**“Phytochemicals in structure-based drug discovery for cancer treatment- a review of the evidence”**

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**Abstract**

Cancer has been one of the leading causes of death worldwide for many years, owing to conventional medicines that have faced numerous hurdles, including multidrug resistance, side effects, and cost-effectiveness. As a result, there is a demand for complementary alternative medicine (CAM) for cancer treatment that improves prognosis while remaining cheap. Plant-based phytochemicals have recently been discovered to have various therapeutic properties such as anticancer, antioxidation, anti-inflammation, immunomodulation, and so on. Taxol, vinca alkaloids (vincristine and vinblastine), and podophyllotoxin are examples of common phytochemicals that have anticancer properties by affecting cancer growth and progression molecular pathways. Furthermore, pioneer phytochemicals have served as models for the design and development of novel anticancer drugs with enhanced pharmacokinetics and pharmacodynamics. The FDA-approved anticancer medicines doxorubicin and idarubicin,  were created by utilising an anthraquinone scaffold and starting ingredients. As a result, the purpose of this chapter is to describe the phytochemicals, modes of action, and structure employed as scaffolds for novel drug development.

**Keywords:** Cancer; Phytochemicals; and Antitumor activity.

**Introduction:**

According to WHO 2011, cancer is one of the top causes of death worldwide, accounting for 7.9 million deaths in 2007. It is also one of the most obnoxious diseases in emerging and impoverished countries because to a lack of effective remedies and care [1]. Every year, around 11 million people are diagnosed with cancer, and millions of people die from it. According to several studies, various forms of cancer (stomach, lungs, cervix uteri, liver, breasts, and colorectal) account for approximately 13% of all deaths each year [2]. Significant attempts were made to identify the epitome technique for cancer medication study, which eventually emerged as the major thrust of study for multiple eras [3]. According to various studies, women have a greater cancer mortality rate than men. Males had a greater occurrence incidence for prostate (15.0%), lung (16.7%), stomach (8.5%), colorectum (10.0%), and liver (7.5%) cancers, whereas females had an elevated occurrence rate of roughly 25.2% - breast, lung -8.7%, colorectum -9.2%, stomach -4.8%, and cervix -7.9% [4].

Malignancy is defined as the uncontrollable proliferation of abnormal cells everywhere in the human body. Malignant cells or tumour cells are the designation given to newly formed abnormal cells. Malignant cells have the ability to infect healthy tissues. Several cancers and the irregular units that form the malignant tissue are then identified by the specific tissue where these irregular cells are created (for instance, cervical cancer, breast cancer, and colorectal cancer). These cells frequently segregate from the initial source of mass cells, proliferate through multiple channels (blood and lymph), and reside in new organs from which they can repeat the cycle. This progression from one section of the body to another is referred to as metastatic disease or metastasis.

**Historical perceptions of phytochemicals as anti-cancer agents:**

Cancer treatment relies heavily on biological products. Particularly Secondary metabolites are essential for the efficient operation of the human body's inherent mechanisms. Several studies have found that phytochemicals decrease highly expressed proteins, amino acids, hormones, and enzymes in a variety of ways. Plant-derived chemicals are being used to inhibit cancerous tumours and reduce treatment resistance. These can control the expression of genetic abnormalities, change in genetic expression of certain genes such as p21 and p53 during mitosis or meiosis, and even carry out DNA repair mechanisms. Scientists are developing semi-synthetic analogues with enhanced pharmacological qualities with the awareness of biological molecules to cure malignancies, Chemical lead molecules, as well as medicinal plants and other natural resources [5]. As a result of significant research by chemists and pharmacologists, several phytotherapeutic procedures have been described [6]. These phytochemicals help to regulate the pace at which protective enzymes are generated, and they have also been shown to have antioxidant and relative oxygen-producing properties by influencing multiple pathways [7]. Some cytotoxic medications inhibit angiogenesis while causing low damage. Surveys on new plants will lead to the development of novel anticancer medications, the success of which will be monumental [8]. Meanwhile, specialised target drugs have been designed to attack tumor-related proteins, and they are the foundation of precise medicine; biological molecules derived from plant resources represent a valuable source for specific remedies because they affect multiple targets at once; and pharmacological combinations behave in a multi-specific manner.

**Enhancement and Application of Synthetic Analogs for Plant-Derived Compounds**

One of the key limiting aspects of secondary metabolites extracted from plants is their low solubility or insufficient bioavailability, which prevents their application in clinical trials. The use of semi-synthetic or synthetic analogues for identifying plant-derived substances has been applied as the ultimate solution to this challenge [9]. Morphine has been transformed to morphine-6-glucuronide, for example, to boost medicinal properties. Paclitaxel (Taxols) and its analogues docetaxel (Taxoteres) and cabazitaxel (Jevtanas) are two examples of scientifically proven synthetic anticancer analogues derived from plants; camptothecin and its analogues belotecan (Camptobells), irinotecan (Camptosars); vinblastine (Vumons).

