Anticancer Activities of Medicinal Plants –An Update

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Abstract:

Aim :
To assess the anticancer activities of certain medicinal plants such as Aloe barbadensis,Azardirachta Indica ,Glycyrrhiza glabra , Curcuma longa, Hypericum perforatum, Acacianialotica -Vachellia nilotica, Acaciacatechu-Senegalia catechu, Camellia sinesis ,Vitis venefera.

Background:
Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body.Not all tumours are cancerous , benign tumours do not spread to other parts of the body.Possible signs and symptoms include a lump, abnormal bleeding, prolonged cough, unexplained weight loss and a change in bowel movements.The causes for cancer include use of tobacco,alocohol, infections such as hepatitis B, hepatitis C and HPV.Cancer is often treated with some combination of radiation therapy, surgery, chemotherapy, and targeted therapy and some drugs made of the plants which have anticancereous properties which can counteract the symptoms as well as capable of acting against the cancerous cells.

Reason :
To explore the anticancer potential of the medicinal plants extracts for isolation and characterisation of the active anticancer principles so that better,safer and cost effective drugs can be developed for treating cancer.

INTRODUCTION:

Cancer has been a constant battle globally with a lot of development in cures and preventative therapies. The disease is characterised by cells in the human body continually multiplying with the inability to be controlled or stopped. Consequently, forming tumours of malignant cells with the potential to be metastatic . Current treatments include chemotherapy, radiotherapy and chemically derived drugs. Treatments such as chemotherapy can put patients under a lot of strain and further damage their health. Therefore, there is a focus on using alternative treatments and therapies against cancer.

For many years herbal medicines have been used and are still used in developing countries as the primary source of medical treatment. Plants have been used in medicine for their natural antiseptic properties. Thus, research has developed into investigating the potential properties and uses of terrestrial plants extracts for the preparation of potential nanomaterial based drugs for diseases including cancer . Many plant species are already being used to treat or prevent development of cancer. Multiple researchers have identified species of plants that have demonstrated anticancer properties with a lot of focus on those that have been used in herbal medicine in developing countries

Compounds which are characteristic to the plant kingdom and are necessary for plant survival and "housekeeping" of the organism are being investigated for their ability to inhibit growth and initiate apoptosis of cancerous cells. This article aims to take an overview of current plant derived compounds that have anticancer therapeutic properties and their developments in the field.

Globally cancer is a disease which severely effects the human population. There is a constant demand for new therapies to treat and prevent this life-threatening disease. Scientific and research interest is drawing its attention towards naturally-derived compounds as they are considered to have less toxic side effects compared to current treatments such as chemotherapy. The Plant Kingdom produces naturally occurring secondary metabolites which are being investigated for their anticancer activities leading to the development of new clinical drugs. With the success of these compounds that have been developed into staple drugs for cancer treatment new technologies are emerging to develop the area further. New technologies include nanoparticles for nano-medicines which aim to enhance anticancer activities of plant-derived drugs by controlling the release of the compound and investigating new methods for administration. This review discusses the demand for naturally-derived compounds from medicinal plants and their properties which make them targets for potential anticancer treatments

ALOE BARBADENSIS:

Several naturally produced herbal formulations are currently available for cancer patients. As most of chemotherapeutic agents were cytotoxic to normal cells and developed drug resistance[1]. Therefore scientific consideration and test of traditionally used herbs for the treatment of different malignancies could be also considered as a very valuable source for new chemotherapeutic drugs.[2] A number of studies carried out over the last few decades on prevention and treatment of HCC have led to the identification of several herbal compounds and formulations that can affect the initiation, promotion as well as the progression processes of HCC. The most important active constituents of the Aloe plants

were anthraquinones like aloin, barbalion, anthranol, cinnamic acid, aloetic acid, emodin, chrysophanic acid, resistanol, and enzymes (including cyclooxygenase and bradykininase), together with Other compounds such as vitamins, saccharides, and amino acids[3] It was reported that the other anthraquinones of Aloe plants had mutagenic and genotoxic effects in bacterial and mammalian test systems [4] the genotoxic effects were illustrated in present research by DNA damage assay and Real Time-PCR. The antitumor activity of 50% ethanol extract (100 mg/ kg) of A. vera was evaluated by Bharath against Ehrlich ascites carcinoma tumor in mice. Ethanol extract of A. vera exhibited antitumor effect by modulating lipid peroxidation and augmenting antioxidant defense system in Ehrlich ascites carcinoma bearing mice Also, Aloe-emodin is one of the active components in the leaves of A. vera which revealed anticancer and cytotoxic activities against neuroectodermal tumors, lung squamous cell carcinoma and hepatoma cell .C. comosum also, has been exhibited anti- inflammatory, anti-ulcer and anti-cancer activities in rat and shrimp animals model Dehydrodicatechin A is an active component of C. comosum which inhibits the growth of Ehrlich ascites[5] Abdel-Sattar et al showed that C. comosum methanolic and aqueous extracts ameliorated haloperidol induced neuro- and hepatotoxicities in male Albino rat. In our study, we have noticed that the cytotoxic activity of A. vera and C. comosum might be through modulation of apoptosis, therefor both extracts demonstrated antitumor effects against HepG2 cells. Gene and protein expressions of both p53 and Bcl2 were significantly altered in response to extracts. Up-regulation of expression of p53 and down-regulation of Bcl2 in a time and dose dependent manner were evident in the human HCC cell line which is a major pathway for regulation of programmed cell death. Both extracts could have cytotoxic and genotoxic activity. C. comosum showed a higher level in inducing morphological changes associated apoptosis, DNA damage, gene and protein expressions.

