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ANTI-CANCER HERBAL DRUGS: AN OVERVIEW

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ABSTRACT

"Cancer" is the term we give to a large group of diseases that vary in type and location but have one thing in common: abnormal cells growing out of control. It continues multiplying uncontrollably and the result of this accumulation of abnormal cells is a mass of cells called a "cancer"[1, 2]. The Plant Kingdom produces naturally occurring secondary metabolites which are being investigated for their anticancer activities leading to the development of new clinical drugs. Vinca Alkaloids, Texans, podo phyllotoxin, Camptothecins have been clinically used as Plant derived anticancer agents[20]. With the success of these compounds that have been developed into staple drugs for cancer treatment new technologies are emerging to develop the area further. New technologies include nanoparticles for Nano-medicines which aim to enhance anticancer activities of plant-derived drugs by controlling the release of the compound and investigating new methods for administration[1]. The purpose of this brief review is to assemble current literature on some herbal drugs and to focus on their beneficial roles and drug targets in cancer therapy and chemoprevention. The present review summarizes the literature published so far regarding herbal medicine used as anti-cancer herbal drugs[20]. This review discusses the demand for naturally-derived compounds from medicinal plants and their properties which make them targets for potential anticancer treatments.

Keywords: 20 Herbal drugs, Cancer, Cell Cycle.

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INTRODUCTION

Cancer is uncontrolled growth of abnormal cells in the body[20]. The idea that simple plants, herbs, and foods can have anti-cancer effects is sometimes a controversial subject. The National Cancer Institute (NCI) has screened approximately 35,000 plant species for potential anticancer activities[22]. For every person who believes that herbs and plants can slow or even kill cancer cells, there is another who will only believe in the merits of chemotherapy. Although there is still work to do in the area of scientific research; here compiled a list of the top 20 herbs and medicinal plants that have had scientific research applied to them and received positive outcomes in the area of fighting cancer[27]. In concept of Immunomodulators, this means that they stimulate your own immune system to fight cancer cells. Others have cytotoxic action, meaning that they do kill cancer cells, but they can also kill healthy cells and should only be used under the supervision of a doctor or herbalist. Anti-cancer is a broad word that can be broken down into three parts:

- Anti-tumor – shown to be toxic to tumors in animal studies
- Cytotoxic – shown to fight tumors in laboratory cell cultures (in vitro)
- Anti-cancer – shown to fight tumors in humans

Cancer usually takes years to develop, so prevention is preferable to any treatment. Avoid all known carcinogens such as tobacco, excessive alcohol, processed foods, and exposure to chemicals. A plant

based diet can help protect you from cancer as plants are rich in antioxidant and anti-inflammatory compounds, both of which are powerful cancer fighters.

CANCER

Cancer is basically a disease of uncontrolled cell division. Cells have many different mechanisms to restrict cell division, repair DNA damage, and prevent the development of cancer. Because of this, it's thought that cancer develops in a multi-step process, in which multiple mechanisms must fail before a critical mass is reached and cells become cancerous. These differences help them grow, divide, and form tumors. For instance, cancer cells gain the ability to migrate to other parts of the body, a process called metastasis, and to promote growth of new blood vessels, a process called angiogenesis (which gives tumor cells a source of oxygen and nutrients). Cancer cells also fail to undergo programmed cell death, or apoptosis, under conditions when normal cells would (e.g., due to DNA damage)[1, 16,17,26,27, 36].

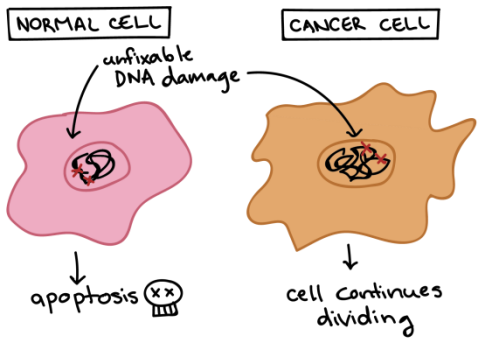

Figure 1: Diagram showing different responses of normal and cancer cells to conditions that would typically trigger apoptosis[16].

In addition, emerging research shows that cancer cells may undergo metabolic changes that support increased cell growth and division start superscript and end superscript. Figure 1 showing different responses of normal and cancer cells to conditions that would typically trigger apoptosis[16].

- A normal cell with unfixable DNA damaged will undergo apoptosis
- A cancer cell with unfixable DNA damage will not undergo apoptosis and will instead continue dividing[16].

