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PLANT DERIVED ANTICANCER AGENTS FOR THE TREATMENT OF CANCER

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ABSTRACT: Cancer is defined as a condition where cancerous cells multiply out of control in the body. It severely affects the human population on a global basis. New therapies are constantly needed to prevent and treat this life-threatening disease. Natural-derived compounds are attracting scientific and research interest due to their substantially fewer side effects than the current cancer treatment. Plants produce secondary metabolites with anticancer properties and are being examined for their potential to be used as clinical drugs. Amazingly, antineoplastic activity has been reported even in most commonly found locally dwelling plants like ginger, turmeric, garlic, and Ashwagandha, besides their use in other illnesses by the local community. However, many medicinal plants are yet to be properly unveiled for their potential as anti-cancerous agents. They need extensive research and valuable resources for in-depth studies like identification, isolation, *in-situ* studies, bioequivalence studies, and *in-vitro, ex-vivo,* or *in-vivo* studies. This review summarizes the role of bioactive compounds in cancer, the mechanism by which compounds show anticancer activity, and the list of plants used for anticancer activity and clinical trials. The scientist will test plant-based anticancer agents and fill the research gap seeking chemopreventive substances.

INTRODUCTION: Today's modern era has significantly improved people's quality of life with newer established technologies and utilities, especially in the healthcare sector, like developing new diagnostic techniques, medical devices, treatment strategies, and surgical procedures. However, there are certain deadly diseases for which no suitable and appropriate treatment is available, although immense research is already on them.

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Cancer is a life-threatening disease that costs about 8 million out of 14 million people worldwide of every age group as per the world health organization, especially in developing and developed countries [1]. Cancer increases the mortality rate every day, with an estimated 13.1 to 17 million fatalities by 2030 [2]. Cancer has been ranked second after cardiovascular diseases for morbidity and mortality in the general population [3].

Cancer is a situation in which the body's normal cells undergo uncontrolled division leading to tumor formation at the affected site, which damages and affects adjacent normal healthy tissues abnormally [4]. The prime reason behind the cancer transformation of normal cells is a mutation in DNA and hence, in genes, leading to the development of oncogenes in them.

These can be caused by physical factors (X-rays), organic compounds, virus-infected pathogenic microorganisms, or behavioural and dietary variables such as a lack of physical activity, smoking, alcohol intake, and an unhealthy diet [5]. The cancer cells can stimulate tumor growth at the local site (benign tumor) or can be significantly transmitted to various parts or organs of the body *via* the bloodstream (malignant tumor) [6]. Cancer can be classified into various types based on affected sites like cells, tissues, or organs, as represented in Table [7].

TABLE 1: CLASSIFICATION OF CANCER

S. no.	Types of cancer	Affected / Associated part
1	Carcinoma	Skin, lungs, breast, pancreas, other organs & glands
2	Sarcoma	Bone, muscle, adipose tissue, blood vessels, cartilage or other soft, connective tissue
3	Melanoma	Melanocytes (pigmentation of the skin)
4	Lymphoma	Lymphocytes
5	Leukemia	Blood

Various methods are used to treat cancer, including traditional drugs 8 as extract of plant 9, chemotherapy 1, radiotherapy, and surgery. Treatment of cancer using certain chemicals, *i.e.*, chemotherapy, tends to cause side effects in cancer patients and severe adverse drug reactions like nausea, vomiting, hair loss, discomfort, and mental distress, simultaneously affecting other normal cells because of its non-selective approach and toxicity on slight over dosage [7].

Patient non-compliance overdosage is also a significant problem in chemotherapy treatment. Nevertheless, surgery needs to be performed on terminal cancer patients. In current years, there has been a substantial shift towards traditional natural herbal medicines and the active compounds obtained after extraction from plants for cancer treatment because of various shortcomings of chemotherapy, as mentioned above.

Since, the herbal medicines are naturally obtained, they have lesser toxic side effects on patient health, are easily affordable, are considered safe to use, and produce deemed positive results [10] Plants produce compounds like volatile oils, resins, gums, alkaloids, terpenoids, saponins, and secondary metabolites. The anti-cancerous evaluation and the efficacy have been determined with the help of various assays performed on several induced tumours as mentioned below:-

1. MTT (3 - (4, 5 - dimethylthiazol - 2 - yl) - 2, 5-Diphenyltetrazolium bromide) Colorimetric Assay: The extract mixed with DMSO is added to a diluted cell culture media (pure cell lines) and seeded for incubation in 96 well-microtiter plates along with the addition of MTT. Cell viability and absorbance were determined at definite time intervals [11].

2. WST - 1 (4 - [3 - (4 - iodophenyl) – 2 - (4 - nitrophenyl) - 2H – 5 - tetrazolio] - 1, 3 - benzene disulfonate) Colorimetric Assay: Firstly, pure cell lines are incubated in 96 well-microtiter plates with culture media. Later, definite concentrations of the extract are added and simultaneously dissolving the contents in DMSO. Finally, adding definite proportions of WST-1 to the above-solubilized mixture. The absorbance was determined at definite time intervals [12].

3. SRB (Sulforhodamine B) Method: Absorbance was determined for cultured RPMI 1640 medium of fetal bovine serum in which extract, TCA, and SRB solution were added simultaneously and kept for incubation [13].

4. Alamar Blue Resazurin Reduction Assay: Serial dilutions of plant extract are prepared with a medium containing pure cell lines suspended in DMEM and seeded for incubation in 96 well-microtiter plates. Afterward, culture media along with resazurin is added and kept for further incubation. The cytotoxic effect of the extract is determined by analyzing the resultant intensity of the fluorescent dye.

Various researchers proposed herbal extract, and the compound derived from the plants showed anticancer effects by numerous mechanisms. They have oxidation-resistant properties or act as antioxidants, resulting in an antiproliferative effect and inducing apoptosis through various subcellular metabolic pathways like decreasing the lipid peroxidation level, acid phosphatase activity, or

inhibition of PI3K/Akt pathway [14] or repairing DNA and enhancing body immunity [15] Some of them are known to cause the arrest of the cell cycle at the metaphase stage by binding to tubulin protein, an essential constituent of microtubules that disrupts its functions and hence, mitotic spindle apparatus.

TABLE 2: FORMULATION OF ANTICANCER DRUG

S. no.	Active chemical constituent of plant	Formulated anticancer drug
1	Taxanes	Paclitaxel (taxol), docetaxel
2	Vinca alkaloids	Vinblastine, vindesine, vincristine
3	Camptothecin	Camptothecin derivatives like irinotecan
4	Epipodophyllotoxins	Etoposide, teniposide

In this way, they prevent cancer cell proliferation and suppress tumor growth. Any plant part like stem, leaves, bark, flowers, shoot, roots, rhizomes, and fruits, which have anti-cancerous properties, can prepare extracts and derive novel compounds for treating cancer *via* various extraction methods [15] Although anti-cancerous activity has been detected in more than 3000 plants [16] till today, in the pharmaceutical market, only four major classes of drugs or medicinal agents obtained from plants [17] are available for cancer treatment with suitable approved formulations for patients which are mentioned in the table below:-

Mechanisms Involved in Anticancer Activity of Herbal Drugs: Numerous herbal drugs show anticancer potential used in cancer therapy. Various mechanisms responsible for the anticancer potential of the herbal medication are described below:

1. Apoptosis: Several cancers are therapeutically targeted by apoptosis, the most common process of programmed cell death. Apoptosis is characterized by morphological changes such as heterochromatin mass core, shrinkage of the cell membrane, and losing cytoplasmic organelles' position. Researchers found that several dietary compounds inhibited carcinogenesis *via* induction of apoptosis. These compounds include curcumin, resveratrol, apigenin, quercetin, and ellagic acid [18, 19]. Apoptosis induction is the most significant marker of the anticancer herbal drug [20].