FIG:1: Aloe barbadensis

AZADIRACHTA INDICA
Neem components inhibit cancer cell proliferation
Uncontrolled cancer cell growth and proliferation are one of the fundamental hallmarks in cancer and play important role in the development of tumor and cancer metastasis [7,8]. Therefore, inhibiting the growth of tumor cells is a common feature of many chemopreventive and therapeutic agents. Extracts of neem suppress the proliferation and growth of tumor cells through disruption of cell cycle progression. For example, neem seed oil inhibits growth of HeLa cervical cancer cells [9], and NLE shows proliferationinhibitory effects in prostate cancer cells [10]. Interestingly, the androgen-dependency status fails to modulate anti-proliferative effects of NLE in prostate cancer cells. For example, neem extract disrupts proliferation of both androgen-dependent and -independent prostate cancer cells.Since androgen-refractory prostate cancer cells are more resistant to apoptosis and lead to prostate cancer recurrence, treatment with active components of neem may provide therapeutic benefits to patients with recurrent prostate cancer. Similar to lack of androgen dependency, the anti-proliferative effects of neem are consistent in both estrogen-dependent and -independent breast cancer cells . Cell cycle progression is tightly controlled by a complex network of regulatory proteins including cyclins, cyclin-dependent kinases (CDKs), CDK inhibitors (CKIs), cell cycle checkpoint proteins, and transcription factors such as E2F.Studies on the effects of neem or its components on cell cycle and proliferation of tumor cells have identified multiple target proteins. For example, treatment of HeLa cells with azadirachtin decreases the levels of cyclin B and cyclin D1, and induces the expression of CKI p21, which collectively led to G0/G1 cell cycle arrest .Analysis of cell cycle distribution in nimbolide-treated colon carcinoma cells revealed that this active neem component induces both G0/G1 and G2/M arrest accompanied by alterations in cyclins, CDKs and CKIs [11]Additional nimbolide targets for G2/M cell cycle checkpoint proteins are CHK2 and Rad17 . Although detailed mechanisms are unknown, nimbolide disrupts cell cycle progression, and thus inhibits proliferation of HeLa breast cancer ,choriocarcinoma , lymphoma leukemia and melanoma cells.. Additional neem components that have been characterized show similar suppressive effects on the growth and proliferation of tumor cells. For example, treatment with NLE or neem-derived gedunin decreases proliferation of pancreatic or ovarian cancer cells, respectively [28]. The subsets of differentially regulated genes induced by gedunin, identified by bioinformatics analysis, encode proteins involved in cell cycle control as well as other cellular processes. Interestingly, the combination of gedunin and cisplatin further decreases the proliferation of treated ovarian cancer cells by almost 50% compared to the cells treated with cisplatin alone. These findings suggest the possibility that gedunin and other potential neem components could enhance the efficacy of chemotherapeutic agents, and such combinatorial therapy may offer additional benefits. In vivo studies of neem extracts or components show significant anticancer properties, confirming the clinical relevance of the in vitro findings. NLE inhibits the process of carcinogenesis in carcinogen 7,12-dimethylbenz[a]anthracene (DMBA)-induced HBP mouse model, which is accompanied by decreased expression of proliferating cell nuclear.
The effects of neem components on cancer cell death
Besides inhibiting cancer cell proliferation, neem components exert anticancer effect by induction of apoptosis as well as other forms of cell death including autophagy. Extracts from seeds and leaves of neem induce apoptosis in different types of cancer cells such as

