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MEDICINAL PLANTS: THEIR USE IN ANTICANCER TREATMENT

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ABSTRACT: 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.

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 [1]. 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 [2].

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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 [3]. 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 [1, 4-8].

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.

2. Epigenetic properties:

The step towards development of cancer involves alterations of epigenetic processes and their deregulation [9]. The control of hypermethylation of tumour-suppressor genes on CpG islands is deregulated in cancer cells. This can result in gene silencing and inactivation of tumour-suppressor genes [10]. Drugs which can inhibit or reverse epigenetic alterations have been in development over recent years [9].

Chemically derived epigenetic drugs have been developed and undergone trials such as 5-azacytidine (azacitidine; Vidaza) and 5-aza-2'-deoxycytidine (decitbine; Dacogen) which are both DNMTi [11] and HDACi such as suberoyanildehydroxamic acid (SAHA, Vorinostat, Zolinza) and FK228 (Romidespin, Istodax) [9]. However, it is difficult to engineer a chemically derived drug which is non-toxic to normal cells and is specific to cytotoxicity of cancer cells. Therefore, development and research into naturally derived compounds to be used for anticancer treatment is becoming high in demand with a focus on those derived from plant species and their natural products.

There are many forms of cancer amongst the human population but they share similar characteristics or genotypes such as insensitivity to signals which inhibit cell growth making their replication limitless. Apoptosis is evaded and never induced in cancer cells and angiogenesis is sustained within the tumour tissue [12] allowing survival of cancer cells. Plant derived compounds have demonstrated properties to inhibit cancer cell activity such as inhibiting proliferation of cancer cells and inducing apoptotic cell death.

3. Plant compounds with anticancer properties:

Medicinal plants have been used for thousands of years in folk medicines in Asian and African populations and many plants are consumed for their health benefits in developed nations. According to the World Health Organisation (WHO) some nations still reply of plant-based treatment as their main source of medicine and developing nations are utilising the benefits of naturally sourced compounds for therapeutic purposes [13]. Compounds which have been identified and extracted from terrestrial plants for their anticancer properties include polyphenols, brassinosteroids and taxols.

a. Polyphenols:

Polyphenolic compounds include flavonoids, tannins, curcumin, resveratrol and gallacatechins and are all considered to be anticancer compounds [14]. Resveratrol can be found in foods including peanuts and grapes and red wine. Gallacatechins are present in green tea. It is thought including polyphenols in a person's diet can improve health and reduce risk of cancers by being natural antioxidants [14-15].

The cytotoxicity of polyphenols on a range of cancer cells has been demonstrated and their antioxidant properties determined [14, 16-17].

Polyphenols are thought to have apoptosis inducing properties showing anticancer properties which can be utilized. The mechanism in which polyphenols are thought to carry out apoptosis initiation is through regulating the mobilization of copper ions which are bound to chromatin inducing DNA fragmentation. In the presence of Cu(II), resveratrol was seen to be capable of DNA degradation [14]. Other properties plant polyphenols show is their ability to interfere with proteins which are present in cancer cells and promoting their growth. Cancer agents may be altered through the polyphenol regulating acetylation, methylation or phosphorylation by direct bonding. For example, curcumin treated cancer cells in various cells lines have shown suppression of the Tumour Necrosis Factor (TNF) expression through interaction with various stimuli [18].

b. Flavonoids:

Flavonoids are from the polyphenolic compounds and constitute a large family of plant secondary metabolites with 10,000 known structures [19]. They are physiologically active agents in plants and becoming of high interest scientifically for their health benefits [20-21].

Various plants have been investigated for their flavonoid content and how these compounds affect cancer cells, such as fern species and plants used in traditional Chinese medicines like the litchi leaf [19, 22]. There is a high content of flavonoid compounds such as anthocyanins, flavones, flavonols, chalcones and many more which can be found in just one structure of the plant like its seed [22]. Coa *et al*., 2013, identified and looked at the anticancer effects of flavonoids on human lung cancer cells (A456 cell line) from the fern species *Dryopteriserythrosora*. They found flavonoids to demonstrate cytotoxicity on cancer cells and to have high free radical scavenging activity [19]. Purified flavonoids have also shown anticancer activities against other human cancers including; hepatoma (Hep-G2), cervical carcinoma (Hela) and breast cancer (MCF-7) [22]. The flavonoids extracted from *Erythrinasuberosa*stem bark (4'-Methoxy licoflavanone (MLF) and Alpinumisoflavone (AIF)) were shown to have cytotoxic effects in HL-60 cells (human leukaemia) [12]. MLF and AIF induced apoptosis through intrinsic and extrinsic signalling pathways. The mitochondrial membrane potential is significantly reduced due to the induction of apoptotic proteins. With mitochondria damage to cells the cancer cells cannot survive [12]. Other studies have looked at flavonoid extracts from fern species and found that even in low concentrations they still demonstrate high percentage of anticancer activity [23].

