

**Research Article**

**Reviews of Natural Products and Herbal Medicines  
in Treatment of Cancer**

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**ABSTRACT**

Chemotherapy is considered a method to treat cancer, but lack of selective cytotoxicity often causes unacceptable side effects. Hence, using herbal medicines and their effective materials in treating cancer is vital. This survey tries to explain some main natural compounds of different plants in cancer treating. This research is an overview study about herbal medicines that are mentioned in different resources, like traditional medicine, educational news press of herbal medicines, different websites with title of herbal medicines and their material key words in treating cancer. Today, potential of using herbal medicine to treat cancer has drawn the researchers` attention. It is hope that this survey be useful as a reliable resource for specialists and those who are interested in research in the field of cancer.

**Keywords:** Herbal Medicine; Cancer; Herbal effective Material.

**INTRODUCTION**

Cancer is a kind of sickness in which the cells loss their natural mitotic and growth capability that results in capturing, destroying, and corrupting the healthy tissues. Gathering these cancer cells and corrupting healthy tissues causes creating a mass called tumor. When the tumor is limited to a layer, not going to other organs and tissues, it is called benign (non-cancer); but when the tumor is widespread and potential to spread and surround

other tissues and organs it is called a cancer tumor or malignant <sup>68</sup>. Using herbal medicine to treat cancer is rooted in past decades; plants are the primary resource of preparing traditional drugs to treat this sickness. Traditional plants are a method in which, after clinic examination and needed diagnosis, herbal elements are used to eliminate the symptoms. Table 1 & 2 show the explained

plants in this survey, with effective material and their mechanisms.

**Table 1 :**Plants studied for anti-cancer potential In vitro model reported

Herbal medicine	Model system	Major mechanisms reported	References
Camellia sinensis (EGCG lower doses of (12.5, 25, 50 µg/ml) highest dose EGCG (100 µg/ml)	brain tumor cell lines: in U-373 MG, U-87 MG, and C6 cells in rat nonfunctioning pituitary adenoma cell line MtT/E	induced apoptosis	92
Camellia sinensis: EGCG	In glioblastomas cell line U-87 UACC-375 melanoma	inhibited MMP activities and proMMP-2 activation cell cycle arrest, induction apoptosis, decrease in proliferation	18 90
Nasturtium microphyllum: isothiocyanates	HT29 cells(Colon)	inhibited metalloproteinase 9 activities suppress the invasive potential of human MDA-MB-231 breast cancer cells protective against the three stages of the carcinogenesis process	72 6
isothiocyanate metabolite	human prostate cancer cells	inhibited proliferation and tumorigenesis	13
Peganum harmala: harmine	B16F-10 melanoma	induced apoptosis by up-regulating Bax and activating Caspase-3, 9 and p53 and down- regulating Bcl-2 up-regulating Caspase-8 and Bid	68
Arctium lappa: Lappaol F	human cancer cell lines: MCF7.( breast), HT29(Colon),DU145(prostate) ,U2OS(osteosarcoma), A375(melanoma)	exhibited antitumor activity in vitro and in vivo induced G(1) and G(2) cell-cycle arrest ,induction of p21 and p27 reduction of cyclin B1 and cyclin-dependent kinase 1	84
Arctigenin	Human ovarian cancer OVCAR3 and SKOV3 cells	inhibition of cell proliferation induces caspase-3-dependent apoptosis	31
Alhagi maurorum: Quercetin& Temozolomide	MOGGCCM astrocytoma cell line(grade III)	programmed cell death induction	38
Catharanthus roseus	MCF (breast cancer) cell lines	antitumor activity	75
Tussilago farfara	human hepatocellular carcinoma cells	induced apoptosis via inhibition of MKK7- TIPRL interaction & increase in MKK7/JNK phosphorylation	52
Nerium oleande: oleandrin	human pancreatic cancer cell line(PANC-1)	inhibited tumor cell proliferation cell death rather through autophagy	61
Hibiscus Sabdariffa	Human Prostate Cancer Cell Invasion human prostate cancer cells(CaP)	suppression of the Akt/NF-κB signaling pathway induction apoptosis	54 55
Capsicum annum	glioma cells (U373)	induction apoptosis	4
Silybum marianum	SCC-4 tongue cancer cells	reduction expression of MMP-2 inhibitory effect on the phosphorylation of ERK1/2	12
Curcuma longa: Curcumin	Glioblastoma:U138MG and C6 cells	decreased the constitutive activation of PI3K/Akt and NFκappaB survival pathways down-regulated the antiapoptotic NFκappaB-regulated protein bcl-xl and induced mitochondrial dysfunction reduced cell survival in a p53- and caspase- independent manner	94
Dendrosomal curcumin	human glioblastoma cells: T98G, U87MG, and T67, rat (C6) glioma cell lines  U87MG cells	inhibition of AP-1 and NFκappaB signaling pathways via prevention of constitutive JNK andAkt activation activation miR-145	88

