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Exploring the Potential of Natural Compounds as Chemotherapeutic Agents: Challenges and Opportunities

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ABSTRACT:

The potential of natural compounds as chemotherapeutic agents has become a focal point in cancer research due to their varied biological activities and unique mechanisms of action. These diverse substances, derived from plants, fungi, and microorganisms, present promising alternatives or adjuncts to conventional cancer therapies. Their multi-targeted nature may lead to reduced side effects and increased efficacy, addressing resistance issues commonly encountered with synthetic drugs. However, the exploration of these natural products faces several challenges, including difficulties in sourcing, standardization, and large-scale production. Additionally, the complexity of their chemical structures necessitates comprehensive understanding and rigorous testing to determine appropriate dosages and potential interactions with existing treatments. Despite these obstacles, advancements in biotechnology and phytochemistry hold promise for enhancing the therapeutic potential of natural compounds. By illuminating their pathways and synergistic effects, researchers can harness these agents more effectively, creating new opportunities for cancer treatment. This exploration not only offers hope for improved therapies but also promotes sustainable practices in drug development, ultimately benefiting both patients and the environment.

***Keywords*:** Chemotherapeutic Agents; Anticancer; Natural Compounds; Phytochemicals; Cancer

1. Introduction

Cancer remains a major public health problem worldwide. It timely leads to about 10 million deaths each year and ranks as the second leading cause of mortality. The development of novel drugs for cancer prevention and treatment has long been a subject of global concern and effort. In previous decades, natural product has been a fruitful reservoir for drug development, with more than fifty percent of the antitumor agents introduced being either natural products or a nature product derivative. Additionally, over 60% of the anticancer compounds approved for clinical use between 1981 and 2014 are natural products based. Unlike the past, the pharmaceutical industry has discontinued the use of natural products as the front-line tool for the drug discovery. This is partially attributed to the historical inefficacy and low technological advancement to standardize production and synthesis of nature compound. However, as with past emerging paradigms such as the combination therapy and the precision pharmacotherapy, the pharmaceutical industry has evolved to locate a new role for natural product in these new paradigms. Prior to this there are multidimensional questions to be tackled to enhance the speed and success rate of drug discovery of nature product.

1.1. Background and Significance

In 1839, the French chemist Leconte isolated taxol (paclitaxel) compound from an endophytic fungus in Sorbus domestica and found that its ethanolic extract was used for the treatment of many diseases, including cancer (Huang et al., 2021). In 1809, the first pure natural-synthesized compound, urea, was obtained from harnstoff, thereby marking the discovery of a range of many important compounds, such as steroids, cephalosporins, and penicillin, which later captured the attention of many researchers to continued effort devoted to the extraction of natural compounds. Natural compounds, including both unmodified molecules containing only C, H, O atoms and compounds modified by hydroxylation, carboxylation, or other processes that are made by life forms, are believed to be endowed with the ability to stimulate some biological activities. For over 50% of anticancer agents applied in the clinic, some chemicals in this class, such as camptothecin, podophyllotoxin, and paclitaxel, have been isolated from plants being examined for antibacterial and anticancer activity. Refinement and an increased orientation for bio-assay processing following the isolation of natural products have persisted over the years.

2. Chemotherapy

Tumor is one of the leading causes of human death worldwide with high mortality and morbidity. Historical records show that as far back as 4000 years ago, ancient Egyptians recognized tumors and attempted to use surgery to remove them. In the early 20th century, dysplastic antimetabolites were the first form of chemotherapy obtained by isolating vinca. In 1947, Sophie Klein discovered the antitumor effect of methotrexate, which led to the start of modern chemotherapy (Wu et al., 2023).

Chemotherapy is the use of chemical drugs to inhibit the progression of tumors. Either alone or in combination with other therapies such as surgery, radiotherapy or biological therapy; It remains the mainstay of tumor treatment and has been shown to improve the survival of patients with specific tumors. Despite this, 90% of patients with solid tumors experience relapses after initial therapy. Especially in advanced tumors, the cure rate is very low. In the past 5 years, death rates in China have increased by 28.99% and morbidity by 28.26%. Although there are many innovative advances in target drugs and immune therapy, traditional chemotherapy still plays an indispensable role in the comprehensive treatment of tumors. In recent years, as large molecules of plant-derived medicine, natural compounds have been recognized after the chemical synthesis drugs that were discovered the earliest.