As previously mentioned polyphenols can inhibit or alter the regulation of proteins and other agents which may be contributing to the survival of cancer cells. Signal Transducer and Activator of Transcription (STAT) proteins are anti-apoptotic and contribute to cancer cell growth. MLF and AIF inhibit members of this family of proteins by preventing their phosphorylation needed for the cancer cells survival [12]. Also, these flavonoids inhibit the expression of NF-κB which is needed for cancer cell survival and angiogenesis and proliferation.

c. Brassinosteroids:

Brassinosteroids (BRs) are naturally occurring compounds found in plants which play roles in hormone signalling to regulate growth and differentiation of cells, elongation of stem and root cells and other roles such as resistance and tolerance against disease and stress. Also, BRs are used for regulation of plant senescence [24]. They are essential for plant growth and development. BRs are another naturally occurring compounds which have demonstrated therapeutic significance in the cause against cancer.

Two natural BRs have been used in investigations with cancerous cells to demonstrate the anticancer properties that these compounds possess. 28-homocastasterone (28-homoCS) and 24-epibrassinolide (24-epiBL) have demonstrated anticancer effects on various cancer cell lines [25-27] and proven to be effective at micromolar concentrations. A characteristic of cancer cells is that they do not naturally undergo apoptosis and proliferate indefinitely. BRs can induce responses necessary for growth inhibition and induce apoptosis by interacting with the cell cycle [25]. BRs have been used in investigations to treat a range of cancer cell lines which include; T-lymphoblastic leukaemia CEM, multiple myeloma RPMI 8226, cervical carcinoma HeLa, lung carcinoma A-549 and osteosarcoma HOS cell lines[25]. Also included are cell lines in breast cancer and prostate cancer. Estrogen receptor (ER), epidermal growth factor receptor (EGFR) and human EGFR-2 (HER-2) are some of the critical proteins which are targeted in treatment of breast cancer as they are abundant in breast cancer cells such as MCF-7, MDA-MB-468, T47D and MDA-MB-231 [26, 28].

In prostate cancer cells (LNCaP and DU-145 cell lines) the androgen receptor (AR) is a critical protein involved in its development and shares a similar structure to ER [27]. BRs will interact or bind to receptors of these proteins and inhibit the growth of both hormone sensitive and hormone insensitive cancer cells [26-27]. Also, BRs can induce cell cycle blockage. Treatment of breast cancer cell lines with 28-homoCS and 24-epiBL showed reduction in cyclin proteins which are involved in G_1 cell cycle phase. At this phase in the cell cycle cells will either under repair or enter apoptosis, treatment with BRs induces apoptosis at this stage which cancer cells would not be able to do naturally without treatment [27]. In prostate cancer cell lines, LNCaP and DU-145, the balance of apoptotic proteins which promote cell survival and those which induce programmed cell death changes with BRs treatment. The levels of the Bax pro-apoptotic protein increase after BRs treatment and anti-apoptotic proteins such as Bcl-2 are reduced [27]. Along with their anticancer properties BRs generate different responses in normal and cancer cells [25]. A key specification in anticancer treatment is for the agent not to be cytotoxic to normal cells and be cell specific to cancer cells; this is where agents of BRs origin are of interest for therapeutic properties.

d. Anticancer plant-derived drugs:

Plant-derived drugs are desired for anticancer treatment as they are natural and readily available. They can be readily administered orally as part of patient's dietary intake [29-30]. Also, being naturally derived compounds from plants they are generally more tolerated and non-toxic to normal human cells [31]. However, there are exceptions such as cyanogenetic glycosides, lectins, saponins, lignans, lectins and some taxanes [31-32]. If plant-derived drugs can demonstrate selectivity in research, are non-toxic to normal cell lines and show cytotoxicity in cancer cell lines, these drugs can be lead into clinical trials for further therapeutic development. Plant-derived drugs can fall under four classes of drugs with the following activities; methytransferase inhibitors, DNA damage preventive drugs or antioxidants, histone deacetylases (HDAC) inhibitors and mitotic disruptors [30]. The compounds being discussed are represented in Table 1 with their origins, anticancer activity and their clinical trial development.