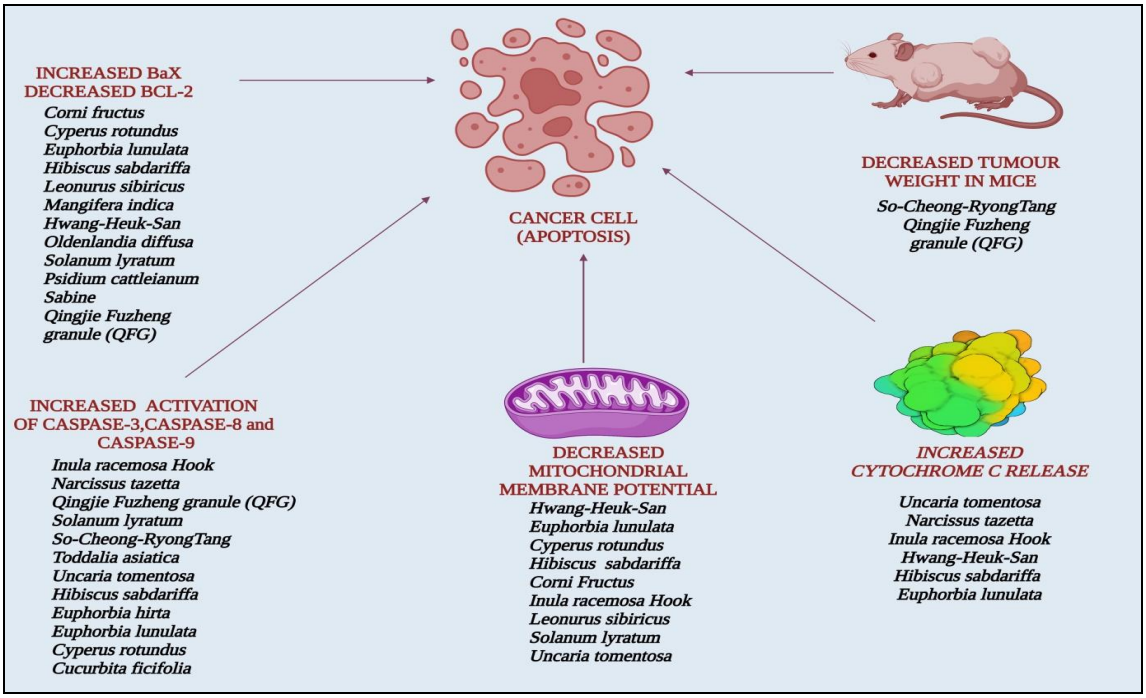

FIG. 1: HERBAL DRUG SHOWING ANTICANCER POTENTIAL *VIA* APOPTOSIS

2. Angiogenesis: It is the process which involves the development of new blood vessels from the old blood vessel resulting in increased blood flow [21]. Angiogenesis plays an essential role in cancer pathogenesis, and targeting is necessary for treating the disease [22]. A variety of natural compounds have been recently shown to modulate tumor angiogenesis by inhibiting angiogenesis-associated cytokines or other mechanisms [23]. These compounds include Resveratrol, Epicatechin,

Epigallocatechin, Genistein, Curcumin, *Triphala churna*, Red ginseng, and Sanguinarine [24]. These plant-derived compounds act on various factors like pro-angiogenic (vascular growth endothelial factor), receptor-mediated signaling pathways (PI3K/Akt), matrix protein, and hypoxia-inducible factor. Different molecular mechanisms have been used to describe many plant-based compounds that exhibit antiangiogenic properties, shown in **figure 2.**

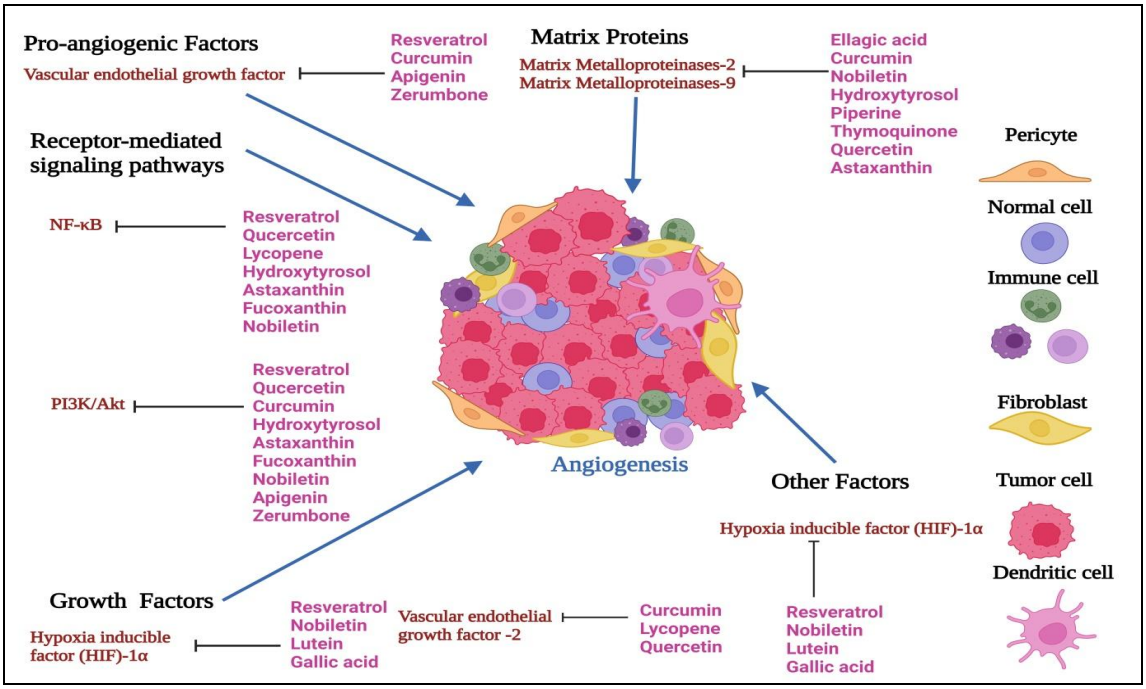

FIG. 2: HERBAL DRUG SHOWING ANTICANCER POTENTIAL *VIA* ANGIOGENESIS

3. Cell Cycle Arrest: In the cell cycle series of events occurs at the macromolecular level, *i.e.*, cell division and formation of two daughter cells [25]. In a cell cycle process, a new piece of DNA is produced, chromosomes must be segregated, cells undergo mitosis, and then they begin to divide [26]. A cell's ability to adapt to a constantly changing microenvironment relies on regulating cell cycle progression [27, 28].

