overall wellness and much-desired longevity. Nonetheless, it would drastically reduce the disease burden and occurrence of negative events in life that in turn would percolate down the ladder leading to robust health. Finally, if we seek peace in life, then we must start believing that peace begins from the self which in turn can be spread in the family, society, state, country, continents, and finally across the world. Needless to mention, a peaceful and relaxed person is a lot less prone to diseases and infection than the one who has an agitated mind. Thus, those of us who preach peace but do not practice will not be able to see the desired results.

This book, **Precision Medicine and Human Health**, has a total of twenty chapters spread

across the spectrum of disciplines. The book includes some of the areas that were less represented earlier in the medical literature. The first chapter dealing with precision medicine provides a critical appraisal encompassing all the key areas that relate to human healthcare systems. For example, emotions, social interactions and life experiences culminating into overall happiness play an important role in the life of a person. Thus, an emotionally strong and happy person is usually healthy. Since everybody, whether diseased or healthy, has a unique genome, this uniqueness must be utilized in selecting the drug molecule, dose, and its long-term effects. Healing and cure strategies should address the root cause of the problem and not the symptoms only to provide short-term relief. Similarly, repurposing of the drug should be explored to cover a much wider number of diseases, cutting down the cost of the development of medicine. Finally, clinicians and doctors should be sensitized to the concept of precision medicine and its sub-disciplines. The medical field, besides being a deep, very deep science is also an art starting from how to deal with diverse types of patients of different backgrounds and educate them by instilling a sense of confidence and then to cure the disease. Clinical psychologists and genetic counsellors particularly in a hospital set up can play their roles too to achieve this goal. Healing requires a combination of medical treatment and a positive environment to achieve faster recovery and long-term benefits for patients.

The second chapter deals with the significance of epigenetics, gene function and putative change or modification in the DNA's sequence. Genes are prone to changes that are brought about by a number of mechanisms encompassing gene conversion, exon/intron reshuffling, alteration in the mutational landscape, and copy number variation. In addition, repeat DNA sequences tend to expand or shrink changing the topology of adjacent genes resulting in their altered functions. Alterations in gene activity, especially those that are brought on by epigenetic errors, frequently cause genetic diseases. Researchers are particularly interested in how epigenetic modifications and mistakes affect gene function, protein synthesis, and human health. It is envisaged that a deeper understanding of the epigenetic modification of the genome or its aberration would augment our understanding of the function of the normal and diseased human genomes.

The third chapter is on Hepatocellular carcinoma (HCC) which is the most common malignancy and is the third leading cause of cancer-related death worldwide. Most HCC patients are diagnosed at the middle or advanced stage, thereby losing surgical resection opportunities. Due to disease heterogeneity, standard treatments such as chemotherapy or radiation are effective only in some patients. Tumors can have underlying genetic differences and may express different proteins across the spectrum of patients. At this juncture, how the PM can provide a better alternative is indeed thought-provoking. Precision medicine relies on matching a patient's molecular profile to an effective and targeted therapy. In clinical practice, the shift from stage oriented to a therapeutic-oriented approach is necessary to direct the selection of HCC treatment towards the potentially most effective option on an individual basis. The clinical application of discoveries in tumor biology holds the promise to improve the treatment outcomes for cancer patients on a large scale. This chapter discusses precision medicine for HCC management and highlights the completed or ongoing clinical trials of novel therapies for treating patients with advanced HCC.

The fifth and sixth chapters are devoted to protein biochemistry encompassing its various forms under varying physical and physiological conditions including folding and misfolding resulting in a wide range of debilitating disorders. These diseases are characterized by the deposition of insoluble plaques consisting of amyloid fibrils rich in β-sheet structures. Many natural proteins form amyloid fibrils or aggregated disease-specific proteins causing human diseases. The role of amyloids and their mechanism of formation, as well as the methods for detecting various types of aggregates, has been examined and discussed. Despite visible

progress in the field of biochemistry, we still have questions regarding the aggregation and co-aggregation of protein molecules. Proteins are functional in their three-dimensional forms. The free amino group of the protein in the body when interacting with the carbonyl group of the reducing sugar follows the Maillard reaction to produce hazardous by-products, referred to as advanced glycation end products (AGEs). Studies have shown different aggregation pathways leading to fibril formation. Thus, the development of large number of therapeutic proteins is envisaged to complement the requirement of precision medicine.

Chapter seven relates to Helicobacter pylori in the human gut biomes playing an important role in our health and wellbeing. *Helicobacter pylori* (*H. pylori*) is a Gram-negative, microaerophilic, and slow-growing bacteria, colonized in more than half of the world's population. This bacterium has co-evolved and migrated with humans from East Africa, the first birthplace of *Homo sapience*, about 58,000 thousand years ago. Special properties of *H. pylori*, like urease, helical shape, and motile flagella, make it a successful resident in the human stomach under extreme stress conditions. The presence or absence of *H. pylori* in the stomach has a good and/or bad relationship with humans depending on host genetic susceptibility, immune responses, and environmental conditions. Usually, *H. pylori*-infected people are asymptomatic; however, about 20% of infected people develop gastric diseases like peptic ulcer (10-15%), gastric adenocarcinoma (1-3%) and mucosa-associated lymphoid tissue (MALT) lymphoma (1%) that are common to elder people. On the other hand, people who have no *H. pylori* infection are more susceptible to other diseases like gastric esophageal disease (GERD), oesophagus carcinoma, diabetes mellitus, and asthma. Clinical manifestations in the infected individuals greatly vary geographically due to the high level of genetic diversity in the bacterial genome and several virulence factors. Eradication of *H. pylori via* antibiotics and proton pump inhibitors is the complete cure for the disease. However, an increase in resistance against antibiotics and lack of effective vaccines are still some challenges to combat the infection. In this context, the effective precision medicine would be the vaccine. This chapter provides an insight into host-pathogen interactions, persistence, prevalence, and pathogenesis of this bacterium in the context of human health and precision medicine.

Chapter eight is devoted to breast cancer which is most common among females. Current data shows more than 1 million women worldwide are affected about ~400 000 patients die every year. Partial success has been achieved by mammography and adjuvant treatment. However, incidences and mortality both are increasing. Of the several sub-categories, one is triple-negative breast cancer (TNBC). This is defined by a lack of expression of oestrogen and progesterone receptors and human epidermal growth factor receptor 2 (HER-2). Several approaches have been undertaken both for speedy and accurate diagnosis and precise treatment. In this context, the precision medicine approach may be of great relevance in ameliorating the suffering of the patients from the menace of breast cancer. However, it may be noted that several drug molecules and strategies need to be developed to cover different stages of breast cancer before a respite may be achieved.

Chapter nine focuses on depression, a pervasive, arduous psychological condition with profound neurological ramifications. Many individuals suffering from depression undertake a recurring or persistent therapy that correlates to a decline in cognitive processing. The underpinning of the exact aetiology and pathogenesis of melancholy is probably the outcome of a variety of mechanisms. These include physiological, behavioural, and socioeconomic variables, all playing their roles. Multiple therapies, medications and medical interventions are employed but depression has yet to find its match in the context of precision medicine. One option is to search for a more effective drug molecule befitting to all the symptoms of depression. The other approach is to find a cure from herbal formulation. In any event, both

approaches need additional research, innovation, and development for ultimate effective interventions.

One of the aspects of precision medicine is to make use of artificial intelligence (AI) which is discussed in chapter ten. The digital ecosystem of AI will have global outreach evoking expert opinion from clinicians in serious conditions of the patients. The AI is envisaged to be the game changer, particularly in case of cancer, which is described as a heterogeneous cellular conglomeration comprising many dissimilar subtypes. The AI involves the use of deep learning which is a part of artificial intelligence (AI) that permits an algorithm to learn itself via the knowledge acquired from a large set of instances that determine the predicted outcomes. The use of AI is continuously growing for the prognosis of various diseases enabling pathologists to accurately diagnose various diseases, and classify them into grades and subtypes keeping in view the process of invasion, mutations, and metastases. AI also contributes to the area of precision medicine to overcome drug resistance and relapse of diseases. This chapter outlines various illustrations for the uses of AI in oncology research, together with circumstances in which deep learning has adequately addressed the difficulties that were earlier assumed to be unsolvable. AI also focuses on resources and datasets that can assist in developing interconnections with AI's intricacies in disease investigation. The expansion of advanced computational methodologies and AI are envisaged to facilitate interactomes studies and help significantly gain insights into the field of oncology fulfilling the concept of personalized medicine.

Chapter eleven relates to Fibromyalgia Syndrome (FMS) which has attracted much attention, especially with the gene discovery pushing towards a newer understanding of disease biology. Potential candidate genes found to be associated with fibromyalgia are SLC64A4, TRPV2, MYT1L, and NRXN3. Fibromyalgia is a widespread musculoskeletal pain disorder accompanied by fatigue, sleep, memory and mood issues. FMS amplifies painful sensations by affecting the way the brain and spinal cord process painful and non-painful signals. Some targeted treatments are now available improving the FMS patients on a short-term basis. This chapter highlights the key breakthroughs focusing on technologies that touch upon personalized or precision medicine in FMS. If FMS is related to brain and spinal cord functioning, work on this line using animal models would prove to be a rewarding proposition as the use of human patients would pose a logistic problem.

The time code is expressed in the form of circadian clocks composed of many transcription, co-activator, and co-repressor factors. These aspects have been covered in Chapter twelve. The transcription-translation feedback loops generated collectively by these factors regulate daily ~24-hour rhythms in physiology, metabolism, and behaviour across divergent phyla. Genome-wide studies reflect that chronic disruption of circadian rhythms provides a plinth for the occurrence and progression of multiple diseases across our lifespan. Increasing epidemiological and experimental evidences are confirming that circadian clocks are compromised in cancer and several other diseases. Altered expressions of circadian clock components are likely to be associated with the onset and progression of cancer and cardiovascular diseases. The concept of targeting circadian clocks at the molecular level is rapidly evolving and opening a new therapeutic window in cancer. Here, we discuss the approaches and recent advancements that have been made for the identification and development of clock-modulating small molecules bearing drug-like properties for the therapeutic management of cancer. Thus, this chapter is envisaged to augment the concepts of precision medicine in general and circadian-related system anomalies in particular.

Of the several diseases that have become the cause of concern, Multiple Sclerosis (Mus) is one that is an autoimmune inflammatory disease affecting roughly 2.8 million people

worldwide which is covered in Chapter thirteen. Mus is a highly heterogeneous disease in term of course, clinical symptoms and drug response. The exact pathogenesis and aetiology of this disease remain unknown. The lack of successful treatment can be explained by the heterogeneous nature of MuS with patients exhibiting widely disparate clinical features and progression pattern resulting in phenotypic heterogeneity. With the introduction of *Omics* approaches, personalized medicine has gained momentum revealing hitherto unseen elements of illness causation, initiation and progression. This chapter highlights the potential role of genomics, transcriptomics, proteomics and metabolomics in MuS for possible identification of biomarkers facilitating and augmenting the concept of precision medicine.

The chapter fourteen deals with the clinical challenge related to metastasis of cancer cells to distant organs forming a secondary tumor. Many cancers are prone to metastasis due to epithelial-mesenchymal transition (EMT), which confers motility and invasive properties to the tumor. EMT is also responsible to chemotherapy resistance and facilitates metastasis by generating cancer stem cells (CSCs). Therefore, the EMT may be an important candidate for therapeutic potential for personalized cancer treatment. This chapter discusses approaches for the design of EMT-based personalized therapies in cancer, summarize the evidence for some of the proposed EMT targets, and review the potential advantages and limitations of each approach.

Yet another rather common cancer is the oral cancer covered in Chapter fifteen. Oral cancer is a type of head and neck cancer mainly caused by poor oral hygiene, alcohol and tobacco abuse, and promotes HPV infection. The conventional approaches for the treatment of oral cancer often rely on surgery, chemotherapy and/or radiotherapy. Now, the precision medicine, with the advent of newer diagnostic techniques, enables healthcare professionals to diagnose the disease early and treat the patient with appropriate medicines with the optimized dose. Targeting specific proteins, such as EGFR and HER2 to suppress tumor growth or make cancer cells more susceptible to the immune system's combat mechanism is also discussed. In addition, this chapter has an overview of various drugs that are being used to treat patients who are positive for HER2 and EGFR. Various challenges and limitations of precision medicine and future prospects for research in this area are highlighted.

The chapter sixteen and seventeen are devoted to herbal medicine. The treatment using plant based medicaments has been prevalent in almost every civilization such as Sumerian, Maya, Red Indian of USA, Greek, Roman and Egyptian for the past seven thousand years. India is blessed with rich medicinal plant biodiversity. Food harnessing and garnishing have become standard practice to enhance the taste and look. Some of the herbs are used directly as food whereas others are used as food additives. Simultaneously, a large number of Phytoconstituents have been characterized for their medicinal properties. In these chapters, Phytoconstituents used for herbal formulation have been discussed with their detailed properties. It is envisaged that such information would be of great use to ameliorate the diseases ensuring better health complementing the concept of personalized medicine.

The Chapter eighteen deals with the human habitat where there is paucity of oxygen (hypoxia). Hypoxia is a condition wherein an organism or a cell of an organ does not receive adequate levels of oxygen to carry out normal life processes. The ability to sense oxygen level and respond appropriately is termed "oxygen sensing" that is used to describe the biological effects of hypoxia. Hypoxia is involved with multiple diseases from high altitude pulmonary oedema to cancer. The oxygen sensing molecular networks is crucial for survival and has a notable impact on human health systems. A very important niche of hypoxia is the study of environmental stressor also called high-altitude hypoxia. High-altitude hypoxia holds multiple molecular similarities with diabetes, cancer, obesity and other diseases like COPD. In

addition, unregulated exposure to hypobaric hypoxia is known to directly cause high altitude illnesses like HAPE/HACE. Acclimatization with the high altitude is known to prevent the occurrence of high-altitude illnesses. This chapter highlights the occurrence of hypobaric hypoxia, its socio-economic impact, molecular underpinnings and correlation with inflammation, cancer, diabetes, obesity and possible therapeutic approaches to these diseases.

Chapter nineteen discusses the advances in nanotechnology and its therapeutic potential. This chapter highlights the promising role of Nanomaterial in Precision oncology where the conventional therapy dwindles. Moreover, the emerging role of Precision Medicine in dentistry genetic diseases and Cystic fibrosis is highlighted which was once a nightmare but now is completely curable with the boon of Precision Nanomedicine. Chapter twenty provides an overview of the current state of the art in nanotechnology-based drug delivery systems and their potential applications. It discusses the various types of nanoparticles that are currently being used or developed for drug delivery, including liposomes, dendrimers, and polymeric nanoparticles, and highlights their advantages and disadvantages. It also covers some of the key challenges and risks associated with the use of nanotechnology in drug delivery, such as toxicity and regulatory issues. Finally, the article explores the future prospects of nanotechnology in drug delivery and highlights some of the areas where further research and development are needed. It is envisaged that this technology will facilitate augmentation of precision medicine for better human health care across the spectrum of diseases.

In this book, chapters have been linked with PM. The book also highlights hitherto less trailed aspects of Ayurveda, a treasure trove of our country. Logic dictates that if already available tried and tested herbal formulations are given as an additive or supplementary medicaments to the patients, that may speed up the process of healing with no or minimal side effect. Simultaneously, research may be conducted to uncover active factors from the still uncharacterized medicinal plants and herbs, synergizing their strength to make them more potent to be used as drug supplement. It is envisaged that the book will provide a conceptual framework for clinician, doctors and researchers in the field of biomedical research augmenting the human health care system and providing additional impetus for future research and innovation complementing the Precision Medicine.

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DEDICATION

Dedicated
To
Late Professor Dr. Mahdi Hasan
PhD, DSc, FNA, FASc, FNASc, FAMS, AvH, DAAD-Germany
Padma Shri, Government of India

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CHAPTER 1

Personalized Medicine (PM) A Critical Appraisal

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Abstract: Personalized medicine, also referred to as precision medicine, deals with a clinical model that delineates patients into different groups based on their ethnicity, lifestyle, food habits, medical history, drug reaction, comorbidity, the robustness of the immune system, age, gender, and proneness to infection, overall psyche and attitude towards life. Further, emotions, social interactions and life experiences culminating into overall happiness play an important role in the life of a person. Thus, an emotionally strong and happy person is usually healthy. Taking all these above factors into consideration and with accurate diagnosis, a drug may be prescribed more in tune with the uniqueness of the patient's genome. Since everybody, whether diseased or healthy, has a unique genome, this uniqueness must be utilized in deciding the drug, dose and its long-term effects. Healing and cure should address the root cause of the problem instead of working only on the symptoms to provide short-term relief. In addition, repurposing of the drug which is not an old concept should also be carefully explored because with this approach, a large number of already available drugs may be used for a much wider number of diseases than the medicine originally developed for. This will also help reduce the cost of the development of medicine. Finally, clinicians and doctors should be sensitized to the concept of precision medicine and its less obvious sub-disciplines. This is envisaged to provide better, more accurate diagnosis and may result in better treatment. The medical field, besides being a deep science is also an art starting from how to deal with diverse types of patients of different backgrounds and educate them all the way to instill a sense of confidence and then to prescribe the medicine to cure the disease. Seemingly, within the realm of precision medicine, it is a huge task. However, it is possible to collect and analyze diagnostic data to reach a consensus. This would require the involvement of clinical psychologists and genetic counselors in a hospital setting ensuring that patient care is holistic, taking

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into account both the physical and psychological aspects of health. This integrated approach can lead to improved patient care and long-term well-being.

Keywords: Demography, Epidemiology, Genome heterogeneity, Human psyche, Pain management, Precise medicine, System biology.

