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Phytochemical Warriors: Investigating Medicinal Plants for Anticancer Effects

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A B S T R A C T

Modern medicine is based on plants, which have been utilized for medicinal reasons since the dawn of human history. The majority of chemotherapeutic medications used to treat cancer are synthetic derivatives of plants or compounds that have been found and extracted from plants. As of right now, cancer is the biggest cause of mortality worldwide, and its death toll is rising every day. Over the years, medicinal plants have been used extensively for the treatment of cancer, especially in Nigeria and the majority of poor nations. There is a lengthy history of traditional medicine that started with the search for plants that may treat a variety of illnesses, including cancer. Many of the plants used in traditional medicine include numerous bioactive chemicals that have the power to cure illnesses and aid in disease prevention. Additionally, plants have made a substantial global contribution to the contemporary pharmaceutical sector. 33 medicinal plants having notable and active anticancer action, together with the anticancer chemicals they contain, are included in this review. For researchers interested in creating a safe, nontoxic, active medicinal plant-based cancer therapy, this article will offer a foundational set of knowledge. The study will provide a rationale for the traditional use of these medicinal plants in the treatment of cancer. Cancer is a dangerous illness that advances very quickly. Cancer is now the second most prevalent cause of death worldwide, after cardiovascular disease. Cancer is caused by a multitude of variables, including genetics, regular actions, environmental influences, and more. Due to the high fatality rate associated with cancer and the unfavorable side effects of radiation and chemotherapy, many cancer patients look for alternative and/or complementary therapies.

Keywords: Cancer; Medicinal Plants, Phytocompounds, Cytotoxicity, Immunotherapies, Himalayas

1. INTRODUCTION

Cancer differs from infectious and environmental illnesses brought on by antigens not found in our body system, as well as diseases linked to microbes and parasites. Human malignancies can arise from a variety of causes, including genetic or epigenetic factors that cause normal cells to mutate [1]. The science of epigenetics examines how variations in heritable gene expression cause aberrant cells to proliferate. Apoptosis malfunctioning, aberrant gene function, altered gene expression patterns, loss of normal cell growth, development, and regulation, commencement of angiogenesis, and metastasizing to other healthy tissue or organs are the causes of cancer. Metastasis is the term used to describe how cancer spreads from its original cells or tissue to a different healthy area of a tissue or organ. The ancient Greeks described cancer as black bile and innate sadness. Early cancer detection, prevention, and therapy are top priorities for a number of cancer research organizations. Globally, there would be 28.4 million new cases of cancer in 2040, up 47% from the average number of cases in 2020, according to GLOBOCAN estimates. Demographic changes are expected to cause a large increase in the rate of transitioning, from 32 to 56 percent to 65 to 95 percent, and this rate may rise even more as a result of rapid economic growth and globalization [2].

The extensive body of knowledge generated by research on cancer cells aids in slowing the disease's progression. Cancer patients experience anxiety and pessimism due to the long-held belief that the disease is incurable, and they may also experience pain and adverse effects from chemotherapy. Therefore, scientific research in the subject of cancer is extremely important for developing a better and sustainable health care system and treatment, as well as for meeting the medical requirements of individuals who have the disease and extending their life expectancy [3]. The cancer treatment regimen that has been used for the last 15 years, which was based on organ origin-based treatment and histomorphology characteristics, is altered by the development of molecular and tumor biology. Understanding the origins of cancer and the ways in which different elements contribute to its growth and progression is crucial for solving complex biological and medical issues associated to the disease [4]. The several cancer therapies that medical professionals, physicians, and oncologists use are depicted in Figure 1. One of the most popular forms of treatment is chemotherapy, which employs one or more anticancer medications to either cure or extend the lives of cancer patients. Immunotherapy is a targeted treatment that interferes with the chemicals in the cancer block and prevents the progression of cancer by artificially stimulating the immune system against cancer cells.

The hormones that promote the growth of malignant cells are inhibited by hormone treatment. The replacement of sick or injured bone marrow occurs through bone marrow transplantation. Cancerous tumors are removed surgically [5,6]. Many medicinal plants have been used in traditional medicine to

treat or cure a variety of conditions, including cancer, diabetes, atherosclerosis, and infectious infections [7, 8]. For almost 80 percent of individuals who use medicinal plants, traditional medicines are their first line of treatment and healthcare across the globe.

