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PHYTOCHEMICALS: A NEW ARSENAL IN DRUG DISCOVERY

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ABSTRACT

In ancient times traditional herbs were used to treat different diseases such as stomach discomfort, toothache, body pain and inflammation, diarrhea, malaria, typhoid, diabetes, and so on. Medicinally important plants are recognized to have chemicals or phytochemicals that could be useful for illness treatment or medication manufacture. These compounds occur naturally in plant parts (leaves, stems, barks, and roots) and are referred to as secondary metabolites because, like primary metabolites, they are synthesized to protect the plant rather than for growth. Fortunately for humans, the majority of these secondary metabolites have therapeutic properties that are useful against a variety of diseases and health problems. Resistance to antibiotics is one of the world's most critical health challenges, with numerous infections rapidly gaining resistance to conventional antimicrobials. There is currently no viable therapeutic agent with the ability to reverse antimicrobial resistance, and several leading laboratories are working hard to find new antimicrobials. Plant-based chemical compounds have received comparatively little attention in the context of antimicrobial medication development. Natural chemicals have piqued the interest of drug development scientists because of their structural diversity, chemical novelty, abundance, and bioactivity. Cancer is currently a major problem. Despite the numerous interventions available, a huge number of patients die each year as a result of cancer disorders. The rising research direction

in healthcare pharmacy is the development of an effective and side-effect-free anticancer medication. Chemical entities found in plants have proven to be particularly promising in this area. Bioactive phytochemicals are preferred because they act differentially on cancer cells while leaving normal cells alone.

This review provides an overview of the utility of medicinal plants as well as secondary metabolites of plants as drug sources, the drug discovery process, the efficacy and safety of phytochemicals, current applications, developments in screening technologies, challenges, and future directions.

INTRODUCTION

Since ancient times, people have utilized plants as remedies for a wide range of illnesses. The oldest (4500 BC) still practiced medical traditions are Ayurveda, Traditional Indian Medicine (TIM), and Traditional Chinese Medicine (TCM). Knowledge of the proper plant selection, when to gather them, and how to prepare drugs for a given purpose were all known in the ancient era. [1] This knowledge is transferred verbally and transmitted from one generation to the next. Every detail on the drugs and their particular use in treating various diseases has been recorded in the folklore system. These medicines were made into powders, tinctures, teas, poultices, decoctions, and other formulations. [2,3] Over the past 200 years, the identification of compounds originating from plants has changed due to the diverse range of knowledge and expertise required. A botanist, ethnobotanist, ethnopharmacologist, or plant ecologist first identifies a plant. A phytochemist then uses plant extracts and biological screening assays to find possible medicinal efficacy before isolating the active ingredient. Ultimately, to identify the mechanism of action and pertinent molecular targets, molecular biology research is necessary. Pharmacognosy is an interdisciplinary approach that is determined by the combination of various subjects. [4] The term "natural products," also known as "phytochemicals," refers only to the substances that are found in living things and are typically referred to as secondary metabolites. Those metabolites do not take part in the survival of that particular living thing. [5] Phytochemicals are plant-based bioactive compounds produced by plants for their protection. They can be derived from various sources such as whole grains, fruits, vegetables, nuts, and herbs, and more than a thousand phytochemicals have been discovered to date. [6] Some of the significant phytochemicals are carotenoids, polyphenols, isoprenoids, phytosterols, saponins, dietary fibers, and certain polysaccharides. These phytochemicals possess strong antioxidant activities and exhibit antimicrobial, antidiarrheal, anthelmintic, antiallergic, antispasmodic, and antiviral activities, etc., [7] Antimicrobial-resistant microorganisms (AMR) and the widespread use of antibiotics are growing global public health concerns. Numerous approaches have been put up to address these issues, such as managing currently available antibiotics, creating substitute substances

with antimicrobial properties, and quickly identifying AMR infections. [8] Out of all of these, using substitute substances like phytochemicals either by themselves or in conjunction with other antibacterial agents seems to be a safe and efficient way to combat these infections. That gives good alternative drug candidates in the fight against the growing drug resistance problem. In short, a detailed study, along with scientific data on the various major aspects of phytochemicals used to treat microbial pathogenesis helps to find out good phytochemicals against it. [9] After drug resistance Cancer is still the primary cause of mortality worldwide and is a serious health issue. An enormous number of anticancer medications have been developed as a result of a growing understanding of the molecular pathways behind the advancement of cancer. Over the past few decades, the general survival rate has not greatly increased due to the usage of chemically synthesized medications. Therefore, to increase the effectiveness of current cancer treatments, new tactics, and cutting-edge chemo-preventive drugs are required. [10] Phytochemicals, which are naturally occurring molecules derived from plants, are important sources for both cancer therapy and innovative medication development. vincristine and vinblastine are a class of different alkaloids, and podophyllotoxin analogues are a few common examples used in controlling different pathways linked to the development and spread of cancer in the body. [11] The process for developing a new medicine is difficult, costly, and time-consuming. A new drug must be discovered and developed over the course of about 10 to12 years, and in today's terms, this requires investments totalling more than $1 billion US Dollars. [12] Medicinal plants are important and well-known worldwide sources of herbal medicine. Medicinal plants are found in many different parts of the planet, including forests, deserts, polar regions, oceans, and freshwater ecosystems. They are also a source of novel medicine compounds. [13] About 1,000 BC, the Indian saints Shusruta and Charak wrote in the Shusruta Samhita and Charak Samhita, respectively, about their knowledge of the habitat of medicinal plants and how to use them to treat a variety of illnesses. Ayurveda has referenced over 197 distinct plant species, along with information on their usage and distribution. [14] Based on a set of criteria, 34 worldwide "Biodiversity Hotspots" have been identified, which also include therapeutic plants. The habitat and distribution of medicinal plants are the main topics of this article, with a focus on biodiversity hotspots.[15] Furthermore, included are the socioeconomic significance of traditional uses of medicinal plants, as well as remote sensing and geographic information system-based methods for distribution research.[16] Natural origin products give an endless source of different compounds to help in the design of pharmacologically important products that work at the molecular level.[17] It is known that medicinal plants may provide for basic human needs including clothing, food, shelter, and health. Humans have developed numerous healthcare systems as a result of their quest for eternal health, longevity, and a means of relieving discomfort. Ancient societies used traditional medicines to treat their illnesses. Natural products have become increasingly significant in the search for new drugs to treat

