Biotechnology and Drug Development for Targeting Human Diseases

Editor:
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PREFACE

Biotechnology weaves its transformational effect across the intricate fabric of life, altering our understanding of illnesses and igniting creative approaches to their treatment. Intricate biological processes and disease mechanisms have been decoded through the groundbreaking use of biotechnology methods. The potential of biotechnology in the context of drug development is considerable. "Recent advances in Biotechnology Vol. 9, Biotechnology and Drug Development for Targeting Human Diseases" is a collection of insightful discussions and in-depth analyses on the use of biotechnology in the treatment of disease.

The chapters in this book provide a thorough examination of the many biotechnology applications, covering topics like the use of multi-omics profiles in disease research and drug development, *in silico* drug design techniques, the use of viruses as carriers, and the investigation of natural products for use in wound healing and as antimicrobials. The notion of drug repurposing, the intersection of omics technologies with biotechnology in drug interaction investigations, and the most recent biotechnological discoveries in disease prevention also receive special emphasis.

Every chapter in this book has been meticulously chosen to provide thorough, up-to-date, and understandable knowledge, backed by a variety of references that let the reader dive deeper into the subject. These chapters work together to give readers a comprehensive picture of how biotechnology is fundamentally changing the field of drug research and disease treatment.

We sincerely thank the authors of each chapter for their contributions to the spirit of this book through their knowledge and thorough study. This compilation was made possible by their perceptions, know-how, and diligence.

We would like to express our sincere gratitude to our families, whose unwavering support has been essential at every stage of the process of writing this book. Their support and faith in this project have been essential.

We really hope that this book will be a helpful resource for individuals who are curious about the field of biotechnology and its applications to the treatment of diseases. This information not only sheds light on the condition of the field now, but also prepares the path for future developments in biotechnology and pharmaceutical research.

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CHAPTER 1

Multi-omics Profiles are Applicable to Human Diseases and Drug Development

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Abstract: Traditional medicine has been a reliable source for the discovery of molecules with therapeutic activity against human diseases of clinical interest. In the past, knowledge of traditional medicine was mainly transmitted orally and in writing. Recently, the advent of "multiomics" tools (transcriptomics, metabolomics, epigenomics, proteomics, and lipidomics, among others) has increased and merged our knowledge, both traditional knowledge and that gained with these new multiomics technologies. In this way, the development of medicines with these 'multiomics technologies' has allowed pharmaceutical advances in the discovery of new drugs. In addition, 'multiomics' technologies have made it possible to uncover new biological activities of drugs that are currently used in clinical therapy. In the same way, 'multiomics' has allowed for the development of 'personalized medicine', that is, a particular and specific treatment and/or diagnosis of a patient with respect to a disease. Therefore, 'multiomics' technologies have facilitated the discovery of new clinical therapeutics for disease, as well as allowing for the diagnosis and/or treatment of diseases in an individual and personalized way.

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Keywords: Drug development, Multiomics technology, Medicinal traditional, Personalized medicine.

INTRODUCTION

In the past, knowledge from original peoples was transmitted only from generation to generation, but today, the knowledge is used in the development of new medicines [1]. Natural products are chemical compounds produced by living organisms, including plants, animals, and microorganisms, and have long been used in medicine and other biological applications [1]. Biological research has undergone many changes since the end of the 20th century and the beginning of the 21st century, with the publication of the complete human genome sequence by the International Genome Sequencing Consortium in 2003 being a crucial step in genetic research [2]. In a similar manner, drug development has been considered a conservative strategy with highly regulated processes. However, medicine is rapidly evolving with the help of different strategies that allow for the development of comprehensive and personalized treatments for different types of diseases and/or patients [3].

The omic sciences are a set of technologies used to study the global molecular components of an organism, such as genes, proteins, metabolites, and lipids. These technologies include genomics, transcriptomics, proteomics, metabolomics, and lipidomics; furthermore, these technologies have been used in a wide variety of applications, including research in biology, medicine, agriculture, and ecology [3, 4]. These "omics technologies" and advances in bioinformatics have generated new knowledge and integrated new technologies such as artificial intelligence (AI) to improve precision medicine [5]. In this "post genomics" era, research is focused on the role of genes, understanding transcriptional regulation, the biochemical roles of gene products and their interactions, and understanding how various chemicals influence metabolic behavior. These new "omics" technologies are based on global and high-throughput analytical methods, such as microarrays, 2D-gel, 2DLC/MS and mass spectrometry, which produce data on a large scale, as well as bioinformatics and computer modeling [2, 3]. In this manner, multiomics sciences are used to identify and investigate new bioactive compounds from natural products [3, 6].

Important factors for the success of precision medicine (or personalized medicine) include early clinical development, the "back translation" of knowledge *via* the development of drugs and the translation of omic signatures into clinically relevant biomarkers, as well as the development of precision diagnostics adapted to each patient [3]. Moreover, multiomics science permits the development of these omic technologies and their application in biomedical research and

pharmaceutical products, thereby offering a broader exploration of the genome, transcriptome, and proteome and with a greater possibility of finding solutions for the discovery and validation of new drugs, evaluating their efficacy, toxicity, safety and personalized access, as well as the availability of new drugs [2].

The goal of this chapter is to describe the development of new drugs used in clinical therapy and their applicability in personalized medicine based on multiomics sciences.

ANCESTRAL KNOWLEDGE: TRADITIONAL MEDICINE IN THE MULTIOMICS ERA

There is a growing interest in the discovery of new drugs from traditional medicine [7]. Ancestrally, knowledge has been transferred from generation to generation, although in modern times, this knowledge that is transferred orally is at risk of being lost [1], not only hindering the development of new drugs but also the discovery of new therapeutic strategies [8]. Ancestral documents such as the 'Shenlong's classis of materia medica' from China describe the use of 365 drugs; moreover, in ancient Greece, Dioscorides described the use of 600 medicinal plants with therapeutic activity [9]. In medieval Europe, traditional medicine comes from the Greeks and Romans such as Hippocrates, Galen, and Dioscorides, and this knowledge was preserved by Benedictine monks through botanical gardens such as the Abbeys of Montecassino and St. Gall, respectively [10]. A convergent referent between traditional medicine and omics science occurred in Japan. In this country, Chinese medical practice was introduced in the 6th century A.D., and eventually the concept of 'KAMPOmics', which represented the merging of omic sciences with traditional Japanese medicine, was developed [11]. The principles of yin (cold) and yang (hot) in traditional Chinese medicine were evaluated using metabolomics on serum from fever rats administered a traditional herbal treatment. The rats had an increase in temperature following treatment with plants that stimulated heat, in contrast to their response following treatment with plants that reduce temperature; certain metabolomic markers could discriminate the samples based on the traditional herbal treatment [12]. In addition, in 2014, the Brazilian government published a book that summarized the traditional medicine of the '*Yanomani people'*, which identifies the botanical species and their preparations that are used as therapeutic material [8]. Furthermore, the 'Herbalomic project', which focuses on new methods to elucidate molecules, establishes libraries of plants in the context of traditional Chinese medicine [13]. Concurrently, China developed the concept of GP-TCM (Good Practice in Traditional Chinese Medicine research in the postgenomic era), which utilizes coordinated actions to regulate interdisciplinary and intersectoral activities in traditional medicine [14].

CHAPTER 2

Utilizing *in silico* Methods in New Drug Design

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Abstract: The current chapter offers a highly informative and enlightening overview of the practical implementation of molecular docking in the field of biotechnology, with a specific focus on drug discovery for a variety of ailments. Molecular docking, an incredibly powerful computational methodology, has increasingly been utilized as an essential instrument in the elucidation of drug-receptor interactions, providing invaluable insights into the process of designing drugs. This chapter delves into the fundamentals of molecular docking algorithms, offering a comprehensive understanding of their theoretical underpinnings, methodologies, and typical applications. Furthermore, this chapter elaborates on how this method is used to predict the binding affinity and orientation of potential small-molecule therapeutics to their protein targets, emphasizing the crucial role that molecular docking plays in the quest for new medications to treat various diseases. By presenting case studies across a range of diseases, this chapter effectively demonstrates the remarkable versatility of molecular docking in advancing our knowledge of disease pathogenesis and therapeutic interventions. In addition, specific diseases and their corresponding drugs are carefully examined, along with an in-depth review of molecular docking studies performed on these drugs. This detailed exploration serves as a robust foundation for researchers seeking to understand the utility of molecular docking in the development of more effective, targeted therapeutics. This chapter thus positions molecular docking as an indispensable tool in the field of biotechnology, propelling drug discovery into a new era of precision and efficiency. Overall, this chapter presents a comprehensive and inf-

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ormative overview of the diverse applications of molecular docking in biotechnology, providing an essential resource for researchers in the field.