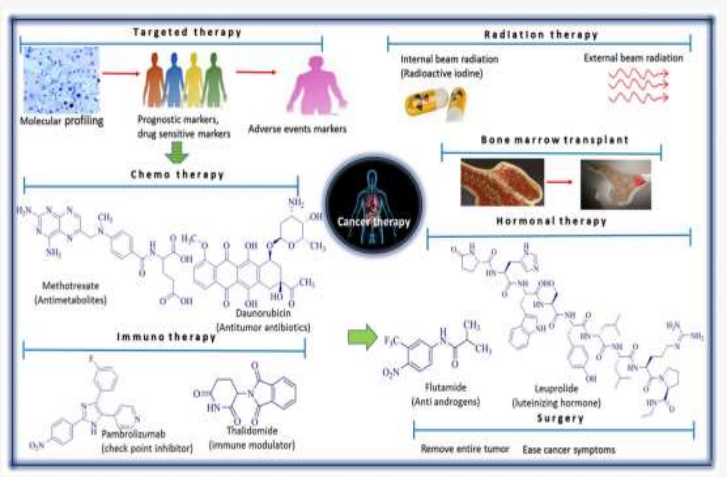

Figure 1. Major types of cancer treatment methods used by physicians and oncologists depending on the cancer type, stage, and severity.

The targeted therapy approach involves the use of medications that recognize and target a particular subtype of cancer cell within the body. An algorithm for molecular profiling identifies the aberrant gene editing within a cancerous cell. Chemotherapy is used to treat inside tumors that are developing quickly. Methotrexate is a chemotherapy medication that inhibits the proliferation of cancer cells. Immunotherapy works by enhancing the body's natural defenses, or immune system, to combat a particular kind of cancer. One treatment option for bone marrow cancer is chemotherapy, and one such drug is thalidomide. Radiation therapy kills cancer by using radiant energy beams similar to X-rays [9]. A bone marrow transplant involves using fresh bone marrow from a donor to replace the damaged bone marrow. An antiandrogen medication called flutamide works to stop testosterone from igniting cancer cells, which is what causes prostate cancer. The process of totally removing a tumor or malignant tissue is called surgery.

Currently, natural products account for around 60% of the medications used to treat cancer [10], with the plant kingdom being the main source. These consist of Podophyllum lignans, Camptotheca alkaloids, Taxus diterpenes, and vinca alkaloids. Thirteen of the sixteen novel plant-derived compounds undergoing clinical trials are in phases I or II, and three are in phases III at the moment. Among these substances, it has been demonstrated that meisoindigo, extracted from the Chinese plant Indigofera tinctoria, and flavopiridol, derived from the Indian tree Dysoxylum binectariferum, both have anticancer properties with lower toxicity than traditional medications. Throughout the world, medicinal plants are a popular substitute for traditional cancer treatments in many nations. There are currently around 3000 plants known to have anticancer activities throughout the globe. Plant-derived products are used to treat cancer at a rate of 10% to 40% worldwide, with a rate of 50% in Asian patients [9–11]. An estimated $5 billion is spent annually on herbal medications with anticancer properties alone in Europe [9]. Approximately 2400 plant species may be found in Israel due to its varied climatic and geographic settings [12]. Israel is home to a wide variety of species, many of which are unique to this region. The country is situated in a transition zone between Mediterranean woodlands in the north, shrubby formations and herbaceous vegetation in the east and south, shrub-steppes and extreme desert areas in the southern Negev, and tropical vegetation in the hottest parts of the country. The medicinal plants of Israel have been utilized for millennia in traditional medicine, making them a special candidate for specialized screening based on ethnobotanical application.

New techniques have made it easier to deal with natural substances, and the pharmaceutical industry is becoming more interested in using these natural components [12, 13]. The World Health Organization estimates that 80% of people worldwide still receive treatment using conventional means [14]. The knowledge of how herbs work on different targets is made possible by contemporary biomolecular science, which has identified several significant qualities in herbs, such as antiviral, anti-inflammatory, and anticancer. The benefits of such herbal therapy against many cancer kinds have also been recognized, as knowledge of their effects grows. Hepatocellular carcinomas (HCCs), for example, are thought to be the fifth most frequent cancer worldwide and are becoming more prevalent [15,16]. Numerous research on the prevention and treatment of HCC using herbal medicine have demonstrated that some herb components may have an impact on the beginning, development, and progression of HCC [17, 18].

2. PLANTS & THEIR ANTICANCER ACTIVITY

WHO recommends cancer is the leading cause of death worldwide, with nearly 10 million deaths predicted in 2020(1) [15]. The bioactivities of phytocompounds for various health benefits have been studied for decades [14]. Synthetic drugs are being replaced by phytocompounds which have great advantages due to their effects on a wide range of target cells with lower cell cytotoxicity effects or side effects compared to synthetic anticancer compounds, which are a single-target effect for prevention and treatment of carcinoma. Various medicinal plants and their nanoparticles have anticancer activity, namely Murraya koenigii leaf extract ZnO nanoparticlets [16]. Most modern drugs used to treat cancer originate from various medicinal plants; 50% of the anticancer drugs originate from medicinal plants.