leukemia, prostate [12] cervical [13], colon [14], stomach [15], and breast as well as choriocarcinoma [16], and hepatocarcinoma cells [17]. These findings suggest a proapoptotic effect of neem extracts on a broad spectrum of cancer cell types. Author Manuscript Author Manuscript Author Manuscript Similarly, the administration of individual neem components also induces cancer cell death. For example, nimbolide induces apoptosis in breast cancer [18], prostate cancer , hepatocarcinoma , cervical cancer [19], choriocarcinoma , colon cancer , lymphoma, leukemia, and melanoma cells [20]. Azadirachtin shows similar effect in cervical cancer cells [21]. An increasing number of less-characterized limonoids that have been recently isolated from different parts of neem also exhibited proapoptotic effects in leukemia and stomach cancer cells Consistent with the anti-proliferative effects of neem, its proapoptotic potentials are not affected by the hormone-dependent status in prostate cancer and breast cancer cells Apoptosis occurs through the intrinsic mitochondrial pathway or the extrinsic pathway mediated by membrane-associated death receptors . Neem limonoids induce apoptosis through the intrinsic pathway in prostate cancer and cervical cancer cells, accompanied by increased release of cytochrome c from mitochondria [23]. The mitochondrial release of cytochrome c is one of the initiating events during apoptosis via intrinsic apoptotic pathway . This cytochrome c release is regulated by proapoptotic members (e.g. Bax and Bad) and antiapoptotic members of the Bcl-2 family (e.g. Bcl-2 and Bcl-xL). Thus Bcl-2 family proteins are important targets for exerting anticancer effects of neem in cancer cells. For example, neem-induced apoptosis in prostate cancer cells is mediated by the concurrent decrease of Bcl-2 and increase of Bax levels [25]. In addition, treatment with individual component nimbolide induces expression of Bad and Bax in breast cancer cells, while decreases the levels of Bcl-2 and Bcl-xL [20]. Similar pattern of modulation of Bcl-2 family proteins has also been observed upon nimbolide or azadirachtin exposure to cervical cancer cells [23], and in nimbolide treated choriocarcinoma cells [26]. Nimbolide and azadirachtin also induce expression of caspases while suppress antiapoptotic protein survivin in cervical cancer cells [23]. In addition to the well-characterized neem components, a newly-isolated neem limonoid, 2,3-dihydro-3α-methoxynimbolide, shows proapoptotic effects in stomach cancer cells through modulation of caspase activities accompanied by modulation of the ratio of Bax/Bcl-2 protein levels . These findings demonstrate that neem components exert anticancer effects by modulating Bcl-2 family proteins, caspases, and additional regulatory proteins. Apoptosis or cell death is a very complex process involving multiple groups of protein, thus targeting multiple components in the apoptotic pathway is likely to improve the anticancer efficacy of neem components or extracts. Interestingly, neem-induced apoptosis occurs through a p53-independent mechanism in colon cancer cells, as loss of p53 fails to prevent neem-induced apoptosis.

FIG 2: **Azadirachta indica**

GLYCYRRHIZA GLABRA :
Anticancer Properties:

Fu Y, et al, investigated Licochalcone (LA) elicited growth control and induction of apoptosis using androgen-independent p53-null PC-3 prostate cancer cells. The findings of this study were-1) LA induced modest level of apoptosis but had more pronounced effect on cell cycle progression arresting cells in G2/M, accompanied by suppression of cyclin B1 and cdc2. 2)It also inhibited phosphorylation of Rb, specifically phosphorylation of S780 with no change of phosphorylation status of T821,3) decreased expression of transcription factor E2F concurrent with reduction of cyclin D1, 4)down-regulated CDKs 4 and 6, but increased cyclin E expression. These findings provided explanation for LA activity and suggested that it might be considered as a chemopreventive agent. [11] B] Kanazawa M, et al investigated the anti-tumor effect of isoliquiritigenin on prostate cancer in vitro. They used DU145 and LNCaP prostate cancer cell lines as targets. In this study, the effects of isoliquiritigenin on cell proliferation, cell cycle regulation and cell cycle-regulating gene expression were studied. The effects of isoliquiritigenin on the GADD153 mRNA and protein expression, and promoter activity were also investigated. The researchers of this study found that isoliquiritigenin significantly inhibited the proliferation of prostate cancer cell lines in a dose-dependent and time-dependent manner. Fluorescence-activated cell sorting (FACS) analysis indicated that isoliquiritigenin induced S and G2/M phase arrest and that isoliquiritigenin enhanced the expression of GADD153 mRNA and protein associated with cell cycle arrest. They have concluded that isoliquiritigenin was a candidate agent for the treatment of prostate cancer and GADD153 might play an important role in isoliquiritigenin-induced cell cycle arrest and cell growth inhibition.[12]

