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Medicinal plants commonly used against cancer in traditional medicine formulae in Sri Lanka

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Abstract

Cancer is a global burden. In low- and middle-income countries around 70% of deaths are due to cancer. For a number of years natural products have been a good source of agents for combatting cancer and plants have played a huge role in anti-cancer product development. For many centuries, indigenous cultures around the world have used traditional herbal medicine to treat a myriad of diseases including cancer. In Sri Lanka, a number of plants have been reported to have anti-cancer properties and some of the commonly used plants are described in this review with an account of their compounds and modes of action. Only a small number of the plants in Sri Lanka have been tested for their bioactivity and more research is required to determine their medicinal activity with the aim of developing novel drugs to fight this disease.

Key words- Plants with anti-cancer properties, traditional medicine, cancer

1.0 Introduction

Currently, one in six deaths are due to cancer worldwide and around 70% of deaths from cancer occur in low- and middle-income countries [1]. This could be due to behavioural and dietary risks such as physical inactivity, smoking, use of alcohol and having an unhealthy diet low in fruit and vegetables. Additional factors contributing to the high incidence rate are aging population and exposure to certain chemicals, metals and infectious agents [2] [3]. This makes cancer an important health problem which requires effective prevention and treatment measures.

Among natural products plants have played a key role in treating a number of diseases including cancer. The sheer variety and number of plants with medicinal properties around the world is quite astonishing. It is estimated that around 70,000 plant species, from lichens to towering trees, have been used at one time or another for medicinal purposes. Ancient cultures respected the curative powers of healing plants, illustrated by findings from the excavation of a 60,000 year old burial site in Iraq. Eight different medicinal plants were

found at this site; the inclusion of the plants in the tomb suggests that they had supernatural significance and medicinal value [4]. Excavations in Sri Lanka have shown that the Balangoda man used plants for medicinal purposes, about 30,000 years ago [5]. Extensive investigations around the globe have revealed that medicinal plants were used by humans in the prehistoric era and that crude extracts or pure molecules isolated from medicinal plants represent the most ancient mode of medications.

Plant-derived agents have played a vital role in the treatment of cancer. Hartwell, in his publications reported over 3000 species that possess anti-cancer properties [6]. The search for anti-cancer agents from plants sources started in the early 1950s and over the years medicinal plants have been exploited as an initial point for the synthesis of new compounds for cancer with different structural parameters in the synthetic, combinatorial and biotechnological sciences. Over 60% of currently used anti-cancer agents are derived from natural sources such as plants [7] [8]. The curative properties originate in different parts of these plants, due to the presence of an array of low-molecular-mass substances known as secondary metabolites. These secondary metabolites are distinct from the components of primary metabolism, as they are not involved in the general metabolism but are used against microbial attacks or animal predation [9] [10]. Examples of secondary metabolites are flavonoids and phenolics, terpenoids, alkaloids and sulphur-containing compounds. Related plant species may produce related chemicals, for instance compounds that have anti-mutagenic and anti-cancer properties may play significant roles in either inhibiting or activating signal transduction pathways in living cells [11].

2.0 Plant-derived anti-cancer agents in clinical use

Vinca alkaloids, are one of oldest class of agent used to treat cancer and are the second-most commonly used agents in the clinic. They were first developed in the 1950s by Canadian scientists Robert Noble and Charles Beer. These alkaloids were isolated from *Catharanthus roseus* (Apocynaceae) and were given to patients with breast cancer, Hodgkin's lymphoma, leukaemia, testicular cancer and lung cancer [8] [12]. The two main vinca alkaloids are vincristine and vinblastine and a few structural analogues such as vinorelbine, vindesine and vinflunine (figure 1) have been developed [3] [12]. Vinblastine, vincristine and vinorelbine are approved for use in the USA and vinflunine was approved in 2008 in Europe. The main mechanism of action of these agents is that they bind to tubulin and disrupt the function of

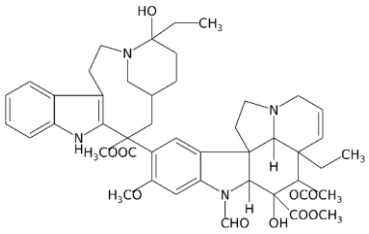
microtubules, particularly those comprising the mitotic spindle apparatus, by arresting metaphase of the cell cycle [13].