Development of Cancer:

Cells have many different mechanisms to restrict cell division, repair DNA damage, and prevent the development of cancer. Because cancer develops in a multi-step process, in which multiple mechanisms must fail before a critical mass is reached and cells become cancerous. Specifically, most cancers arise as cells acquire a series of mutations (changes in DNA) that make them divide more quickly, escape internal and external controls on division, and avoid programmed cell death. Figure 2 showing mutations leading to cancer. An initial mutation inactivates a negative cell cycle regulator. A new mutation takes place, making a positive cell cycle regulator overly active. In one of the descendants of this second cell, a third mutation takes place, inactivating a genome stability factor. Once the genome stability factor is inactivated, additional mutations accumulate rapidly in the cell's descendants (because mutations are no longer prevented or repaired as efficiently) [16]. Once a critical mass of mutations affecting relevant processes is reached, the cell bearing the mutations acquires cancerous characteristics (uncontrolled division, evasion of apoptosis, capacity for metastasis, etc.) and is said to be a cancer cell. Cancer is one of the principal causes of mortality and morbidity around the globe and the number of cases are constantly increasing estimated to be 21 million by 2030 [23, 24]. It is estimated that in 2017, the United States alone will have approximately 1 688 780 new cancer diagnoses cases and 600 920 cancer deaths [25, 26].

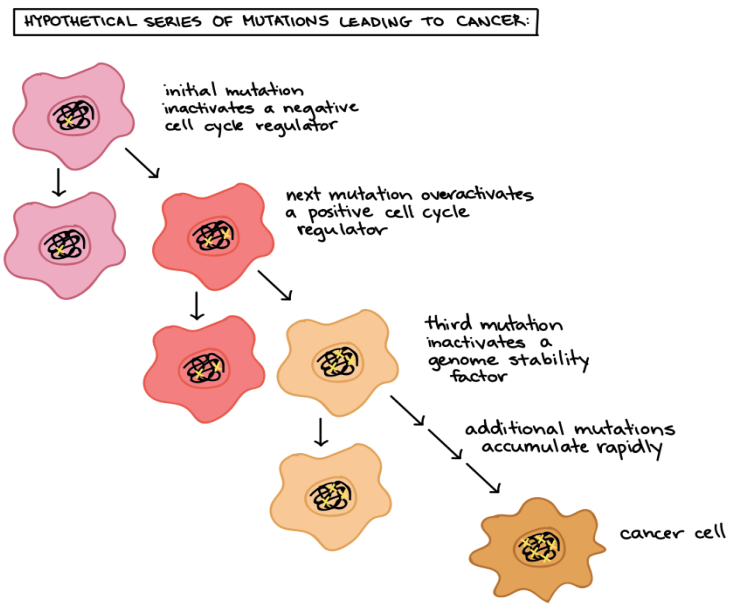

Figure 2: Mutation leading to cancer[16]

CELL CYCLE OF CANCER

Specifically, most cancers arise as cells acquire a series of mutations (changes in DNA) that make them divide more quickly, escape internal and external controls on division, and avoid programmed cell death, start superscript, end superscript. These include both external cues (like molecular signals) and internal cues (like DNA damage) (such as G_11start subscript, 1, end subscript) triggers the onset of the next phase (such as S). Core cell cycle regulators: proteins called cyclins, enzymes called cyclin-dependent kinases (Cdks) [35], Maturation-promoting factor (MPF), and an enzyme complex called the anaphase-promoting complex/ cyclosome (APC/C) [29].

1) Cyclins: Each cyclin is associated with a particular phase, transition, or set of phases in the cell cycle and helps drive the events of that phase or period. For instance, M cyclin promotes the events of M phase, such as nuclear envelope breakdown and chromosome condensation [f]igure 3 showing Cyclin Expression Cycle.

2) Cyclin-dependent kinases: In order to cell cycle forward, a cyclin must activate or inactivate many target proteins inside of the cell. Cyclins drive the events of the cell cycle by partnering with a family of enzymes called the cyclin-dependent kinases (Cdks)[34]. A lone Cdk is inactive, but the binding of a cyclin activates it, making it a functional enzyme and allowing it to modify target proteins. Its works as Cdks are kinases, enzymes that phosphorylate (attach phosphate groups to) specific target proteins. The attached phosphate group acts like a switch, making the target protein more or less active[28]. When a cyclin attaches to a Cdk, it has two important effects: it activates the Cdk as a kinase, but it also directs the Cdk to a specific set of target proteins, ones appropriate to the cell cycle period controlled by the cyclin. For instance, S cyclins send Cdks to S phase targets (e.g., promoting DNA replication), while M cyclins send Cdks to M phase targets (e.g., making the nuclear membrane break down). Figure 4 showing functioning of cyclin-dependent kinases (Cdks) [34,39,40]

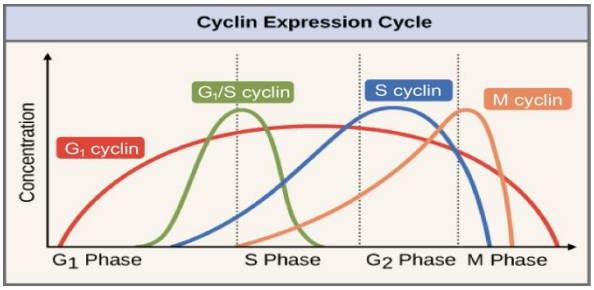

Figure 3: Cyclin Expression Cycle[16]