INTRODUCTION

Every human genome is unique as mentioned earlier with respect to its organization, gene expression, regulation, signal transduction, immune system, and response towards different drugs. The genome is a dynamic ensemble of several attributes and constantly adopts and adjusts to maintain cellular homeostasis. During the course of duplication of about 7 billion diploid sequences in a single cell, the genome must ensure that it remains error-free. However, the genome is constantly getting affected by the environment and therefore the possibility of newer mutations may not be ruled out. It is therefore relevant to uncover genetics and environmental bases of diseases. How the concept of PM is viewed across the globe, is another important issue because the world has become small though the healthcare system has become big. Since quality management of patients is possible only when we have a deeper understanding of the disease heterogeneity together with the genome heterogeneity of the patients, we have included demography, epidemiology, ethnicity and genome heterogeneity in our discussion. Finally, we have taken into consideration the prevalent healthcare system and its management, not only in India but in other countries as well. It is envisaged that our attempt at PM will enhance awareness of this theme evoking sufficient interest amongst clinicians and doctors to become more multidisciplinary in their approaches, bringing several healthcare systems on a single platform. This will be a win-win situation for both doctors and researchers. Since medicine is manufactured by pharmaceutical companies, it would be befitting to keep them in the loop so that more fruitful results are obtained. In the context of PM, drug repurposing and titration are two main aspects that must be seriously considered as a topic of research. When adequate data is available on this line, innovation will continue to trickle into the realm of the human healthcare system. Finally, we all agree that prevention is better than cure; we should therefore try to sensitize the masses to make a change in their lifestyle from an unhealthy one to a healthy one. If this calls for some sacrifice at a personal level, so be it. It has been largely believed that our life revolves around genetics and environment with a ratio of 50:50. However, a recent closer scrutiny suggests that the role of genetics is only 10% and the rest all is the environmental impact. Thus, the scope of the environment in the human health care system is expanded with new found knowledge. Clearly, the environment includes a lot more things than we have envisaged so far. Cancer now is considered a preventable disease but 1

million Americans and more than 10 million people worldwide are at risk of cancer. Significantly, 5-10% of cancers have a genetic basis; the remaining ones are based on lifestyle and environmental factors. The lifestyle includes cigarette smoking, diet (fried food meat), alcohol, sun exposure, environmental pollutants, infections, stress, obesity, and lack of physical inactivity. About 25-30% of cancer-related deaths are due to tobacco alone, 30-35% are linked with diet, about 15-20% are due to infections and the rest are because of radiation, noise pollution, lack of sleep, and substance abuse. Prevention is possible in most of the cases, like quitting the use of tobacco, regular uptake of fruits and nuts, moderate or better still, no use of alcohol, restricted intake of calories, use of whole grains, use of timely vaccination, avoidance of too much sun exposure, regular exercise and routine medical checkup. Such changes amongst masses may reduce the genome heterogeneity facilitating the development of PM. There has been a history behind the origin of precision medicine but the concept is now gaining momentum with the availability of better research tools, more awareness, and faster communication.

ORIGIN AND CONCEPT OF PERSONALIZED MEDICINE (PM)

A teenage boy and his grandmother would not buy the same clothes because their bodies will have different size requirements. However, during sickness, they may receive the same medical treatment and so will everyone else. At this juncture, the differences and now fully established genome heterogeneity are not taken into consideration.

That's because even the world's best scientists and doctors do not fully understand how different people develop diseases and respond differently to treatments. The "one-size-fits-all" approach in medicine has been going on but this has never been rationalized let alone challenged. Why population study, demography, epidemiology, population structure, genetic makeup, genotypes, mutational load, food habits, region, religion, susceptibility and resistance, liking and disliking, thought processes, customs and tradition, choice of mating partners, day-to-day activities, the timing of food intake and retiring to bed, disciplined/ undisciplined lifestyle and change in the weather are not taken into consideration before prescribing the medicine. This is because what is practiced by the doctors is what they have been taught. Perhaps doctors do not have time to think beyond their defined hours of duty. During their studies, they were not asked not to think and use their own imagination. The so-called common sense is highly uncommon, because, in the majority of the cases in every field, this is simply lacking. Thus, based on broad population averages, and decade-old drug trials, medicine is prescribed. There is no information on how the same medicine in two different persons will be metabolized. However, after the intake of the drug, this can be

CHAPTER 2

An Integrative Approach to Bioinformatics and Epigenetics Toward Personalized Medicine

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Abstract: Studies on epigenetics have shown cell control, gene function, and putative change or modification in the DNA's sequence. Genes are prone to changes that are brought about by a number of mechanisms encompassing gene conversion, exon/intron reshuffling, alteration in the mutational landscape, and copy number variation of the genes. In addition, repeat DNA sequences tend to expand or shrink changing the topology of adjacent genes resulting in a change in their functions. Alterations in gene activity, especially those that are brought on by epigenetic errors, frequently cause genetic diseases. Researchers are particularly interested in how epigenetic modifications and mistakes affect gene function, protein synthesis, and human health. Precise mapping and evaluation of epigenetic biomarkers will enhance treatment approaches by enabling more accurate and early diagnosis prior to a change in the genetical landscape. This chapter covers the topics of genomics, bioinformatics and epigenetic clocks that pave the way to personalized medicine. It is envisaged that a deeper understanding of the epigenetic modification of the genome or its aberration would augment our understanding of the function of the normal and diseased human genomes.

Keywords: Disease diagnosis, Epigenetic modification, Epigenetic clocks and protein misfolding, Gene expression, Precision medicine.

INTRODUCTION

The fields of medicine and healthcare are rapidly expanding, ushering in a continuous stream of advanced treatments aimed at enhancing patients' well-being. Nevertheless, alongside these advancements, we are confronted with the challenges of side effects and limited treatment effectiveness. This has prompted a critical re-evaluation of the traditional “one-size-fits-all” approach to healthcare.

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In response, healthcare management is undergoing a transformation towards a more personalized approach. This shift is driven by the realization that previous methods, such as genomics, proteomics, and transcriptomics, while impressive, have not provided a complete understanding of why some individuals exhibit altered characteristics. To truly revolutionize healthcare management and personalized medicine, there is an urgent need for a comprehensive, systematic approach that integrates various disciplines. This integration cannot be achieved without proactive collaboration between bioinformatics, epigenetics, and genomics.

Recent developments in epigenomics and the emerging field of omics offer promising paths for enhancing clinical care. These fields enable us to directly connect biomarkers to observable traits or characteristics, potentially leading to more effective and personalized treatments. Several variables are now driving epigenomic medicine research. The first is the field's overall high level of interest. Second, reference epigenomes are continuously being characterized to advance and amplify research efforts. The third is the accessibility of effective tools for characterizing epigenomes, such as next-generation sequencing (NGS).

Bioinformatics and computational biology have provided effective methods for understanding epigenetic mechanisms and analysing epigenomic data. These are becoming increasingly crucial in unraveling the mysteries of gene regulation both in normal and diseased conditions. Bioinformatics tools and techniques aid in the field of epigenetics in a variety of ways. The most important one is to understand the biology of diseases caused by the epigenome enabling optimization of therapies. The large-scale analysis of epigenetic datasets has affected almost all the fields of the human health care system including cancer and various heritable alterations.

In this chapter, we aim to shed light on the significance of epigenetic data and its possible use in personalized medicine. Specifically, we delve into topics such as epigenetic alterations of the human genome, epigenetic biomarkers, personalized medicine, and the pivotal role of bioinformatics in advancing the field of personalized medicine. This chapter is envisaged to enhance our better understanding of bioinformatics and epigenetics towards personalized medicine leading to improved diagnosis, prognosis, and therapeutics of a diseased phenotype.

EPIGENETIC ALTERATIONS OF THE HUMAN GENOME

Our genes play a significant role in our health, but the gene expression itself is modulated by our behaviour, like what we eat and the level of exercise that we do, and the environment to which we are exposed [1]. The field of epigenetics deals

with how cells regulate gene activity without altering the DNA sequence. In Greek, “epi-”means “on or above,” and “epigenetic” refers to factors other than the genetic code [2]. It is, thus, the study of how environmental factors and behaviour can alter the functions of the gene (Fig. **1**). While epigenetic changes are reversible and do not alter our DNA sequence as genetic changes do, they can alter how our body interprets a DNA sequence [3]. Because epigenetic modifications regulate whether genes are switched on or off, they have an impact on protein production in cells. This regulation ensures that each cell generates only the proteins required for its activity. Proteins that promote bone formation, for example, are not generated in muscle cells. Patterns of epigenetic change vary amongst persons, the tissues within an individual, and even between the cells within a tissue [4]. Environmental factors such as a person's nutrition and exposure to contaminants can affect the epigenome.

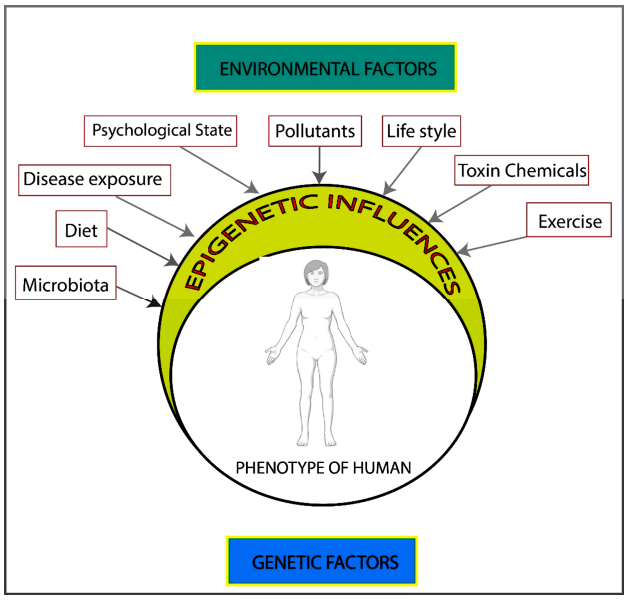

Fig. (1). The phenotype of humans is influenced by environmental factors and genetic factors.

Epigenetic alterations can be passed down *via* families or acquired in response to the environment. Decisions about one's way of life enhance exposure to factors (such as pollution and cigarette smoke) that alter our epigenome [5]. Monozygotic or 'identical' twin studies have revealed insightful information into the genetics and environmental factors that control epigenetic pathways, indicating that our genes cannot be solely responsible for regulating the development of complex phenotypic traits. Similar to this, biochemical signals from the womb during fetal development or hormones released after puberty cause epigenetic alterations that

CHAPTER 3

Precision Medicine in Improving Treatment Outcomes in Hepatocellular Carcinoma: Clinical Outcomes and Advancements

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Abstract: Liver cancer ranks sixth among the most commonly diagnosed malignancies and 90% of liver cancer cases are of Hepatocellular carcinoma (HCC). Treatment options for HCC include resection, radiotherapy, and systemic therapies with chemotherapeutic drugs. The late diagnosis of HCC prevents successful treatment by surgical resection. Further, conventional treatment modalities such as chemotherapy and radiotherapy are ineffective in all patients as tumors are heterogeneous. The heterogeneous nature of tumors enables them to have genetic variations and express specific proteins in different patients. This inherent variability of cancer creates the need to move to a growing field of medicine, *i.e.*, precision/personalized medicine. Precision medicine is based on complementing the molecular profile of a patient to a targeted therapy. In clinical practice, the transition from a stage-based approach to a targeted therapy-based approach is necessary for determining the most appropriate treatment plan for a patient. The clinical outcomes for patients could be improved on a large scale if the discoveries in tumour biology are applied efficiently in clinics. This chapter discusses the research on precision medicine for improving treatment outcomes in HCC patients, especially advanced cancers. It also includes the clinical studies of novel therapeutics used for the targeted therapy of advanced liver cancer patients. Concisely, we summarize the recent studies on the applications of precision and personalized medicine.

Keywords: Cancer management, Clinical trials, Hepatocellular carcinoma, Precision/personalised medicine, Targeted therapy.

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INTRODUCTION

Among the various cancer types, liver cancer ranks sixth among the most frequently diagnosed malignancies and the third leading cause of death globally [1]. Among other primary liver cancers, 90% of cases are of HCC and result from exposure to a carcinogen, alcohol abuse, obesity, and hepatitis B and C viral infections [2 - 4]. HCC is characterized by uncontrolled growth, low resection capability, recurrence, inadequate response to treatment, and poor prognosis. Currently, >850,000 cases of HCC are diagnosed annually, and it is anticipated that this incidence will rise to 1 million cases in the future [3, 5]. Further, the mortality rate due to HCC is the highest among other cancers [2]. Due to the high incidence and mortality rate, HCC is not easily manageable despite improvements in diagnosis and therapies.

Surveillance programs in developed nations have facilitated the timely detection of HCC in ~40-50% of affected patients, thereby allowing potentially remedial treatments [3, 6]. However, intermediate- and advanced-stage HCC patients are manageable only with loco-regional, ablation, and systemic treatments. Generally, ~50% of patients are treated with systemic therapies (chemotherapeutic drugs) during disease progression [3, 6]. Sorafenib/Nexavar is a Tyrosine Kinase Inhibitor (TKI) used to treat advanced HCC patients. It has been reported that the administration of sorafenib increased the overall survival from 8 to 11 months. Moreover, Sorafenib is associated with a tolerable safety profile and manageable side effects [7, 8]. From 2007 to 2016, Sorafenib remained the only chemotherapeutic treatment option for late-stage HCC patients. However, recent randomized Phase III clinical studies have demonstrated improvement in treatment outcomes in patients given Lenvatinib as a frontline treatment [7] followed by the second-line treatment of Regorafenib [8], Cabozantinib [10], and Ramucirumab [11] after the patients have experienced HCC progression on Sorafenib. Currently, the second-line treatment for HCC management is Regorafenib. Recently, Immunotherapy is another emerging personalized therapeutic option for HCC patients, for instance, a monoclonal antibody (Nivolumab) targeting the immune checkpoint protein 1 (PD-1). The use of Nivolumab in Phase I/II study resulted in favorable responses and survival rates in patients who have undergone treatment with Sorafenib [12], granting increased FDA approval. Despite extensive efforts, several kinase inhibitors, including Brivanib and Erlotinib, and treatments such as Doxorubicin and radio-embolization using Yttrium 90 (90Y)-microspheres, have failed to demonstrate a significant improvement in the survival rate for patients with unresectable HCC [13]. Also, therapeutic outcomes in patients receiving systemic therapies have been reported to be low.

In the past decade, research evidence has highlighted that every individual's cancer is unique, indicating that their response to conventional therapies (like chemotherapy and radiation) may vary significantly [14]. The conventional treatment methods are often too simplistic and may result in treatments that are expensive, not effective, and associated with significant side effects, causing patients to experience adverse outcomes. Therefore, precision medicine is a more effective approach that aims to shift away from the "one-size-fits-all" approach to cancer therapy. Precision medicine involves developing specialized treatments for each specific cancer subtype by critical analysis of various types of data, including genetic, metabolomic, transcriptomic, proteomic, and other relevant patient data. The majority of healthcare facilities worldwide rely on the BCLC staging system to determine the most effective therapeutic approach for HCC patients [15, 16]. A detailed analysis/investigation of tumor burden, liver function, and overall health status guides in selecting the most specific and personalized treatment option for HCC patients [15]. However, due to the late diagnosis of patients, only a few patients (one-third) are eligible for curative-intent treatments. The majority of HCC patients are diagnosed in the advanced stage, leaving only limited treatment options, resulting in poor treatment outcomes.

The implementation of precision medicine against HCC challenges the traditional "one-size-fits-all" approach to treatment. It focuses on the molecular targets specific to a patient's tumor biology to develop individualized treatment plans. Precision medicine recognizes that each patient's cancer is unique, and treatment should be tailored to their specific needs to achieve better outcomes (Fig. **1**) [17, 18]. In this regard, molecular insight into the disease biology can enable HCC management and help advance the therapies through a complete understanding of the disease etiology; an approach termed a biomarker-driven approach. This approach is crucial at this hour when HCC incidence is increasing alarmingly. This chapter discusses precision medicine for advanced-stage HCC management from the perspective of its clinical implications.

THERAPEUTIC APPROACHES EFFECTIVELY MANAGING HEPATOCELLULAR CARCINOMA (HCC)

In the past decade, various staging systems have been proposed for HCC [19 - 21]. Among them, the BCLC staging system is the most widely used for patient staging and treatment administration [22 - 24]. In developed countries, treatment options including liver resection, transplantation, or localised ablation are possible only in ~50% of the patients, which could be diagnosed at early stages (BCLC stage 0-A) [24]. The available therapeutic options for early-stage HCC have shown a median overall survival of over 60 months [24]. However, it has been reported that ~70% of such patients experience cancer relapse within five years of

CHAPTER 4

Protein Structures, Aggregation, Misfolding, Induction Factors and Precision Medicine

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Abstract: The aggregation of protein is a complex process influenced by various factors resulting in a wide range of debilitating disorders. These are characterized by the deposition of insoluble plaques consisting of amyloid fibrils rich in β-sheet structures. Many natural proteins form amyloid fibrils and build-up misfolded or aggregated disease-specific proteins in the tissues causing human diseases. The present chapter deals with protein structures, aggregation, misfolding, induction factors, and their involvement in human disease and implications in precision medicine. We have discussed the role of functional amyloids in portraying the mechanism of its formation, highlighting the method of detection of diverse types of aggregates. Moreover, we also contextualized therapeutic strategies to combat the process of aggregation keeping in view that this is a broad field of research that ranges from biophysics to clinical trials. Despite visible progress in the field of biochemistry, we still have questions regarding the aggregation and co-aggregation of protein molecules. However, with the present level of knowledge, it is envisaged that accurate treatments against diseases related to aggregation would be feasible in near future.

Keywords: Human diseases, Induction factor, Protein aggregation, Protein misfolding, Precision medicine, Proteins structures.

INTRODUCTION

Protein misfolding is a detrimental process that is interconnected with aggregation and is known to be involved in a large variety of localized, systemic, non-neuropathic, and neurodegenerative diseases [1, 2]. Owing to its implications in several human diseases, these processes have attracted much attention and have become a dynamic field of research. In some cases, the disease arises when a specific protein adopts a misfolded conformation or encounters trafficking impairment and is no longer functional, resulting in loss-of-function diseases [3]. In contrast, if misfolding and aggregation occur concomitantly resulting in a pathological state then this is regarded as a gain-of-function diseases [4]. Alth-

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ough protein polymerization can be a physiological process in case of the formation of muscles F-actin filament. However, in several instances, native protein oligomerization has been reported to be connected to specific pathological conditions underlying several human disorders [5, 6]. The diseases in which the misfolded protein aggregates formed are termed "Protein misfolding diseases". The accumulation of diverse proteins in various organs of a human body is the hallmark of protein misfolding disorders (PMDs). Table **1** comprises the list of human diseases linked with the misfolded proteins. The most known protein misfolding disease (PMD) is Amyloidosis, which is known to be caused by the building up of insoluble amyloid fibrils in the extracellular space [7]. Amyloidosis are difficult to diagnose and complicated to study because one or more organs like heart, liver, kidney, pancreas, and the central nervous system may be involved [8]. In localized amyloidosis, intracellular or extracellular deposition of amyloid takes place only in the organ/tissue where the precursor protein synthesis occurs [9]. For example, the accumulation of Aβ and α-synuclein occurs outside of the cells, whereas insoluble toxic protein aggregates of misfolded SOD1 form inside the cells [10]. In contrast to localized amyloidosis, all the systemic amyloidoses remain extracellular. Their onset occurs when the expression and secretion of the precursor protein take place at one site but it gets deposited at distinct sites. The diverse systemic disorders include light chain amyloidosis (AL), heavy chain amyloidosis (AH), secondary amyloidosis (AA), lysozyme amyloidosis (ALys), familial amyloid polyneuropathy (FAP or ATTR), dialysis-related amyloidosis (Aβ2M), *etc* [11].