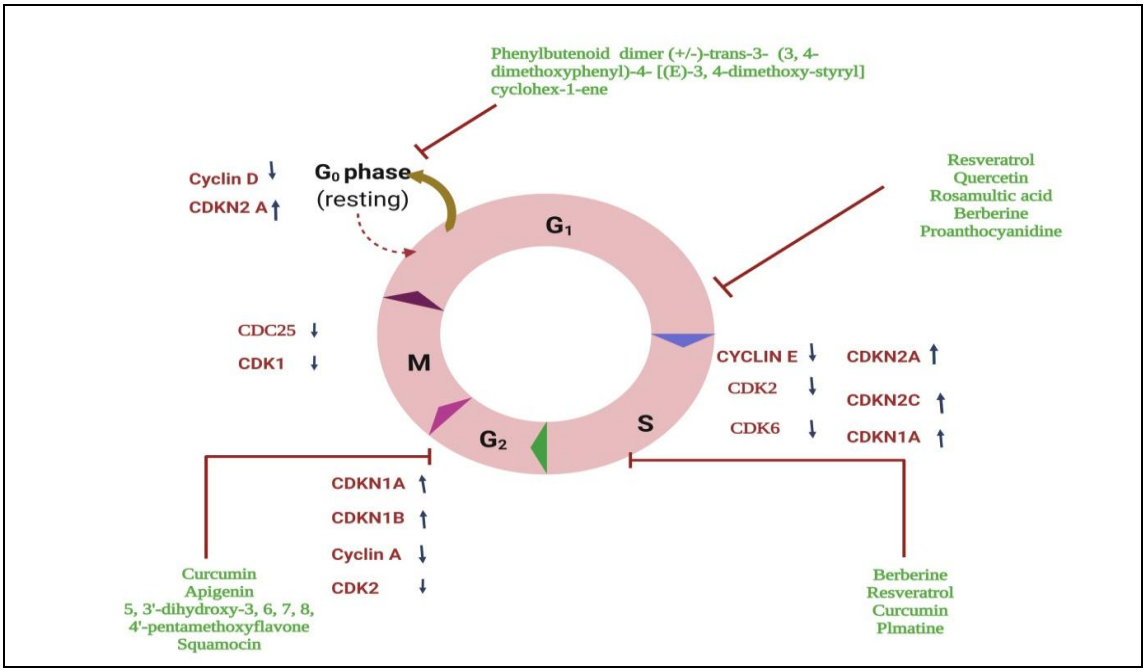

FIG. 3: HERBAL DRUG SHOWING ANTICANCER POTENTIAL *VIA* CELL CYCLE ARREST

Understanding how uncontrolled and rapid cell division contributes to cancer development is the key factor in selecting the anticancer drug. It has been shown *in-vivo*, *in-vitro* and in clinical studies that it is possible to kill cancer cells with natural compounds that inhibit the cell cycle arrest.

Various natural compounds berberine, quercetin, apigenin, chebulagic acid, squamocin, rosamultic acid, silibinin, bufotalin palmatine, paclitaxel, rhizoxin, and tryprostatin acting on the cell cycle at different checks point of the cell cycle. Different checkpoints are affected by various herbal drugs, as shown in diagram 4.

4. Autophagy: Autophagy is a catabolic process that evolved and delivered cytoplasmic components to the lysosome for degradation in lysosomes [29]. The main objective of autophagy is to maintain cell vitality by eliminating damaged proteins [30, 31]. There has been evidence that natural products play an essential role in modulating autophagy, co-related to pro-survival autophagy or autophagic cell death [32, 33].

These compounds include Quercetin, Kaempferol, Genistein, Resveratrol, Rottlerin, Ursolic Acid, Camptothecin, Neferine, and Thymoquinone [34].

To develop novel therapeutic approaches, autophagy targets must be identified. Several natural products can induce or inhibit autophagy and target various stages of autophagy, as shown in the figure.

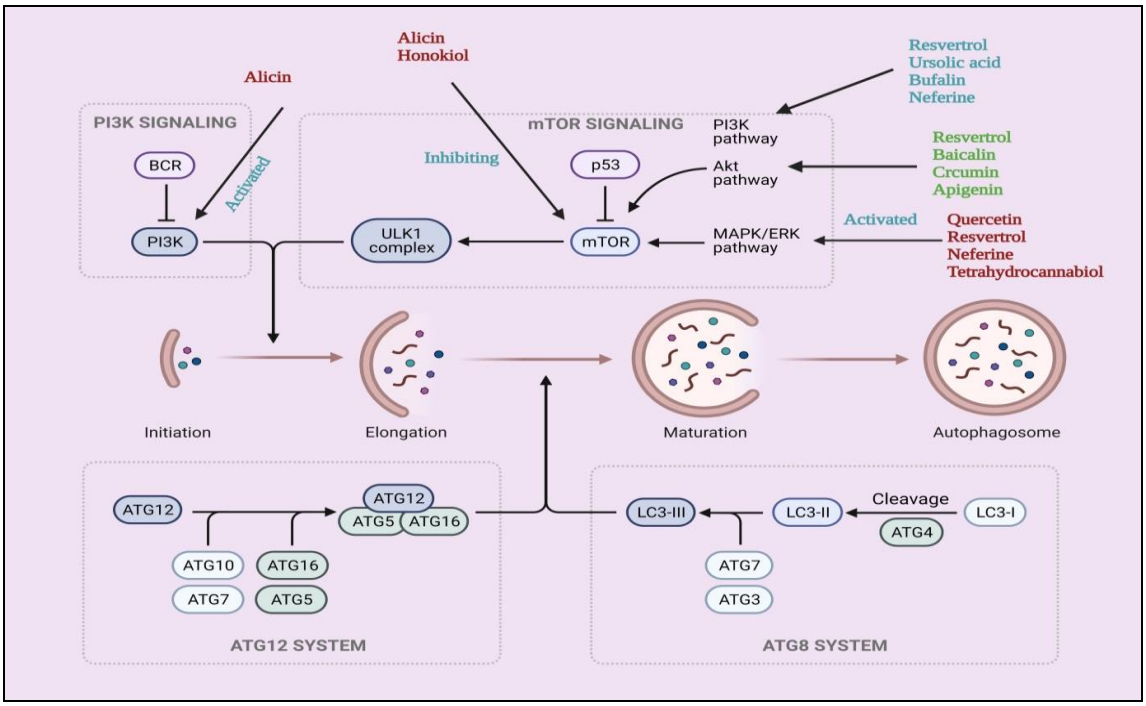

FIG. 4: HERBAL DRUG SHOWING ANTICANCER POTENTIAL *VIA* AUTOPHAGY

Phytochemicals and the active constituents derived from different plant parts, *i.e.*, leaf, stem, rhizome, fruit, seed, root, pericarps, and fruit, show different pharmacological properties and therapeutic potential.

The different experimental studies found that plant extracts and their isolated phytoconstituents can exert chemopreventive actions [35].

These herbal drugs act by different approaches, i.e., made more responsive cancer cells to herbal chemotherapeutic drugs, increase the accumulation of herbal drugs in cancerous cells, and reduce the adverse effects of chemotherapeutic agents [36].

Herbal drugs from natural sources are excellent candidates for cancer treatment because of their capacity to affect different targets such as migration and growth of cells and numerous molecular pathways.