Keywords: Biotechnology, Binding affinity, Drug discovery, Drug-receptor interactions, Disease pathogenesis, Molecular docking, Molecular docking algorithms, Protein targets, Precision medicine, Therapeutic interventions.

INTRODUCTION

With its broad range of applications in the areas of drug design and target molecule identification, molecular docking has become an essential tool for the creation of novel treatments for a variety of diseases, including but not limited to infectious diseases, neurodegenerative disorders, and chronic illnesses. To carefully assess the binding affinities between the possible pharmacological ligands and the matching target molecules in a three-dimensional space, this advanced methodology makes use of the power of computational algorithms. The ultimate goal is to get the two entities to fit together as well as possible, opening the door for the successful creation of novel therapeutic approaches. A potent computational method for structure-based drug design is molecular docking. It is employed to predict the interactions of tiny compounds with protein targets, such as prospective medicines. With the help of this method, the computational prediction of protein-ligand binding entails determining the binding mode first and then assessing how strong the protein-ligand interactions are. These interactions are directly correlated with ligand binding affinities, which increases the possibility of successful drug development. Numerous studies have shown that molecular docking simulations are becoming a common method for creating new medications [1].

Based on the idea of free energy, molecular docking determines the stability of a system by estimating the energy required to bind a tiny molecule (ligand) to a protein (target). It consists of two primary phases: a search process in which a number of potential ligand-target orientations are investigated to locate a stable one and a scoring process in which the orientations are ranked according to energy to determine the most likely ligand-protein configuration [2]. The utilization of state-of-the-art technology has exhibited significant triumph in hastening the revelation of pharmaceuticals for various ailments, specifically in the realm of cancer treatment. Through the combination of molecular docking and *in vitro* investigations, the procedure of identifying potential drugs to combat cancer has been notably hastened [3]. In addition to the aforementioned information, it is imperative to note that the development of new and innovative agents that combat the HIV virus has undergone substantial improvement *via* the utilization of an integrated approach. This strategy includes a wide range of

methods, including molecular docking studies, virtual screening, 3D-QSAR (quantitative structure-activity relationship), and pharmacophore modeling. In a deliberate attempt to increase the effectiveness and potency of anti-HIV drugs, many techniques have been used. Recognizing the importance of these strategies in the creation of new HIV therapy drugs is crucial [4]. Similarly, molecular docking has shown efficacy in the domain of malaria research. Numerous studies have reported the identification of diverse molecules using this method, further consolidating its utility in drug discovery [5]. These findings reinforce the pivotal role molecular docking plays in biotechnology, heralding a new era of drug development for these, and potentially, numerous other diseases. Additionally, it is being used to create new medicine delivery systems, antibiotics, and vaccines. One of the crucial processes in drug creation is now the identification of therapeutic candidates against infectious diseases using a molecular docking technique, Because it is used to screen virtual libraries of drug-like molecules to identify potential leads for further drug development, the prediction of the ability of small molecules to bind to proteins has unique practical significance [6] (Fig. **1**).

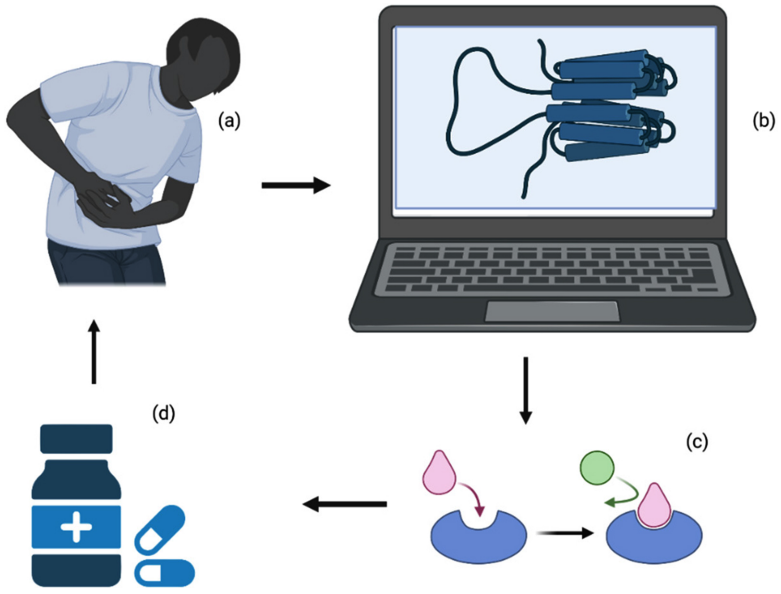

Fig. (1). Overview of the Molecular Docking-Based Drug Development Process: This flowchart illustrates a typical drug development process and highlights the critical function of molecular docking. (**a**) Determining the disease that will be targeted. (**b**) Performing molecular docking analysis to determine the binding affinity between prospective medication compounds and the identified target. (**c**) Conducting *in vitro* and *in vivo* experimental tests to confirm the outcomes of the molecular docking. (**d**) Further developing the novel medication after successful validation, and then authorizing it for therapeutic use.

CHAPTER 3

The Roles of Farnesol and Farnesene in Curtailing Antibiotic Resistance

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Abstract: In the extensive domain of "biotechnology and drug development for targeting human diseases", essential oils have long been revered for their therapeutic potential. Among these, farnesol and farnesene stand out due to their pharmacological attributes. As the challenge of antibiotic resistance intensifies, the scientific community is increasingly exploring the potential of these traditional remedies. Using the Kirby-Bauer agar diffusion method, a qualitative assessment was conducted on two gram-positive and two gram-negative bacterial strains. The broth microdilution technique further determined the Minimum Inhibitory Concentration (MIC), Minimum Bactericidal Concentration (MBC), and the sensitizing impacts of these compounds. Both farnesol and farnesene exhibited antibacterial efficacy against all evaluated strains. Their synergistic potential was highlighted when combined with clavulanic acid, cefuroxime, and cefepime. Among these combinations, farnesene paired with cefepime showed pronounced efficacy against *Escherichia coli* 82 MR, with an MIC of 0.47 µg/mL. In contrast, in the investigation of *Staphylococcus aureus* 23MR, it was observed that this particular strain exhibited an increased sensitivity when exposed to combinations containing farnesol. Notably, the Minimum Inhibitory Concentration (MIC) was determined to be 0.03 µg/mL in the presence of both antibiotic agents. To gain deeper molecular insights, docking experiments were performed with the *β*-lactamases of *E. coli* and *S. aureus*, focusing on the most effective combinations. All tested compounds—cefuroxime, cefepime, farnesene, and farnesol—acted as non-competitive inhibitors, suggesting their potential mechanisms of action.

Keywords: Antibacterial, Antibiofilm, Essential oils, Farnesol, Farnesene.

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INTRODUCTION

In the realm of microbiology, the emergence of antibiotic resistance serves as a compelling illustration of the remarkable adaptability and tenacity exhibited by bacterial organisms. As they naturally evolve, bacteria undergo mutations, acquire genetic material, and modify their genome expression. Such evolutionary changes empower them to counteract the effects of antibiotics [1]. While this evolutionary process is a natural occurrence, human activities have accelerated its pace. Within the broader context of microbial evolution, several determinants have been identified as contributors to the proliferation of antimicrobial-resistant bacterial strains. These encompass the imprudent utilization of medications in both human and veterinary medicine, suboptimal infection prevention protocols in healthcare establishments, and lapses in fundamental hygiene and sanitation standards. This challenge is further intensified by the declining discovery of new antibiotics [2].

Due to this situation, there has been a significant rise in the search for complementary treatments or alternatives to conventional antibiotics. Natural antimicrobial products have emerged as substances of significant scientific interest due to their vast chemical diversity and biological characteristics. Among these, essential oils include a group of components with unique qualities that distinguish them in the healthcare, cosmetics, and food industries [3].

