

Traditional Botanicals that Restore Cellular Function

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Discussion

Plants naturally contain a wide array of secondary metabolic compounds produced as defense against predators and environmental stressors. Research reports that these plant constituents work through multiple pathways to modulate cellular and physiological functions. Researchers around the world are investigating botanical medicines that have been used safely and successfully for thousands of years in order to discover new compounds with potential therapeutic benefits. About about one in four current pharmaceutical drugs was discovered through researching these traditional herbs.¹

Historical Traditions

In traditional herbal medicine, a clear distinction is drawn between classes of herbs in relation to their toxicity. Many herbs are classified as suitable for daily, long-term use as foods, spices, herbal teas, or medicine. Other herbs are used only during illness for specific periods of time. Ancient herbalists worldwide identified the toxicity of certain herbs and recognized their medical benefits. They utilized these toxic herbs safely for specific conditions, in the same way that many Western medical drugs are not be suitable for daily use but are beneficial when used correctly. Only highly knowledgeable herbalists, trained in their correct use and indications, employed these more toxic herbs. They were valued for serious illnesses including cancer, which was well-known to practitioners in ancient China, India, the Americas, and other areas. These herbs include the Himalayan Yew, Madagascar Periwinkle, Camptotheca, Paw Paw, Poke Root, and Mayapple.

In the late 19th and early 20th century the Eclectic physicians and other herbalists, drawing on the knowledge of indigenous peoples, utilized many of these herbs, including Poke Root and Mayapple, to treat the cancers of their time.

In this century, researchers have been investigating the plant world to discover potential anti-tumor agents from botanicals. They found beneficial compounds that led to the development of drugs successfully used as part of Western medicine protocols. This includes the taxane family of

compounds derived at first from the Pacific Yew tree and later produced synthetically so as to preserve the Yew species.

The anticancer alkaloid camptothecin is derived from the Camptotheca tree and vincristine and vinblastine are from Periwinkle vinca alkaloids. The lignans of Mayapple and acetogenins from Paw Paw are also highly-studied and clinically-utilized. While the amount of toxic compounds in the whole plant is relatively small, even minute, researchers extract specific constituents to create new and powerful therapeutic agents.

Studies report that the antitumor influence of herbs can be attributed to their multi-faceted actions including enhancing immune function, inducing cell differentiation, inhibiting cell division and telomerase activity, and inducing apoptosis of cancer cells.² Many herbal constituents, such as phenolic and other compounds, exert antioxidative and anti-inflammatory activity. Flavonoids and other compounds are known to modulate biological processes and promote homeostasis at all physiological levels. While herbal medicine is not a replacement for modern therapeutic treatments, it offers a beneficial adjunct to help promote allostasis.²

While scientists research single constituents, they recognize the complexity and synergy of the multiple compounds within a plant. Both Pacific Yew and Poke Root are known for their anticancer, anti-inflammatory, and immune-stimulant activity.³ The actions of Pacific Yew are attributed to its taxanes, flavonoids, and lignans. The actions of Poke Root are attributed to its unique combination of saponins, tannins, astragalins, triterpenes, lectins, alkaloids, and protein PAP-R.³

In their papers, researchers often comment that the whole concert of compounds in plants works together synergistically in way that isolated compounds cannot. Some plant components often work to balance and modulate the influence of its more toxic constituents. For example, flavonoids are being studied for their protective ability and researchers often recognize the bioactive complexity of whole plant foods and medicines.^{4,5}

Compounds of Interest

The main groups of compounds described as exerting antitumor influence include taxanes (from Yew), saponins (including terpene compounds), lignans, lectins, alkaloids, and flavonoids. These all exert an array of activity working through multiple mechanisms at the cellular level.

