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Phytochemicals in Antitumor Herbs and Herbal Formulas

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Additional information is available at the end of the chapter

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1. Introduction

Cancer is an uncontrolled proliferation of anaplastic cells, which tend to invade surrounding tissues and metastasize to other tissues and organs. A hundred years ago, cancer was not a common disease, but today, it is one of the leading causes of death worldwide, and one of three persons is having a lifetime risk of developing cancer. The incidence of cancer has risen alarmingly in the last few decades: in 2008, 12.7 million people were diagnosed with cancer globally, and about 7.6 million people died of it [1]; in 2012, 14.1 million cases of cancer were diagnosed, with 8.2 million deaths; in 2030, more than 21 million new cancer cases are estimated and 13 million deaths are expected. Considering the above data, it confirms the hypothesis that cancer seems to be a civilization disease. The major type of cancer diagnosed among females is breast cancer, accounting for 23% of the total cancer cases; in males, 17% of the total cancer cases are caused by lung cancer [2]. More than 60% of all cancer deaths occur in low- and middle-income countries, many of which lack the medical resources and health systems to support the disease burden [3]. However, cancer mortality surprisingly increased in U.S. population as well, and cancer metastasis attributes to approximately 90% of cancer-related deaths [4].

After years of intense biomedical research on understanding the mechanisms of tumor genesis and biology of cancer, usual cancer treatment still consists in surgery, radiation, and chemotherapy, each having its own limitations: surgery and radiation therapy could be effective especially for the primary tumor; chemotherapy with serious side effects associated with severe toxicity to normal cells is commonly used for the whole-body treatment of recurrent disease. Considerable research activity is devoted to the discovery of more potent treatments, while minimizing their toxic side effects and to discover selective drugs that can kill malignant tumor cells without affecting normal cells [5, 6].

Recently, there is a greater global interest in nonsynthetic, natural medicines derived from natural sources due to better tolerance and minimum adverse drug reactions as compared to synthetic medicines. Many cancer patients prefer complementary and alternative medicine; herbal medicines were by far the most commonly used group of treatments because they are believed by the general public to be safe, cause less side effects, and less likely to cause dependency [7].

When we are considering natural antitumor compounds, generally we refer to secondary metabolites. Secondary metabolites are the products of metabolism not essential for normal growth, development, or reproduction of an organism. Many of them have proved invaluable as antibacterial or antifungal agents, anticancer drugs, cholesterol-lowering agents, immunosuppressant, antiparasitic agents, herbicides, diagnostics, and tools for research [8]. Nowadays, the increased interest in the obtaining of considerable amounts of secondary metabolites has led to intensive research in the field of cell cultures technology. A lot of efforts have been put into plant cell, tissue, and organ culture as an alternative method to whole plant cultivation for the production of pharmacologically important plant secondary metabolites [9].

Getting plant metabolites is not the only problem; the delivery of biologically active substances in the human body is also subjected to innovative research such as nanotechnology that has been used for tumor diagnosis and to design and development of targeted drug delivery [10-11].

2. What is cancer?

Cancer is ultimately the result of cells that uncontrollably grow and do not die. Normal cells in the body follow an orderly path of growth, division, and death. There are three major types of cell death:

- a. Apoptosis—a naturally occurring programmed and targeted cause of cellular death that may occur in multicellular organisms. Biochemical events lead to characteristic cell changes (morphology) and death [12].
- b. Autophagy—the basic catabolic mechanism that involves cell degradation of unnecessary or dysfunctional cellular components through the actions of lysosomes. Autophagy allows the degradation and recycling of cellular components [13].
- c. Necrosis—a form of cell injury that results in the premature death of cells in living tissue by autolysis, caused by factors external to the cell or tissue, such as infection, toxins, or trauma that result in the unregulated digestion of cell components. Necrosis is almost always detrimental to the organism and can be fatal [14].

Cancer results from a multistage carcinogenesis process that involves three distinguishable but closely connected stages: initiation (normal cell → transformed or initiated cell), promotion (initiated cell → preneoplastic cell), and progression (preneoplastic cell → neoplastic cell). The malignant tumor has the abilities to invade surrounding tissues (metastasis), migrate around

the body in the blood or the lymphatic system, and set up secondary foci of cancerous growths at distant sites. Metastasis is responsible for 90% of the deaths caused by cancer [1].

Every living cell in the human body has the potential to become cancerous. A generic name is usually given to a group of cancers, depending on the type of cells of their origin, which include carcinoma, sarcoma, leukemia, lymphoma, and myeloma.

- Carcinoma: a type of cancer that develops from epithelial cells. About 80% of the human cancers are carcinomas.
- Sarcoma: cancer arising from a mesenchymal cell (connective tissue cell). Sarcoma may arise from the bone, cartilage, muscle, fat, and fibrous tissue.
- Myeloma: a cancer of plasma cells, a type of white blood cell normally responsible for producing antibodies.
- Leukemia: cancer arising from a blood forming cell (hematopoietic stem cell).
- Lymphoma: cancer arising from a cell of the lymphatic tissue (lymphocytes) [15].

When cancer begins, it invariably produces no symptoms. Signs and symptoms only appear as the mass continues to grow or ulcerates. General symptoms may include unintentional weight loss, fever, being excessively tired, and changes to the skin. The symptoms of metastatic cancers depend on the location of the tumor and can include enlarged lymph nodes, enlarged liver or enlarged spleen, which can be felt in the abdomen, pain or fracture of affected bones, and neurological symptoms [16].

3. What causes cancer?

Cancer results from a mutation in the chromosomal DNA of a normal cell under the action of carcinogens. The mutated cell proliferates indiscriminately (pathological mitosis), usually forming a mass known as neoplasm or malignant tumor. Cancer can be triggered by both internal factors (nutritional imbalance in the diet, aging, immune conditions, hormones, and mutations occurring in metabolism) and external factors (tobacco, alcohol, chemicals, infectious agents, and radiation). These causal factors may act together or in sequence to initiate or promote the development of cancer [1, 2, 15, 17].

3.1. Carcinogens

A carcinogen is any substance, radionuclide, or radiation that is an agent directly involved in causing cancer. Carcinogens include a wide range of possibilities: chemical and physical pollution, unhealthy lifestyle, stress, aging, viruses, bacteria, heredity, etc.

3.1.1. Chemical carcinogens

Most of the human cancers are caused by certain chemical agents.

- *Tabacco*. Among the dangerous factors leading to cancer, cigarette smoking (also second-hand tobacco smoking) is essential. Smoke contains several carcinogenic pyrolytic products that bind to DNA and cause many genetic mutations. Tobacco smoke generates more than 2000 chemical compounds, and more than 45 are known or suspected as chemical carcinogens; nicotine is one of the major cancer promoters [18].
- *Polluted environment* is another major source of chemical carcinogens. Industrial toxic chemicals and heavy metals having carcinogenic activity may enter and get accumulated in the human body and damage DNA [2].
- *Contaminated food*. The food containing residues of pesticides, insecticides, and herbicides is one of the three major causes of cancer. Most of the food additives including preservatives (butylated hydroxytoluene), sweeteners (saccharin and cyclamates), and synthetic colorants have carcinogenic activity [15].
- *Chlorine*, used to purify drinking water, may produce certain carcinogenic compounds in the treated water, including chloroform and trichloroethylene, which have carcinogenic activity [15].
- *Reactive oxygen species* (ROS—superoxide, hydrogen peroxide, hydroxyl radical) are also major causes of DNA, protein, and lipid damages, which lead to cancer or aging [19].

3.1.2. Physical carcinogens

Ionizing radiation emitted by radioactive substances ruptures the DNA strands, leading to mutations in the genes. Ultraviolet radiation induces skin cancer. The electromagnetic fields generated by electrical appliances, power lines, and cell phones emit 30-100 times higher electromagnetic fields than the maximum permissible limits. Studies have revealed that prolonged exposure to electromagnetic fields causes mutations in the genes [15].

3.1.3. Biological carcinogens

Certain viruses are suspected to cause cancer in human: for example, the Epstein-Barr virus is linked to Burkitt's lymphoma; testicular tumors and leiomyoma in children; viruses of hepatitis B and hepatitis C are known to enhance risk of the hepatocellular carcinoma; human papilloma virus is a major risk factor of the cervical and of anal cancers [15].

3.1.4. Lifestyle

The World Cancer Research Fund and the American Institute for Cancer Research assess that 30-40% of all cancers could be prevented by appropriate diet and physical activity to avoid overweight and obesity. Many lines of evidence demonstrate that a diet based on abundant and various foods of plant origin protects against epithelial cancers, particularly those of the gastrointestinal tract [2].

3.1.5. Age factor

The incidence of cancer is three times higher in women as compared to men during 30 to 50 years of age, whereas men have a greater risk of cancer as compared to women during 60 to 80 years of age. Cancer is generally considered as the disease of middle-aged and elderly people, but some cancers are known to affect the children [15].

3.1.6. Genes (hereditary factor)

Extensive evidence indicates that only 5-10% of cancers are genetically determined. It is believed that members of those families, who are predisposed to a particular cancer, have one or more activated oncogenes in their genome; therefore, fewer additional mutations are required in such persons to develop the cancer. Genetic mutations are commonly seen in the breast and the ovarian cancers, especially in cancers occurring below 30 years [15].

4. How do natural remedies work?

The plants act on several fronts in the fight against cancer, such as nourishing the body with minerals, vitamins, enzymes, and micronutrients; increasing the immune system of the body; inducing antioxidant action and protecting the body from oxidative stress; enhancing detoxification functions of the body; alkalizing the body fluids; inhibiting cancer-activating enzymes; promoting production of protective enzymes; stimulating DNA repair mechanism; and modulating the activity of specific hormones and enzymes to inhibit growth of cancer.

4.1. Immunomodulatory properties of plant

The immune system is a complex defense network that protects the host from disease and has a large impact on antitumor resistance. Most of the anticancer drugs currently used in chemotherapy are cytotoxic to normal cells, leading a low immune function of organism and can result in development of the tumor, and difficulty of tumor patients' recovery [20].

A major research interest has focused on the immunomodulatory properties of plant-derived medicines. Several studies have reported that many flavonoids, such as quercetin, catechins, resveratrol, green tea polyphenols, grape seed proanthocyanidins, silymarin, and curcumin, have anti-inflammatory and immunomodulatory properties [2].

