

## Research Article

# Anticarcinogenic Activity of Plant Bioactivity Compounds

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### Abstract

Cancer is the first leading cause of mortality in the world. Patients who are diagnosed at earlier stage are good related with diagnosed at late stage, there are no choice of treatment (cancer patients who are at a late stage are unable to cope with chemical therapy) at the late stage. It has been proven plant bioactive compounds are able to prevent cancer, inhibit NF-κB, Nrf2, PI3K, STAT, Wnt, signaling pathways, angiogenesis and induce cancer cell death by several studies those are in vivo and in vitro. Therefore, we are going to study the possibilities of using plant bioactive compounds for cancer treatment.

**Keywords:** Angiogenesis; Cancer stem cell; Plant bioactive compounds; Signaling pathways

### Introduction

In the earth, by 2018, approximately 18,1 million population are diagnosed with cancer and mortality rate is 9,6 million [1]. Successful cancer treatment has not been achieved yet although there has been progress. Furthermore, the standard treatment of cancer (chemotherapy, radiotherapy, immunotherapy) has high cost, treatment quite often causes suffering, and various side effects for patients [2]. Due to that, there is need to search a new approach which is less toxic, highly effective and has low cost. Plant bioactive compounds are able to act against bacteria and virus and inhibit cancer cell signaling pathways. Since thousands of years ago, plants have been used for prevention and treatment of cancer various diseases. The Red Emperor, or Shen Nung of the ancient Chinese emperor, compiled the first medicinal herbal literature, the Pentsao in 2,800 B.C. In United States, 50-60%

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of cancer patients get combination of standard cancer treatment and additional herbal medicine. These additional therapeutic products (EGCG, idroxycecol, resveratrol, sulforaphane etc) are the target therapy for colon cancer, breast cancer, lung cancer, liver cancer, NF-κB, Hedgehog, Wnt pathways and angiogenesis [3,4]. Due to anti-cancer plant bioactive compounds have higher probability to affect cancer stem cell, there might be a chance to make new cancer treatment approach to cancer stop or eliminate, which is the combination of plant bioactive compounds and chemotherapy. In the review, study on the effect of plant bio-actvie compounds for anti-cancer service will be studied.

### Materials and Methods

We have performed our search by using key word “lung cancer, cancer stem cell, signaling pathway” from www.Pubmed.gov and other medical journals. Performed our study (Table 1) by translating materials that came out from key word search, and by using decomposition analysis, summary conclusion methods.

### Mechanism










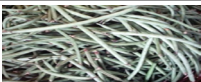




#### Cell death




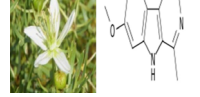













Apoptosis is a programmed cell death. During this highly regulated process unnecessary cells die off. Numerous conditions active the apoptotic pathway, including DNA damage and unregulated cellular division. Apoptotic process is activated by intracellular (intrinsic) and extracellular (extrinsic) signaling pathways. This is also known as mitochondrial pathway and death receptor pathway. Intrinsic pathway regulation includes DNA damage, growth factor deficiency, cytokine depletion, whereas extrinsic pathway regulation includes cytotoxic T cell damage of immune system response induced cell death stimulating signal. In order to proceed apoptosis through hundreds of proteins, the intrinsic and extrinsic signalling pathways use proteins called caspase. All these pathways unite in caspase protein [46].





#### Cancer cell death

Cancer cells go under unregulated cellular division and stimulate angiogenesis in order to evade from apoptosis. Apoptosis is the process that prevents from cancer and becoming the promising objective of target therapy against cancer. Loss of apoptotic control enables the longevity and mutation process of cancer cells. Moreover it also increases invasive feature of cancer cell and stimulate angiogenesis and regulate nutritional status of the cells. Cancer cells have many ways to evade the apoptosis. Including supressing caspase function and inactivating apoptotic stimaling factors [46].