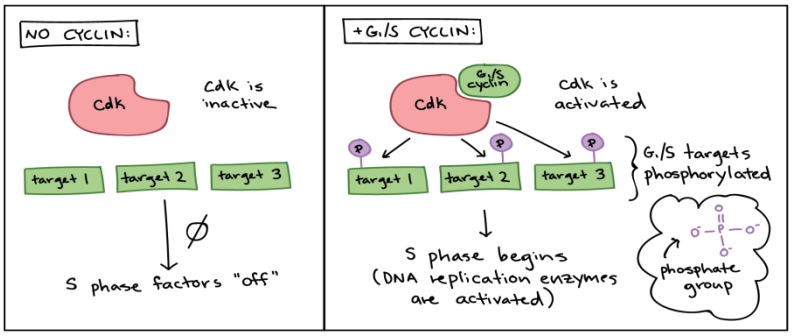

Figure 4: functioning of cyclin-dependent kinases (Cdks)[16]

3) Maturation-promoting factor (MPF): Cyclins and Cdks work together to control cell cycle transitions is that of maturation-promoting factor (MPF) [38]. The MPF complexes add phosphate tags to several different proteins in the nuclear envelope, resulting in its breakdown (a key event of early M phase), and also activate targets that promote chromosome condensation and other M phase events. The role of MPF in nuclear envelope breakdown is shown in simplified form in the diagram below[16].

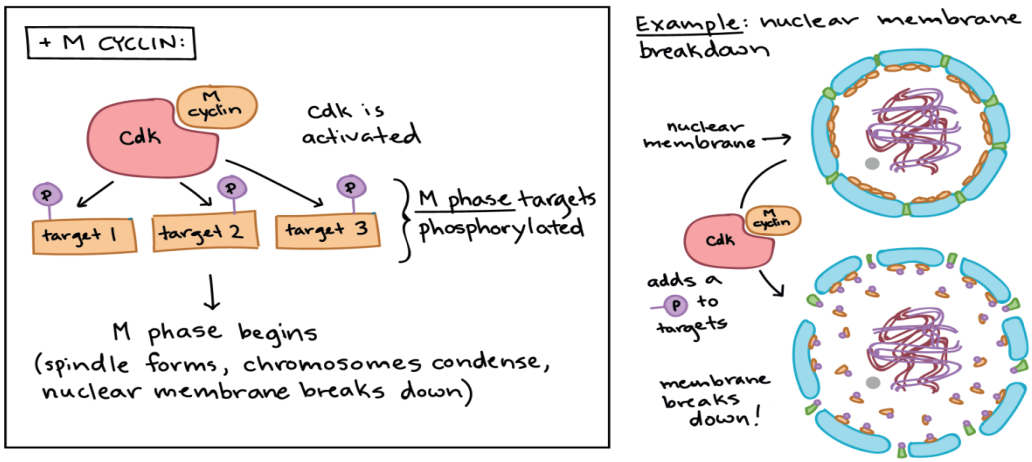

Figure 5: combining of Cdk and M cyclin[16].

Figure 5 showing how Cdk and M cyclin combine to form MPF:

Left panel: The MPF complex phosphorylates various targets specific to M phase, and the phosphorylated targets cause spindle formation, chromosome condensation, nuclear membrane breakdown, and other events of early M phase.

Right panel: Specific example of MPF triggering nuclear envelope breakdown. The MPF complex phosphorylates proteins in the nuclear envelope, resulting in the fragmentation of the nuclear membrane into vesicles (and release of some of the proteins from the membrane) [16].

4) The anaphase-promoting complex/cyclosome (APC/C): In addition to driving the events of M phase, MPF also triggers its own destruction by activating the anaphase-promoting complex/cyclosome(APC/C), a protein complex that causes M cyclins to be destroyed starting in anaphase. Function of APC/C is phosphate group to its targets, it adds a small protein tag called ubiquitin (Ub). When a target is tagged with ubiquitin, it is sent to the proteasome, which can be thought of as the recycle bin of the cell, and destroyed[18].

- The APC/C first adds a ubiquitin tag to a protein called securin, sending it for recycling. Securin normally binds to, and inactivates, a protein called separase.
- When securin is sent for recycling, separase becomes active and can do its job. Separase chops up the cohesin that holds sister chromatids together, allowing them to separate[16].

5) Checkpoints and regulators: Cdks, cyclins, and the APC/C are direct regulators of cell cycle transitions. Positive cues, like growth factors, typically increase activity of Cdks and cyclins, while negative ones, like DNA damage, typically decrease or block activity. If DNA damage is not fixable, p53 will play its third and final role: triggering programmed cell death so damaged DNA is not passed on[34,35,45].