FIG 3 : **Glycyrrhiza glabra**

CURCUMA LONGA

The anticancer activity of turmeric when evaluated prophylactically and therapeutically i.e., pre-induction treatment and post -induction treatment respectively, by two different routes of administration i.e., per oral and topical application. Though post-induction per oral treatment with turmeric demonstrated a significant anticancer activity against MNU-induced mammary cancer in rats, the degree of anticancer activity was more prominent in prophylactic treatment groups and was more effective particularly with topical application. It was clearly evidenced by the decreased drastic reduction in mean tumor volume and higher degree of tumor growth inhibition in prophylactic topical application of turmeric when compared to the therapeutic treatment of groups. Our study demonstrated similar results with the previous work reported (21). Prophylactic topical application of turmeric has shown superior efficacy when compared to all other groups in reduction of the incidence rates of tumor induction, prolongation of mean latency periods of tumor development, reversal of mean tumor volume and inhibition of tumor growth. Hence, interesting findings in this study are i) Preventive role of turmeric against MNU induced mammary cancer was more predominant than the therapeutic role of turmeric on MNU induced mammary cancer. ii) Preventive role of turmeric was more pronounced with topical application though it has demonstrated moderate prophylactic effect with per oral administration of turmeric. In an in-vivo study, dietary administration of 1% turmeric, 0.05% ethanol extract of turmeric, when administered during initiation and post initiation periods significantly inhibited the 7, 12 – dimethyl benz (a) anthracene (DMBA) induced mammary tumorigenesis by reducing tumor multiplicity, tumor burden and tumor incidence. Simultaneous administration of 1% curcumin-free aqueous turmeric extract as the sole source of drinking water during the initiation phase did not suppress DMBA-induced mammary tumorigenesis but suppressed the DMBA-induced mammary tumorigenesis when administered during post initiation period by reducing tumor multiplicity and tumor burden but not the tumor incidence. Till date, there was no evidence of anticancer activity with topical application of turmeric in breast cancer model. In two in vivo studies reported earlier, topical application of 100 or 3000 nmol curcumin in CD-1 mice and 0.2% or 1% curcumin in diet significantly reduced the tumor incidence and tumor volume in dimethyl benz (a) anthracene (DMBA) initiated and 12,0tetradecanoylphorbal -13-acetate (TPA) promoted skin tumors (22). The general anti-carcinognic effect of Curcumin involves the mechanisms like induction of apoptosis and inhibits cell-cycle progression, both of which are instrumental in preventing cancerous cell growth in rat aortic smooth muscle cells (23). The antiproliferative effect is mediated partly through inhibition of protein tyrosine kinase and c-myc mRNA expression and the apoptotic effect may partly be mediated through inhibition of protein tyrosine kinase, protein kinase C, c-myc mRNA expression and bcl-2 mRNA expression (23). Specifically, Curcumin suppresses human breast carcinoma through multiple pathways. Its antiproliferative effect is estrogendependent in ER (estrogen receptor)-positive MCF-7 cells and estrogenindependent in ER-negative MDA-MB-231 cells (9). Curcumin also down regulates matrix metalloproteinase (MMP)-2 and upregulates tissue inhibitor of metalloproteinase (TIMP)-1, two common effector molecules involved in cell invasion (9). It also induces apoptosis through P53-dependent Bax induction in human breast cancer cells (10). Since major side effect of anti-cancer drugs is bone marrow depression, the present study has investigated the effect of chronic turmeric treatment on hematological parameters. There was no significant difference in hematological parameters among the different treatment groups and control group. Hence it was evident that no bone marrow depression with turmeric treatment was observed, which is a major side effect with cytotoxic chemotherapy. In conclusion, the turmeric acts effectively both orally and topically initiation stage of mammary cancer than in the promotion stage of mammary carcinoma. This stage specificity of turmeric's anticancer activity must be established by further investigations.

FIG 4: **Curcuma longa**

HYPERICUM PERFORATUM:

Hypericum perforatum (St. John's wort) is a perennial flowering plant, preparations of which are popular as an anti-depressant and are also being promoted as an alternative cancer therapy. Even though some preliminary pre-clinical investigations have generated encouraging findings, there are no clinical studies to show that St. John's wort would change the natural history of any type of cancer. St. John's wort may reduce the blood levels of many conventional drugs, including some cancer medicines. Rare adverse effects include psychological symptoms, allergic reactions and visual disturbances.

Anticancer effects

The anti-depressive effects of St. John's wort seem to rely on the inhibition of the re-uptake of serotonin, noradrenalin, glutamate and dopamine in the central nervous system . Other known mechanisms of action include the modulation of interleukin-6 activity and gamma-aminobutyric acid receptor binding and antioxidant effects . There is preliminary evidence from in-vitro studies to suggest that constituents of St. John's wort have anti-cancer effects 33-35 . A range of mechanisms have been proposed based on results of pre-clinical studies, e.g. cytotoxic, apoptosis-inducing and anti-angiogenic effects. St. John's wort extracts exhibit cytotoxic and apoptosis-inducing effects in neoplastic cell lines . 11 They thus inhibit the growth of leukaemia and glioblastoma prostate