Terpene Compounds

Terpene compounds occur throughout the plant world and are found in Yew and in Poke root.⁶ Triterpene saponins are known to exert a multitude of biological activities. They demonstrate anti-inflammatory, vasoprotective, gastroprotective, and antimicrobial influence. They are found to exert cytotoxic, cystostatic, pro-apoptotic, and anti-invasive activity. Studies are exploring these compounds and activities in relation to dose and concentration. They also influence gene expression and are noted to be cytoprotective of normal cells.⁶⁻⁹

The Yew tree naturally contains a unique group of diterpene compounds called taxanes. This includes taxol and paclitaxel. Taxanes are found to halt cancer cell replication through cross-linking microtubules.^{3,6,10,11}

Lignans

Lignans, natural plant compounds, are found in the Yew tree, Mayapple, and other plants. They are found to exert antioxidant, anti-inflammatory, and antitumor influence. Lignans are found to induce apoptosis and suppress tumor growth.³

Lectins

Plant lectins are highly studied for potential antitumor activity. Lectins from different plants and even from the same botanical plant from different regions have slightly different specific actions.^{12,13} Lectins, proteins that specifically bind to carbohydrates, are ubiquitous in all living organisms. In plants, lectins are part of the plant's defense system; in animals, lectins usually benefit cellular interactions. They are known for diverse activity including antitumor, antibacterial, antiviral, and antifungal. They are found to exert anti-proliferative influence on cancer cells and to exert an immunomodulatory influence with the ability to induce production of anti-inflammatory cytokines.

As immune-modulators, lectins are found to influence production of certain interleukins and other factors. Lectins interface with the immune system and are widely known for their ability to induce apoptosis through a number of pathways and mechanisms. They bind with carbohydrates in the cell membrane and to cell receptors where they can cause

cytotoxicity. They influence the cell cycle through various mechanisms and are found to promote programmed cell death through several mechanisms. Plant lectins are found to influence cell adhesion and cell proliferation. They bind with ribosomes and can inhibit protein synthesis.¹²⁻¹⁵ Lectins are found in Mistletoe and in Poke Root.

Alkaloids

The alkaloids of Madagascar Periwinkle and camptothecin are of specific interest to researchers. Scientists used these alkaloids to create plant-derived, semisynthetic, and synthetic compounds that have been used for many years as anticancer agents.^{10,11} Periwinkle contains the vinca alkaloids used to develop many drugs including vinblastine and vincristine.^{10,16} Camptothecin, from *Camptotheca*, is a pyridoindole alkaloid used to develop a variety of anticancer agents.¹⁰

Vinca alkaloids are found to work directly to inhibit multiplication of cancerous cells through influencing various structures and activities of the cells involved with cell reproduction.^{10,17} Camptothecin alkaloids induce cell death through targeting the enzyme DNA topoisomerase, which catalyzes changes in DNA topology.¹⁸ Other actions include selective inhibition of angiogenesis, induction of apoptosis, and modulation of immune and inflammatory responses that influence the formation, growth, and spread of tumors.^{2,10}

Flavonoids

Botanicals are especially rich in polyphenols, a vast family of naturally-occurring biochemical compounds produced by plants as part of their defense system. Vegetables, fruits, whole grains, and herbs provide a complex diversity and abundance of these plant micronutrients known as polyphenols. Diets high in plant polyphenols are found to correlate with increased health and decreased incidence of chronic degenerative disease.^{19,20,21}

Research reveals that polyphenolic compounds act as antioxidants working through multiple pathways. They exert a powerful influence to normalize cell signaling and support healthy cellular function. They are known to exert anti-inflammatory and immunomodulatory influence. Many plant phenolic compounds are widely studied for their role in preventing both the occurrence and progression of tumor growth.^{19,22-24}

Flavonoids are found to be cytoprotective, protective against the development of numerous human cancer cell lines, and to help reduce tumor numbers and tumor growth.²¹ Working through multiple pathways, polyphenols are found to influence hormonal activity, inhibit cell proliferation,

induce cell cycle arrest, prevent oxidative conditions, induce antioxidative enzyme systems, modulate cell signaling, and also to modulate inflammatory and immune response.²¹

Inflammation and Disease

A vast body of research investigates the interrelationship between inflammation and disease. Scientists report that an inflammatory cellular microenvironment is conducive to tumor formation. Inflammatory processes and responses play key roles in the development and progression of tumors and also influence response to therapeutic interventions.²⁵ Inflammation and oxidative stress drives genetic and epigenetic changes that leads to dysregulation of fundamental cellular and biological processes. This includes disruptions in cell division, cell differentiation, angiogenesis, and other processes.¹⁹

Excess generation of ROS (reactive oxygen species) and other radicals at the cellular level causes lipid oxidation and reduces cellular membrane fluidity. This causes loss of enzyme and receptor activity, damages proteins in the cellular membrane, and can cause cell inactivation. As free radicals attack and damage cellular DNA, mutational changes occur which can lead to cancer.²²⁻²⁴

A great deal of research is focused on the role and efficacy of botanicals in this capacity and to support the return of dysregulated biochemical pathways to normal and thus restore health.²⁶ The actions of herbal compounds are scientifically attributed to their specific constituents. Since each botanical species is unique, each offers a unique and specific group of compounds and actions. Synergistic combinations of the herbs outlined below offer even greater influence.