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Ocimum basilicum: methyl thiazol tetrazolium	human cervical cancer cell line (HeLa), human laryngeal epithelial carcinoma cell line (HEp-2), NIH 3T3 mouse embryonic fibroblasts	cytotoxicity	41
Marijuana Delta9- tetrahydrocannabinol	human breast cancer cells	inhibited cell cycle progression through Cdc2 regulation	10
Cuminum, Carum carvil: Monoterpenes	neuro-2A cells neuroblastoma cell model	cytostatic effect, ability to inhibit ubiquinone syntheses in	81
caryophyllium aromaticus	human colon cancer cells HCT-15, HT-29	activation PARP (polyadenosine diphosphate-ribose polymerase), p53 and caspase-3	36
Cinnamomum verum: Cinnamic Aldehyde	A375 cells	G1 cell cycle arrest induced an oxidative stress response inhibited NFκB transcriptional activity TNFα-induced IL-8 production	9
Saffron( Crocus sativus )	MCF-7 human breast cancer cell line	decreased in the expression of VEGF- A, specific biomarker of angiogenesis Inhibition cancer cells	60
saffron	Breast Cancer Cell Line (4T1)		80
Urtica dioica	MCF-7 human breast cancer cell line	increase of the amount of calpain 1, calpastatin, caspase 3, caspase 9, Bax and Bcl-2, all proteins involved in the apoptotic pathway	21
Coriandrum sativum	MCF-7 human breast cancer cell line	cell cycle arrest at the G2/M phase and apoptotic cell death	89
Gossypol	human prostate cancer cells DU-145	induced apoptosis by the regulation of the Bcl-2 and caspase families	29
Nigella sativa: Thymoquinone	cervical cell lines: Siha cells C33A cells	p53-mediated apoptosis activation of caspase-3	31
Viola odorata Extract	Breast Cancer MDA-MB-468 Cells	reducing tumor volume	32
ACA1 Extract 5mg/ml	melanoma cell lines( SK-MEL3)	highest cytotoxicity	24

**Table 2:** Plants studied for anti cancer potential in vivo model reported

Herbal medicine	Model system	Major mechanisms reported	References
Camellia sinensis:	breast cancer-induced osteolysis mouse model	anti-tumor, anti-metastasis and anti-osteolysis	56
Tussilago farfara	inbred strain ACI rats	Carcinogenicity due to senkirkine, a hepatotoxic pyrrolizidine alkaloid.	30
Catharanthus roseus	Ehrlich ascites carcinoma (EAC) tumor model	antitumor activity	75
Hibiscus Sabdariffa	LNCaP cells in xenograft tumour studies	inhibited the growth	14
Silybum marianum	Lewis lung carcinoma (LLC) cells (C6 implants) models of GBM	inhibition of the metastasis	12
Curcuma longa: Curcumin	colon cancer -induced with drug azoxymethane in male Fischer rats	decreased brain tumors	
nano-curcumin curcumin & dendrosomal curcumin	male Fischer rats	antiproliferation Reducing the amount of COX-2 inflammatory markers	94
		Reduction betacatenin expression Increase expression Bax	45
			78
Cuminum, Carum carvil: Thujone	B16F-10 melanoma cells in C57BL/6 mice	inhibition of tumor cell proliferation, adhesion, and invasion	83
caraway essential oils ( Cuminum )	Male Wistar rats to induce colon cancer in animal models with 1,2- dimethylhydrazine (DMH)	regulating expression of MMPs, VEGF, ERK-1, ERK-2, TIMPs, nm23, and levels of proinflammatory cytokines and IL-2 in metastatic animals	
			3