4.2. Chemoprevention

Chemoprevention is defined as the use of natural or synthetic chemical agents to reverse, suppress, or prevent carcinogenic progression to invasive cancer. Many chemopreventive agents are phytochemicals (secondary metabolites) and nonnutritive plant chemicals that have protective or disease-preventive properties [2, 21]. Several commonly used herbs such as coriander, cumin, garlic, ginger, mint, oregano, and turmeric have been identified by the National Cancer Institute as possessing cancer-preventive properties.

4.3. Impact on cancer induction: antimutagenesis

During the initiation phase, natural chemopreventive agents can inhibit the absorption of a carcinogen into the organism through the antioxidant activity, prevent inflammatory-induced damage or enhance neutralization, and remove carcinogens through metabolic enzymes [3].

4.4. Anti-inflammatory activity

Long-term inflammation leads to the development of dysplasia [22]. Many phenolic substances, including phenolic acids (e.g., gallic, ellagic, caffeic, chlorogenic), flavonoids (e.g., genistein, kaempferol, quercetin, daidzein, isorhamnetin, naringenin), anthocyanins (e.g., pelargonidin), and catechins, have potent anti-inflammatory properties, affecting different stages of the inflammation. Flavonoid aglycones have been shown to exert higher activity than adequate glycosides [2].

4.5. Antioxidant properties

Oxidative stress has been proven to be one of the main factors that lead to the formation of cancer. Oxidative stress is defined as a discrepancy between production of free radicals and reactive metabolites, so-called reactive oxygen species [ROS, e.g., hydrogen peroxide (H_2O_2), superoxide anion ($O_2^{\cdot-}$), and hydroxyl radical ($\cdot OH$)], and their eradication by defending mechanisms, referred to as antioxidants. Excessive oxidative stress in the body for extended periods of time activates inflammatory pathways, which cause the transformation of normal cells into cancer cells, support the survival of cancer cells, and finally lead to cancer cell proliferation [23].

Many herbs are known to contain large amounts of phenolic antioxidants having the capacities to quench lipid peroxidation, prevent DNA oxidative damage, and scavenge reactive oxygen species (ROS) [24].

4.6. Pro-oxidative activity

The pro-oxidant behavior of phenolics is observed in the presence of transition metal ions such as copper or iron. Many studies suggest that the antitumor activity of some polyphenols (e.g., resveratrol, gallic acid, delphinidin, baicalin, quercetin, epicatechin, and epigallocatechin-3-gallate) is also a consequence of their pro-oxidant properties. It seems that while the antioxidant activity lowers the risk of cancer induction by protecting normal cells from oxidative injury, pro-oxidative properties of polyphenolics are more relevant for apoptosis induction and destruction of existing tumor cells [2].

4.7. Modulation of activity of xenobiotic-metabolizing enzymes

A carcinogen is a xenobiotic, and generally, biotransformation involves modification, conjugation, and excretion and is strictly involved in the detoxification of carcinogens. Many plant-derived phenolic compounds such as flavonoids, including kaempferol, daidzenin, genistein,

diosmetin, and theaflavin, have been reported to affect the activity of metabolizing enzymes leading to faster carcinogen detoxification [2].

4.8. Changing multidrug resistance

Multidrug resistance is a significant challenge in the treatment of infectious diseases and cancer. The antitumor treatments currently in use often fail at some stage of the sickness because many types of cancers develop resistance to chemotherapeutic drugs. Some plants can change the resistance of tumor cells to antitumor drugs [25].

4.9. Suppression of angiogenesis

Angiogenesis is the process of formation of new vessels (vascularization) from the preexisting microvascular network. This is as an essential step in tumor dissemination and formation of metastases. Many plant-derived phenolics have been reported to restrain angiogenesis and, consequently, cancer invasion and metastasis [2].

4.10. Apoptosis induction

The activation of apoptosis in preneoplastic cells is one of the crucial mechanisms of cancer chemoprevention. Polyphenolic compounds have been shown to induce selective promotion of apoptosis in cancerous or precancerous cells, by affecting different cellular mechanisms [2].

5. Which are the phytochemicals with antitumor activity?

Plant secondary metabolites and their semisynthetic derivatives are playing today an important role in anticancer drug therapy. In this chapter, the main classes of natural compounds are presented, which have been identified to contain substances with antitumor activity.

5.1. Terpenes

Terpenes are a large and diverse class of organic compounds, often strong-smelling, produced by a variety of plants, particularly conifers. Many terpenes are aromatic hydrocarbons and thus may have had a protective function. The difference between terpenes and terpenoids is that terpenes are hydrocarbons, whereas terpenoids contain additional functional groups. Terpenes are derived biosynthetically from units of isoprene, which has the molecular formula C_5H_8 . The basic molecular formulae of terpenes are multiples of $(C_5H_8)_n$, where n is the number of linked isoprene units.

- **Diterpenes** are composed of four isoprene units and have the molecular formula $C_{20}H_{32}$. Taxanes are diterpenes produced by the plants of the genus *Taxus* and are widely used as chemotherapy agents although present difficulties in formulation as medicines because they are poorly soluble in water. The principal mechanism of action of the taxane class of drugs is inhibition of the process of mitosis [26]. Taxane agents include taxol (or paclitaxel) and docetaxel (Figure 1).

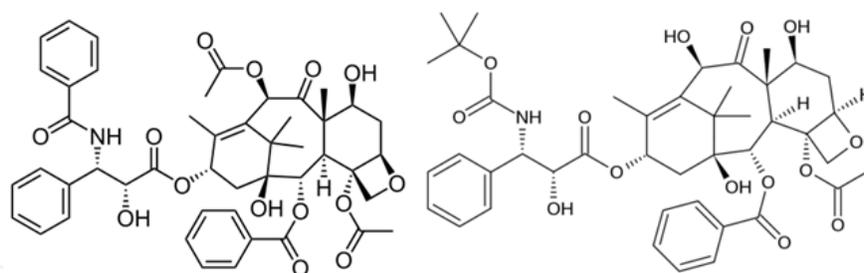


Figure 1. Taxol (or paclitaxel, left) and docetaxel (right).

Taxol, originally isolated in 1971 from the bark of Pacific Yew, *Taxus brevifolia*, is a strong anticancer drug approved by the U.S. FDA to treat a variety of tumors, including breast, ovarian, and AIDS-related Kaposi's sarcoma, among others. Among the conifers apart from the genus *Taxus*, only two other species have been reportedly claimed to produce taxanes: *T. brevifolia* and *Taxus baccata* or the European yew.

- **Triterpenes and triterpenoids**

Triterpenes consist of six isoprene units and have the molecular formula $C_{30}H_{48}$. Triterpenes are widespread in nature and are highly abundant in medicinal plants, especially in the leaves, bark, fruits, and seeds of the herbs. The pentacyclic triterpenes can be classified into lupane, oleanane, or ursane groups. Triterpenoids are structurally diverse organic compounds, more than 20,000 known members, widespread in nature. Several triterpenoids, such as ursolic and oleanolic acid, betulinic acid, and lupeol, possess antioxidative and anti-inflammatory, antidiabetic properties, and have been suggested to be potentially promising anticancer agents. Triterpenoids exist in free form or combined with sugar into glycosides—the triterpenoid saponins. In anticancer mechanisms, triterpenoids are multitargeted agents that induce apoptosis, inhibit cell proliferation, suppress angiogenesis, cause mitochondrial dysfunction, and modulate genes and proteins [27].

- **Boswellic acid** (Figure 2), a triterpene isolated from *Boswellia serrata* (native in India and Pakistan), has been found to possess potent anti-inflammatory and anticancer activity. Boswellic acid have been used to treat Crohn disease, ulcerative colitis, bronchial asthma, endotoxin-induced hepatitis, and arthritis. Boswellic acid is a mixture of four major pentacyclic triterpene acids. Beta-boswellic acid (Figure 2), keto-beta-boswellic acid, and acetyl-keto-beta-boswellic acid have been indicated in apoptosis of cancer cells, in particular, brain tumors and cells affected by leukemia or colon cancer, melanoma, hepatoma, and prostate cancer [28].
- **Oleanolic acid** (Figure 3) is a triterpenoid widely found in several dietary and medicinal plants. Oleanolic acid is abundant in ginseng root and in olive plant (*Olea europaea*), which is the primary commercial source for the compound. Oleanolic acid can be easily obtained in high yield from olive pulp remaining after crushing of the olive fruit and also from olive leaves.

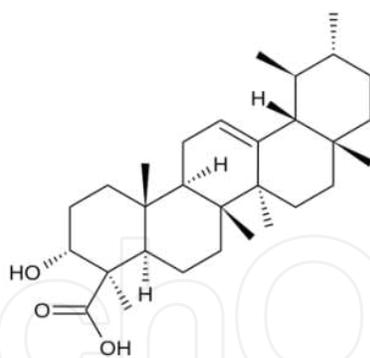


Figure 2. β -Boswellic acid.

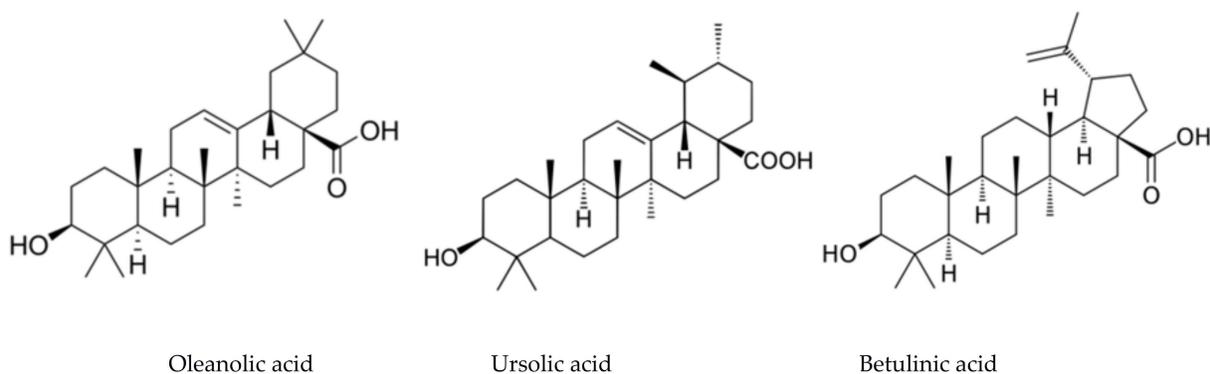


Figure 3. Structure of oleanolic, ursolic acid and betulinic acid.