serious illnesses like cancer, malaria, diabetes, and heart disorders. [18] More attention has recently been paid to the discovery of novel anticancer medications from plants, including vincristine, paclitaxel, docetaxel, topotecan, irinotecan, and vinblastine, etc. [19] Plants naturally generate a wide range of compounds with varying chemical properties that are essential to their growth and development. The materials needed for activities like photosynthesis, translocation, and respiration are provided by primary metabolites. [20] Secondary metabolites are those formed from primary metabolites that are not directly connected to growth and development. Secondary metabolites are typically generated by biosynthetic modifications such as methylation, glycosylation, and hydroxylation and are the result of primary metabolites. When compared to primary metabolites, secondary metabolites undoubtedly have more complicated side chains and structural compositions. [21] The use of natural products and the recognition of their beneficial health benefits currently face a number of difficulties, such as a lack of standardization procedures and the difficulty of isolating pure chemical compounds or components. Lack of clarity regarding the biological mechanism and the irregular completion of so-called controlled and documented clinical studies by "standards" As previously said, there is historical scientific data that supports the effectiveness of natural ingredients as medicines. which paved the way for the creation of several popular conventional medications. [22] The complexity of the molecular combinations in natural goods frequently makes searching for new therapeutic candidates challenging. Plant extracts typically have therapeutic effects because of the synergistic and concurrent actions of several compounds. [22,23]

Phytochemicals in drug discovery

Due to a decline in new drug approvals and rising costs, new drug innovation is encountering significant obstacles. Many novel medications and pharmaceutical active components come from natural items. Finding the appropriate candidate plants through the application of Ayurvedic knowledge, traditional recorded beneficial use, tribal non-documented use, and thorough literature search should be the first step in the development of new plant-based drugs. [24] An in-depth understanding of the predominance of specific Ayurvedic characteristics may be obtained by frequency analysis of the ingredients of the ancient documented formulations and analysis of their Ayurvedic attributes. This will help select appropriate candidate plants for bioactivity-based fractionation. The combination of drug research and Ayurvedic wisdom necessitates a paradigm change in the extraction method from sequential to parallel extraction. The foundation of new drug discovery and lead compound development is the use of phytochemicals derived from various plant sources in drug discovery processes. Preclinical and clinical studies are conducted after biochemical characterization, phytochemical identification, separation, and purification from the chosen

plant species, and pharmacological research. Drug discovery also necessitates the use of state-of-the-art analytical methods including mass spectrometry, high-performance liquid chromatography, and gas chromatography for structural elucidation. [25] Occasionally, the natural structure of phytochemicals needs to be altered to improve their biological activity and stability. As a result, finding new drugs and leads is a crucial arsenal for combating antibiotic resistance and many more diseases. Currently, the discovery of novel drugs and the revolution in the pharmaceutical business rely heavily on phytochemicals. As a result, more prospects for novel drug discovery utilizing phytochemicals should materialize soon. [26] Modern drug discovery techniques and treatment are focused on single-compound medication and reject the use of whole plant extracts. Using whole plants or extracts instead of separating their constituent parts, as is done in conventional medicine, results in a more potent therapeutic impact. This is significant since the majority of plant metabolites probably function simultaneously or in concert to provide the therapeutic action of the plant extract. Scientists must research the application of entire plant extracts to identify the molecular underpinnings of the extracts' medicinal effects. [27] With the aid of technological progress, creative drug development from natural ingredients is required to fight serious health concerns across the globe. Primarily, novel and inventive computational and analytical techniques are required to recognize the chemical constituents of unrefined plant extracts. [28] This is necessary to pinpoint the chemicals responsible for the intended medicinal outcome and refine the extraction process to eliminate any disruptive elements. In the end, rather than concentrating only on individual components, more research ought to be done on the combinational effects of phytochemicals from various plant extracts. Through existing "-omics" platforms, the effects of this combined strategy on gene level and protein level involved in numerous cellular processes need must be studied. Microfluidics and computational analysis advances have made it possible to generate and test compounds derived from plant extracts for use in drug discovery. [29] Isolating individual components of a medical extract may not be beneficial because the majority of extract components often function in concert to produce their therapeutic benefits. To properly research and exploit these molecules and develop novel medications, creative methodologies are required. Furthermore, a systems biology-guided approach offers an alternative perspective in the field of natural product pharmacology. [30] This goes beyond identifying a particular bioactive molecule with a targeted target and supporting an overall balance of a human body system experiencing coordinated processes on several gene targets. Better drug candidates may result from creative drug design enabled by a systems biology approach combined with the use of current technology like transcriptomics, proteomics, metabolomics/metabonomic, genomics, automation, and bioinformatics or computer-based techniques. Lead chemicals and herbal tinctures for novel medications will be sourced from various databases of potent bioactive compounds from natural product research and development. When utilizing