ARTEMISIA ANNUA

There are over 400 species in the genus Artemisia globally, which is found widely in Europe, Asia, North America, and South Africa [19]. For ages, the genus's plants were employed in traditional medicine. The annual, short-day plant Artemisia annua is a member of the Asteraceae family and has a stiff, brownish stem. In India and Pakistan, A. annua is referred to as "dona" in the Urdu language and as "sweet wormwood" (Qīnghāo in Chinese).A. annua also produces 1,8-cineole molecules and scopoletin. Similar to this, artemisinin's semi-synthetic derivatives, such as arteether, artemether, and artesunate, are also produced. Research has shown that artesunate is a highly potent anticancer agent. Eighty percent ethanol and water were used to extract the stem and leaves of A. annua. Using high-performance liquid chromatography, many quantifiable phenolic compounds from A. annua were discovered (HPLC). HeLa and AGS cell lines were used in the tests of the extracts. Compared to leaf extracts, stem extracts have less ability to suppress cell proliferation. At 500 mg/mL, the ethanolic extracts of leaves suppress the development of HeLa and AGS cells by 57.24% and 67.07%, respectively. The stem extract of A. annua has less phenolic acids than the leaf extract, according to HPLC analysis.

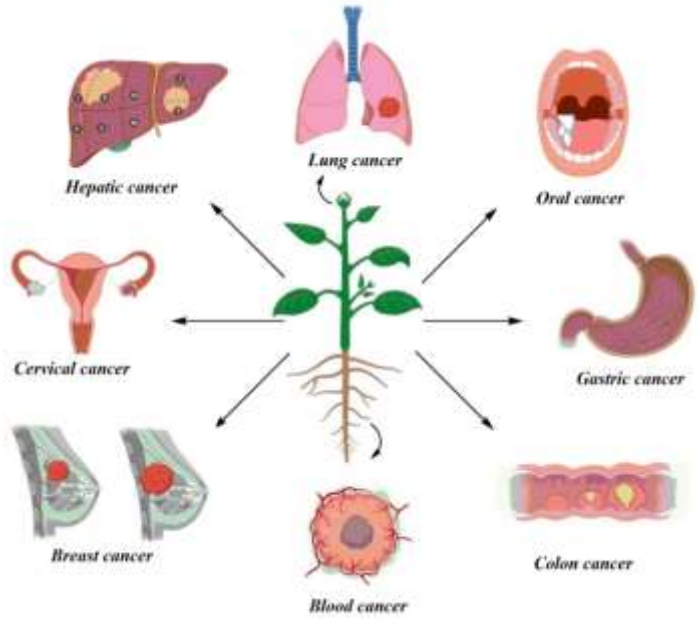

Figure 2: An example of how plants may fight against different kinds of cancer

FAGONIA INDICA

Locally referred to as "dhamasa," fagonia indica is a blooming plant that is a member of the Zygophyllaceae family of caltrops. The Fagonia genus is well-known for its traditional medicinal use, where it is used to treat a wide range of skin conditions. It has been discovered that the aqueous extracts of F. indica are highly efficient against many malignancies, particularly breast tumors. For example, Waheed et al. separated the powerful and active fraction of the F. indica extract using bioactivity-guided fractionation. Three cancer cell lines were used to evaluate the activity: Caco-2 colon cancer cells, MDA-MB-468 estrogen-independent breast cancer, and MCF-7 estrogen-dependent breast cancer (Figure 2). Apoptosis was triggered in MDA-MB-468 and Caco-2 cells, according to the results of many pieces of evidence, including the action of the pan-caspase inhibitor Z-VAD-fmk, caspase-3 cleavage, and DNA ladder tests. Additionally, a novel steroidal saponin glycoside induced necrosis in MCF-7 cells by lysing the cells. Similarly, an aqueous extract of F. indica was shown by Lam et al. [21] to exhibit substantial activity against the breast cancer cell line MCF-7.