Table 1. List of human diseases linked with protein misfolding and aggregate formation.

Serial Number	Neurodegenerative Diseases	Aggregating Proteins	Nonneuropathic Systemic Amyloidosis	Aggregating Proteins	Nonneuropathic Localized Diseases	Aggregating Proteins
1	Alzheimer's disease	β-Amyloid (plaques),Tau (neurofibrillary tangles)	Light chain amyloidosis	Immunoglobulin light chain	Type II diabetes	Amyloin (IAPP)
2	Parkinson's disease	α-Synuclein	Heavy chain amyloidosis	Immunoglobulin heavy chain	Medullary carcinoma of thyroid	Calcitonin
3	Dementia with Lewy bodies	α-Synuclein	Lysozyme amyloidosis	Mutants of lysozyme	Injection-localized amyloidosis	Insulin
4	Huntington's diseased	Huntington with polyQ Expansion	Senile systemic amyloidosis	Wild-type transthyretin	Cataract	γ-Crystalline
5	Spongiform encephalopathies	Prion protein or fragments thereof	Familial amyloidotic polyneuropathy	Mutants of transthyretin	Lattice corneal dystrophy	Mainly C-terminal fragments of kerato epithelin
6	Amyotrophic lateral sclerosis	Superoxide dismutase	Cardiac arrhythmias	Fragments of serum amyloid A protein	Corneal amyloidosis associated with trichiasis	Lactoferrins

(Table 1) cont.....

7	Spinocerebellar ataxia	Ataxins with polyQ Expansion	Hemodialysis-related amyloidosis	β2-microglobulin	Atrial amyloidosis	Atrial natriuretic factor
8	Frontotemporal dementia	Hyperphosphorylated TDP-43	Fibrinogen amyloidosis	Variants of fibrinogen α-chain	Aortic medial amyloidosis	Medin
9	Familial British dementia	ABri	Finnish hereditary amyloidosis	Fragments of gesolin mutants	Pulmonary alveolar proteinosis	Lung surfactant protein C
10	Familial Danish dementia	ADan	Cystatin amyloidosis	Cystatin C	Cutaneous lichen amyloidosis	Keratins

When the proteinaceous deposits occur on the neuronal cells resulting in progressive damage to the neurons, then this leads to the onset of neurodegenerative diseases. One of the most studied neurodegenerative disorders is Alzheimer's disease (AD) that affect sizable older populations. AD is a fatal diseases caused by 40-42 amino acids long amyloid beta aggregates [12]. Others include widespread illnesses like Parkinson's disease, Huntington's disease, transmissible spongiform encephalopathies (TSE), and amyotrophic lateral sclerosis (ALS) [13 - 15]. Fig. (**1**), illustrates the diagrammatic representation of the several organs of the human body that are affected by neuropathic as well as non-neuropathic diseases.

Despite diversity at a molecular level, all the proteins have a common property of rapid and spontaneous self-assembly into functional three dimensional structures. However, native conformation is not the only fold available to a polypeptide chain but an alternative state termed as Amyloid may represent primordial of protein folding. Studies have shown that folding of protein and fibril formation are competitive processes that operate parallelly. Basically, the intermediate states determine the diversion of molecules between the folding and aggregation landscapes. We still have a lot to learn to better understand the balance that lies between protein folding and aggregation. The complete understanding regarding the structural properties of different stages of all the proteins folding and aggregation is a major task.

Thus, studying protein aggregation is important to understand the structural and mechanistic basis of the conformational changes and factors that promote the precursor states' conversion into aggregates. In the current review, we tried to delineate the mechanism of amyloid aggregation and the underlying factors that assist in *in vivo* and *in vitro* aggregation of proteins. The strategies to combat protein aggregation have also been discussed. There are several organs that are affected due to protein aggregation as illustrated in the following diagram.

CHAPTER 5

Resiliency of Protein Dictates Human Health

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Abstract: Proteins are functional in their three-dimensional form; any type of modification in the conformation of the protein affects its functions. Thus, the role of the proteins in the body depicts the functional ability and ensures health of an organism. Besides its presence in the body, proteins are consumed by the body in the form of dietary uptake. The free amino group of the protein in the body when interacting with the carbonyl group of the reducing sugar follows the Maillard reaction to produce hazardous by-products which is an advanced glycation end products (AGEs). The process of AGEs formation routes towards the aggregation process. Different studies have shown different aggregation pathways, some restricting the partial unfolding of the protein and the other oligomerization leading to fibril formation depending upon the conditions of the study. It is noteworthy that in *in-vivo* cases, glycation and aggregation are the two sides of the same coin because it is obvious that we have seen the diseased condition due to AGEs formation that also shows aggregation or *vice versa*. Hence, the two causative agents depend upon each other.

Keywords: Advanced glycation end products (AGEs), amyloid fibrils, human diseases, oligomer, protein.

INTRODUCTION

Proteins are the most adaptable macromolecules in living systems and are essential to practically all biological processes. The term “protein” coined from the Greek word “proteios”, means primary. This term is quite dependable in nourishment because of its fundamental role in the tissues of animals and humans. They act as catalysts, carry and store molecules such as oxygen, offer immunological protection, mechanical support, produce movement, conduct nerve impulses, and regulate the growth and differentiation of the cells. To support this wide variety of proteins’ functions, they are constituted by varied permutations and combinations of the 20 amino acids; the highest for any biomolecule. These amino acids are connected by peptide bonds [1].

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DIETARY PROTEINS

Non-essential amino acids and essential amino acids both are synthesized by our body from the abundance of food. Unless they are digested by peptidases and proteases to simpler amino acids in the lumen of the small intestine, these proteins have no nutritional value. The combination of amino acids can have an impact on health, “pure” protein, sourced from plant and animal nutrition, and has equal impacts on health. There are certain “complete proteins” in food, which means they have all the twenty types of amino acids, required by the body. Apart from the complete proteins, others lack one or more necessary amino acids, which our bodies cannot synthesise on their own or even from other amino acids. Edibles from plants frequently lack one or more important amino acids, but foods derived from animals typically provide a complete protein (Fig. **1**) [2, 3].

Fig. (1). Pictorial representation of dietary proteins. Source: Internet.

The oxidation of amino acids is enhanced following the substrate-enzyme relationship of Michaelis-Menton kinetics. Thus, this should be taken into account when determining the human diet's needs for amino acids and proteins. Overabundant amino acids are oxidised to carbon dioxide (CO_2), water (H_2O), and urea, except glutamine in the skeletal muscle. There is very little amino acid

oxidation when the intake of protein is at the perfect level for protein synthesis The oxidation of amino acids is decreased to spare amino acids for protein synthesis when the animal's nutritional requirements for protein or amino acids are not met. This is because the enzymes responsible for the synthesis of proteins, such as tRNA-amino acid synthases, have substantially lower K_M values and thus, a higher affinity for amino acid substrates than the enzymes responsible for amino acid degradation. Amino acids are largely directed to the pathway of protein synthesis compared to amino acid catabolism. Hence, only a little amount of dietary amino acids are accessible for oxidation in animals nourished with a balanced diet.

The quantity of the protein required by the human diet can be ascertained using a variety of approaches. These methods include nitrogen balancing studies, which examine the relationship between nitrogen intake from food and nitrogen excretion in various forms; factorial analysis, which examines the amount of nitrogen excreted in the urine and faeces in response to a diet low in protein (maintenance); amino acid deposits in the body; and amino acid excreted as animal products (such as milk and foetal growth); and tracer studies, which use the direct and indirect oxidation of the amino acids to detect specific amino acids.

Protein and amino acid requirements are influenced by dietary factors, such as amino acid content, its proportions, the presence of other substances in the food, energy intake; physiological characteristics of the individual, such as genotypic and phenotypic traits, enzymes, hormones, pregnancy, lactation, and physical activity; pathological conditions, such as infection, trauma, diabetes, obesity, cardiovascular disease, and foetal growth restriction; and environmental factors *e.g*., temperatures, air pollution, sanitation, and personal hygiene, toxic agents and dietary habits [4].

Role of Dietary Proteins

Chemically, the human body is made up of proteins, lipids, minerals, and water. The metabolism of the body is predominantly influenced by the protein component, which is frequently measured as Lean Body Mass (LBM). Protein content in the diet is metabolically significant because it supplies the amino acids needed for the body to synthesize new proteins. They are essential to body metabolism as well as a source of non-communicable or self-styled diseases commonly as diabetes, hypertension, and cardiovascular disease that are ultimately related to disturbances in body metabolism. Dietary protein is necessary for the body's growth and LBM maintenance. It also plays a crucial role in the maintenance of overall health, muscle mass, and strength [2].

CHAPTER 6

Status of *Helicobacter pylori* in Gut Microbiome and Precision Medicine

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Abstract: *Helicobacter pylori* (*H. pylori*) is a Gram-negative, slow-growing microaerobic bacterium that infects over 50% of the global population. Around 58,000 years ago, *H. pylori* and humans co-evolved and migrated from East Africa, the original birthplace of *Homo sapiens*. Its distinct characteristics, such as urease, helical structure, and motile flagella, allow it to survive in the human stomach under stressful conditions. The occurrence of *H. pylori* in the stomach can be beneficial or detrimental to human health, depending on the host's genetic vulnerability, immunity, and environmental factors. Although most of the *H. pylori*-infected patients are asymptomatic, about 20% develop stomach illnesses such as peptic ulcer (10-15%), gastric adenocarcinoma (1-3%), and mucosa-associated lymphoid tissue (MALT) lymphoma that is common to aged people. People who do not have *H. pylori* infection, on the other hand, are predisposed to a variety of diseases, including gastric esophageal disease (GERD), oesophageal cancer, diabetes mellitus, and asthma. Clinical symptoms in infected patients vary significantly geographically due to the high level of genetic variation in the bacterial genome and the presence of numerous virulence factors. The entire sickness is treated by eradicating *H. pylori* with antibiotics and proton pump inhibitors. However, the rise in antibiotic resistance and a lack of effective vaccinations make it tough to combat the infection. This chapter aims to shed light on host-pathogen interactions by analysing the bacterium's persistence and pathogenesis in the context of human health and precision medicine.

Keywords: CagA, Gastric ulcer, Gastric cancer, Gut microbiota, *Helicobacter pylori*, Standard triple therapy, Virulence factors.

INTRODUCTION

H. pylori is one of the most successful colonizing bacteria in the human stomach which is found in over 50% of the global population. Bizzorero first time in 1893 emphasized the existence of spiral-shaped microbes in biopsy samples of mammalian stomachs [1] (Fig. **1**). Almost a century later, in 1984, Barry Marshall

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and Robin Warren isolated a spiral-shaped bacterium from the gastric biopsy of a human stomach and proved its role in the development of gastritis after the ingestion of microbial culture. In 2005, Warren R. and Marshall B. got a Nobel Prize in Physiology or medicine for the discovery of *Helicobacter pylori* and its association with gastric disease. Initially, it was named "C*ampylobacter pylori*" and latter following its thorough characterization renamed as *Helicobacter pylori* [2]. Human is the only host for *H. pylori*; however, other *Helicobacter* species have also been reported in cattle (*Helicobacter bovis*), pigs (*Helicobacter suis*), cats (*Helicobacter felis*), and dogs (*Helicobacter canis*) as well as for many other mammalian species which are mostly asymptomatic.

Scientific classification

Kingdom:	Bacteria
Phylum:	Proteobacteria
Class:	Epsilon Proteobacteria
Order:	Campylobacterales
Family:	Helicobacteraceae
Genus:	*Helicobacter*
Species:	*pylori*

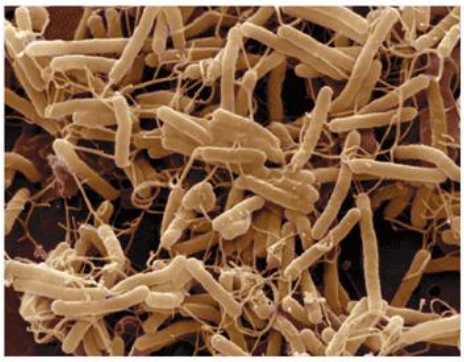

Fig. (1). Scanning micrograph shows several *H. pylori* (Adapted from: Meridian Bioscience: Europe website).

H. pylori transmits during childhood or early adolescence and persists throughout the life span of the host. *H. pylori* remains largely asymptomatic in infected people even after decades of infection or throughout the lifetime. However, about 20% of the infected people become symptomatic, including most of them as elder people who are above 40 years old. Long-term infection of *H. pylori* is responsible for chronic inflammation that leads to the development of gastritis, gastric ulcer, gastric adenocarcinoma, and gastric mucosal-associated lymphoid tissue (MALT) lymphoma. In 1994, the International Agency for Research on Cancer (IARC), a unit of the World Health Organization (WHO) classified *H. pylori* strain as a class I carcinogen [3]. *H. pylori* strain encodes cagA (cytotoxin-associated gene A), also known as an 'oncogene', which is predominantly responsible for the occurrence of chronic inflammation and subsequent gastric cancer.

Around 58,000 years ago, geographical analysis revealed that *H. pylori* moved from East Africa to Western Europe, Eastern Asia, and Southern Africa. It is believed that modern human was already infected with this bacterium before

leaving East Africa as both have similar migration history. The bacterium is well-transformed and adapted accordingly to survive in the gastric mucus during the course of co-evolution. It is evident that people without *H. pylori* infections are more at risk for other diseases like Gastroesophageal reflux disease (GERD), esophagus carcinoma, gastric atrophy, diabetes, and asthma. This association hints towards the symbiotic behaviour of the bacterium with humans. The frequency and/or severity of disease outcomes with *H. pylori* infection is variable geographically among humans depends on multiple factors including bacterial genetics and virulence factors, host epigenetics as well as environmental factors. *H. pylori* infection is identified using various tests and successfully treated with one or more medicines. Unfortunately, the rise in antibiotic resistance and the lack of vaccine development are the key impediments to creating more effective medicines for this common but deadly pathogen. This chapter will cover disease diagnosis and treatment methods as well as the persistence and pathophysiology of *H. pylori* with respect to human health.

BACTERIOLOGY

H. pylori is a Gram-negative, spiral-shaped, small (3.5µm x 0.5 µm), micro-aerophilic, and non-spore-forming bacteria. It is able to survive in a high acidic environment (~pH 2) of the gastric lumen [4] and can grow at pH 6-8. It is a slow-growing bacterium with a generation time of 4–6 hours and requires low oxygen environmental conditions (*i.e.*, 5% O_2, 10% CO_2, 85% N_2, and high humidity) and 37°C for optimal growth [5]. There is no requirement for H_2, although it is not detrimental to bacterial growth. The organism has 2-6 sheathed flagella at one end that allow rapid movement in a highly viscous condition across the gastric mucus layer [6]. Typically, bacterial colonies are quite visible and grow well on blood or serum containing solid agar media like Columbia blood or Brain heart infusion (BHI) media with specific growth supplements. *H. pylori* is spiral-shaped and appears as a rod under normal physiological conditions, however, it transforms from spiral to coccoid form during prolonged *in vitro* culture or under stressed conditions like antibiotic treatment and/or the presence of high oxygen level [7]. The coccoid form of the organism is viable but non-culturable [8, 9]. *In vitro*, the coccoid form can attach to and colonise stomach epithelial cells [10 - 12].

GENOME AND GENETIC DIVERSITY

The genome sequences of several strains including *Helicobacter pylori* 26695, J99, HPAG1, and G27 are annotated. The genome size varies among different strains of the organism like the size of the *H. Pylori* 26695 genome is ~1.7 Mb, however, it is 24 kb larger than the J99 strain and about 71 kb larger than HPAG1

CHAPTER 7

Prevalence of Triple Negative Breast Cancer and its Therapeutic Challenges

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Abstract: Breast cancer (BC) is the most common among females. The current status of BC worldwide shows that more than 1 million women are affected and ~400 000 die every year. Partial success has been achieved by mammography coupled with adjuvant treatment. However, its incidence and mortality both are increasing. Several sub-categories of BC have been reported; of which, one is triple-negative breast cancer (TNBC). This is defined by a lack of expression of oestrogen and progesterone receptors and human epidermal growth factor receptor 2 (HER-2). Several approaches have been used for speedy and accurate diagnosis and precise treatment of BC. In this context, precision medicine approach is of great relevance in ameliorating the suffering of the patient's from the menace of BC. The present chapter aims to provide background information, different types of BC and its sub-types and molecular mechanisms for therapeutic intervention required for precision medicine.

Keywords: Breast cancer, Human epidermal growth factor receoptor-2 (HER-2), Triple-negative breast cancer, Therapeutic intervention.

INTRODUCTION

Abnormal cell growth and multiplication are referred to as cancer. Normal cells divide and multiply in a regular manner but cancer cells do not follow the regular process instead they ignore signalling and molecular events which control the abnormal growth. After heart-related issues, cancer ranks as the second most common cause of death worldwide (WHO report). Globally, 20 million incidences of cancer were reported in 2020 resulting in 1 million deaths. Thus, one in every six fatalities was caused due to the cancer [Globocan report 2020]. Despite recent major advances in the field of cancer biology, metastasis continues to pose a challenge because it is the leading cause of mortality for both the sexes globally.

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In metastasis, cancer cells leave the primary tumour site and invade other parts of the body proliferating to develop secondary tumours. Metastasis accounts for about 90 percent of cancer-related mortality [1]. With time, these metastatic cells experience many molecular modifications that alter the characteristics of such cancerous cells [1]. There are currently ten known features of cancer that tumour cells use to continue their unchecked multiplication and progress while evading increasing inhibition signals [2].