Updated information about plant binomial name, common name, family name, part of the plant used, active constituents, and the mechanism responsible for anticancer activity are given in **Table 3.**

TABLE 3: MEDICINAL PLANT USED AS ANTICANCER DRUG

S. no.	Plant binomial name	Common name	Family	Plant part used	Effective against specific cancer type	Active chemical constituent	Mechanism of action	Ref.
1.	*Zingiber officinale*	Ginger, inguru	Zingiberaceae	Rhizome	Gastrointestinal, esophageal, liver	Gingerols converted to shogaols, paradols, zingerone	Suppresses TNFα & reduces the expression of NF_kB	37
2.	*Curcuma longa*	Turmeric, kaha	Zingiberaceae	Rhizome	Colon, hepatocellular, MCF-7 & ZR-75 breast type, renal, prostate, T-cell leukemia, B cell lymphoma	Curcumin	Downregulation of COX-2 enzyme, apoptosis via caspase-3 activity & increasing level of ROS, Ca^{2+}	38
3.	*Hemidesmus indicus*	Indian sarsaparilla	Apocynaceae	Root , leaves	Leukemia, liver, uterine breast, HepG2	Ledol, nerolidol, caryophyllene, camphor, borneol, lupeol, dodecanoic acid	Upregulation of CD83 and activation of caspases 3&9, inhibition of glutathione S-transferseP expression	39-42
4.	*Munronia pinnata*	Bin kohomba	Meliaceae	Leaves, root & even whole plant	Lung, brain, LLC, T47D, S-180, MethA, PANC-1	B-caryophyllene, caryophyllene oxide ganoderiol F	Inhibits PI3K, AKT, Mtor, stat3 responsible for cell proliferation	43-44
5.	*Smilax zeylanica*	Kumarika, kabarossa	Smilacaceae	Root, stem	Lung cancer, Breast cancer (MDA-MB 231, MCF-7)	Diosgenin, smilagenin, β-sitosterol, phenolics, flavonoids, tannins	Antioxidant activity, upregulation of p53 tumor suppressor gene, downregulation of Bcl2	45
6.	*Tinospora cordifolia*	Heart-leaved moonseed	Menispermaceae	Stem	Leukemia, Hela	Berberine, choline, tembetarine, tetrahydropalmatine, β-sitosterol, cordiofolioside A,giloinsterol, furanolactone, palmatine.	Inhibit cell cycle at G_1 & G_2 by suppression of cyclin D1, anti-apoptotic protein Bcl-xL	46-47
7.	*Adenanther apavonina*	Red lucky seed, madatiya	Leguminosae	Bark	Leukemia (HL-60), lymphoma, Hela cells, HCT-116 cells	β-sitosterol, arginine, cysteine, arachidonic acid, dulcitol, lignoceric acid, malonic acid	Free radical scavenger activity, antioxidant effect, arrest of G_2 phase (prevents cell proliferation)	48
8.	*Thespesiapopulnea*	Malvaceae	Tulip tree, gansuriya	Leaves	Leukemia, lymphoma, B16-F10 melanoma	,Lupeol, β-sitosterol, Kaempferol.	Reduction of glutathione level, apoptosis, antioxidant activity by quenching free radicals	49-50
9.	*Phyllanthus emblica*	Phyllanthaceae	Gooseberry, nelli	Fruit or fruit juice	Throat, lung cancers, A549 (lung), HepG2, Hela, SW620 (colon)	Pyrogallol, quercetin, Kaempferol,geraniin.	Induces caspase 3/7 & upregulated Fas protein, inhibiting NF_kB	51-52
10.	*Boerhavia diffusa*	Nyctaginaceae	Hog weed, karichcharani	leaves	Gastric, liver, MCF-7 cells	Rhamnoside,quercetin, borhaavone.	Inhibits S, G_1 phase of cell cycle, apoptosis Inducement	53
11.	*Ziziphusnum mulariawight*	Rhamnaceae	Harbor, wild jujube	Root, bark, stem, flowers, seeds	p53 mutant cells	Botulin, betulinic acid	Generation of ROS, Topoisomerase-I inhibited, MAP kinase activated	54-55
12.	*Andrographispaniculata*	Acanthaceae	The king of bitters, kiryat	Roots, leaves	KB, P388, MCF7, HCT-116, HT29	Diterpenes, flavonoids, stigmasterols, andrographolide	Alterations in the levels of glutathione, Glutathione-S-transferase activity increased	56-59

13.	*Centella asiatica*	Apiaceae (umbelliferae)	Brahmamanduki, Asiatic pennywort, gotu kola	Leaves, whole plant	Ehrlich ascites cells	Vallerine, pectic acid, sterol, flavonoids, ascorbic acid,asiaticoside,	DNA synthesis inhibition, increase the level of Ca^{2+} ATPase	60-61
14.	*Annona atemoya*	Annonaceae	Sour-sop of America, mamaphal	Root, bark, leaf, fruit	A-549, MCF-7, HT-29, HepG2	Bullatacin, annomuricin A&B,	Induces apoptosis *via* antitoxidant activity	62-64
15.	*Mappia foetida*	Icacinaceae	Amruta, kalgur, narkya	Whole plant, leaves	Hela cells, L-120 cells, breast carcinoma	Camptothecin	Inhibits nucleic acid synthesis, DNA topoisomerase-I	65-68
16.	*Withania somnifera*	Solanaceae	Ashwagandha, winter cherry	Roots, leaves	HL-60, sarcoma	Withanolide A, withaferin A	Apoptosis activated and generation of NO, increase in production of inflammatory mediators ($CD4^{+}$, IFN-ϒ, IL-2)	69-73
17.	*Cedrus deodara*	Pinaceae	Devdar (timber of gods), Himalayan cedar	bark	HL-60 cells, leukemia	Oleo-resin, wikstromal, matairesinol, dibenzylbutyrolactol	Activation of caspase 3,8,9, increase in level of NO, sub G_0 cells concentration and formation of apoptotic body.	74-75
18.	*Boswellia serrata*	Burseraceae	Indian oli-banum, salaiguggul	Stem, bark,	Hela cells, carcinoma	Oleo gum resin, boswellic acid	Excessive OS, NO formation, increased sub G_0 fraction, Bcl-2 cleavage, expression of CDR4, apoptosis	76-80
19.	*Aloe barbadensis*	Cape aloe, mussabar	Asphodelaceae (liliaceae)	Whole plant	HepG2, breast and cervical cancer	Aloin, emodin, volatile oil, barbaloin, chrysophanic acid, β-barbaloin, isobarbaloin	Downregulation of cyclin D1, CYP1A1, CYP1A2	81
20.	*Arbutus andrachne*	Greek strawberry tree	Ericaceae	Leaves,aerial parts	MCF-7 cell line, CACO-2 and HRT18 cell line	Arbutin, flavanoids, polyphenols	Antioxidant activity, antiproliferative and lipid peroxidation	82
21.	*Aristolochia longa*	Barraztam	Aristolochiaceae	Roots	VCREMS, breast cancer	Aristolochic acid, aristolctams, aporphines, isoquinolones, flavanoids, coumarins, terpenoids	Induced apoptosis	83
22.	*Asplenium nidus*	Bird's nest fern, langsuyar	Aspleniaceae	Whole plant	HepG2, HeLa	Gliciridin-7-O-hexoside, phenols, flavanoids, quercetin, kaempferol, myricetin-3-O-rhamnoside	Atiproliferative effect	84
23.	*Averrhoa bilimbi*	Star fruit, carambola	Oxalidaceae	Fruit, leaves	MCF-7	B-sitosterol, apigenin, fucopyranoside, flavanoids	Induced apoptosis *via* antioxidation and inhibits DNA replication	85-86
24.	*Azadira chtaindica*	Neem, idian lilac, margosa	Meliaceae	Leaves, seeds	EACC, HBP carcinoma	Nimbin, nimbolide, nimbidin,limonoids, β-sitosterol, quercetin, ascorbic acid, polyphenolic compounds, azadirachtin	Antioxidant activity, Modulated the activity of VEGF, p53 and NF-kB	87-88
25.	*Barleria grandiflora*	Devkaranti, shemmuli	Acanthaceae	Leaves	A-549, DLA	Alkaloidal, phenolics, flavanoidsbalarenone, barlerinoside, lupulinoside, lupeol, β-sitosterol	Antioxidant activity leading to induced cell death via ROS generation, decline in tumor growth by antiproliferative effect	89
26.	*Berberis aristata*	Indian barberry, daruhaldi, tree urmeric	Berberidaceae	Root, stem	Colo205, Hop62, HT29, SiHa, MIA-PA-CIA-2, DWD, T24, PC3, A549, ZR75-I, A2780, DU145,	Alkaloidal, flavanoids, berberine, berbamine, columbamine, oxyacanthine, chelidonic acid	Influencing the mitochondrial Transmembranepotential, MMP regulation, p53 activation, NF-kB signal activated ,	90

