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A brief review on plant-derived natural compounds as an anti-cancer agents

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Abstract

Cancer is one of the leading causes of death and globally the figures of cases of cancer are increasing progressively. There are a number of medicines available in the market to treat the different kinds of cancer but no medication is found to be fully effective and safe. The foremost problem in the cancer chemotherapy is the toxicity of the conventional drugs. However, plants and plant-derived compounds have shown effective and safe in the treatment and management of cancers. These days most of the research work on cancer drugs is targeted on plants and plants derived natural compounds. Numerous natural compounds and their analogs have been identified as effective anti-cancer agents and day by day the anti-cancer property of various plants is being identified. Here an attempt is being made through this review to highpoints the natural compounds namely Turmeric, Neem, Tulasi and Ginger and their analogs established as anti-cancer agents.

Keywords: Cancer, medicinal plants, natural compounds, anti-cancer potential, turmeric, neem, Tulasi, ginger

Introduction

Cancer is a major public health burden in both developed and developing countries. It is an abnormal growth of cells in the body that can lead to death. Cancer cells usually invade and destroy normal cells. These cells are born due to an imbalance in the body and by correcting this imbalance, cancer may be treated. According to the American Cancer Society, deaths arising from cancer constitute 2–3% of the annual deaths recorded worldwide. Several chemo preventive agents are used to treat cancer, but they cause toxicity that restricts their usage ^[1].

Immunomodulatory and medicinal properties of herbal and traditional/indigenous drugs

Herbs or Botanical plants are considered as God's gift to human beings in the form of natural medicines. Among the 21,000 medicinal plants listed by the World Health Organization (WHO), 2500 species are native to India, which stands first in the production of medicinal herbs. Natural dietary agents including fruits, vegetables, and spices have drawn a great deal of attention from both the scientific community and the general public owing to their demonstrated ability to suppress cancers ^[2]. Dietary agents consist of a wide variety of biologically active compounds that are ubiquitous in plants, many of which have been used in traditional medicines for thousands of years. Possess potent anti-inflammatory, antibacterial, antiviral and antifungal benefits and also helpful in preventing or suffering from infectious and systemic diseases. Multiple immunomodulatory actions including modulation of cytokine secretion, histamine release, immunoglobulin production, immunoglobulin class switching, cellular co-receptor expression, lymphocyte proliferation and phagocytosis promotion.

- Gives relief from ear infections, wounds, bums and skin irritations.
- Effective in treating and fighting the deadly malady of cancers.
- Exhibit beneficial biological activity-anti-stress, adaptogenic and cytoprotective.
- Improving mental functions and preventing diseases and Enhances vaccine responses.
- Easily accessible, safer, easy to prepare and administer, Environment-friendly and are cost-effective ^[4].

Use of natural compounds in the prevention of cancer

Cancer cells are easy to kill using drug therapy however; they are hard to kill without damaging normal cells. This is because cancer cells rely on processes that are fundamentally similar to the processes used by normal cells. Their differences are in activity, not function. It is like two clocks, one that keeps the right time and one that is fast. Both clocks use the same mechanisms, but one works at a higher speed.

Any treatment that harms the structure of the fast clock as given in common route also affects to the normal clock, which harms its structure as well. Regarding the cellular level Then, the best way to inhibit a cancer cell (and to spare normal cells) is not to destroy its structural properties but to normalize the signals that drive it. These signals derive from its genetic instability, abnormal expression of genes, abnormal signal transduction, and abnormal communication with healthy cells [5]. Why we need to switch to natural compounds, there are three main reasons for it. First is, natural compounds that show anticancer potential fit into the

mechanism-based approach as perfectly as a hand fits into a glove. Second is, although the future does look bright for eventual success in the fight against cancer, we are not there yet. As a science, the field of natural compound research can contribute to a greater understanding of cancer and a faster development of successful therapies. The third is, we must use natural compounds because for better or for worse, hundreds of thousands or millions of patients around the world are experimenting with natural compounds in their efforts to heal themselves of cancer [6].