Oleanolic acid exists in nature as free acid but also serves as an aglycone of triterpenoid saponins, linked with one or more sugar moieties to form glycosides. Effects of oleanolic acid on cancer cells have been demonstrated in chemoprevention and therapy of breast, colorectal, non-small cell lung, epithelial ovarian, pancreatic, prostate cancer, and melanoma. Oleanolic acid inhibited the proliferation of cancer cells and induced apoptosis via ROS-mediated mitochondrial mechanism [29].

- **Ursolic acid** (Figure 3), an isomer of oleanolic acid, is found in combination with oleanolic acid and has similar pharmacological properties. Ursolic acid is easily obtained in very high purity by methanol extraction of rosemary leaf [29].
- **Betulinic acid** (Figure 3) is a naturally occurring pentacyclic triterpenoid found in the bark of several species of plants, principally the white birch (*Betula pubescens*, *Betulaceae*), but also the ber tree (*Ziziphus mauritiana*), self-heal (*Prunella vulgaris*), rosemary (*Rosmarinus officinalis*), and *Pulsatilla chinensis*. Betulinic acid exhibits various biological activities such as anti-HIV, antimalarial, antibacterial, and anti-inflammatory properties, as well as a more recently discovered potential as an anticancer agent by inhibition of topoisomerase and apoptosis in the tumors [3]. A major inconvenience for the future clinical development of betulinic acid and analogues resides in their poor solubility in aqueous media such as blood serum and polar solvents used for bioassays. In order to solve the solubility and to enhance

pharmacological properties, many derivatives were synthesized and evaluated for cytotoxic activity [30-33].

- **Triterpenic saponins**

Saponins are a group of naturally occurring plant glycosides, characterized by their strong foam-forming properties in aqueous solution. Originally named for soapwort plants (*Saponaria* spp.), saponins consist of a hydrophobic aglycone linked to a hydrophilic carbohydrate. The presence of saponins has been reported in more than 100 families of plants, out of which at least 150 kinds of natural saponins have been found to possess significant anticancer properties. Saponins are common in a variety of higher plants and usually found in roots, tubers, leaves, blooms, or seeds. The amphipathic nature of the class gives them activity as surfactants that can be used to enhance penetration of macromolecules such as proteins through cell membranes. Saponins have also been used as adjuvant in vaccines [34]. Based on the carbon skeletons, saponins were classified into triterpenes and steroids. Their glycone parts were mostly oligosaccharides, arranged either in a linear or branched fashion, attached to hydroxyl groups through an acetal linkage. The considerable variety of aglycones, carbohydrates, and their different attachments results in many different saponins. Modern research found that saponins have antitumor effect on many cancer cells at least by cell cycle arrest and apoptosis. Meanwhile, saponins in combination with conventional tumor treatment strategies result in improved therapeutic success [35].

- **Oleananes** are the most common saponins in nature. Their antitumor effect worked through various pathways, such as anticancer, antimetastasis, immunostimulation, chemoprevention, etc. Some of the most studied triterpene saponins are soybean saponin, saikosaponins, avicins, and tubeimoside [35].
- **Cycloartane saponins** could be used as chemotherapeutic agent in the treatment of tumors. For example, total *Astragalus* saponins possess antitumor properties in human colon cancer cells. In addition, *Astragalus* saponins could be used as an adjuvant in combination with other orthodox chemotherapeutic drugs to reduce the side effects of the latter compounds [35].

5.2. Phenols and polyphenols

Phenolic phytochemicals represent the largest category of phytochemicals widespread in different fruits and vegetables and one of the major groups of secondary metabolites in plants. Numerous phenolic compounds have been reported to demonstrate selective activity, destroying cancer cells without damaging normal cells. Many clinical trials have been made on cancer prevention of breast, colon, gastric, reproductive, head and neck, and prostate cancers by using plant polyphenols such as epigallocatechin-3-gallate, curcumin, resveratrol, genistein, and quercetin [2, 36].

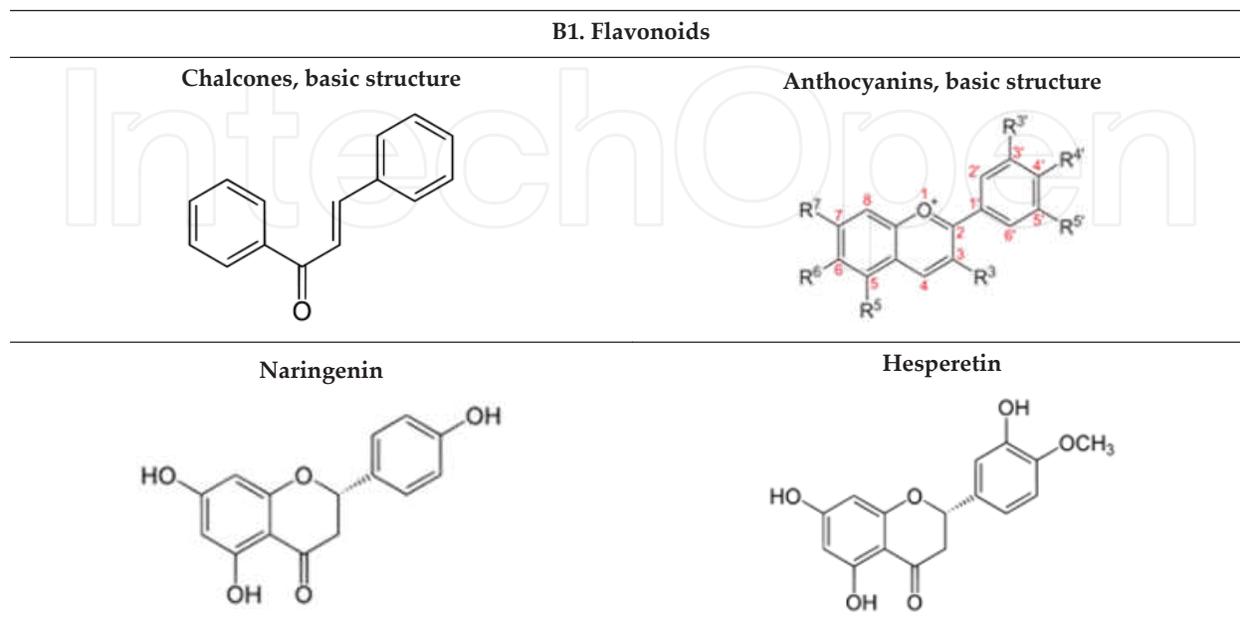
Most of the studies with plant polyphenols showed that cancer-preventing mechanisms include antioxidant activity (the strength of this property is influenced by the number and location of hydroxyl groups, the size and shape of molecules, and steric properties), radical scavenging activity, inactivation of carcinogenic substances, antiproliferation, cell cycle arrest,

induction of apoptosis and differentiation, inhibition of angiogenesis, modulation of tumor suppression genes, and others [36].

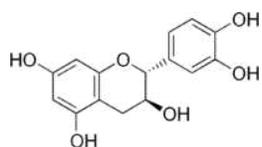
Plant polyphenols are divided into two major groups (Table 1)—flavonoids (chalcones, flavanols, flavones, flavanones, isoflavones, and anthocyanins) and nonflavonoids (phenolic acids, e.g., caffeic acid, gallic acid; stilbenes, e.g., trans-resveratrol, tannins, lignins) [21]. Flavonoids and phenolic acids account for the majority (60% and 30%, respectively) of total dietary polyphenols. The average daily intake of flavonoids alone is 1-2 g [2].

A. Flavonoids		B. Nonflavonoids	
Chalcones and dihydrochalcones	Butein, cardamonin, phloretin	Stilbenoids	Resveratrol
Anthocyanines	Cyanidin, pelargonidin, delphinidin	Hydroxycinnamic acids	Caffeic acid
Flavanones	Naringenin, hesperitin, baicalein	Phenolic acids	Gallic acid, protocatechuic acid, ellagic acid
Flavanols	Catechins, gallic esters of catechins, teaflavons	Curcuminoids	Curcumin
Flavones	Wogonin, luteolin, apigenin, diosmin	Tannins	Hydrolysable and condensed tannins
Flavonols	Quercetin, kaempferol, myricetin		
Isoflavones	Genistein, daidzein		

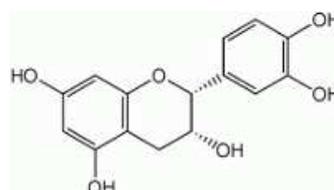
Table 1. Main classes of plant polyphenols