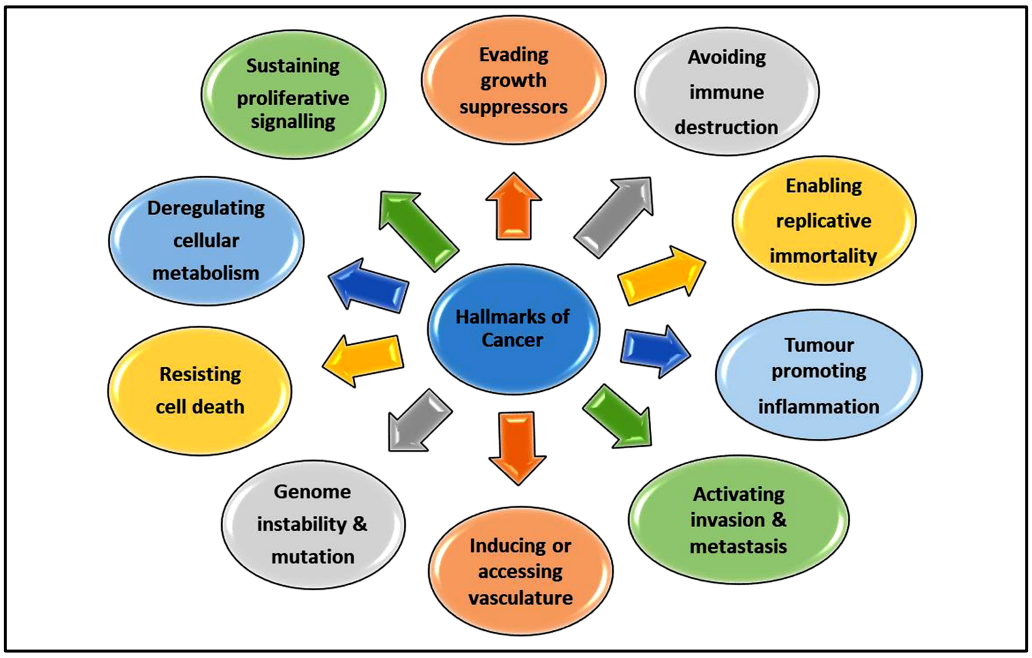

Fig. (1). Hallmarks of the cancer include several aspects in a well-orchestrated manner.

BREAST CANCER (BC)

The most aggressive form of tumour across the globe in females is breast cancer. About 2.6% women that is 1 in every 38 will develop breast cancer in their lifespan. In America, 12% women that are 1 in 8 may develop aggressive breast cancer. BC is an aggressive tumour that can originate from cells in the breast lobule or glandular milk duct. The degree to which a tumour has started to grow within the luminal surface determines if it is aggressive or non-aggressive. Lobular carcinomas are those breast cancers that originate from the lobules of mammary gland whereas ductal carcinomas originate from epithelial cell of the duct of the breasts. Tumorous cells in non-metastatic (non-invasive) breast cancer are confined to the milk ducts or lobules, whereas in metastatic breast cancer (invasive), the altered cells spread to the surrounding tissues and metastasis to the

liver, lungs, brain, and bones [3]. Breast cancer is a complex disease consisting of many functionally diverse components with specific medical and therapeutic ramifications [4]. According to studies, breast cancer with different anatomical and biological features exhibit distinct characteristics that lead to different clinical results and thus warrant to be treated with a wide range of therapies [5]. With the aim of maximising clinical results, it is crucial to classify breast carcinoma into therapeutically relevant groups. Using cancer immune-histochemical and gene expression analyses, the following subgroups of BC have been classified [6].

INCIDENCE AND MORTALITY

World-wide Status of Breast Cancer

BC continues to be one of the main causes of death in women, accounting for an estimated 2.3 million new cases diagnosed and 684996 mortalities reported globally in 2020. In terms of global death, BC is the sixth worldwide cause and the second among women in developed nations. GLOBOCAN 2020 database shows all types of cancers, with the incidence of BC in females being the highest that is 47.8/100000 with the highest mortality rate of 13.6/100000. In 2020, France had the highest incidence (99.1/100000 females) and mortality rate (15.6/100000) followed by New Zealand with 93/100000 incidence and 14.1/100000 mortality (Globocan 2020).

National Status of Breast Cancer

BC has the highest incidence and fatality rates among all the females in India. The expected rate of new incidences in India is 3465951 out of 14388382 cases. This represents 24.1% of all female cancer cases, and the expected number of fatalities is 11214132 out of 7302147 cases, representing 15.4% of all cancer-related deaths (Globocan-2020). Hyderabad has India's highest incidence of breast cancer (48.0 per 100000 women), Chennai (42.2), followed by Bangalore (40.5) and Delhi (38.6) according to the National Cancer Registry Programme (NCRP). During the last 5 years, BC mortality all over the world has reached the highest among all the other cancer types. Thus, BC is the world’s most common cancer as 7.8 million females are diagnosed with this type of malignancy. More than 90% of the developed countries have better survival rates of BC (at least five years) after diagnosis compared to India and South Africa having survival rates of 66% and 40%, respectively (Globocan-2020). In developed nations with advanced diagnostics, early assessment and treatment have proven more successful than in poor countries. Age-standardized mortality rates for BC reduced by 40% in high-income countries between the 1980s and 2020. In women under the age of 70, a 2.5% annual mortality reduction would result in a reduction of 25% by 2030 and 40% by 2040, preventing roughly 2.5 million BC-related deaths between 2020

CHAPTER 8

Molecular Mechanisms Implicated with Depression and Therapeutic Intervention

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Abstract: Depression is a pervasive, arduous psychological condition with profound neurological ramifications. The parameters for leveraging depression involve the diagnosis and evaluation of depression, the endorsement to implement substantiated therapies and rigorous follow-up of the patients. Many individuals suffering from depression undertake a recurring or persistent therapy that correlates to a decline in cognitive processing. The underpinnings of exact aetiology and pathogenesis of melancholy are probably the outcome of a variety of mechanisms. These include physiological, behavioural, and socio-economic variables, all playing their roles. Multiple refinements to the treatments encompassing therapies, medications and medical interventions are employed, in relation to effective approaches reassuring the brighter side. In this chapter, we discuss more integrative and multifaceted aspects of psychological health, minimizing the segmented understanding to achieve a consensus on multiple possibilities for effective interventions.

Keywords: Heterogeneous, Health disorder, Resource-based economies, Trial-and-error strategy.

INTRODUCTION

The term “depression” was coined in the 19th century to describe “mental depression,” an enervating ailment that is predominantly syndromal, distressing individuals all over the globe. Depression or Major Depressive Disorder is among the most pervasive, highly heterogeneous and often disabling syndrome with relatively higher lifetime prevalence rates, yet very difficult to recognise. Depression bears modest correlations from being a neuropsychiatric disorder to its anchored biological roots, motivating interest in diagnosing depression for treatment and research purposes.

MDD is epitomized by a cluster of signs and manifestations which allude to a distinct illness with discrete aetiologies. The aphorism “No health without mental health [1]” rationalizes depression as being an illness of hindered mental well-being. Anguish, diminished motivation, protracted melancholy, suicidal ideation, and psychosocial impairment are the critical attributes of the cognitive and

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somatic facets of depressive episodes. Besides these, circadian rhythm disruption and hormonal imbalances, notably cortisol and melatonin release, are among other major markers of depression disorders [2].

Depression departs from regular mood swings and fleeting emotional reactions, specifically when recurrent with moderate or severe intensity. Depression has proven to be a significant drain on workforces in knowledge-based industries and resource-based economies with exceptionally high rates of debility and abridged productivity. It is prophesied that by 2030, depression will be the utmost debilitating and prevalent health disorder. An estimated 50% of depressed patients do not present any emotional variability despite manifold health care visits, and often misdiagnosed and thereby incompetently treated with available interventions. There are multiple non-invasive treatments, evidence-based psychotherapies, and antidepressant therapies for treating depressed patients, nevertheless, the therapy response rates are relatively lower [3].

Even with an ensuing recovery, several patients may necessitate a trial-and-error strategy, as there are no reliable guidelines for optimal treatments, with patients developing treatment resistance over time. This scenario stems from the heterogeneity of depression and the lack of biomarkers for subtype-specific stratification. The principles of upkeep for this condition are quite simple, relying on early detection, accurate diagnosis, appropriate therapy selection and post-intervention monitoring. Regardless of advances, a number of significant issues have emerged regarding depression diagnosis and novel therapy. To address these known challenges, this chapter aims to address the basic precepts of depression, the implicated brain circuits with molecular dysfunction, and the diagnostic parameters with accessible therapies. Taking these points into consideration, one can then chalk out the program for precision medicine, the titration of dose, and the one that has no side effects. Several drug molecules are available to treat neurological disorders. However, a great deal of additional work is required to achieve a consensus on drugs, treatment and the duration of follow-up of the patients.

EPIDEMIOLOGICAL BURDEN

Depressive malaises foray approximately 3.8% of the global population, encompassing primarily 5.0% of adolescents and individuals over the age of 60 [4]. Depression affects nearly 280 million people across the globe. Annually, around 700 000 people commit suicide, mostly amongst those who are 15 to 29 years of age, making suicide the fourth leading root of mortality. Despite the widespread availability of established, budget-friendly drugs, about 75% of people in low and middle-income nations do not receive treatment for mental

health issues. Inadequate funding, unsatisfactory healthcare, a shortage of competent workers, and undeniably the stigma allied with psychological ailments are the foremost impediments in the direction of efficacious care.

Prevalence

Depression typifies one of the utmost predominant chronic conditions universally, having a detrimental impact on the emotions, thoughts, and social interaction abilities of individuals. Approximately 2-6% of people globally suffer from depression, affecting roughly 1 in every 15 adults annually and 1 in every 6 people may happen to pass through depressive episodes at some phase in their lifespan. Prior to 2020, psychological illness, precisely anxiety and depression, were the key causes of global health burden. Nevertheless, the COVID-19 predicament has fostered a scenario where frequent variables of meagre mental state have been accentuated. As a consequence, there is a heightened urge to strengthen mental health treatment by initiatives to include in the mitigation [8].

In accordance with the "Global Burden of Diseases, Injuries, and Risk Factors Study (GBD)" 2019, both depression and anxiousness are the two major incapacitating mental conditions, explicitly labelled among the top 25 major contributing factors for escalating mental health globally. This pressure was great across the spectrum, affecting both genders, in a plethora of settings [7]. Despite mounting evidence of interventions that mitigate the impact, there has been no decline in global prevalence rates since 1990. The frequency of DALYs globally due to mental diseases surged from 80.8 million in 1990 to 125.3 million in 2019, while the overall percentage of all DALYs rose from 3.1% to 4.9%. In 2019 approximately 125.3 million YLDs were ascribed to mental disorders, who were in 17361.5 YLLs attributable to eating disorders [6].

According to WHO projections, the 10 leading nations with the maximum and minimum (Table **1**) prevalence rate of depression are enlisted. However, the percentages mentioned over and under are completely substantial and relevant [7]. However, it may be noted that the real figures are apparently far larger and are heavily influenced by age and gender.

Table 1. Prevalence of depression across some leading countries of the world.

S. No.	%Highest Prevalence	%Lowest Prevalence
1	Ukraine-6.3%	Solomon Islands-2.9%
2	United States-5.9%	Papua New Guinea-3.0%
3	Estonia-5.9%	Timor-Leste-3.0%
4	Australia-5.9%	Vanuatu-3.1%

CHAPTER 9

Artificial Intelligence, Deep Learning and Precision Medicine

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Abstract: Cancer is often described as a complex and diverse collection of cells, encompassing many distinct subtypes. To address the challenges presented by this heterogeneity, artificial intelligence (AI) has emerged as a pivotal technology for advanced cancer research and clinical management. AI leverages computer systems to perform tasks that traditionally rely on human cognitive abilities. One integral component of AI is Deep Learning (DL), which empowers algorithms to autonomously acquire knowledge from vast datasets, enabling them to make accurate predictions. The application of AI in cancer research has witnessed continuous growth, particularly in the realm of disease prognosis. This advancement has empowered pathologists to precisely diagnose various cancer types, and classify them into different grades and subtypes while considering factors such as invasion patterns, genetic mutations, and metastasis. Such precise characterization of cancers facilitates the implementation of tailored treatment strategies, ultimately leading to more favorable clinical outcomes. Moreover, AI plays a pivotal role in the field of precision medicine, aiding in overcoming challenges like drug resistance and cancer relapse.

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In comparison to traditional methods, AI offers superior predictive accuracy and enhances the overall clinical perspective. This chapter aims to showcase the evolving roles of AI in diagnosing and prognosticating various cancer types and their subtypes. The applications of AI in cancer prediction warrant further assessment and validation, supporting not only routine tasks for pathologists but also complex diagnostic scenarios. Within these pages, we will highlight various instances where AI, particularly DL, has effectively addressed challenges that were previously deemed insurmountable. Additionally, we will focus on the resources and datasets available to foster a deeper understanding of the intricacies of AI in cancer research. The continued expansion of advanced computational methodologies and AI is expected to facilitate the study of interactomes, significantly enriching our insights into oncology and advancing the concept of personalized medicine.

Keywords: Artificial Intelligence, Cancer, Diagnosis, Deep Learning, Machine Learning.

INTRODUCTION

An interdisciplinary approach involves the fusion of two or more fields of research, enabling a more comprehensive, expansive, and innovative perspective, and developing a coherent understanding of a subject. Recent advancements in both biological and computer sciences have spurred scientists to explore the role of computational methods in cancer research. According to the Center for Disease Control and Prevention (CDC), cancer ranks as the second leading cause of death on a global scale [1]. In 2022, the National Cancer Institute (NCI) reported an estimated mortality rate of 609,360 in the United States alone, with 194,451 individuals succumbing to lung cancer, 42,260 to breast cancer, 31,620 to prostate cancer, and 17,760 to brain malignancies (as per the American Cancer Society's 2020 new cancer release report) [2].

Timely cancer detection emerges as an imperative goal that has the potential to save countless lives worldwide. Early detection not only significantly enhances survival rates but also reduces mortality and minimizes the chances of its future recurrence. Initial and accurate diagnosis of cancer is one of the major challenges for the treatment as misdiagnosis is caused because of the lack of molecular markers [3]. Recent studies have shown that nearly 46% of cancer cases have missed diagnosis at the primary health care centre [4] due to the use of traditional pathology techniques. Historically, the diagnosis of malignant disorders has relied heavily on the visual examination of clinical images and the judgment of pathologists. However, this traditional approach is plagued by both time-consuming processes and susceptibility to errors.

Since malignant growth can occur due to a variety of reasons, the genesis is often not clearly known. Ever since, the first malignant cells were detected from sputum

in 1851, several devices and systems have been developed to recognize malignant growth at an early stage. A brief history of diagnosis of malignant growth is shown in Fig. **(1)**. It depicts the significant leaps that changed the course of cancer diagnosis and treatment over the century. Early prediction of any chronic ailment is useful in limiting complications of the disease. It also helps in determining treatment options available to the patients leading to better management. Multiple analyses and treatment conventions have established that AI is a beneficial approach having great implications in the healthcare sector. The fundamental premise of this area of research is to make computers progressively helpful in elucidating complex healthcare challenges and decipher the correct inference using data from different pathological conditions. In the mid-1980s, computer-aided diagnosis (CAD) was developed to aid specialists in improving the interpretation of medical images with precision and within the limit of time [5].

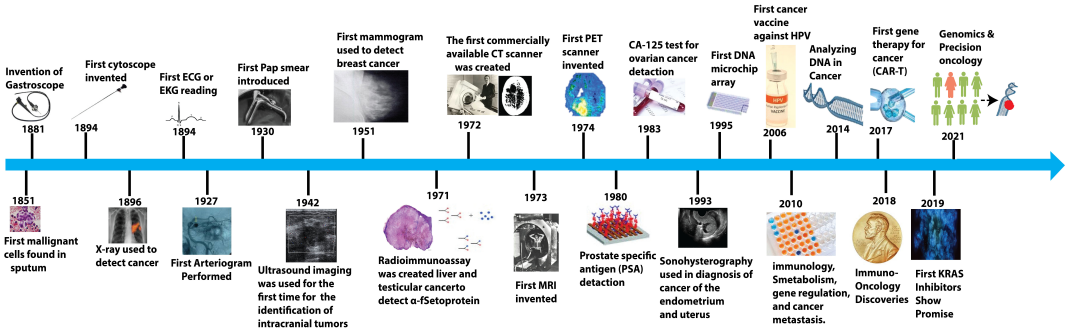

Fig. (1). History of cancer diagnostics [10].

Machine learning (ML) is an interdisciplinary field that complements AI and use computer resources focusing on different disciplines such as neurology, psychology, and statistics to create mathematical algorithms. This in turn facilitates the diagnosis and provides possible treatment options that may vary for different patients [6]. Feature extraction is the key principle that underlines ML reducing the resources and data dimensions while dealing with large datasets. Feature extraction also plays crucial role in over and under fitting of desired models [7]. Several techniques for feature extraction in different types of cancers have been reported in the literature [8, 9], and they have demonstrated their utility. Here we discuss interdisciplinary approaches of cancer detection/prognosis in the context of AI and ML.

However, these extraction-based approaches have their flaws. To address these flaws and enhance quality, a new paradigm known as (DL) has been developed [11]. DL is therefore, a sub-area of ML aimed at permitting abstract portrayal of data through multilayer neural network systems or deep neural systems. From

CHAPTER 10

Precision Medicine in Fibromyalgia Syndrome

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Abstract: Individualized remedy for patients is a middle objective of today's clinical approach and the need of our society. Many elements, starting from genes to proteins, all stay unknown for their unique roles in human physiology. The accurate prognosis, monitoring, and remedy of various problems require dependable biomarkers, for the development of correct healing interventions. Precision medicine within the treatment of Fibromyalgia Syndrome (FMS) has attracted a whole lot of attention, particularly with the gene discovery pushing toward more modern know-how of the biology of disorders. Genome-huge association research has proven that in fibromyalgia pathogenesis, genetic factors are accountable for as much as 50% of the sickness susceptibility. Candidate genes determined to be associated with fibromyalgia are SLC64A4, TRPV2, MYT1L, and NRXN3. Fibromyalgia is an extensive musculoskeletal pain disorder followed by fatigue, sleep, memory, and mood troubles.