Compounds including sulforaphane, isothiocyanates, isoflavones and pomiferin are considered to be HDAC inhibitors. They inhibit the activity of carcinogenic proteins. For example, sulforaphane has shown to inhibit important targets in breast cancer proliferation. Decreased expression of ER, EGFR and HER-2 resulted from HDAC inhibition by sulforaphane treatment in breast cancer cell lines [28]. In cancer cells, epigenetically-silenced genes which are functional for chromatin acetylation are reactivated by HDAC inhibitors and cancer cells are then able to enter programmed cell death (apoptosis). Plant-derived compounds which show inhibition of HDAC can enhance chemotherapeutic sensitivity in human cancrs [28, 30]. Derivatives of vinca alkaloids, vincristine, vinblastine, vinorelbine, vindesine and vinflunine are drugs which will inhibit the dynamics of microtubules by binding to β-tubulin. Taxanes such as paclitaxel and its analogue docetaxel are also microtubule disruptors. These compounds inhibit cell cycle phase transitions from metaphase to anaphase causing cell cycle arrest and apoptosis. Replication of cancer cells is reduced by paclitaxel as it stabilizes or polymerizes microtubules in the cells[33-35]. Paclitaxel was one of the first drugs to have a huge impact on cancer treatment and vincristine and vinblastine were two of the initial drugs to be isolated [35].

Combinations of drugs derived from vinca alkaloids, Taxusditerpenes, Podiphyllumlignans and Camptotheca alkaloids in plant extracts may enhance their anticancer effects and improve their efficacy as therapeutic agents [35-36]. Extracts from *Urticamembranaceae*, *Artemesia monosperma* and *Origanumdayi Post* in Solowely *et al*., 2014 were investigated to test their effects on a wide range of cancer cell lines from lung, breast, colon and prostate cancers. The investigation showed the plant extracts with a combination of anticancer compounds were able to have killing activity which was specific to cancer cells and showed no effect on normal human lymphocytes and fibroblasts. This makes plant extracts more desirable as therapeutic agents than those that are chemically derived which cause toxic complications in cancer treatment. The plant extracts induced apoptosis which was demonstrated by an increased sub-G_1 phase population of cells with lower DNA content and condensation of chromatin. Also an increase in caspase 3 activation was seen after extract treatment which is a key stage in apoptotic cell death [36].

Discovery of anticancer cancer agents which show specificity towards cancer cells and can induce cell death and inhibit growth of tumours may be considered for clinical trials (**Table 1**).

e. Enhancing drug administration:

With advancements and discoveries in naturally derived drugs new technologies are emerging for the application and dosage of these anticancer compounds. Administration of new drugs needs to be effective for the compound to be a successful alternative to current treatments such as chemotherapy. Through the field of nanotechnology the use of nanoparticles (NPs), as a delivery system for drugs to reach target sites, is developing. Some compounds that have demonstrated anticancer activities may be limited in their clinical development due to the need for high dosages [37]. Bromleain, isolated from *Aanascomosus* was shown to be more effective as an anticancer agent in formulation with NPs than free bromelain [37].

This research demonstrated a safe and biocompatible method using bromelain NPs to sustain release of the drug at the target site whilst also protecting the drug. These bromelain loaded polyllactic-co-glycolic acid NPs (BL-PLCG NPs) showed to trigger apoptosis of benign cells more so than free bromelain by regulating the expression of pro-apoptotic and anti-apoptotic proteins in 2-stage skin turmorigenesis in mice. Other NPs synthesized have also been investigated such as; gold NPs of *Antigonoleptopu s*powdered extract and copper oxide NPs of *Acalyphaindica* [3, 38]. These formulations of plant extract and NPs showed cytotoxicity against MCF-7 breast cancer cell lines. Paclitaxel has been through clinical trials and early treatment settings. Research and development is aiming to use NPs to control release of the drug and enhance target specificity [39] by using magnetic mesoporous silica NPs with a gelatine membrane; Paclitaxel can be controlled externally using a magnetic field.

This has shown to be successful in increasing the drug's ability to inhibit growth of tumours and reduce unwanted effects of other tissue areas as the drug's distribution is controlled [39]. Success has also been seen with the drug quercetin using superparamagnetic magnetite NPs against breast cancer (MCF-7) cell lines [40]. This research demonstrated enhanced activities of the NPs in cytotoxicity of MCF-7 cells compared to free or pure quercetin. NPs in their use for anticancer treatment are of growing interest and show promise as a natural alternative to current treatments.