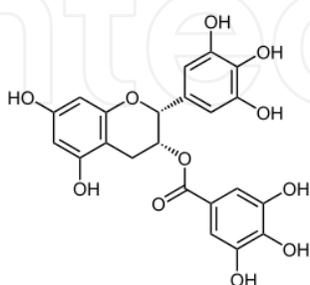
(+) - Catechin



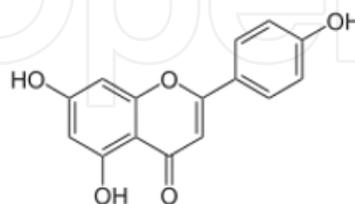
(-) - Epicatechin



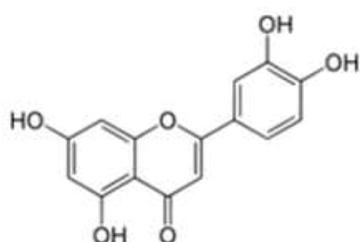
Epigallocatechin gallate



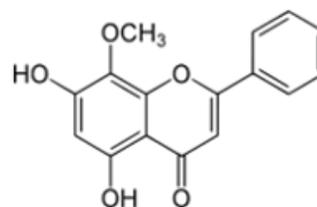
Apigenin



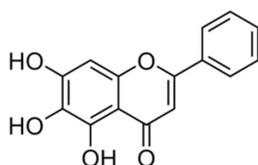
Luteolin



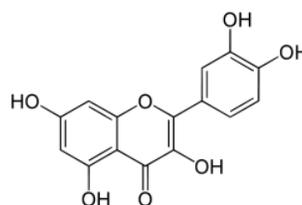
Wogonin



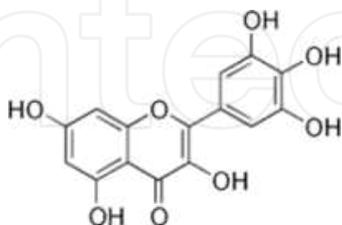
Baicalein



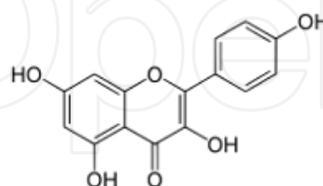
Quercetin



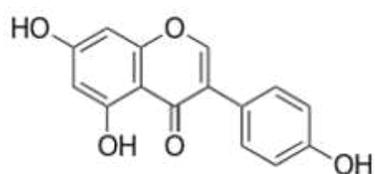
Myricetin



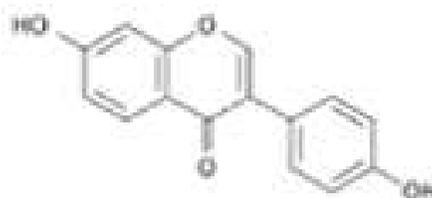
Kaempferol



Genistein



Daidzein



B2. Nonflavonoid phenols

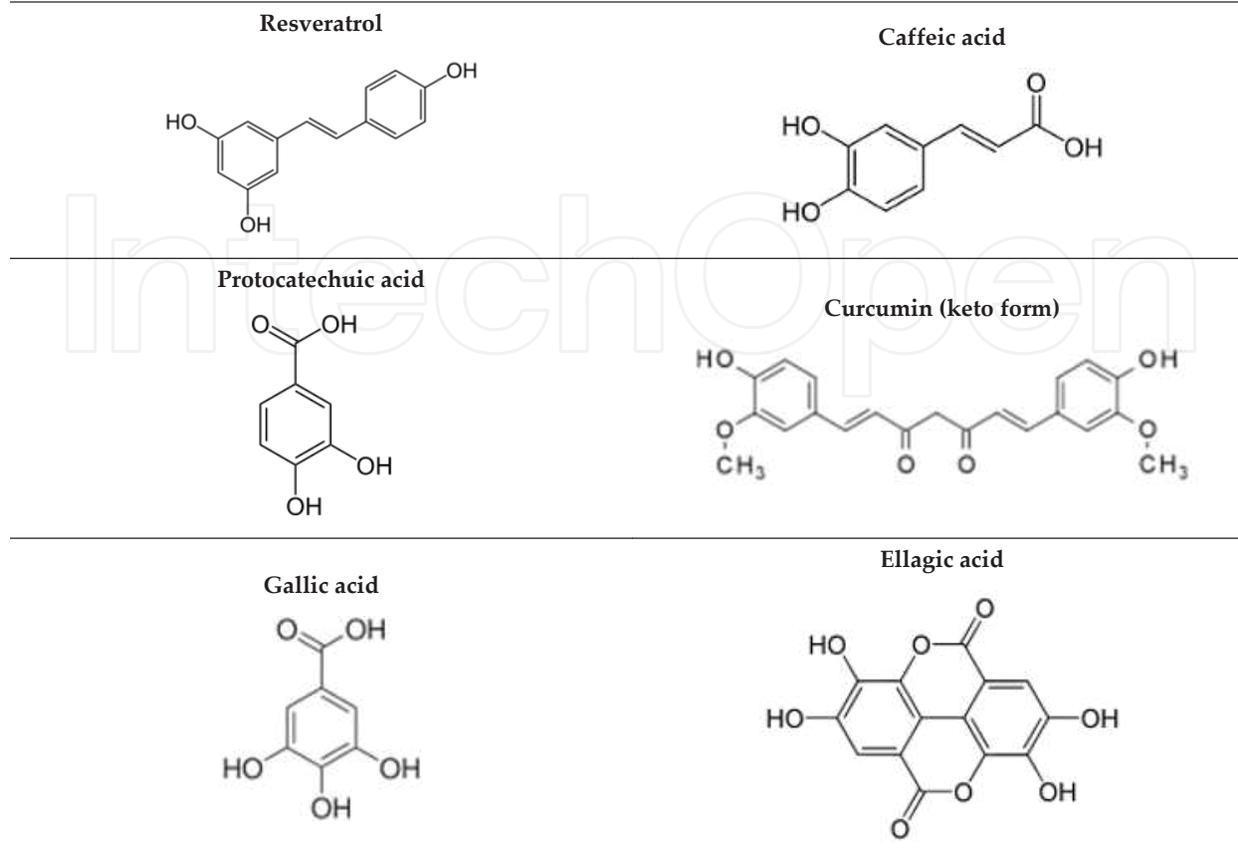


Table 2. Chemical structure of some plant polyphenols with antitumor activity

Flavonoids commonly share the same generic structure, the flavan nucleus consisting of two aromatic rings linked by a pyran ring. Differences in the location of the right phenolic ring to pyran ring make it possible to distinguish between flavonoids (2-phenylbenzopyrans) and isoflavonoids (3-phenylbenzopyrans). 2-Phenylbenzopyran group may be further divided into 3-hydroxyflavonoids (flavonols, flavanols, and anthocyanidins) and flavonoids without substituent at C3 (flavanones and flavones). Flavones differ from flavanones by a C2-C3 double bond [19].

5.2.1. *Flavonoids as anticancer agents*

• **Chalcones as anticancer agents**

Chalcone (Table 2) is an aromatic ketone that forms the central core for a variety of important biological compounds, which are known collectively as chalcones or chalconoid. They are a group of plant-derived polyphenolic compounds belonging to the flavonoids family even if the chroman ring is not yet formed (they are precursors of flavonoid structure). Some of the most significant chalcones identified from plants include flavokawin, butein, xanthoangelol, 4-hydroxyderricin, cardamonin, 2',4'-dihydroxychalcone, and naringenin chalcone (phloretin). These chalcones have been linked with immunomodulation, antibacterial, antiviral, anti-inflammatory, antioxidant, and anticancer activities [36].

- **Anthocyanins as anticancer agents**

Anthocyanins (also named anthocyanins; Table 2) are water-soluble vacuolar pigments that may appear red, purple, or blue depending on the pH. Anthocyanins occur in all tissues of higher plants, including leaves, stems, roots, flowers, and fruits. Dietary intake of anthocyanins has been estimated at up to 200 mg/day, which is higher than other flavonoids. More than 550 different anthocyanins are discovered until now. Anthocyanins are derived from anthocyanidins by adding pendant sugars and are mostly 3-glucosides of the anthocyanidins. From various studies, it is found that some plants or their parts containing anthocyanins have anticancer property, and their analogues may be helpful in synthesizing newer effective anticancer agents in future. The number of hydroxyl groups and presence of sugar moiety is crucial for the specific modulatory actions of anthocyanins. Numerous *in vitro* and *in vivo* studies showed that anthocyanins can affect basic cell functions related to cancer development. They may inhibit the formation and growth of tumors by induction of cell cycle arrest and apoptosis, thus eliminating damaged cells or tumor cells [36].

- **Flavanones as anticancer agents**

The consumption of citrus fruits and juices has been widely investigated for its possible role in the prevention of cardiovascular disease and cancer. These beneficial effects are mainly attributed to flavanones, the typical polyphenols of citrus species. Major flavanones in plant species include hesperetin, naringenin, eriodictyol, isosakuranetin, and their respective glycosides. Hesperetin and its derivatives are characteristic flavanones of sweet orange, tangelo, lemon, and lime, while naringenin and its derivatives are those of grapefruit and sour orange. The major citrus flavanones can be effective in fighting carcinogenesis by minimizing DNA damage (protecting effect of naringenin against UV-induced damage of DNA), tumor development, and proliferation [19].

Naringenin (Table 2) is found in high concentrations in citrus fruit while low concentrations are also found in tomatoes and their products. Naringenin can be found as aglycone and/or as glycosides, such as naringin (naringenin-7-neohesperidoside) and narirutin (naringenin-7-rutinoside). Naringenin was successfully investigated for its cell antiproliferation effect on colon cancer cell line. In a comparative study, flavanones showed a significant antiproliferative activity against lung, colon, breast, prostate, and melanoma cancerous cell lines [19].

Hesperetin (Table 2) and its glycosides are also mainly present in citrus fruit. The aglycone is less dominant in nature than the glycosides. The most widely distributed glycosides of hesperetin are hesperidin (hesperetin-7-rutinoside) and neohesperidin (hesperetin-7-neohesperidoside), which are conjugates with rutinose and neohesperidose, respectively [19]. Recent study shows that hesperetin exhibits a potential anticancer activity against human cervical cancer cell lines *in vitro* through the reduction in cell viability and the induction of apoptosis. Altogether, these data sustain our contention that hesperetin has anticancer properties and merits further investigation as a potential therapeutic agent [37].

- **Flavanols as anticancer agents**

Flavan-3-ols (flavanols) possess two benzene rings (called the A- and B-rings) and a dihydropyran heterocycle (the C-ring) with a hydroxyl group on carbon 3 and have been shown to

have the ability to scavenge free radicals, reduce the rate of LDL oxidation, inhibit lipid peroxidation, modify enzymes that activate or detoxify, and participate in the modulation of the immune response in several biological systems. The hydroxylation pattern of the B-ring appears to have a critical influence on their activities, particularly in the inhibition of protein kinase, which can induce antiproliferate activities [38]. **Catechins** belong to flavan-3-ols and there are two chiral centers on the molecule on carbons 2 and 3 (they are four diastereoisomers). Two of the isomers are in *trans* configuration and are called catechin, and the other two are in *cis* configuration and are called epicatechin. The most common catechin isomer is the (+)-catechin (Table 2). The most common epicatechin isomer is (-)-epicatechin (Table 2). Catechins and epicatechins are found in cocoa (108 mg/100 g), prune juice (25 mg/100 ml) and broad bean pod (16 mg/100 g), açai oil (67 mg/kg), argan oil, barley grain, peaches, green tea, and vinegar [39-42].

The results of a recent study show that catechin present in the extract of *Ligaria cuneifolia*, a hemiparasite species that belongs to Argentine flora, can reduce proliferation and induces apoptosis of lymphoma cell line [38]. The recent data show that catechins also affect the molecular mechanisms involved in angiogenesis, regulation of cell death and multidrug resistance in cancer. Catechins present antioxidant activity by scavenging free radicals, chelating redox active transition-metal ions, inhibiting redox active transcription factors, inhibiting pro-oxidant enzymes, and inducing antioxidant enzymes [43].