		Activation Wnt/b-catenin signaling pathways & expression of colonic b-catenin	
Saffron	induced skin carcinogenesis in Swiss albino mice.	radical scavenging, anti-mutagenic and immunomodulating effects	17
melatonin (40 mg/kg) and Viola odorata at 250 mg/ml	Balb/c mice received subcutaneous injection of 100 µl of cell suspension (4T1 cells) in the left hind flank	inhibited increasing of tumor volume after 21 days	2
Olive Leaf Extract (doses of 150 & 225 µg/kg/days) dose of 150 µg/kg/days	breast cancer-induced 4T1 cells in Balb/c mice model	Reduction tumor volume Increase activities of catalase	57

## Natural Products and Herbal Medicine against Cancer

### 1. Camellia Sinensis

Camellia Sinensis is an antioxidant against cancer due to containing some materials like Catechins; it is more effective than other antioxidants like vitamins E and C. Catechins involve Epigallocatechins (EGC), Epicatechins 3-gallate, Epigallocatechins (EGC) 3-gallate (EGC G) which have anti-proliferation on cancer cell-lines<sup>90</sup>. EGC and EGCG prevent growth of CH-0566, MB-1133, and LF-0023 cell-lines. It is believed that the most effective cell anti-growth and cell-death are the ones mentioned above. Cancer cells of ovary and prostate are mostly sensitive to EGC and EGCG. But, melanoma cells are mostly sensitive to EGCG. The results show that a composite of Catechins may show relief and even show an anti-tumor behavior<sup>73</sup>. Recently, matrix of Meta-proteinase-9 (MMP-9) is reported as one of the marker genes for most of the cancers<sup>96</sup>. Additionally, increase in activity and matrix of metallo-proteinase-9 and -2 in tumor tissues and malignant cells has been reported<sup>91</sup>. Also, Catechins control matrix of meta-proteinase<sup>18</sup>. MicroRNA as biomarker are used to diagnosis cancer. Natural products like EGCG, Curcumin can change multi-aim genes and MicroRNA at the same time. Cancer is created in lack of these genes. So, it can be considered to control cancer. Accordingly, natural products can decrease explanation of MicroRNA in causing cancer and again they can cause increase of explanation of MicroRNA<sup>65</sup>. In a study it was reported that  $\beta$ -adrenergic receptors in tumor cells with low grade (Astrocytoma 1321N1) via increasing connexin level-43 and MiR146a and decrease in 155-MiR

and a27-MiR are explained. So it can be a useful method to control astrocytoma. connexin 43 and MicroRNA 21 have a role in growth of glioma. In some studies it is believed that Camp signaling way can be affective in connexin 43 and microareans. Results show that signaling way of  $\beta$ -adrenergic-Epac increases the explanation of connexin 43 and decreases the explanation of miR-21<sup>59</sup>. Another result showed that stimulating signaling way of  $\beta$ -adrenergic-Epac and more explanation of miR-451 has synergic effect on cell level of 1321N1<sup>58</sup>.

### 2. Nasturtium Microphyllum

Phenol compounds in the leave of this plant are reported like Coumaric Acid, Caftaric Acid, Quercitin. Phenol compounds in phenolic elements are mostly aqueous extract. So this plant has anti-oxidant role<sup>83</sup>. There have been lots of studies regarding Nasturtium Microphyllum its role toward being anti-cancer. In 2010, in South Hampton University, studies showed that only after a while after consumption of 80 g Nasturtium Microphyllum, the amount of anti-cancer cells increased and controlled growth of breast cancer cells<sup>75</sup>. So, Nasturtium Microphyllum controls breast cancer and reliefs this sickness. In 1991, in a study in title of "Cancer Epidemiology", it was shown that consuming 57 g Nasturtium Microphyllum, daily, decreases lung cancer in smokers<sup>26</sup>. In 2007, another study, "American Clinical Nutrition Journal", showed that consuming 85 g Nasturtium Microphyllum- for 8 week, daily- controls 23% of destroying white blood cells. Positive effect of Nasturtium Microphyllum is noticeable on smokers that are due to lack of anti-oxidants in their body<sup>23</sup>. A study showed that Nasturtium Microphyllum may