In the broader discourse on essential oils featured in botanical literature, the sesquiterpene alcohol, farnesol ($C_{15}H_{26}O$), emerges as a notable compound. It has been cataloged in a range of plant families, prominently among Lamiaceae [4, 5], Asteraceae, Poaceae [6], and Pittosporaceae [7], among others [8]. In a parallel vein, farnesene ($C_{15}H_{24}$), another representative of the sesquiterpene class, is traced back to its origin in the mevalonic acid biosynthetic pathway. Essential oils from various families like Lamiaceae [4, 5], Lauraceae [9], Meliaceae [10], Asteraceae [6, 11], Verbenaceae [12], and Euphorbiaceae [13] have been found to contain several isomers of farnesene. These isomers encompass a range of properties, including antimicrobial activities, attractant capabilities, signaling functions, and hormonal attributes.

Terpenes, the broader category to which both farnesol and farnesene belong, possess a plethora of biological properties. Their potential therapeutic applications span from antifungal, antibacterial, antiviral, antitumor, antiparasitic, hypoglycemic, anti-inflammatory, to analgesic effects. Such a diverse range of properties underscore the increasing interest in terpenes within the scientific community [14].

Recent studies have shed light on the antimicrobial potential of farnesol. For instance, its efficacy against strains of *Paracoccidioides brasiliensis* was

evaluated, revealing its ability to induce cytoplasmic degeneration and inhibit germ tube formation [7]. Furthermore, the combined use of *tt*-farnesol and minocycline demonstrated a significant inhibitory effect on the growth of *S. aureus* ATCC43300 [15].

The potential of farnesol to influence antibiotic activity has been a topic of academic inquiry. Notably, in experiments where farnesol was paired with antibiotics such as ampicillin and oxacillin, evidence emerged of its capacity to augment the effectiveness of these drugs against methicillin-resistant strains of *S. aureus* [16]. Such findings suggest that farnesol could play a pivotal role in overcoming antibiotic resistance, especially in bacterial strains like methicillin-resistant *S. aureus* [15].

MATERIALS AND METHODS

In the expansive domain of biotechnology and drug development, the quest to unearth natural compounds and their potential synergy against bacterial strains is a pressing endeavor. This chapter embarks on an investigative journey into two such intriguing compounds, farnesol and farnesene, and their prospective roles in the battle against antibiotic resistance.

Our narrative commenced with the foundational elements. The compounds under investigation, including farnesol (CAS 4602-84-0), farnesene 90% (CAS W383902), and several other chemical agents, were procured from Sigma–Aldrich, a reputable supplier in Toluca, Mexico. The bacterial protagonists for this study included strains of *Escherichia coli* ATCC25922, *Staphylococcus aureus* ATCC29213, *E. coli* 82 MR, and *S. aureus* 23 MR multi-resistant strains. These strains were diligently handled, maintained at 4°C in Mueller Hinton agar, and primed for subsequent experiments.

The first experiment conducted was the antibacterial activity assay. The Petri dish is an environment where bacteria interact and respond to various compounds. The disc diffusion method, a time-honored technique in microbiology, was employed to determine the response of our bacterial strains to the presence of farnesol, farnesene, and other agents [17, 18]. Clear zones of inhibition, representing areas where bacterial growth was notably suppressed, serve as an indicator of the antibacterial efficacy of the compounds.

However, we had additional experiments to perform. To quantify the efficacy of these compounds, the broth dilution method was used [19, 20]. This technique facilitated the determination of the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) – in essence, the minimal quantities of the compounds needed to inhibit or stop bacterial growth.

CHAPTER 4

Application of Viruses as Carriers in Biotechnology

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Abstract: Currently, the development of new vaccine technologies for the treatment of diseases is vital. The use of biotechnology in the application of viruses for the development of vaccines is a relatively new research platform. Viruses have become an important tool in biotechnology, and they are being used in the development of vaccines and anticancer drugs. Some of the viral vectors commonly used to develop vaccines are adenoviruses, adeno-associated viruses, herpes simplex viruses, retroviruses and lentiviruses, among others. Viral vectors have been used as vaccines against a variety of infectious diseases, such as COVID-19, influenza, HIV and malaria. Viruses have also been used to target drugs to cancer cells by using engineered viral vectors that can selectively target and infect cancer cells. In this way, viral vectors can also be used to deliver antitumor drugs. This will selectively target cancer cells. Thus, vectors can be used to deliver therapeutic drugs directly to the tumor, resulting in reduced side effects and improved efficacy.

Keywords: Anticancer viral vectors, Biotechnology, Carriers, Virus-based delivery systems, Viral vectors, Vaccines.

INTRODUCTION

Small infectious agents called viruses penetrate and spread within living cells. They are made of genetic material and protein coats [1], as shown in Fig. (**1**). The definition of a virus is an infectious entity that lacks several essential life activities, such as metabolism or reproduction [2, 3].

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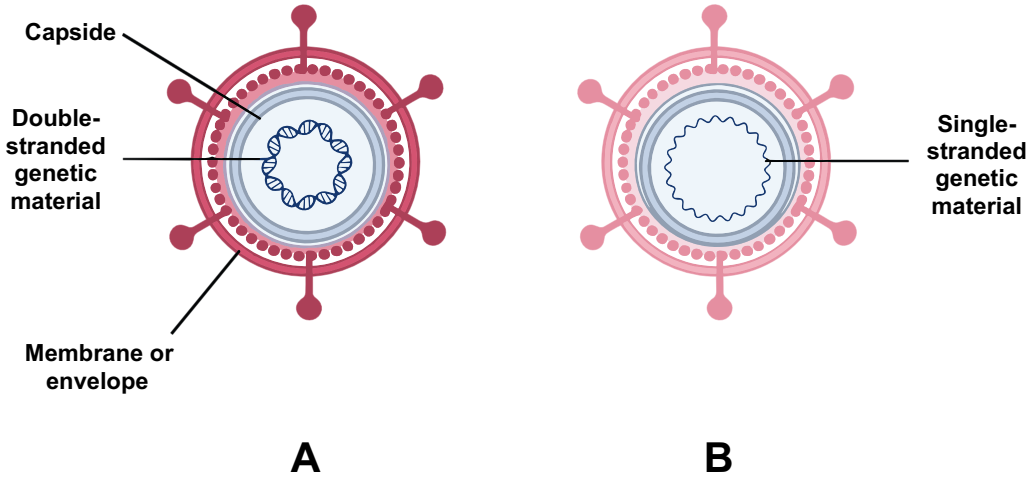

Fig. (1). Basics of virus structure. (**A**) Double-stranded genetic material, and (**B**) Single-stranded genetic material.

To complete their life cycles, viruses might use or abrogate specific cellular machinery components [4, 5]. A replicon, which permits genome duplication, and a capsid, a complex structure that not only protects the viral genome in the extracellular space but also plays a role in how virions enter and exit cells, are the two "organs" that the simplest viruses express [3].

In fact, viruses protect their genetic material by enclosing the viral nucleic acid in a protein shell known as a capsid [6], and their capsid proteins associate to produce globally stable structures through locally weak interactions [6]. Genetic engineering can be employed to modify the genetic makeup of the protein capsid [7].

Host ribosomes are enlisted by viruses to translate viral mRNAs. The objective is to ensure that cellular ribosomes are recruited to viral mRNAs, regardless of whether their genomes are made of RNA or DNA or how their mRNA is produced [8]. Host cells may eventually burst as they gather newly generated virus particles. This causes progeny virions to be released, which can subsequently infect other cells and continue the infectious cycle [9]. In tolerant cells, approximately 10,000 progeny virions are created [10]; however, many deficiencies can affect steps between transcription and the formation of new virions as well. Target cells could be infected in the first cycle, but progeny virions would fail to form or be released. Additionally, defective genomes could be incorporated into particles with functional proteins [9].

The host cell may eventually experience lysis when offspring virions accumulate

during viral replication. This will release the newly created viral particles, which can then infect nearby cells and continue the infectious cycle [11]. Virus-induced cell lysis releases up to 10,000 virions from a single cell [12]. One mechanism for controlling the generation of mutations in viral populations is thought to be variations in lysis time [5].

