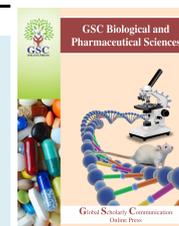


Available online at [GSC Online Press Directory](https://www.gsconlinepress.com/)

GSC Biological and Pharmaceutical Sciences

e-ISSN: 2581-3250, CODEN (USA): GBPSC2

Journal homepage: <https://www.gsconlinepress.com/journals/gscbps>

(REVIEW ARTICLE)



Herbal therapeutics for cancer control: an overview

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Publication history: Received on 17 July 2019; revised on 12 September 2019; accepted on 16 September 2019

Article DOI: <https://doi.org/10.30574/gscbps.2019.9.1.0172>

Abstract

Cancer is said to be an uncontrolled cell proliferation or metastasis of abnormal cells in the body. Modern chemotherapy, radiotherapy, and other antineoplastic regimens have limitation of multiple drug resistance (MDR) and high rate of cancer recurrence after initial chemotherapy treatments. Natural products (NPs) have been a historically rich source of biologically active compounds for the pharmaceutical industry. These natural products serve as rich sources of bioactive metabolites including alkaloids, phenol compounds, and monoterpenes. In addition to these, compounds such as vinblastine, vincristine, curcumin, Taxol, boswellic acid, and umbelliprenin and compounds such as quercetin, catechin, cucurbitacin, kaempferol, thymol, carvacrol, 1 and 1, 8-cineole, a-pinene, myrecene, and b-sitosterol have been reported for anticancer effects. These compounds have antioxidant properties, and inhibition of damage to DNA, cell cycle arrest (especially at the G2/M), induction of apoptosis, inhibition of angiogenesis in tumor cells, and its anticancer effects are well reported. Using natural products for the control and management of cancer is an assurance of a safe, cost effective and complete treatment for cancer with no significant physical side effects that crop up with other treatment options for cancer treatment.

Keywords: Cancer; Plants; Conventional therapy; Phytochemicals; Herbal therapy

1. Introduction

Cancer is considered to be one of the most dreaded diseases in the world today. It is said to be an uncontrolled cell proliferation or metastasis of abnormal cells in the body [1]. According to Kasthuri and Ramesh [2], cancer is said to be one of the major factor causing mortality in almost all parts of the world. They add up to say that more than one-third of the world's population is affected by cancer, accounting for more than 20% of all deaths.

Cancer is responsible for one in eight deaths worldwide even more than AIDS, tuberculosis, and malaria together [3]. The overall cancer incidence and mortality are higher in North America, Australia, New Zealand and Western Europe compared to the rest of the world. In the United States, one in four deaths is attributed to cancer. Globally, the number of cancer deaths is projected to increase from 7.1 million in 2002 to 11.5 million in 2030 [4]. The International Agency for Research on Cancer (IARC) in 2010 estimated that 7.6 million deaths worldwide were due to cancer with 12.7 million new cases per year being reported worldwide. A significant proportion of this burden is borne by developing countries; 63% of cancer deaths are reported to be from developing countries [5]

The era of cancer chemotherapy began in the 1940s with the first use of nitrogen mustards and antifolate drugs. Modern chemotherapy, radiotherapy, and other antineoplastic regimens have made the treatment of many solid tumors possible and have given hope to those diagnosed with cancer [1]. However, the prognosis for many cancer

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patients remains bleak due to the high rate of cancer recurrence and multiple drug resistance (MDR) seen after initial chemotherapy treatments [6]

Many researches in the plant kingdom has shown a great place in the treatment of diseases with no ill effect [7-9]. Numerous plant products are now used for the remedy of cancer. According to a WHO estimates in 2005, more than 80% of people living in developing countries depend on traditional medicine for their primary health needs [10]. Kooty *et al.*, [11] made an ascertainment on the most important problem in cancer treatment, being that destroying tumor cells in the presence of natural cells, without damaging natural cells is the main challenge of cancer treatment. This is the reason why there is a shift into the use of natural products and this review seeks to highlight the roles of natural products in controlling and managing cancer.