be effective in decreasing the danger of cancer in human beings. Poly-phenols, isothiocyanate, resorcinol, limonene and alium control the tumor of chemical material in rodents<sup>56,74</sup>. In another survey it was shown that phenyl- isothiocyanate has anti-tumor role. The mice with lack of immunity that received zincography from prostate-cancer PC-3, received biphenyl isothiocyanate conjunctive with PEITC-NAC (8 micromole in nutritional supplement for 9 weeks), showed a decrease in tumor volume. Subsequently, in this survey it was found that the above compound controls tumor creation by prostate cancer cells. In fact, this compound regulates carcinogen and the next phase by aiming regulating cell cycle and apoptosis<sup>11</sup>.

### 3. Peganum Harmala and Arctium. Lappa

Recently, alkaloids of beta-carboline like harmalol, harmaline, and harmine in the plants and Peganum Harmala are considered because of their anti-tumor effect. Spinal-Z is produced of Peganum Harmala. It has controlling effect in cell mitosis. It stops the cancer cell in mitosis. It has anti-tumor effect on cell lines like A2789-cp, HeLa, Saos-2, MCF-7, K562, KB, HL60, A2780-s, A172, A375, A549, HFFF. Harmine has anti-toxicity on HL60 and K562<sup>3</sup>. Harmaline is the strongest compound against HL60 in some tumor cell line like Hepatocarcinoma, Fibro-sarcoma, Myeloma, and Breast Cancer, Ovarian Cancer, and Melanoma<sup>32,3</sup>. Lappol-F5 in Arctium. Lappa is potentiated to control cancer. In a study it was shown that the nude mice which received tumor zincograph graft, the mice first got injected subcutaneous cancer cells. The results show that a meaningful control against cancer cells<sup>73</sup>.

### 4. Alhagi maurorum and Catharanthus Roseus

Catharanthus roseus contains non-saturated sterols, teriterpene, Tanins, Flavonoids like Quercetin and Catechin that have anti-oxidant effect. Also, Flavonoids glycosides like Alhagidin, Alhagitin, etc<sup>7,63,82</sup>. In a study Sorafenib-5 and Quercetin are effective in controlling MGC823 and multi-form glioblastoma (T98G)<sup>37</sup>. It was shown that Quercetin causes cell death via apoptosis in U373MG cell lines<sup>46</sup>. Resveratrol and Quercetin cell number in glioma, not in rat-

astrocytes. Also, it was reported that a compound of poly-phenols there is an anti-tumor effect. These two are strong in activating caspase 3/7 when they are in the level of glioma cells<sup>93</sup>. Alkaloids like vinblastin, vincristin exist in Catharanthus Roseus plant that is used to control human beings cancer<sup>77</sup>.

### 5. Tussilago farfara and Nerium Oleander

Using apoptosis via activation of TOR signaling pathway regulatory-like is a kind of strategy against cancer. It has got the ability to use selective apoptosis method in selected cancer cells. Tussilago farfara plant because of using apoptosis via TOR as an anti-cancer factor is considered as an anti-cancer element. In this study Tussilago farfara was introduced as a sensitive plant against cancer. Also, it was known as a new strategy to control cancer<sup>52</sup>. In another study, it was reported that Nerium Oleander was used to synthesize Nano-particles. It was shown that it has anti-oxidant effect<sup>87</sup>. Oleandrin in Nerium Oleander, also, is a strong anti-oxidant to cure all kinds of cancers like colon, lung, prostate and so on<sup>61,50</sup>.