Because of their distinct qualities, viruses cannot be categorized as either living things or inert objects [13]. Although they have genetic material and are capable of reproducing, they require a host cell to carry out their basic life functions [3].

Viral nanomaterials can be utilized to transport drugs and genes that can be used to treat and prevent a variety of diseases [7]. The utilization of engineered virus-based nanomaterials as three-dimensional scaffold materials for diagnostic and therapeutic delivery systems as well as technological equipment has greatly advanced recently, demonstrating that viruses can also have advantageous properties [7].

New vaccines based on live recombinant vectors may induce robust, long-lasting immune responses while maintaining acceptable safety profiles [14]. Inducing strong immune responses against the encoded target antigen is possible with viral vector-based vaccinations. Indeed, numerous clinical studies have shown how effective viral vector-based vaccines such as VSV-ZEBOV are at eliciting protective responses in people. However, antigen distribution in a virus-unrelated situation makes this technique extremely difficult to execute [15].

Oncolytic virotherapy is a technique for directly delivering anticancer medications to malignant cells through the use of engineered viruses that can stop the growth of these cells or even kill them [16, 17]. The delivery of the virus to the tumor and the propagation of the virus infection are the two critical phases of effective oncolytic virus therapy, both of which are active areas of preclinical research innovation [18].

In addition, viruses are used to deliver therapeutic drugs since they can infect tumor cells [19]. Adenoviruses, adeno-associated viruses, herpes simplex viruses, retroviruses, lentiviruses, paramyxoviruses, and poxviruses are a few examples of viral vectors frequently employed in biotechnology. Adenoviruses are DNA viruses that do not integrate into the host genome, whereas retroviruses are RNA viruses that integrate their genome into the DNA of the host cell. Herpesviruses are large DNA viruses that cause lifelong latent infections in their hosts, whereas adeno-associated viruses are small DNA viruses that require a helper virus for reproduction [20]. Although not exclusively, many naturally occurring viruses show a preference for tumors and tumor cells. Since most cancers have evolved to evade immune identification and killing as well as to withstand apoptosis and

CHAPTER 5

Phenolic Compounds with Photo-Chemoprotective Activity

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Abstract: Skin cancer has one of the highest incidence rates among all types of cancer and is predominantly caused by exposure to ultraviolet radiation from the sun, which reaches the Earth's surface due to the well-known phenomenon of thinning of the ozone layer in the stratosphere. To reduce the risk of developing this malignancy, the use of sunscreens is recommended; however, the synthetic compounds in sunscreens can cause side effects and harm the environment. To avoid damage to human health and the environment, the use of different plant secondary metabolites with photochemoprotective potential has been investigated in recent decades. For this reason, phenolic compounds are useful alternatives since many of them are capable of absorbing ultraviolet radiation (UVR). Moreover, some of these compounds have anti-inflammatory, antioxidant, and even anticancer activities. This chapter explores the progress in the study of different phenolic compounds extracted from plants with potential for use in sunscreen formulations.

Keywords: DNA photodamage, Erythema, Flavonoids, Inflammation, Lignins, Natural products, Oxidative damage, Oxidative stress, Phenylpropanoids, Phenolic acids, Photoaging, Photocarcinogenesis, Photochemoprotection, Photoprotection, Reactive oxygen species, Secondary metabolites, Skin cancer, Sunscreens, Tannins, Ultraviolet radiation.

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INTRODUCTION

Skin cancer has a rate of high incidence in North America, Europe, and Australia, with at least 1.5 million cases reported worldwide in 2020 [1]. In Latin America, cases have increased due to the higher prevalence of fair-skinned individuals, while Africa and Asia have lower incidence rates due to greater skin pigmentation. The International Agency for Research on Cancer, an institution operated by the World Health Organization, has officially classified ultraviolet radiation (UVR) in group I of carcinogens with the strongest evidence of carcinogenicity in humans, especially skin cancer [2].

UVR is in the nonionizing radiation region of the electromagnetic spectrum, representing approximately 9% of the emitted solar radiation. For study purposes, UVR has been divided into three types: UV-C (200-280 nm) the shortest wavelength of radiation; UV-B (280-320 nm) which includes the mid-wavelength range and covers 5% of the total UVR spectrum; and UV-A (320-400 nm), which is known as longwave UV radiation, which comprises about 95% of the total ultraviolet spectrum [3]. The ozone (O_3) present in the planet's stratosphere, also known as the ozone layer, efficiently filters much of the UV-C radiation. Nevertheless, absorption by the ozone layer is rapidly decreasing, particularly the absorption of radiation with wavelengths greater than 280 nm, with an absorption rate of 0% for wavelengths greater than 330 nm [4]. Under normal conditions, the ozone layer filters approximately 80% of UV-B radiation, however, human activities have caused a reduction in the concentration of stratospheric ozone through the emission of compounds such as chlorofluorocarbons (CFCs). This has led to UV-C radiation and a higher percentage of UV-B radiation reaching the Earth's surface, affecting all living organisms. UVR that reaches the Earth varies due to factors such as geography, altitude, ground reflectance, cloud cover, and seasonal variation in ozone concentration in the stratosphere [5].

The mildest skin damage caused by prolonged exposure to UVR is erythema (sunburn), which is characterized by vasodilation and subsequent infiltration of neutrophil leukocytes that activate melanogenesis, the proliferation of epidermal cells, as well as the release of prostaglandins, nitric oxide (NO) and cytokines [6]. One factor that contributes to the development of skin cancer is the accumulation of reactive oxygen species (ROS), which leads to an imbalance in endogenous antioxidant systems, provoking oxidative damage, inflammation, and remodeling of the extracellular matrix [7]. In addition, exposure to UVR-A leads to an increase in ROS within cells, provoking oxidation chain reactions. The damage caused by UVR-B is mediated by ROS and by the increase in reactive nitrogen species, which triggers an increase in peroxidized lipids and a reduction in catalase and glutathione peroxidase levels [8]. Subsequently, ROS attacks lipids,

proteins, and DNA. Oxidative damage includes the formation of the 8-oxo-7 and 8-oxo-dG photoproducts that cause transversion mutations during DNA replication, the formation of cyclobutane pyrimidine dimers (CPDs), and inflammatory mediators derived from peroxidized lipids [9].

Inflammation caused by UV radiation is a defense mechanism of the body; however, when inflammation becomes chronic, it can lead to a higher probability of developing skin cancer [10]. ROS act as inducers of proinflammatory genes. Proinflammatory mediators are released from keratinocytes, fibroblasts, tumor cells, leukocytes, and the endothelial lining of blood vessels. Plasma mediators include those of a protein nature, such as bradykinin, plasmin, and fibrin; lipid mediators, such as prostaglandins, leukotrienes, and platelet-activating factors; and the inflammatory cytokines IL-1, IL-6, as well as TNF-α, histamine, and active phospholipase [11, 12].

Although enzymatic and nonenzymatic antioxidant systems are sufficient to decrease the damage caused by oxidative stress, when found at low levels, even small concentrations of ROS can trigger the inflammatory process through the activation of NF-kB and AP-1 [13]. NF-kB is a family of five structurally related proteins that function as central mediators of inflammatory responses [14, 15].

Additionally, UVR causes skin photoaging, which is characterized by fewer collagen fibers and fibroblasts, the loss of elasticity, and a reduction in wound-healing capacity [16]. UVR directly activates cell surface receptors, initiating signaling cascades that increase the transcription of different matrix metalloproteinase (MMPs) genes and reduce the expression of procollagen I and III genes, which regulate collagen synthesis and its subsequent degradation. During the photoaging process, the density of Langerhans cells and T lymphocytes is reduced considerably [16, 17]. These changes increase susceptibility to photocarcinogenesis and chronic skin infections. Clinically, signs of photoaging include wrinkles, irregular pigmentation, dryness, roughness, and a variety of premalignant lesions such as actinic keratoses [18].