cutting-edge technology in conjunction with systems biology, the goal should be to consider the compounds' synergistic effects rather than taking a reductionist approach to finding a single active ingredient. It is imperative to underscore that inventive medicine discoveries emanating from natural products will require a non-reductionist strategy to understand their complex mechanisms of action at the molecular level. [31]

Phytochemicals in Pre-clinical Trail Studies

While developing drugs from bench to bedside, comprehensive data on preliminary efficaciousness, toxicity, pharmacokinetic, and safety information, preclinical screening models may provide prospective lead compounds for drug development. This information is useful in determining if a molecule should proceed with clinical trials. Plenty of data on the preclinical effectiveness of several phytochemicals has been gathered in this review.

Brief information on selected each phytochemical (Table No. 1) is as follows:

Sr No	Phytochemical Name	Phytochemical class	Plant Common name	Scientific family	Biological action	Citation
1.	Diferuloylmethane	Phyto polyphenol	Turmeric	Zingiberaceae	Alters cell signaling and functional gene expression regulatory pathways	[31]
2.	Epigallocatechin-3-gallate	Flavonoids	Green tea	Theaceae	Controls cell proliferation and Programmed cell death	[32, 33]
3.	Andrographolide	Diterpenoids and their derivative	Green chiretta	Acanthaceae	HIF-1a, VEGF, and PI3K pathway	[34]

4.	Ursolic acid	Isoprenoids	Snake-Needle Grass	Rubiaceae	Ki-67, CD31, and miR-29a	[35,36]
5.	Physapubescin B	Natural Steroid	Cape-gooseberry, Goldenberry	Solanaceae	Ki-67, Cdc25C, and PARP	[37]
6.	Glycyrrhizic acid	Triterpenes	Licorice	Fabaceae	Controls JAK/STAT pathway	[38]
7.	1-isothiocyanato-4-(methylsulfinyl)-butane	Organo-sulfur	Cabbage	Brassicaceae	caspase 8, p21, hsp90	[39]

Table No.1 *(Brief information on selected each phytochemical along with compound class and plant source name.)*

1. **Curcumin:** One of the phytochemicals found in Curcuma longa (Zingiberaceae) is called curcumin (phytopolylphenol). Curcumin has been shown in several studies to have anticancer potential through the regulation of several signaling and gene expression regulatory pathways [31]. When mice models were examined with human A375 melanoma cells, curcumin altered the formation of the tumors. Research revealed that curcumin may inhibit different cell cycle phases, self-degradative process, and downregulation of the human uveal melanoma cells pathway, an important intracellular signaling pathway linked to both cell survival and death, to prevent the growth of melanoma cells [40]. Along with this, It helps in the treatment of anxiety, arthritis, metabolic syndrome, oxidative and inflammatory diseases, and hyperlipidemia. It might also aid in the control of inflammation and muscle pain caused by exercise, improving recovery and function in those who lead active lives. Furthermore, individuals without medical diagnoses may benefit from the complex at

very low dosages. The majority of these advantages are related to its anti-inflammatory and antioxidant properties. [41,42]