### 6. Hibiscus sabdariffa and Capsicum annum

In a study was found that Hibiscus sabdariffa uses apoptosis in cancer cell lines in prostate cancer in in-vivo and in vitro<sup>54</sup>. Hibiscus sabdariffa controls breast cell lines MCF-7 because of selecting it as an anti-cancer medicine<sup>42</sup>. Capsaicin is a chemical material in group of capsicum. It can be found in red peppers. It causes the special taste of peppers. It has anti-oxidant advantage. It controls the cells of body against free-radical molecules. In a study it was found that capsaicin in red pepper uses apoptosis in glioma Vanniloid cell via TRV1 receptor by help of p53<sup>3</sup>. It was also reported that capsaicin is causing activation of skin cancer via signaling epidermal growth factor receptor (EGFR)<sup>33</sup>. In a study it was reported that a compound of capsaicin and TRAIL tumor necrosis factor-related apoptosis-inducing ligand is a vital strategy to control malignant glioma<sup>47</sup>. Capsaicin causes releasing apoptosis in glioma cell lines A172 via ROS (Reactive oxygen species)<sup>53</sup>. Hibiscus sabdariffa L., a local soft drink material and medicinal herb, is usually

used effectively in native medicines against breast disorders. Again, they reported an extract, HSE (H. sabdariffa extract), which was designed to exhibit hypolipidemia and antiatherosclerotic effects with experimental atherosclerosis<sup>39</sup>. Capsaicin involves in some kinds on cancers like brain, prostates, lung, and so on; it is uses molecule regulating signaling in signaling ways like stressing cell cycles<sup>66</sup>.

#### 7. *Silybum marianum* and *Curcuma longa*

Seed of *Silybum marianum* contains about 4-6% and its extract contains 65-80% silymarin and 25-30% fat acids<sup>27</sup>. In a study it was shown that synergic effect of flavonoids in some plants like luteolin and silibinin causes hopeful control of immigrating the cells and apoptosis in glioblastoma cells like SNB19<sup>11</sup>. Cylimyarin in *Silybum marianum* has anti-cancer behavior<sup>70</sup>. Syndrome of cushing is created because of existing a tumor in pituitary<sup>72</sup>. High potential of Curcumin in *Silybum marianum* in attracting and gathering free radicals and controlling inflammation introduces this plant as an anti-cancer and tumor controller material<sup>19,94</sup>. In a study it was shown that three plants like *Polygonum Cuspidatum*, *Withania Somnifera*, and *Curcuma. Longa* have most effects on prostate cell lines and some medium effects on skin fibro-plasts BG-9<sup>71</sup>. Curcumin stops tumor creation and removes brain tumor cells<sup>68</sup>.

#### 8. *Ocimum basilicum* and *Marijuana*

A type of *Ocimum basilicum* has anti-cancer behavior. In a study it was shown that using *Ocimum basilicum* increases anti-cancer activity<sup>28</sup>. Extract of *Ocimum basilicum* has anti-metastasis via activating oxidative enzymes like super oxidative dismutase, Catalase, glutathione, and peroxidaz<sup>48</sup>. Active Eugenol in Tulsi (Holy Basil) is responsible controlling chronic cancer. It was reported that *Ocimum basilicum* protects brain cells by electromagnetic Field via regulating anti-oxidant enzymes in serum.  $\Delta^9$ -Tetrahydrocannabinol via activation of receptors (CB) canabioids controls cancer cells division by using apoptosis<sup>10</sup>.

#### 9. Caraway and Cumin

Different compounds of caraway are limonene, gama -terpen, Cuminaldehyde, etc<sup>16</sup>. in a survey it was shown that monoterpens of D-limonene may be effective in chemotherapy of malignant tumor in human beings<sup>83</sup>. It was also considered that Thujone controls which is result of injecting B16f-10 in lungs<sup>22</sup>. Seed of caraway can prevent cancer and it can regulate metabolism carcinogen<sup>81</sup>. Perillyl Alcohol is a strong Neuro-2A product of Neuroblastoma. It was again shown that Cuminaldehyde controls melanin in rat- melanin. But these effects were not seen in cell levels of melanoma A375<sup>62</sup>.

#### 10. Bergamot, *Allium sativum*, and *Allium cepa*

In a study it was shown that bergamot extract by lacking monoterpens like limonene cause death of cancer cells<sup>76</sup>. Also, garlic was useful in removing free radicals so it has a anti-oxidant behavior<sup>51</sup>.