At the cellular level, exposure to UVR-A induces DNA modifications, due to the oxidation of guanine to 8-oxo-dG, and the creation of DNA strand breaks [19]. UVR-B more efficiently produces mutations and DNA lesions, such as the formation of CPDs and pyrimidine-pyrimidone (6-4) photoproducts. CPDs are the predominant photoproduct induced by UVR [20, 21]. However, both types of lesions mentioned above are highly mutagenic, and they accumulate due to the excessive rate at which repair mechanisms occur, causing abnormal cell proliferation and tumor development [22].

CHAPTER 6

Natural Products in Wound Regeneration

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Abstract: The skin is the largest organ in the body that provides protection. When a wound occurs, the skin structure and its function are damaged, and it can even compromise life. Damage repair can occur through two mechanisms: healing and regeneration. When a scar forms, fibrosis occurs in the area, and the skin appendages, which include the glands and hair follicles, are lost. In regeneration, the functionality of the skin is partially or totally recovered. Medicinal plants and their active principles favor the regeneration of skin wounds because they have direct effects on the different phases of the process. They favor hemostasis, and modulate inflammation, which allows the following stages of healing to occur in less time, such as proliferation and remodeling. They favor hemostasis, modulate inflammation, and that the following stages of healing to occur in less time (proliferation and remodeling). Natural products can also reduce the risk of wound infections by having antibacterial activity. However, the bioavailability of the extracts and their metabolites may be limited, and a solution to this problem is to integrate them into preparations such as hydrogels, nanoparticles, nanofibers, and nanoemulsions. Research on the therapeutic properties of various natural products and their integration into the formulations mentioned above for wound regeneration is described below according to their effect on epithelialization, regeneration of epidermal appendages, vascularization, and in some cases their mechanism of action.

Keywords: Hair follicles, Hydrogels, Nanoemulsions, Nanofibers, Nanoparticles, Natural products, Wound regeneration.

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INTRODUCTION

The largest organ in the body is the skin; one of its main functions is to maintain the integrity of the individual. It has two main tissues: a) the outermost is the epidermis, a keratinized squamous epithelium composed mainly of keratinocytes, and the thickness varies from 0.04 to 1.6 mm depending on the location; b) the dermis is made up mainly of fibroblasts that synthesize and remodel the extracellular matrix (ECM) such as type I collagen fibers, elastic fibers, and ground substance; this layer is thicker than the epidermis -15 to 40 times-epidermis [1, 2].

In the dermis, there are two important compartments: a) the papillary dermis (PD) which is located below the epidermis, and is rich in papillary fibroblasts, with a high proliferative and synthetic capacity; and b) the reticular dermis (RD) which is much thicker with a parallel organization of connective tissue fibers to the surface of the skin, below the fatty layer called the hypodermis and later the fascia. In these layers, we find the radicular fibroblasts that oversee the synthesis of the ECM and participate in the generation of adipocytes. The epidermis and dermis are the hair follicle (HF) associated with sebaceous glands and the erector pili muscle, known as epidermal appendages [1]. It has been reported that papillary fibroblasts participate in the regulation of the maintenance and growth of the epidermis, as well as of the follicles. Mesenchymal stem cells are found in PD located at the base of the HF [2].

When the integrity of the skin is altered, a wound occurs. The damage repair process is carried out through the formation of scars or fibrotic repair that do not present HF, sebaceous glands or sweat glands. The wound healing process comprises four interposed phases: a) hemostasis (generation of a clot), b) inflammation (debridement of the wound), c) proliferation (activation of fibroblasts with collagen III synthesis), and d) remodeling (restoring type I collagen), resulting in a scar [2].

The process of healing wounds on the skin occurs in several stages and there are no specific time limits between them, they overlap each other. This process is dynamic and highly regulated by cellular, humoral, and molecular mechanisms that participate in each of the phases. It begins immediately after the injury and can last for years. Closure of skin wounds can be achieved through scarring or regeneration. Healing occurs through a nonspecific form of fibrosis and scar formation [3].

On the other hand, skin regeneration consists of the replacement and specific proliferation of tissues, such as the epidermis, and dermis with their annexes such as HFs [3, 4]. The role of papillary fibroblasts is crucial in skin regeneration by

preventing fibrotic effects, and promoting the development of the epidermis, and neoformation of HFs and blood vessels [2]. After an injury, PD fibroblasts respond to Wnt/β-catenin and Sonic Hedgehog (Shh) signals. Transforming epidermal growth factor beta (TGF-β) stimulates DR fibroblasts to proliferate and secrete ECM in regeneration [5]. The epidermal Shh signaling pathway is involved in reseating dermal papillae with the regenerative niche that promotes hair follicle neogenesis (HFN). The involvement of different pathways is complex and can lead to scarring or regeneration; for example, sustained Wnt expression is associated with fibrosis, but Shh signaling in Wnt-active cells promotes dermal papillae [6]. The temporal and spatial regulation of signals that can induce fibrotic scar formation or regeneration is complex and continues to be the subject of extensive research (Fig. **1**).

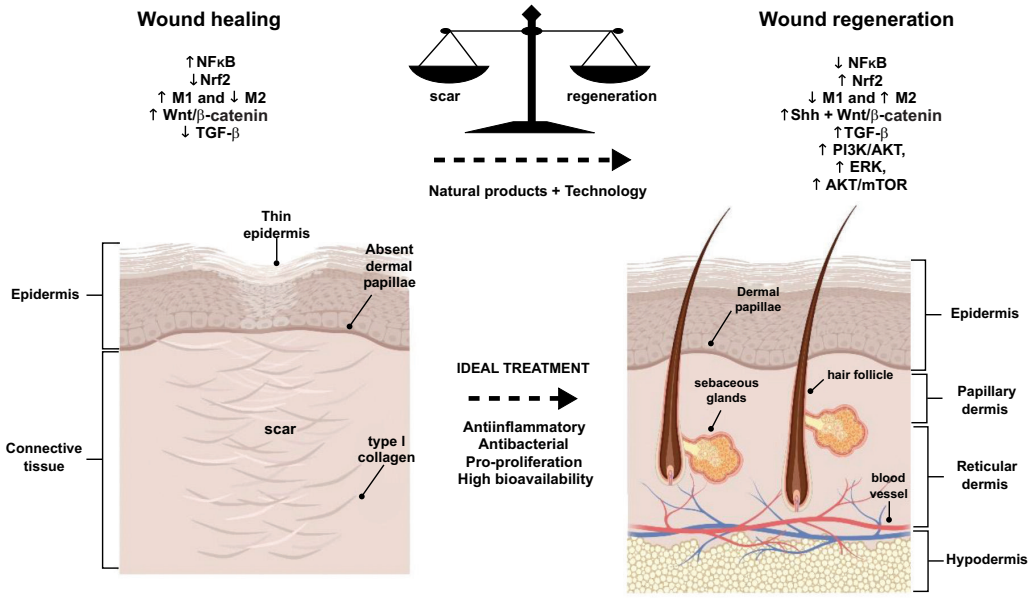

Fig. (1). Differences between wound healing and wound regeneration. ↑: increase; ↓: decrease, M1: type 1 macrophage, M2: type 2 macrophage. Created in BioRender.

NATURAL PRODUCTS: EXTRACTS AND SECONDARY METABOLITES

Treatments for wound healing are diverse and with them, the aim is to promote the healing phases and regeneration of tissue. In addition, it is recommended that treatments help maintain humidity around the wound, promote gas exchange, prevent infection, and be biocompatible, biodegradable, and non-toxic. In this

CHAPTER 7

Antimicrobial Effect of Natural Products against Bacteria, Fungi, and Yeasts

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Abstract: Antibiotics are compounds that either halt or destroy bacterial growth. They may be natural, semi-synthetic, or synthetic. Secondary metabolites, such as those produced by plants, animals, and microorganisms, are known as natural antimicrobials. The antibacterial/antimicrobial properties of secondary metabolites have been investigated over the past 30 years. Compounds derived from plants and culinary seasonings, including essential oils (EOs), are widely utilized in the food industry as organic agents to inhibit microbial growth in foods and prolong the shelf life of food products. Animal peptides (*i.e.*, polypeptides) also exhibit antimicrobial properties. Certain pathogenic and decaying bacteria may be inhibited by various chemicals produced by numerous microorganisms. Most microbially-derived antibacterial compounds are produced as intermediate byproducts of food fermentation. Numerous factors influence the antibacterial efficacy potential of natural products, including the source of the biological agent, harvesting time, the stage at which it is cultivated, and production methods.