2. **Epigallocatechin 3-gallate (EGCG):** Green tea extract contains an abundant polyphenolic component called epigallocatechin 3-gallate (EGCG), which has a variety of bioactivities and can be used to treat a wide range of illnesses. In the past ten years, studies using experimental models of Parkinson's disease (PD) have demonstrated the efficacy of EGCG. The pleiotropic neuroprotective properties of EGCG have been demonstrated by a number of experimental studies, which has increased its attractiveness as a PD treatment approach. [43] Through the induction of apoptosis and the inhibition of multiplication of clusters with the basal subtype of breast cancer in a mouse model, epigallocatechin (EGCG), a primary catechin present in green tea, successfully delayed the onset of tumours and decreased tumour burden [32]. In a different study, EGCG prevented the reactive oxygen species that are formed through the reaction of guanine with reactive oxygen species compounds resulting from oxidative stress in mouse lung DNA, which prevented lung carcinogenesis caused by nitrosamine (NNK) [44].
3. **Andrographolide:** A bicyclic diterpenoid lactone called andrographolide was extracted from Andrographis paniculata (Acanthaceae) Nees, which is widely utilized in traditional Chinese medicine. With its anti-inflammatory, antibacterial, antiviral, anticancer, and immune-regulating properties, andrographolide is used to treat cardiovascular and cerebrovascular illnesses as well as to protect the liver and gallbladder. Because andrographolide has modest pharmacological effects and poor water solubility and bioavailability, there are stringent production requirements. [45] It was discovered that andrographolide prevented tumor adaptability, thereby preventing tumor growth to a state of hypoxia. A dose of Andrographolide (1 mg/gm) gives the inhibition of hypoxia-inducible factor (HIF)-1a activity and its upstream PI3k/AKT/mTOR pathway [34]. Islam et al. have evaluated further information regarding andrographolide's potential as a cancer treatment [46].
4. **Ursolic Acid:** Ursolic Acid and Its Derivatives as used as a Bioactive analog it has been determined that one class of secondary metabolites from medicinal plants, called pentacyclic triterpenoids (PT), may be extremely important for managing and treating several non-communicable diseases (NCDs). One such PT is ursolic acid (UA, 3 β-hydroxy-urs-12-en-28-oic acid), which has significant biological benefits such as antibacterial, anti-inflammatory, anticancer, and antidiabetic properties, but its solubility and bioavailability restrict its clinical use. Major sources of UA have been identified as Glechoma hederacea, Ilex paraguarieni, and Mimusops caffra. [47] Many naturally occurring plants contain the terpene molecule ursolic acid (UA). Since UA has a well-established anticancer effect, new research has shown that it could be used as

a cancer chemosensory to conventional chemotherapy medications [48] In one study, it was demonstrated that UA improved the therapeutic benefits of oxaliplatin in a CRC mice model by suppressing the tumor and raising the rate of survival. According to the in vitro mechanistic investigation, treating CRC cells with UA and oxaliplatin dramatically reduced the expression of drug-resistant genes, enhanced apoptosis, and ROS generation, and considerably hindered cell growth. [49] Since the UA nanoparticles synthesized would be used to target p53 and caspases, they reduced the size of the tumor including cIAP and Bcl-2 downregulation causing apoptosis and cervical cancer cell death. [50]

5. **Physapubescin B:** It's a naturally occurring substance that was isolated from the plant Physalis pubescens L. (Solanaceae), had anticancer efficacy against prostate cancer both in vivo and in vitro. Prostate cancer cells treated with Physapubescin B accumulated in the G2/M phase, correlated with elevated levels of Cyclin B1, P21, and p-Cdk1 (Tyr15) and decreased levels of Cdc25C. Additionally, PC-3 cells treated with Physapubescin B produced more reactive oxygen species (ROS). Moreover, antioxidant NAC and GSH dramatically reversed the G2/M phase cell cycle arrest and the physapubescin B-induced decrease in Cdc25C protein expression. Additionally, our research showed that physapubescin B has a significant antitumor efficaciousness in vivo in a human prostate cancer PC3 xenograft. Physapubescin B (0.005gm/1000gm) inhibited PC3 tumor growth in nude mouse models containing Box 1 Prostate cancer by lowering the expression levels of full-length PARP, Cdc25C, and Ki-67 as well as raising the proportion of apoptotic cells in the tumor tissue [51]. Moreover, physapubescin (30 mg/kg) suppressed in vivo angiogenesis and reduced vimentin protein expression in renal cell carcinoma 786-O cells [52].
6. **Glycyrrhizic acid:** Glycyrrhizic acid (GA) is one of the most commonly utilized medications in these cultures. The primary medicinal ingredient in licorice root, glycyrrhizic acid, has long been recognized in traditional Chinese and Japanese medicine. However, it wasn't until the twenty-first century that the GA's unique and uncommon ability to increase the effectiveness of other medications was found. [53] GA (135 mg/kg) inhibited the expression of proliferating cell nuclear antigen (PCNA) and thromboxane synthase (TxAS) in athymic BALB/c nude mice xenografts with human lung adenocarcinoma A549 cells that were stably transfected with TxA2 receptor (TPa). This was achieved by blocking the TxA2 pathway. [54] More recent research revealed that Glycyrrhizic acid (0.1gm/1000gm) slowed the growth of NSCLC in patient-derived xenograft (PDX) mice by inhibiting JAK/STAT and reducing the amount of hematopoietic malignancies [55]

7. **sulforaphane (SFN):** One member of the iso-thiocyanate class belonging to organo-sulfur biomolecule is sulforaphane. SFN modulates important signaling pathways, including induction, to produce its anticancer actions inducing apoptosis, suppression of the cell cycle, suppression of angiogenesis, and enhancing the anti-cancer properties of other antiproliferative drugs, such as paclitaxel. [56,57] Potent chemopreventive agent sulforaphane (SFN) is commonly used as a dietary supplement or in food. It alters the II and III metabolic phase enzymes. [58]
8. **Oleocanthal:** Previous researchers observed that among these flavonoids oleocanthal is effective in preventing Aß aggregation and destabilising preformed fibrils. Olive oil, the main source of monounsaturated fatty acids and phytochemicals such polyphenolic compounds, squalene, and a-tocopherol, are the key component of the Mediterranean diet. Polyphenols are responsible for olive oil's bitterness, pungency, and astringency. The antioxidant components in olive oil are responsible for several health advantages [59].