Tea (*Camellia sinensis*), one of the most popular beverages in the world, is manufactured as black (78%), green (20%), or oolong tea (2%) [43]. Catechins are the major group of bioactive compounds found in green tea, meaning about 25% of the dry weight of fresh tea leaf [44], which contains characteristic polyphenolic compounds, such as epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin (EC). The chemopreventive properties of this beverage are mostly connected with EGCG that EGCG and includes induction of apoptosis, promotion of cell growth arrest, inhibition of cell proliferation and transformation, inhibition of angiogenesis, and metastasis [2]. Tea polyphenols inhibited in experimental studies the growth of lung, mammary, and stomach human cancer cell lines [45].

Also, red wine containing higher levels of catechin showed significant reducing powers, thereby confirming the antioxidant potential of red wine due to catechin content. It is obvious that drinking green tea or red wine helps in improving the general well-being in humans.

Epigallocatechin gallate (EGCG, Table 2), also known as epigallocatechin 3-gallate, is the ester of epigallocatechin and gallic acid. EGCG has been shown to inhibit the growth of different human hepatoma cell lines at concentrations of 50-100 µg/ml and increased tumor necrosis [21]. Various clinical studies have revealed that treatment by EGCG inhibits tumor incidence and multiplicity in different organ sites such as liver, stomach, skin, lung, mammary gland, and colon. Preclinical research data in recent studies show promising results, and EGCG has great potential in cancer prevention because of its safety, low cost, and bioavailability [36].

Theaflavins are antioxidant polyphenols that are formed from the condensation of flavan-3-ols in tea leaves during the enzymatic oxidation (fermentation) of black tea [46]. Theaflavin-3-

gallate, theaflavin-3'-gallate, and theaflavin-3,3'-digallate are the principle of theaflavins. Previous research studies led in mice showed beneficial inhibitory effects of topically applied black tea theaflavins (e.g., theaflavin-3,3'-digallate) providing a good promise for chemoprevention (e.g., decreased occurrence of melanoma and nonmelanomas such as squamous cell carcinoma and basal cell carcinoma) [47].

- **Flavones as anticancer agents**

Apigenin (Table 2) is a flavonoid present in various fruits, vegetables, and spices like onions, parsley, oranges, thyme, celery, and sweet red pepper. It possesses several chemopreventive properties, including induction of apoptosis, inhibition of cancer cells proliferation, and involvement in angiogenesis [2].

Luteolin (Table 2) is most often found in leaves, but it is also seen in celery, parsley, broccoli, onion, carrots, peppers, cabbages, apples, thyme, dandelion, chamomile tea, carrots, green pepper, olive oil, peppermint, rosemary, oranges, and oregano. The chemopreventive mechanism of action of luteolin includes induction of apoptosis, inhibition of proliferation of cancer cells, and suppression of angiogenesis and metastasis. Luteolin has been reported to inhibit growth of tumors in human skin, hepatoma, and ovarian cancer cells; in lung and breast cancer, luteolin has been shown to inhibit the invasion of cancer cells [2]. Among 68 plant polyphenols examined for their inhibitory ability against hepatocellular carcinoma cells, luteolin was one of the most potent [21].

Wogonin, baicalein (Table 2), and baicalin (baicalein 7-*O*-glucuronide), all naturally occurring flavonoid extracted from *Scutellaria baicalensis* Georgi (*Lamiaceae*), were reported to have potential antitumor effects in several studies. These phytochemicals are not only cytostatic but also cytotoxic to various human tumor cell lines *in vitro* and inhibit tumor growth *in vivo*. Numerous studies demonstrated that wogonin had a cytostatic effect due to the apoptotic cell death on various tumor cell lines (such as sarcoma, hepatoma cells, breast cancer, and nasopharyngeal carcinoma cells) and antimetastatic ability as well [48, 49].

- **Flavonols**

Quercetin (Table 2) is the most abundant flavonoid in foods. It is present in different fruits (apples, berries, and grapes), vegetables (onions, broccoli), as well as in tea and red wine, mostly in glycosylated forms. The daily intake of quercetin has been estimated at 30 mg. Quercetin is probably the most studied flavonoids, and antioxidant properties are known as outstanding. This flavonol was found to have antiproliferative activity in many situations, such as adenomatous polyposis [36] and breast cancer [2].

Myricetin (Table 2) is the next flavonol occurring in fruits, vegetables, or red wine exerting anticancer activity. In lung cancer, this compound has been observed to block invasion and migration of human lung adenocarcinoma cells. According to the study with human leukemia cell line, myricetin induced apoptosis in these cells [2].

Kaempferol (Table 2) is another flavonol present in tea, broccoli, grapefruit, brussels sprouts, apples, and other plants. This compound exerts antioxidant, anti-inflammatory, and anticancer effects on several types of cancer. Kaempferol has been reported to inhibit the invasion of the

human invasive breast carcinoma cell line, angiogenesis, and human ovarian cancer cells. The available data indicate that kaempferol could be a potential chemopreventive agent against various cancers such as lung, colon, prostate, liver, pancreas, and skin [2].

- **Isoflavones as anticancer agents**

Isoflavone (3-phenyl-4H-1-benzopyr-4-one) differs from flavone in location of the phenyl group. Most members of the *Fabaceae* family contain significant quantities of isoflavones. Genistein and daidzein (Table 2), the most prevalent compounds of isoflavonoid class, were found in various legumes including soybean, green bean, alfalfa sprout, mung bean sprout, cowpea, kudzu root, and red clover sprout. Due to the estrogen-like structure of isoflavones found in soybeans and the known role of estrogens in breast carcinogenesis, most soy research has focused on the hormonal activity of these compounds [50]. Some studies showed that daidzein can inhibit hepatoma cell growth and induce apoptosis [21]. Regarding genistein, the major isoflavone in soy, laboratory studies have demonstrated different mechanisms of action, including antiproliferative activity and induction of apoptosis in both animal and human cell lines. In addition, genistein possesses antioxidant activity and the ability to scavenge free radicals, protecting the body against oxidative DNA damage. The chemopreventive activity of genistein has been investigated mainly against breast and prostate cancer.

- **Influence of glycosilation in flavonoid family**

The dietary flavonoids in nature almost all exist as their O/C-glycosides, such as glucoside, galactoside, rhamnoside, arabinoside, and rutinoside. The most abundant flavonoid glycosides in plants are flavone and flavonol O-glycosides. The glycosidation are found mainly as their 3 or 7 O-glycosides, although the 5, 8, and 4' O-glycosides were also reported in some cases. Regarding the antioxidant and antitumoral properties, it was illustrated that the flavonoid aglycones showed higher anticancer potential than their glycosides in cell level; e.g., rutin did not inhibit cell proliferation of any of the cancer cell lines tested; C/O-glycosylation of apigenin significantly weakened the inhibition of cancer cells; genistein and daidzein glycosides exhibited no noticeable activity on human breast carcinoma cell. It was demonstrated that cellulase can remarkably transform baicalin and wogonoside to their aglycones (baicalein and wogonin) with enhance of antiproliferative effects [51]. Generally, glycosylation reduced the antiproliferative activity in flavonoid classes, and a C2-C3 double bond seems important for the antiproliferative activity of flavonoids, and indeed flavones are typically more potent than flavanones [19].

5.2.2. Nonflavonoids as anticancer agents

- **Stilbenoids**

Stilbenoids are hydroxylated derivatives of stilbene with a C6-C2-C6 structure. They are secondary metabolites occurring naturally in various families of plants; grapes and related products are considered the most important dietary sources of these substances. Trans-resveratrol (3,4',5-trihydroxystilbene, Table 2), a hydroxylated stilbene, is today a well-known chemopreventive substance for cardiovascular diseases, antiaging, antiviral, and several

malignant neoplasms [36]. High amounts of trans-resveratrol can be found in grapes and grape skins used for wine production, raspberries, mulberries, blueberries, cranberries, peanuts, and certain types of pine [21]. All anticancer data obtained on preclinical animal studies showed that resveratrol affects all three discrete stages of carcinogenesis (initiation, promotion, and progression) by modulating signal transduction pathways that control cell division and growth, apoptosis, inflammation, angiogenesis, and metastasis [36]. A synthetic stilbene derivative, tamoxifen, is currently used for the treatment of several types of breast cancer in women, and as a hormone treatment for male breast cancer [52].

- **Caffeic acid**

Caffeic acid (Table 2) is a hydroxycinnamic acid found in most plants, including coffee beans, nuts, berries, and grains. Several studies have investigated the antitumor potential and hepatoprotective activity of the caffeic acid derivative, which have been identified in particular in honey and propolis [21]. Data showed that caffeic acid phenethyl ester (CAPE), a component of propolis, induces cell cycle arrest and has antiproliferation effect on glioma cells *in vitro* and *in vivo*. In addition, CAPE inhibited the metastasis of glioma cells [53].

Caffeic acid 3,4-dihydroxy-phenethyl ester (CADPE), a natural polyphenol from *Sarcandra glabra*, has potent *in vitro* anticancer activity through multiple targets. This compound significantly decreased tumor growth in hepatoma and sarcoma tumor-bearing mice, and also significantly inhibited ascites development. CADPE did not show any toxicity *in vivo* and anticancer efficacies were equivalent to those of 5-fluorouracil and cyclophosphamide (drugs in cancer treatment). The tested 59 human cancer cell lines from leukemia and nine different solid tumors, including colon cancer, gastric cancer, breast cancer, CNS cancer, ovarian cancer, melanoma, lung cancer, renal cancer, and prostate cancer, are sensitive to CADPE that suppresses tumor growth and angiogenesis [54].

- **Protocatechuic acid**

Protocatechuic acid (Table 2), a dihydroxybenzoic acid widely distributed in the plant kingdom, is the major metabolite of antioxidant polyphenols found in green tea. Protocatechuic acid has antioxidant and anti-inflammatory activity and has been shown to inhibit HepG2 (human liver carcinoma cell line) cell growth and induce apoptosis [21].