Keywords: Animal origin, Antimicrobial origin, Byproducts, Essential oils, Natural products, Plant origin, Secondary metabolites.

INTRODUCTION

Initially hailed as “miracle medications,” antibiotics have quickly become overused due to their widespread use. Over the past decade, pathogenic microorganisms have developed resistance to several antibiotic medications, which is difficult to overcome. To address this, pharmaceutical companies are attempting to create new antibiotics [1].

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Natural products refer to chemicals that are produced by organisms or are acquired from the environment and have pharmacological or biological activity [2]. Primary and secondary metabolites produced by living things have diverse biological roles. Primary metabolites exert vital functions within the organism; by contrast, secondary metabolites may be superfluous byproducts or they may confer a substantial benefit to the organism. Secondary metabolites can be advantageous for human use and are used to treat several conditions, including cancer, bacterial infections, and inflammation, among others [3], with many compounds identified as having antibacterial properties. The majority of secondary metabolites with antimicrobial action originate from [1] plants such as fruits, vegetables, seeds, herbs, and spices [2], animal-based products such as milk, eggs, and tissue, and [3] microbes such as bacteria and fungi [4, 5].

Approximately 30,000 antimicrobial molecules have been identified in plants, and over 1340 species have known antibacterial properties [4]. Numerous naturally occurring antimicrobial compounds are derived from a diverse range of organisms, such as plants, animals, minerals, bacteria, and other distinct species [6]. Botanicals, which are commonly referred to as herbal products, are composed of an assortment of diverse plant components, such as seeds, bark, stems, leaves, flowers, fruits, wood, and even the whole plant itself [7]. A variety of animal-derived products exist, including beef, milk, eggs, meat, marine fish, sponges, curd, cow urine, cow dung, and other marine organisms [8]. In addition, natural products can be derived from honey and other sweeteners. They can also come from minerals, bacteria, and various other sources. The aim of the scientific field known as ethno-pharmacology, which explores substances such as natural antibiotics, is to apply the extensive pool of knowledge accumulated by indigenous individuals from specific communities and regions in relation to the numerous flora and fauna they have utilized to protect their well-being [8].

The term “antimicrobial activity” pertains to the ability to kill or inhibit microorganisms, thus halting their associated ailments. Various substances, such as alkaloids, tannins, terpenoids, essential oils, flavonoids, lectins, proteins and polypeptides, quinones, coumarins, polyphenols and phenolic compounds, enzymes, lysozymes, phagocytic cells, and numerous other organic constituents, possess active principal or secondary metabolites (or in the case of plants, phytochemicals) that exhibit antimicrobial properties [8]. Interest in natural antimicrobials has been reignited due to elevated public awareness surrounding the limited efficacy of synthetic pharmaceutical products in the management of numerous infectious diseases, which is attributed to drug resistance that has arisen from the incorrect usage and overprescription of antibiotic medications [8]. Additionally, several synthetic compounds can be harmful and are associated with unintended consequences. Increasingly, individuals are seeking better alternatives

in order to maintain control over their medical treatment and avoid unnecessary toxins and chemicals [8].

Natural antimicrobial agents appear to be a feasible solution to address the numerous issues associated with increasing antibiotic resistance. Compared to synthetic antimicrobial agents, which are formed *via* amalgamations of chemicals and other synthetic methodologies [9, 10], there is a significant demand for new kinds of potent and healthful antibacterial chemicals that could avoid contamination in food and protect consumers from illness. This chapter aims to provide an overview of recent research on naturally occurring antimicrobial compounds derived from plants, animals, and microorganisms. The primary objective is to investigate the feasibility of using these compounds as a potential treatment option for microbial pathogens responsible for causing various human diseases [10].

EXPLORING THE ORIGINS AND DIVERSITY OF NATURAL ANTIBIOTICS

Botanical Origins: Natural Antimicrobial Substances

Since ancient times, humans have been aware of the healing powers of plants. Throughout history, the knowledge of utilizing plants and their byproducts for medicinal purposes has been passed down over generations in diverse regions of the world [11]. This has greatly influenced the growth of diverse traditional medical systems. According to the World Health Organization (WHO), nearly 80% of people worldwide regularly utilize traditional herbal remedies [12].

Plants generate a vast array of diverse chemical compounds, several of which do not have indispensable requisite functions in fundamental metabolic processes, but represent adaptation of the plant's adverse biotic and abiotic conditions [13]. Such chemicals that are categorized as substances with physiological activity are sometimes referred to as secondary metabolites since they are produced as byproducts or intermediates of secondary plant metabolism. These ancillary compounds proficiently exert their role within the plant system and are associated with biological and pharmacological effects in humans in addition to defining distinctive botanical attributes such as the hue and fragrance of flowers and fruits, the zestful flavor of spices, and the savory taste of vegetables [11]. Consequently, the medicinal properties of plants are associated with plant secondary metabolites [14].

Extracts of culinary, therapeutic, and herbal plants are used to create essential oils (EOs), which are also products of secondary metabolism [15]. Antibiotics produced by plants can be divided into two categories: phytoanticipins, which are

CHAPTER 8

Human Diseases and Recent Biotechnology Breakthroughs in Curbing Diseases

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Abstract: Medical biotechnology represents a field in continuous progress and today has revolutionized how illnesses are diagnosed and treated. A look at the latest medical biotechnological breakthroughs shows how biotechnology innovations are changing medicine. Recently, we saw how biotechnology affected efforts to combat the coronavirus disease 2019 (COVID-19) pandemic on the world's health. The scientific community has been working assiduously to develop effective treatments for the prevention and management of other diseases, such as cancer, human immunodeficiency virus (HIV), cardiovascular disease, diabetes mellitus, and neurodegenerative disorders such as Alzheimer's disease, along with other dementia variants that stand out among the leading causes of mortality worldwide. This effort has recently resulted in the development of RNA vaccines. Some of the most promising biotechnological developments include gene therapy to alter an individual's genetic makeup through diverse techniques, immunotherapeutic methods that bolster the body's natural immune defense mechanisms, and precision medicine strategies in which treatment is personalized to a patient's genetic profile. This chapter provides an overview of the most prevalent and deadly human diseases with a focus on recent biotechnological breakthroughs.

Keywords: Biotechnological breakthroughs, Gene therapy, Immunotherapy, Medical biotechnology, Precision medicine.

INTRODUCTION

In recent years, medical biotechnology has emerged as a highly progressive discipline that utilizes living organisms, cells, cell products, or materials to gene-

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rate innovative healthcare solutions [1]. Biotechnology enterprises and the scientific community are employing the most recent advancements in molecular biology, genetics, and nanotechnology to fabricate innovative medicinal products, vaccines, diagnostic instruments, and other healthcare commodities to improve human welfare. The present role of medical biotechnology can be seen in precision medicine and the utilization of progressive technologies such as gene manipulation and cellular therapy (Fig. **1**) [2]. Precision medicine can potentially revolutionize the healthcare industry for both collectives and individuals by enabling early disease detection, enhancing diagnostic accuracy, and customizing therapeutic interventions [3].

This field of study employs various essential technologies, such as big data, artificial intelligence, diverse omics, and pharmaco-omics, as well as environmental and social factors. Additionally, it involves integrating these technologies with tools from preventive and population medicine, all of which are critical components of this field [4]. A personalized approach to medicine needs to be supported by the utilization of cutting-edge technologies, including gene manipulation. The landscape of gene therapy technology has advanced significantly [5].

A gene-editing method called clustered regularly interspaced short palindromic repeats (CRISPR) was developed for increased robustness and is based on the innate immune system of bacteria. Due to its increased specificity and effectiveness, CRISPR/Cas9 has been widely used in the treatment of a variety of genetic and nongenetic diseases, including but not limited to cancer, genetic hemolytic diseases, acquired immunodeficiency syndrome, cardiovascular disease (CVD), ocular diseases, neurodegenerative diseases, and some X-linked diseases. Additionally, some researchers have used the CRISPR/Cas9 methodology in the context of gene therapy and immune therapy for cancer treatment to treat or mitigate cancer [6]. Cancer immune therapy is a biological procedure that uses several immune system elements to protect the host from the development of primary tumors or improve the chances of cancer evasion. Cancer immunotherapy has led to significant improvements for patients in terms of survival and quality of life when compared to chemotherapy, radiotherapy, and surgery. Immunotherapy has recently gained acceptance in the field of cancer treatment as a cutting-edge foundational therapy, applicable from the metastatic stage to the adjuvant and neoadjuvant environments in a variety of disease categories (Fig. **1**) [7].