2.1. Overview of Chemotherapy

The word 'chemotherapy' incorporates a broad variety of pharmacological procedures employed in cancer remedial which serve to kill or retard the propagation of cancer cells in an individual. There are a host of diverse chemotherapy drugs accessible, most of which derive from the combinatorial use of a number of drugs. Conversely, there are currently a small number of chemotherapy drugs which are single agents and are employed in monotherapy. Some naturally occurring compounds have been proven to obliterate cancer cells in test tube and animal studies (S. Choudhari et al., 2020). The question is if they can obliterate the cancer when taken in large enough quantities by humans. Nevertheless, the data presented herein arrives at the conclusion that the majority of these compounds have no therapeutic efficacy in humans and might even be detrimental to the patient's health.

Chemotherapy serves to obliterate cancer cells through the process of attacking cell components actively participating in mitosis. This is why cancer cells are most sensitive to chemotherapy particularly when they undergo mitosis (the M stage of the cell cycle) but are also susceptible to cancer toxins during replication (the S stage of the cell cycle). Normal, differentiated cells are protected to an extent from the cytotoxic effects of chemotherapy seeing they do not divide as frequently as cancer cells (Sun et al., 2021)(Raghani et al.2024). Nevertheless, as stated earlier, chemotherapy does not only target M stage cells. Consequently, the drug also eliminates normal, rapidly dividing cells in tissues for example hair follicles, skin, bone marrow, and the gastrointestinal tracts, which are common sites of drug toxicity.

2.2. Types of Chemotherapeutic Agents

According to the pharmacology of action, the main chemotherapeutic agents are divided into 9 categories including alkylating agents, antibiotics, anthracyclines, plant alkaloids, hormone antagonists, enzyme inhibitors, antimetabolites, topoisomerase inhibitors, and biological agents (Anand et al.2023). Surgery, a traditional practice for treating tumors, has become more mature. However, it is easy to damage the growth at the surgical site and possibly spread tumor cells to other parts of the body. Radiotherapy is a method to use artificial radiation to damage tumor cells and stop their growth and division. However, normal cells can be easily damaged due to their precise sensitivity and will make the patient feel pain (Gong et al.2021). With the development of immunotherapy drugs, as well as the continuous introduction of more targeted therapy drugs, these drugs have slowed the progression of tumors and improve the quality of life of patients significantly.

Natural compounds, on account of their broad compatibility and low side effects, have been widely condensed and viewed as chemical models for synthesizing organic compounds. These secondary compounds produced by plants in response to biotic and abiotic stress conditions have the ability to inhibit plant parasitic infections, including bacteria, viruses and herbivores. Nutrients such as carbohydrates, lipids, amino acids, vitamins and minerals play an essential role for the growth, development and inheritance of plants (Wu et al., 2023). Even there are quite a few secondary metabolites with no direct role in growth, development, or reproduction process. Effected compounds are involved in signaling and defense mechanisms against herbivores and pathogens, in responses to ultraviolet light, oxidative stress and wound healing, and in the attraction for pollinators, or in the defense against other plants (Kumar et al.2023)(Divekar et al.2022). After many years of installation, breakdowns, developments of Q Selective Reaction and Gas Liquid Chromatography techniques, and the increase of the human population, the Industrial Revolution has occurred, causing industry and chemical contamination to sources of freshwater. These natural compounds, most of which are harmful to aquatic organisms, can have different ecotoxicological effects on ecosystem function, structure and community composition.

