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HERBAL-DERIVED ANTICANCER PHYTOCONSTITUENTS: TRADITION TO MOLECULAR MECHANISMS

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ABSTRACT: This article reveals a detailed review of important constitutes of herbal drugs which will be useful to treat various types of cancer. Cancer is the second leading cause of death in both developed and developing countries as the number of mortalities is increasing day-by-day and year after year. Herbal drugs have contributed for the discovery of new anticancer drugs due to conventional cancer therapies cause's serious side effects. Therefore, the fear of side effects patient prefer to use of herbal drugs or compound isolated from the medicinal plants for cancer treatment. An ideal phytochemical is one that possesses anti-tumor properties with minimal toxicity, side effects and has a defined mechanism of action. Several anticancer agents including taxol, vinblastine, vincristine, the camptothecin derivatives, topotecan, irinotecan, and etoposide derived from epipodophyllotoxin are in clinical use all over the world. A number of promising agents such as flavopiridol, roscovitine, combretastatin A-4, betulinic acid, silvestrol, apigenin, curcumin, fisetin, and crocetin are in preclinical or clinical development stage.

INTRODUCTION: Plants have been used for the treatment of various diseases for thousands of years. Phyto-chemicals have proved to be an excellent reservoir of new medical formulations. Our ancestors have used these plants for thousands of years to alleviate their ailments. For a long period of time medicinal plants or their secondary metabolites have been directly or indirectly playing an important role in human society to combat diseases.

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Extracts of plants were used for the treatment of various diseases and this forms the basis of all the Indian systems of medicine. Cancer is a general term applied to a series of malignant diseases which may affect many parts of the body. It is characterized by a rapid and uncontrolled cell proliferation leading to abnormal growth or tumor. If the abnormal growth is not arrested, it may progress to the death of the patient. It is world's second biggest killer after cardiovascular diseases.

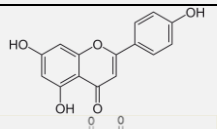
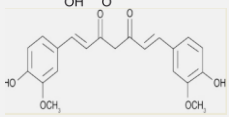
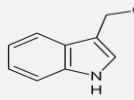
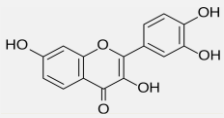
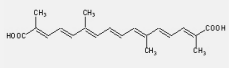
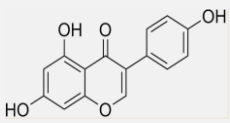
Cancer is life threatening and a dreadful disease [1]. It is the leading cause of death in economically developed countries and the second leading cause of death in developing countries [2]. Consumption of tobacco is the cause of about 22% of cancer deaths [3]. Another 10% are due to obesity, poor diet, lack of physical activity and excessive drinking of

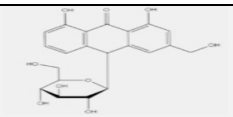
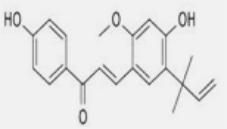
alcohol. Other factors include certain infections, exposure to ionizing radiation and environmental pollution. Natural products play a major role in cancer prevention and treatment. Plants have been the chief source of natural compounds used for medicine [4]. During long term folk practice, a large number of anticancer medicinal herbs and relevant prescriptions have been screened and used for treatment and prevention of various cancer types of cancers [5]. There are certain bioactive compounds extracted from plants that possess anticancer activity. The National Cancer Institute collected about 3500 plants samples from 20 countries and has screened around 114000 extracts for anticancer activity [6].

Initially, cancer drugs were discovered through large scale testing of synthetic chemicals and natural products against rapidly proliferating animal tumors systems. Many clinical trials are ongoing on the use of nutritional supplements and modified diets to prevent cancer [7]. Dietary plants such as fruits, vegetables, spices, cereals and edible tubers/roots- which also contain significant level of bioactive natural compounds, may provide human health benefits beyond basic nutrition to reduce risk of many chronic diseases including cancer [5, 8]. Phyto-chemicals are defined as bioactive nonessential nutrients derived from plants. It is estimated that more than 5000 individual phyto-chemicals have been identified in fruits, vegetables, grains and other plants which have mainly been classified as phenolic, carotenoids, vitamins, alkaloids, nitrogen containing compounds and organosulphur compounds.

The Garhwal Himalayas has been a center of spiritual knowledge, religiosity and biodiversity from ancient times. The region is rich in its flora and fauna due to its distinct meteorological, geographic, geological and ecological patterns. More than 8000 species of flowering plants grow in the Himalayas, with nearly 4000 species identified from the Garhwal Himalayan Region along with great diversity. Local people of Uttarakhand are partially or completely dependent on forest resources for medicines, food and fuel. Following section provide details of various phytoconstituents having anti-cancer property. The review displayed in **Table 1** describes the chemistry, occurrence and structure of certain bioactive constituents from medicinal herbs that possess anticancer activity.