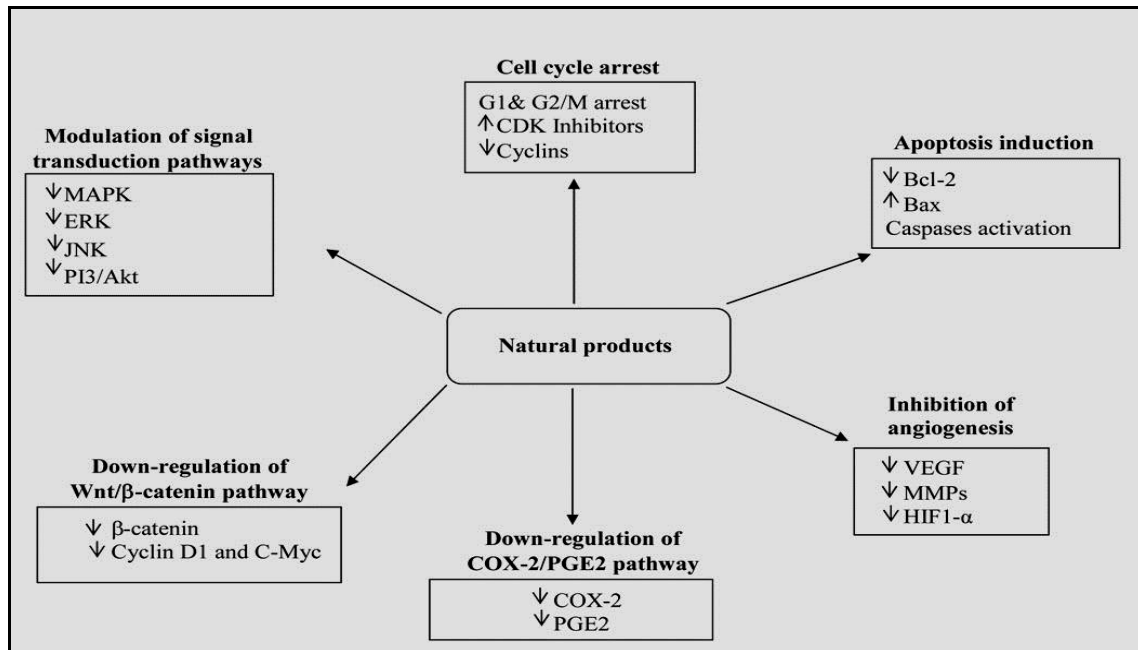


Fig 1: Role of Natural Compound in Prevention of Cancer [3].

Table 1: List of Indian Medicinal Plants, Their Family, Part and Solvents Used for Extraction and Assay Employed for Anti-cancer Studies [7].

No.	Scientific Name (vernacular name, family)	Part/s used	Extract	Type of the Tested Cancer Cells and Method	Traditional and Reported Uses
1	<i>Azadirachta indica</i> Juss. (Neemeliac, Meae)	L	80% ET	Prostate cancer / <i>In vivo</i>	Immunomodulatory, anti-inflammatory, antiulcer, antimalarial, antifungal, antibacterial, antiviral, antioxidant, antimutagenic and anticarcinogenic properties
2	<i>Curcuma longa</i> L. (Haldi, Zingiberaceae)	Rh	-	Colon Cancer Cells / <i>In vitro</i> / Lactate	Antimutagenic, anticarcinogenic
3	<i>Ocimum sanctum</i> L. (Tulsi, Lamiaceae)	L	ET	Skin cancer / <i>In vivo</i>	Anti-stress, antioxidant, hepatoprotective, anti-inflammatory, antibacterial and radio protective properties
4	<i>Zingiber officinale</i> Rosc. (Adu, Zingiberaceae)	Rh	50% ET	Prostate cancer cellline / <i>In vitro</i> and <i>In vivo</i> / MTT test	Carminative, antioxidant, diaphoretic, antispasmodic, expectorant, peripheral circulatory stimulant, astringent, appetite stimulant, anti-inflammatory agent, diuretic and digestive
5	<i>Punica granatum</i> L. (Dadam, Lythraceae)	J,P	70% AC	Prostate carcinoma cell / <i>In vivo</i> and <i>In vitro</i> / MTT test	Antioxidant and anti-inflammatory
6	<i>Ocimum gratissimum</i> L. (Damro, Lamiaceae)	S,L	AQ	Breast cancer / <i>In vivo</i> and <i>In vitro</i> / MTT test	Chemopreventive, anticarcinogenic, radioprotective and numerous others pharmacological uses
7	<i>Allium sativum</i> L. (Lasan, Liliaceae)	P	-	Oral cancer cell, sarcoma 180 cancer cell / <i>In vivo</i>	Antioxidant properties, anti-asthmatic, anticholesterolemic, antiseptic, antithrombotic, cancer, cholagogue, diaphoretic and diuretic
8	<i>Berberis vulgaris</i> L. (Barberry, Berberidaceae)	RB	ME	Breast cancer / <i>In vitro</i> / SRB test	Antioxidant, diarrhea, gallbladder, liver dysfunctions, leishmaniasis, malaria, stomach problems and urinary tract diseases
9	<i>Beta vulgaris</i> L. (Beet, Chenopodiaceae)	J	95%ET	Skin and lung cancer / <i>In vivo</i>	Antioxidant, leukaemia, cancer such as breast, oesophagus, glands, head, intestines and leg
10	<i>Mangifera indica</i> L. (Keri, Anacardiaceae)	Fr,B,L	-	Lung cancer / <i>In vivo</i>	Antitumour, antioxidant, antiviral, antibacterial, analgesic, antiinflammatory, antidiarrhoeal, antiamebic, spasmolytic, immunostimulant and Immunomodulatory properties