3. Natural Compounds

Natural compounds are biologically active substances that are derived from a wide variety of sources, encompassing plants, microorganisms, and even marine life. These exceptional compounds have played a pivotal role in shaping the ever-evolving field of drug development, particularly within the critical and complex realm of cancer treatment (Chopra & Dhingra, 2021). Their diverse and intricate structures, along with their remarkable ability to interact with numerous biological processes, render them particularly valuable to researchers and clinicians alike. Many prominent and widely used chemotherapy drugs, including well-known examples such as paclitaxel, vincristine, and camptothecin, trace their origins back to these natural sources. These essential drugs display a broad and impressive spectrum of pharmacological effects, which include not only anti-inflammatory and antimicrobial

properties but also potent anticancer effects that are fundamental to modern medicine (Shah et al.2023). The inherent potential of these natural compounds for reduced toxicity, alongside their unique capability for selective targeting cancer cells, positions them as highly promising candidates for the development of new and innovative therapeutic strategies. However, despite the numerous advantages that these natural compounds present, considerable challenges continue to exist. Issues such as low bioavailability, complexities involved in large-scale production, and various regulatory hurdles must be effectively navigated and addressed in order to fully exploit their multiple therapeutic benefits and to maximize their impact within the treatment landscape. Overcoming these barriers is essential for the realization of their full potential in enhancing patient outcomes and improving therapeutic efficacy in a meaningful way (Dehelean et al.2021)(Huang et al., 2021). Continued research and development efforts are crucial to unlocking the vast capabilities of these natural compounds in pharmacology and thus advancing the future of cancer therapies.

3.1. Diverse Bioactivity and Mechanisms of Action

The extraordinary diversity in nature is a rich source of bioactivity, with plant compounds acting as secondary metabolites that play crucial ecological roles, particularly in defense against predators. This unique profile of natural bioactive molecules highlights the potential for drug discovery, as many are utilized as templates in commercial drug development (Salam et al.2023). The bioprospecting potential of these complex chemicals has led to widespread plant-initiated compound databases for virtual screening in industry and academia. However, several challenges hinder the translation of natural compounds into clinical practice: i) While many natural chemical entities in plants and related organisms have been characterized, many more remain unobserved. The resulting diversified metabolomic profile contrasts with the high costs of thorough chemical and biological inspections; ii) Information on the bioactivity mechanisms of natural compounds is often sparse and incomplete (Atanasov et al.2021).

Pure compounds may interact with multiple target pathways, with many relevant interactions remaining unknown. Understanding how bioactives influence the TCL metabolome and communication systems is still in its infancy, posing bioinformatics challenges; iii) Identifying bioactives with desired profiles may require drug-likeness filtering, which could inadvertently exclude real bioactive compounds, especially those rich in alkyl, epoxy, hydroxyl, or metal groups. Some unobserved bioactive compounds may represent new, effective treatments (Zhang et al.2022)(Najmi et al., 2022). Many computational methods have been developed to study single molecular signaling, yet the death rate associated with TCL remains high, with most patients dying within five years of diagnosis. Despite advances in medical treatments, including surgical and radiological interventions as well as various therapies, TCL continues to be one of the deadliest malignancies, ranking fifth in global causes of death (approximately 450K fatalities annually) with a nearly equal incidence in men and women. (P. Chavda et al., 2021)

3.2. Synergistic Effects and Multi-Target Activity

Traditionally, composite mixtures, including drug combinations and herbal formulations, have been utilized for cancer treatment globally. However, their complexities challenge scientific investigation and regulatory approval. Advances in drug discovery have led to more purified active compounds developed as single-component drugs. Herbal medicine often uses multiple herbs to improve efficacy and minimize side effects, but understanding its mechanisms through Western medicine theory remains difficult (Gao et al.2022). Modern technology attempts to standardize and control quality, although assessing therapeutic outcomes through molecular targets is still limited. Major pharmaceutical firms favor isolation of bioactive compounds as single drugs, complicating the entry of complex mixtures into the market. Regulatory challenges and the lack of suitable business models hinder the development of composite drugs, and protecting commercial rights for commonly shared mixtures poses further difficulties (Chavda et al.2022). Efforts in Europe and China to standardize traditional herbal products seek to ensure manufacturing processes and product characterization for efficacy and safety. This has been positively received by regulatory authorities, fostering the continued use of traditional remedies, particularly among migrant populations. Growing recognition exists regarding the potential for appropriate combinations of bioactive constituents in complex mixtures to provide synergistic therapeutic effects at various cellular or molecular levels. (P. Chavda et al., 2021)