TABLE 1: PHYTOCONSTITUENTS HAVING ANTICANCER ACTIVITY

Name of the compound	Chemical Formula	IUPAC Name	Molar Mass	Melting Point	Sources	Chemical Structure	Reference
Apigenin	$C_{15}H_{10}O_5$	5,7-Dihydroxy-2-94-hydrophenyl)-4H-1benzopyran-4-one	270.24 g/mol	345-350 ºC	Parsley, celery, chamomile tea.		9, 10, 11, 12, 13
Curcumin	$C_{21}H_{20}O_6$	(1E,6E)-1,7 Bis (4hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione	368.39 g/mol	183 ºC	Turmeric (*Curcumin longa*)		14, 15, 16, 17, 18, 19
Indole-3-Carbinol	C_9H_9NO	1-H-indole-3-ylmethanol	147.18 g/mol	96-99 ºC	Cabbage, radishes, cauli-flower, broccoli, Brussels sprout		20, 21, 22, 23, 24
Fisetin	$C_{15}H_{10}O_6$	3-(3, 4-dihydroxyphenyl)-3, 7-dihydroxy-chromen-4-one.	286.24 g/mol	330 ºC	Strawberries, apples, grapes		25, 26, 27, 28
Crocetin	$C_{20}H_{24}O_4$	(2E,4E,6E,8E,10E,12E,14E)-2,6,11,15-Tetramethylhexadeca- 2, 4, 6, 8, 10, 12, 14-heptaenedioic acid or 8, 8- diapo-8, 8-carotenoic acid	328.41 g/mol	- 285 ºC	Crocus flower and *Gradenia jasminoides* fruits		29, 30, 31
Genistein	$C_{15}H_{10}O_5$	5,7-Dihydroxy-3-(4-hydroxyphenyl)chromen-4-one or 4', 5, 7-Trihydroxy isoflavone	270.24 g/mol	297-298 ºC	Soy bean, kudzu, fava beans		32, 33, 34, 35, 36, 37

Aloin	$C_{21}H_{22}O_9$	10-Glucopyranosyl-1,8-dihydroxy3-(hydroxymethyl)-9(10H)-anthracenone	418 g/mol	148 ºC	Leaves of *Aleo vera*		38, 39, 40
Lico-chalcone A	$C_{21}H_{22}O_4$	(E)-3-[4-Hydroxy-2-methoxy-5-(2-methylbut-3-en-2-yl) phenyl]-1-(4-hydroxyphenyl)prop-2-en-1-one	338.40 g/mol	101-102 ºC	Liquorice root		41, 42, 43, 44, 45, 46

Phytoconstituents:

Apigenin: Apigeninis a member of the flavone subclass of flavonoids present in fruits and vegetables and is considered to have various biological activities such as being anti-inflammatory, anticancer and it also has free-radical scavenging properties [9]. Apart from having anticancer activity it may also stimulate adult neurogenesis.

Mechanism of Action: Apigenin can effectively inhibit proliferation in various breast cancer lines MDA-MB-453. [10] Several mechanisms have been proposed to explain the inhibition of cancer cell growth by apigenin; these include the arrest of the cell cycle, the induction of apoptosis and the modulation of signal transduction [11, 12]. It has been suggested that apigenin- induced apoptosis results from the depletion of ErbB2 following the dissociation of a complex containing ErbB2 and GRP94. [13]

Curcumin: Curcumin is a diarylheptanoid belonging to the group of curcuminoids, which are natural phenols responsible for turmeric's yellow color. It is a tautomeric compound existing in enolic form in organic solvents, such as a keto form in water [14]. Curcumin was first isolated in 1815 and its chemical structure was determined by Roughley and Whiting in 1973. [15] Curcumin has effect on gastrointestinal system, anemia, diabetes, hepatitis, skin diseases, inflammation, urinary diseases, cough, liver disorders, carcinogenesis, *etc*.

Mechanism of Action: Curcumin acts as a potent anticarcinogenic compound. Induction of apoptosis plays an important role in its anticarcinogenic effect. It induces apoptosis and inhibits cell-cycle progression, both of which are instrumental in preventing carcinogenic cell growth in rat aortic smooth muscle cells [16]. Curcumin induces apoptotic cell death by DNA- damage in human cancer cell lines, TK-10, MCF-7 and UACC-62 by acting as topoisomerase II poison [17].