Alternatively, research investigating application using nanocochleates and nanolipososmes demonstrates achievement in anticancer activities through oral or inhalable intake [41-42]. Paclitaxel taken orally is most cost effective and more comfortable for the patient. A formulation of paclitaxel-loaded nanocochleates which can been administered orally showed controlled drug release and effective activities against lung, ovarian and breast cancer cell lines [41]. Also, noscapine was limited in clinical trials due to insoluble properties until derived analogues were developed [43]. Jyoti *et al*., 2015 investigated the noscapine analogue 9-bromo-noscapine in formulation with nanostrucutured lipid particles. Here they showed enhanced cytotoxicity and apoptosis in lung cancer cell lines with increased uptake of drug into cancerous cells of the formulated noscapine analogue compared to the free drug.

5. Medicinal plant demands:

With successful clinical trials drugs being developed from plant origins are popular for clinical development. Their non-toxic effects on normal cells and their cytotoxic effects on cancer cells put them in high demand. A lot of the species investigated are selected from developing countries in Africa and Asia where herbal therapies are practiced and medicinal plants are relied upon for primary treatment [1, 4-8].

The World Health Organisation estimated in 2007 that the plant-derived drugs trade was worth US$100 billion. The trade is expected to reach US$5 trillion by 2050 [13].

There is a huge demand for medicinal plants in developing countries putting high pressure on the plant populations. Many medicinal plants are cultivated from wild populations for informal trade but this cultivation is not regulated [44]. With rapid population growth, deforestation and increasing urbanisation the protection of medicinal plants is becoming an issue in need of addressing [45]. With constant increase in demand, high-value medicinal plants are threatened by extinction if over exploitation continues. Conservation of these plants is vital. When wild medicinal plants are harvested only specific parts of the plant are used in treatment such as the bark of a tree or bulbs and tubers from bulbous and tuberous plants. Extracting only segments of a plant may damage and reduce its survival [44]. To increase the sustainability of medicinal plants in developing countries, utilization of all plant parts including the stem, leaf, root and bark should be included in the treatment. Other methods of conservation include germplasm conservation; storing viable seeds, cryopreservation; preserving biological material in liquid nitrogen and tissue culture; propagates plants in sterile conditions and can produce mature plants clones quickly of rare species [45-46]. These preservation methods will also allow for industrial utilization in developed countries [45].

In developed areas such as Europe and parts of India and China some medicinal plants are being cultivated on a large scale to keep up with increasing demands for alternative natural drugs [44]. Cultivating sustainable species may release pressure on other wild species and prevent loss of plant biodiversity. However, mass cultivation could lead to strain on land available for other resources in agriculture.

Attention is being drawn towards foods with medicinal properties, such foods include cruciferous vegetables and fruit berries [21, 29]. Raw by-products from industries could be utilized to extract anticancer agents from sources possess these agents. For example, one of the biggest crops grown globally are grapes (*Vitrisvinifera*) and 'grape seed extract' is often added in ingredients of food products due to its human health benefits. In the winery industry grape stems are a raw by-product of wine making. This high organic load can be acidic to the environment surrounding the winery. However, its high polyphenolic content may make it advantageous for anticancer drug development and make a profitable scheme to solve environmental issues. Grape stem extracts have demonstrated to have antioxidant properties, prevent DNA damage from reactive oxygen species and shown anti-carcinogenic potential against an array of cancer cell lines from cervical cancer, thyroid cancer and many more [47-48].

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 [49]. 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 [50]. Cancer Research UK said in 2012 14.1 million adults were diagnosed with cancer and 8.2 million people were killed by cancer globally [51]. 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 [11]. However, current methods such as chemotherapy have their limitations due to their toxic effects on non-targeted tissues furthering human health problems [1]. Therefore, there is a demand for alternative treatments with naturally-derived anticancer agents with plants being the desired source.

The secondary metabolites in the plant kingdom such as polyphenols, flavonoids and brassinosteroids have been studied for their potential use as anticancer agents. Collectively they have been shown to possess anticancer activities which include; antioxidant activity; inhibition of cancer cell growth; induction of apoptosis; target specificity; cancer cell cytotoxicity [18-19, 25, 40]. Plant-derived drugs have been developed from positive results in research and have progressed into clinical trials (**Table 1**). Drugs derived from vinca alkaloids were some of the first compounds to be utilized and are developing in clinical Phase III trials along with Pacitaxel and other anticancer agents (**Table 1**). These compounds are readily available from the natural environment and are relatively non-toxic to healthy human cells. Also there are currently developments using new technologies such as nanoparticles to be used in administration of anticancer compounds and therapies. Their development could be applied to control sustained drug release and help in aims to create drugs that are tissue specific reducing severe side effects of treatments.