Cell death is an essential for cancer treatment. The standard treatments for cancer which are being used in clinic (chemotherapy, radiotherapy, target therapy and immunotherapy) are directed to kill cancer cells [3,46]. Furthermore, plant bioactive compounds have effect against inflammation; virus and cancer induce cell death. In comparison with chemotherapy, natural phytochemical compounds are able to cell signaling pathways as target induce cell death factors such as transcriptional factor, growth factor, cancer cell survival

Plant name	Plan picture	Mechanism of phytochemicals	Phytochemicals	Cancer suppressed	Reference
<i>Camellia sinensis</i>		anti-proliferative	EGCG (Epigallocatechin Gallate)	Brain, prostate, cervical and breast cancer	[5,6]
淫羊藿 <i>Herba epimedii</i>		Apoptotic, inhibit multiple signaling pathways	Icariin, icaritin, icaraside II	Prostate, lung, kidney and gastric cancer, skeletal disease	[5,7,8]
<i>Allium wallichii</i>		Cytotoxic activity	Steroids, terpenoids, flavonoids, reducing sugars and glycosides	Prostate cancer, breast cancer, cervical cancer	[5,9]
<i>Silybum marianum</i>		inducing apoptosis, anti-proliferative, anti-angiogenesis	Silibinin	Lung, liver, skin, colon and prostate cancer	[5,10]
<i>Paeonia suffruticosa</i>		anti-inflammatory, induce apoptosis	Polysaccharides (HBSS, CHSS, DASS, and CASS)	Prostate, colon, human breast, and cervical cancer	[5,11]
<i>Ocimum sanctum</i>		anti-proliferative, anti-angiogenesis	Eugenol, orientin, vicenin	Breast and liver cancer	[5,12]
<i>Ginkgo biloba</i>		reduces the risk of cancer	Ginkgetin, ginkgolide A & B	Hepatocarcinoma, ovary, prostate, colon and liver cancer	[5,13]
<i>Camellia sinensis</i>		anti-proliferative	EGCG (Epigallocatechin Gallate)	Brain, prostate, cervical and breast cancer	[5,6,14]
<i>Solanum nigrum</i>		anti-proliferative	Solamargine, solasonine	Breast, liver, lung and skin cancer	[5,15]
<i>Vigna unguiculata</i>		anti-carcinogenic	Black-eyed-pea trypsin/Chymotrypsin inhibitor	breast cancer	[5,16,17]
<i>Ziziphus spina-christi</i>		Anti-cancer	Doxorubicin, spinanine-A, rutinine, quercetin	Lung cancer and breast cancer	[5,18]
<i>Glycyrrhiza glabra</i>		pro-apoptotic, anti-proliferative,	Licochalcone-A, licoagrochalcone	Prostate, breast, lung, colon, stomach and kidney cancer	[5,19, 20]
<i>Nigella sativa</i>		anti-proliferative, pro-apoptotic, anti-oxidant, anti-mutagenic, and anti-metastatic	Thymoquinone	Colon, prostate, breast and pancreas cancer	[5,21]
<i>Artemisia annua</i>		anti-angiogenesis, inhibition signaling pathways(Wnt/β-catenin, AMPK)	Artemisinin	Liver, breast and pancreatic cancer	[5,22,23]