2. Conventional cancer treatment

The era of cancer chemotherapy began in the 1940s with the first use of nitrogen mustards and antifolate drugs. Modern chemotherapy, radiotherapy, and other antineoplastic regimens have made the treatment of many solid tumors possible and have given hope to those diagnosed with cancer [1]. However, the prognosis for many cancer patients remains bleak due to the high rate of cancer recurrence and multiple drug resistance (MDR) seen after initial chemotherapy treatments [6]. Metastatic cancers affecting multiple organ systems are particularly difficult to treat and oftentimes demand the partial or complete surgical resection of multiple tissues. Cancer stem cells (CSCs) potentially explain many of the shortcomings of established chemotherapy treatments [12].

According to the CSC model, cancer recurrence after treatment is due to the superior resistance of CSCs to cellular toxins and insults. While current treatments are capable of eradicating the bulk of the tumor mass, the lingering CSCs are able to form new, fully developed tumors from a small number of cells or even a single cell. CSCs are thought to resist treatment through several cellular mechanisms including the overexpression of drug efflux pumps, quiescence, and detoxifying enzymes [13]

Current methods for the treatment of cancer have been demonstrated to be insufficient in eliminating CSC populations from a number of cancer types. Treatments targeting a specific molecule or surface marker are likely to fail to eliminate CSCs due to the multiple survival pathways activated in CSCs in addition to the ambiguity of CSC markers across different tissue types, the presence of commonly used CSC markers in healthy tissues, and the often required combination of markers used to denote CSC populations. Treatments capable of reducing CSC populations will therefore require the development of novel, diverse, and multi-targeted approaches for cancer treatment. Due to the numerous, still poorly understood characteristics of CSCs, the discovery of CSC targeting therapies will likely be the result of opportunistic screening of new or known compounds against CSC populations [14].

3. Natural products

The term natural products (NPs) has been defined by Gurnani *et al.*, [15] as any naturally occurring substance, but, is generally taken to mean a secondary metabolite; small molecule that is not involved in the main life processes. NPs may be the key to discovering novel treatments demanded by the difficulty of treating CSCs. NPs have been a historically rich source of biologically active compounds for the pharmaceutical industry [16]. The value of NPs in medicine is a result of their ability to influence multiple signaling pathways simultaneously while producing diminished, benign side effects. The success of these compounds, especially as they relate to cancer treatment, has led researchers to investigate the effect of a number of NPs on CSCs [15]

Reddy *et al.*, [17] described a recent United States study which was said to be conducted involving about six hundred and twenty-eight (628) men under the age of sixty-five (65) years with newly diagnosed prostate cancer. The men were said to be placed on a trial of fruit and vegetables for a period of five (5) years. It was reported that while fruit was not protective, vegetables, especially cruciferous vegetables such as cabbage, broccoli, brussels sprouts, and cauliflower, reduced the risk. Tomatoes containing lycopene are protective against prostate cancer, and when a tocopherol which is a variety of vitamin E, is added to lycopene, the prostate cancer progression may be curtailed by almost 90% [6]. Other research has found that plant sterols and sterolins found in pumpkinseeds, the African potato, and some vegetables have a beneficial effect on prostate health.

The literature indicates that many natural products are available as chemo protective agents against commonly occurring cancers occurring worldwide [17]. A major group of these products are the powerful antioxidants, others are phenolic in nature, and the remainder includes reactive groups that confer protective properties. These natural

products are found in vegetables, fruits, plant extracts, and herbs. Although the mechanism of the protective effect is unclear, the fact that the consumption of fruit and vegetables lowers the incidence of carcinogenesis at a wide variety of sites is broadly supported [17].

4. Some cancer chemotherapeutic agents derived from natural products

From history, plants have been primary sources of natural product in drug discovery, and in the anticancer area, plant-derived agents, such as vinblastine (VBL) and vincristine (VCR), etoposide, paclitaxel, docetaxel, topotecan, and irinotecan, are among the most effective cancer chemotherapeutics currently available [18]. Nevertheless, many suffer from the liabilities of poor solubility in aqueous media and significant toxic side effects. Thus, there continues to be considerable research devoted to diminishing the impact of these factors, and numerous analogues and prodrugs of these agents have been synthesized, and methods devised for increasing aqueous solubility and targeting specific tumors [19].