Table 1 : Some of the important anticancer medicinal plants, their active components

S.No.	Plant Name	Parts Used	Extract Used (Aqueous/Methanolic etc.)	Active Components Used	Dose Concentration	References
1	Allium sativum	Leaves	Aqueous extracts	Allicin, flavonoids, and phenolic components	20 mg/kg/0.2 mL	[22]
2	Alpinia galangal	Rhizomes	Ethyl acetate extract	Chrysin	1.3 mg/kg	[23]
3	Alstonia scholaris	Stem bark	Ethyl Alcohol extract	--	210 mg/kg	[24]
4	Andrographis paniculata	Aerial parts	Methanolic extract	Diterpenes	10 µg/mL	[25]

5	Angelica archangelica	Root and rhizome	Ethanolic extract	Angelicin	500mg/kg	[26]
6	Aralia elata	Leaves	Ethanol extract	--	300 mg/kg	[27]
7	Artemisia annua	--	--	Artemisinin	0.02%	[16]
8	Asclepia scurassavica	Shade dried leaves	Ethyl acetate and methanolextract	B-sitosterol	10–20 mg/kg b.w.	[28]
9	Astragalus membranaceus	--	--	Polysaccharide	400 mg/kg	[29]
10	Copaifera multijuga	Trunk of the tree	Oil resin	Clerodane Diterpenes	2 g/Kg	[21]
11	Coptidis rhizoma	--	--	Berberine	200 µM and 400 µM	[11]
12	Curcuma longa	--	--	Curcumin	75 µM	[32]
13	Elephantopus scaber	--	Dimethyl sulfoxide extract	Deoxyelephantopin (doe)	25mg/kg	[22]
14	Fagonia schweinfurthii	Whole plant	Ethanolic extract	Carbon tetrachloride (ccl4)	200 µg/mL	[13]
15	Garcinia indica	Fruits	Ethanol extract	Garcinol	<1 µM	[20]
16	Garcinia oblongifolia	Branch	Methanol extract	Xanthone	1000 µg/mL	[19]
17	Garcinia preussii	Fruits and leaves	Meohextract	Benzophenones		[14]
18	Hedyotis diffusa	--	--			[15]
19	Hedyotis spp.	Aerial parts, stem and leaves	Methanol extract	--	20 µM	[34]
20	Kaempferia parviflora	Rhizomes	Ethanolic extract	--	1 mg/mL	[21]

3. CONTEMPORARY PATTERNS IN CONVENTIONAL MEDICINE PLANT PRODUCTS WITH ANTICANCER PROPERTIES AND INFORMATICS PROSPECTS

Building tools and databases that provide knowledge on herbal formulations, the active ingredients in herbs, and related topics is becoming more and more popular as information technology and bioinformatics progress. Numerous initiatives exist, such as the Encyclopedia of Traditional Chinese Medicine (ETCM) [186], SymMap [25], Chinese Medicine Integrated Database (TCMID), Collective Molecular Activities of Useful Plants (CMAUP) [184], etc. Furthermore, a number of researchers have created methods for analyzing the pharmacokinetic characteristics of molecules and medications in silico. Phytochemicals and plant-based active therapeutic components can also benefit from these kinds of methods for enhanced drug development, virtual screening, and potential mechanisms of action. Systems pharmacology and in silico methods have been used to assess a number of plant-based anticancer drugs. The current study promotes more research on plant-derived anticancer active components for their pharmacokinetic and in silico screening properties. Taking into account the fact that plant-based medication formulations typically contain many phytochemicals or even multiple plants. Predicting the function of phytochemicals other than active ingredients found in conventional medicine will be the main obstacle in this path.

4. CONCLUSION

On a variety of human-derived hematological and solid tumor cell lines as well as primary cultures established from patient biopsies, whole cell extracts (ethanol extraction) from Urtica membranacea (Urticaceae), Artemesia monosperma (Asteraceae), and Origanum dayi post (Labiatae), plants native to the coastal plain and desert areas of Israel, demonstrated dose- and time-dependent killing capabilities. Since the plant extracts had no effect on initial cultures of healthy human cells, the killing activity was limited to tumor cells. The whole plant extracts killed the cells by apoptosis. Because Urtica

membranacea plant extract really stopped the growth of tumors in a mouse model of breast adenocarcinoma, it demonstrated especially potent anticancer properties. According to our findings, entire plant extracts have promise as anticancer medicines. His thorough examination of several plants revealed that medicinal herbs had a significant anticancer potential. This page provides a thorough overview of the antitumor activity mechanism of several significant plants. Usually, signaling pathways are regulated to do this. Numerous studies have documented the suppression of enzymes that halt the development of tumors. Human cell lines are typically used in these investigations. It is emphasized that these plants' many kinds of secondary metabolites have a significant anticancer effect. The investigation of a wide variety of anticancer plants, some of which are still undiscovered, should not be restricted by the research of these plants. Research is required to elucidate the anticancer activity mechanism of several previously studied and unstudied plants.

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