<i>Ocimum sanctum</i>		inducing apoptosis, inhibit angiogenesis, inhibit metastasis	Eugenol, orientin, vicenin	Breast, liver and fibrosarcoma	[5,24]
<i>Moringa oleifera</i>		inducing apoptosis	Moringa oleifera protease inhibitor (MoPI)	breast ,colorectal cancer	[25,5,26]
<i>Glycine max</i>		Anti-cancer	Bowman-Birk inhibitors	Colorectal, breast, prostate and colon cancer	[5,27]
<i>Peganum harmala</i>		anti-angiogenesis	Harmine	Breast cancer	[5,28]
<i>Curcuma longa</i>		Anti-proliferative, NF-κB inhibitor and downstream gene products (c-myc, Bcl-2, COX-2, NOS, Cyclin D1, TNF-α, interleukins and MMP-9)	Curcumin, ascorbic acid	Leukemia, Head and neck squamous cell carcinoma (HNSCC), glioblastoma and colon cancer	[5,29]
<i>Alstonia scholaris</i>		Anti-cancer, anti-neoplastic	O-methylmacalstonine, talcarpine,villalstonine, pleiocarpamine	Lung cancer	[5,30]
<i>Andrographis paniculata</i>		Anti-tumor,Anti- metastasis	Andrographolide	Colon cancer	[5,31]
<i>Panax ginseng</i>		Inducing apoptosis	Panaxadiol	Breast, colon cancer	[5,32]
<i>Plumbago zeylanica</i>		Inducing apoptosis	Plumbagin	Liver, pancreatic, fibrosarcoma, leukemia and breast cancer	[5,33]
<i>Oldenlandia diffusa</i>		Inducing apoptosis, inhibit cancer cell growth	Ursolic acid	Lungs, ovary, uterus, stomach, liver, colon, rectum and brain cancer	[5,34]
<i>Glycyrrhiza uralensis</i>		Inducing T lymphocyte	Isoliquiritigenin	lung cancer	[5,35]
<i>Boerhavia diffusa</i>		Inhibit Bcl2	Punarnavine	Malignant melanoma cancer	[5,36]
<i>Vitis vinifera</i>		Anti-cancer	Procyanidins	Human colon cancer	[5,37]
<i>Aloe vera</i>		anti-neoplastic, inhibit cancer cell growth	Alexin B, emodin	Leukemia, stomach cancer	[5,38]
<i>Argemone gracilenta</i>		anti-proliferative	Argemone and berberine	B-cell lymphoma, leukemia	[5,39]
<i>Centella asiatica</i>		Inducing apoptosis	Asiatic acid	Melanoma, glioblastoma, breast	[5,40]
<i>Allium sativum</i>		Anti-carcinogenic	Allylmercaptocysteine, allicin	Lymphoma, cervix cancer	[5,41]

<i>Saffron crocus</i>		inhibit cancer cell growth, cancer-preventive	Saffron	Liver, lung cancer and pancreatic cancer	[5,42]
<i>Taxus brevifolia</i>		Arrest in the G2/M phase of the cell cycle	Paclitaxel	Ovarian, breast, endometrial, cervical, prostate, and head and neck cancers	[5,43]
<i>Tabernaemontana divaricate</i>		anti-proliferative	Cononitarine B, Conophylline	Liver, lung, breast and colon cancer	[5,44]
<i>S.Smilax chinensis</i>		Anti-cancer, anti-inflammatory	Tannin, saponins and flavonoid	Sarcoma-180 and ascites sarcoma	[5,45]

**Table 1:** Herbal bio-activity components of anti-cancer.

factor, inflammation cytokines, protein kinases and angiogenesis. Due to simultaneous target signaling pathways, there is the ability to kill cancer cells selectively [47].

- In the cell death cycle: <blebbing>, cell shrinkage and nuclear fragmentation occur [3]. Cell death is divided into inner and outer regulation.
- Inner regulation: as DNA is injured, P53 protein activates, eliminate BAX protein, mitochondria makes a hole on its membrane, eliminate cytochrome C protein, activates apoptotic protease activating factor-1 (Apaf-1) and ATP, as a result, caspase 3 is activated by effect of caspase 9, breaks DNA and finally, cell death occur [46,3].
- Outer regulation: Fas ligand of CTL cell (transmembrane protein of TNF) interacts with Fas molecule (Apo-1 or CD95) of target cell and activates caspase 8. As a result, caspase 8 activate caspase 3 and cell death occur [46,3].

### Cell signaling pathway

There are 12 main pathways and in some type of cancer, these pathways have abnormal function [4]. Hedgehog signaling pathway leads to cell differentiation, growth and determines embryonic normal function [48]. On the other hand, due to an abnormal activation of the Hedgehog (Hh) pathway, cancer of brain, lung, prostate, leukemia, gastric and skin develop [3,49]. Moreover, transforming adult stem cells to cancer stem cell, as a result, cancer [3] and drug resistance can be developed. The Hedgehog signaling pathway is three ligand (Sonic hedgehog-Shh, Indian hedgehog-Ihh, Desert hedgehog-Dhh), has two of receptors (PTCH1, PTCH2), key signaling converter smoothed (SMO) and 3 of transcription factors (Gli1, Gli2, Gli3) [49]. The sonic hedgehog (SHH) contains ~20 kDa N-terminal signaling domain (SHH-N) and ~25 kDa C-terminal signaling domain (role of its is unknown). As SHH is attached to Patched-1 (PTCH1) receptor, then Smoothed (inhibited by PTCH1) is activated and GLI transcriptional factor is activated. The activated GLI is accumulated in nucleus and hedgehog target gene transcription, as a result hedgehog signaling pathway is activated, Fas and apoptotic gene decrease and angiogenesis increase [3].