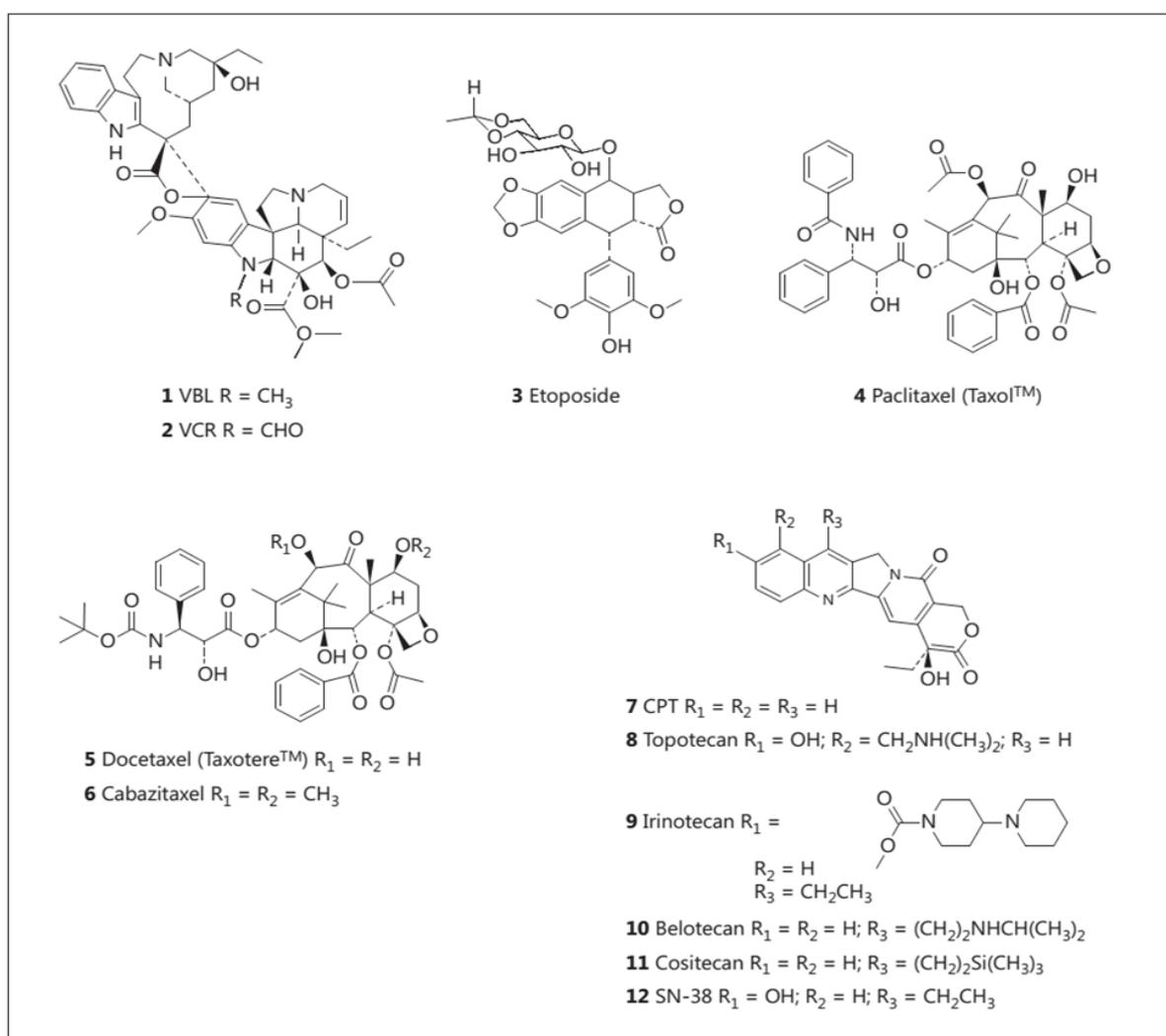


Figure 1 Vinca alkaloids, etoposide, taxanes, and CPTs as Adapted from Cragg et al. [18].