Another important class of anti-cancer agents are the taxanes. Paclitaxel (Taxol) (figure 1), derived from extracts of the Pacific yew tree *Taxus brevifolia*, is given to patients with breast, ovarian, lung, head and neck, oesophageal, prostate and bladder cancers. This compound acts by binding to microtubules and enhancing tubulin polymerization, leading to microtubule stabilization, cell cycle arrest and aberrant mitosis. Docetaxel (figure 1) is a semisynthetic taxane, derived from extracts of European yew tree *Taxus baccata*. This agent is similar to paclitaxel with a related mechanism of action, but better solubility in water. Docetaxel is effective in breast, ovarian, head and neck, lung, gastric and bladder cancers [14]. Several different analogues of taxanes have been clinically evaluated. A nanoparticle albumin-bound form of paclitaxel (Abraxane), having greatly reduced systemic toxicity, was approved in 2005 for the treatment of metastatic breast cancer. Another analogue, cabazitaxel (figure 1), was approved in 2010 for the treatment of metastatic prostate cancer. Further, larotaxel, milataxel, ortataxel, and tesetaxel (figure 1) are currently under clinical evaluation [3] [15] [16].

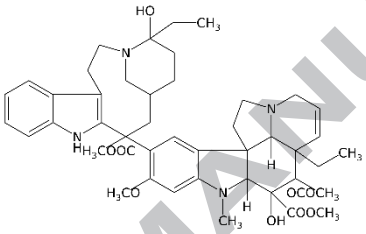
Camptothecin (figure 1) a quinoline alkaloid, was obtained in 1966 from the stem of *Camptotheca acuminate*, a Chinese ornamental tree. It binds to topoisomerase I, allowing DNA cleavage but inhibiting subsequent ligation which results in DNA strand breaks. This agent proved unsuccessful in the clinic due to severe bladder toxicity but extensive research led to the discoveries of irinotecan and topotecan (figure 1) which are derivatives of camptothecin. Irinotecan is approved for treating colorectal cancer and topotecan is approved for the treatment of ovarian, cervical and small cell lung cancers [8] [17].

Etoposide, a semisynthetic derivative of *Podophyllum peltatum*, was first synthesized in 1966 and was approved for cancer therapy in 1983. This agent targets topoisomerase II and forms a complex with topoisomerase II and DNA. The complex induces breaks in double-stranded DNA and prevents repair by topoisomerase II binding. Etoposide is used to treat Hodgkin's and non-Hodgkin's lymphomas, lung, gastric, breast, and testicular cancers [18] [19]. A number of novel etoposide derivatives are undergoing clinical evaluation [20] [21]. Teniposide, another semisynthetic derivative of *Podophyllum peltatum*, has a similar mechanism of action to etoposide but is insoluble in water [22].

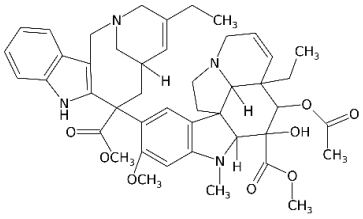
Harringtonine and Homoharringtonine (figure 1) are also plant-derived agents with anti-leukaemic properties. They are isolated from *Cephalotaxus harringtonia* (harringtonine was first isolated in 1963). These agents inhibit protein translation by preventing the initial elongation step of protein synthesis via an interaction with the ribosomal A-site. A racemic mixture of these two agents has been given to patients with acute myelogenous leukaemia and chronic myelogenous leukaemia in China and in 2012 homoharringtonine was approved by the US Food and Drug Administration for the treatment of chronic myeloid leukaemia [8] [23] [24].