					MCF7, K562		inhibition of telomerase.	
27.	*Caesalpinia sappan*	Sappan wood, brazil wood	Caesalpiniaceae (fabaceae)	Heartwood, leaves	MCF7, A549 cell lines	Ombuin, quercetin, rhamnetin, sappanchalcone, sappanol, 8-methoxy bonducellin, chromanomones, brazilein, brazilin	Induced S phase & G_2/M phase accumulation, acts on p53 independent pathway & induce apoptosis	91-92
28.	*Calligonum camosum*	Fire bush, arta	Polygonaceae	Whole plant	HepG2	Catechin, dehydrocatechin, kaempferol, quercetin, isoquercetrin, mequilianin, β-sitosterol, lauric acid, myristic acid, palmitic acid	Apoptosis induced *via* ROS generation, induced G_0/G_1 , antioxidant enzyme catalase	93-95
29.	*Cenchrus ciliaris*	African foxtail grass	Poaceae	Aerial parts, roots	HepG2, CACO, A-549	Glycosides, flavanoids, steols, triterpenes, anthraquinones	Antioxidant and antiproliferative activity	96-97
30.	*Cenchrus antiochia*	Sand burs, sand spur	Asteraceae	Aerial parts	Vero , HeLa	Alkaloidal, phenolics, sterols, anthraquinones	Antioxidant activity and altering the caspase enzyme avtivation	98
31.	*Vitexagnus castus*	Monk's pepper, abrahm's balm	Lamiaceae	Fruits, leaves	MCF-7 breast cancer	1,8- cineole, phenolic compounds, sabinene, β-caryophyllene, flavanoids (vitexin, casticin), iridoid glycoside (agnuside, aucubin)	Potent antioxidant, cytotoxic & apoptotic activity	99-100
32.	*Chrysanthemumcoronarium*	Chop-suey greens	Asteraceae	All parts	T47D, HRT18, CACO-2, A375.MCF-7	Camphor, α-pinene, lyratyl acetate, β-pinene, chrysanthenylactetae, β-farnesene, germacrene, camphor, perillaldehyde, isoitalicene	Radical scavenging activityrelative to the strong antioxidant effect, also exhibits antiproliferative effect	101-102
33.	*Cocculus hirsutus*	Broom creeper, patalgarudi	Menispermaceae	Aerial parts	MCF-7, Dalton's lymphoma ascites	Flavanoids rutin, liquiritin, quercetin, hirsudioltrilobine, magnofluorine, ginnol, β-sitosterol	Endogenous antioxidant mechanism	103
34.	*Cordadichotoma*	Indian cherry, bird lime tree	Boraginaceae	Leaves	PC3, MCF-7	Stearic acid, betulin, octacosanol, oleic acid, α-amyrins, lupeol-3rhamnoside.	Antioxidant activity leading tot decrease in cell viability	104
35.	*Cotynuscoggygria*	Smoke tree	Anacardiaceae	Leaves	Vero , HeLa	Quercetin, gallic acid, disulfuretin, myricetin, taxifolin, phenolics, flavanoids, tannins, limonene, α-pinene	Lipid peroxidation inhibition	105
36.	*Crataegus microphylla*	Hawthorn	Rosaceae	Leaves	Vero , HeLa	phenolic compounds, chlorogenic acid, hyperoside and epicatechin	Potent antioxidant effect leading to apoptosis	106
37.	*Croton caudatus*	Scandent shrub	Euphorbiaceae	Leaves	DL, MCF7, HeLa	ethyl hexatriacontanoate, palmic acid, stearic acid, zheberiesinol, vanillin, vanillic acid, syringic acid, octacosanoic acid, succinic acid, inosine, isosinensetin	Antioxidant effect, free radical scavanging activity leading to cellular toxicity	106
38.	*Delphinium staphisagaria*	Stavesacre	Ranunculaceae	Seeds	H56, N2A	Isoazitine, azitine,19-oxodihydroatisine, dihydroatisine, 22-O-acetyl-19-	Used for hair loss treatment in cancer patients and have cytotoxic and	107-108