cancer cells in vitro . Ex-vivo experiments have demonstrated anti-angiogenic activity effects . which theoretically could contribute to anticancer These effects may not be linked purely to hypericin but also to other ingredients of St. John's wort . Animal experiments have shown that St. John's wort inhibits pro-inflammatory cytokines . Hypericin also 19 18 has phototoxic effects, and St. John's wort could thus have potential as a photodynamic agent for some types of skin cancer . Collectively the evidence indicates that the threshold for phototoxicity of hypericin 20 is between 100 and 1000 ng/ml . Since serum and skin concentrations of hypericin after oral1 administration of recommended doses are below 100 ng/ml, photosensitivity is unlikely . Nevertheless, it was reported that 3 μM of activated hypericin induced a necrotic mode of cell death in pigmented melanoma cells and melanocytes and an apoptotic mode of cell death in non-pigmented cells and keratinocytes .

FIG 5: **Hypericum perforatum**

ACACIANIALOTICA -VACHELLIA NILOTICA :

Cancer is a multi-mechanistic second largest disease in the world require a multidimensional approach for its treatment, control and prevention. Plant based drugs form an important component of total medicines available for treating various human diseases. The use of phytochemicals in cancer prevention has received considerable interest in the past few decades owing to certain discoveries with specific properties include antioxidant and anti-inflammation. Recently, a number of anti-cancer agents have become recognized therapies in the clinical setting which include: vinca alkaloids, taxanes, podophyllotoxin, camptothecin and its derivatives (Otsuki et al., 2010). A number of additional plant-derived agents are currently under investigation for example Homoharringtonine, 4-Ipomeanol and ß-lapachone (Adriana et al., 2001). Among the Acacia species, especially A.nilotica, a plant with established medicinal properties was chosen for this study. It has been reported as important medicinal plant used in folk medicine to treat various ailments. Based on this information and previous biological studies, we decided to investigate its anticancer effect against DAL induced solid and ascitic tumor condition. The reliable criteria for judging the quality of any anticancer drug are prolongation of lifespan and its effect on hematopoietic system (Isha et al., 2011). Administration of A.nilotica extract at concentration of 10 mg/kg.bw showed increase in mean survival time and

percentage increase in life span, decrease in percentage of increase in body weight (due to reduction of tumor burden) when compare to control DAL bearing ascitic tumor group. Myelosuppression and anemia have been frequently observed in ascites carcinoma condition. and similar findings were observed in our present study. In DAL bearing tumor control animals, elevated total WBC count and reduced hemoglobin content was observed. Moreover, A.nilotica extract showed a protective effect on hematopoietic system by reversal of total WBC cells and hemoglobin content in DAL bearing animals towards the value of normal group animals when compare to DAL bearing ascitic tumor animals. To investigate the inhibitory effect on ascitic tumor was local or systemic, the effect of administration of A.nilotica extract was tested against solid tumor induced by DAL cell lines. The abnormal mass of tissue that does not contain cyst or liquid is referred as solid tumor and is mostly epithelial in nature (Kushi et al., 2011). We observed significant inhibition of solid tumor volume and reduction of body weight in solid tumor bearing animals when compare to control DAL induced solid tumor animals undoubtly suggests that the inhibitory effect of A.nilotica is systemic, not only related to its local cytotoxic effect. This inhibitory effect on tumor volume and protection of hematopoietic system was comparable with the result produced by the standard drug methotrexate. AST and ALT were found in serum and various body tissues but are mostly associated with liver parenchymal cells. The elevated level of AST and ALT will be observed in acute liver damage condition. In addition, the level of ALP will rise with intrahepatic cholestasis and infiltrative diseases of the liver (Gaze, 2007). Similarly in our present study, we observed elevated level of AST, ALT and ALP in DAL induced ascitic tumor animals when compare to DAL induced tumor alone group. Administration of A.nilotica extract and standard drug methotrexate exerted a protective effect by reversal of these enzyme levels nearly towards normal value of animals. Gamma glutamyl transferase, an enzyme involved in cellular glutathione homeostasis which is often increased in level in tumor condition. The membrane bound enzyme GGT is expressed highly in embryo livers and decreases rapidly to lowest levels after birth. GGT is highly re-expressed during the development of (HCC) Hepatocellular carcinoma (Pompella et al., 2006; Lei et al., 2012). Treatment with A.nilotica significantly lowered the enhanced level of γ- GT in tumor bearing animals when compare to tumor control. The major non-protein thiol, GSH is required for the tumor cell proliferation and its metabolism (Guruvayoorappan and Kuttan, 2007). Cancer cells have higher GSH levels than the surrounding normal cells, which is characteristic of higher cell proliferation rate and resistance to chemotherapy. Scientific evidence shown that combining GSH depletion using 1,3-Bis(2chloroethyl)-1-nitrosourea chemotherapy with superoxide dismutase gene therapy could be considerably successful in the treatment of breast cancer. When the intracellular GSH levels are low, the cells are more susceptible to ROS attacks. Increased ROS might activate