- **Curcuminoids**

A curcuminoid is a linear diarylheptanoid, with molecules such as curcumin (Table 2) or derivatives of curcumin with different chemical groups that confers increase solubility and make them suitable for drug formulation. Curcumin is the principal curcuminoid of the spice turmeric, which is a member of the ginger family. It has been traditionally used for centuries for treating numerous diseases. Over the past few years, a number of studies uncovered several pharmacological properties of curcumin. It has been shown that curcumin inhibited HepG2 cell growth by inducing apoptosis [21]. Recent studies showed substantial evidence that curcumin inhibited proliferation, migration, invasion and metastasis, and induced apoptosis via modulating multiple signaling pathways in head and neck cancer [36].

- **Gallic acid**

Gallic acid (Table 2) is a hydroxybenzoic acid occurring mostly in certain red fruits, black radish, onions, and also fresh tea leaves containing up to 4.5 g/kg. Gallic acid has been shown to exhibit biological activity, including anticancer and chemopreventive potential, capacity to induce apoptosis in human leukemia. Because gallic acid exhibits anti-invasive and antimetastatic activities in various cancer cells, it might be a potential preventive and therapeutic agent against gastric cancer metastasis [2].

- **Ellagic acid**

Ellagic acid (Table 2) is a dimeric derivative of gallic acid occurring mostly in fruits and berries (such as raspberries, strawberries, blackberries, and pomegranates) and a primary constituent of ellagitannins. The data demonstrate that ellagic acid inhibits carcinogenesis, induces apoptosis in pancreatic and leukemia cancer cells, and also can delay the tumor latency and significantly reduce the estrogen-induced mammary tumors in rats. As a consequence, ellagic acid as well as gallic acid may be considered in a promising new class of cancer chemopreventive and therapeutic agents [2, 55].

- **Tannins**

Tannin (also known as tannoid) is an astringent, bitter plant polyphenolic compound that binds to and precipitates proteins and various other organic compounds, including amino acids and alkaloids. The tannin compounds are widely distributed in many species of plants, where they play a role in protection from predation, and perhaps also as pesticides, and in plant growth regulation. They showed antimutagenic activity without any obvious toxicity. Pentagalloylglucose and geraniin were among the most active tannins. Geraniin was isolated from the dry leaf of *Geranium thunbergii*. The plant is an official medicine in the Japanese Pharmacopoeia and is used for the treatment of diarrhea and for controlling intestinal function [45]. The grape (*Vitis vinifera*) skin mostly contains the highest amount of condensed tannins, alongside monomeric flavanols and flavonols, phenolic acids, and resveratrol. The grape skin extract induced prostate tumor cell line apoptosis, and the extract from pomace has a significant antiproliferative effect on human colon adenocarcinoma cells [56].

5.3. Polysaccharides

Polysaccharides are biopolymers with linear or branched side chains, composed of monosaccharides linked together through glycosidic bonds. Considering that the repeating units in the polymer backbone are often six-carbon monosaccharides, the general formula can be represented as $(C_6H_{10}O_5)_n$, where $40 \leq n \leq 3000$. Natural polysaccharides can be obtained from various organisms, such as plants, algae, microorganisms, and animals, and exist in a variety of chemical compositions, molecular weights, and structures [1]. Most polysaccharides derived from higher plants are relatively nontoxic and do not cause significant side effects; thus, plant polysaccharides are ideal candidates for therapeutics with immunomodulatory and antitumor effects and low toxicity [20]. Natural polysaccharides isolated from herbal plants have been

shown to possess bioactivities. For example, the immune-stimulatory properties of *Aloe vera* glucomannan have been confirmed and used for treatment of immune-related diseases [23].

The type of linkage between saccharide units—the glycosidic linkage—seems to be important in immunomodulatory and anticancer activities. The literature also demonstrates that most of antitumor polysaccharides contain B-1,3-glucans, β -1,6-glucans, and α -1,3-glucans [23]. Although today is investigating especially polysaccharides of bacterial, algae, and fungi origins, plants have an important as sources of bioactive polymers especially because they are nontoxic. Here are some examples in the following lines:

- The genus *Actinidia* (*Actinidiaceae*) consists of over 58 species widely distributed in the Asian continent (China, Taiwan, Korea, Japan, southeast Siberia, and south of Indochina). Some *Actinidia* species, such as *A. macrosperma*, are the important in traditional medicine being used as health foods and medical products. In temperate climate zones, roots of *Actinidia eriantha* Benth (a commonly liana plant) have been used for gastric carcinoma, nasopharyngeal carcinoma, breast carcinoma, and hepatitis in traditional Chinese medicine. The water extracts of this drug possess antitumor and immunopotentiating activities. Four polysaccharides were isolated and purified from the roots of *A. eriantha*, and the chemical composition of these polysaccharides could affect their antitumor and immunomodulatory activity [20].
- *Rhizoma arisaematis* comes from the rhizome of *Pinellia pedatisecta* Schott, which has bitter, warm, pungent, and toxic properties. It has been recorded in Chinese Pharmacopoeia as a traditional Chinese medicine, displaying sedative, stomachic, analgesic, anticoagulant, anti-inflammatory, antiemetic, and antitumor activities. The pharmacognostical study identifies the active components of *R. arisaematis* to be beta-sitosterol, total alkaloids, guanosine, gamma-aminobutyric acid, dipeptides, and recently a water soluble polysaccharide composed of rhamnose, fucose, arabinose, mannose, galactose and glucose, with molar ratios of 0.4:0.5:0.3:0.6:0.9:5.3. This polysaccharide significantly inhibits the growth of tumor in animal experiments; immunomodulation might be the mechanism of the antitumor activity [57].
- *Rhodiola rosea* L. belongs to the family Crassulaceae that grows in the Arctic and in the mountainous regions of Europe, Asia, and North America. The rhizome and roots has been widely used for a long time in Russian and Chinese folk medicine to increase human physical and mental performance, longevity, and resistance to high-altitude sickness and to treat fatigue, anemia, cancer, bacterial infection, impotence, nervous system disorders, and cardiovascular diseases. Phytochemical studies of *R. rosea* have revealed the presence of glycosides, flavonoids, essential oils, fats, waxes, sterols, organic acids, tannins, proteins, and polysaccharides. A homogeneous polysaccharide (composed of glucose, galactose, manose, and rhamnose with a relative molar ratio of 4.2:2.4:1.6:1.0) from *R. rosea* was tested for its immunomodulation and anticancer activity *in vitro* and *in vivo* experiments on sarcoma cells. The results showed that this polysaccharide could be used as a novel promising immunotherapeutic agent in cancer treatment [58].

- *Astragalus membranaceus* is commonly used in Chinese herbalism, where it is considered to be one of the 50 fundamental herbs. The plant, used especially for treatment of the kidneys and also to avoid senility, has been shown to be effective in immune enhancement and in the treatment of diabetes, viral infections, and cancers as well. The polysaccharides isolated from the radix of *A. membranaceus* are an active anticancer component. Structural analysis indicated that the polysaccharides were mainly composed of α -(1 \rightarrow 4)-glucan with α -(1 \rightarrow 6)-linked branches or α -(1 \rightarrow 3)-glucan with side-chains containing arabinose and xylose [1].
- Polysaccharides from ginseng (*Panax* genus) possess preventive and inhibitory effects against tumors by enhancing immunological functions and induction of apoptosis. A ginseng polysaccharide injection has been developed in China as a useful adjuvant for irradiation therapy and chemotherapy for cancer patients [1].
- *Solanum nigrum* is a species in the *Solanum* genus, native to Euroasia and introduced in North and South America, South Africa, and Australia. Parts of this plant can be toxic to livestock humans, and it is considered a weed. The toxicity of *Solanum* species varies widely depending on the species and the plant's growing conditions. *S. nigrum* is a widely used plant in oriental medicine where it is considered to be antitumorigenic, antioxidant, anti-inflammatory, hepatoprotective, diuretic, and antipyretic [59]. Chinese experiments confirm that the plant inhibits growth of cervical carcinoma in mice [60]. Polysaccharides isolated from *S. nigrum* L., mainly containing galactose and arabinose, have significant antitumor and immunomodulatory activities; the anticancer activity was mediated by increasing cell apoptosis, inducing cell cycle arrest and activating host immune responses [1].
- *Artemisia argyi* (Asteraceae), the Chinese mugwort, is a herbaceous perennial plant native to China, Japan, and far-eastern Siberia. It is used in herbal medicine for conditions of the liver, spleen, and kidney. In Chinese traditional herbal medicine, it is used for the treatment of cancer, microbial infections, inflammatory diseases, diarrhea, hepatitis, malaria, and circulatory disorders. In a recent study, a water-soluble polysaccharide was isolated from *A. argyi*, and its antitumor activity was evaluated *in vivo*. This new hetero-polysaccharide had clear antitumor and immunomodulatory activities [61].
- The *Angelica sinensis* commonly known as "female ginseng" is a herb from the family *Apiaceae*, grows in cool high altitude mountains in China, Japan, and Korea. The root of the plant, a well-known Chinese medicine, has been used as a tonic, hematopoietic, and anti-inflammatory agent for thousands of years. Pharmacological experiments have proved that polysaccharide is one of the major active ingredients in *A. sinensis* possessing antitumor effects on experimental tumor models *in vivo* and inhibitory effects on invasion and metastasis of tumor cells *in vitro* [62].
- Tea plant (*Camellia sinensis*) is mainly cultivated in tropical and subtropical climates, in areas with enough rainfall. The flowers of *Camellia sinensis* have been used for deodorization, skin care, cough suppressant, and expectorant in China. Recent studies have demonstrated that the extract of tea flower had various bioactivities, including antiproliferative and apoptotic effects against human breast cancer. A regular use of green tea protects the body against many cancers including those of the liver, esophagus, stomach, intestine, and lungs. Tea

polysaccharides, one of the main components of tea extracts, have been demonstrated to have immunological, antiradiation, antioxidant, anticancer, and hypoglycemic effects [63].

Although they are not derived from plants, we must remember some polysaccharides that have been demonstrated to have powerful antitumor activity: chitin, the most abundant renewable natural resource after cellulose, a homopolymer of *N*-acetyl-d-glucosamine, is active on bladder human cancer cells and colon carcinoma [64]; a water-soluble polysaccharide from *Inonotus obliquus* has immunomodulatory and antitumor activity [65]; the polysaccharides extracted from *Pleurotus eryngii* have been demonstrated to have multiple functions, such as antitumor, antioxidant, hepatoprotective activity, and enhance immunity [66]; gamma-carrageenan sulfated polysaccharides extracted from marine red alga, with different molecular weight, has antitumor and immunostimulating activities [67].