3.3. Lower Toxicity and Reduced Side Effects

Chemotherapy is a common cancer treatment, but its low drug specificity can lead to adverse reactions and toxicity, making patients intolerant to side effects. In Asia, natural products from medicinal plants have been used for thousands of years to treat diseases. Evidence shows that these natural products and herbal compounds may influence critical cancer pathways, emphasizing the need for strategies to mitigate chemotherapy's negative effects. Recent studies involving cell lines, animals, and clinical trials reveal that various natural substances can alleviate side effects induced by chemotherapy. Compounds, single herb extracts (SHE), and composite herbal formulas (CHF) have improved quality of life for cancer patients (Chaughule & Barve, 2024)(Moreira et al.2023). Multi-component extracts, often used in Asia, help manage chemotherapy or radiation side effects and assist in post-treatment tissue repair. Much of the relevant research is published in Chinese journals, frequently studying specific herbal formulas like PHY906. The unique components and bioactivities of these herbs differ from common edibles, hindering further research outside China. Understanding the anti-cancer effects of natural products necessitates studying their influence on chemotherapy efficacy. Breast cancer remains the most common type, with many natural compounds being isolated and explored for therapeutic potential (Almukram et al.2024). Natural product-based chemotherapy has received approval for cancer treatment due to its unique structures and ability to target biological molecules while sparing normal cells. Cancer cells often evade apoptosis, a regulated cell death, through oncogene hyperactivation, making restoring these pathways a goal of effective chemotherapy. Natural compounds like epothilone-B and ursolic acid demonstrate promise by disrupting tumor cell adhesion, encouraging cell death and presenting new strategies in cancer treatment. (Fu et al., 2018)(Zhang et al., 2018)

3.4. Potential for Overcoming Drug Resistance

Despite significant advances in cytotoxicity against cancer cells, drug resistance remains a major obstacle to chemotherapy effectiveness. This resistance results from cumulative cellular and physiological processes. The search for new chemotherapeutic agents is active, with numerous candidates approved for trials, including fortified paclitaxel analogs from Cryptotheca acuminate and desacetyl vinblastine amide sulfate (Sharma et al.2022). However, the number of FDA-approved drugs has decreased since the 1990s, exacerbated by rising drug resistance. Consequently, there is a shift from drug discovery to re-exploring potent compounds from natural resources. Since 1983, about 55% of approved anti-tumor agents have originated from nature or natural product derivatives. This underscores the importance of nature as a source for new therapeutic agents. Natural products from plants, marine organisms, and microbial fermentation are being developed as potential chemotherapy candidates (Dehelean et al.2021). Traditional plant herbals, rich in medicinal properties, include curcumin, resveratrol, and vinblastine, which have demonstrated efficacy in clinical studies. Approximately 150 compounds from marine organisms are in clinical or preclinical studies, including dolostatins and kahalalides. Additionally, the fermentation of basidiomycetes has isolated lead compounds like echinocandin B and cyclosporin A. The quick growth and ease of modification of Saccharomyces cerevisiae further enhance its role in fermentation for therapeutic compound production, with ongoing genomic studies enhancing our understanding of yeast metabolic pathways for this purpose (Wang et al., 2015)