different intracellular oncogenic pathways which lead to activation of tumorigenesis process (Weydert et al., 2008). However, the excessive levels of ROS stress can also be toxic to the cancer cells. Therefore, changing ROS levels by GSH modulation is a way to selectively kill cancer cells without causing toxicity to normal cells (Makiya, 2008; Trachootham et al., 2009). Administration of A.nilotica extract significantly reduced the level of intracellular GSH in extract treated DAL tumor cells when compare to the non-extract treated DAL bearing animals. Moreover, the treatment with extract also reduce the level of Nitric oxide production in serum and tumor cells when compare with tumor control animals. Since, nitric oxide is an important regulator of tumor growth and involved in various pathophysiological process includes inflammation and carcinogenesis (Hong, 2002). Phenolics and flavonoids display a wide range of biological and pharmacological properties and normally scavenge the free radicals and play an essential role in prevention and therapy of cancer. It is well documented that A.nilotica is one of the rich source of these flavonoids and phenolics. For example, the polyphenolic compound Kaempferol displayed radical scavenging activity in different in vitro assays (Rajbir et al., 2008). Niloticane isolated from the bark of the A.nilotica showed antiinflammatory property by inhibition of Cyclooxygenase enzymes which is involved in inflammatory process (Eldeen et al., 2010). ß-sitosterol also showed antioxidant and anti-inflammatory activity, which is used in the treatment of inflammatory disorders, breast cancer and colon cancer (Padmasri and Sarada, 2011). Similarly, gallic acid and catechin showed protective effect against N-nitrosodiethylamine-induced hepatocarcinogenesis (Brahma et al., 2009). Umbelliferone is also reported as potential scavenger of free radicals which is present in bark and leaves of A.nilotica (Rajbir et al., 2010). Recently, a report indicates that apigenin can act as potential chemopreventing agent due to induction of leukemia cell cycle arrest. Apigenin inhibited phosphoinositide 3-kinase/protein kinase B (PI3K/ PKB) pathway in HL60 and induced caspase-dependent apoptosis (Rajbir et al., 2010). Androstene also exhibits dose dependent anti-inflammatory property against TPA (12-O-tetradecanoylphorbol-13-acetate) induced mouse ear edema (Chaubal et al., 2006). The anti-angiogenic effect of rutin and its regulatory effect on the production if VEGF, IL-1β and TNF-α in tumor associated macrophages was also demonstrated (Guruvayoorappan and Kuttan, 2007). the treatment with A.nilotica was effective on inhibiting the tumor progression in in vivo models, most likely because of high content and synergistic activity of specific constituents present in the extract such as umbelliferone, gallic acid, niloticane, catechin, kaempferol, rutin, apigenin, androstene and β-sitoterol derivatives may exert these preventing effects. However, the exact molecular mechanism by which A.nilotica mediates its antitumor activity is still not clear.

FIG 6: **Vachellia nilotica**

ACACIACATECHU- SENEGALIA CATECHU

Recently, there has been renewed interest in botanically derived products as sources of therapeutic agents, due to safety concerns with synthetic drugs. Lack of characterization of agents with specific actions, especially in supplements from natural products; have made clinicians and scientists wary of their efficacy. [14] In the present study we report on the anticancer activity of the methanolic extract of the bark of Acacia catechu. The plant from the family leguminosea is popular in Indian subcontinent as well as in various other Asian countries for 'katha 'preparation. Katha is extracted from the hardwood and bark of Acacia catechu. However as per our findings the bark appears to be of great importance. The anticancer activity of Acacia catechu was evaluated in different cell lines viz. KB, MCF-7, U-87, HeLa, NCLH46, and HEK. Different extracts of the bark were tested for cytotoxic activity. Among all the extracts tested, the methanolic extract caused significant inhibition in the growth of cancerous cells. It caused inhibition of growth of KB cell line by ~83% (p<0.01) at 200µg/ml. The methanolic extract also inhibited the growth of MCF-7 cells by ~63%, U-87 by~73%, HeLa by~66% and NCL H-46 by ~58% (p<0.01) with effective concentration of 200 µg/ml while aqueous extract inhibited KB cells by ~49%, MCF-7 cells by~ 40%, U-87 cells by~ 52%, HeLa by~ 54% and NCL H-46 by ~41% (p<0.01). Acetone, chloroform and hexane extracts did not show significant cell growth inhibition at this concentration. The results were further confirmed by cell proliferation assay using trypan blue dye. The methanolic extract showed no cytotoxicity in normal cell line (HEK) at 200µg/ml. These finding suggest that the active components are polar in nature and the mechanism by which they induce cytotoxicity may be same for all cell lines. Epigallocatechin-3 gallate is found in Acacia catechu and it is known for its cytotoxic action. We have also performed a study with epigallocatechin-3 gallate as reference compound in KB and NCL-H46 cell line. The results showed that the methanolic extract was more cytotoxic than epigallocatechin-3 gallate.. To study the effect of extract on cell migration scratch assay was carried out with effective dose of 200 µg/ml and lower concentrations of methanolic extract on KB cell line, we found that 100µg/ml of methanolic extract was able to stop cell migration. The rate of cell migration was observed at every 3 hours for 12 hours under phase contrast microscope. The migration rate of the cells treated with