**Classification of Phytochemicals:**

In pharmaceutical treatment, natural compounds play a key role, particularly in the case of antitumor drugs. Beneficial component classes such as steroids, fatty acids, glycosides, terpenes, flavonoids, alkaloids, tannins, and phenolics have been identified in ethnomedicine plant analysis. [10]. They are responsible for enhancing DNA repair pathways and directly affect the central hallmark of cancer progression and metastasis. The pure, chemically well-defined drugs obtained naturally have been used in before being used as a drug, advanced medicines are either transformed directly or through chemical processes.

Plant alkaloids have an impact on a variety of underlying signalling mechanisms. [11]., Some alkaloids (capsaicin, piperine) appear to enhance tumour growth and metastasis, or to act as co-carcinogens, whereas others appear to be genotoxic (caffeine, sanguinarine, harmine). Consequently, cancer-curing medications must not be genotoxic or carcinogenic. Caffeine has been known to help the development of mammary glands in addition to DNA damaging chemicals that induce cancer. This finding could be regarded as a proliferative impact, which is undesirable in anticancer medicines as well.

Phenols, flavonoids, and their derivatives, stilbenes and lignans are among the many antioxidants that fall under this category. Polyphenols have various targets in carcinogenesis, drug and radiation resistance mechanisms, tumour cell proliferation and apoptosis, inflammation, invasive dissemination, angiogenesis, and drug and radiation resistance and processes. [12]. Polyphenols inhibit platelet activation, capillary permeability, lipid peroxidation, and enzyme systems like lipoxygenase, among other biological activities. The following phytochemicals have been found to be useful in the chemoprevention of cervical cancer in experimental investigations.

**Phytochemical**

**Thiols**

**Free alkaloids Eg.** Atropine, Nicotine

**Terpenoids**

**Polyphenols**

**Alkaloids**

**Carotenoids Eg.** Lycopene Lutein

**Phenolic acids**

**Benzoic acid derivatives Eg.** Gallic acid

**Protoalkaloids Eg.** Ephedrine, Berberine

**Non-Carotenoids Eg.** Saponin

**Cinnamic acid derivatives Eg.** Coumaric acid

**Polyamine Alkaloids Eg.** Spermine, Spermidine

**Flavonoids**

**Pseudoalkaloids Eg.** Capsaicin, caffeine

**Indoles** Eg. Indole-3-carbibnol

**Flavanones Eg.** Hesperitin, naringenin

**Cyclopeptide alkaloids Eg.** Nummularine A

**Anthocyanidin Eg.** Pelargonidin naringenin

**Stilbenes Eg.** Resveratrol, Phytoalexin

**Flavonols Eg.** Quercetin

**Allylic Sulfides** Eg. Allicin

**Isoflavones Eg.** Glycetein, genistein

**Flavones Eg.** Apigenin, chrysin

**Flavanonols Eg. Silibinin, Silymarin**

**Flavan-3-ols Eg. Catechin.**

Terpenoids are categorized into various groups, depending on the amount of building unitss, such as monoterpenes (e.g., carvone, perillyl alcohol , limonene-*d*, and geraniol), diterpenes (e.g. trans-retinoic acid and retinol ), triterpenes [e.g., lupeol, ursolic acid, oleanic acid, and betulinic acid], and tetraterpenes (e.g., lutein, α-carotene, , and β-carotene lycopene [13]. Many triterpenoids have been found to inhibit the growth of a wide variety of cell types while causing no harm to healthy cells [14].

Thiols are a group of highly reactive chemicals that play an important role in maintaining the cellular redox equilibrium [15]. The thiol moiety is one of the cell's most powerful nucleophilic groups. It has taken part in a variety of biochemical process., where thiol-containing compound have an important function in maintaining intracellular redox balance, commonly known as oxidative stress, Apoptosis is another well-known role for the phytochemical [16].

**Phytochemicals from plants are currently used in cancer treatment:**

Phytochemicals, or naturally occurring plant substances, are employed in the development of new drugs and in the treatment of cancer. It is classified based on its chemical structure [17]. Some examples include taxol analogues, vinca alkaloids such as podophyllotoxin, vinblastine, vincristine, and analogues. Phytochemicals typically interact by influencing the molecular pathways of cancer growth and progression. Individual techniques include increased antioxidant levels, suppression of proliferation, encouragement of cell cycle arrest and apoptosis, carcinogen inactivation, and immune system regulation [18]. They perform a wide range of activities on a wide range of biological targets and signalling pathways, including membrane receptors [19]. Phytochemicals' anti-cancer properties have been studied in vitro and in vivo. They have separate and overlapping processes that scavenge free radicals in order to cut down carcinogenic activity [20]. Figure 1 depicts the chemical structures of numerous chemicals produced from plants that are utilised to treat cancer in this chapter,