Fibromyalgia syndrome (FMS) exacerbates painful sensations by altering the way the brain and spinal cord process both painful and non-painful signals. While some targeted treatments have shown promise in improving the condition of FMS patients in the short term, there is an opportunity to delve deeper into the mechanisms at play. With the aid of animal models, we can further explore the intricate interplay between the brain and the spinal cord, identifying specific genes, loci, and potential failures within the spinal cord that contribute to FMS.

Additionally, FMS has been linked to biogenic amine depletion and mitochondrial dysfunction. These factors represent crucial avenues for investigation. This chapter aims to spotlight the significant advancements in technology that facilitate personalized or precision medicine approaches for FMS. Since FMS is closely tied to the functioning of the brain and spinal cord, research using animal models offers a promising avenue, as conducting experiments on patients presents logistical challenges.

Keywords: Animal model, Anxiety disorders, Amine depletion, Fibromyalgia prognosis, Precipitated fibromyalgia, Sleep aetiology.

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INTRODUCTION

Precision medicine (PM) is defined as an approach to an individual's genetics, environment, and lifestyle to help determine the exceptional preventable method to treat a disorder [1]. PM was well-documented [2] and has now and again proven an excellent impact on some diseases inclusive of FMS [2]. Dramatic progress in the area has enabled achievements in FMS genetics [4]. PM in the narrower aspect assumes that a drug concentrated on a molecular stage might be the satisfactory possible method to attain accuracy, justifying the term “precision remedy. The primary issue is that the definition of what is particular and what is not can most effectively consult with the present-day (molecular and pathogenetic) information. The feasibility of diagnostic tests and their ability to provide additional precision directly influences the accuracy of treatment. The application of genetics has recognized the cause of many severe, regularly treatment-resistant diseases producing a paradigm for PM extending from genetic discovery to *in vitro* and *in vivo* models. Further, this enabled rational drug selection, repurposing, or the discovery of the more recent drug molecules for human beings with mutations within the gene that can be used for clinical trials. Fibromyalgia syndrome (FMS) is a commonplace sickness, characterised by way of persistent generalized aches with an anticipated prevalence of one–5% of the population [5]. FMS is likewise related to a variety of somatic and mental issues, which include fatigue, sleep disturbances, stiffness, anxiety, and cognitive disorder [6].

Over the last couple of decades, research has been devoted drastically closer to the development of newer pharmacological solutions for the fibromyalgia spectrum. This fact is properly predicted in view of the overpowering financial burden posed by using persistent pain in popular and FMS. These efforts have led to 3 medications gaining FDA acclaim for the FMS treatment. nevertheless, at the same time as reviewing the progress made on this location of untreated FMS disease, it should be acknowledged that pharmacological remedy has been met, in widespread, with rather modest prices of success. Actual-lifestyles data published over recent years [7], showed that only a minority of FMS patients took drug treatments for a quick time period both due to lack of efficacy or aspect results, or each. Current suggestions published regarding the remedy of this disorder, unanimously propose, a multidisciplinary approach, with the aid of combining pharmacological remedy with complementary modalities, inclusive of cognitive behavioral therapy (CBT), aerobic and strengthening bodily training, and meditative movement cures [8, 9].

However, studies have proven the reason for a few treatments to be extra powerful than others and proven to be a possible remedy earlier than the identification of

the cause of the disorder. The capacity of PM seems big and huge and the enthusiasm is comprehensible: The PM provides rational powerful care for each person affected by FMS [10]. Throughout human diseases, PM has attracted tons of attention in the direction of the discovery and progress of genetics as this line of work is envisaged to assist in picking out and broadening the makers by using know-how the disorder biology. The rise and the autumn of the preceding revolutions inside the field of FMS bear witness to the idea that a particular exhilaration can also be the simplest quick-lived dream [11].

PM perhaps gets towards disease biology more than any other previous efforts made for sickness diagnosis. However, PM for FMS requires clarity of experimental strategies to increase markers reliable enough to be useful across the spectrum of FMS patients. The modern status of PM in FMS for diagnosis, diagnosis, choice of remedy, and choice to lessen remedy could be discussed here. Development of markers for analysis of FMS involves several additives encompassing genomics, genetics, environmental publicity, assessment of epigenetic amendment, imaging, and radiological surveillance, and getting admission to to health care device (Fig. **1**). Prognostic precision (P.P) is properly set up for FMS, such as markers of sickness activity or its shape, as well as autoantibodies and genetics. Eventually, the latest, and most reliable markers for a secure remedy continue to be inside the lower ranges of disease activity and longer presence of remission of the sickness.

PURPOSE OF PRECISION MEDICINE IN FMS

Character and behavioral environmental exposure get the right of entry to Healthcare Genetics and Genomics customized medicinal drug modifications in Epigenetic Biomarkers Imaging and Radiology (Fig. **1**). An outline of personalized medicine for understanding the underlying factors of Fibromyalgia Syndrome (FMS) should encompass multiple aspects. Purpose of Precision Medication in FMS-vital unmet want of remedy in FMS is the identity of biomarkers that predict which of the medications can be only for a man or woman suffering from FMS, which will decrease sickness activity. Here we strive to outline goal measures for remedy and response therein for the development of personalised medicine for FMS [12].

CHAPTER 11

Circadian Clock Modulation: A Novel Therapeutic Approach to Cancer Treatment and Management

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Abstract: There is a time code to the genome instructing temporal regulation of cellular activities. The time code is expressed in the form of circadian clocks composed of many transcription, co-activator, and co-repressor factors. The transcription-translation feedback loops generated collectively by these factors regulate daily ~24-hour rhythms in physiology, metabolism, and behavior across divergent phyla. Genome-wide studies reflect that chronic disruption of circadian rhythms provides a plinth for the occurrence and progression of multiple diseases across our lifespan. Increasing epidemiological and experimental evidence are confirming that circadian clocks are compromised in cancer. Altered expression of circadian clock components is likely to be associated with the onset and progression of cancer. The concept of targeting circadian clocks at the molecular level is rapidly evolving and opening a new therapeutic window in cancer. Here we discuss the approaches and recent advancements that have been made for the identification and development of clock-modulating small molecules bearing drug-like properties for the therapeutics and therapeutic management of cancer. It is envisaged that this chapter will augment the concepts of precision medicine in general and circadian-related system anomalies.

Keywords: Cancer, Circadian clock, Clock-modulating small molecules, Drug-like properties, Precision medicine, System anomalies, Time code.

INTRODUCTION

Circadian clocks refer to the internal biological timing systems that regulate various physiological and behavioral processes in organisms. These clocks operate on a roughly 24-hour cycle and are found in a wide range of organisms, including humans, animals, plants, and even some microorganisms [1].

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The circadian clock enables organisms to synchronize their biological activities with the Earth's daily cycle of light and dark. Circadian clocks are molecular systems consisting of various transcription factors, co-activators, and co-repressors [2, 3]. These components work together to create transcription-translation feedback loops, which play a crucial role in regulating daily rhythms lasting approximately 24 hours. These rhythms affect diverse aspects such as physiology, metabolism, and behavior across different phyla. The circadian timing system plays a crucial role in regulating sleep-wake cycles, hormone production, body temperature, metabolism, immune function, and many other physiological processes. Disruptions to the circadian timing system, such as shift work, jet lag, or certain sleep disorders, can have significant impacts on overall health and well-being [2].

In mammals, the circadian timing system encompasses the interconnected network of biological processes and mechanisms that regulate the body's circadian rhythms. It includes the central clock (pacemaker), known as the suprachiasmatic nucleus (SCN), located in the hypothalamus of the brain [1]. The SCN, consisting of around 20,000 neurons, is synchronized by the natural light-dark cycle, acting as the dominant zeitgeber (time giver). The SCN receives light input from the eyes and coordinates the timing of various physiological and behavioral functions. In addition to the SCN, the circadian timing system involves peripheral clocks found in various tissues and organs throughout the body. These peripheral clocks are influenced by signals from the SCN and help synchronize the timing of local processes with the central rhythm. Fig. (**1**) represents the general organization of the circadian timing system in mammals. In mammals, light signals are detected by special cells in the retina called intrinsically photosensitive retinal ganglion cells (ipRGCs). These cells transmit chemical messages, like glutamate and pituitary adenylate cyclase-activating polypeptide, to the suprachiasmatic nucleus (SCN) through a pathway known as the retinohypothalamic tract [2]. These chemical messages trigger the influx of calcium ions into the SCN, leading to the activation of specific protein kinases. Consequently, the Ca2+/cAMP-response element binding protein (CREB) becomes phosphorylated [3]. The phosphorylated CREBs then bind to specific regions called Ca2+/cAMP-response elements (CREs) within gene promoters. This binding initiates the expression of certain genes called early immediate genes (EIGs), which include Per1 and Per2 [4]. The expression of these EIGs drives neuroendocrine signals that communicate with cell-autonomous peripheral clocks instructing temporal regulation of cellular activities [3, 4]. In addition, peripheral clocks are likely to be influenced by feeding [5, 6], activity [7], and strong social interactions [8].

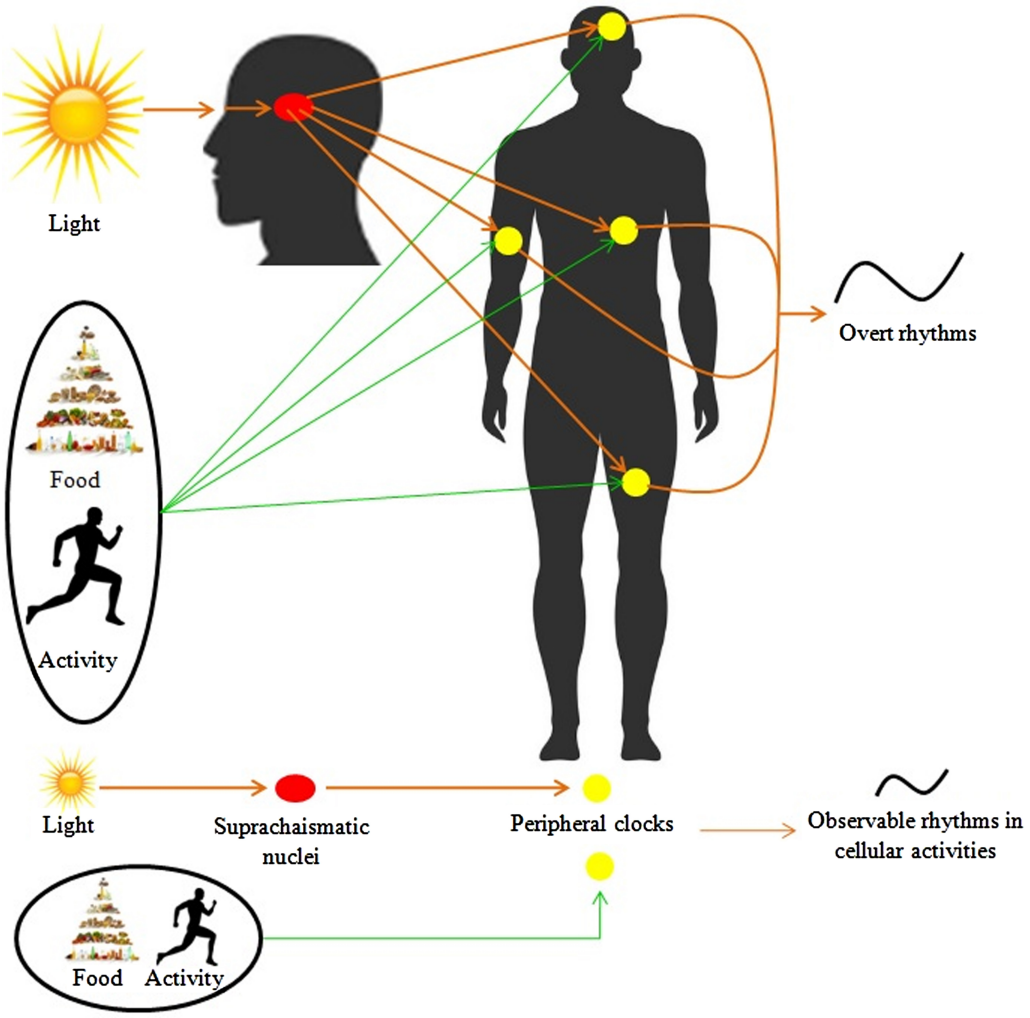

Fig. (1). Circadian clocks system in mammals. Circadian clocks in mammals are organized in a hierarchical system. The master clock "suprachaismatic nuclei (SCN)" is present in hypothalamic region of brain. Light signals are received in eyes by the photosensitive cells. These cells generate chemical messages that travel through retinohypothalamic tract to reach SCN. SCN communicate with peripheral clocks to transducer them the "internal day" and generates overt rhythms in cellular activities. High degree of intercellular coupling of SCN neuronal cellular clocks is a key feature to orchestrate circadian programme. Clocks in peripheral organs also respond to signals generated by feeding, activity, and strong social interactions.

Genome-wide transcriptome, proteome, and metabolome studies reflect that optimized daily rhythms sustain health; their disruption increases the risk of humans to multiple diseases including cancer [9 - 18]. Increasing epidemiological and experimental evidence supports the idea that circadian rhythms are disrupted in various types of cancer, including breast cancer [19 - 21], oral cancer [22],

CHAPTER 12

A Roadmap towards Precision Medicine for Multiple Sclerosis

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Abstract: Multiple Sclerosis (MS) is an autoimmune inflammatory disease and this affects roughly 2.8 million people worldwide. This is a highly heterogeneous disease in terms of course, clinical symptoms and response treatment. The exact pathogenesis and aetiology of this disease remain unknown. The lack of successful treatment can be explained by the heterogeneous nature of MS with patients exhibiting widely disparate clinical features and progression patterns resulting in phenotypic heterogeneity. Therefore, there is a need for the development of biomarkers for MS. The "Omics" approaches have been exploited for the development of biomarkers although the system biology was taken into consideration. With the introduction of Omics approaches, personalized medicine has gained potential revealing hitherto unseen elements of illness causation, initiation and progression. This chapter will focus on the potential role of genomics, transcriptomics, proteomics and metabolomics in MS for the possible identification of biomarkers facilitating and augmenting the concept of precision medicine.

Keywords: Biomarkers, Early diagnosis and precision medicine, Multiple sclerosis, Omics approaches.

INTRODUCTION

The term "Personalized medicine" (PM) refers to the medical treatment that takes into account factors such as the disease status of the patient and their background to select the most appropriate treatment. This strategy gives patients and medical staff the chance to gain from more focused and efficient treatments, potentially increasing healthcare gains and boosting the effectiveness of the healthcare system. Finding the right drug for the right patient at the right time is the main aim of personalised medicine [1, 2].

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OMICS covers genomics, transcriptomics, proteomics, metabolomics, epigenomics and lipidomics, among other high-throughput technologies that have rapidly grown in recent years, allowing us to elucidate the complex pathophysiology behind complicated biological events (Fig. **1**). Additionally, it is concentrated on the customization and timing of therapeutic and preventive actions based on biological data, omics biomarkers and molecular disease pathways. The non-invasive, high-throughput and cost-effective methods of metabolomics and proteomics study of biomarkers show promise for diagnosing early-stage prognosis, monitoring therapy effectiveness, and contributing to the creation of innovative targeted medicines. Therefore, "omics" has seen a sharp increase in studies on biomarkers' discovery in recent times and it is very important to understand system biology. With the introduction to Omics approaches, personalised medicine has gained momentum and now has potential to uncover hitherto 'unseen' elements of illness causation, initiation, and disease progression [3].

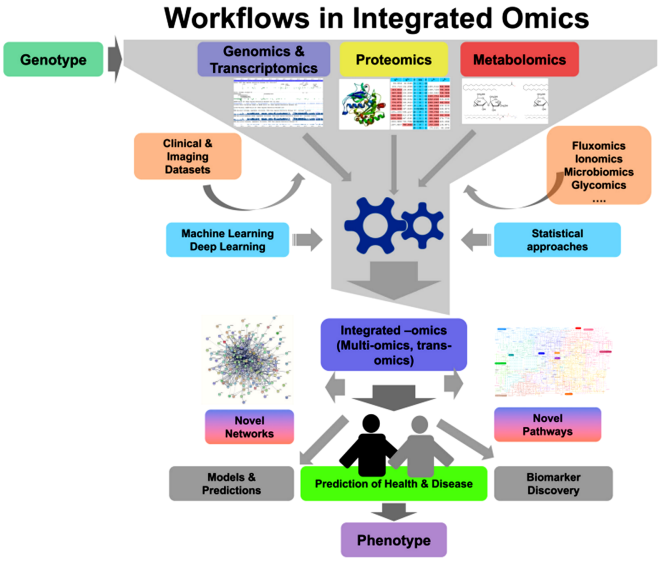

Fig. (1). Integrated Omics workflow adapted from B.B. Mishra *et al*., 2019 [3].

Multiple Sclerosis **(**MS) is an inflammatory, chronic, autoimmune disease of the central nervous system (CNS) resulting in neuronal demyelination and axonal damage in the brain and spinal cord. MS affects roughly 2.8 million people worldwide. The MS is a leading cause of non-traumatic medical disability in young people of 20-45 years. This disease commonly affects women (Female to male ratio 3:1) though the cause is still unknown.

The scientific community generally agrees that various environmental conditions in genetically susceptible persons produce an aberrant activation of the immune system against CNS myelin. MS is a highly heterogeneous disease in terms of course, clinical symptoms and response to treatment. It is characterized by inflammatory demyelinating relapsing-remitting multiple sclerosis (RRMS) which progresses over time to a progressively degenerative stage characterized by scar formation and axonal loss, resulting in cognitive disability [4, 5].

MS complexity has been characterised more thoroughly using epigenetic, transcriptomic, proteomic, and metabolomic techniques. A combination of techniques provides unique insights into the molecular underpinnings of disease pathogenesis. This enables its integration and translation into clinical neurology. Given the scarcity of prognostic markers for MS, the importance of "omics" techniques that can build a fingerprint for each patient appears to be a suitable approach for accomplishing "ad hoc" therapeutic therapy [4]. However, according to available data, personalized therapies for MS are still at the preliminary stage. This chapter will concentrate on the potential role of genomics, transcriptomics, proteomics and metabolomics in MS, for the possible identification of biomarkers useful in the context of personalized medicine.