S: Stem, P: Peel, L: leaves, R: root, RB: root bark, J: juice, Rh: rhizomes, Fr: fruits, B: bark
 ET: Ethanol, ME: Methanol, AQ: Aqueous, AC: Acetone

Phytoconstituents or Natural compounds as an anticancer agent

Fruits and vegetables are recommended for prevention of cancer and other diseases. Numerous agents identified from fruits and vegetables can interfere with several cell signaling pathways. The agents include curcumin (turmeric), resveratrol (red grapes, peanuts and berries), genistein (soybean), diallyl sulfide (allium), S-allyl cysteine (allium), allicin (garlic), lycopene (tomato), capsaicin (red chili), diosgenin (fenugreek), 6-gingerol (ginger), ellagic acid (pomegranate), ursolic acid (apple, pears, prunes), silymarin (milkthistle), anethol (anise, camphor, and fennel), catechins (green tea), eugenol (cloves), indole-3-carbinol (cruciferous vegetables), limonene (citrus fruits), beta carotene (carrots) [8]. The medicinal plants maintain the health and vitality of individuals, and also cure various diseases, including cancer without causing toxicity. They are one of the main sources of biologically active ingredients. These medicinal plants possess good immune-modulatory and antioxidant properties, leading to anticancer activities. The antioxidant phytochemicals protect the cells from oxidative damage [9].



Fig 2: Rhizome of Turmeric

Turmeric (*Curcuma longa*)

Family: Zingiberaceae.

Common names: Haldi/Indian saffron/yellow ginger.

Active principle/compound: Zingiberene, curcumin, curcuminoids

Biological Properties: Curcumin the most active ingredient of turmeric is an orange-yellow crystalline powder practically insoluble in water and ether but soluble in alcohol, di-methyl-sulfoxides and acetone. Besides curcumin turmeric contains other chemical constituents known as curcuminoids. Commercial curcumin contains about 77% curcumin, 17% demethoxy-curcumin (DMC) and 3% bis-demethoxy-curcumin (BDMC) as its major components. Curcumin inhibits the growth of ovarian cancer cells and induces apoptosis in lung cancer cell lines. Anti-cancer effects are also observed in various cancer cell types including skin, colon, duodenal and ovary in the laboratory animals. Anti-cancer properties of curcumin may be mediated, at least in part by inhibition of inducible form of NO synthase. It is useful in mouth blisters, sprains, internal parasites, skin disease, constipation, internal injury, eye diseases, wounds, galactagogue, external parasites, mastitis, cough-cold, bone fracture, heatstroke, haematuria, broken horn and stomach-ache. The anti-inflammatory effect gives relief from rheumatoid arthritis and osteoarthritis. It is also an anti-Alzheimer's agent. It also acts as HIV-I and HIV-2 protease inhibitor, hepatoprotective, hypoglycemic and hypolipidemic agent [10].

Anti-cancer potential

The mechanism by which curcumin manifests its effect on NF-kappaB (nuclear factor) and NF-kappaB-regulated gene expression. Curcumin inhibits NF-kappaB activation and NF-kappaB-regulated gene expression through inhibition of IKK (IKappaB kinase) and Akt (also known as protein kinase B) activation [11]. Curcumin can be cytotoxic to cervical cancer cells in a concentration-dependent and time-dependent manner. The cytotoxic activity was selectively more in HPV16 and HPV18 infected cells compared to non-HPV infected cells. It also induced apoptosis in cervical cancer cells. Morphological hallmarks of apoptosis such as nuclear fragmentation and inter nucleosomal fragmentation of DNA were observed. It blocked Ikb-alpha phosphorylation and degradation, leading to abrogation of NF-kappaB activation and also down regulated the expression of COX-2, a gene regulated by NF-kappaB. Binding of AP-1, an indispensable component for efficient epithelial tissue-specific gene expression of HPV was also down regulated by curcumin. These results provide use of curcumin in the prevention of HPV associated tumors [12]. Curcumin has potential for the prevention and therapy of cancer and also it is well tolerated and may produce antitumor effects in people with precancerous lesions or who are at a high risk for developing cancer. Curcumin may also alter the effectiveness of radiotherapy and chemotherapy. Preclinical data have also shown that curcumin can both inhibit the formation of tumors in animal models of carcinogenesis and act on a variety of molecular targets involved in cancer development. *In vitro* studies have demonstrated that curcumin is an efficient inducer of apoptosis [13]. It is found that curcumin also down regulates cyclin D1, cyclin E and mdm2 (murine double minute oncogene) and up regulates p21, p27, and p53. Most human cancers over express epidermal growth factor receptor (EGFR) and HER2/neu, which ultimately stimulates the proliferation of cancer cells. Cellular experiments *In vitro* have shown that short term treatment with curcumin inhibits EGFR kinase activity and EGF-induced tyrosine phosphorylation of EGFR in A431 cells and depletes cells of Her2/neu protein. Curcumin may down regulate bcl-2 expression, thereby contributing to anti proliferative activity. Curcumin has also been shown to induce apoptosis in acute T cell leukemias by inhibiting the phosphatidylinositol 3 kinase/AKT pathways and to induce G2/M arrest and non apoptotic autophagic cell death in malignant glioma cells by abrogating Akt and Erk signaling pathways [14]. Curcumin also regulating the activities of additional molecular targets that control cell adhesion, apoptosis, and invasion. It inhibits the expression of caspases both *In vitro* and *in vivo*. Other anti-apoptotic proteins that are inhibited by curcumin include bcl-2, bclxL, X-linked inhibitors of apoptosis (XIAP), and surviving. The inhibitors of apoptosis (IAP) proteins has been discovered recently as new class of caspase inhibitors that selectively bind and inhibit caspase 3, 7 and 9. These inhibitors have great potential in the treatment of malignancy. Curcumin induce the expression of p53 in various cell lines such as glioma and prostate cancer. p53 is a tumor suppressor and transcription factor and is a critical regulator in many cellular processes including cell signal transduction, cellular response to DNA damage, genomic stability, cell cycle control, and apoptosis [15]. Curcumin [(1E,6E)-1,7-bis(4-hydroxy-3 methoxyphenyl) hepta-1,6-diene-3,5dione] is the major yellow pigment extracted from turmeric, a commonly used spice, derived from the rhizome of the plant *Curcuma longa*. Curcumin has broad spectrum cancer chemopreventive