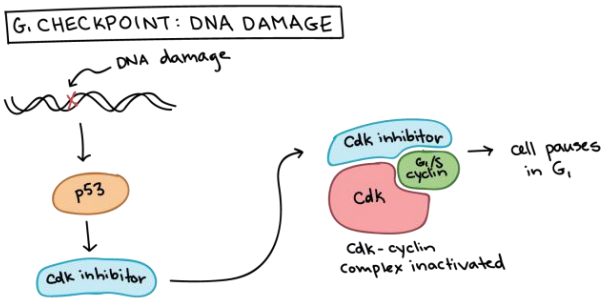

Figure 6: DNA Damage[16]

p53 is activated by DNA damage and causes production of a Cdk inhibitor, which binds to the Cdk-G1/S cyclin complex and inactivates it. This halts the cell in G1 and prevents it from entering S phase, allowing time for the DNA damage to be fixed. p53 prevents mutations (changes in DNA) from being passed on to daughter cells (figure 6 showing how DNA damaged). When p53 is defective or missing, mutations can accumulate quickly, potentially leading to cancer[16, 45].

Cell cycle regulators and cancer: In general, mutations of two types of cell cycle regulators may promote the development of cancer: positive regulators may be over activated (become oncogenic), while negative regulators, also called tumor suppressors, and may be inactivated[17].

ANTICANCER HERBLE DRUGS

Burdock Root Family: Asteraceae Biological Name: Arctium lappa		Grapes Family: Vitaceae Biological Name:Vitis vinifera L.	
Ginger Root Family: Zingiberaceae Biological Name: Zingiber officinale		Goldenseal Root Family: Ranunculaceae Biological Name: Hydrastis canadensis	
Aloe Vera Family: Asphodelaceae Biological Name: Aloe Vera (L.) Burm.f.		Clove Family: Myrtaceae Biological Name: Eugenia aromaticum	

Licorice Sticks Family: Fabaceae Biological Name: Glycyrrhiza glabra		Turmeric Root Family: Zingiberaceae Biological Name: Curcuma longa	
Red Clover Family: Fabaceae Biological Name: Trifolium pratense		Bloodroot Flower Family: Papaveraceae Biological Name: Sanguinaria canadensis	
Artemisia Annua Family: Asteraceae Biological Name: Artemisia annua		Barberry Family: Berberidaceae Biological Name: Berberis vulgaris	
Tea Family: Theaceae Biological Name: Camellia sinensis		Onions Family: Amaryllidaceae Biological Name: Allium cepa	
Dandelion-Flower Family: Asteraceae Biological Name: Taraxacum officinale		Foxglove-Flower Family: Plantaginaceae Biological Name: Digitalis purpurea (Common foxglove)	
Graviola Family: Annonaceae Biological Name:Annona muricata		Milk-Thistle-Flower Family: Asteraceae Biological Name: silybum eburneum	
Mistletoe Leaves Family: Santalaceae Biological Name: viscum album		Dried- Saffron Family: Iridaceae Biological Name: saffron crocus	

PHYTOCHEMICAL SCREENING AND THEIR MECHANISM OF ACTION

1) Burdock Root:

Burdock root is native to northern Asia and Europe. The applicable parts of burdock are the root, seed, and leaf. Extracts of burdock root appear to have antitussive activity, antibacterial, anticandidal effects and may increase immunological activity, anti-inflammatory and free radical scavenging activity, protect the liver from toxicity caused by ethanol and carbon tetrachloride, possibly due to its antioxidant activity, blood purifier[5].

Treating gout, pneumonia, arthritis, venereal diseases, kidney problems, skin conditions, and respiratory issues with this root[5]. Burdock seeds contain arctiin, which may have a protective effect against cancer. Preliminary research suggests arctiin converted into estrogenic and antiestrogenic compounds by intestinal bacteria[8]. Burdock leaf may have Lappaol F was shown to induce G(1) and G(2) cell-cycle arrest, induce cell death in several cancer cell lines, and to activate caspases. In other studies, arctigenin inhibited the proliferation, and induced caspase-3-dependent apoptosis of ovarian cancer cells via suppression of inducible nitric oxide synthase (iNOS)/nitric oxide (NO)/signal transducer and activator of transcription-3 (STAT3)/survivin signalling pathway[13]. Recent research shows that burdock root is very effective at removing the cancer causing toxins that accumulate in our digestive systems when certain foods are not properly digested[15]. There are several anti-cancer herbal compounds that have used burdock root as a base including "Flor-Essence," and "Essiac." In fact, one anti-cancer formula sold and marketed in 1919, called "Hoxsey," was burdock root. Specially treating Breast cancer[14]. Some herbalists state that burdock root can stop cancer cells from metastasizing. It is often used in India and Russia for the treatment of cancer. Burdock can be used safely, except for those who are on potassium lowering diuretic therapy, as it contains fairly high quantities of potassium[8-15].