DIAGNOSTIC CRITERIA FOR MULTIPLE SCLEROSIS

MS is classified into four subtypes based on empirical evidence which includes relapsing-remitting multiple sclerosis (RRMS), primary progressive multiple sclerosis (PPMS), secondary progressive multiple sclerosis (SPMS), and progressive relapsing multiple sclerosis (PRMS). Thus far, there is no specific laboratory marker for the diagnosis of MS. McDonald criteria for diagnosis were first developed in 2001. The International Panel on Diagnosis of MS developed the McDonald criteria in 2001, giving magnetic resonance imaging (MRI) increasingly more weight in the diagnosis of MS as a result of the technology's increased availability. These criteria were subsequently revised in 2005 and 2010, with the most recent revision occurring in 2017. The 2017 revisions to the McDonald criteria allow for early diagnosis of MS, and an increasing number of approved disease-modifying therapies (DMTs) provide the best treatment for MS patients by altering the disease course [6]. Presently, there are 13 MS disease-modifying therapies for MS that have received FDA approval [7]. MS is diagnosed through clinical evaluation and supported by laboratory findings such as MRI, and CSF analysis. Another important examination is lumbar puncture for CSF examination, cytopathological evaluation, microbiological test, test for IgG index and qualitatively oligoclonal band analysis. The risks of misdiagnosis MSt be weighed against the advantages of early diagnosis [8].

CHAPTER 13

Role of Epithelial-Mesenchymal Transition (EMT) Therapy in Personalized Cancer Treatment

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Abstract: A major clinical challenge in treating cancer patients is the metastasis of cells to distant organs forming secondary tumors. Many cancers are prone to metastasis due to epithelial-mesenchymal transition (EMT), which confers motility and invasive properties to the tumor. EMT also contributes to chemotherapy resistance and facilitates metastasis by generating cancer stem cells (CSCs). Therefore, the EMT program has therapeutic potential for personalized cancer treatment. In more severe situations, this might destroy metastatic cancer cells that are already present or stop tumour progression in high-risk patients who are at risk of developing metastatic tumours. The options for developing EMT-based personalised cancer therapeutics are covered in this chapter, along with a summary of the evidence supporting some of the suggested EMT targets and a discussion on the possible benefits and drawbacks of each strategy.

Keywords: Biomarkers, cancer stem cells, epithelial-mesenchymal transition, personalized cancer therapy, tumor metastasis.

INTRODUCTION

Epithelial cells depart from their non-invasive characteristics during the EMT process and gain a more mesenchymal and invasive nature. The EMT process is characterized by the loss of apical-basal polarity and cell-to-cell adhesion and the transition into spindle-like cells with motility [1]. This process is regulated by various EMT inducers and activators whose role is to induce an EMT program in epithelial cells. At the molecular level, EMT involves the down regulation of epithelial proteins such as E-cadherin and cytokeratin, and the up regulation of mesenchymal protein markers such as vimentin. EMT infers placentation, healing of wounds, tissue fibrosis, and cancer metastasis in adults [2].

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The most common reason for mortality of cancer patients is metastasis. EMT plays a crucial role in cancer metastasis, as it converts an immobile epithelial phenotype into a motile invasive phenotype, which can metastasize into distant organs as secondary tumors [3]. It is critical to create novel therapeutic approaches to stop the metastasis of organ-confined tumours in patients at high risk for them, as well as to get rid of metastatic cells already present in patients with more advanced disease states. Such a technique might be made easier by the pharmaceutical targeting of the EMT process in particular cancer types [2]. In recent years, cancer treatment has been revolutionized following the identification of several molecular alterations that are responsible for cancer development. Instead of focusing on the anatomic site of tumor development as the target for treatment, biomarkers are now appropriate candidates for therapeutic intervention [4]. This change has resulted in a single targeted drug treating large groups of patients with cancer that has a specific molecular feature. This opened the door to personalized therapy. In addition to genomics, it is clear that molecular phenotyping measurements and characterization are critical for improving personalized therapy for cancer patients [5]. Further, proteomic analysis may be useful when several molecular alterations are detected, making the identification of the most critical one. Another crucial area to advance a personalised treatment strategy is metabolomics. It is crucial for not only identifying targetable biomarkers but also for developing pharmacological phenotypes that make it easier to comprehend how differently each patient responds to treatment. Additionally, metabolomics can aid in assessing drug resistance and illness relapse, resulting in the creation of fresh treatment approaches [6].

There is mounting proof that EMT, which focuses on cancer metastasis, is a clinically useful mechanism for cancer treatment. However, important issues about the viability of preventing or reducing metastasis by targeting EMT still need to be resolved. Targeting EMT as a potential adjuvant therapy for cancer treatment is covered in this chapter.

EPITHELIAL AND MESENCHYMAL PHENOTYPES

The building blocks of life are cells, which can take on a variety of morphological phenotypes and sustain the intricate intracellular and extracellular processes required for the survival and operation of the organism. One such classification of cellular phenotype is the epithelial and mesenchymal phenotype both having unique characteristics [7].

The epithelium is composed of specialized membrane junctions, including tight junctions (TJ), adherent junctions (AJ), desmosomes, and gap junctions that hold the epithelium together. Owing to localized distribution of adhesion molecules,

such as cadherins and integrins, a lateral belt of intercellular junctions is formed as a result of apical-basolateral polarization. An apical structure is defined by the polarized arrangement of the intracellular actin cytoskeleton, while a lining is formed by the basement lamina, which divides the epithelium from the mesenchyme [8].

On the other hand, mesenchymal cells have no structural organisation of cell surface molecules or actin cytoskeleton, lack apical-basolateral polarity, and lack cell layer organisation. Mesenchymal cells are scattered haphazardly across the extracellular matrix and lack junctional integrity. They are distinguished by front-rear polarity, a characteristic that makes them more mobile and invasive [9]. While epithelial cells grow as "clusters" or "islands" of cells with intact intercellular cell-cell adhesion, mesenchymal cells exhibit a spindle-like, fibroblastic shape in *in-vitro* cell culture [10].

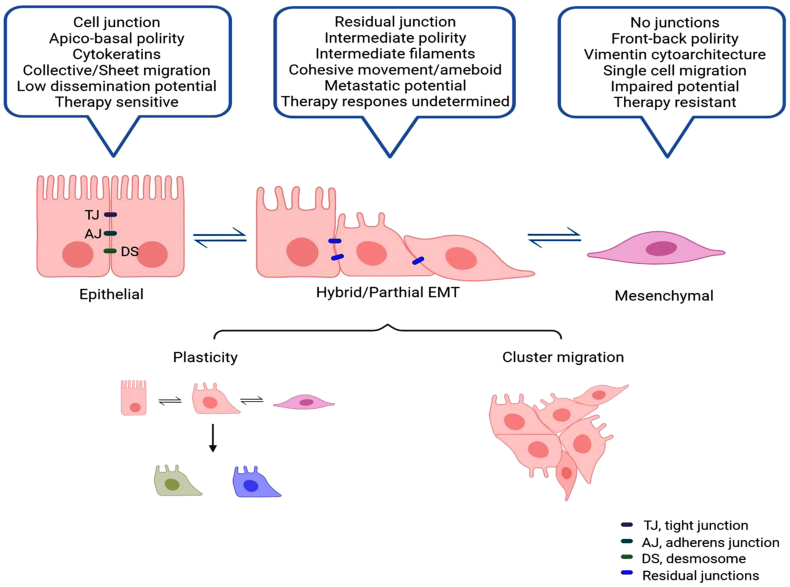

Fig. (1). Epithelial to mesenchymal transition [63].

A PERSPECTIVE ON THE TRANSITION FROM EPITHELIAL TO MESENCHYMAL CELLS

Epithelial-to-Mesenchymal Transition (EMT), a conserved evolution process, has been shown to be able to convert polarised, non-motile epithelial cells into motile mesenchymal cells. As a result of EMT, epithelial cells gradually lose many of their epithelial characteristics, including apical-basolateral polarity and dissolution of cell-cell junctions, and they consequently acquire motility-invasive

CHAPTER 14

Oral Cancer and Prospects of Precision Medicine

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Abstract: Precision medicine is a systematic therapeutic approach that tailors the overall treatment process as per an individual's unique characteristics; taking into account the genomic makeup and lifestyle. This approach has shown promising results in treating certain types of cancers, including that of highly heterogeneous oral cancer. Oral cancer is a type of head and neck cancer mainly caused by poor oral hygiene, alcohol, and tobacco abuse, and promotes HPV infection. The conventional approaches for the treatment of oral cancer often rely on surgery, chemotherapy, and/or radiotherapy. Now, precision medicine, with the advent of newer diagnostic techniques, enables healthcare professionals to diagnose the disease early and treat the patient with appropriate medicines and optimized doses. This ensures overall safety while minimizing undesirable exposure to not-so-effective drug regimes. After a brief introduction to precision medicine, this chapter details genetic mutations as targets for precision medicine and the advantages of this approach in oral cancer treatment. It is envisaged that this approach offers improved efficacy, safety, reduced side-effects, and prepares the body's immune response against oral cancer. Targeting specific proteins, such as EGFR and HER2 to suppress tumor growth or make cancer cells more susceptible to the immune system's combat mechanism is also discussed followed by an overview of various drugs that are being used to treat patients who are positive for HER2 and EGFR. Various challenges and limitations of precision medicine and future prospects for research in this area are highlighted.

Keywords: Chemotherapy, EGFR, MAb, Oral Cancer, Precision Medicine, Small molecule inhibitors, Targeted Therapy.

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INTRODUCTION

Though the history and origin of the term "precision medicine" remain unclear, it has a clear impact on increasing the overall survival rate in a large number of diseases. Moving forward from treatments designed for "average patients" and the "one drug fits all" hypothesis, precision medicine is developed on the basis of the genetic makeup of an individual which decides the molecular and genetic properties governing the development and progression of disease along with the responses to a particular drug [1]. This response and development are the results of the expression of different proteins at different levels. Along with genetics, an individual's lifestyle choices like diet and exercise also play a critical role in developing precision medicine. We observe phenotypic effects in patients which is a combination of both genetics and the environmental factors to which they are exposed [2].

In order to develop precision medicine, the first step requires the identification of specific biomarkers, genes, or any other factor that is unique in a way that may increase or reduce the chance of occurrence of a disease or may affect the path of progression of disease in a patient. The identification of such markers is utilized to divide patients into subpopulations. This is done in such a way that their susceptibility to disease is established and their targeted treatment response is as per the expectation [3]. This way, a person is given the best-suited treatment with limited side effects at a reduced cost of diagnosis and treatment. Thus on the basis of the lifestyle, clinical phenotype, and molecular diagnostics of a patient, precision medicine is developed in accordance with an individual's medical requirement [4]. The overall environment seems to play major roles in overpowering the genetic makeup of the patients. Thus, a healthy environment together with a healthy lifestyle, healthy foods coupled with healthy attitudes, and healthy work conditions will ensure a healthy life. Nothing can be done with the genotype one inherits. However, phenotype can be fine-tuned following the set rules of nature and nurture including regular exercise.

Oral Cancer

Cancer is one of the leading causes of death among non-communicable diseases. According to WHO, 19.3 million new cases were reported and around 10 million deaths were caused by all cancers in the year 2020. Oral cancer is among one of the leading contributors to it with around 3,77,713 new cases and 1,77,757 deaths in the year 2020 [5]. The common causes of oral cancer include poor oral hygiene, use of alcohol and tobacco, use of betel quid, an infection caused by the human papillomavirus, and Epstein Barr Virus, besides occupational hazards like exposure to radiation [6, 7]. These factors are augmented in some individuals with

a genetic predisposition. Fanconi anemia is a rare genetic disorder that is characterized by a mutation in any of the 22 FANC gene families and is known to increase the possibility of oral cancer [8]. Thus, an early diagnosis of oral cancer is crucial for the survival of the patient. A large number of options are available for the purpose of diagnosis. This includes some common, non-technical but very effective approaches like a physical examination conducted by physicians and some highly advanced non-invasive methods that are not even accessible in many developing countries [9].

Genetic Mutations in Oral Cancer

A large number of genetic mutations are known to accumulate in cancerous cells. A number of studies are being conducted to identify these mutations in order to develop markers based on such mutational load and to design precision medicine targeting common mutations among subpopulations of patients. Most of these mutations are present in signaling pathways and some are present as chromosomal abnormalities [10]. Around two-thirds of oral cancer cases are known to have deletions in 9p21-22 [11]. TP53, a tumor suppressor gene involved in the regulation of the cell cycle is most commonly found to be mutated in oral cancer and plays a fundamental role in oral cancer progression. The nature of the mutation in TP53 can also be used to assess the status of exposure to tobacco, as G>T transversions are reported to show a high presence in tumors that are caused by exposure to tobacco [12]. TP53 mutations reduce the overall survival rate of patients compared to those without TP53 mutations. Mutations in tumor suppressor genes are more common among smokers while mutations in oncogenes are more frequent in non-smoker oral cancer patients [13]. Also, TP53 is found to have a lower rate of mutation in Asian patients as compared to Caucasians [14].

Thrombospondin 1 (TSP 1) and deleted in oral cancer (DOC-1) are the only known tumor suppressor genes after TP53, which are found to be mutated in oral cancer. DOC-1 gene mutation reduces the transcription and translation of the proteins. The reintroduction of wild type DOC-1 gene in tumors has shown the reversal of cancerous phenotype to normal keratinocyte cells. TSP-1 gene mutation is correlated with angiogenesis in oral cancer. TSP 1 transfection in oral cancer cells has been shown to suppress angiogenesis in the tumor [15, 16].

Epidermal growth factor receptor (EGFR) is an oncogene that is frequently found to be overexpressed in oral cancer and also in breast cancer. Aberrant expression of EGFR has been correlated to the development of oral cancer. EGFR has been shown a 5 to 50-fold increased expression in oral cancer [17]. EGFR serves as a receptor for the epidermal growth factor (EGF) and transforming growth factor

CHAPTER 15

Therapeutic Potential of Phytoconstituents and Personalized Medicine

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Abstract: India has a rich tradition of the use of herbal medicine since the time immemorial. The treatment using plant-based medicaments became possible owing to the rich medicinal plant biodiversity. Several spices used on a regular basis in food preparation offer protection from a variety of ailments. Further, food consumption in different parts of the country has evolved based on culture, tradition, weather, and availability of resource materials. In a rural set-up, generally, the food is cruder but natural and thus healthier. Food harnessing and garnishing have become a standard practice to enhance the taste and look. Some of the herbs are used directly as food whereas others as food additives. Simultaneously, a large number of phytoconstituents have been characterized for their medicinal properties. In this chapter, we report on Phytoconstituents used for herbal formulation and discuss their therapeutic potential in human diseases. It is envisaged that such information would be of great use for ameliorating diseases ensuring better health complementing the concept of personalized medicine.

Keywords: Food additives, Human diseases, Medicinal plants, Phytoconstituents, Personalized medicine.

INTRODUCTION

Natural remedies represent plant-derived compounds that have traditionally been used to prevent sickness maintaining the indigenous or regional therapeutic traditions. These plant-derived ingredients have undergone minimal or no major alteration. In the context of health care, traditional herbal medicines have attracted a great deal of attention. In the absence of doctors, clinicians, hospitals, and health centers, traditional medicines proved to be a lifeline for human civilization. Literature shows China's attempt to prevent or cure severe acute ailments through the traditional system [1]. Similarly, about eighty percent of the African popula-

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tion has used traditional herbal medicine [2]. From the ancient period till now, Indians have relied upon six well-articulated systems which are recognized as Ayurveda, Siddha, Unani, yoga, Naturopathy, and Homeopathy. Besides these, there are many folklore medicines in Indian homes which are not registered. However, in the past, limited studies have been conducted on several aspects of these systems [4].

Previous research on traditional herbal remedies has shown their potential for the well-being of the people world over. Traditional herbal studies have received significant financial support from several government bodies such as China, India, Nigeria, and the United States of America and the efforts of these countries have been endorsed by WHO [2]. Additionally, in search of herbal medicine, private sectors have spent millions of dollars on the exploration of new bioactive molecules from plants [3]. In this chapter, we elucidate the overall potential of herbal formulations particularly phytoconstituents, their active factors wherever possible and future prospects in the context of personalized medicine. The concept of personalized medicine is based on the fact that every individual is unique with respect to his/her genomic constitution, mutational landscape, metabolic activities, lifestyle, food habits, regions, religion, faith, and the choice of mating partners. All these attributes affect the body and therefore one single prescription works well for someone but the same prescription does not work for another person. In addition, the drug may have side effects in one person but the same drug does not affect the other person. This heterogeneous response of the patients towards a single drug, therefore, may be made more uniform if we are able to generate the consensus keeping in view all the variables. Since there are several sub-disciplines of personalized medicine, generating consensus will involve additional efforts in research and development. Many times, the drug needs to be titrated to be able to uncover the most effective dose for a patient. While drug titration may not be possible for every situation, past observation clearly suggests that drug titration must be taken seriously. A diabetic patient for example was found to have unstable glucose levels despite the correct medicine he was prescribed. Upon a careful investigation, the same drug was titrated and the quantity was increased. The result was very positive as his glucose level stabilized. This suggests that *one-size-fits-all* is not the correct approach. Since in this chapter we are dealing with herbal medicaments, we will remain confined to this realm only. Other chapters in the book will cover additional aspects of personalized medicine.