activity in preclinical animal models. The study of anticancer activity of the curcumin and ethanolic extract was done *in vivo* on mice and *In vitro* on cell line. The extract showed a considerable anticancer activity against the cell line of human hepato cellular liver carcinoma [16]. The cytotoxic effects of the crude methanol and fractionated extracts (hexane, ethyl acetate) of *C. manga* against six human cancer cell lines, namely the hormone-dependent breast cell line (MCF-7), nasopharyngeal epidermoid cell line (KB), lung cell line (A549), cervical cell line (Ca Ski), colon cell lines (HCT 116 and HT-29), and one non-cancer human fibroblast cell line (MRC-5) were conducted using an *in-vitro* neutral red cytotoxicity assay. The crude methanol and fractionated extracts (hexane and ethyl acetate) displayed good cytotoxic effects against MCF-7, KB, A549, Ca Ski and HT- 29 cell lines, but exerted no damage on the MRC-5 line [17]. It is proposed that curcumin is a potent anticancer agent and suppresses the cancer of the skin, mammary gland, oral cavity, lung, liver, fore-stomach, oesophagus, stomach, intestine and colon and others. Curcumin has the activity to inhibit cell proliferation. It inhibits cytochrome P450 isoenzymes, suppress certain oncogenes e.g. cHa-ras, c-jun and c-fos and also inhibits cell-cycle-related proteins (cyclin E, p34, cdc2). It inhibits tumor implantation and biotransformation of carcinogens and Induction of glutathione S-transferase (GST) activity [18]. Some research worked on apoptotic effects of curcumin (diferuloyl methane) on squamous cell carcinoma of the cervix. Caspase3 and TNF-alpha assay were performed on monocytes isolated from cervical carcinoma patients and cultured with curcumin. Also cyto-smears and sections from cervical carcinoma tissue cultured with curcumin for the morphological evidence of apoptosis. Curcumin in the doses of 500 micron/ml increased the caspase-3 levels and decreases the level of TNF-alpha in human cells. Cyto-smears and sections from cervical carcinoma tissue cultured with curcumin showed better differentiation and increased number of apoptotic cells as compared to non-curcumin controls [19]. It is well known that curcumin (Di-feruloyl methane) is a natural compound extracted from *Curcuma longa* that allows suppression of carcinogenesis. The molecular mechanism of curcumin induced apoptosis in HPV positive cervical cancer HeLa, SiHa and CaSki cells. Curcumin causes distinct inhibition of human telomerase reverse transcriptase (hTERT) the catalytic core of telomerase thereby reducing proliferation of cancer cells. Curcumin mediated apoptosis in these cells appears to be due to upregulation of pro-apoptotic Bax (Bcl-2-like protein 4), AIF, release of cytochrome-C and down regulation of anti-apoptotic Bcl-2, Bcl-XL in HeLa and SiHa. This was accompanied by an increase in caspase3 and 9 activities [20]. Curcumin selectively eliminates a variety of HPV (+) cervical cancer cells (HeLa, ME-180, SiHa, and SW756), suppresses the transforming antigen E6, dramatically inhibits the expression of the pro-cancer protein epidermal growth factor receptor (EGFR), and concomitantly induces p53. Additionally, vacurin, a uniform colloidal solution of curcumin is used amphipathic vaginal cream, eliminates apposed HeLa cells while suppressing the expression of EGFR [21]. Some research work related within *silico* studies indicate that curcumin and its natural analogs have effective binding with different active sites on HPV 16 E6 protein, ideal target for restoring the tumor suppressor function of p53 and thus allowing the apoptosis of infected cells. The main limitation in the use of curcuminoids as therapeutic agents is their low bioavailability. Although curcumin has been found

to have strongest binding with target and the two curcuminoids, demethoxy and bisdemethoxy curcumin have lower but comparable good affinity, chlorogenic acid have best binding affinity amongst all the analogs [22].