5.4. Alkaloids

Alkaloids are a group of naturally occurring chemical compounds that contain mostly basic nitrogen atoms.

- Camptothecin (Figure 4) is a naturally occurring pyridoindole (quinoline) alkaloid isolated from the seeds of Chinese plant *Camptotheca acuminata* and *Mappia foetida*. Camptothecin and some of its analogs have shown a broad spectrum of antitumor activity against many solid tumors including colorectal, breast, lung, and ovarian cancers. Derivatives of camptothecin such as 18-OH-camptothecin, 11-OH-camptothecin, and 10-OH-camptothecin have been found to possess a strong antileukemic activity [3, 68].

The primary limitations of camptothecin are its extremely low water solubility, and the hydrolysis of the active lactone ring to the inactive carboxylate, which reduces the drug efficacy and can lead to side effects. To overcome these stability and solubility problems of camptothecin, several new approaches have been investigated such as using drug delivery technologies, e.g., incorporation in liposomes, polymer micelles, microemulsions, and microspheres [69]. Specifically, camptothecin nanocrystals were prepared with a sonication-precipitation method with promising results [68].

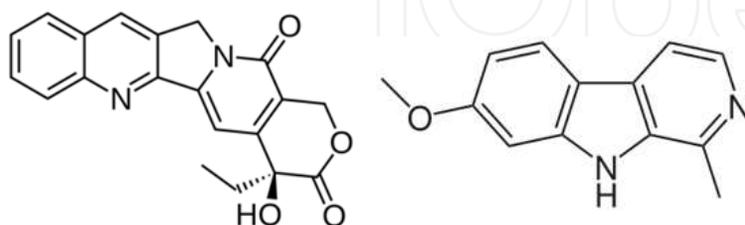


Figure 4. Camptothecin (left) and harmine (right).

- Harmine (Figure 4), the most representative naturally occurring beta-carboline alkaloid, was originally isolated from *Peganum harmala*, which is being widely used as a traditional herbal drug in the Middle East and North Africa. In Northwest China, the extracts of the seeds of

P. harmala have been used for hundreds of years to treat the gastrointestinal cancers and malaria. Harmine was reported to exhibit a diverse range of pharmacological properties such as hallucinogenic, antitumor, antiviral, and antiparasitic activities. In order to search for novel leading compounds with better antitumor activities and less neurotoxicities, a series of harmine derivatives were designed and synthesized by modification of β -carboline nucleus [70].

5.5. Peptides, proteins, and lectins

- Peptides are short chains of amino acids linked by peptide bonds. They are naturally, abundantly occurring biological molecules. Many plants are an enormously rich source of peptides with potential antitumor effect, e.g., *Violaceae*, *Rubiaceae*, and *Cucurbitaceae* families. The mechanism of anticancer peptides action consists of inhibition of tumor angiogenesis, induction of tumor apoptosis, induction of tumor necrosis, immunomodulation. Studies have shown that peptides from plants exhibit marked inhibitory effects on the proliferation of various tumor cell lines, such as murine leukemia, rat osteoblast-like sarcoma, human nasopharyngeal carcinoma, lung, liver, and mammary gland cancer and ovarian neoplasm [71].
- Studies have shown that most peptides isolated from plants are cyclic peptides, so-called cyclopeptides (which usually consist of less than 14 amino acid residues with no disulfide bond). More than 450 cyclopeptides have been discovered in higher plants. They exhibit more potent biological activities, possibly due to the stable configuration provided by their cyclic structure. Some cyclopeptides have been reported to have powerful antitumor activities, for example, cherimolacyclopeptide, a cycloheptapeptide from *Annona cherimola* seeds [72].
- Cyclotides are small disulfide rich peptides isolated from plants, consisting of 28-37 amino acid residues. They have been found in the plants of *Rubiaceae*, *Violaceae*, and *Cucurbitaceae*. Cyclotides are exceptionally stable and are resistant to denaturation by thermal, chemical, or enzymatic treatments and have a wide range of biological activities, including anti-HIV, antitumor, antimicrobial, hemolytic, neurotensin antagonism, trypsin inhibitor, uterotonic, and insecticidal activity [72].
- Lectins are members of a super family of proteins that express the capacity to bind reversibly to a specific carbohydrate. Lectins are present in many plant families and are most abundantly seen in the leguminosae family: 10-15% of the total protein content. Foods with high concentrations of lectins, such as beans, cereal grains, seeds, nuts, and potatoes, may be harmful if consumed in excess in uncooked or improperly cooked form. Adverse effects may include allergies, autoimmune diseases, or even interfere with the absorption of nutrients, thereby acting as antinutrition molecules.

However, plant lectins attracted increasing attention from cancer biologists due to their possible antitumor properties. A large-scale study in colorectal cancer patients and a control group showed some beneficial effects of consuming plant lectins, but the pathways remain unclear [73].

Astragalus membranaceus lectin displays antiproliferative properties toward human leukemia cells *in vitro*. Mistletoe lectin, which is used as an adjuvant in cancer therapy, is known to activate caspases, enzymes involved in the self destruction of cells [74].

Concanavalin A, a member of the legume lectin family with a mannose/glucose-binding specificity, was reported to induce apoptosis in human melanoma cells and demonstrated potent therapeutic effect in liver cancer [75].

Recently, some antitumoral lectins have been discovered and researched, such as mistletoe (*V. album*) lectins, rice (*Oryza sativa*) bran agglutinin with remarkable antitumour activities, wheat (*Triticum* spp.) germ agglutinin, a typical chitin-binding lectin with strong inhibitory effects on the growth of the pancreatic tumour cells, and garlic (*Allium sativum* L) lectin, isolated from garlic which induced apoptosis at a low concentration [76]. *Phaseolus vulgaris* lectin can also induce apoptotic cell death toward various types of cancers; more interestingly, induces autophagic cell death in hepatocarcinoma [77].

5.6. Quinones

Quinones are secondary metabolites generally having a hexacyclic di-ketone system derived from the oxidation of hydroquinones, and isolated principally from plants. Naturally occurring quinones are widely distributed and include benzoquinones, naphthoquinones, anthraquinones, and polyquinones. Quinones exhibit numerous biological activities, such as neurological, antibacterial, antioxidant, antitumor, and anti-HIV activities that have been proven to be related to the redox properties of their carbonyl functions. Quinones, in general, and naphthoquinones, in particular, are well known for antibacterial, antifungal, and antitumoral activities.

- Lapachol (Figure 5), the most studied substance of natural quinone class, is the main constituent in Pau D'Arco (a natural remedy) and has been extracted from the bark of South American tree, *Tabebuia impetiginosa*. Lapachol possesses strong biological activity against liver, kidney, breast, prostate, cervix cancer, and leukemia. Unfortunately the toxic effect limits the use of lapachol [78].
- Plumbagin (Figure 5) is a naphthoquinone compound that displayed antiproliferative activity on a panel of 60 cancer cell lines. However, plumbagin, identified in the Cameroonian plants *Diospyros crassiflora* and *Diospyros canaliculata*, was suggested as a promising anticancer lead drug [79].

Plumbagin has been shown to have activity against breast, prostate, ovarian, pancreatic, lung, liver, renal, cervical, and skin cancer, in addition to having activity against myeloma and leukemia. It has been shown to inhibit cell proliferation and cell invasion and effectively induces apoptosis and causes cell cycle arrest [80].

- Emodin (Figure 5), isolated from *Rheum emodi*, a Himalayan rhubarb, is also produced by many species of fungi, including *Aspergillus* fungi. The pharmacological studies have demonstrated that emodin when isolated from rhubarb exhibits anticancer effects on several human cancers, including human pancreatic cancer [81].

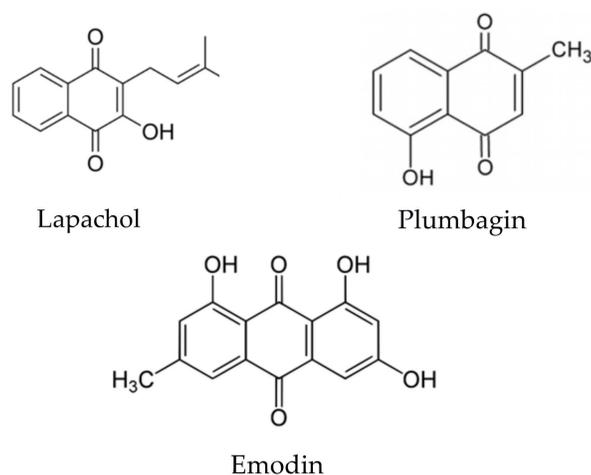


Figure 5. Chemical structures of quinones with antitumoral activity.

5.7. Isothiocyanates

Cruciferous vegetables are a rich source of glucosinolates (natural chemicals most likely contribute to plant defense against pests and diseases), which are converted to isothiocyanates. Evidence supports that consumption of cruciferous vegetables has substantial chemopreventive activity against various human malignancies, including pancreatic cancer. Benzyl isothiocyanate (Figure 6), an agent that is present in cruciferous vegetables such as watercress, cabbage, cauliflower, mustard, and horseradish, is widely consumed as part of a routine diet. Benzyl isothiocyanate is quite effective in suppressing pancreatic tumor growth by inhibiting various key signaling pathways [82].

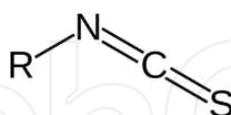


Figure 6. Benzyl isothiocyanate (R=benzyl).

6. Herbs and herbal formulas with antitumor activity

6.1. Aloe vera

Aloe vera is one of the most impressive herbs, called by many people “a miracle.” The plant works on multiple plans purifying, strengthening, and healing the body. In a single plant, aloe vera offers potent, natural medicine that nourishes the body with minerals, vitamins, enzymes,

and saccharides; alkalizes the body, helping to balance overly acidic dietary habits; prevents and treats *Candida* infections; protects the body from oxidative stress; boosts the oxygenation of your blood; reduces inflammation; purifies the blood, repairs “sludge blood”; halts the growth of cancer tumors; stops colon cancer, heals the intestines and lubricates the digestive tract [83].