						oxodihydroatisine.	angiogenic potential	
39.	*Dillenia pentagyna*	Dog teak	Dillenaceae	Stem, bark	DL, MCF7, HeLa	phenolics, flavonoids, tannin, saponin, alkaloid, and terpenoids	apoptosis via NF-Kb pathway through the increase of the bax to Bcl_2 ratio, leading to fall of MMP & subsequently induced release of cytC , activation of caspase-3 followed by nuclear fragmentation in A549 cells	109
40.	*Euphorbia tirucalli*	Indian tree spurge, pencil tree, finger tree, petroleum plant	Euphorbiaceae	Leaves, stem	MiPaCa2	Terpenes, sterols, taraxasterol, tirucallol, euphol, α-euphorbol, tigliane, ingenane	Inhibition of protein kinase activity, induce genotoxicity, and changes in antioxidant gene expression	110-111
41.	*Ficus racemosa*	Goolar, cluster fig	Moraceae	Roots, bark	HL60	α-amyrin acetate , tannin, wax, cerylbehenate,saponinglluanol acetate, β-sitosterol (A).	Antioxidant effect observed in-vitro	112-113
42.	*Helicteres isora*	Enthaniavartani, marodphali,	Sterculiaceae	Plant (Whole)	H60, PN-15,HeLa-B75.	Cucurbitacin b ,gallic acid, vanillin.	Induced apoptosis, generation of ROS & antioxidation activity	114-115
43.	*Hibiscus micranthus*	Tiny flower hibiscus, rose mallow	Malvaceae	Aerial parts	HepG2, MCF-7	β-sitosterol, phenolic acids, fatty alcohols and acids	Increase oxidative stress, decrease MMP, selectively induced apoptosis via ROS production, though the exact mechanism is not known	116
44.	*Hypericium kotshcyanum*	St. john's wort, goat weed	Hypericaceae	Aerial parts	Vero , HeLa	Hypericin	Apoptosis Induce	117-118
45.	*Inulavis cosa*	False yellowhead, woody fleabane	Compositae	Flowers	MCF-7, Hep-2	Sesquiterpene lactones (tomentosin, inuviscolide)	Inhibition of cell proliferation	119-121
46.	*Jasmium sambac*	Arabian jasmine	Oleaceae	Flowers	MCF-7, Hep-2	benzyl acetate, benzyl alcohol, linalool, geraniol.	Dose dependent tumor cell proliferation inhibition activity	122-123
47.	*Lavandulaangustifolia*	True lavender, narrow-leaved lavender, garden lavender	Lamiaceae	Flowers	MCF-7, Hep-2	Camphor,linalool, terpine-4-ol,	Antiproliferative effect as the main mechanism	124
48.	*Leea indica*	Bandicoot berry	Vitaceae	Leaves	DU-145, PC-3	Phthalic acid, palmitic acid, ursolic acid, gallic acid, β-sitosterol	Augmentation of bax/Bcl2 ratio, induced mitochondrial-mediated apoptosis	125
49.	*Limonium densiflorium*	Sea-lavender, marsh-rosemary	Plumbaginaceae	Shoots	A549, DLD-1	3-hydroxycinnamic acid, myricetin, isorhamnetin	Highest antioxidant effect recorded	126
50.	*Luffa cylindrica*	Sponge guard	Araceae	Aerial parts	MCF-7, Hep-2	Lucyosides C, Lucyosides F, Lucyosides H	Minimise recurrence and metastasis through antiproliferative effect	126–130
51.	*Manilkara*	Chiku,	Sapotaceae	Flower,	MCF-7	Lupeol acetate,	Induce apoptosis *via*	131

	zapota	sapodilla, naseberry, chicle gum		leaves		caffeic acid oleanolic acid	antioxidant effect	
52.	*Mirabilis jalapa*	Marvel of peru, four o'çlock flower	Nyctaginaceae	Roots, stem	Hep-2, MCF-7	Phytosterols, β-sitosterols, stigmasterol, brassicasterol, ursolic, oleanolic acid, betulinic acid, Miraxanthin-III,II,V, vulgaxanthin-I	LDHA inhibition activity in silico	132
53.	*Morus nigra*	Black mulberry, blackberry	Moraceae	Leaves	HeLa, MCF-7	β-Sitosterol, flavanoids	Antioxidant & cytoprotective effect, decrease tumor growth via antiproliferative effect	132
54.	*Narcissus tazetta*	Daffodil, Chinese sacred lily	Amaryllidaceae	Aerial parts, flowers	MCF-7, Hep-2	Heptanal, myrcene, cineole, ocimene, linalool, nonanal, benzyl acetate, terpineol	Antioxidant as the major mechanism	133
55.	*Nepetaita lica*	True catnip	Laminaceae	Aerial parts	Vero , HeLa	α-Pinene, 4αβ,7α,7αβ-nepetalactone, 4αα,7α,7αβ-nepetalactone, α-amorphene, ϒ-cadinene, cis-calamenene, β-pinene, β-caryophyllene	Effect on lipid peroxidation, functions of oxidative enzymes	134-135
56.	*Ocimum sanctum*	Tulsi, holy basil	Laminaceae	Leaves	HFS-1080	Oleanolic acid, ursolic acid, linalool, carvacrol, eugenol	Cytotoxic effect on leukemia cell lines	136-138
57.	*Oldenlandia corymbosa*	Flat-top mille grains, dimond flower	Rubiaceae	Leaves	K562	Geniposide, 6-α-hydroxygeniposide	Significant cytotoxic effect with *Parthenium hysterophorus* on cancer cell lines	139
58.	*Olea europea*	Common olive, Indian olive	Oleaceae	Leaves	MCF-7, B16F10, HeLa	Secoiridoids such as oleuropein, ligstroside, methyloleuropein, flavanoids	Antiproliferative effect leading to decrease in tumor growth	140-141
59.	*Ononis hirta*	Restharrows	Fabaceae	Parts (Aerial)	Breast cancer cell line MCF-7	Flavanoids, terpenoids, phenolic compounds, alkaloidal	Solid tumor necrosis on combination with *Bifiridobacteriumlongum*	142
60.	*Origanum sipyleum*	Amaracusgled, Turkish oregano	Laminaceae	Aerial parts	Vero , HeLa	ϒ-Terpinene, pcymene	Inhibition of cancer cell migration, proapoptotic activity, inhibit tumor growth	143
61.	*Parthenium hysterophorus*	Santa-maria, white top weed, famine weed, congress grass	Asteraceae	Leaves	K562	Germacrene- D, trans-β-ocimene	Considerable potential effect as cytotoxic & antioxidant action, inhibits lipid peroxidation, increase activity of caspase-3,6,9.	144
62.	*Phagna lonrupstre*	Gnaphalonlowe	Asteraceae	Aerial parts	MCF-7, Hep-2	Dimethylallyl-hydroquinone glucoside,	Antioxidation effect leading to generation of ROS, induces apoptosis	145
63.	*Picrorhiza kurroa*	Kutki, katuka, picrorhiza	Plantaginaceae	Root	Colo205, Hop62, HT29, SiHa, MIA-PA-CIA-2, DWD, T24, PC3, A549, ZR75-I, A2780, DU145, MCF7, K562	Picoside I, II, d-mannitol, kutkiol, kutkisterol, apocynin, androsin	Regulate the expression of cyclinD1 &CDKs help protect cells against carcinogenesis, inhibition of NF-Kb	146
64.	*Piper longum*	Pipli, Indian long pepper	Piperaceae	Fruit	Colo205, Hop62, HT29, SiHa, MIA-PA-CIA-2, DWD, T24, PC3,	α-pinene, caryophyllene,Limonene, α-copaene,	Selectively induced caspase independent apoptosis	147