2. Grape Seed:

Grape seed proanthocyanidins inhibit colon cancer-induced angiogenesis through suppressing the expression of growth factors such as vascular endothelial growth factor (VEGF) and angiopoietin-1 (Ang-1). Grape seed proanthocyanidins (GSPs) are widely consumed dietary supplements that have antitumor activity. The mechanisms of their action were related to inhibiting the expression of both VEGF and Ang1 through scavenging reactive oxygen species[6]. Previous studies have demonstrated that the chemopreventive effects of GSPs on colon cancer are associated with their growth inhibitory and apoptosis-inducing effects. Results demonstrate another mechanism by which GSPs inhibit colon tumor growth, which will be helpful for developing GSPs as a pharmacologically safe angiopreventive agent against colorectal cancer. The phytochemicals in grape seeds have anti-tumor or strong potential cancer preventative abilities that can be isolated from the seeds themselves[5]. Proanthocyanidins are especially worth noting, as these have been found to stop pancreatic cancer cells from spreading or migrating. One research team at the University of Colorado showed evidence that grape seed extract was effective against colorectal cancer. Extract from grape seed extract induced the death of these types of cancer cells. The more advanced the cancer cells were, the better the grape seed extracts seemed to work at limiting the growth and survival of cancer cells. Grape seed extract was not only causing the death of cancer cells, but it did not harm healthy cells. The proanthocyanidins in grape seed extract have also been reported to inhibit the creation of new blood vessels and to arrest the growth of colon tumors. Proanthocyanidins accumulate in large amounts in the colon because they are not well absorbed in the stomach. This is good news, as the proanthocyanidins can stop cancer cells more efficiently as they build up in the colon[51].

3. Ginger Root:

Gingerol, the active ingredient in ginger root, has gotten a great deal of attention, especially in clinical trials, in an attempt to determine its potential to stop or prevent certain cancers. Results from these pharmacological experiments show that ginger might inhibit the growth of tumors in human beings. In cases of ovarian cancer, researchers found that gingerol caused cancer cell death, reduced inflammation, and improved immune function[5]. Research also shows that gingerol might offer protection from colon cancer as well. In many Asian countries, especially in India, ginger root is a part of their everyday diet. India has some of the lowest cancer rates of any country in the world. Ginger is a natural anti-viral, anti-fungal, anti-parasitic, antioxidant, and antibacterial. Ginger is best consumed from the fresh, organic root. Use it in tea or grate some into vegetable dishes. If the flavor of ginger is not to your liking, almost all health foods stores sell ginger supplements. The mechanism involved in the chemopreventive effects of ginger are contribute by free radical scavenging, antioxidant pathways, alteration of gene expressions and induction of apoptosis and thus cause decrease in tumor initiation, promotion and progression[7].

4. Goldenseal:

Goldenseal is native to North America and has been used for hundreds of years by the Native American people to treat numerous infections, including infections of the mouth, throat, or gums. Goldenseal is a key ingredient in many mouthwashes and toothpastes due to its antibacterial compounds which prevent tooth decay and kill bacteria[5]. The powerful compound in goldenseal, berberine, has antibiotic compounds. This herb is currently undergoing scientific tests to see it lowers the risk of developing certain types of cancer. Care should be taken with goldenseal and it is best used under the supervision of a doctor or herbalist as high doses can become toxic[30]. Goldenseal has been shown to have antimicrobial effectiveness against intestinal protozoa such as Entamoeba histolytica, Trichomonas, and Giardia lamblia in addition to Salmonella, Shigella, Klebsiella, Escherichia, Proteus, Staphylococcus, Leishmania, and Vibrio[30, 31]. Since Goldenseal was able to decrease P-gp protein (paraglycoprotein) function in colon cancer cell lines, if the same effect translates to in vivo clinical colon cancers leading to a decrease in P-gp function, this could lead to an increase in the availability of orally administered drugs with the added benefit of goldenseal conferring anti-intestinal pathogen effects as well[32].

5. Aloe Vera:

Aloe vera as being therapeutic for burns or skin irritations, but there have been very promising treatments using aloe vera for the treatment of certain types of cancer. Aloe vera contains a compound called 1.8 dihydroxy-3 (hydroxymethyl) – anthraquinone

which has been proven to cause cell death amount human bladder cancer cells. It has impressive anticancer effects. It stops cell viability as well as stopping the G2/M of the cell lifecycle[5]. In conclusion, the present study demonstrated that the herbal extracts of aloe vera could induce cytotoxic and genotoxic activites on human hepatocellular carcinoma (HepG2) cells through induction of apoptotic pathway.[31] aloe vera with a longstanding history of safe use, has anti-neoplastic and anti-proliferative effects on multiple cancer types and cell lines. Aloe-emodin has great potential to serve as an adjunct to conventional chemotherapeutic regimens, as these data demonstrate potential for synergy with selected chemotherapeutic agents, allowing for a reduction in drug dose[33].