From developing new treatments for diseases to creating diagnostic tools that can detect illnesses earlier, medical biotechnology significantly impacts how we approach healthcare. Overall, the current state of biotechnology in healthcare is dynamic and ever-evolving, and the field continues to push the boundaries of

medical science. The prospect of utilizing gene therapy to treat chronic ailments necessitating lifelong care and medical supervision has sparked scientific interest. CVD and neurodegenerative diseases are considered appropriate models for the comprehensive utilization of precision medicine technologies throughout the various stages of disease progression [8].

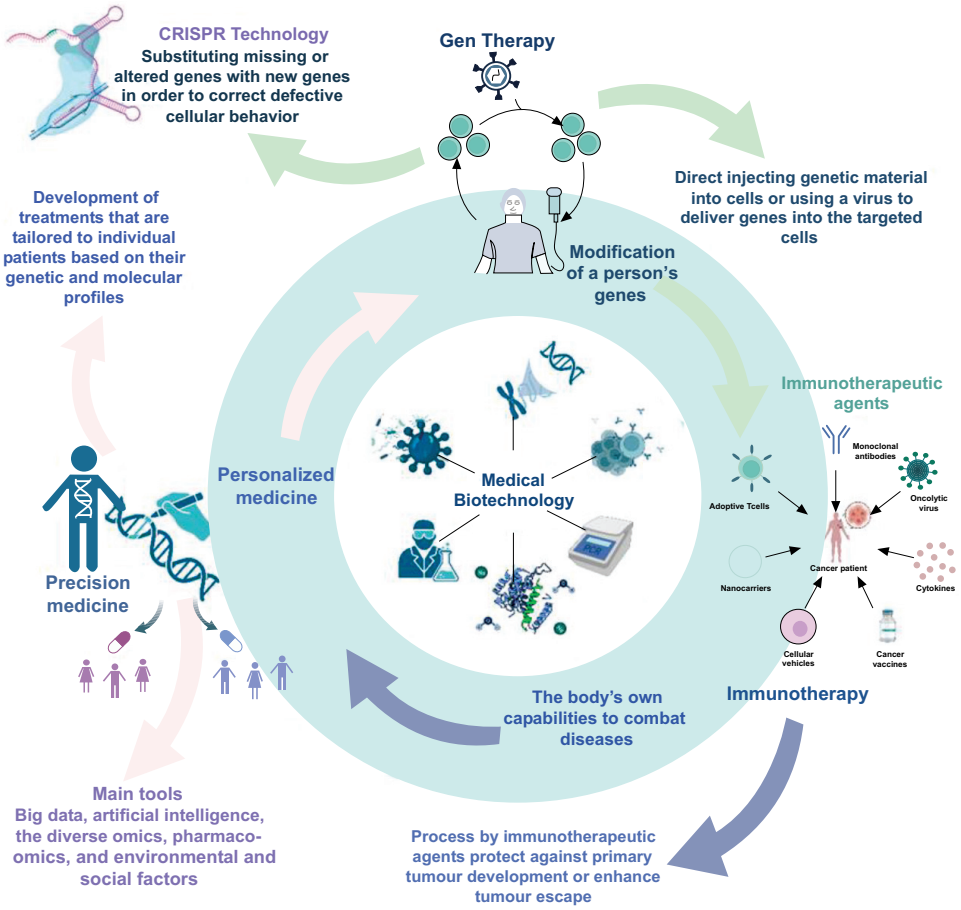

Fig. (1). Medical biotechnology as a central scientific area for the development of promising advancements in targeted therapies such as gene therapy, precision medicine and immunotherapies. Created with BioRender.com.

In 2019, noncommunicable diseases were responsible for 74.36% of all deaths worldwide. CVDs, neoplasms, and chronic respiratory disorders (CRDs) are a few of the prominent non-communicable diseases (NCDs). In 2019, deaths from these three diseases made up a sizable fraction of deaths worldwide from all causes [9].

CHAPTER 9

Exploring the Intersection of Omics Technologies and Biotechnology in Drug Interaction Studies

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Abstract: The integration of omics tools with biotechnology has led to a paradigm shift in our comprehension of drug interactions, providing profound insights into the molecular mechanisms underlying these interactions. We explore the crucial functions of genomes, transcriptomics, proteomics, and metabolomics in this chapter to decode pharmacological interactions at various molecular levels. Notably, significant emphasis is placed on the application of omics tools in areas such as high-throughput screening for unveiling novel drug targets, personalized medicine, pharmacogenomics, understanding drug-drug and drug-metabolite interactions, drug repurposing, polypharmacology, and systems biology. Furthermore, the paper explores the potential of integrating omics data with computational approaches to study complex biological networks, highlighting the instrumental role of microbial biotechnology in drug interactions. Importantly, alongside these advancements, there is also an in-depth discussion of the ethical, legal, and societal ramifications of the use of omics technologies in biotechnology. Moreover, the text presents an in-depth examination of the emerging trends, challenges, and prospective developments in the realm of omics research. As the field continues to evolve, overcoming challenges related to data integration, reproducibility, and standardization are underscored as crucial for the translation of these pioneering discoveries into improved patient care and the development of more effective, personalized therapeutic strategies. It is crucial to remember that the combination of omics tools and biotechnology will have significant effects on how medicine and healthcare are delivered in the future. As a result, it is essential to maintain research and development in this field to ensure that all future healthcare-related exigencies can be met with the most advanced and innovative solutions possible.

Keywords: Biotechnology, Drug interactions, Drug repurposing, High-throughput screening, Systems biology, Microbial biotechnology, Omics tools, Personalized medicine, Pharmacogenomics, Polypharmacology.

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INTRODUCTION

The study of metabolites and metabolism, often known as metabolomics, occupies a distinctive position in the rapidly changing field of drug interaction research. Researchers can use this field as a conduit to investigate the complex intersections of gene-environment interactions. Notably, this particular focus stands in stark contrast to the emphasis on genes and genetic risk scores, which predominantly indicate potential future outcomes. Rather, metabolic profiling and phenotyping reflect ongoing processes in the present. In summary, metabolomics not only makes it easier to identify illness indicators such as endogenous metabolites (those produced by genes) and exogenous metabolites (those produced by environmental variables) but also offers previously unattainable insights into the underlying causes of diseases. With enhanced accessibility to metabolomics assays, these fresh perspectives are catalyzing a seismic shift in the way drugs are discovered, developed, delivered, and dosed. It is clear that this paradigm shift has the potential to transform the process of finding new drugs and cause a major shift in the medical industry [1].

In the realm of scientific research, a considerable obstacle that arises pertains to the unification of diverse omics data sets, a crucial procedure that facilitates the generation of more knowledgeable decisions about therapeutics. Despite the intricate nature of this process, it has become a rather commonplace occurrence to incorporate and blend exome and RNA-seq data, namely, through the fusion of genomics and transcriptomics, particularly when examining a tumor, as a means of unearthing profound insights into prospective therapeutic targets that can be influenced by drugs. This process, which is referred to as pharmacogenomics, is progressively gaining traction [2].

Pharmacogenomics is the field of study characterized by the discerning application of genomics data and other “omics” information for the purpose of guiding, informing, and individualizing drug therapy. A long time has passed since the initial introduction of the concept of pharmacogenetics by Arno Motulsky, and the progressions that have been achieved in this realm since then are noteworthy. It is undeniable that genetics has a significant impact on therapeutic efficacy and the likelihood of unexpected drug reactions and that genomics data can be used to enhance efficacy and reduce adverse reactions [2].