Traditional Botanicals that Restore Cellular Function



Pacific Yew Leaf/Bark (*Taxus brevifolia*)

Historically, the Yew tree was valued by traditional Indian medicine in both Ayurvedic and Unani traditions. They used it to treat infections, common cold, cough, fever, and pain.²⁷ Modern studies find that the Yew demonstrates antipyretic, anti-inflammatory, immunomodulatory, and antibacterial activity.²⁷ The Pacific Yew and other members of the species are widely studied for their therapeutic potential.^{11,27}

A botanist collected bark, twigs, and leaves from the Pacific Yew tree in 1962 as part of a National Cancer Institute program. Scientists discovered Yew taxanes and found them to exert cytotoxic activity.²⁸ The isolate taxol was the first of several drugs developed.²⁸ Later, scientists produced paclitaxel (Taxol) and other compounds semisynthetically.²⁹

Pacific Yew is found to contain lignans, polyphenols, tannins, saponins, anthraquinones, alkaloids, steroids, and diterpenes; all of which contribute to the natural synergy of the plants activity.²⁷ The antitumor effects of Pacific Yew are attributed to its taxanes, flavonoids, and lignans for which researchers report anticancer influence both *in vitro* and *in vivo*.³

Taxanes, unique to Yew trees, are found to inhibit cell division through several pathways.^{3,29,30} They are known to disrupt the microtubule function essential to mitosis.³ Taxanes are found to interact with regulatory proteins and oncogenes involved with the process of mitosis. They are able to induce apoptosis through several mechanisms and are found to modulate genes that regulate apoptosis and microtubule dynamics.²⁹



Madagascar Periwinkle Aerial (*Catharanthus roseus*)

The Madagascar Periwinkle (MP), also known as the Rosy Periwinkle, is native to Madagascar. It was traditionally used in folk medicine for diabetes and blood pressure.^{16,31,32} The main bioactive compounds in MP are alkaloids and tannins. First discovered in the 1950s, scientists have identified 150 alkaloids in the leaves that are found to be medicinally active compounds. Leaf extracts of Periwinkle are found to exert antihyperglycemic and cytotoxic activity.^{10,16,31-33} The vinca alkaloids vinblastine and vincristine in MP were the first plant isolates used to treat cancer.¹⁰

Vinca alkaloids are noted for their wide range of influence throughout the cells and tissues of the body. Vinca alkaloids are found to exert cytotoxic influence through multiple

pathways. They influence the cell cycle and arrest cell division of cancerous cells. They bind to tubulin, which is a microtubule protein, and cause breakdown of the microtubules. This inhibits the formation of the mitotic spindle during the metaphase of cell division.^{10,16,31,32,34} Vinca alkaloids are found to inhibit protein and nucleic acid synthesis, modulate lipid metabolism and membrane lipids, and are able to elevate oxidized glutathione and cAMP (cyclic adenosine monophosphate).³⁴

While the chemical agents vinblastine and vincristine, derived from Periwinkle, are highly toxic to both cancer cells and normal cells, the plant extract is found to be non-toxic. This is because the plant only contains minute amounts of the alkaloids which naturally occur with many other beneficial plant compounds.^{16,32}



Camptotheca Seed (*Camptotheca acuminata*)

Native to Southern China and Tibet, *Camptotheca* is known as the Happy Tree or the Tree of Life. Traditional peoples of Southern China have used *Camptotheca* for generations, making a paste from all parts of the tree mixed with rice wine.¹ It is valued for its ability to alleviate stubborn phlegm (i.e. difficult or deep-seated) conditions and other diseases. It is known for its bitter, cool nature, which works through enhancing the liver, gall bladder, and stomach systems according to Chinese medicine principles.¹

Traditional herbalists primarily use the leaves but also used the bark, seeds, and stem to help normalize cell activity.³⁵ Its antitumor components were discovered in 1957.¹ In the early 1970s many Han Chinese doctors began to use the fruit, bark, and leaves of *Camptotheca* to treat some types of cancer in hospitalized patients.¹