Developments in screening technologies, challenges, and future directions

Nowadays, metabolomics is regarded as a broad, sensitive, and effective method for learning about the makeup of a metabolite pool found in any organism, including plants. [60] The field of metabolomics is a multidisciplinary study area that combines the strengths of analytical chemistry, statistics, and biochemistry. Its continuous development offers methods for comprehending quantitative variations in metabolite levels in a methodical manner. When using metabolomics, one can typically focus on a single cell, a single tissue, or the complete organism. Over the past three decades, significant advancements in science and technology entered the scientific community into the new edge of multiple cellular level-based drugs, where metabolomics offers the unique advantage of studying the cellular entities that have the greatest influence on end phenotype, despite being in a more developed state than genomics, transcriptomics, and proteomics. [61]

The conventional method of finding plant-based medications frequently takes a long time and costs a lot of money. These labor-intensive methods have found it difficult to stay up with the high-throughput technology's rapid growth. Bioinformatics is essential in the age of large volume, high throughput data creation in the biosciences. This has typically been the case when it comes to the creation and discovery of new drugs. On the other hand, the prospective application of plant-based knowledge-leveraging bioinformatics techniques have received little attention up to this point. [62]

CONCLUSION

Research into the potential value of phytochemicals in the prevention and treatment of disease has increased as a result of a greater understanding of the methods by which they can affect upstream endogenous cellular defense processes. Traditionally, pharmaceutical medicine has looked to find the building blocks for new drugs; in contrast, nutraceutical medicine aims to preserve plant's bioactive nature as near to their original state as possible. The molecular structure of bioactive phytochemicals to a large extent determines the molecule's bioavailability.

The mid-18th and beginning of the 19th centuries saw the pursuit of analyzing the study of the bioactive ingredients of medicinally important plants and herb-based treatments.

During the 19th century developments in various techniques used in phytochemistry which made it possible to isolate, purify, and characterize several plant's bioactive components.

Innovative drug development methodologies necessitate a paradigm shift due to the poor success rate of medication discovery. The first step in developing novel drugs is to take inspiration from natural goods to create remedies for medical ailments. It is impossible to overstate the importance of using natural products to develop novel medications for both communicable and non-communicable diseases. Thanks to technological advancements, it is now possible to comprehend the profiles of these intricate natural compounds, which may lead to the discovery of novel therapeutic agents. Lead compounds found in natural products have been used to isolate or synthesize an astounding number of blockbuster medications. This presents the discovery of new therapeutic medications through natural products as a highly effective approach. In this day of rapidly developing science and technology.

REFERENCES

1. Choudhari, A. S., Mandave, P. C., Deshpande, M., Ranjekar, P., & Prakash, O. (2020). Phytochemicals in cancer treatment: From preclinical studies to clinical practice. Frontiers in pharmacology, 10, 1614.
2. Ogbonna, J., Kenechukwu, F., Attama, A., & Chime, S. (2012). Different approaches to formulation of herbal extracts/phytopharmaceuticals/bioactive phytochstituents-a review. Int. J. Pharm. Sci. Rev. Res, 16(1), 1-8.
3. Fridlender, M., Kapulnik, Y., & Koltai, H. (2015). Plant-derived substances with anti-cancer activity: from folklore to practice. Frontiers in plant science, 6, 799.
4. Anand, U., Jacobo-Herrera, N., Altemimi, A., & Lakhssassi, N. (2019). A Comprehensive Review on Medicinal Plants as Antimicrobial Therapeutics: Potential Avenues of Biocompatible Drug Discovery. Metabolites, 9(11), 258. https://doi.org/10.3390/metabo9110258.