However, curcumin affects different cell lines differently, whereas leukemia, breast, colon, hepatocellular and ovarian carcinoma cells undergo apoptosis in the presence of curcumin, lung, prostate, kidney, cervix and CNS malignancies and melanoma cells show resistance to cytotoxic effect of curcumin [18]. Curcumin also inhibits proliferation of rat thymocytes. These strongly imply that cell growth and cell death share a common pathway at some point and that curcumin affects a common step, presumably involving modulation of AP-1 transcription factor [19].

Indole- 3- Carbinol (I3C): Indole-3-Carbinol is produced by members of the family Cruceferae and particularly members of the genus *Brassica*. Glucoinolate glucobrassicin breakdowns to produce Indole-3-Carbinol [20].

Mechanism of Action: I3C has been shown to suppress the proliferation of a wide variety of cells, including breast cancer cell [21], colon cancer cells [22], prostate cancer cells [23] and endometrial cancer cells. DIM (3, 3'-Diindolymethane derived from the digestion of I3C) inhibits DNA synthesis and cell proliferation in both ER positive (MCF-7) and ER-deficient (MDA-MB-231) human breast cells [21]. Bonnesen and his colleagues, found that I3C can both stimulate apoptosis and confer protection against DNA damage in human colon cell lines [22]. The naturally occurring DIM, ascorbigen (ASG), I3C and ICZ stimulate apoptosis in human colon adenocarcinoma LS-174 and $CaCO_2$ cells. These phytochemicals may prevent colon tumorigenesis by both stimulating apoptosis and enhancing intracellular defenses against genotoxic agents.

Chinni's laboratory demonstrated G1 cell cycle arrest in prostate cancer cells by I3C, which

correlated with the upregulation of p21WAF1 and p27kip1 CDK inhibitors, followed by their association with cyclin D1 and E, and the down-regulation of CDK6 protein kinase level and activity [23]. Numerous studies have indicated that I3C also has a strong hepatoprotective activity against various carcinogens. It has incredible potential both for prevention and treatment of cancer [24].

Fisetin: Fisetin is a plant polyphenol from the flavonoid group. It can be found mainly in fruits, vegetables, nuts and wine and displays a variety of biological effects including antioxidant and anti-inflammatory [25]. It serves coloring agent in fruits and vegetables like strawberries, apple, persimmons, onion and cucumber.

Mechanism of Action: Fisetin has been shown to exhibit anticancer activities in various types of tumor cells, with the capability to induce cell cycle arrest and apoptosis [26, 27]. The cytotoxic and apoptotic effects induced by fisetin in human breast cancer MCF-7 and MDA-MB-231 cells exhibit a robust anticancer activity in caspase-3 deficient MCF-7 cells and fisetin induced apoptosis did not display typical features of apoptosis such as DNA fragmentation and PS externalization but instead triggered plasma membrane rupture, mitochondrial depolarization, activation of caspase-7, -8 and -9 and PARP cleavage in MCF-7 cells, which can be intensively blocked by caspase inhibition [28].

Genistein: Genisteinis an isoflavone that is described as an angiogenesis inhibitor. It was first isolated in 1899. Genistein occurs as a glycoside (genistin) in the plant family Leguminose which includes soybean.

Mechanism of Action: Genistein can arrest tumor growth, proliferation, cell cycle, invasion, metastasis and angiogenesis. Genistein at low concentration stimulates growth and at high concentration inhibits growth of estrogen-positive MCF-7 and estrogen-negative MDA -MB -438 breast cancer cells [29]. A number of studies suggest that genistein induced cell cycle arrest may involve up regulation of P21WAF1 and consequent down regulation of cyclin B1 [30]. Genistein can decrease the vessel density and can cause the release of vascular endothelial growth factor (VEGF) and TGF-β1. [31] Genistein as a food supplement can be given to women from pre-pubertal stage of life so that it would be beneficial in arresting tumor initiation. Genistein may avoid the risk of developing cancer in both men and women who have risk factor for gender-based cancers, such as familial expression of BRCA 1 and 2.

Crocetin: Crocetin is a natural apocarotenoid dicarboxylic acid that is found in saffron (derived from the dried stigma of the *Crocus sativa* flower). Crocetin exhibits antio-xidant [32], antihyperlipidemic, cardio protective [33] and neuroprotective effects [34]. Crocetin causes cell growth inhibition and induces cell death in several malignant cells including pancreatic cancer cells and breast cancer cells.

Mechanism of Action: Crocetin has two distinct certified anticancer functions. First one is to inhibit cell proliferation at an initial stage by inducing the cell cycle arrest indifferent human cancer cell type *via* a p53-dependent and -independent p21 mediated mechanisms. The second function is to kill the cancer cells *via* apoptosis [35]. It has been confirmed that HepG2 cells treated with the saffron extract contains crocin and safranal increased cleavage of caspase-3, as well as DNA damage and cell cycle arrest [36]. Also, crocetin decreases CDK2 and cyclins levels in the cells that are sensitive to crocetin, which contributes to increased p21 accumulation. Crocetin activates p21 through a p53- independent mechanism which could be one of the main mechanisms of antitumor [37].