Fig 3: Rhizome of Ginger

Family: Zingiberaceae

Common names: Adu, Adarak

Active principle/ compound: Citral, curcumin (sesquiterpene) and de-hydrozingerone

Ginger (*Zingiber officinale*)

Biological Properties: Ginger is a widely used herbal supplement. It is a rhizome of the herb *Zingiber officinale*, which belongs to the family *Zingiberaceae*. Due to its diverse healing properties it is extensively used in alternative medicines such as Chinese medicine, Ayurveda, Siddha and Unani. The Indian systems of medicines recommend the use of ginger as a *kaya karpam* or rejuvenator. It is used both in fresh and dried form to treat nausea and vomiting, osteo and rheumatoid arthritis, diabetes mellitus, indigestion and some cardiovascular disorders. Various studies have demonstrated the anti-oxidant, anti-inflammatory, anti-cancer and anti-microbial properties of ginger [23].

Anti-cancer potential

Ginger supplemented rats had a significantly smaller number of tumors and cancer incidence. In addition, supplemented rats had significantly less lipid oxidation and higher level of enzymatic and non-enzymatic antioxidants and when mice were injected with [6]-gingerol, the growth of cancerous melanoma cells was reduced. [6]-gingerol does inhibit angiogenesis and may be useful in the treatment of tumors and other angiogenesis-dependent diseases. It is concluded that ginger extract significantly reduced the elevated expression of NF-kB and TNF- α in rats with liver cancer. Ginger may act as an anti-cancer and anti-inflammatory agent by inactivating NF-kB through the suppression of the pro-inflammatory TNF- α [24]. It is observed that treatment of human cervical carcinoma cell line, HeLa with ethanolic ginger extract in combination with gemcitabine resulted in significant dose-dependent decrease in cell viability. Use of ginger extract increased the efficacy of gemcitabine and importantly, it was found to be minimally toxic to normal cells. Together, these results suggest a novel mechanism may be involved in the synergistic effect of this combination and it is useful in the treatment of cervical cancer [25]. Research conducted on leaves and rhizomes extract from two Malaysian young ginger (*Zingiber officinale* Roscoe) varieties namely: Halia Bentong and Halia Bara grew under ambient (400 $\mu\text{mol/mol}$) and elevated (800 $\mu\text{mol/mol}$) CO₂ concentrations were studied for

their antioxidant and *In vitro* anticancer activities against two human cancer cell lines (MCF-7 and MDA-MB-231). The results showed that CO₂ enriched Halia Bara exhibited the highest anticancer activity on MCF-7 cancer cells with IC₅₀ values of 25.3 and 27.31 µg/ml respectively for rhizomes and leaves extract. IC₅₀ values for MDA-MB-231 exhibitions were 30 and 32.81 µg/ml, respectively for rhizomes extract of Halia Bara and Halia Bentong. Results showed that Halia Bentong and Halia Bara possessed anticancer and antiradical properties especially when grown under elevated CO₂ concentration [26]. Some scientists found that antioxidant and anticancer activities of two Bangladeshi ginger varieties (Fulbaria and Syedpuri) at young age grown under ambient (400 µmol/mol) and elevated (800 µmol/mol) CO₂ concentrations against two human breast cancer cell lines (MCF-7 and MDA-MB-231). The effects of ginger on MCF-7 and MDA-MB-231 cell lines were determined using TBA (thiobarbituric acid) and MTT [3-(4, 5-dimethylthiazolyl)-2, 5-diphenyl-tetrazolium bromide] assays. Antioxidant activities in both varieties found increased significantly ($P \leq 0.05$) with increasing CO₂ concentration from 400 to 800 µmol/mol. The results showed that enriched ginger extract (rhizomes) exhibited the highest anticancer activity on MCF-7 cancer cells with IC₅₀ values of 34.8 and 25.7 µg/ml for Fulbaria and Syedpuri respectively. IC₅₀ values for MDA-MB-231 exhibition were 32.53 and 30.20 µg/ml for rhizomes extract of Fulbaria and Syedpuri accordingly [27]. To investigate the cytotoxicity, toxicity, and anticancer activity of a crude ethanolic extract of ginger (*Zingiber officinale* Roscoe) against CCA cell line. Cytotoxic activity against a CCA cell line was assessed by calcein-AM and Hoechst-33342 assays and anti-oxidant activity was evaluated using the DPPH assay. Investigation of apoptotic activity was performed by DNA fragmentation assay and induction of genes that may be involved in the resistance of CCA cells to anticancer drugs (MDR1, MRP1, MRP2, and MRP3) was examined by real-time PCR. Results from these *In vitro* and *in vivo* studies indicate anticancer activity of the crude ethanolic extract of ginger against CCA with the absence of any significant toxicity [28]. Ginger treatment suppressed the proliferation and colony formation in breast cancer cell lines, MCF-7 and MDA-MB-231. Treatment resulted in sequences of events marked by apoptosis, accompanied by loss of cell viability, chromatin condensation, DNA fragmentation, activation of caspase 3, and cleavage of poly (ADP-ribose) polymerase. Ginger treatment down regulated expression of pro survival genes, such as NF-κB, Bcl-X, Mcl-1, and Survivin, and cell cycle-regulating proteins. It also inhibited the expression of the two prominent molecular targets of cancer, c-Myc and the human telomerase reverse transcriptase (hTERT) [29]. Whole ginger extract (GE) exerts significant growth-inhibitory and death-inductive effects in a spectrum of prostate cancer cells. Comprehensive studies have confirmed that GE perturbed cell-cycle progression, impaired reproductive capacity, modulated cell-cycle and apoptosis regulatory molecules and induced a caspase-driven, mitochondrial mediated apoptosis in human prostate cancer cells. Most importantly, GE did not exert any detectable toxicity in normal, rapidly dividing tissues such as gut and bone marrow [30]. Research work investigated the metabolism of 10G (10mg concentration of ginger) in zebra fish embryos, and then explored the biotransformation of 10G in humans. Results show that 10G was extensively metabolized in both zebrafish embryos and in humans, in which two major metabolites, (3S,5S)-[10]-gingerdiol and (3R,5S)-[10]-