6. Turmeric:

Turmeric is native to India and Southeast Asia. Turmeric has been used for inflammation, allergies, rheumatism, and liver problems. The active compound in turmeric, curcumin, causes cancer cell death without harming healthy cells. It does this through the suppression of an activation pathway, kappaB, which is linked to numerous diseases caused by inflammation, including cancer. Some studies done recently show that curcumin has anti-cancer potential. When given to laboratory rats orally, turmeric was effective in preventing cancer of the stomach, lung, colon, breast, and skin. Rodents in an in vivo study done in 2001 showed that when turmeric was given as a dietary supplement throughout their life cycle, it showed a significant reduction in cancerous cell activity when compared to the control group. Curcumin was determined to be a gene regulator when it comes to the formation of cancer. In clinical trial, it was found to stop the migration of lung cancer cells. More recently, turmeric has been studied for the possible treatment of breast cancer and myeloma[5].

7. Clove:

Clove is actually the dried flower buds from trees native to India, Pakistan, Zanzibar, and Madagascar. Clove oil from cloves has been studied for their ability to improve immune function, which means it offers cancer protection or prevention. Clove oil has antioxidant compounds that have the potential to act as an anticancer agent, according to the American Pharmaceutical Association's Practical Guide to Natural Medicines. Cloves possess antiseptic, antibacterial, antifungal, and antiviral properties, but their potential anticancer activity remains unknown[41]. Clove oil has the highest concentration of antioxidant activity of any single ingredient tested by the ORAC (Oxygen Radical Absorbance Capacity); it is a lab test that attempts to quantify the "total antioxidant capacity"). The American Cancer Society says that there is currently insufficient evidence to show that clove oil can either treat or prevent cancer; however its high antioxidant levels show that it is a powerful supplier of anthocyanins, which are known to stop the growth of tumors, as well as kill existing cancer cells[5].

8. Licorice Root:

Licorice root has been used by Ancient Chinese medicine as an anti-virus, anti-inflammatory, and anti-ulcer agent. DNA damage is often done by carcinogens, and licorice root provides protection from that type of damage. Licorice root also contain polyphenols that encourage apoptosis (automatic death) in cancer cells. Licorice regulates the production of hormones from your adrenal glands, and it reduces stress chemicals. Chronic stress often triggers the growth of cancer cells. Licorice root stops the proliferation of breast cancer cells in humans, according to a study done in South Korea. It modulates the expression of Bcl-2/Bax (B-cell lymphoma 2) apoptotic regulatory factors[5]. Licorice root dose-dependently increased the expression of the tumor suppressor genes p53 and p27 and down-regulated the expression of cell cycle-related genes. The finding suggests that licorice root can mitigate the tumorigenic effects of TCDD (2,3,7,8- tetrachlorodibenzodioxine) in breast cancer cells by suppression of AhR (aryl hydrocarbon receptar) expression and cell cycle arrest. Thus, licorice root can be used as a potential toxicity-alleviating agent against EDC (electric daisy carnival) mediated diseases[46, 42].

9. Red Clover:

An American Indian remedy, Flor Essence, is still a popular herbal tonic consumed by cancer patients. Its main ingredient is red clover (trifolium pretense). The University Of Maryland Medical Center found that red clover help to prevent certain types of cancer. These same scientists mention in their article that they believe red clover should not be consumed by women with breast cancer or women with a history of breast cancer in their family. Red clover supplements are available in most health food stores as tables, capsules or in a tincture. Dried red clover leaves are often brewed into a tea with a typical daily dose being about 4 grams of dried red clover to 30 milliliters of water. Red clover is another ingredient in Hoxsey Herbal Treatment, sold around the turn of the century as a cancer treatment[5].

10. Bloodroot:

Bloodroot is native to Canada, eastern North America, and Nova Scotia. Externally, it has been used as a home remedy for skin cancer and is possibly the most well-known anti-cancer herb around. There have been several publications showing that bloodroot has the potential to be a powerful anticancer agent. Bloodroot has been shown in several studies to have consistent anti-neoplastic activity; it can shrink tumors, and has shown itself to be useful when dealing with sarcomas. The sap is toxic if consumed in anything more than minute amounts but all parts of the plant can be used externally. It's often used in naturopathic treatments for skin cancer[5].

11. Artemisia Annua:

Artemisia annua also called sweet Annie, sweet fern, sweet wormwood or annual wormwood. This little known plant recently became wormwood had the potential to become a powerful anti-cancer herb. Artemisia annua was noted by these scientists because it

was highly effective against breast cancer cells. One compound extracted from this plant, called artemisinin, has been shown to have a positive effect against cancer cells and malaria, along with numerous viruses including hepatitis B and C, along with herpes simplex[5]. Artemisinin has been to promote cancer cell death in colon cancer, breast cancer, leukemia, and other types of cancers. It shows promise for the development of both preventative measures as well as therapeutic ones. The flavonoids present in A. annua leaves have been linked to suppression of CYP450 enzymes responsible for altering the absorption and metabolism of artemisinin in the body, but also have been linked to a beneficial immunomodulatory activity in subjects afflicted with parasitic and chronic diseases[43].