#### 11. *Caryophyllium aromaticus* and *Cinnamomum verum*

Extract of *Caryophyllium aromaticus* has Eugenol, Caryophyllin, alcohol, benzilic, benzoate Demotil, furfury, and ethylene<sup>25</sup>. Eugenol is a main material is used to control pain in dentists. It has anti-cancer affects in in-vivo and in-vitro. It was shown that this compound causes apoptosis in cancer cells on human beings colon<sup>36</sup>. It can control melanoma, too. Chemical compound of *Caryophyllium aromaticus* contain mostly Linalool, aldehyde, arimethoxy, Cinnamic, Caryophyllin, betacinol, and Eugenol. In a study it was reported that extract of *Caryophyllium aromaticus* controls growth factor of endothelial of vessels sub-type VEGFR2. So, it controls Angiogenesis in cancer. It was also reported that CB403 is a chemical material that is derivative of cinnamyl aldehyde, that is able to control cancer. The studies of in-vitro and in-vivo show that *Caryophyllium aromaticus* has the potential ability to control cancer<sup>39</sup>. It was shown that level of cinnamyl aldehyde of *Caryophyllium aromaticus* causes stopping cells growth and increasing apoptosis<sup>20</sup>. Extract of *Cinnamomum verum* is a kind of hormone stimulator. It controls melanine production so it controls oxidative stress in melanoma B16<sup>15</sup>.

## 12. Saffron and *Urtica dioica*

The main part of saffron is crocin, croctin, and saffronal. In a study it was shown that saffron controls colon of cancer cells. It has no role in growth of healthy cells. Consuming saffron as an element in foods controls cancer. It reduces speed of growth of tumor<sup>64</sup>. It was also shown that long time consuming of crocin in rats with colorectal tumor caused long time life of the rats with reduce in tumor growth<sup>23</sup>. *Urtica dioica* contains tanon, licitin, formic acid, nitrate-potassium, and calcium. It contains also ironic compounds and vitamins. *Urtica dioica* contains a kind of glycoside that makes skin red color. A material can be extracted from *Urtica dioica* in title of Urticin. It was reported that leaves of *Urtica dioica* has the effects of controlling breast cancer MCF-7 cells<sup>21</sup>. The affects of anti-cancer ability of *Urtica dioica* was shown in in-vivo and in-vitro<sup>49</sup>. Again, they resulted that *Urtica dioica* controls the cells in colon cancer HCT-116<sup>6</sup>.

## 13. *Coriandrum sativum*, Gossypol, and *Nigella Sativa*

Effective compounds in *Coriandrum sativum* involve aldehyde, P.Cymen, Pinenes, :inalool (70-80%), Geranoil, Terpenin, and Phellanderin. In a study it was shown that extract of has anti-cancer ability in MCF-7 cancer cells<sup>89</sup>. In a review it was reported that extract of Gossypol has a role in curing chronic illnesses like Malaria, Aids, and Psoriasis<sup>7</sup>. Again it can control and cure protective tumors. Autophagy curing is a strategy in curing tumor. In a survey it was reported that Thymoquinone is a autophazhe controller in level of glioblastoma<sup>69</sup>

## CONCLUSION

Cancer is cause of death in current societies and it is one of the mortal illnesses with different types. Today, some different medicines are introduced but they have not been effective and were not able to control cancer, yet. Using natural and herbal materials is one strategy to cure cancer. This strategy has rooted in past decades to cure cancer<sup>97</sup>. About 50% of medicines are derived from plants; hence plants can be investigated more because considering them is increasing. According

to the past researches in the field of these effective materials and their effects on cancer and according to primary researched on plants and lack of fundamental knowledge on plants, more researches can improve their usage<sup>98-101</sup>. There are different methods to stop cancer. In this study, our aim was to introduce important medical plants to control cancer and also, to introduce the plants that are potential to do that. Although, a lot of plants have been searched for anticancer activity, however, clinical trials and the researches to investigate the mechanism actions of these plants are scarce. Cancer is associated with increase free radicals which induce oxidative stress. Most of these plants have phenolic compounds with antioxidant activity. Hence, they may have acted by their phenolic components and by antioxidant activity and other plants which have these compounds<sup>102,105</sup> may have anticancer, too.

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