gingerdiol, were identified by analysis of the MSn(mass spectrometry) spectra. The reductive pathway is a major metabolic route for 10G in both zebrafish embryos and in humans [31]. Ginger possesses chemo preventive and antineoplastic properties. Ginger is also effective in ameliorating the side effects of γ-radiation and of doxorubicin and cisplatin; to inhibit the efflux of anticancer drugs by P-glycoprotein (P-gp) and ginger also possess chemo sensitizing effects in certain neoplastic cells *In vitro* and *in vivo* [32].

Neem (*Azadirachta indica*)

Biological Properties: Various parts of the neem tree such as leaves, flowers, seeds, roots and bark are used as traditional remedies for a number of ailments in the Indian systems of alternative medicine. However, the medicinal value of the neem leaves stands out in comparison with other parts of the tree. Various studies have indicated that the neem leaves have anti-microbial, anti-inflammatory, analgesic, anti-diabetic, Immunomodulatory, anti-oxidant and anti-cancer properties. Neem plant extract stimulates phagocytic activity and antigen presenting ability of macrophages. It stimulates cytokines and thereby the immune system. They are also effective against allergic disorders and limiting anaphylactic reactions [36,35].



Fig 4: Leaves of Neem

Family: Meliaceae.

Common names: Nimba, holy tree, vembu.

Active principle/componnd: Azadirachtin, nimbin, gedunin, gallic acid, catechin, NB-II peptidoglycan.

Anti-cancer potential

Neem is a potent inducer of apoptosis in biopsies of cervical cancer patients. Theneem treated monocytes from cervical cancer patients showed high activity levels of caspase 3, 8, and 9. A decrease in TNF-α and an increase in IFN-γ levels were seen in culture supernatant of monocytes. Cyto and histomorphology of neem treated cervical cancer cells exhibited increased apoptosis [33]. The effects of leaf extracts from *Azadirachta indica* and *Terminalia arjunah* have been investigated on HeLa cells. When the plant extracts-treated HeLa cells were seen under the microscope, we observed significant morphological changes of the cells. The adherent HeLa cells were detached from the culture plate and become floated resulting in rounding up of cellular shape. This degenerative morphological change ultimately led the cells to death. The percentage of dead cells was then calculated by counting the cells after stained with trypan blue. Higher concentration (50 µg/ml) of *A. indica* extract induced only 55% of cell death. Whereas lower concentration (5 µg/ml) of *A. indica* extracts could not induce cell death significantly [34]. The cytotoxic effects of nimbolide, a limonoid present in