Withaferin A Quercetin

Taxol Curcumin

Resveratrol Berberine Camptothecin

**Recent cancer therapy against phytochemicals:**

Since ancient times, nature has provided medicinal herbs, which have played a critical role in human progress. Phytochemicals derived from various portions of medicinal plants have a variety of therapeutic properties, including inhibiting development and progression of cancer. Secondary metabolites play a key role in hindering signalling pathways of such as cyclooxygenase activity, topoisomerase enzyme, and CDK4 kinases activity, as well as DNA repair mechanisms activation and enhancing protective enzymes formation such as capase-3, resulting in strong anticancerous effect. Table 1 provides thorough information about several medicinal plants and their parts that are used to treat a specific type of cancer .

**Table 1: Phytochemicals of some medicinal plants against particular type of cancer**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Name of the Plant** | **Family** | **Part used** | **Phytochemicals** | **Specific cancer suppressed** | **References** |
| Curcuma longa | Zingiberaceae | Rhizomes | Curcumin, ascorbic acid | Leukemia, glioblastoma and colon cancer (In vitro) | (21) |
| *Artemisia annua* | Asteraceae | Whole plant | Artemisinin | Liver, breast and pancreatic cancer (Both *in vitro* and *in vivo*) | (22) |
| Paeonia suffruticosa | Paeoniaceae | Seed | Polysaccharides (HBSS, CHSS, DASS, and CASS) | Prostate, colon, human breast, and cervical cancer (In vitro) | (23) |
| Allium wallichii | Amaryllidaceae | Whole plant | Steroids, terpenoids, flavonoids, reducing sugars and glycosides | Prostate cancer, breast cancer, cervical cancer (In vitro) | (24) |
| Ziziphus spinachristi | Rhamnaceae | Flowers, leaves | Doxorubicin, spinanine-A, rutnine, quercetin | Lung cancer and breast cancer (In vivo) | (25) |
| Ziziphus mauritiana | Rhamnaceae | Leaves, bark, fruit | α-linolenic acid, Methyl stearate | Leukemia, human cervical and liver cancer (In vitro) | (26) |
| Camelia sinesis | Theaceae | Leaves | Epicatechingallate, picatechin, epigallocatechin | Lung, bladder, skin, prostate and breast cancer (Both in vitro and in vivo) | (27) |
| Peltophorum dubium | Fabaceae | Seeds | Peltophorum dubium trypsin inhibitor | Rat lymphoma cells, human leukemia cells | (28) |
| Vicia faba | Fabaceae | Seeds | Field bean protease inhibitors | Skin cancer (Both in vitro and in vivo) | (29) |
| Broussonetia papyrifera | Moraceae | Fruits, leaf, bark | 2S-abyssinone Ⅱverubulin | Glioblastoma and brain cancer (In vitro) | (30) |
| Vigna unguiculata | Fabaceae | Seeds | Black-eyed-pea trypsin/Chymotrypsin inhibitor | Human breast cancer (In vitro) | (31) |
| Ziziphus jujuba | Rhamnaceae | Fruits, seeds, leaves | Linoleic acids, triterpenoids | Breast cancer, human Jurkat leukemia T cells (Both in vitro and in vivo) | (32) |
| Sylibum marianum | Asteraceae | Flower, leaves | Silibinin | Lung, liver, skin, colon and prostate cancer (Both in vitro and in vivo) | (33) |
| Psoralea corylifolia | Leguminosae | Seeds | Bavachanin, corylfolinin, psoralen | Lung, osteosarcoma, ﬁbrosarcoma and liver cancer (In vitro) | (34) |
| Viscum album | Santalaceae | Sprouts | Viscumin, digallic acid | Breast, cervix, ovary, stomach, colon, kidney, lung cancer (Both in vitro and in vivo) | (35) |
| Liriodendron tulipifera | Magnoliaceae | Stem | Costunolide, tulipinolide, liriodenine, germacranolide | KB (Oral cancer), HT29 cell line (Both in vitro and in vivo) | (36) |
| Crocus sativus | Liliaceae | Dry stigmas | Crocetin | Hippocampal cell death and lung cancer (In vivo) | (36) |
| Dioscorea colletti | Dioscoreales | Rhizomes | Dioscin | Liver and human gastric cancer (In vitro) | (37) |
| Bleekeria vitensis | Apocynaceae | Leaf | Elliptinium | Myelogenous leukemia and breast cancer (In vivo) | (38) |
| Tylophora indica | Combretaeae | Bark, Kernel fruit | Tylophorine | Breast cancer (In vivo) | (39) |