methanolic extract was much slower in comparison to the untreated cells. Even at the end of 12 hours the cells were not able to fill up the artificial gap upon treatment while the gap was filled successfully by untreated cells. The above study proved the fact that the plant extract has the potential to slow down the process of metastasis. Along with the cell migration assay, morphological changes in the cells during treatment with the methanolic extract were also studied. The cells were observed after every 6 hours under phase contrast microscope. Cells were found to lose their adherent ability and shrinkage in cells was observed upon treatment with methanolic extract. The cells loose their adherent projections and come on the surface and become aggregated which finally leads to their death. A vast variety of naturally occurring substances have been shown protection against experimental carcinogenesis. Some anti-inflammatory chemopreventive agents have been found to suppress growth and proliferation of transformed or malignant cells through apoptotic induction.[15] Our results demonstrated that methanolic extract from Acacia catechu induced apaptosis in KB cells at concentrations of 100 µg/ml and 200 µg/ml, as demonstrated by DNA fragmentation assay. The induction of apoptotic cell death was also accompanied by characteristic morphological and structural changes. The western blot analysis clearly illustrates the inhibitory effect of the methanolic extract on Cyclooxygenase-2 enzyme (COX-2) level activity. The expression of the COX-2 protein is lowered to a significant extent upto 75% in oral cancer cells, which were treated with the methanolic extract as compared to those cells which were untreated. COX-2 is related to the formation of carcinogens, tumor promotion, apoptosis inhibition, angiogenesis development, and metastatic process.[10] The inhibition in metastatic potential and cytotoxicity in oral cancer cells could be correlated to COX-2 inhibition. We propose here that the methanolic extract of the bark of Acacia catechu not only has cytotoxic action on cancerous cells, but also prevents metastasis. The study also revealed the fact that

the extract leads to apoptosis in the cancerous cells as indicated by DNA fragmentation and inhibition in the COX-2 enzyme activity. Therefore the methanolic extract causes cells to aggregate, decrease proliferation and to enter apoptosis.

FIG 7: **Senegalia catechu**

CAMELLIA SINESIS:

Several mechanisms involved in GTCs inhibition of cancer formation/progression are recently reviewed by numerous Authors [12–15]. Certainly, GTCs, through their antioxidant activity, are able to quench ROS and chelate transition metals, produced during all the carcinogenesis stage. However, it has been reported that also GTCs can be a source of ROS generation, inducing oxidative stress and consequently activating apoptotic pathways [16]. GTCs, and especially EGCG, are capable of modulating a plethora of cell signalling pathways crucial for cancer cells transformation and survival, including, but not limited to, the mitogen-activated protein kinase (MAP-kinase), the nuclearfactor-kappaB(NFκB), and the insulin-like growth factor (IGF)/IGF-1 receptor pathways. With regard to the prostate-specic processes GTCs are able to affect androgen receptor (AR) downregulation and prostate-specic antigen (PSA) expression [14, 17]. Here below, we report the most probable GTCs mechanisms of action in some PCa cell lines. 2.1. Inhibition of Cell Proliferation and Cell Cycle Arrest. GTCs exhibit ant-proliferative effects versus both androgensensitive and androgen-insensitive human PCa cells. The effect is mediated by cell cycle deregulation and cell death induction [18]. We showed that GTCs action is cancer specic, since GTCs is capable of inducing growth arrest both in SV40 immortalized prostate epithelial cells (PNT1a) and in tumorigenic androgen-independent PCa cells (PC3), while normal human prostate epithelial cells were not signicantly affected, even when EGCG was administered at higher doses [19]. The IC50 of EGCG ranges from about 40 to about 200µM, depending on the cell line type (LNCap < PNT1a < DU145 < PC3), as well as the length of the experiment, ranging from 24 to 72 hours [18, 20]. Our results were conrmed by other authors in normal broblasts [20, 21].