12. Barberry:

Mostly used for fevers, fatigue, and stomach upsets, barberry (berberis vulgaris) has recently been recognized as a powerful anti-cancer herb. Barberry has strong anti-inflammatory, antibiotic, and antioxidant properties. It is often used interchangeably with goldenseal, as the two plants share a similar composition. Recent studies show that barberry improves immune functions and can lower high blood pressure. According to Ayurveda tradition, barberry is an effective treatment for liver tumors. One study done in Taiwan shows that when barberry is administered in high doses to cancer patients over time, the alkaloid in barberry, berberine, killed cancer cells in tests done with humans. Barberry is another of the ingredients in the Hoxsey herbal formula for cancer treatment.

13. Tea:

One study performed by the USDA in 2006 found that tea had more than 700 different compounds, many of which were already known for their ability to fight disease. Among these compounds known to fight disease are polysaccharides, flavonoids, certain vitamins, and amino acids[17]. All varieties of tea, including green white, black, and oolong, were found to contain high levels of antioxidants, which are powerful anti-aging and anti-tumor agents[5]. Tea has high levels of vitamin C, which is known to fight cancer causing free radicals. Tea has a low glycemic index and has strong cleansing properties. Regular consumption of tea has long been associated with the prevention of diabetes and heart disease[43].

14. Onion:

Onion has a high antioxidant activity and is associated with a variety of pharmacological items including being anti-inflammatory, antibiotic, and anti-carcinogenic. One study showed greater antioxidant activity of older rats that were fed onion. There is a definite relationship between the consumption of onions and the risk of common cancers. Researchers from the Italian Mario Negri Institute for Pharmacological Research compiled data from both Italian and Swiss controlled studies and multivariate logistic regression models for onion consumption and cancer rates. The risk rates vary, but onions lowered the risk of colorectal cancer, ovarian cancer, renal cell cancer, prostate cancer, esophageal cancer, mouth cancer, and breast cancer. Onions are high in polyphenols, which prevent diseases, including cancer. Onions are also high in antioxidants, which are also known cancer fighters. These popular veggies also contain a compound called quercetin, which has been shown to decrease cancer tumor cells[5].

15. Dandelion:

There has been strong evidence lately that dandelion, that weed in your garden, can inhibit the development and growth of numerous types of cancer, including stopping their metastasizing capabilities. Dandelion leaves have long been used by Chinese medicine and Ayurvedic practitioners to treat abscesses, water retention, tumors, and cysts. A study done in 2008 provided some scientific proof that dandelion (taraxacum officinale) extracts had anti-cancer compounds. Dandelion selectively reduced the metabolic activity of aggressive colon cancer cells, irrespective of their p53 status[44, 45]. During this study, three extracts were made from mature dandelion leaves, roots, and flowers. All parts were tested for their activity on the progression of tumors. This study showed that the leaf of this common weed blocked the growth of breast cancer cells and the invasions of prostate cancer cells. Dandelion root extract stopped the invasion of breast cancer cells. The flower of this plant has high antioxidant compounds as a Canadian study showed in 2005. This study showed that dandelion extract stopped hydroxyl and superoxide radicals, which means that dandelion has the potential to be a powerful, yet novel, cancer fighter[5].

16. Foxglove:

There have been several studies done regarding foxglove and its possible anti-cancer capabilities. There are two varieties of this plant, Digitalis purpurea L and Digitalis lanata ehrh. These two have been looked at for their vitro cytotoxicity after polypeptide isolation and extraction. Both have been shown to have strong anti-tumor possibilities. A study performed in Spain in 2003 look at the cytotoxic activity from the leaves of the strain D[5]. purpurea against human cancer cells. The extracts used (C50 0.78-15ug/ml) especially the methanolic extract, had high cytotoxic action. Acteoside, which can be extracted from the leaves of this common flower, have a hepatoprotective effect from a toxin called aflatoxin B1. This makes this plant cytotoxic and a strong potential chemo-preventative possibility. It's the chemical in the foxglove flower called digoxin that is known to slow the spread of breast cancer cells, as well as prostate cancer by as much as 24 percent. Keep in mind this is an extract that has been removed professionally[5]. "foxglove", is the main source of cardenolides, which have various pharmacological properties effective against certain pathological conditions including myocardial infarction, arterial hypertension, cardiac dysfunction, angina, and hypertrophy. Togehter with a prime effect of controlling the heart rhythm, many workers demonstrated that lanatoside C and some other cardiac glycosides are effective in several cancer treatments such as prostate and breast cancers[49].