**Different strategies for the development of anticancer phytochemicals**

Plants with medicinal properties play a important role especially in the field of pharmaceutical industry for the treatment of various diseases. They might vary with longitude, latitude, altitude, climate, age, and seasonal diversity from species to species. Each plant parts contain many numbers of pharmacological functions. These bioactive phytochemicals are majorly used as anticancer drugs. Phytochemical purification involves many stages i.e., isolation assays, bioassay-guided fractionation and combinatorial chemistry. For the separation of bioactive compounds, various analytical techniques have been used. The process starts with natural extracts analysis by using dry or wet plant material by confirming the biological activity. Then, followed by fractionation of active plant extracts, tested for biological activities and also various analytical techniques such as GCMS, LCMS, HPLC, TLC, UV-vis, NMR and FTIR, etc. are used for the separation of active compounds. For some of the polarity orders, different solvents are used. Sephadex, Superdex, Silica, or any other suitable matrix can be used for fractionation purposes. Even some of the dyeing agents are used for the detection of natural compounds in endangered species or even in medicinal plants (e.g. Vanilline sulfuric acid). These protocols may vary from species to species. However quality, purity, and quantity of the bioactive compounds must be very high and this can be done by using the highly pure solvents, and matrices, and also with careful handling. Once the purification is done for the phytochemicals, they should undergo in-vitro or in-vivo anticancer effects. If the compound showed anticancer activity then it has to undergo various tests such as pharmacokinetics, pharmacodynamics, immunogenicity, metabolic fate, biosafety, side effects, drug interactions, dose concentration , etc. for future drug design. A detailed schematic diagram is shown below of bioactive compound synthesis, optimization, characterization, testing, and potential application as a cancer therapeutic agent is shown in Figure 2.

**Fig. 1: Illustration of activity of plants against several types of cancers.**



**Figure 2. Detailed scheme of anticancer phytochemical synthesis, optimization, characterization and prospective use as cancer therapeutic agent.**

**Bioactive Compounds and Their Anticancer Functions**

Previously, many varieties of food which includes vegetables and fruits were determined to have a great impact on human health. Bioactive compounds contain many secondary metabolite and help in the prevention of diseases thereby protecting human health [40]. Most of the secondary metabolites vary in their structure and functions and also have the potential to act as chemotherapeutic and chemopreventive agents, especially in the treatment of cancer [41-44]. The bioactive compounds that will be discussed and the food sources of these compounds Table [2](https://www.hindawi.com/journals/omcl/2022/1429869/tab2/) [45].

|  |  |  |  |
| --- | --- | --- | --- |
| **Bioactive compounds** | **Examples** | **Sources** | **Supposed anticancer effects** |
| Polyphenolic compounds | Quercetin, resveratrol, catechin | Red wine, chocolate, flaxseed oil |

|  |
| --- |
| Carcinogen detoxification, inhibit tumor initiation/promotion, antimutagen |
|  |

 |
| Carotenoids | Lycopene, lutein, cryptoxanthin | Tomatoes, carrots, leafy vegetables | Antimutagen |
| Sulfur-Containing compounds | Allicin, diallyl sulfide, allyl mercaptanSulforaphane | Garlic, onion, leek | Carcinogen detoxification, inhibit tumor initiation/promotion |
| Terpenoid | Perillic acid, d-limonene | Cherries, mint, herbs | Carcinogen detoxification, inhibit tumor initiation/promotion |

**Conclusion:**

Cancer is the leading cause of death worldwide. It is necessary to develop new drugs for the prevention of cancer disease. Around 60% of the current anticancer drugs are derived from the natural sources. Nature continues to be an abundant source of biologically active and diverse chemotypes, and while relatively only a few of the actual isolated natural products are developed into clinically effective drugs in their own right. Most of the bioactive compounds are identified as chemo preventive and chemotherapeutic agents in the treatment of cancer. These unique molecules often serve as models for the preparation of more efficacious analogs and prodrugs through the chemical methodology, such as total or combinatorial (parallel) synthesis, or the manipulation of biosynthetic pathways. A novel approach for the drug discovery was ethnopharmacological knowledge which is supported by the broad spectrum which involves pharmacology, biochemistry, medicinal chemistry, molecular, and cellular biology including natural product chemistry which is essential to harvest the potentials of phytochemicals. In addition, improvements in the formulation may result in the more effective administration of the drug to patients, or conjugation of toxic natural molecules to monoclonal antibodies or polymeric carriers specifically targeting epitopes on tumors of interest can lead to the development of efficacious targeted therapies. The essential role played by natural products in the discovery and development of novel anticancer agents, and the importance of multidisciplinary collaboration in the optimization of novel molecular drugs from natural product sources have been extensively reviewed.

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