leaves and flowers of the neem tree (*Azadirachta indica*) on human choriocarcinoma (BeWo) cells. Treatment with nimbolide resulted in dose and time dependent inhibition of growth of BeWo cells with IC(50) values of 2.01 and 1.19 microM for 7 and 24 hrs respectively, accompanied by down regulation of proliferating cell nuclear antigen. Examination of nuclear morphology revealed fragmentation and condensation indicating apoptosis [35]. Neem (*Azadirachta indica*), a member of the *Meliaceae* family. Because of it is tremendous therapeutic, domestic, agricultural and ethno-medicinal significance, and its proximity to human culture and civilization, neem has been called "the wonder tree" and "nature's drug store." All parts of this tree, particularly the leaves, bark, seed-oil and their purified products are widely used for the treatment of cancer [36]. Neem extracts and its purified products have been examined for induction of apoptosis in multiple cancer cell types. neem oil, which contains the majority of neem limonoids including azadirachtin, induced apoptotic and autophagic cell-death. Neem induced the release of cytochrome C and apoptosis-inducing factor (AIF) from mitochondria, suggesting the involvement of both caspase-dependent and AIF-mediated apoptosis. p21 deficiency caused an increase in caspase activities at lower doses of neem, whereas p53 deficiency did not modulate neem-induced caspase activation [37]. Some work based on restriction of the murine sarcoma growth by the therapeutic intervention of neem leaf glycoprotein (NLGP). In order to evaluate the mechanism of tumor growth restriction, they analyzed tumor microenvironment (TME) from sarcoma bearing mice with NLGP therapy. Analysis of cytokine milieu within TME revealed IL-10, TGF β , IL-6 rich type 2 characters were switched to type 1 microenvironment with the dominance of IFN γ secretion within NLGP-TME. The proportion of CD8+ T cells was increased within NLGP-TME and these T cells were protected from TME-induced energy by NLGP and also inhibit downstream signaling. Also, research studies on tumor-microenvironment (TME) from NLGP treated mice (NLGP-TME) and suggests that anti-tumor effect is directly associated with enhanced CD8+T cell activity, dominance of type 1 cytokines/chemokine network with down regulation of suppressive cellular functions. NLGP-TME educated CD8+T cells showed higher perforin and granzyme B expression with greater *In vitro* cytotoxicity against B16 melanoma. These CD8+T cells showed proportionally lower FasR expression, denotes prevention from activation induced cell death by NLGP [38]. The anti-proliferative activity of ethanolic neem leaves extract (ENLE) alone or in combination with cisplatin by cell viability assay on human breast (MCF-7) and cervical (HeLa) cancer cells. The effects of different concentrations of ENLE on MCF-7 cells, HeLa cells, and lymphocytes were evaluated by the MTT assay. MCF-7 and HeLa cells treated with increasing concentrations of ENLE ranging from 10 to 500 $\mu\text{g}/\text{mL}$ showed a dose and time dependent increase in cell death. In comparison to untreated cells, ENLE-treated cells showed typical features of cell death at the morphological level such as rounding of cells, cell shrinkage, and detachment from the substrate which accumulated in a dose and time-dependent manner, thus indicating that ENLE induces cell death by apoptosis in these cells [39].

Tulasi (*Ocimum sanctum*)

Biological Properties: Tulasi is an analgesic, anticancer, adaptogen or antistress agent and also having antidiabetic property. Its antioxidative property and inhibition of lipid

peroxidation are due to the presence of eugenol. Immunostimulant potential of tulasi is helpful in the treatment of immunosuppression and also shows its immunomodulatory effect by an increase in IFN- γ , IL-4, T-helper cells, NK cells thus reducing total bacterial count increasing neutrophil and lymphocyte count and enhancing phagocytic activity and phagocytic index. Aqueous extract showed immunotherapeutic potential in bovine sub-clinical mastitis. It inhibits mast cell degranulation and histamine release in presence of an allergen. It is useful in constipation and wounds. It is more potent than dexamethasone in the treatment of acute viral encephalitis [40].



Fig 5: Leaves of Tulasi

Family: Lamiaceae

Common names: Tulasi/holy basil

Active principle/compound: Oleanolic acid, ursolic acid, rosmarinic acid, carvacrol, eugenol, b- caryophyllene

Anti-cancer potential

The seed oil of *Ocimum sanctum* was evaluated for chemopreventive activity against subcutaneously injected 20-methylcholanthrene induced-fibrosarcoma tumors in the thigh region of Swiss albino mice and they show good chemopreventive activity result. The potential chemopreventive activity of the oil is partly attributable to its antioxidant properties [41]. The aqueous extracts of the medicinal herb *Ocimum gratissimum* (Og) inhibit the proliferation of several cancer cell lines, especially prostate adenocarcinoma (PC-3) cells. Therefore, Og-leaf extracts may harbor novel cancer-fighting compounds that need to be isolated, purified and characterized. Partially purified Og fractions were obtained from sequential extraction of Og powder with organic solvents of different polarities which shows good inhibition of prostate adenocarcinoma (PC-3) cells [42]. The sulphorhodamine Blue (SRB) assay was used for evaluating *In vitro* cytotoxic potential of three medicinal plants namely *Ocimum sanctum*, *Zingiber officinale* and *Momordica charantia* against eight human cancer cell lines via ethanolic, 50% ethanolic and aqueous extracts. Results demonstrated that ethanolic extract from *Ocimum sanctum*, ethanolic and 50% ethanolic extract from *Zingiber officinale* and aqueous extract from *Momordica charantia* possess selective anti-proliferative effect on human cancer cells taken from different tissues. However, ethanolic extract *Ocimum sanctum* was most effective against lung, liver and oral cancerous cells. Ethanolic extract of *Zingiber officinale* inhibited the growth of the central nervous system, lung and colon cancer cells whereas aqueous extract of *Momordica*