5. Dias, D. A., Urban, S., & Roessner, U. (2012). A historical overview of natural products in drug discovery. Metabolites, 2(2), 303–336. https://doi.org/10.3390/metabo2020303.
6. Kumar, A., P, N., Kumar, M., Jose, A., Tomer, V., Oz, E., Proestos, C., Zeng, M., Elobeid, T., K, S., & Oz, F. (2023). Major Phytochemicals: Recent Advances in Health Benefits and Extraction Method. Molecules (Basel, Switzerland), 28(2), 887. https://doi.org/10.3390/molecules28020887.
7. Sheneni VD, Muhammad SS, Shaibu IE. Natural chemicals for healthy living: plant secondary metabolic compounds. MOJ Food Process Technols. 2023;11(2):98–104. DOI: 10.15406/mojfpt.2023.11.00286
8. Prestinaci, F., Pezzotti, P., & Pantosti, A. (2015). Antimicrobial resistance: a global multifaceted phenomenon. Pathogens and global health, 109(7), 309–318. https://doi.org/10.1179/2047773215Y.0000000030.
9. Khameneh, B., Eskin, N. A. M., Iranshahy, M., & Fazly Bazzaz, B. S. (2021). Phytochemicals: A Promising Weapon in the Arsenal against Antibiotic-Resistant Bacteria. Antibiotics (Basel, Switzerland), 10(9), 1044. https://doi.org/10.3390/antibiotics10091044.
10. Choudhari, A. S., Mandave, P. C., Deshpande, M., Ranjekar, P., & Prakash, O. (2020). Phytochemicals in cancer treatment: From preclinical studies to clinical practice. Frontiers in pharmacology, 10, 1614.
11. Dhyani, P., Quispe, C., Sharma, E., Bahukhandi, A., Sati, P., Attri, D. C., ... & Cho, W. C. (2022). Anticancer potential of alkaloids: a key emphasis to colchicine, vinblastine, vincristine, vindesine, vinorelbine and vincamine. Cancer cell international, 22(1), 1-20.
12. Hughes, J. P., Rees, S., Kalindjian, S. B., & Philpott, K. L. (2011). Principles of early drug discovery. British journal of pharmacology, 162(6), 1239–1249. https://doi.org/10.1111/j.1476-5381.2010.01127.x
13. 1Petrovska B. B. (2012). Historical review of medicinal plants' usage. Pharmacognosy reviews, 6(11), 1–5. https://doi.org/10.4103/0973-7847.95849.
14. Bhavana, K. R., & Shreevathsa (2014). Medical geography in Charaka Samhita. Ayu, 35(4), 371–377. https://doi.org/10.4103/0974-8520.158984
15. Stephen, A., Suresh, R., & Livingstone, C. (2015). Indian Biodiversity: Past, Present and Future. International Journal of Environment and Natural Sciences, 7, 13-28.
16. Aziz, M. A., Adnan, M., Khan, A. H., Shahat, A. A., Al-Said, M. S., & Ullah, R. (2018). Traditional uses of medicinal plants practiced by the indigenous communities at Mohmand Agency, FATA, Pakistan. Journal of ethnobiology and ethnomedicine, 14, 1-16.
17. Thomford, N. E., Senthebane, D. A., Rowe, A., Munro, D., Seele, P., Maroyi, A., & Dzobo, K. (2018). Natural Products for Drug Discovery in the 21st Century: Innovations for

Novel Drug Discovery. International journal of molecular sciences, 19(6), 1578. https://doi.org/10.3390/ijms19061578

18. Sofowora, A., Ogunbodede, E., & Onayade, A. (2013). The role and place of medicinal plants in the strategies for disease prevention. African journal of traditional, complementary, and alternative medicines : AJTCAM, 10(5), 210–229. https://doi.org/10.4314/ajtcam.v10i5.2.
19. Asma, S. T., Acaroz, U., Imre, K., Morar, A., Shah, S. R. A., Hussain, S. Z., Arslan-Acaroz, D., Demirbas, H., Hajrulai-Musliu, Z., Istanbullugil, F. R., Soleimanzadeh, A., Morozov, D., Zhu, K., Herman, V., Ayad, A., Athanassiou, C., & Ince, S. (2022). Natural Products/Bioactive Compounds as a Source of Anticancer Drugs. Cancers, 14(24), 6203. https://doi.org/10.3390/cancers14246203
20. Twaij, B. M., & Hasan, M. N. (2022). Bioactive secondary metabolites from plant sources: Types, synthesis, and their therapeutic uses. International Journal of Plant Biology, 13(1), 4-14.
21. Cragg, G. M., & Newman, D. J. (2013). Natural products: a continuing source of novel drug leads. Biochimica et Biophysica Acta (BBA)-General Subjects, 1830(6), 3670-3695.
22. Thomford, N. E., Senthebane, D. A., Rowe, A., Munro, D., Seele, P., Maroyi, A., & Dzobo, K. (2018). Natural Products for Drug Discovery in the 21st Century: Innovations for Novel Drug Discovery. International journal of molecular sciences, 19(6), 1578. https://doi.org/10.3390/ijms19061578
23. Kiyohara, H., Matsumoto, T., & Yamada, H. (2004). Combination effects of herbs in a multi-herbal formula: expression of Juzen-taiho-to's immuno-modulatory activity on the intestinal immune system. Evidence-Based Complementary and Alternative Medicine, 1, 83-91.
24. Katiyar, C., Gupta, A., Kanjilal, S., & Katiyar, S. (2012). Drug discovery from plant sources: An integrated approach. Ayu, 33(1), 10–19. https://doi.org/10.4103/0974-8520.100295.
25. Atanasov, A. G., Waltenberger, B., Pferschy-Wenzig, E. M., Linder, T., Wawrosch, C., Uhrin, P., ... & Stuppner, H. (2015). Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnology advances, 33(8), 1582-1614.
26. Ashraf M. A. (2020). Phytochemicals as Potential Anticancer Drugs: Time to Ponder Nature's Bounty. BioMed research international, 2020, 8602879. https://doi.org/10.1155/2020/8602879.
27. Chan, K.; Shaw, D.; Simmonds, M.S.; Leon, C.J.; Xu, Q.; Lu, A.; Sutherland, I.; Ignatova, S.; Zhu, Y.P.; Verpoorte, R.; et al. Good practice in reviewing and publishing studies on herbal medicine, with special emphasis on traditional Chinese medicine and Chinese materia medica. J. Ethnopharmacol. 2012, 140, 469–475.