5. Vinca alkaloids

These are said to be the first plant-derived agents to advance into clinical use and were classified as VBL and VCR as shown in 1 and 2 of Fig. 1 above. Isolated from the Madagascar periwinkle, *Catharanthus roseus* G. Don. (Apocynaceae). This plant was said to be used by various cultures for the treatment of diabetes and while under investigation as a source of potential oral hypoglycemic agents, it was noted that extracts of the plant reduced white blood cell counts and caused bone marrow depression in rats, and subsequently they were found to be active against lymphocytic leukemia in mice [20]. This led to the isolation of VBL and VCR as the active agents, so their discovery

may be indirectly attributed to the observation of an unrelated medicinal use of the source plant. The mechanism by which they act is to disrupt microtubules, causing the arrest of the cells at metaphase and leading to apoptotic cell death [21].

6. Podophyllotoxins

The structure of the major active constituent, podophyllotoxin, was said to be first isolated in 1880, and was only reported in the 1950s. Podophyllotoxin inhibits the polymerization of tubulin and develop diverse derivatives of podophyllotoxin, such as, etoposide (3 Fig. 1), etopophos and teniposide, which have been developed and are currently used in clinics for treatment of a variety of malignancies and in combination with other drugs [22].

The clinical trials of several closely related podophyllotoxin-like lignans, however, were said to have failed due to lack of efficacy and unacceptable toxicity. For mechanism of action, while podophyllotoxin reversibly binds to tubulin, etoposide and teniposide inhibit topoisomerase II, inducing topoisomerase II-mediated DNA cleavage. In treatment, etoposide and teniposide are said to be used for lymphomas, bronchial and testicular cancers. The history of the development of these agents and some related analogues under clinical investigation has been reviewed [23].

7. Taxanes

Taxanes are considered one of the most important classes of cancer chemotherapeutic drugs in clinical use. Currently, the two most clinically effective drugs of this class are paclitaxel (Taxol®) (4 Fig. 1), originally isolated from the bark of the Pacific yew, *Taxus brevifolia* Nutt. (Taxaceae), and docetaxel (Taxotere), a semisynthetic analogue synthesized from DAB (10-deacetylbaaccatin III) isolated from the leaves of the European yew, *Taxus baccata*. DAB has also been semi synthetically converted to paclitaxel, thereby providing a sustainable source of the drug [24]

Regarding the mechanism of action, it has been found that paclitaxel and other taxanes promote the polymerization of tubulin heterodimers to microtubules, thereby suppressing dynamic changes in microtubules resulting in mitotic arrest. Paclitaxel is used in the treatment of breast, ovarian, and non-small cell lung cancer (NSCLC), and has also shown efficacy against Kaposi's sarcoma, while docetaxel is primarily used in the treatment of breast cancer and NSCLC. A comprehensive review of the taxanes as well as ongoing research into the development of improved analogues and methods of delivery has been published by Kingston [25].

8. *Artemisia absinthium* L

Artemisia is a plant native of Asian moderate areas, north of Africa, and vast areas of America, the size of which is 80 to 120cm. It has flowers that are yellow and clustered. Bora and Sharma, [26], reported a research on breast cancer cells MCF-7. A similar result related to the anticancer characteristics of the plant on 3 cancer cells HeLa, HT-29, and MCF7 have also been reported. In a study about the mechanism of Artemisinin effect of this plant on breast cancer cells, it was determined that plethoric reaction in cancer cells involves inhibiting cell's growth, apoptosis, preventing angiogenesis, preventing cell migration, and decreasing responses of core receptors [27].

Quercetin, isorhamnetin, kamfrolinalol, alphapinin, limonene, and myrcene are said to be the other compounds of this plant. Quercetin has been found to inhibit the growth of many cancer cells such as MCF-7, and isorhamnetin inhibits growth of many cancer cells such as MB-435, SKMEL-5, Du-145, MCF-7, and DLD. In other research, alpha-pinene, beta-pinene, limonene, and myrcin that are available in the plant are probable factors of inhibiting the growth of human breast cancer and hepatic and melanoma [28].