Increasing demand for plant-derived drugs is putting pressure on high-value medicinal plants and risking their biodiversity [44]. 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 [46]. Mass cultivation of medicinal plant species and utilizing raw by-products in industries may also help with conservation [32, 48]. Plant-derived anticancer agents are effective inhibitors of cancer cells lines [3], making them in high demand. Exploitation of these agents needs to be managed to keep up with demands and be sustainable.

TABLE 1: PLANT-DERIVED DRUGS IN RESEARCH AND CLINICAL TRIALS

Anticancer agent	Isolated or derived from:	Compound activity	Research and clinical development	References
Sulphoraphane	Isotiocynanate in cruciferous vegetables *Brassica*	Induces phase 2 detoxification enzymes; inhibits tumor growth in breast cancers; antiproliferate effects	Clinical trials with oral administration of cruciferous vegetable preparation with sulphoraphane	28-29, 52
Paclitaxel (Taxol)	Taxane; *Taxusbrevifolia* L	Microtubule disruptor; block mitosis; induce apoptosis; microtubules are polymerized and stabilized; disruption of spindle formation; inhibition of translational machinery	In clinical use; Phase I-III clinical trials; early treatment settings; non-small lung cancer, breast cancer, ovarian cancer, Kaposi sarcoma. Research and development in alternative drug administration using nanoparticles, naocochealtes and nanoliposomes.	34, 39, 41, 53-54
Epipodophyllotoxin	*Podophyllumpeltatum*L.; Podophyllotoxin isomer	Pro-apoptotic effects; cell cycle interference	Lymphomas and testicular cancer trials	31, 36, 53
Vincristine			Lymphomas, sarcomas and leukaemias; in clinical use; combination trials	30, 34, 36, 53, 55
Vinblastine	*Catharanthusroseus* G. Don; Vinca alkaloids	Anti-mitotic; microtubule inhibitor; bind to β-tubulin; microtubule stabilizers or destabilizers; pro-apoptotic properties and induce cell cycle arrest; anti-tumour activity	Testicular cancer, Hodgkins disease and lymphoma; in clinical use; combination trials	30, 34, 36, 55
Vinorelbine			Non-small cell lung cancer; single and combination trials; Phase I-III	30, 34, 36
Vindesine			Clinical trials for acute lymphocytic leukaemia	30, 36
Vinflunine			Clinical trials for activity against solid tumors; Phase III clinical trials	30-31, 34
Pomiferin	Isoflavonoidisolatated from *Maclurapomifera*; *DereeisMalaccensis*	Pro-apoptotic effects; DNA fragmentation; inhibits oxidative damage of DNA; antioxidant activity; inhibits histone deacetylases; cytotoxicity of cancer cells	Growth inhibition in six human cancer cell lines: ACHN (kidney), NCI-H23 (lung), PC-3 (prostate), MDA-MB-231 (breast), LOX-IMVI (Melanoma), HCT-15 (colon)	30, 56

Epigallacotechin-3-gallate	Catechin; green tea	Antioxidant; decrease DNA damage from oxidative stress; anti-proliferative effects; inhibition of specific kinases; inhibit carcinogenesis induced chemically or by UV	Clinical trials in prostate cancer treatment ; Phase I clinical study for oral dose administration	30, 57-58
Combretastatin A-4 phosphate	Water-soluble analogue of combretastatin; *Combretumcaffrum*	Anti-angiogenic; vasuclar shut-down of tumors; tumor necrosis	Early trials; mimics developed; clinical and preclinical trials	31,54
Roscovitine	Derived from olomucine; *Raphanussativus*L. (*Brassicaceae)*	Inhibition of cyclin dependent kinases; reduction of cell cycle progression	Phase II clinical trials in Europe	31, 54
Flavopiridol	Synthetic flavonoid derivative; rohitukine based structure; *Dysoxylumbinectariferum*Hook.f. (*Meliaceae*)	Anti-inflammatory; immunamodulatory activity; tyrosine kinase activyt; growth inhibitory effects	Phase I and Phase II clinical trials in solid tumors, lymphomas, leukaemias	31, 54, 59
Noscapine	Opium poppy (*Papaver somniferum*)	Antiproliferative properties; microtubule interfering; inhibits tumour growth and progression	Phase I and Phase II clinical trials; limited progression due to its limited solubility; research into alternative administration of drug using analogues and nanotechnology.	42-43, 60

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