28. Medema, M. H., & Fischbach, M. A. (2015). Computational approaches to natural product discovery. Nature chemical biology, 11(9), 639-648.
29. Kim, E., Moore, B. S., & Yoon, Y. J. (2015). Reinvigorating natural product combinatorial biosynthesis with synthetic biology. Nature chemical biology, 11(9), 649-659.
30. Buriani, A.; Garcia-Bermejo, M.L.; Bosisio, E.; Xu, Q.; Li, H.; Dong, X.; Simmonds, M.S.; Carrara, M.; Tejedor, N.; Lucio-Cazana, J.; et al. Omic techniques in systems biology approaches to traditional Chinese medicine research: Present and future. J. Ethnopharmacol. 2012, 140, 535–544.
31. Kunnumakkara, A. B., Bordoloi, D., Harsha, C., Banik, K., Gupta, S. C., & Aggarwal, B. B. (2017). Curcumin mediates anticancer effects by modulating multiple cell signaling pathways. Clinical science, 131(15), 1781-1799.
32. Thangapazham, R. L., Singh, A. K., Sharma, A., Warren, J., Gaddipati, J. P., & Maheshwari, R. K. (2007). Green tea polyphenols and its constituent epigallocatechin gallate inhibits proliferation of human breast cancer cells in vitro and in vivo. Cancer letters, 245(1-2), 232-241.
33. Xu, Y., Ho, C. T., Amin, S. G., Han, C., & Chung, F. L. (1992). Inhibition of tobacco-specific nitrosamine-induced lung tumorigenesis in A/J mice by green tea and its major polyphenol as antioxidants. Cancer Research, 52(14), 3875-3879.
34. Li, J., Zhang, C., Jiang, H., & Cheng, J. (2015). Andrographolide inhibits hypoxia-inducible factor-1 through phosphatidylinositol 3-kinase/AKT pathway and suppresses breast cancer growth. OncoTargets and therapy, 427-435.
35. Prasad, S., Yadav, V. R., Sung, B., Reuter, S., Kannappan, R., Deorukhkar, A., ... & Aggarwal, B. B. (2012). Ursolic acid inhibits growth and metastasis of human colorectal cancer in an orthotopic nude mouse model by targeting multiple cell signaling pathways: chemosensitization with capecitabine. Clinical cancer research, 18(18), 4942-4953.
36. Zhang, Y., Huang, L., Shi, H., Chen, H., Tao, J., Shen, R., & Wang, T. (2018). Ursolic acid enhances the therapeutic effects of oxaliplatin in colorectal cancer by inhibition of drug resistance. Cancer Science, 109(1), 94-102.
37. Ding, W., Hu, Z., Zhang, Z., Ma, Q., Tang, H., & Ma, Z. (2015). Physapubescin B exhibits potent activity against human prostate cancer in vitro and in vivo. Journal of agricultural and food chemistry, 63(43), 9504-9512.
38. Deng, Q. P., Wang, M. J., Zeng, X., Chen, G. G., & Huang, R. Y. (2017). Effects of glycyrrhizin in a mouse model of lung adenocarcinoma. Cellular Physiology and Biochemistry, 41(4), 1383-1392.
39. Qazi, A., Pal, J., Maitah, M. I., Fulciniti, M., Pelluru, D., Nanjappa, P., ... & Shammas, M. A. (2010). Anticancer activity of a broccoli derivative, sulforaphane, in barrett

adenocarcinoma: potential use in chemoprevention and as adjuvant in chemotherapy. Translational oncology, 3(6), 389-399.