4. Pharmacokinetics and Pharmacodynamics of Natural Compounds

Natural compounds are vital in developing healthcare products that can save lives, yet research into medicinal plants is hindered by limited access to active ingredients. A notable example is a plant from Meghalaya, India, recognized for its anti-inflammatory and anti-cancer properties and used to treat lung cancer. Unfortunately, conservation efforts for these natural resources are threatened, with many species nearing extinction. Medicinal plants serve as a cost-effective method for managing chronic diseases, increasingly integrated into healthcare systems (Wang et al., 2022). Their importance in pharmaceuticals is linked to the side effects of synthetic drugs, rising pathogen resistance, and growing consumer preference for health-oriented solutions. The WHO estimates that about 80% of the global population uses traditional medicine, primarily herbal remedies, due to cultural acceptance. These plants typically enhance natural defenses against pathogens and toxins, addressing root causes of ailments and enabling recovery, with extracts treating various health issues. However, 30% of displayed compounds are ineffective, and 50% do not succeed in becoming approved drugs due to pharmacokinetic issues and toxicity (Mao et al.2022). Many drugs are later withdrawn for inadequate properties or unforeseen side effects. Hence, developing effective and safe drugs is imperative. Oral administration, preferred for its sustained therapeutic effects, relies on bioavailability, often hindered by poor drug molecule solubility. Many compounds fail pre-clinical trials due to adverse effects, being unsuitable based on properties like absorption and toxicity. ADME-related properties explain many active compounds' abandonment. According to Lipinski's rules, successful orally active compounds should meet specific criteria: a molecular weight <500 Da, log P ≤5, ≤5 hydrogen donors, and ≤10 hydrogen acceptors. ParaMax pharma ADME software analysis concluded that halogens in compounds significantly enhance oral bioavailability, suggesting structural modification via halogenation could improve it significantly. (Huang et al., 2021)(Ntie-Kang et al., 2013)(Kumar Mondal et al., 2009)

Plant-derived compounds and dietary molecules have enabled the discovery of novel therapeutics with strong pharmaceutical properties. Recently, there has been significant interest in natural products and their role as antineoplastic agents, exemplified by successful plant-based drugs like vinblastine, topotecan, and etoposide. The pursuit of new, accessible bioactive natural agents for curative and preventive effects is vital for researchers (Shaik et al.2022)(Talib et al.2021). Plant-based drugs are known for their potency and efficacy, enhanced by controlled herbal drug usage. Plant-derived compounds, including alkaloids, coumarins, flavonoids, glycosides, surfactants, sterols, and terpenes, offer structural diversity that supports bioactivity, influencing metabolic pathways and enzymatic processes. Phytochemicals also stimulate cellular activities that promote cell proliferation by involving different regulatory mechanisms. With about 60% of prescribed synthetic anticancer drugs derived from natural or semi-synthetic plant compounds, efforts continue to isolate new chemical entities from the world’s 350,000 plant species, of which 15-20% have been studied for their bioactive potential. (P. Chavda et al., 2021)

5. Efficacy and Safety of Natural Compounds

Cytotoxic drugs, also known as chemotherapy, are the predominant, first-line treatment for all types of cancer. However, significant obstacles to treating cancer with cytotoxic drugs are the severe side effects and intrinsic or acquired ability of cancer cells to readily develop drug resistance. As a result, ongoing research seeks to identify new drugs capable of combating cancer’s resistance to chemotherapy. A substantial proportion of these studies evaluate plant-derived natural compounds (Ji et al., 2014). Many researchers remain committed to exploring the potential of natural compounds rather than pursuing the chemical synthesis of anticancer agents.

Plant-derived natural compounds account for a very substantial portion of the high number of successful anticancer agents developed. The significant role that natural compounds have played in anticancer drugs discovery illustrates the therapeutic potential of these compounds. It is fine that numerous commercial anticancer drugs derive from or are modelled after plant-derived natural compounds. For centuries, many different cultures have discovered and utilized a wide array of plants for various medicinal purposes. In fact, numerous plant species synthesize various compounds for protection from the threat of predators, infections, and so forth. Because of their mechanism of action, cancer chemopreventive drugs function synergistically when administered with chemotherapeutic drugs, providing even more support for the need for continued research in this field (Muhammad et al., 2022). Such

research should evaluate the efficacy and/or mechanism of action of individual plant-derived natural compounds, as well combinatorial treatments of non-chemotherapeutic agents, i.e., synthetic drugs, with plant-derived natural agents.