TRADITIONAL REMEDIES

Traditional medicine has its much deeper roots in India and has undergone a constant process of evolutionary transition since the Vedic age. A single drug or

mixtures in crude shape are valued above multiple-fold preparations. Traditional Medicine has evolved into several systems because of which differences in the origins and historical development are found. However, they share a common background and their foundation is based on the plants and at times, some other additives such as (*Bhasma*). Medicinal plants have roots, shoots, leaves, bark, and flowers and fruits each one having a different property and potency. This warranted in-depth characterization to uncover their active factors and then monitor health potentials as therapeutic agents. Plants are important parts of our civilization and have been used extensively for a variety of fruits production, beautification, ornamentation, wine cheese, pickle, jam, and essential oil preparation. Plants have been used as traditional medicine since 2600 BCE as Mesopotamia recorded 1000 plant-based products. These include the use of extracted oils of *Cupressus arizonica* Greene, *Commiphora acuminata Mattick, Cedrus libani* A. Rich., *Glycyrrhiza glabra L*., and *Papaver somniferum L*., which are still used to treat common colds, coughs and swelling [5]. Egyptian pharmaceutical, which dates back to about 2900 BCE, claims to be the oldest form of modern medicine. The "Ebers Papyrus" is the best-known record from 1500 BCE, and lists more than 700 drugs, most of which were made from plants [6]. Over the course of many centuries, traditional Chinese medicine has gained widespread recognition, as evident from the record of around 2000 years ago (1100 BCE; Wu Shi Er Bing Fang; 52 medicines), followed by the herbal Shennong (100 BCE; 365 medicines) and the herbal Tang (659 CE; 850 medicines). On the other hand, records of traditional Indian medicine go back more than 5,000 years (Charaka and Sushruta Samhitas hold 341 and 395 herbal medicines separately 1,000 BCE ago) [7].

From across the globe, Romans and Greeks contributed a lot to the development of traditional medicine in the ancient Western world. Dioscorides, a Greek physician who lived around 100 BCE, wrote about how traditional medicine was collected, stored, and used in the "known world" at the time. About half of the top 50 drugs sold in European pharmacies are NPs (natural products) that are sold as herbal or food supplements. Although the modern pharmaceutical industry all over the world relies on synthetic drugs, however, close to about 25% of the drugs in the modern pharmacopeia come from plants. Several synthetic drugs are made using original formulations based on plants representing naturopathy (NPs) [8 - 10]. Thus, in the true sense, overall plant-based drug formulation would be more than 25%. Realizing the merit and potential of the plant-based drugs, the World Health Organization (WHO) has taken note of it. Thus, as per the WHO, "the entire understanding, abilities, and methods based on the hypotheses, convictions, and experiences of indigenous drugs used in different cultures, whether logical or not, actually provide substantial support to the human healthcare system. It may be noted that plant-based formulations have found their use for animals,

CHAPTER 16

Phytoconstituents and their Therapeutic Potential in Precision Medicine

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Abstract: Spices and herbs have been an integral part of Indian cuisine since ancient times. They are not only cherished for improving the flavor and taste of Indian food but also confer their health benefits. Instant herbal remedies prepared from spices and herbs found in the kitchens of Indian homes have been used to treat many ailments and infections in a natural way. Most of the spices and herbs have high nutritional and anti-oxidant properties responsible for their medicinal effects. This is because of the presence of phytochemicals in the plants. The emphasis of the current article is to provide an overview of the therapeutic potentials elucidating the phytochemical compositions of the key Indian plants. Many such plant products are used mainly as spices in Indian cuisine. In this review, we aim to highlight the chemical constituents and active factors of some of these spices and their pharmacological potential. We believe that in-depth molecular characterization of these spices for all their chemical constituents and their impact on cells, organs, and different organelles will provide a wealth of information useful for human health. These findings may further be chiseled in the form of personalized medicine.

Keywords: Indian Spices, nutritional values, personalized medicine, phytochemicals, therapeutic properties.

INTRODUCTION

Life without spices is dull and insecure because spices are known to regulate gut microbiomes. Spices are the aromatic components of plants, such as seeds, stalks, bark or flowers. They are hardly used in fresh form but frequently used in the dried form. Due to their exceptional medicinal value in traditional therapies, they are regarded as safe, reliable, affordable, and are efficient against a wide range of illnesses and ailments. Depending on their composition, different spices exhibit varying amounts of anti-bacterial and anti-oxidant activity, making them powerful scavengers of free radicals and fighters against microorganisms.

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As a result, they are referred to as "Potent therapeutic agents" [1, 2].

Flavonoids and phenols are known to act as primary anti-oxidants that can scavenge free radicals and strengthen the immune system. Alkaloids richly present in the spices are beneficial as they impart anti-rheumatic, anti-cancerous, and anti-spasmodic activity. While these properties are well documented in the context of human health, what still remains unknown is the precise quantity of these plant derivatives to be given to the patients. Since each patient is unique owing to genome heterogeneity, the herbal formulation needs to be adjusted and readjusted accordingly. This would fulfill the much desired aspirations of personalized medicine augmenting the human health care system in an affordable manner. India claims to have a large number of species in addition to an equally large number of medicinal plants. Some have been characterized whereas others still need to draw the attention of the researchers. Owing to the presence of tannins in the spices mainly in Clove and Ajwain, they exert anti-hemorrhoid and anti-diarrheal activity. The presence of terpenoids in large quantities particularly in Clove, Pepper and Cinnamon enhances the therapeutic properties. Hence they exert antiseptic, diuretic, analgesic, anti-rheumatic and anti-microbial activities [3] (Fig. **1**).

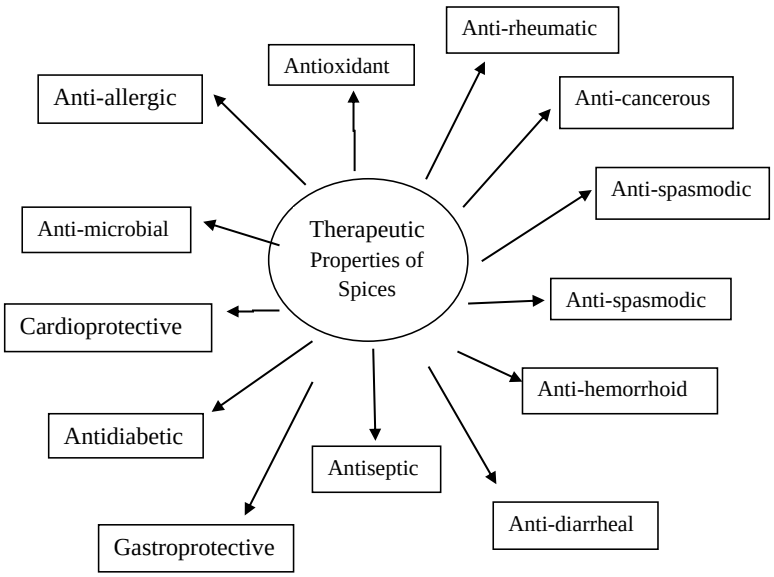

Fig. (1). Therapeutic properties of some common Spices used routinely for culinary preparation.

Consequently, phytochemicals derived from plants are crucial for maintaining human health and preventing disease. Due to the presence of such

phytochemicals, spices and herbs have attracted a great deal of attention for their therapeutic and medicinal properties [4, 5] (Table **1**).

Table 1. Medicinal properties of some known spices and their chemical constituents.

S. No.	Name of the Spices	Part Used/ Common Name	Different Chemical constituents	Medicinal Properties	References
1	Turmeric (*Curcuma longa*)	Rhizome/ Haldi	Curcumin	anti-bacterial, anti-inflammatory, hypocholesteremic, anti-histaminic, anti-hepatotoxic, anti-fungal, and anti-arthritic	[6-7]
2	Black Cumin (*Nigella sativa* L.)	Seeds/ Kalonji	thymoquinone (TQ), thymohydroquinone, thymol, carvacrol, nigellidine, nigellicine, and –hederin	anti-oxidant, anti-inflammatory, immunomodulatory, anti-cancer, neuroprotective, anti-microbial, anti-hypertensive, cardioprotective, antidiabetic, gastroprotective, and nephroprotective and hepatoprotective	[8-9]
3	Fenugreek (*T. foenum-graecum*)	Leaves and Seeds/ Methi	Galactomannan,neutrallipids,Steroidalsaponins and alkaloids	Diuretic, galactogogue, anti-microbial, useful in heart diseases, Anti-diabetic, Gastroprotective and Hepatoprotective	[10-11]
4	Cumin (*Cuminumcyminum*)	Seeds/ Zeera	Cumaldehyde, vitamin A, vitamin C, cuminal, cuminicalcohol, γ-Terpinene, Safranal, p-Cymene, volatile oils, and β-Pinene.	Antispasmodic, carminative, digestive stimulant, anti-oxidant, hypocholesterolemic, anti-inflammatory.	[6, 12]
5	Cloves (*Syzgiumaromaticum*)	unopened flower buds/Laung	Caryophyllene, eugenol, salicyclic acid, tannin,, sterols, triterpenes, and flavonoids	Anti-inflammatory, anaesthetic, pain-relieving, anti-viral, anti-fungal, anti-microbial, anti-diabetic, anti-thrombotic, and anti-microbial effects.	[13-15]
6	Cinnamon (*Cinnamomumzylanicum*)	Bark/ Daalcheeni	Cinnamaldehyde, cinnamate, cinnamic acid, and a number of essential oils	Anti-inflammatory, anti-bacterial, anti-fungal, anti-oxidant, and antidiabetic properties and anti-cancer agent.	[16-17]

CHAPTER 17

High Altitude Hypoxia Stressor Associated Diseases and Precision Medicine

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Abstract: Hypoxia is a condition wherein an organism, a cell or a region of an organ does not receive adequate levels of oxygen to carry out normal life processes. The ability to sense oxygen levels and respond appropriately is termed "oxygen sensing" which might be used in certain cases to describe the biological effects of hypoxia. Hypoxia is an important facet involved in multiple diseases. Ranging from high-altitude pulmonary edema to cancer, oxygen-sensing molecular networks are crucial for survival and have a notable impact on human health systems. The type, duration, and intensity of hypoxic episodes have been found to have a multitude of effects ranging from beneficial to harmful in diverse conditions like obesity, type 2 diabetes and obstructive sleep apnea. A very important niche of hypoxia is the study of environmental stressors also called high-altitude hypoxia. High-altitude hypoxia holds multiple molecular similarities with diabetes, cancer, obesity, and other diseases like COPD. In addition, unregulated exposure to hypobaric hypoxia is known to directly cause high-altitude illnesses like HAPE/HACE. An interesting facet of high-altitude hypoxia is the ability of the molecular and physiological systems to acclimatize to the high altitude. This acclimatization is known to prevent the occurrence of high-altitude illnesses. This review highlights the previous studies to build a framework that elucidates the occurrence of hypobaric hypoxia, its socio-economic impact, molecular underpinnings, and correlation with inflammation, cancer, diabetes, obesity and possible therapeutic approaches to these diseases.

Keywords: Disease, Hypobaric hypoxia, High altitude acclimatization, Inflammation, Therapeutics.

INTRODUCTION

Human life revolves around genetics and the environment. Genetics contributes only about 10% whereas environment plays major roles.

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There are several aspects of environment that include our lifestyle, food habits, ethnicity, choice of mating partner, social and religious practices, demography, epidemiology, social interactions, genetic susceptibility and resistance, and environmental living condition. A large number of environmental conditions tend to affect our physiology and immune system. Lack of exercise, and the use of substances (marijuana, heroin, cocaine, or methamphetamine and alcohol) invariably affect our health and often result in comorbidity. Living at higher altitudes is part of the environment that causes stress and affects our body although the body tries to acclimatize with its surrounding.

Table 1. List of major high altitude cities worldwide and their populations.

Average height	Country	Population	Est. year
4,150 m	El Alto, Bolivia	1,184,942	2014
4,090 m	Potosi, Bolivia	170,000	2007
3,836 m	Shigatse, China	117,000	2013
3,825 m	Juliaca, Peru	225, 146	2007
3,819 m	Puno, Peru	120, 229	2007
3,706 m	Oruro, Bolivia	250,700	2011
3,658 m	Lhasa, China	373,000	2009
3,640 m	La Paz, Bolivia	845,480	2010
3, 399 m	Cusco, Peru	358,052	2011
3,053 m	Huancayo, Peru	425,000	2012
3,050 m	Huaraz, Peru	135,000	2011

ENVIRONMENTAL-INDUCED STRESS AND ITS EFFECTS ON HUMANS

A change in the environmental factors/conditions either natural or man-made causes undesirable impact on the organismal fitness and performance of essential tasks. This may result in endangering the survival of the organism in that particular environment. The stress caused due to any environment becomes an environmental stressor and the effects are termed environmental stress [1]. Environmental stress has several forms that include everyday air and noise pollution observed in urbanized areas, high pressure at depths of 30 m or more in oceans, and low visibility combined with treacherous roads at high altitude areas. The WHO, in line with multiple human studies [2 - 7], recognized environmental stress and stressors as a significant cause of many diseases like diabetes, cardiovascular diseases, and cancer [8]. Cardiovascular diseases, according to WHO, are the leading cause of deaths globally (https://www.who.int/news-

room/fact-sheets/detail/cardiovascular-diseases-(cvds); accessed on 17th January 2019). A majority of environmental stressors activate the hypothalamic-pituitary-adrenocortical axis and the sympathetic nervous system subsequently cause the onset of inflammation and oxidative stress leading to disease and mortality [9 - 11]. Environmental stressors and their significant effect on health and quality of life have been a focus of research since the late 70s. Thus, irrespective of the types of environmental exposure, the management of stressors present in that environment is of prime importance. It becomes all the more important when the environment happens to be of a very high altitude.

The environmental stressors at high altitudes consist of rough uneven terrain, cold temperature, UV radiation, low humidity levels, and risk of avalanches and landslides. However, the most pertinent stressor is hypobaric hypoxia. Hypobaric hypoxia refers to the decline in partial pressure of oxygen in the atmosphere owing to the decline in barometric pressure. All known high altitude illnesses (HAIs) are purported to be patho-physiological responses to hypobaric hypoxia. These include acute mountain sickness (AMS), high altitude pulmonary edema (HAPE), and high altitude cerebral edema (HACE).

SOCIO-ECONOMIC ASPECTS OF HIGH-ALTITUDE AREAS

High altitude has no precise definition but any geographical entity with an elevation of at least 8,000 ft (~2438 m) is termed a high altitude area. In India, as per Army order No. 110/80, high altitude is considered to be an elevation of 2700 m (8859 ft) or above. Extreme altitude may be defined as one exceeding 5800 m (19028 ft) where permanent residence is practically not feasible (Army orders No.110/80, New Delhi, 1980). The highest permanent human settlement is La Rinconada, Peru at 16,700 ft (5100 m) [12]. Only a handful of urbanized places exist at such elevations and interestingly most of them lie in the South American countries like Bolivia, Peru and Ecuador. In Asia, only Lhasa (in Tibet) is a major city at high altitude. Even though countries like India, China, Nepal and Bhutan are well-documented to have multiple native populations in their high-altitude regions [13, 14]. The highest percentage of the world's high altitude native populations [15] lack major cities point and live in remote and difficult areas. The names and populations of some high-altitude cities are shown below in Table **1**.

According to Moore *et al*, till 1983, there were 140 million people living permanently above 2500 m (~8,000 ft) constituting about 2% of the world's population then [16]. In 1998, a study published by Cohen and Small reported that about 33% of the world population lived within 100 m (328 ft) of mean sea level and the median altitude of residence worldwide was 194 m (636 ft) above the sea level [16]. They further determined a greater than an exponential decline in

CHAPTER 18

Nanomaterials in Precision Medicine

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Abstract: The exigency for the most accurate form of diagnosis and treatment to challenge the failure of evidence-based medicine unlocked new avenues for tailored treatment. Precision Medicine encompasses the novel techniques and methods of therapy considering the genetic complexity, variations, and mutations in the human population. Recent advances in nanotechnology have paved a new path in therapeutics. The fusion of Precision Medicine with cutting-edge nanotechnology has offered unique headways into the healthcare management system. Novel approaches of nanoparticle synthesis and drug delivery techniques to cure heterogeneous populations with varied genetic alterations is now possible through precision medicine. This chapter highlights the promising role of nanomaterials in precision oncology where conventional therapy dwindles. Moreover, we discuss the emerging scope of precision medicine in dentistry to cure genetic diseases. Cystic fibrosis, which was once a nightmare, is now completely curable with the boon of Precision Nanomedicine. Precision medicine has revolutionized the medical world with a ray of hope to achieve the pinnacle of human health.

Keywords: Cystic Fibrosis, Human Health, Nanomedicine, Precision Dentistry, Precision Medicine, Precision Oncology.

INTRODUCTION

Healthcare practitioners have long been concerned with making their therapies as efficient and suitable for the particular patient as possible. The traditional one-size-fits-all paradigm involves identical treatment to patients presenting with a similar array of symptoms. The quest for a more precise diagnosis and therapy to overcome the shortcomings of evidence-based medicine resulted in new possibilities for tailored and personalized treatment. Precision Medicine (PM) is synonymically referred to as personalized medicine in certain arenas of therapeutics [1]. However, the United States National Research Council, expr-

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esses a broader concept that, while it may not be feasible to design therapies explicitly for individual patients on an individual level, subsets of patients should be able to be demarcated and treated [2]. Precision medicine does not indicate the development of drugs or medical devices tailored to the needs of a specific patient. Instead, it refers to the segregation of people into sub-groups, depending on their vulnerability to a specific disease, the biology of the disease and their responses to a specific treatment [3]. The concept of PM has existed for the past 2500 years since the time of Greek philosopher Hippocrates, but now it has gained momentum. Several Scientists have contributed to this field with the passage of time. Archibald E. Garrod (1857-1936) is the most prominent name who is considered as the father of precision medicine. He demonstrated genetic variations as the fundamental source of diseases such as alkaptonuria, albinism, cystinuria, and pentosuria. He suggested that all individuals differ from one another, even the uniovular twins are genetically distinct warranting the requirement of precise treatment for each person [4]. In 2015, the Precision Medicine Initiative was launched by President Barack Obama, for "providing the right treatment at the right time to the right person and taking into account patients' health history, genes, environments, and lifestyles" [5].