9. *Allium sativum* L

Allium sativum is a garmineous and permanent plant, with a stem size of 40 cm and an underground part that is inflated and composed of 5 to 12 parts enclosed in fine and slender membranes in gray-white. Its leaf is thin and filet in dark green, and its flowers are small and pink like an umbrella at end of the stem. *Allium sativum* have been reported to be safe upon acute and sub-acute administration [29] and organosulfuric compounds has been found to reduce the risk of cancer in breast, larynx, colon, skin, womb, gullet, bladder, and lungs [30]. One of the most important *Allium sativum* compound, that is, Allicin, plays an important role in antitumor characteristics on breast and prostate cancer. This compound induces planned death of cells and has an anticancer role. When *Allium sativum* is crushed and cracked up, Allicin 1, under the effect of an enzyme, changes to Allicin 2. Allicin is a proliferation inhibitor of malignant human cells [31].

10. *Avicennia marina*

Avicennia marina is a species of mangrove plants which are halophyte plants that are resistant to sea salt. The plant is likened to a bush or shrub with a height of 1 to 10 meters and has a white shell or gray or yellowish green, with leaves that are oval or sharp. Its flowers have 4 white or yellowish orange petals. Flavonoid compounds of its leaf extract have anticancer effect on human breast cancer BT-20 cells. In another study, by separating naphthoquinone from leaf of the plant, anticancer effect of this compound on laryngeal cancer cells (kb) was shown [32]. A cytotoxic effect of the extract on breast cancer cells (row 231MDA-MB) is said to be confirmed according to Momtazi *et al.* [33].

11. *Boswellia serrate*

Boswellia serrata is a medical plant from Spindales order and Burseraceae family with names Olibanum or Frankincense. It is obtained from specie B sacara, B frereana, and B serratein Bosoolia. Hydroalcoholic extract of this plant causes death of cervical cancer cells (HeLa cell) and this effect is dependent on dosage and time [34-35] In another study, alcoholic extract of frankincense resin caused disorder in the biosynthesis of DNA and RNA and proteins inhibit the tumor growth and induce apoptosis in cancerous cells in mice. In a research on leukemic cells HL60, it was shown that frankincense reduces viability of the cells [36]. Monoterpene, diterpene, and triterpene and boswellic acid are the main ingredients of frankincense resin, which can induce apoptosis in cancerous cells. In fact, it is recorded that frankincense extract, by increasing production of reactive oxygen species and by activating caspases, leads to apoptosis and severe damage to cells [37-38].

12. Turmeric (*Curcuma longa* Linn)

Turmeric (*Curcuma longa* Linn) is a member of the Zingiberaceae family and is cultivated in tropical and subtropical regions around the world and it is originates from India, Southeast Asia and Indonesia [39]. It has traditionally been used for medical purposes for many centuries in countries such as India and China for treatment of jaundice and other liver ailments [40]. Turmeric is one of the most popular medicinal herbs, with a wide range of pharmacological activities such as antioxidant [40], anti-tumor [41] and anti-aging [42] properties. The pharmacological activity of turmeric has been attributed mainly to curcuminoids, which consists of curcumin (CUR) and two related compounds demethoxy curcumin (DMC) and bisdemethoxycurcumin [43].

Table 1 Various herbal ingredients useful for natural treatment of cancer as adapted from Korrapati *et al.*, [45].

Sr. No.	Name of herbal product	Type of cancer cured	Uses	Key ingredients
1	Astragalus	All types of cancers	Immune system booster	Astragloside, triterpeneglycosides, polysaccharides
2	Berberis	Ovarian cancer, prostate cancer	Slowactive purgative	Alkaloids
3	Bloodroot	Breast and skin cancer	Anti-neoplastic, anti-angiogenic, cytotoxic, antioxidant	Sanguinarine, alkaloids
4	Butchers broom	Breast cancer	Laxative, diuretic, anti-Inflammatory	Ruscogenins and related saponins
5	Cat's claw	Skin cancer	Phagocytosis, adaptogen, immune stimulant	Astragalus and Echinacea
6	Chapparal	Breast cancer	Anti-oxidant, anti-microbial with low toxicity	oak, chamise, Manzanita, ceanothus, red shanks
7	Curcumin	Colon cancer	Anti-oxidant, anti-microbial, anti-inflammatory	Nicotinamide, ferulic acid, hydroquinone, p-hydroxy benzoic acid, L-tartaric acid