The Wnt signaling pathway does not involve in normal physical functions of adult human and animals and it only involves in embryogenesis and cancer development [3,50]. Wnt signaling pathway

regulates embryonic cell migration, cell polarization, neuronal differentiation and organogenesis and affects renewing of stem cell. Due to loss of normal Wnt signaling pathway regulation, embryogenesis interrupt, cancer of breast, colon, gastric, leukemia, melanoma, dermal cancer and bone damage are develop [50,51]. The Wnt signaling pathway is divided into  $\beta$ -catenin (canonical) and non  $\beta$ -catenin (non-canonical) [50].

- $\beta$ -catenin (canonical): Wnt protein connect to Frizzled receptor of cell surface at that time Dishevelled (DSH) complex is activated, GSK is inhibited,  $\beta$ -catenin enters to cell nucleus freely which activates TCF, as a result, gene expression gets improved [50,51].
- Non  $\beta$ -catenin (non-canonical): due to deficiency of Wnt protein, DSH complex is not activated, therefore, secondary protein complex which are GSK, axin and APC are activated and break  $\beta$ -catenin [3,50,51].

NF- $\kappa$ B signaling pathway NF- $\kappa$ B (Nuclear factor kappa-light-chain-enhancer of activated B cells) controls cell inflammation, change, proliferation, angiogenesis, metastasis, resistance of chemotherapy and radiotherapy. NF- $\kappa$ B is active in most of cancer cells and the cell activation induces cancer cell growth, inhibit cell apoptosis and induces angiogenesis [52,53]. TNF $\alpha$  induces cell death and inflammation mechanism. Although the process of inflammation is innate immunological protective mechanism, if it continues (chronic) for a long period of time, it leads to tissue damage, autoimmune disorder, excess in cell loading, collect inflammation factors is makes DNA damage, as a result various types of cancer develop and support the growth of cancer by changing the genetic sequence, damaged tissue epigenetic, its micro environmental [53]. TNF $\alpha$  is connected to cell surface receptor TNFR-1, as a result TRADD (TNF receptor type 1-associated death domain protein), TRAF-2 (TNF receptor-associated factor 2), IAP (inhibitor of apoptosis protein), RIP/RIPK (receptor-interacting protein kinases) proteins are activated, as a result IKK (inhibitor of nuclear factor kappa-B kinase subunit alpha) complex is activated and due to that I $\kappa$ Ba (inhibitor of kappa-B) deficiency occur. Due to the deficiency of I $\kappa$ Ba, NF- $\kappa$ B enters to cell nucleus, pre inflammation gene, anti-apoptotic gene and cytokines are released.

### Angiogenesis

Angiogenesis is the new vascular formation physiological process and also is the cancer cell prognostic general marker that indicates cancer prognosis, invasion, metastasis, growth, nutritional status and



oxygen supply. Thus inhibiting angiogenesis has a great importance. Angiogenesis inhibitors are classified into direct inhibitors and indirect inhibitors [54,3].

### Direct inhibitors of angiogenesis

Angiogenesis direct endogen inhibitors include angiostatin, endostatin, arrestin, canstatin and tumstatin etc., These are certain parts are from extracellular matrix protein proteolysing process. Endogens inhibitors prevents from endothelial cell division. Direct inhibition process against angiogenesis uses certain intracellular signalling pathways that uses endothelial surface integrin proteins. These includes, PI3K, Akt, mammalian target of rapamycin (mTOR) etc., [54].