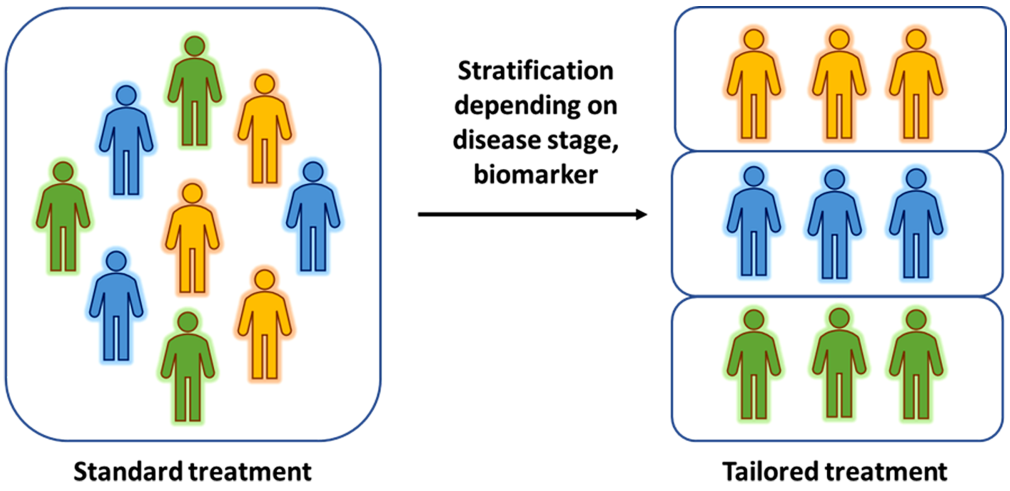

Fig. (1). Schematic representation showing stratification of the patients useful for precision medicine deviating from *one-size-fits-all* conventional treatment [45].

Precision public health (PPH) is a contemporary approach that accompanies the growth of precision medicine by harnessing improved newer technology and information available through big data to effectively aim public health initiatives for the communities. A vital function of PPH is the utilization of population-level data to create a larger group of individuals who may be subjected to precision medicine. This can be achieved by a surge in the understanding of the biochemical processes involved in various illnesses [6].

PRECISION NANOPARTICLES

Nanomaterials have a promising role in disease diagnosis and treatment. To maximize safety and efficacy, nanomaterials enhance the stability and bioavailability of encapsulated cargos, facilitating transport across the biological membranes, and extending the circulation time [7]. However, the paucity of knowledge of the pathophysiological variations in animals and humans nanomaterials especially with the way these differences impact the activity and effectiveness of nanomedicine is not clear. Individual heterogeneity potentially hinders the efficacy of nanomedicine. Moreover, there is an inadequate study on the interplay of nanomedicine with stratified patient groups [8]. Consequently, a limited number of nanomedicines is suggested as first-line therapy choices, although several benefits have been demonstrated only in a minor proportion of the patients. The reason is that the diseased tissue exhibits altered proliferation, morphology, and physiology affecting the pharmacokinetic properties of the NPs. Advancements in the synthesis strategy and design of nanoparticles, incorporating bio-responsive molecules possessing intricate structures and targeting agents offer great hopes. The rising pre-dominance of PM can be linked in particular to the development of NPs to circumvent biological barriers unique to patient sub-groups or pathological conditions [9].

Types of Nanoparticles

Lipid-based Nanoparticles

Lipid-based NPs are FDA-approved drug delivery vehicles, having several benefits including the ease of fabrication, self-assembly, excellent bioavailability, and biocompatibility and having the potential to bear substantial payloads. Moreover, a variety of physical and chemical properties may be tuned to regulate their biological character [10]. Liposomes are lipid-based structures composed of one or more phospholipid bilayers, capable of encapsulating drugs along with aqueous media. The stability of the lipid bilayer and the therapeutic material contained are determined by the lipid content and cholesterol concentrations. Their size range from 25 to 100 nm and these are regulated by the maximum amount of drug retained inside the bilayer retaining their flexibility [11].

CHAPTER 19

Nanotechnology, Drug Delivery and Prospects in Precision Medicine

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Abstract: Nanotechnology has the potential to revolutionize the field of drug delivery by enabling targeted and controlled release of drugs within the body. This article provides an overview of the current state of the art in nanotechnology-based drug delivery systems and their potential applications. It discusses the various types of nanoparticles that are currently being used or developed for drug delivery, including liposomes, dendrimers, and polymeric nanoparticles, and highlights their advantages and disadvantages. It also covers some of the key challenges and risks associated with the use of nanotechnology in drug delivery, such as toxicity and regulatory issues. Finally, the article explores the future prospects of nanotechnology in drug delivery and highlights some of the areas where further research and development are needed. Overall, the article demonstrates that nanotechnology-based drug delivery systems hold great promise for improving the efficacy and safety of drug treatments and that on-going research in this field has the potential to transform the way we approach drug delivery in the future. Finally, it's envisaged that this technology will facilitate the augmentation of precision medicine for better human health care across the spectrum of diseases.

Keywords: Dendrimers, Drug delivery, Liposomes, Nanoparticles, Nanotechnology, Precision medicine, Polymeric nanoparticles, Stimuli-responsive micelles.

INTRODUCTION

Nanotechnology is the study and application of very small particles or structures, typically those that are smaller than 100 nanometers in size [1]. A nanometer is one billionth of a meter, or about 1/100,000th the width of a human hair. Nano-

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technology has applications in a wide range of fields, including electronics, medicine, energy, and materials science [2].

For example, nanotechnology is being used to develop more efficient solar cells, drug delivery systems that can target specific cells in the body, and stronger and more durable materials for use in construction and manufacturing [3]. Nanotechnology also poses some potential risks, such as the possibility of toxicity or environmental harm if nanoparticles are not properly handled or disposed of [2]. As a result, there is ongoing research and discussion about the ethical, social, and environmental implications of nanotechnology. Nanotechnology involves manipulating and engineering materials at the atomic or molecular level, often using specialized tools and techniques such as scanning probe microscopes, electron microscopes, and other sophisticated instrumentation [4]. This allows researchers to create materials and devices with unique properties and characteristics, such as increased strength, conductivity, or reactivity.

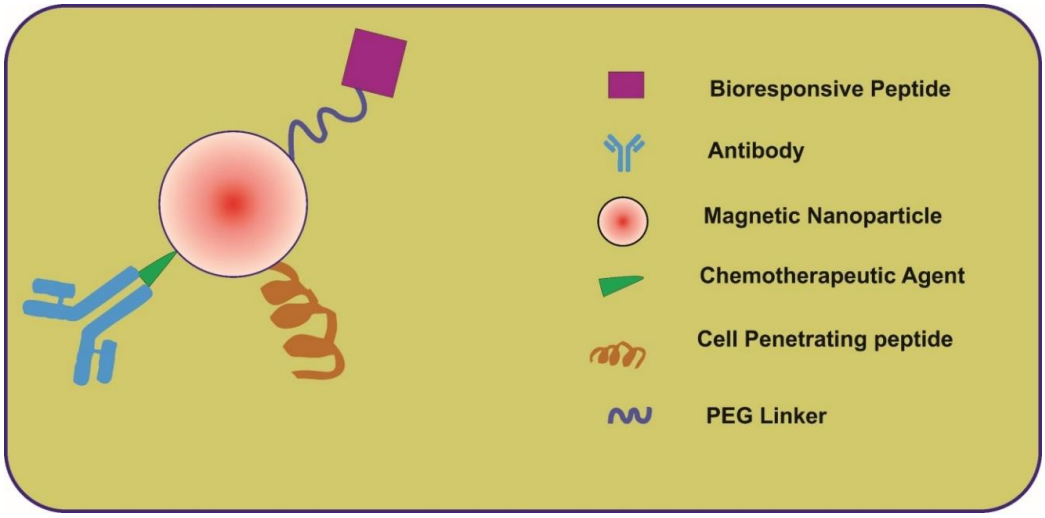

Fig. (1). Schematic diagram showing the functionalization of magnetic nanoparticles with bio responsive peptide, chemotherapeutic agent, PEG linker, antibody, and cell-penetrating peptide [34].

NANOTECHNOLOGY IN MEDICINE

Nanotechnology has the potential to revolutionize medicine by enabling the development of new diagnostic and therapeutic tools with unprecedented precision and efficiency [1 - 4]. Some potential applications of nanotechnology in medicine include:

Drug Delivery

Nanoparticles can be engineered to carry drugs and target specific cells or tissues in the body, which can increase the effectiveness of the treatment while minimizing side effects.

Imaging

Nanoparticles can be used as contrast agents to enhance the resolution and sensitivity of medical imaging techniques such as MRI and CT scans.

Tissue Engineering

Nanotechnology can be used to create scaffolds or matrices that mimic the structure and function of natural tissues, which can be used to repair or replace damaged or diseased tissues.

Diagnostics

Nanoparticles can be used to develop highly sensitive and specific diagnostic tests that can detect diseases at an early stage.

Therapeutics

Nanoparticles can be used to develop new therapies that target specific disease pathways or cellular processes, such as cancer or viral infections.

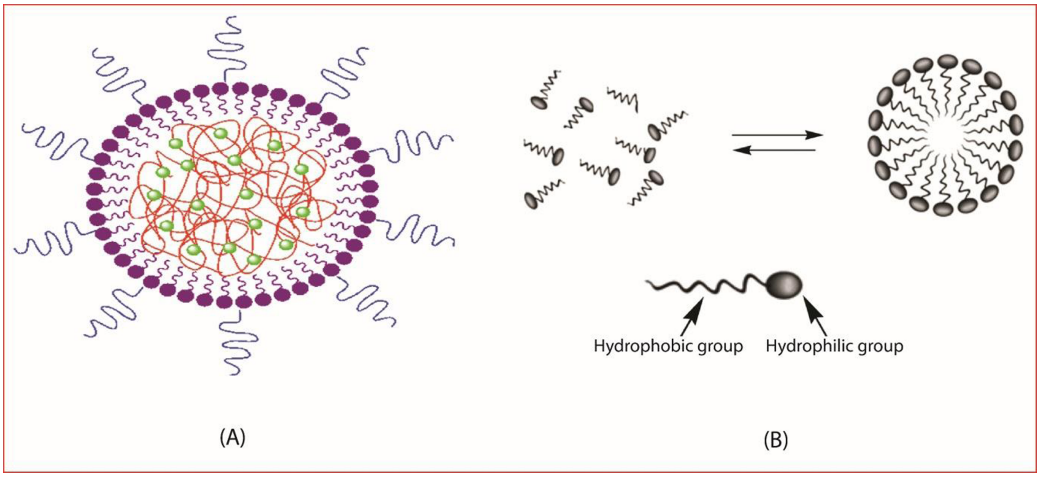

Fig. (2). Schematic diagram showing; (A) the structure of polymeric nanoparticle, and (B) the structure and reversible formation of micelles [54].

CHAPTER 20

Therapeutic Dynamics of Tannin Interaction and Significance in Precision Medicine

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Abstract: Personalized medicine is a targeted therapy that aims to provide people suffering from complex illnesses with tailored-made healthcare. Taking this into consideration, foods with diverse bioactive compounds have recently gained widespread scientific interest as alternatives to modern drugs for developing therapeutic agents against human diseases. Tannins are an important group of polyphenol compounds in foods that have both beneficial and anti-nutritional effects. As an anti-nutrient, they can reduce element bioavailability, and protein absorption, and inhibit enzymatic actions during metabolism. If tannin-rich foods are consumed in sufficient quantities and at the appropriate time, they may act similarly to natural drugs that ameliorate a range of metabolic disorders. Thus, the types of tannin-rich foods and the timing of consumption before or after meals should be considered for maximum physiological importance in maintaining human health. In this chapter, we compiled the different types of tannins and their food sources, as well as their beneficial and anti-nutrient effects on human health.

Keywords: Micronutrients, Macronutrients, Personalized medicine (PM), Polyphenols, Tannins, Tannins-rich foods.

INTRODUCTION

In the 21st century, personalized medicine (PM) is continuing to attract the attention of medical researchers and healthcare practitioners. PM is a novel concept in the medical sector that has the ability from mass targeting to the one-person target by providing effective, tailored therapeutic strategies on the basis of the genomic, and proteomic profile of an individual. PM provides both treatments

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as well as preventive options. The assessment of proteogenomic along with mutations that give rise to resistance against treatment opens the doors for healthcare practitioners to decide which treatment is right for a particular person. Generally, it has been seen and happens that if there is no relief from one medication, then another medication is started. These types of trial-and-errors lead to side effects, drug interactions and worsen the disease state in the patients, which also affects the patient's mental health. To rule out the adverse effects of trial-and-error prescription specified treatment by PM approaches is more powerful. The development of PM will provide better treatment at a specific dose that will increase drug efficacy and minimize the patient's casualties [1]. The main focus of the PM is raise the advantages and prevent the risk to the patients by targeting the biological markers such as clinical, genetics, and genomic that intervene to develop therapeutic drugs [2]. Pharmacogenomics, pharmacoproteomics, and pharmacogenetics are major divisions of personalized medicine that have crucial roles in developing drugs and determining their efficacy on patients based on molecular diagnostics studies. In the current scenario, several biotechnological and pharmaceutical companies have announced personalized medicine will prime target to expand the individualized treatment for diseases in future [3]. In recent years, nutritional and lifestyle changes have gained attention in both developed and developing countries. Good nutrition is of utmost importance to maintain normal body function and to mitigate the dysfunction of metabolic pathways which are induced by various factors [4, 5].

Adequate nutrition provides both macronutrients and micronutrients to fulfil the physiological needs of human body. Macronutrients include carbohydrates, proteins, and fats that are necessary to provide cellular energy whereas micronutrients such as minerals and vitamins are needed for growth, development and metabolism for proper functioning of body [6]. Foods contain a complex system of both nutrients and non-nutrients components which are required for plants and animals because they have the abilities to modulate epigenetic, gene expression and protein functions [7, 8]. In plants foods, non-nutrients components are natural and synthetic compounds that can be beneficial, non-beneficial or even toxic. Natural compounds such as polyphenols, flavonoids, alkaloids and steroids have the beneficial effects for plants and human both. Among them, some of the group of compounds such as tannins, saponins, lectins and phytic acid may be considered as anti-nutrients because they cause adverse effect in human such as reduced bioavailability of elements and digestibility of protein if they are not taken at right time [9].

Tannins are the important class of polyphenols that provide beneficial effects such as anti-inflammatory, antioxidant, or anti-cancer properties [10]. Many of them are in foods like coffee, chocolate, olive and berries [11]. Anthocyanins, an

important class of polyphenols are also responsible for berries colour such as red, blue, or purple color [12]. Non-extractable polyphenols form dietary fibers *via* polymerization reactions, which influence the gut health [13]. Lentils, and beans especially red kidney beans and black beans contain good number of polyphenols having antioxidant and anti-inflammatory activities [14]. Literature revealed that tannins might be good for human health if they are taken in particular quantities. Generally, they have beneficial effects but anti-nutrients effects cannot be ignored. Therefore, all the anti-nutrients effects of tannins should be studied before making any suggestion for possible consumption of those foods which are tannin rich. Thus, the aim of this chapter is to summarize the current knowledge based on tannins, their chemical structure, dietary sources and health benefits with adverse effects. The molecular mechanism of tannins in foods is also discussed in details, highlighting which food should be avoided or recommended for beneficial effects in human.

TANNINS: STRUCTURE AND CLASSIFICATION

Tannins are different types of polymeric compounds of phenols that are abundantly found in numerous plant-based foods and medicinal plants in their different parts such as fruits, leaves, seeds, stem and roots. Generally, tannins are of four types: (1) hydrolysable tannins, (2) condensed tannins, (3) pseudo-tannins, and (4) phlorotannins [15]. Hydrolysable tannins are synthesised from Shikimate pathway which is derived gallic acid metabolism. On hydrolysis, hydrolysable tannins *e.g*. gallotannins and ellagitannins yielded phenolic acids (*e.g*., ellagic acid and gallic acid) along with carbohydrate (*e.g*. glucose) or their derivatives in basic units [16]. Condensed tannins, also known as proanthocyanidins, are polymers of the flavan-3-ols that yielded anthocyanidins *via* oxidation reactions. They are non-hydrolysable tannins. Condensed tannins are very complex in structure, which are formed by C-4 linkage of one catechin with C-6 or C-8 linkage of the adjacent monomeric catechin. Having catechin or epicatechin as building blocks of condensed tannins, they are from flavonol pathways originated [17]. Phlorotannins are oligomers of phloroglucinol, which are mainly found in algae. Phloroglucinol, an aromatic ring with 1, 3, 5 hydroxyl groups, is the constituted unit of various phlorotannins that undergo polymerisation at C1-C3 positions. Three distinctive classes of phlorotannins are fucols, phloroetols and fucophloroteols, which are made by coupling in between C-C, C-O-C, C-C and C-O-C units respectively. Pseudo tannins are polyphenols of gallic acid and falvan-3-ols units in their basic skeletons [18].

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Farzana Mahdi

Professor Farzana Mahdi is working as Pro-Vice-Chancellor of Era University, Lucknow. She has several other key responsibilities which include director of academics, at Era's Lucknow Medical College and Hospitals (ELMC&H) and dean of academics, at the American University of Barbados. She is the general secretary of the Indian Society of Personalized Medicine and Director, of the Department of Personalized and Molecular Medicine. Her most noble contribution has been the extraordinary commitment to providing treatment to COVID-19 patients during the pandemic which saved about 3200 COVID-19 patients. Her field of specialization includes molecular genetics, free radical biology, toxicology, clinical biochemistry, autism, metabolic syndrome, etc. She has received several grants and massive extramural research funding from the Union Government of India and has published more than 150 papers in journals of repute. She made remarkable contributions to the development of the clinical skills lab in the medical college. As a coordinator, she looks after the curriculum committee and clinical skill laboratory. Her devotion and deep involvement with medical college have augmented the cardiovascular and diabetic research at Era University.

Abbas Ali Mahdi

Prof. Abbas Ali Mahdi is currently helming the Era University, Lucknow as a Vice-Chancellor. He has made seminal contributions during the last 35 years and has 415 publications including 32 book chapters, and twelve books, to his credit. He has guided 27 Ph.D. 04 MPhil, and over 200 MD/MS/MDS/DM students. He has supervised more than 50 research projects, including the prestigious DST – -FIST and that of The World Academy of Science, Italy (TWAS). His name has been listed in the worldwide ranking of the top 2% of scientists from India as recorded by Stanford University, USA. Prof. Mahdi has received several awards and recognitions for his academic and research contributions, including a fellowship from the National Academy of Medical Sciences (India), the Association of Clinical Biochemists of India, and the Indian Academy of Biomedical Sciences. He has delivered more than 200 invited talks at various national and international institutions/conferences. Prof. Mahdi has been the editor-in-chief/editor/board member and reviewer of a number of national and international journals of repute. He has been the president of 4 National Scientific Societies. He is known for his research contribution in the area of natural products, metal toxicity, and free radical biology.

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