8	Dangshen root	Cancer	Anti-oxidant, anti-inflammatory, anti-microbial, anti-bacterial	Rosmarinic acid, salvianolic acid, dihydrotanshinone, cryptotanshinone, tanshinone IIA
9	Echinacea	Brain cancer, pancreatic and colon cancer	Immune system booster, anti-viral, anti-inflammatory	Alkylamides
10	Fever few	Different types of cancers	Anti-inflammatory and kills leukemia cells	Parthenolide, eudesmanolides, germacranolides and guaianolides
11	Golden seal	Different types of cancers	Anti-bacterial, anti-microbial, anti-catarrahal, laxative, oxytotic	Berberine
12	Milk thistle	Liver cancer	Anti-hepatotoxic	Silymarin
13	Pau d'arco	Blood and lymph Cancers	Anti-bacterial, anti-yeast, anti-microbial	Lapachol
14	Red clover	Breast, skin and prostate cancer	Chemo protective	Herb of Hippocrates, Salicylic acid, sitosterol, genistein, flavonoids, phytoestrogens
15	Sheep s sorrel	Different types of cancers	Anti-inflammatory, antibacterial, diuretic, anti-oxidant	Oxalic acid, beta carotene, Na, K, Fe, Mn, P
16	Skull cap (scutellabarbata)	Lung, stomach and intestinal cancer	Anti-microbial	Hexahydrofamesylacetone, menthol, tetramethylhexadecenol, octenol
17	Sutherlandia	Drives out waste in cancer patients	Anti-inflammatory, anti-viral and anti-fungal	L-canavanine, pinitol, gaba and asparagine
18	Thorowax	Bone cancer	Anti-inflammatory, hepatoprotective, mid sedative, anti-pyretic, analgesic, antitussive and adaptogen	Fatty acids, glycosides, oleic acid, palmitic acid, quercetin, narcissi
19	Wheat grass	Breast cancer and some other cancers	Anti-bacterial and removes cancer causing agents from body	Ca, Mg, aminoacids, chlorophyll, minerals, vitamins, enzymes
20	Sweet worm wood	Breast cancer	Anti-microbial, anti-yeast, antioxidant	Sesquiterpenetrioxane lactone, artemisinin
21	Ashwagandha	Slows down growth of cancer cells	Anti-inflammatory, stimulates immune system, anti-oxidant, anti-ulcer, anti-septic	Iron, glycowithanolides, tannins, glucose, potassiumnitrate, alkaloids, fatty acids and some other substances
22	Garlic	Brain and colon cancers	Anti-oxidant, anti-microbial, anti-cancer, anti-diabetic and immune system booster	Phytonutrients, minerals, vitamin
23	Green tea	Colon, breast, prostate and colorectal cancers	Anti-oxidant, anti-bacterial and anti-diabetic	Caffeine, polyphenols like flavonoids, catechins
24	Celandine	Colon, esophagus, testes, ovary, breast, cervix, colo rectal cancers	Sedative, anti-spasmodic, antibiotic, anti-tumour agent, analgesic, diuretic, purgative	Alkaloids, berberine, chelidonic acid, ergosterol, sanguinarine

13. Conclusion

Nature provides ample sources for effective treatment of cancer. Researchers are still working to discover more ways to utilize natural products in treating cancer because plant products have proven to contain many biologically active compounds that mediate cell apoptosis. As chemotherapy has proven to be effective in the management of cancer, it

has not done so without posing risk to the patients hence, natural products which are good in treatment without posing much effects proves to be the way forward. By using the herbs and the treatment options discussed above there can be assurance of a safe, cost effective and complete treatment for cancer with no significant physical side effects that crop up with other treatment options for cancer treatment.

Compliance with ethical standards

Acknowledgments

We acknowledged the mentorship of Dr. Adeniyi A.K of Animal Biology, Federal University of Technology, Minna, Nigeria.

Disclosure of conflict of interest

No conflict of interest exists.

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How to cite this article

Kure B Taliya, Mayaki A Muhammad, Oyinloye G Yemisi, Dauda J Michael, Ayeni A Wemimo and Abdulkaddir Sayyadi. (2019). Herbal therapeutics for cancer control: An overview. *GSC Biological and Pharmaceutical Sciences*, 9(1), 15-23.