### Indirect inhibitors of angiogenesis

Angiogenesis indirect inhibitors are used in common chemo therapeutic substances, target therapy against oncogene, micro environment of cancer and other target therapeutic pathway. These inhibitors prevent from formation and expression of angiogenesis and inhibits the pro-angiogenesis protein function [54]. VEGF (vascular endothelial growth factor) induce angiogenesis of cancer. Due to VEGF is connected to VEGFR (VEGF receptor), MAP kinase signaling pathway is activated and MMP, uPA, uPAR, Plasminogen activator proteins are released. By influence of VEGF, signaling cascade in epithelial cell occur. VEGFR-2 (VEGF receptor-2) activates cascade of tyrosine kinase signal and makes chance to create maturely developed vessel, maintain transcription, growth and survival [3]. Using angiogenesis inhibitors along with chemotherapy and targeted anti cancer therapy is showing a great promise. Depending on the cancer type, anti angiogenesis drug, and chemotherapy, the angiogenesis inhibitors can be used before chemotherapy or after chemotherapy. These combined therapy has showed some result in numerous precilical and clinical study.

### Immune system against cancer

The main goal of immunotherapy is eliminate cancer and reduce cancer mass [2]. Currently, the immunotherapy is intended to inhibit cancer cell surface marker, induce non specific immune cells such as dendritic cell, T cell, NK cell, CTL, NKT cells, and cytokines IFN $\alpha$ , IL12, IFN $\gamma$ , IL2, IL7 function. As a result, immune reaction rate increases. Although the standard treatment of cancer is able to destroy cancer cell, the mainstem cell of cancer is not destroyed. Therefore, post treatment resistance, recurrence and metastasis occur. Cancer stem cells are the small part of total cancer cells and it is potential to renew itself and grow unlimitedly in an accumulation of gene population. Furthermore, they lack of nutrients, oxygen content and they take nutrients from adjacent cells and they have high flexibility, and are potential to cope with strain [54-56]. One of the protecting and survival methods of cancer cell is cell surface marker (Table 2). Currently, It has not yet studied comprehensively that cancer cell surface markers and their activities.

From surface markers above, the uppermost in the mind is CD133 and CD44. CD133 /Prominin 1/ is in group of Prominin and with 5 of transmembrane and 2 glycosylation capsule in outer environment. Excess growth of CD133 protein in cancer cell surface lead to drug resistance and ability of cancer development [62]. This protein is detected in numerous types of cancer, but currently, it is not studied comprehensively and having debate [62,60] CD133 is commonly

Tumor types	Surface marker on the CSCs	References
Breast	CD44+/CD24-, CD133+, EpCAM+, CD29,	[57,58,14]
Colon	CD133+, EpCAM+, CD44+, CD166+, CD24+	[57,58,59]
Glioma (brain)	CD133+, CD15+, CD49f+, CD90+	[57,59]
Leukemia (AML)	CD34+, CD38-, CD123, CD117, CD90, CD71	[57,59]
Lung	ABCG2, CD133+, CD147+, CD117+, ATP+, CD34+/CD44+, ALDH1+, OCT4+, CD24-, CD45-, CD166+CD44+, CD166+EPCAM+, CXCR4+	[60,14,59]
Melanoma	ABC5, CD133+, CD20+, CD271+, CD166, Nestin+	[57,59]
Ovarian	CD44+, CD117+, CD133+, CD24+, ALDH1A1+	[57,59]
Pancrease	EPCAM+, CD44+, CD24+, CD133+, ESA	[60,14,59]
Cervical	CD133+	[61]

**Table 2:** Cancer stem cell surface markers in human cancer.

detected in stem cell surface of neuronal, prostate, brain, colon, lung, liver and ovarian cancer [60]. CD44 is in group of non kinase and it is cell surface transmembrane glycoprotein. It is contained a bit or it does not contained in healthy individual. The excess detection of CD44 induce cancer stem cell growth and negatively affect the patient's prognosis [63]. If CD44 is detected in cancer stem cell surface commonly, which reduces glutathione synthesis, increase an active oxygen capability, as a result various types of treatment resistance occur. The main role of CD44 is pump to put cystine into chancer stem cell. Therefore, due to inhibition of glutamatcystine transportation, CD44 dependent cancer growth is decreased and sensitiveness for treatment increases [59]. CD44 has an essential role to start MAPK, Hippo,  $\beta$ -catenin, AKT, TGF- $\beta$ , Emmprin, MMPs and STAT3 signaling pathways [63].