While the field of transcriptomics has been successful in elucidating gene expression modifications following drug exposure, proteomics has enabled researchers to delve into the intricate interactions between drugs and targets and the subsequent impacts on protein expression. However, the study of metabolomics involves a thorough characterization of metabolites and metabolism

in biological systems. This field of "omics" science is quickly expanding. Numerous new biomedical applications have been made possible by recent developments in metabolomics technology. In particular, the study of metabolomics is beneficial for identifying novel drug targets, detecting diseases, understanding disease mechanisms, determining individual treatment plans, and precisely tracking therapeutic outcomes [1].

USING HIGH-THROUGHPUT SCREENING TO FIND NEW DRUGS

With the emergence of high-throughput technologies, there has been a proliferation of genome-scale datasets that have come to be known as multiomics data. The landscape of drug discovery research has undergone considerable upheaval as a result of this advancement, which has had a profound impact on the discipline. This vast collection of data comprises different types of data, such as genome sequencing data, which is known as genomics. Additionally, there are genome-wide RNA-sequencing data, which are referred to as transcriptomics. Furthermore, there are methylation and histone modification data, which fall under the category of epigenomics. Last, there is mass spectrometry protein data, which is known as proteomics [3].

Over the past four decades, the prevailing pattern for the exploration and establishment of drugs has typically involved an array of intricate stages. The procedure starts with the identification and determination of disease-triggering genes using technologies such as whole-genome sequencing, genome-wide association studies (GWAS), or pedigree analysis. The next step in development is the cloning of the discovered genes. High-throughput screening is performed on the purified target proteins to find potential therapeutic leads. These leads are then improved upon and evaluated in animal models, ultimately leading to human trials [1].

The field of metabolomics, despite being primarily focused on metabolites, has a multitude of applications that extend across a vast array of domains. Human and animal health, the identification of biomarkers, the development of new drugs, plant biology, microbiology, food chemistry, and environmental monitoring are just a few of these domains. Metabolomics' versatility in being able to evaluate a wide variety of substrates is the reason for its broad applicability. These substrates include liquids such as water, effluent, and biofluids as well as solids such as tissues, soil, and biological waste [1].

Genomics and transcriptomics approaches have unquestionably played a crucial part in the identification of prospective therapeutic targets and biomarkers that are suggestive of treatment response. The multiomics approach has been widely employed to supplement these methodologies [1]. Furthermore, proteomics and

CHAPTER 10

Sharing is Caring: Drug Repurposing among Leading Diseases

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Abstract: The process of drug development is time-consuming and resource-intensive, but drug repurposing offers an alternative by using already approved drugs to treat different diseases. Drug repurposing candidates can be identified through computational and experimental approaches, which are often combined. Traditionally, drug repurposing is considered when developing a custom drug is not feasible, but recent findings regarding the cross-talk between cellular mechanisms and pathways that are altered among disease states suggest that multipurpose drugs may be the key to simultaneously treating multiple diseases. This chapter reviews published reports on drug repurposing for five of the most threatening diseases to human health today: Alzheimer's disease, arthritis, diabetes mellitus, cancer, and COVID-19, highlighting promising candidates, challenges, and potential future directions for research.

Keywords: Alzheimer's disease, Arthritis, Cancer, COVID-19, Diabetes mellitus, Drug development, Drug repurposing.

INTRODUCTION

Drug development is a complex process that can take years to complete. After its discovery, which alone can take several attempts spanning years, candidate drugs must undergo a series of trials to deem them safe, effective, and practical to use as a therapy. These tests can take close to twenty years and have a low probability of success. Drug repurposing, also known as drug repositioning, offers an alternative

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to this resource-intensive process. The rationale behind drug repurposing is to discover new uses for existing drugs that have already been tested to be safe, effectively bypassing at least the first set of tests and saving substantial amounts of time and resources [1]. This approach has succeeded in finding novel uses for several drugs. For instance, the PDE5 inhibitor sildenafil, initially intended as a treatment for systemic hypertension and later discovered to be an effective treatment for erectile dysfunction, has found new applications in breast and prostate cancer, among other cancer types [2]. Another successful, albeit noncanonical, example is thalidomide, a nonaddictive sedative marketed to pregnant women in the 1960s. After being infamously teratogenic, it was banned; however, it is now used as a treatment for various cancers and inflammatory skin disorders [3].

Drug repurposing is a relatively recent concept and has only been documented since the mid-1980s. Since then, approaches to this potentially beneficial concept have moved from serendipitous to systematic. Today, drug repurposing strategies are broadly classified into computational and experimental approaches. Computational strategies use big data analytics to find repurposing candidates through their association with gene or pathway regulation, large-scale drug screen results, and molecular docking. Experimental approaches encompass binding assays such as affinity chromatography and *in vitro* experiments to evaluate the effectiveness of a repurposing candidate [4]. Repurposed drugs are great alternatives to treat rare diseases where no licensed treatment is available, and the resource-intensive process of developing a custom drug is unfeasible [5].

Nevertheless, as the community searching for repurposing candidates and applications widens and the amount of available information increases, it has become evident that drugs can be repurposed even among the leading, most studied diseases, exploiting the crosstalk between the cellular mechanisms and pathways altered in them. This crosstalk indicates that a few already-approved drugs may be able to simultaneously treat several diseases. In this chapter, we reviewed published information about drug repurposing for five of the most threatening diseases to human health today: Alzheimer's disease [6], arthritis [7], diabetes mellitus [8], cancer [9], and the recently emerged COVID-19 [10].

THE PANDEMIC IN THE ROOM

Although the strict lockdown measures have been lifted, the world is still dealing with the pandemic caused by the SARS-CoV-2 virus, the etiological agent of COVID-19. Several groups rushed to find treatment strategies for the novel disease [11], and as the average number of severe cases dwindles, concerns about its sequelae have become increasingly important [12, 13].

Due to its relative but substantial reduction in processing time, drug repurposing excels as a search strategy for COVID-19 treatments. For instance, Mirabelli *et al*. [14] found that amiodarone, ipratropium bromide, lactoferrin, lomitapide, remdesivir, and Z-FA-FMK, out of a library of over a thousand US Food and Drug Administration (FDA)-approved compounds, inhibited SARS-CoV-2 infection in a panel of cell lines. Of these compounds, lactoferrin stood out since it blocked viral attachment and enhanced the interferon response at concentrations as low as the nanomolar range.

Sonkar and colleagues [15] took a bioinformatic approach based on observed structural similarities between SARS-CoV-2 RNA-dependent RNA polymerase (RdRP) and familiar kinases such as JAK, ITK, PERK, and p38-MAPK. From a suite of 12 kinase inhibitors currently employed to treat gastric cancer, brepocitinib, decernoitinib, filgotinib, and ibrutinib bound SARS-CoV-2 RdRP with sufficient affinity to block its function, thus making them candidates for repurposing. A similar machine-learning approach suggested that baricitinib, an inhibitor of the AAK and JAK1/2 kinases, was effective against SARS-CoV-2 entry because AAK is involved in endocytosis. This mechanism was tested *in vitro* and in patients [16]. However, a 648-sample clinical study showed that treatment with the tyrosine kinase inhibitor imatinib did not necessarily lead to quicker COVID recovery. While strong evidence suggests that imatinib inhibits the Arg/Abl2 kinases, its administration was not associated with a better clinical outcome. The authors do not rule out the effectiveness of imatinib; instead, they argue that the metabolic variants within their sample may have affected the results [17].

A different bioinformatic approach, taken by Lucchetta and Pellegrini [18], was used to compare the gene expression patterns of patients with several conditions, including prostate and colorectal cancers and COVID-19. These authors developed DrugMerge, a software application capable of analyzing expression signatures and finding drugs that similarly affect them, ranking them according to their degree of similarity. Etoposide, a topoisomerase II inhibitor used to treat prostate cancer, was shown to affect a similar subset of genes in patients with COVID-19 infection. DrugMerge software is still in the process of being developed, and its developers are yet to incorporate considerations of pharmacological therapy, such as dosage, tissue specificity, and possible adverse side effects.

Given that COVID-19 can have broad systemic effects [19], several groups evaluated the repurposing of antimetabolic drugs for COVID-19 treatment. The results showed that several of these drugs can indeed aid in COVID-19 treatment.

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The published chapters in this book about multi omics applications from different research groups at UNAM, explores health from a variety of perspectives. Interpreting scientific studies and communicating the findings in an easy to understand way is a gift that keeps on giving.

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