17. Graviola:

Graviola (guanabana), also known by the name of its fruit, sour sop, has received a great deal of attention lately because of its promising compounds as possibly being a natural anti-cancer agent. Graviola is an evergreen tree that is used as a remedy for coughs, bacterial and parasite infections, herpes, and arthritis. In lab experiments, guanabana selectively hunts down and kills 12 different types of cancer cells including colon, breast, prostate, pancreatic, and lung cancer[56]. However there haven't been any large scale studies in humans. These types of cells are extremely resistant to conventional therapies. By inhibiting several signaling pathways that pancreatic cancer cells use to regulate their survival and metastatic lifecycle, graviola kills these cells when they are unable to complete their normal function. Once they are inhibited in this manner, the rate at which pancreatic cancer cells spread to other organs to make new cancers becomes incredibly slow. Still another study done in Virginia at Virginia Tech, found that sour sop extracts also stopped the growth of breast cancer cells. Sour sop extract also inhibited the growth of EGFR (The EGFR gene provides instructions for making a receptor protein called the epidermal growth factor receptor). Cell mutation result in the overproduction of EGFR has been strongly connected to several cancers. It has cancer killing abilities[5].

18. Milk Thistle:

The extract of the seed coating of milk thistle has anti-cancer effects. Milk thistle has an active ingredient in their seeds contain a wide mixture of flavonolignans such as silibinin, silidianin, silicristin, and isosilibinin. The main active ingredient, silibinin has shown the strongest in vitro effects against human prostate cancer cells, human colon cancer cells, human lung cancer cells, and estrogen dependent and estrogen independent human breast cancer cells[5]. Silibinin, the active ingredient in the seeds from milk thistle plants, has efficacy from both UVB (ultraviolet-B) and UVA (ultraviolet-A) induced skin cancer and photo-aging. These studies, done in 2012 and 2013, showed the amazing ability of silibinin to selectively kill skin cells mutated by UVA but were nontoxic to healthy skin cells. It also accelerated the repair of UVB damaged noncancerous cells. Milk thistle has anti-cancer activity against numerous cancer cell types: prostate cancer, breast cancer, cervical cancer, ovarian cancer, colon cancer, lung cancer, liver cancer and skin cancer[57].

19. Mistletoe:

The extracts from mistletoe and the products that come from this extract, especially iscador, is one of the most commonly used oncological drug in Europe. It's been used as an overall treatment for cancer for years. One randomized and nonrandomized matched pair study that involved more than 10,000 cancer patients, iscador was shown to prolong the survival time of cancer patients[5]. Amazingly, this study showed that the overall survival time of the group that took iscador was as much as 40 percent longer when compared to the control group. Mistletoe extract is also known as having a better survival among cancer patients and there are numerous studies that show the positive effects of this plant on cancer patients[16].

20. Saffron:

Saffron contains a carotenoid compound called crocetin. The results of studies done, both in vivo and in vitro, show that this compound has the potential to be a strong anti-tumor agent. Saffron was found in another study to inhibit skin cancer in mice[53]. New research shows that this popular spice has a powerful chemo-preventative effect against liver cancer in tests done with animals. A number of undesired side effects sometimes occur during chemotherapy. Natural therapies, such as the use of plant-derived products in cancer treatment, may reduce adverse side effects. Currently, a few plant products are being used to treat cancer.[22]

Crocus sativus L belongs to the family of Iridaceas, the line of liliaceas and is mainly cultivated in several countries of mild and dry climate. There are established documents of *in vivo*and *in vitro* studies on the anticarcinogenic and antitumor actions of saffron and its main components [54,55] Biomedical findings have been demonstrated that saffron and its ingredients may be useful as a treatment for neurodegenerative disorders and related memory impairment, ischemic retinopathy and/or age-related macular degeneration, coronary artery disease, blood pressure abnormalities, acute and/or chronic inflammatory disease, mild to moderate depression, seizure, Perkinsonism. Furthermore, antioxidant, antimutagenic, antigenotoxic, tumoricidal and antioxidant activity of saffron and its ingredient have been found[53].

CONCLUSION

Cancer is becoming a high profile disease in developed and developing worlds. In 2007 the WHO published that in 2005, 7.6 million people died from cancer related diseases with the majority of these people living in low-income countries. In the United States cancer is the cause of 1 in 4 deaths and in 2010 it was estimated there were over 1.5 million new cases of cancer. Cancer Research UK said in 2012 14.1 million adults were diagnosed with cancer and 8.2 million people were killed by cancer globally. Therefore, the demand for a cure and the prevention of cancer is extremely high. Chemically-derived drugs have been developed and other cancer treatments pre-exist. Medicinal plants have contributed a rich health to human beings. Plant extracts and their bioactive compounds present in them which are responsible for anticancer activity have to be screened for their valuable information. This review had given some of the plants possessing anticancer activity for various types of cancer. This review can help others to explore herbs to further extent and its use in various other disease and toxicity studies along with clinical trials[21]. Mass cultivation of medicinal plant species and utilizing raw by-products in industries may also help with conservation.[50, 51, 52]

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