charantia conquered the growth of 72% infected cells [43]. The treatment of a squamous cervical cancer cell line, SiHa with the ethanolic extracts of leaves of *Ocimum sanctum* and *Azadirachta indica* and roots of *Withania somnifera* at IC₅₀ values for 48 h resulted in formation of inter nucleosomal fragments of DNA and study of morphological changes also showed the formation of apoptotic bodies after treatment with these plant extracts. The IC₅₀ values were determined using the cell proliferation assay, MTT assay [44]. A methanolic extract of *Ocimum* varieties have been shown to possess cancer preventive activities through reduction of an excess amount of nitric oxide. Ethanolic tulsi leaves extract has been found to produce significant reduction in the values of tumor incidence (Papillomas) in the skin. A methylthiazol tetrazolium assay was used for *In vitro* cytotoxicity screening against the human cervical cancer cell line (HeLa), human laryngeal epithelial carcinoma cell line (HEp-2) and NIH 3T3 mouse embryonic fibroblasts. The IC₅₀ values obtained were 90.5 and 96.3 µg/ml respectively, and the results revealed that basil oil has potent cytotoxicity [45]. The histopathological examination of skin tumors treated with *Ocimum* leaf extract showed increased infiltration of polymorpho nuclear, mononuclear and lymphocytic cells, decreased ornithine decarboxylase activity with concomitant enhancement of interleukin-1beta (IL-1beta) and tumor necrosis factor-alpha (TNF-alpha) in the serum, implying the *in vivo* anti-proliferative and immunomodulatory activity of *Ocimum* leaf extract. The leaf extract of *O. sanctum* provided protection against chemical carcinogenesis by three mechanisms, (i) by acting as an antioxidant (ii) by modulating phase I and II enzymes (iii) by exhibiting anti-proliferative activity [46]. The efficacy of novel flavonoid vicenin-2 (VCN-2), an active constituent of the medicinal herb *Ocimum Sanctum* Linn. In combination with docetaxel (DTL) in carcinoma of prostate shows VCN-2 effectively induced anti-proliferative, anti-angiogenic and pro-apoptotic effect in CaP cells (PC-3, DU-145 and LNCaP) irrespective of their androgen responsiveness or p53 status. The treatment of a squamous cervical cancer cell line, SiHa with the ethanolic extracts of leaves of *Ocimum sanctum* at IC₅₀ values for 48hrs resulted in the formation of inter nucleosomal fragments of DNA [47]. Cytotoxicity induced by carvacrol in HeLa and SiHa cells was determined by different assays like MTT assay and LDH assay and apoptosis was measured by DNA fragmentation assay. Carvacrol could have a potential therapeutic significance in treating cancer. Treatment of SiHa cell line with the ethanolic extracts of leaves of *Ocimum sanctum* and *Azadirachta indica* and roots of *Withania somnifera* at IC₅₀ values for 48hrs resulted in formation of internucleosomal fragments of DNA. Morphological changes also showed the formation of apoptotic bodies after treatment with *Ocimum sanctum* extracts [48]. Tulsi and some of its phytochemicals eugenol, rosmarinic acid, apigenin, myrethenal, luteolin, β-sitosterol, and carnosic acid prevented chemical-induced skin, liver, oral, and lung cancers and to mediate these effects by increasing the antioxidant activity, altering the gene expressions, inducing apoptosis, and inhibiting angiogenesis and metastasis. The other important phytochemicals like eugenol, rosmarinic acid, apigenin, and carnosic acid are also preventing radiation-induced DNA damage [49]. The combinatorial chemopreventive efficacy of *Azadirachta indica* (AI) and *Ocimum sanctum* (OS) against N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-induced gastric carcinogenesis, based on changes in oxidant-antioxidant status, cell proliferation, apoptosis and angiogenesis.

chemoprevention by AI and OS combination may be mediated by their antioxidant, antiangiogenic, antiproliferative and apoptosis inducing properties [50].

Conclusion and prospect

This review paper provides information on natural compounds with the potential to decrease the growth of cancer or be used as adjuvant with cancer treatments for patients who already have or have had cancer. It is renowned that medicinal herbs have rich anticancer potential, and on the forefront whenever we talk about anticancer remedies, are significant sources of synthetic and/or herbal origin. Natural compounds discovered from medicinal plants have played an important role in the treatment of cancer. They have exhibited anticancer activity in animal models of leukemia, skin cancer and sarcomas. By generating awareness regarding usage of herbs and exploring natural compound properties, healthcare professional, can play significant clinical roles as knowledge resources for masses. Selected plants have been explored for biological activity and further investigations into the anticancer activity of the plants showing promising activity, must be undertaken. Cancer is associated with high mortality rates if herbs can be used even in the palliative care or to reduce the side effects associated with cancer would be of great relief for the sufferer.

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