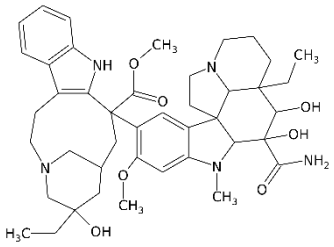


Vincristine

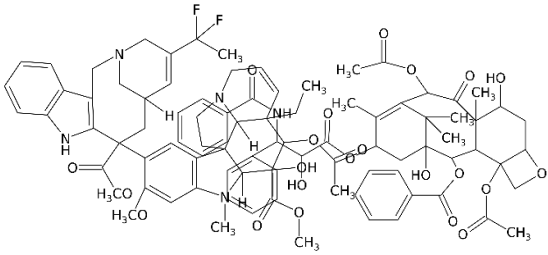


Vinblastine

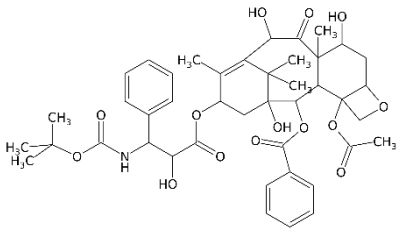




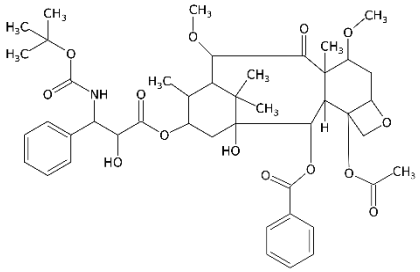
Vindesine



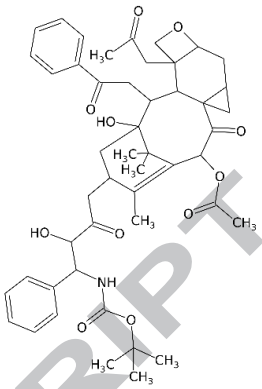
Vinflunine



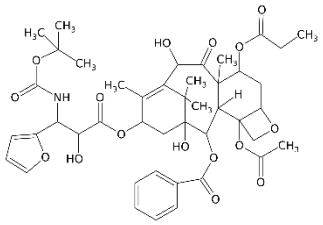
Docetaxel



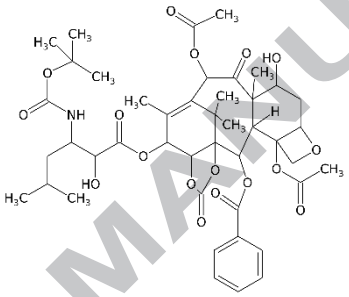
Cabazitaxel



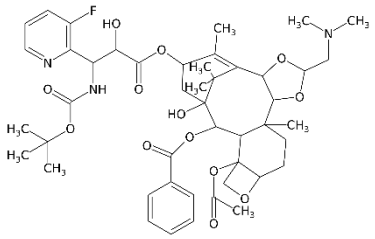
Larotaxel



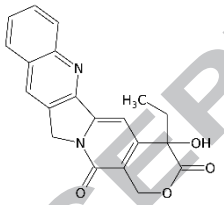
Milataxel



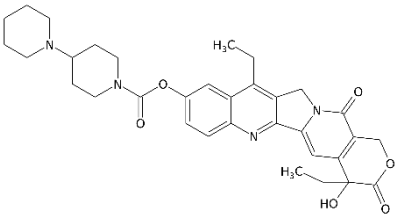
Ortataxel



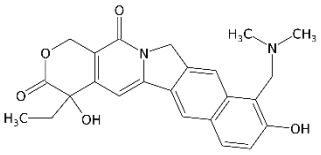
Tesetaxel



Camptothecin



Irinotecan



Topotecan

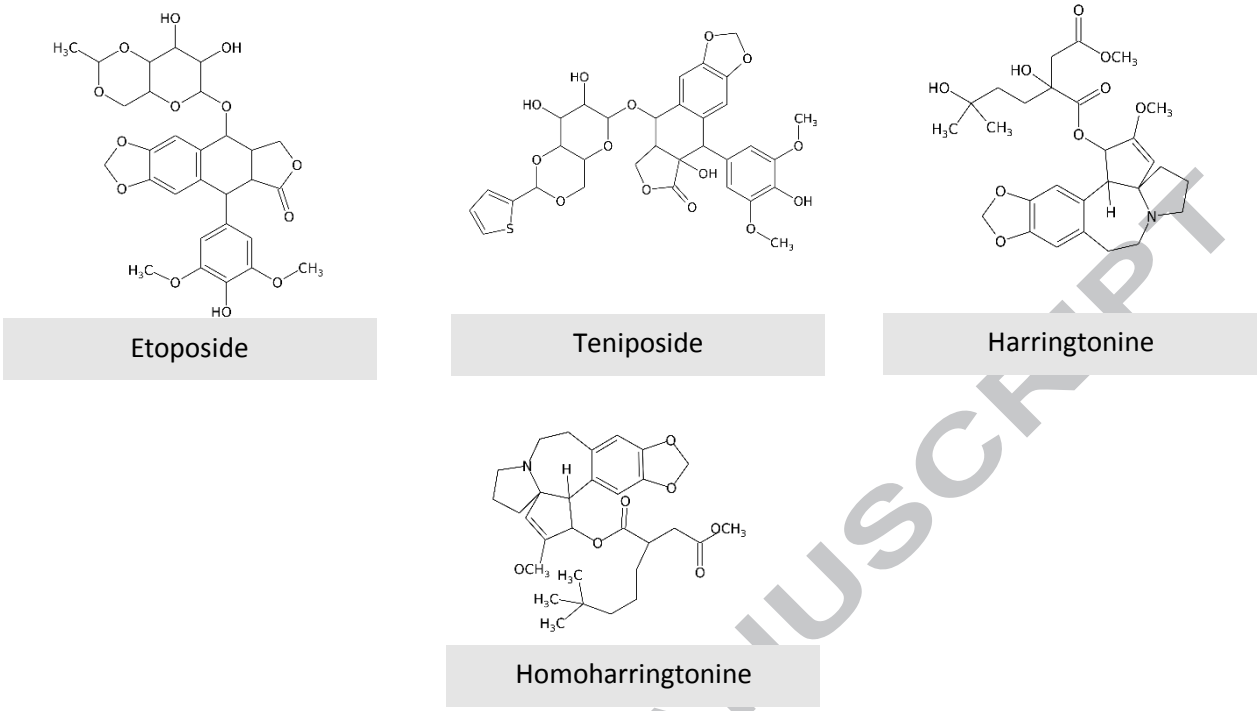


Figure 1- Chemical structures of anti-cancer drugs derived from plants that are in clinical use

3.0 Sri Lankan plants that have anti-cancer properties

Sri Lanka has a rich history of traditional medicine practice dating back many centuries. This practice is a mixture of the Sri Lankan indigenous medicine system "deshiya chikitsa" ayruveda and siddha systems, introduced by India, and the unani system that originated in Greece and introduced by the Arabs to Sri Lanka. Currently, 70% of the population of the country uses this traditional medicine system [25], which is popular for treating tumours both benign and malignant. The Sri Lankan herbal preparations or traditional medicine formulae used against cancer typically contain extracts from more than one plants species; very rarely is an extract of just a single plant given to patients having cancer, unless it is very potent. A single plant may contain one or more active compounds, working together synergistically with compounds of other plants to offer a combinatorial approach that would deliver an enhanced therapeutic effect. This combinatorial approach may also overcome resistance by reducing the activity of cross talk of signalling pathways activated in cancer. Sri Lanka which is a biologically diverse country, is home to around 1430 medicinal plants [26], giving rise to numerous herbal preparations for cancer. The primary mode of administration of such preparations is oral. Various parts of the plant (leaves, bark, stem, roots, flowers, seeds) are used in these medicinal preparations. Further, a specific plant may have various morphotypes