					A549, ZR75-I, A2780, DU145, MCF7, K562			
65.	*Plectranthus stocksii*	Spur-flower	lamiaceae	Stempart and leaves,	MCF-7, RAW 264.7, Caco cell line	Ferulic acid, caffeic acid, catechin	Antioxidant effect as the major mechanism	
66.	*Populous alba*	Silver poplar, white poplar	salicaceae	Flowers	MCF-7, Hep-2	Tremuloidin, populin, chaenomeloidin, salicin, tremulacin, catechol, benzoic acid, salicylol	Strong antiproliferative, cytotoxic & potent antioxidant properties	148
67.	*Pterocephaluspulverulentus*	Wing head shaped	Dipsacaceae	Aerial parts	MCF-7, Hep-2	Flavanoids, alkaloidal, polyphenols, quercetin	Antioxidant effect and antimigratory effect shown against cancer cell lines	149
68.	*Rosa damascena*	Damask rose, bulgarian rose	Rosaceae	Flowers	Vero , HeLa	Flavanoids, carboxylic acid, glycosides, quercetin	Cell viability decreased	150
69.	*Diplotaxis harra*	Middle east harra, forssk.	Brassicaceae	Whole plant, aerial parts	HCT116, HepG2, MCF7	Quercetin	Antioxidant effect	151
70.	*Salvia officinalis*	Culinary sage, garden sage	Lamiaceae	Aerial parts	MCF-7, B1610, HeLa	Thujone, β-caryophyllene, cineole, α-humulene, β-pinene, β-thujone, camphor, allo-aromadendrene, borneol, α-pinene	Regulates p53 signalling, cell cycle regulation by G_1/S phase arrest	152-153
71.	*Saururus chinensis*	Lizard's tail	Saururaceae	Roots	MCF-7	Glucosides, hydrolyzable tannins, indolealkaloidal, sitosterols, aristolactam A, ellagic acid, corilagin, lyoniside, neolignans	Antiproliferative activity and antiangiogenetic action	154-155
72.	*Scorzonerat omentosa*	Scorzonera	Asteraceae	Aerial parts	Vero, HeLa	Flavanoidaglycones, glycosides, phenolic acids, triterpenoids, bibenzyl derivatives	Antioxidant activity leading to apoptosis	156-158
73.	*Senecio scandens*	Climbing senecio, sai-ek-hlo	Asteraceae	Leaves	MCF-7, DL, HeLa	Senecainin A, 3-methoxyisonicotinic acid, monoepoxylignanolide, pinoresinol	High ration of Bax/Bcl-2 promotes apoptosis activity, upregulation of capase-3,9 proteins	159-160
74.	*Solanum khasianum*	Nightshade	Solanaceae	Fruit	MCF-7, DL, HeLa	Dillapiole, α-cardinol, para-cymene, β-damascenone, α-phellandrene, β-pinene, α-bisabololactate	Cytotoxic effect on cancerous cells and induces cell death and arrest of cell division	161
75.	*Citrullus colocynthis*	Vine of Sodom, bitter apple, bitter cucumber, desert gourd	Cucurbitaceae	Root, bark, leaves	HepG2 hepatoma cells, colorectal cancer	Cucurbitacin, flavanoids, alkaloidal, phenoli acids	Increase in caspase-3 activity and inhibiting STAT3 function	162-163
76.	*Syringa vulgaris*	Common lilac	Oleaceae	Seeds	MCF-7 cell line, Hep-2	Iridoids, lignans, phenylpropanoids, phenylethanoids	Oxidative stresses induces apoptosis in cancer cells	164-165
77.	*Syzygium cumini*	Indian blackberry, jamun	Myrtaceae	Seeds	A2780, MCF7, PC-3, H460	Anthocyanins, glucoside, ellagic acid, isoquercetin, kaemferol, myrecetin	Antiproliferative and antioxidant activity	166-168
78.	*Tabernaemontana divaricata*	East Indian rosebay, moon beam, coffee rose	Apocynaceae	Flowers	NIH3T3, HeLA	A-amyrin acetate, α-amyryloctadecanoate, taraxasterol acetate, calycosin, formononetin, farnisin	Superoxide anion scavenging activity, reduced GSH levels	169-170

79.	*Tecoma stans*	Yellow trumpetbush, yellow bells	Bignoniaceae	Leaves, flowers	A549	Alkaloidal, flavanoids, phenylbenzopyrone	inhibit aromatase & disturbs cell division at telophase	171-172
80.	*Terucrium polium*	Felty germander	Laminaceae	Stems, Leaves	MCF-7, CACO-2, Hep-2,	Agarospirol, caryophyllene, β-caryophyllene, α-humulene, β-bisabolene, β-sesquiphellandrene, dolichodial	Inhibition of DNA oxidation, lipid oxidation	173-175
81.	*Tillandsia recurvata*	Ball moss	Bromeliaceae	Plant	HL60	Caffeic acid	FMS-like tyrosine kinase 3 get inhibited	176-177
82.	*Verbascums inuatum*	Wavy-leaf mullein	Scrophulariaceae	Aerial parts, flowers	MCF-7, Hep-2	Verbathasin A, luteolin, 3-O-fucopyranosylsaikogenin F, verbascoside	Apoptosis enhanced	178-179
83.	*Vitisv inifera*	European wine grape, common grape	Vitaceae	Sap of stem	MCF-7, HeLa	Phenolic compounds, flavanoids	Antioxidant, antiproliferative effect because of epicatechin-3-O-gallate present	180-181
84.	*Zea mays*	Indian corn	Gaminaea	leaves	Hep2	Quercetin diglucoside, maizenic acid, rutin, chlorogenic acid, hydroxycinnamic acid, flavanoids, saponins, phytosterol, eugenol	Oxidative stress induces apoptosis, upregulation of p53	182-183
85.	*Allium savitum*	Garlic	Amaryllidaceae	Bulb	Skin, colon, lung, prostate, leukemia, breast cancer	S-allylcysteine, allicin, S-allylmercapto-L-cysteine	High radical scavenging activity, antiproliferative growth, inhibits tumor growth	184-186
86.	*Acronychia baueri*	Chakkimaram, mootanari, aspen	Rutaceae	Bark	Carcinoma, colon cancer	Alkaloids (normelicopidine, melicopine, acronycine), triterpenelupeol	Antiproliferative and antioxidant effect	187
87.	*Alstonia boonei*	Cheese wood, pattern wood, stool wood	Apocynaceae	Stem, bark, leaf, root	Pancreas, lung, prostate, colon cancer	Echitamine, eugenol, 1,2 benzene dicarboxylic acid, alstiboonine	Antiproliferative and cytotoxic effect	188-189
88.	*Thymus vulgaris*	Thyme	Lamiaceae	Bulb, leaves	MCF-7 cell lines, HeLa	Diallyl disulphide, diallyltrisulphide, allicin, tannins, triterpenes, styerols, flavonoids, glycosides	By controlling interferon signalling, biosynthesis of N-glycxan	190-191
89.	*Tithonia diversifolia*	Gaint Mexican sunflower	Composiae	leaves	HL-60, U373, Col2 colon cancer cells	Tagitinin C, 1-β-methoxydiversifolin, 3-O-methyl ether, 1-β- & 2-α-epoxytagitinin C	Inhibit cell proliferation, induces cell death	192

Clinical Trials on Isolated Constituents (https://clinicaltrials.gov/): Herbal drugs are integral to the health care system. Clinical trials are essential to assess the risks associated with herbal drugs.

In clinical trials, herbal medicines must be proven safe and effective before their effectiveness can be determined. Clinical studies about herbal anticancer are interventional, observational, and other types mentioned in the literature. In this article, we consider the clinical studies related to herbal drugs used in cancer.

An early phase 1 (NCT01568996) study on Sulforaphane was done to determine the chemopreventive action and modulate the melanoma.