6. Synergistic Combinations with Conventional Chemotherapeutic Agents

Some natural compounds may circumvent apoptosis resistance by activating intrinsic or extrinsic apoptotic pathways, leading to cancer cell death alongside chemotherapeutic drugs. These agents can downregulate anti-apoptotic proteins, either directly or indirectly. In addition to inducing apoptosis, they can also downregulate transcription factors, reactivating tumor suppressor protein expression. Research indicates three additional modes of action: 1) modulation of phosphorylation levels in cancer signaling pathways, 2) high-affinity natural ligands for Bcl-2 and p53 proteins that inhibit anti-apoptotic complex formation, and 3) arresting the cell cycle at G0/G1 or G2/M phases (Rajabi et al.2021)(Neophytou et al., 2021)

The choice of plant compounds considered for the treatment of cancer is defined by their ability to 1) chemosensitize cancer cells (by enhancing their susceptibility to chemotherapeutic drugs); 2) induce apoptosis also in various types of cancer in a concentration which has no effect on their normal counterparts, and 3) work with drug combinations, reducing the dosages at which the chemotherapeutics lose any effective activity in inducing death in cancer cells. There is laboratory evidence of synergistic interactions between a number of natural compounds. It seems that the choice of natural compounds must be carefully made, as there are some poorly water-soluble compounds which may interfere favorably with the activity of not beneficially other compounds (Gavrilas et al.2022)(Bouyahya et al.2022). It can also be found that the design of special liposome particles, which have been proven particularly effective for the encapsulation of these agents, may not only improve the stability, bioavailability, and better cell distribution of natural compounds but also result in highly selective transfer to tumors.

7. Challenges in Development and Commercialization

The exploration of natural products as anticancer agents has a long history, and a series of successful cases have led to the development and commercialization of several drugs. Many other proto-drug natural agents are undergoing clinical trials and new drugs are bound to be released to the market in the coming years. As drug leads from a natural source are structurally distinct from current commercial drugs, they could provide a way to find new chemical entities that maintain innovation and curb the decline in approved entities. In addition, synthetic modification of natural products is becoming increasingly popular; such structures can guide the design of synthetic compounds, combining the best frameworks of nature with enhanced drug-like properties (Huang et al., 2021). However, there are multidimensional problems that need to be tackled in order to increase the speed and success rate of the drug discovery development of natural products. Firstly, how to select a suitable model to fully reveal the anticancer potential of nature products. Given the heterogeneity of cancer, it is well-accepted that one compound failing to show activity towards a specific model is not necessarily inactive towards other tumor models. Moreover, the anticancer effects of natural compounds could stem from its impacts on the tumor microenvironment or even of the whole human body. Thus, the selection of the right tumor model could be a critical key point in the early stages of evaluation (Haddad et al.2021)(Yaqoob et al.2023). The second fundamental question is how to efficiently identify the direct targets and MOA (mechanisms of action) of the activity. Precise cancer treatment will require a full understanding of the MOA of the natural compounds. As it is common that nature products exhibit multi-faceted mechanisms, how to get the whole picture of the MOA of the natural compounds will need to be addressed. The third common question of the research is how to accelerate the process from that time a promising candidate compound is found to the preclinical stage to being a marketed drug (Kalachaveedu et al.2023)(Trapotsi et al., 2022). At present many types of bioactive nature products are facing the issues of large-scale production to meet the manufacturing needs, which constitutes a major hurdle for those promising candidates eventually reaching the bedside. The continuous conceptual advancement in cancer therapy and implementation of innovative technologies will be needed to resolve the already existing issues and thus reinforce the historic transformation of the entire filed that leads to more clinical success.

7.1. Regulatory Hurdles

Drug discovery from natural products is enjoying a rekindled interest and a revitalized status in the past two decades, with a plethora of successful efforts that have moved a vast number of candidates from the bench to the bedside. Nevertheless, the attrition rate in preclinical and clinical tests was observed to be high, with numerous promising candidates failing along the way. This has prompted multidisciplinary examinations by researchers to distill and delineate the challenges of identifying more effective anticancer nature products and to conceive innovate sequence of experiments, in silico modeling protocols, and efficacy pharmacological analyses that could help unravel the therapeutic potential of S. leucotricha and aid in the production of more clinically successful nature product candidates in the future (Huang et al., 2021).