It is proved that plant bioactive compounds have less toxicity, high effect against cancer by several studies. For instance, paclitaxel which is extracted from barks of yews in Pacific ocean [64] in the experimental model MDA-MB-231 xenograft, it inhibits CD133 and has effectiveness to inhibit cancer growth. But after stopping treatment, cancer develops faster [55]. In APCMin $+/+$  mouse model, dasatinib and curcumin reduced cancer stem cell surface markers (LDH, CD44, CD133, CD166 ) by 80-90 % [65]. Although Curcumin was proved having able to kill [66] cancer stem cell by clinical trial, it has low bioavailability. Therefore, it was hard to use in treatment [67,68].

### Result and Discussion

Long ago, it was known that cancer cells continuously proliferate, and metastasize however recently researchers have proven that cancer cells have stem cell population responsible for drug resistance and metastasis. In worldwide, currently we are using gene therapy, anti angiogenic therapy for patients with cancer. These have multiple effects such as maintaining remission without relapse after standardized treatment of cancer, reducing tumor size etc. However, expense of chemotherapy is high (unable to be used in poor countries), high toxicity (damages other healthy organs) and does not have effect on cancer stem cells. Plant based bioactive compounds decrease risk of cancer development risk, and increase drug effects through synergetic manner, suppress progress of cancer, and able to be used with solely or with other drugs and thus is possible low cost variation. To eradicate cancer completely, it is necessary to eradicate cancer stem cells, and by eradicating cancer stem cells there is possibility to stop progression of cancer, and maintain remission without relapse. In recent

years research on cancer stem cell have been performed intensively, and by 2015 there are up to 5000 research studies have been published on this topic. From several pathways to treat cancer stem cells, most effective methods are signal pathway and suppression of surface markers.

Through many studies, CD44 a cancer stem cell surface marker has been proven that it is possible target treatment. Current treatment strategy is directed to reducing CD44 detection. Thus current treatment strategy is directed to reducing CD44 detection load. Furthermore, signal transduction pathways of cancer stem cells play major role for cancer cells and microscopic environment of tumor, therefore this topic have been studied for last 10 years. Through many epidemiology and in vitro studies, it was proved that green tea has effect on cancer cells and support tumor radiation treatment. Currently international research centers are testing tumor effecting ability of plants based bio-active compound are often used in in vitro, in vivo cancer prevention, treatment studies. Some of these clinical trials have been successive. Plant based bio-active compound research are interesting and thus we should understand their potential, pharmacokinetic indicators, pharmacokinetic interaction, metabolism, toxicity, drug interaction and polymorphism. Thus to study importance of plant based bio-active compounds, there are several issues we are confronting. These include: It is necessary to develop model for cancer stem cells and cell, and test plant based bioactive compound mechanism and dose. Through these, we can clarify important mechanism of treatment, and has responsibility to develop better treatment methods. Signal transduction pathways of cancer cells play important role of biologic activity, thus to develop treatment we should thoroughly assess. Recently, clinical trials of the signal transduction pathway during pancreas, colon, and ovary cancer have been unsuccessful. Furthermore, information of detailed biochemical understanding of signal transduction is insufficient. Inhibition of signal transduction pathways has poor results if used solely, and interaction suitability of chemotherapy drug or other treatment targets should be determined. In recent years, possible plant based bioactive compound that can suppress self-renewal, survival of cancer stem cells are being performed. Starting from now, we face need for new studies on complex effect of CSC and performing testing of bioactive compounds for treating for metastatic cancer. We assume that in future through clinical trial studies, an additional treatment strategy of using signal transduction inhibitors will be developed.

## Conclusion

Signal transduction pathways are associated to multiple types of cancer, thus it shows it signal transduction has high importance. Even though there is advancement in studies on signal transduction, we should thoroughly study signaling pathway mechanisms. From the information above, It can be concluded that the use of plant bioavailability in cancer treatment can be effective in patients who unable to cope with chemotherapy in the last stage of cancer, there is lack of clinical trial. Therefore, it is necessary to carry out further research in this field.

## Conflicts of interest

There are no conflicts of interest.

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