FIG 8: **Camellia sinesis**

VITIS VENEFERA.:

Antioxidant activities of GSE and grape phenolic compounds (mainly resveratrol and procyanidins), have been extensively investigated in vitro and in vivo.GSE possesses strong free radical scavenging activity prevents ROS-induced DNA damage and displays a relevant chelating effect on transition metal ions, thus reducing lipid peroxidation . Those effects have been deemed even more potent than known antioxidants such as vitamin E and

ascorbic acid. Some studies have reported an enhancing effect of GSE or of its polyphenolic constituents, on several anti-oxidant enzymes as glutathione (GSH) super-oxide dismutase (SOD) catalase and other detoxifying/antioxidant enzymes . GSE-induced antioxidant enzyme expression is associated with activation of the redox-sensitive transcription factor nuclear factor erythroid-2 p45 (NF-E2)-related factor (Nrf2), through its interaction with the antioxidant-response element (ARE) or the electrophile-responsive element (EpRE) . Indeed, Nrf2 plays a key role in up-regulation of many phase II antioxidant/detoxifying enzymes, including glutathione peroxidase (GPx), glutamate cysteine ligase (GCL), glutathione S-transferase (GST), SOD, and NADPH/quinone oxidoreductase 1 (NQO1) .In vivo, dietary supplementation of GSE was shown to reduce oxidative stress and improve the glutathione/oxidized glutathione ratio, as well as the total antioxidant in a double-blinded randomized crossover human trial .Though those results have been often confirmed , other studies have been unable to do so, showing that GSE exhibits either only a moderate or negligible antioxidant effect . Oxidative stress, resulting from enhanced production of ROS overcoming the cellular antioxidant defence, is a key phenomenon in chronic degenerative diseases (diabetes mellilitus, cardiovascular illness, cancer) ROS participate in triggering the apoptotic process, as programmed cell death is tightly regulated by the oxidative environment [19]. Dietary GSE strongly reduces rat mucosal apoptosis via modulation of both mitochondrial and cytosolic antioxidant enzyme systems together with an increase in cellular GSH, thus protecting normal colonic mucosa from ROS injury [21]. Given that GSE exerts a protective antioxidant effect in normal cells exhibiting deficiency of catalase activity or glutathione level, it can be hypothesized that grape polyphenols participate in controlling intracellular peroxide production [23]. Hence, anti-oxidant properties of GSE treatment may efficiently counteract the onset of ROSdependent disease, as documented by several studies. Yet, despite the popular version diffused by mass-media, it is hardly conceivable that GSE or polyphenols may exert a significant effect against cancer development by displaying anti-oxidant actions . Indeed, several studies have reported that GSE in cancer cells paradoxically enhances ROS production in a significant manner. GSE and many polyphenolic compounds induce a relevant increase in ROS and in superoxide radical generation, at both the cytosolic and mitochondrial site, that could eventually lead to GSH depletion . It is worth noting that GSE does not induce hydroxy peroxide (H_2O_2) increase, thus evidencing a deficiency in SOD activity, at least in the cancer cell lines studied. Indeed, in SOD-deficient cells, GSE treatment induce ROS-mediated cytotoxicity, evidencing that GSE-dependent increase in ROS activity is not efficiently counteracted by SOD-dependent transformation in hydroxy peroxide, leading to GSH depletion, cellular damage, and increased apoptosis (27) Moreover, pro-oxidant effects of GSE are enhanced in cells lacking SOD activity meanwhile co-exposures of polyphenols-treated cancer cells with SOD

largely prevented ROS formation and DNA damage Considering that the oxidant-dependent toxicity of polyphenols is efficiently rescued by co-treatment with SOD, but not with catalase, it is unlikely that flavonoids-related pro-oxidant effects could be mediated.

FIG 9: **Vitis venefera**

CONCLUSION:

Cancer is becoming a high profile disease in developed and developing worlds. In 2007 the WHO published that in 2005, 7.6 million people died from cancer related diseases with the majority of these people living in low-income countries . In the United States cancer is the cause of 1 in 4 deaths and in 2010 it was estimated there were over 1.5 million new cases of cancer. Cancer Research UK said in 2012 14.1 million adults were diagnosed with cancer and 8.2 million people were killed by cancer globally . Therefore, the demand for a cure and the prevention of cancer is extremely high.

Chemically-derived drugs have been developed and other cancer treatments pre-exist. However, current methods such as chemotherapy have their limitations due to their toxic effects on non-targeted tissues furthering human health problems. Therefore, there is a demand for alternative treatments with naturally-derived anticancer agents with plants being the desired source.

Increasing demand for plant-derived drugs is putting pressure on high-value medicinal plants and risking their biodiversity.Increasing populations, urbanization and deforestation are contributing to species endangerment in developing countries. To aid conservation of these species germplasm conservation, cryopreservation, tissue cultures and plant part substitution strategies need to be in place. Mass cultivation of medicinal plant species and utilizing raw by-products in industries may also help with conservation.

Plant-derived anticancer agents are effective inhibitors of cancer cells lines, making them in high demand. Exploitation of these agents needs to be managed to keep up with demands and be sustainable.

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