Scientific research shows strong immunomodulatory and antitumor properties for aloe vera polysaccharides. Acemannan (Figure 7) is the name given to the major carbohydrate fraction obtained from the gel of the aloe vera leaf. This compound has several important therapeutic properties including acceleration of wound healing, immune stimulation, and antiviral and anticancer effects. The research results suggest that acemannan accelerates the destruction of cancer tumors, improves survival time and results in far better recovery from toxic cancer treatments [83, 84]. Acemannan is currently being used for treatment and clinical management of fibrosarcoma in dogs and cats. Administration of acemannan has been shown to increase tumor necrosis and prolonged host survival [85].

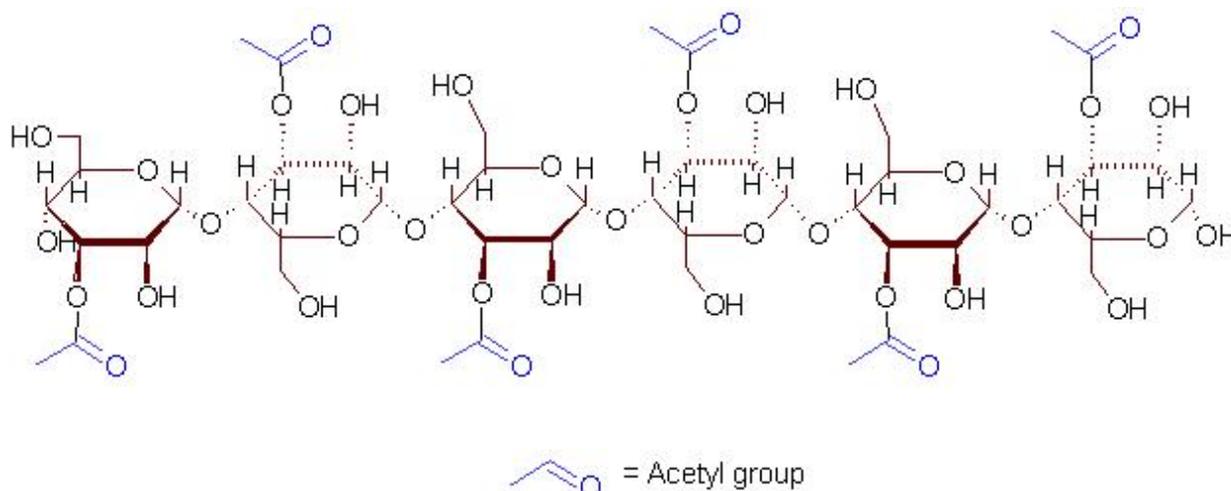


Figure 7. Acemannan structure

Also, *Aloe vera* amplifies the antioxidant effects of vitamins C and vitamin E probably due to its effect on enhancing blood quality and allowing the blood to more effectively transport oxygen and nutrients to the body's cells [83].

6.2. *Catharanthus roseus* or *Vinca rosea*

This contains vinca alkaloids, which were the first phytoconstituents ever used to treat cancer. Intense work on *C. roseus*, a folklore hypoglycemic drug, led to isolation of more than 70 dimeric indole alkaloids, which include vinblastine, vincristine, alstonine, ajmalicine, and reserpine. Vinca alkaloids execute anticancer effect by arresting division of the cancerous cells. Vinblastine is used in the treatment of Hodgkin's disease, non-Hodgkin's lymphoma, and cancers of the kidney and the testis. Vincristine is usually given in combination with other anticancer agents to treat acute lymphocytic leukemia, Wilm's tumour, neuroblastoma,

rhabdomyosarcoma, Ewing's sarcoma, lymphoma, and cancers of the breast, lung, bladder, and the cervix [15].

6.3. Garlic (*Allium sativum*)

Garlic has been used for thousands of years to treat various diseases. Garlic contains approximately 33 sulfur compounds (alliin, allicin, ajoene, allylpropyl disulfide, diallyl trisulfide, sallylcysteine, vinyldithiines, S-allylmercaptocystein, and others), several enzymes (allinase, peroxidases, myrosinase, and others), 17 amino acids (arginine and others), and minerals (selenium, germanium, tellurium, and other trace minerals). Garlic has shown significant therapeutic effect in stomach, colorectal, and breast cancer in humans. Biological effects of garlic are attributed to its characteristic organ sulfur compounds [86]. The constitutive compounds of garlic can selectively inhibit tumor proliferation by a number of factors, e.g., controlling DNA repair mechanisms, chromosomal stability, and cell cycle regulation. Garlic constituents can suppress carcinogen formation, carcinogen bioactivation, and tumor proliferation [87, 88].

6.4. Parsley (*Petroselinum crispum*)

Parsley has a variety of nutrients that protect against developing cancer. It is an excellent source of vitamin C and a good source of beta-carotene, folic acid, vitamin K, flavonoids, and volatile oil components—including myristicin, limonene, eugenol, and alpha-thujene. Parsley's volatile oils—particularly myristicin—have been shown to inhibit tumor formation in animal studies, and particularly tumor formation in the lungs. The flavonoids include apiin, apigenin, crisoeriol, and luteolin [89]. Luteolin have been shown to function as antioxidants that combine with ROS and help prevent oxygen-based damage to cells. Apigenin research studies have associated it with a decreased risk of pancreatic cancer, leukemia, cervical, and ovarian cancer. Apigenin has also been shown to interfere with cancer cell proliferation, exhibiting strong antitumor properties [90].

6.5. Chaparral (*Larrea divaricata* Cav.—Zygophyllaceae)

This contains five species of evergreen shrubs that are native to the Southwestern United States, and it is a herb derived from the common desert shrubs *Larrea tridentata* and *Larrea divaricata*. It is a plant widely used in popular medicine to treat tumors, infections, and inflammatory diseases. Many studies have shown that chaparral possesses antioxidant properties and exhibits cytotoxic properties in a variety of cell types. The principal ingredient in chaparral is nordihydroguaiaretic acid that is an anticancer agent and a potent antioxidant [91]. This herb also has anti-inflammatory, analgesic, expectorant, emetic, and diuretic properties. Chaparral chelates remove heavy metals in the body and offer protection against the harmful effects of radiation, sun exposure, and the formation of tumors and cancer cells. The lignans found in chaparral that are very similar to estrogen; they are isolated from the flowering tops of *Larrea tridentata* and are effective against human breast cancer, human colon cancer, and human melanoma cell lines [92].

6.6. Essiac

Essiac is an herbal formula that was originally known to an American tribe and was renamed Essiac in 1920 by a Canadian nurse, Rene Caisse. Essiac is a tea prepared from a mixture of herbs: burdock root (*Arctium lappa*), sheep sorrel (*Rumex acetosella*), slippery elm bark (*Ulmus rubra*), and turkey rhubarb (*Rheum officinale*), and it has been used in alternative medicine for over 50 years. The phytochemicals found in these ingredients are antioxidants protecting cells against oxidative damage manifest interference with DNA replication and have antibacterial effects. Essiac enhances activity of the immune cells and reduces toxic side effects of chemotherapy and radiotherapy. Essiac has been used in the treatment of malignant melanoma, lymphoma, and cancers of the pancreas, breast, ovary, esophagus, bladder, bile duct, and bone. Despite a lack of clinical studies reporting efficacy, 72% of the patients taking Essiac reported a positive opinion of the product [93].

6.7. Hoxsey herbal formula

Hoxsey herbal formula was discovered incidentally in by Elder Hoxsey, when one of his horses suffering from cancer on the leg, got cured after grazing certain herbs. Later, his grandson Harry Hoxsey tried these herbs on the human cancer. The cancer treatment practiced by Harry M. Hoxsey is one of the longest-lived unconventional therapies of this century. Hoxsey herbal formula contains *Arctium lappa*, *Berberis vulgaris*, *Glycyrrhiza glabra*, *Larrea tridentata*, *Picramnia antidesma*, *Rhamnus purshianus*, *Stillingia sylvatica*, *Trifolium pratense*, and *Xanthoxylum americanum*. Hoxsey herbal formula has been used to treat malignant melanoma, lymphoma and cancer of the skin [94].

6.8. Iscaddor

Iscaddor is a fermented extract of *Viscum album* (mistletoe) that was discovered by the Austrian scientist, Rudolf Steiner, and has been used in the treatment of cancer by European physicians since 1920s. Mistletoe extracts are complex multicomponent mixtures, containing various biologically active substances such as glycoproteins, in particular the mistletoe lectins, polypeptides, amino acids, and oligo- and polysaccharides. More than 20 prospective clinical trials using mistletoe extracts in patients with various malignancies have been reported, and in most of these studies, it was concluded that mistletoe extracts had therapeutic benefit in terms of response rate, overall survival, quality of life, and reduce side effects [95].

7. Conclusion

Conventional chemotherapy, radiotherapy, and surgical treatments of cancer mainly focus on mass cell killing without high specificity and often cause severe side effects and toxicities. Because of these reasons and high mortality rate associated with cancer, many cancer patients seek alternative methods of treatment and herbal medicines have a vital role to play in the prevention and treatment of cancer.

Over the past decade, there has been an increasing demand of drug development against cancer; at the same time there is considerable scientific and commercial interest in the continuing discovery of new anticancer agents from natural product sources, especially herbs. Already a great number of modern drugs in clinical use, having the ability to control cancer cells, are of natural product origins; with advanced knowledge and modern device in isolation and structure elucidation techniques and in molecular science, a more efficient research for finding new plant remedies is possible. There are an impressive number of higher plants, and it is estimated that only 10% of all plants have been examined for their chemical composition and only about 100,000 types of chemical structures have been identified. Thus, there is still a lot to be done in the search for novel natural chemopreventive compounds.

Chemically speaking, it can notice a large structural diversity in herbs: alkaloids, polyphenols, tannins, fatty acids, terpenes, polysaccharides, etc. We can say that nature has cures for serious diseases, in every place all around the globe; most of them are waiting to be discovered and used for the good of people.

Until now, the scientific researchers have investigated mainly particular herbs well known in worldwide alternative medicine ; far less have been investigated the mixtures of plants, e.g., some recognized herbs formulations (e.g., Essiac, Hoxsey, Iscador) that proved to be effective on hundreds of patients. The synergisms arising among the biologically active compounds are waiting to be demonstrated.

In scientific terms, no magic overall formula has been found so far to be applicable to all types of cancer. However, there are enough people who had a longer life or even healed with plants; therefore, medical and herbal research must continue.

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