Aloin: Aloinis also known as barbaloin, is a bitter, yellow-brown colored compound found in *Aloe species*. The compound is present as the aloe latex that exudes from cells adjacent to the vascular bundles, found under the rind of the leaf. It is used as a stimulant-laxative, treating constipation by inducing bowel movements. Aloin also prevents the colon from re-absorbing water from the gastrointestinal tract, which leads to softer stools. Aloin also has an anticancer effect.

Mechanism of Action: Aloin showed a pronounced anti-proliferative effect on human uterine carcinoma HeLaS3 cells [38] at physiological concentration, caused cell arrest in the S phase and markedly increased HeLa S3 cell apoptosis. The cytotoxic activity of aloin from *Aloe* plant against

two human breast cancer cell lines, without (MCF-7) and with (SKBR-3) ervB-2-topolla coamplification, was reported [39]. MCF-7 cell line was more sensitive to aloin than SKBR-3, as demonstrated by the MTT and colongenic assays. Aloin at higher concentration reduced the proportion of cells undergoing mitosis by induction of apoptosis, inhibition topoisomerase type IIA expression, and down regulated cyclin B1 protein expression in the MCF-7 cell line, whereas erbB-2 protein expression was not affected [40].

Licochalcone A: Licochalcone A is a chalconoid, a type of natural estrogenic flavonoid. It can be isolated from root of *Glycyrahiza glabra* or *Glycyrrhiza inflate*. Roots of *Glycyrahiza glabra* is known as liquorice, it has ant parasitic, antibacterial and antitumor properties [41, 42, 43]. However, few studies have shown that LCA has a significant anticancer activity in various malignant human cell lines [44].

Mechanism of Action: LCA is a potent antitumor promoting agent, which has cancer chemo preventive activity by inducing the apoptosis of cancer cell [45]. LCA can reduce the cell viability, enhance mitochondrial ROS, induce oxidative stress, mitochondrial dysfunction, apoptotic cascade activation and ER stress in T24 cells [46].

Hence, indicates that ROS plays a prominent role in LCA-induced T24 cell apoptosis through mitochondria-dependent and ER stress activated apoptotic signals. LCA can trigger oxidative stress by mitochondrial ROS to induce T24 cell apoptosis through mitochondrial dysfunction, leading to the cleavage of PARP and activation of the caspase cascade-mediated signaling pathway [46].

TABLE 2: ANTICANCEROUS PLANTS OF UTTARAKHAND

Plant	Compounds or Extracts	Plant part used	Reference
Acorus calamus	Ethanolic extract	Rhizome	47, 48, 49
Aleo vera	Aloemodin, aloesin	Leaves	50, 51, 52
Asparagus racemose	Histone	Roots	53, 54, 55
Betula utilis	Betullin	Bark	56
Cassia fistula	Ethyl acetate extract	Flowers, fruits	57, 58
Curcuma domestica	Curcumin	Rhizomes	59, 60, 61, 62
Kaempferia rotunda (Linn.)	Methanolic extract	Rhizome	63, 64, 65
Ocimum tanuiflorum	Ethanolic extract	Leaves	66, 67, 68, 69
Phyllanthus amarus	Methanolic extract	Whole plant	70, 71, 72
Piper longum	Ethyl acetate extract	Fruits	73, 74
Rubia manjith	Methanolic extract	Leaves	75, 76, 77
Taxus baccata	Taxol and taxotere	Leaves	78
Terminallia arjuna	Casuarinin	Whole Plant	79, 80
Tinospora cordifolia	Alcoholic extract	Whole Plant	81, 82, 83
Trigonella foenum-graecum	Ethanolic extract	Leaves	84, 85
Withania somnifera	Withaferin A and withaferin B	Root	86, 87, 88

CONCLUSION: Herbal drugs have been contributed to cure different ailments including cancer for thousands of years herbal extracts and their bioactive compounds are play a significant role for prevention cancer activity and many compounds have to be screened for their valuable information, but a large number of medicinal plants having anticancer properties are available in nature and they are not fully phyto-chemically investigated. This review has given some of the herbal bioactive constituents possessing anticancer activity for various types of cancer with mechanism of action. The review can help others researchers to explore herbs for further evaluation and its use in various other disease and toxicity studies along with preclinical, clinical trials. It should be of particular interest to explore the anticancer potential of the herbal drugs for isolation and characterization of the active anticancer principles so that better, safer and cost-effective drugs can be developed for treating cancer.

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