Drug discovery from natural products has regained high interest and respectability among scientists and companies in the pharmaceutical industry. As clinical and technological methodologies advance, nature products frequently take a role as exclusive lead compounds in anticancer drug discovery. The renewed interest has resulted in an extraordinary renaissance in anticancer natural-product-based drug discovery and preclinical and clinical testing over the last three decades with several bioactive candidates proceeding to the drug-marketing phase (S. Choudhari et al., 2020). This shift of paradigm has marked the appearance of miracle cancer cures from nature products and rekindled hope for the suffering multitude from this dread disease. But under the surface of these fortuitous events, there have been profound problems that remain unresolved and unabated. In addition, when a priori reasonable questions are scrutinized, a plethora of lace is discovered under the drug discovery largesse that the general public rarely sees.

7.2. Intellectual Property Rights

There are two aspects associated with the IPR on species due to a plant. Biological material derived from natural sources other than microorganisms is patentable subject matter in the US and several other countries, provided that it satisfies the usual patent requirements of novelty, utility, inventiveness and usefulness. This development, combined with the growth of biological and chemical knowledge and research, resulted in a proliferation of different terms used to define different kinds of biotechnologies. Industry and also the general public are eager to obtain patents or property rights on the basis of these new developments, thus attempting to secure their investment and markets. Ownership of certain types of invention can be an incremental step leading to conflicts among various firms, thereby hampering research progress and technologies. On the other hand, some societal groups contend that exclusive patents on living organisms stifle competition and the access of consumers to goods, including food and medicines, and endanger human health and the environment. Presently, the legal structure offers a framework of patents which aim at protecting biotechnological inventions. An effort to explain and discuss aspects of the new field of biotechnology and plant patents with respect to the protection of genetic resources and plants is made with particular reference to agriculture. At the moment, intellectual property rights refer to patents, utility models or plant variety certificates which are protected by the UPOV convention (Gadiya et al., 2024)

8. Future Perspectives and Opportunities

Professionals in synthetic chemistry, parasitology, chemical biology, and agronomy are encouraged to develop feasible ways to derive novel therapeutic agents from natural products, which could be transiently synthesized or produced as gene-edited plants with chemically modifiable pathways. There is a need to produce new entities at a sufficiently fast pace, rather than trying a single compound due to low capacity to increase sufficient mass and diversity in terms of structural type (Beane & Leonardi, 2022). Once a natural product of interest is able to be generated at a reasonable level and eventually used in a screening campaign (it is largely accepted to screen libraries with a few thousand known molecules previously optimized for drug-like properties), the chances of finding suitable compounds arrives, which will be reduced by applying the same rule for the various subsequent steps. Given the structural complexity and novelty of natural products, a really large number of compounds should be screened to maximize the chances to find good hits, which is not feasible for most academic research (Huang et al., 2021).

Positively in the field of health, it is generally expected that growth in efficiency of technologies developed for drug discovery may lead in the short medium term to a position where so far disabling and pathological conditions could be effectively treated. Modulation of the metabolism of host with specifically functionalized pools should add some possibilities. For example, mixing several types of interference compounds such as small molecules, proteins, semiochemicals, apart from gene-expression modulators themselves, through adequate may represent a feasible path to eventually suppress one pathogen or at least slow down infections (P. Chavda et al., 2021). Broadly speaking, compounds activated hypothetically in a given organ or tissue may target pathogens developed after the activation step occurring there, or constitute a starting starting material converted in-site into a therapeutic agent. Though the process appears complex, both synthesis and automation of treatments are sufficiently developed at present to ensure feasibility.