40. Zhao, G., Han, X., Zheng, S., Li, Z., Sha, Y., Ni, J., ... & Song, Z. (2016). Curcumin induces autophagy, inhibits proliferation and invasion by downregulating AKT/mTOR signaling pathway in human melanoma cells. Oncology reports, 35(2), 1065-1074.
41. Hewlings, S. J., & Kalman, D. S. (2017). Curcumin: A Review of Its Effects on Human Health. Foods (Basel, Switzerland), 6(10), 92. https://doi.org/10.3390/foods6100092.
42. Al-Karawi, A. S., Alawssi, Y. F., & Khadhum, M. K. (2023). Immunological Insights into Rheumatoid Arthritis: A Comprehensive Review of Diagnosis and Assessment Approaches. African Journal of Advanced Pure and Applied Sciences (AJAPAS), 151-159.
43. Wang, Y., Wu, S., Li, Q., Lang, W., Li, W., Jiang, X., Wan, Z., Chen, J., & Wang, H. (2022). Epigallocatechin-3-gallate: A phytochemical as a promising drug candidate for the treatment of Parkinson's disease. Frontiers in pharmacology, 13, 977521. https://doi.org/10.3389/fphar.2022.977521.
44. Xu, Y., Ho, C. T., Amin, S. G., Han, C., and Chung, F. L. (1992). Inhibition of tobacco-specific nitrosamine-induced lung tumorigenesis in A/J Mice by green tea and its major polyphenols as antioxidants. Cancer Res. 52, 3875–3879. doi.10.1016/0169-5002(93)90327-T
45. Yan, Y., Fang, L. H., & Du, G. H. (2018). Andrographolide. Natural Small Molecule Drugs from Plants, 357–362. https://doi.org/10.1007/978-981-10-8022-7_60.
46. Choudhari, A. S., Mandave, P. C., Deshpande, M., Ranjekar, P., & Prakash, O. (2020). Phytochemicals in Cancer Treatment: From Preclinical Studies to Clinical Practice. Frontiers in pharmacology, 10, 1614. https://doi.org/10.3389/fphar.2019.01614.
47. Mlala, S., Oyedeji, A. O., Gondwe, M., & Oyedeji, O. O. (2019). Ursolic Acid and Its Derivatives as Bioactive Agents. Molecules (Basel, Switzerland), 24(15), 2751. https://doi.org/10.3390/molecules24152751.
48. Prasad, S., Yadav, V. R., Sung, B., Gupta, S. C., Tyagi, A. K., & Aggarwal, B. B. (2016). Ursolic acid inhibits the growth of human pancreatic cancer and enhances the antitumor potential of gemcitabine in an orthotopic mouse model through suppression of the inflammatory microenvironment. Oncotarget, 7(11), 13182.
49. Shan, J., Xuan, Y., Zhang, Q., Zhu, C., Liu, Z., & Zhang, S. (2016). Ursolic acid synergistically enhances the therapeutic effects of oxaliplatin in colorectal cancer. Protein & cell, 7(8), 571–585. https://doi.org/10.1007/s13238-016-0295-0.
50. Wang, Y., Wei, Z., and Wang, X. (2018). Enhancement of anti-tumor activity of ursolic acid by nanostructured lipid carriers. China Nanomed. 2016: Nanotechnol. Biol. Med. 14, 1743–1885. doi: 10.1016/j.nano.2017.11.366
51. Ding, W., Hu, Z., Zhang, Z., Ma, Q., Tang, H., & Ma, Z. (2015). Physapubescin B Exhibits Potent Activity against Human Prostate Cancer In Vitro and In Vivo. Journal of

agricultural and food chemistry, 63(43), 9504–9512. https://doi.org/10.1021/acs.jafc.5b03045.

52. Chen, L., Xia, G., Qiu, F., Wu, C., Denmon, A. P., & Zi, X. (2016). Physapubescin selectively induces apoptosis in VHL-null renal cell carcinoma cells through down-regulation of HIF-2α and inhibits tumor growth. Scientific reports, 6(1), 32582.
53. Selyutina, O. Y., & Polyakov, N. E. (2019). Glycyrrhizic acid as a multifunctional drug carrier - From physicochemical properties to biomedical applications: A modern insight on the ancient drug. International journal of pharmaceutics, 559, 271–279. https://doi.org/10.1016/j.ijpharm.2019.01.047.
54. Deng, Q. P., Wang, M. J., Zeng, X., Chen, G. G., & Huang, R. Y. (2017). Effects of glycyrrhizin in a mouse model of lung adenocarcinoma. Cellular Physiology and Biochemistry, 41(4), 1383-1392.
55. Wu, X., Wang, W., Chen, Y., Liu, X., Wang, J., Qin, X., ... & Pei, D. (2018). Glycyrrhizin suppresses the growth of human NSCLC cell line HCC827 by downregulating HMGB1 level. BioMed Research International, 2018.
56. Qazi, A., Pal, J., Maitah, M. I., Fulciniti, M., Pelluru, D., Nanjappa, P., ... & Shammas, M. A. (2010). Anticancer activity of a broccoli derivative, sulforaphane, in barrett adenocarcinoma: potential use in chemoprevention and as adjuvant in chemotherapy. Translational oncology, 3(6), 389-399.
57. Su, X., Jiang, X., Meng, L., Dong, X., Shen, Y., & Xin, Y. (2018). Anticancer activity of sulforaphane: the epigenetic mechanisms and the Nrf2 signaling pathway. Oxidative medicine and cellular longevity, 2018.
58. Lubelska, K., Milczarek, M., Modzelewska, K., Krzysztoń-Russjan, J., Fronczyk, K., & Wiktorska, K. (2012). Interactions between drugs and sulforaphane modulate the drug metabolism enzymatic system. Pharmacological reports : PR, 64(5), 1243–1252. https://doi.org/10.1016/s1734-1140(12)70920-9.
59. Mohammed, A. A., & Sonawane, K. D. (2022). Destabilizing Alzheimer's Aβ42 protofibrils with oleocanthal: In-silico approach. BIOINFOLET-A Quarterly Journal of Life Sciences, 19(3), 288-295.
60. Patel, M. K., Pandey, S., Kumar, M., Haque, M. I., Pal, S., & Yadav, N. S. (2021). Plants Metabolome Study: Emerging Tools and Techniques. Plants (Basel, Switzerland), 10(11), 2409. https://doi.org/10.3390/plants10112409.
61. Shen, S., Zhan, C., Yang, C., Fernie, A. R., & Luo, J. (2023). Metabolomics-centered mining of plant metabolic diversity and function: Past decade and future perspectives. Molecular Plant, 16(1), 43-63.
62. Sharma, V., & Sarkar, I. N. (2013). Bioinformatics opportunities for identification and study of medicinal plants. Briefings in bioinformatics, 14(2), 238–250. https://doi.org/10.1093/bib/bbs021.