Another phase 1 (NCT03980509) study is performed on curcumin to study its effect on breast cancer. Effect of qucertein (NCT03980509) has been tested on polyphenols uptake subject's suffering from prostate cancer. Similarly, clinical trials on the herbal drug used as an anticancer drug are listed in **Table 4.**

TABLE 4: CLINICAL TRIAL ON HERBAL DRUGS

Description	Type of study	Phase of study	Design of study	Age (years)	Subject participated	Status of study	Reference
Traditional Chinese Medicine in breast and other cancers	Interventional	Phase 2	Randomized	≥21	80	Recruiting	NCT04104113
Teng-Long-Bu-Zhong-Tang herbal along With Chemotherapy in Colorectal cancer patients	Interventional	Phase 1	Randomized	18-70	72	Completed	NCT01975454
Herbal drug products in patients of breast cancers for reduction of dermatitis induced by radiation	Interventional	Phase 2	Randomized	≥20	150	Completed	NCT02922244
TPE-1 herbal formula effect in breast cancer patients	Interventional	Not Applicable	Randomized	18-70	60	Completed	NCT01142479
KD018 and Sorafenib in patients with hepatic carcinoma	Interventional	Phase 2	Not applicable	≥18	18	Completed	NCT01666756
Dendrobium Huoshanense Granules effects in rectal cancer patients	Interventional	Phase 3	Randomized	18-70	210	Recruiting	NCT04394598
Traditional Chinese Medicine regulation in cancer patients	Interventional	Phase 1	Not applicable	≥20	300	Recruiting	NCT04438564
Da Huang Gang Tsao Tang effect for improving appetite in patients of cancer at late-stage	Interventional	Phase 2	Not applicable	≥20	4	Completed	NCT01503346
Effect of Chinese herbal therapy in women of breast cancer undergoing chemotherapy	Interventional	Not Applicable	Randomized	≥18	Unknown	Completed	NCT00028964
Herbal drug therapy in patients of prostate cancer	Interventional	Phase 2	Not applicable	≥18	43	Completed	NCT00669656
Effect of ACAPH in patients of Intraepithelial neoplasia having smoking history	Interventional	Phase 1	Randomized	45-75	90	Completed	NCT00522197
Effect of combination of chinese and western medicine in cancer patients having constipation	Interventional	Phase 2	Randomized	≥18	60	Completed	NCT02795390
TCM-TSKSR effects in patients having cancer at different stages	Interventional	Phase 2	Randomized	18-75	400	Recruiting	NCT03716518
Herbal Mouth rinse in patients of cancer having mucositis	Interventional	Phase 2	Randomized	18-89	50	Completed	NCT01898091
Angelica Sinensis effect in prostate cancer for treatment of hot fleshes	Interventional	Phase 2	Randomized	≥18	44	Completed	NCT00199485
Traditional and complementary medicine effect in Ovarian Cancer	Interventional	Phase 3	Not applicable	≥18	28	Completed	NCT01419210
Food supplements in cancer threapies	Interventional	Phase 2	Non-Randomized	≥18	60	Recruiting	NCT04474951
Effect of KD018 in colorectal cancer	Interventional	Phase 4	Randomized	≥18	33	Completed	NCT00730158
Sho-Saiko in hepatic cancer	Interventional	Not Applicable	Not applicable	≥18		Completed	NCT00040898
Traditional chinese medicine effect in triple-negative breast cancer	Interventional	Not Applicable	Randomized	18-70	200	Recruiting	NCT04403529
Effect of SH003 in Solid Cancer	Interventional	Phase 2	Sequential Assignment	≥19	11	Completed	NCT03081819
Blue Citrus in breast cancer	Interventional	Phase 2	Randomized	≥18	30	Completed	NCT00702858
Dietary supplement effect in breast cancer	Observational	Phase 3	Cohort	≥18	200	Completed	NCT03959618
FuzhengYiliu effect in chemotherapy patients	Interventional	Phase 1	Non-Randomized	18-75	189	Recruiting	NCT04459754
Chemotherapy and Traditional chinese medicine effect on Lung Cancer	Observational	Not Applicable	Not Applicable	65-80	82	Completed	NCT01780181
Sipjeondaebo-tang in patients of cancer having anorexia	Interventional	Not Applicable	Randomized	20-80	32	Completed	NCT02468141

Siliphos in hepatic cancer patients	Interventional	Phase 2	Non-Randomized	≥18	3	Completed	NCT01129570
Artemi Coffee in Patients of ovarian cancer at advanced stage	Interventional	Not Applicable	Non-Randomized	≥18	18	Recruiting	NCT04805333
Oligo-Fucoidan effect in hepatic cancer	Interventional	Not Applicable	Randomized	≥18	100	Recruiting	NCT04066660
Chamomile gel in prevention of oral mucositis induced by chemotherapy	Interventional	Phase 1	Randomized	20-70	45	Recruiting	NCT04317183
Effect of curcumin on radiation induced dermatitis among the person suffering from breast cancer	Interventional	Phase 1	Randomized	21	35	Completed	NCT01042938
Effect of curcumin on pancreatic cancer was studied.	Interventional	Phase 2	Not applicable	18	50	Completed	NCT00094445
Resveratrol effect on patients with colon cancer.	Interventional	Phase 2	Not applicable	18	11	Completed	NCT00256334
Artesunate effect in Colorectal Cancer at different stages.	Interventional	Phase 2	Randomized	18-70	200	Recruiting	NCT03093129
The effect of Chinese herbs on syndrome differentiation with reduced side effects and increased antitumour effect was studied.	Interventional	Phase 2	Randomized	18	200	Unknown	NCT02737735
This study aims to know the effect of berberine to prevent colorectal adenomas in patients with previous colorectal cancer.	Interventional	Phase 1	Randomized	18-80	1000	Unknown	NCT03281096
To study the effect of lycopene in colorectal carcinoma patients.	Interventional	Phase 2	Randomized	18	28	Completed	NCT03167268
This study aims to know the chemoprevention effect of Sulforaphane in lung cancer in former smokers.	Interventional	Phase 1	Randomized	55-75	72	Recruiting	NCT03232138
The effect of Chinese herbs on syndrome differentiation with reduced side effects and increased antitumour effect was studied	Interventional	Phase 2 Phase 3	Randomized	18	200	Unknown	NCT02737735
This study aims to know the effect of berberine to prevent colorectal adenomas in patients with previous colorectal cancer.	Interventional	Phase 2	Randomized	18-80	1000	Unknown	NCT03281096
This study aims to know the chemoprevention effect of Sulforaphane in lung cancer in former smokers.	Interventional	Phase 2	Randomized	55-75	72	Recruiting	NCT03232138
To study the effect of epigallocatechin gallate colorectal cancer patients.	Interventional	Early Phase 1	Randomized	≥18	50	Recruiting	NCT02891538
A Phase 1 Dose Escalation of Artemi Coffee in Patients With Advanced Ovarian Cancer	Interventional	Phase 1	Non-Randomized	≥18	18	Recruiting	NCT04805333
Kanglaite (Coix Seed Oil) in head and neck Cancer	Interventional	Phase 2	Not applicable	18-80	53	Completed	NCT03101514
Effect of Kanglaite Injection with gemcitabine in pancreatic cancer	Interventional	Phase 2	Randomized	18-75	85	Completed	NCT00733850

CONCLUSION: Throughout the world, cancer threatens millions of lives each year. Aside from affecting a patient's physical health and quality of life, treatments such as surgery and chemotherapy do not dramatically improve the chances of survival. Even though modern medicine has greatly influenced people's lives and synthetic drugs have become more readily available; still, most of the people depend on plant remedies. WHO data shows that greater than 75% of the population rely on plant remedies or extracts for health care needs. Research results have directed to expanding plant-derived products after achieving excellent results and are now conducting clinical trials. An effective

way to inhibit cancer cells is with plant-derived anticancer agents, making them highly valuable. To meet demand and remain sustainable, herbal drugs must be exploited efficiently. The current review may provide researchers with a great deal of information about herbs, their effects on disease, and the safety of using them.

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