Camptotheca contains quinolone alkaloids, the most notable being the pyridoindole alkaloid camptothecin (CPT). While initially isolated from the wood bark, CPT is also highly concentrated in the leaves, fruit, and seeds of the plant. CPT, well-known for its anticancer activity, is found to induce cell death through inhibition of topoisomerase I, an enzyme needed for DNA replication.^{10,18,35,36} CPT also inhibits retroviruses such as HIV.³⁶

CPT is the precursor of the semisynthetic derivatives topotecan and irinotecan, and other compounds clinically used as anticancer agents.^{10,36,37} CPT derivatives are used worldwide for treatment of various cancers and many CPT analogues are in various stages of clinical development.³⁷



Mistletoe Thallus (*Viscum album*)

European Mistletoe, an evergreen parasitic plant that grows in trees, has been well-known in folk medicine for centuries. In traditional European herbal medicine it was widely used as a nervine, antispasmodic, and circulatory tonic.^{32,38} In the 16th century it was used for various ailments including blood circulation, asthma, nervous disease, and heart failure. In 1920, Rudolf Steiner began using injections of fermented Mistletoe for treatment of certain tumors. Due to the popularity of these injections, scientists began to study Mistletoe.³⁹ European Mistletoe is now widely used in Europe in various forms as adjuvant cancer therapy.⁴⁰

Mistletoe is found to exert cytotoxic activity and to increase natural killer cells. The polysaccharides in Mistletoe are found to stimulate nonspecific immune function.⁴¹⁻⁴³ Mistletoe lectins are some of the most researched lectins in studies and in clinical trials.¹² These studies show that Mistletoe lectins influence immune response and DNA stability. They demonstrate cytotoxic and antiangiogenic activity.¹²

Mistletoe lectins are especially known for their antitumor activity, protective ability against cancer, and their potent ability to induce apoptosis.⁴⁰ Both *in vivo* and *in vitro* research reports that Mistletoe lectins demonstrate antitumor influence and exert widespread influence on various cancer cells.¹⁴ Mistletoe lectins are found to induce apoptosis in some cancer cell lines *in vitro* and show antitumor activity in animal studies. Mistletoe is found to inhibit cell growth and induce apoptosis through modulation of various pathways.⁴⁴

Mistletoe contains multiple immune-stimulating and immunomodulatory compounds including lectins, viscotoxins, low-molecular weight proteins, oligosaccharides, polysaccharides, flavonoids, and triterpenes. All these constituents contribute to the plant's cytotoxic actions. The glycoprotein lectins mediate cellular regulation and exert immunomodulatory influence.^{39,45} Lectins are found to activate monocytes, macrophages, NK cells, T-cells, cytokines and other immune factors both *in vitro* and *in vivo* studies.⁴⁰



Paw Paw Seed/Bark (*Asimina triloba*)

Paw Paw is a small tree native to Northeast America. The nutritious edible fruits are sometimes called Indiana Bananas and have been used as food for centuries. Over 200 acetogenins have been identified from this plant. These complex compounds are derivatives of long-chain fatty acids. Naturally-occurring acetogenins are highly studied due to their unique biochemical structure and biological activity.⁴⁶⁻⁴⁸

Acetogenins are found to be potent inhibitors of mitochondrial and cytoplasmic production of ATP (adenosine triphosphate) and other nucleotides. They act selectively to inhibit cellular energy (ATP).^{46,49} This action is thought to contribute to its cytotoxic, antitumor, antimalarial, anthelmintic, antiviral, and antimicrobial activity.^{46,47,49}

Acetogenins are found to inhibit growth in multi-drug resistant tumor cells. This is attributed to its suppressive influence on cellular energy production, especially in cancer cells which have a higher metabolic level. This suppressive influence contributes to apoptosis in these cells.⁴⁸ Purified acetogenins are found to influence cell-signaling pathways.⁴⁹



Poke Root (*Phytolacca americana*)

Poke is a common perennial weed native to south China and the eastern United States. The young shoots and leaves are eaten as a cooked vegetable and the berries can be made into jelly or pie. The seeds are highly toxic to livestock and humans. Poke root has long been used in traditional herbal medicine to treat many diseases including cancer.⁵⁰ In China, the dried roots were used to treat tumors, edema, bronchitis, and abscesses.⁵¹