8.1. Emerging Technologies

Since ancient times, the medicinal use of plants has been preferred due to fewer side effects than synthetic drugs. Modern research into natural products has led to isolating biologically active compounds from diverse sources (plants, fungi, marine life) with a broad range of pharmacological properties. Computer-aided molecular modeling enhances these compounds into more effective derivatives. The extensive chemical diversity of natural products supports ongoing drug discovery, with secondary metabolites' biological activity assessed through endophyte interactions. Natural products crucially impact human health, emphasizing biologically active compounds from non-plant sources for drug development (Okaiyeto and Oguntibeju2021)(Hussain et al.2021). Studies on plant endophytic fungi have unveiled unique bioactive metabolites with therapeutic potential, especially in inhibiting protein kinases. Cancer, a leading cause of death, arises from disrupted cell behavior related to genetic information. Many natural compounds aid cancer treatment, with over 60% of today's cancer drugs originating from natural sources. Key compounds include anti-cancer agents from endophytic fungi like camptothecin derivatives. Marine products like Ziconotide and rare insect-derived compounds also show anti-cancer effects. Endophytes are crucial for producing compounds with anti-biofilm and antiviral properties (Dzobo, 2022)(Chaachouay & Zidane, 2024). The drug discovery process from natural products is complex, requiring time, effort, and resources. Natural compounds often target multiple molecular pathways, displaying diverse pharmacological activities. New prediction methodologies, such as target fishing, show promise in anticancer drug analysis. A multitarget approach could reduce the need for diverse drug regimens, minimizing side effects by focusing on specific receptors. Network pharmacology involves systematic analysis of potential target combinations, representing biological pathways as graphs that connect genes and proteins. Studying drug action mechanisms through network pharmacology aids discovery, serving as a quantitative modeling platform for intricate systems, simplifying complex phenomena into precise models through mathematical methodologies. (P. Chavda et al., 2021)(Huang et al., 2021)

8.2. Precision Medicine Approaches

There is reasonable now to consider natural compounds as complex mixtures for integration with synthetic compounds and molecular targeted therapy in a consciously formulated synergism with delivery through nano-formulation. No other competition may be more appropriate than phytotherapy for the personalized therapy practiced by the Greek physician of antiquity. Such an idea enjoys recent theoretical validations through Bayesian computer modelling of malignant transformation-host interaction (Efferth et al., 2017). These efforts indirectly lead to a new experimental method for selection of

individually optimized blends of multiple compounds for cancer therapy viewed as a "system of systems." Interested, however, should not deceive themselves to anticipate any quick arrival of an efficient approach. An implementation of this new concept, built up from such distant bases and embracing a wide spectrum of diversity, is confronted by enormous technological and methodological problems as well as by huge amount of initial research. The fact that chemosensitivity testing was not established as a routine laboratory method during the integrated syntheses is dictated by historical reasons (Henrich et al., 2021)(Zhang et al.2022). The advent of combination chemotherapies makes the formulation of the testing material difficult, and it remained thus on the level of simplistic trials. Yet the major factor is that several early clinical attempts to use chemosensitivity testing yielded negative. However, the lack of immediate success with the early attempts to apply chemosensitivity testing in the clinic (for a variety of not always well understood reasons) is no valid argument per se to deny the validity of the testing principle. Close to the same time, findings about cell resistance phenomena involving multigenic mechanisms were published (van et al.2023)(du et al.2021). This fast growing literature was too overwhelming to pale-scale research resources, especially when the dominant belief in the essential reward of immediate pay-off directed grants toward mostly clinically oriented studies.

9. Conclusion

Attempts to develop antitumor chemotherapeutic agents have reached an impasse due to limited cancer cell selectivity and toxic side effects. In general, exposure to chemotherapeutic drugs is long and can result in different types of resistance, producing a decrease in drug efficacy. This has led scientists to continue scanning natural products as a possible alternative to the finest chemotherapeutic agent frontier. The rapid development of laboratory techniques has revealed a variety of new compounds, naturally occurring host secondary metabolites (P. Chavda et al., 2021).

Phytochemicals have been demonstrated to have significant beneficial effects on various forms of cancer. Plant secondary metabolites have been the source of many medications. Plant chemicals owe their pharmacological properties to a large variety of mechanisms. There is growing interest in the acceptance of natural origin as the first source of new chemotherapeutic agents. However, a characteristic herbal item contains many chemicals. It is now difficult to identify the active principal component of the plant and the molecular pharmacology. Furthermore, in the medicinal plants sold in the market, many of the biological activities linked to the chemical composition are found to be dose-dependent and are therefore generally ineffective and of little chemical concentration. These inherent difficulties can be surmounted by technical approaches (Huang et al., 2021). So, an alternative way to expose the fruitful studies of unearthing novel anticancer compounds is recommended.

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