Used as an alternative in traditional herbal medicine, Poke's role in treatment of cancer can be dated to the 18th century.³ Poke root is highly revered by the Eclectic Physicians who used it as a primary alternative herb for the lymphatic-glandular system. Poke root is a powerful and active lymphatic remedy, acting chiefly on the skin, mucous membranes, and lymph glands. Eclectic physicians found it beneficial to calm inflammation, calm ulceration of the mucous membranes, and to stimulate immune response.⁵²⁻⁵⁴

Poke root is found to exert antitumor, anti-inflammatory, and immune-stimulating activity. *In vitro* and *in vivo* studies show Poke root exerts antitumor activity. Poke root contains betain-type alkaloids, triterpene saponins, protein PAP-R, and a number of mitogenic-acting cysteine-rich glycoprotein lectins.^{3;52-58} The toxicity of Pokeweed is attributed to the mitogens and to the saponin glycosides.³

Triterpene compounds are known for their wide array of bioactivity, including antiviral, antitumor, anti-inflammatory, and immunodulatory influence. One of the triterpene saponins in Pokeweed, known as oleanolic acid, is studied for its antitumor influence against specific cancer cells. Oleanolic acid is also found to inhibit NF-kB activation.³

Poke mitogen is a lectin from *P. americana* found to stimulate B-cell proliferation and immunoglobulin secretion.⁵⁵ Mitogen exerts immunomodulatory influence and stimulates T- and B-cell lymphocytes. The proteinaceous mitogens include

phytolaccatoxin and phytoaccagenin.³ Another component of Poke root is protein PAP-R, which is studied for its biological activity and therapeutic potential in several areas.³



Mayapple Root (*Podophyllum peltatum*)

The Mayapple plant has a long history of use in both Himalayan and Native American medicinal traditions. Mayapple grows in the Himalayas and throughout North America.^{59,60} Both cultures used it as a purgative, emetic, cholagogue, and as a salve to clean wounds. Native Americans used Mayapple as an antidote for snakebites, as a poison, anthelmintic, local antifungal, and as a laxative.⁶¹ Native Americans and the Eclectic physicians used Mayapple for its powerful influence on the glandular and lymphatic systems. For this, it is most often used in conjunction with other alterative herbs. Traditional herbalists used Mayapple as a gentle stimulant tonic to improve appetite, benefit digestion, and help restore intestinal and hepatic secretions.^{52,59}

Mayapple is high in lignans and flavonoids.⁵⁹ Many lignans, such as podophyllotoxin, are known for their antitumor and antiviral activity. Podophyllotoxins are found to possess antitumor activity in both human and animal studies. The most well-known of these is podophyllin.^{59,60-63} Podophyllin was included in the 1820 US Pharmacopoeia as an antitumor and antiviral agent.⁵⁹ The antitumor activity of the natural podophyllin resin used in traditional herbal medicine and its antitumor activity was confirmed in the 1940s, which led to the study of podophyllotoxin and development of its semisynthetic derivatives etoposide and teniposide.^{62,63}

Podophyllotoxin exerts cytotoxic activity working through several mechanisms including its ability to block mitosis.⁵⁹⁻⁶⁴ It binds with microtubules, inhibits microtubule assembly, and causes mitotic arrest in metaphase.^{59,61} It attaches to cell proteins and directly affects the mitochondria.⁶¹ Podophyllotoxin exerts potent antiviral activity through many of these same processes that disrupt cellular activity.⁶¹



Ginger Root (*Zingiber officinale*)

This world-renowned herb has been used as cooking spice, herbal remedy, and revered medicine for centuries. It is a daily household remedy for digestive upset, sore throat, colds, and flu. Known as a valuable anti-nausea remedy, it is also a digestive carminative. Ginger is traditionally known to exert a thermogenic and diaphoretic effect. Ginger aids circulation and is used to warm the system during cold weather. Herbalists also use Ginger to enhance the effectiveness of other herbs in a formula by supporting digestion and circulating the herbs.⁶⁵ Ginger demonstrates impressive antioxidant and anti-inflammatory activity.⁶⁶⁻⁶⁸ It is found to inhibit expression of COX-2 and activation of NF-kB inflammatory pathways.^{67,68}

For more information on any of the ingredients listed here, including extensive research or individual monographs compiled by Donnie Yance, please email info@naturaedu.com.

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