in different localities in the country, where one particular type would be widely used therapeutically [27]. Ten terrestrial plant species commonly found in anti-cancer herbal preparations of the traditional medicine system of Sri Lanka are described below.

3.1 *Zingiber officinale*

Zingiber officinale (belongs to the family Zingiberaceae), commonly known as ginger or 'inguru' (in Sinhalese), is widely used in anti-cancer traditional medicine preparations for gastrointestinal, liver and oesophageal cancers [28]. The rhizome is used in medicinal preparations and it is mostly used in poly herbal preparations. It is commonly used as a culinary ingredient in Sri Lankan cuisine [29] [30]. Many active ingredients are present in this plant, including gingerols, which are converted to shogaols, zingerone and paradol [31]. *Zingiber officinale* exerts its anti-cancer effects via multiple pathways. For instance, an extract of *Zingiber officinale* was found to significantly reduce the expression of NFκB through suppression of proinflammatory TNFα in liver cancer induced rats [32]. NFκB is a transcription factor that plays a role in biological processes such as inflammation, cell growth and survival, and TNFα is a cytokine which exerts its biological functions through activating NFκB [33]. Another study showed that when gingerol was given to male F344 rats at a concentration of 0.02% for around 3 weeks, azoxymethane-induced intestinal cancer was significantly suppressed [28]. Research has suggested that gingerol in ginger could be an effective chemo-preventive and/or chemotherapeutic agent for colorectal cancers. Ginger showed significant efficacy in mice were fed with ginger before and after tumour cells were injected and also when ginger was fed after tumours had grown to a certain size [28]. Gingerol, has demonstrated anti-angiogenic activity *in vitro* and *in vivo*, suggesting that it might have a possible role in preventing metastasis [34]. Other than for cancer, *Zingiber officinale* is often used as an antibacterial agent for infections, it is also used for nausea and diarrhoea, loss of appetite, and for inflammation [30].

3.2 *Curcuma longa*

The rhizome of *Cucurma longa* (Zingiberaceae) is commonly used in poly-herbal preparations used to treat a wide range of cancers. This plant, known as turmeric or "kaha" in the Sinhalese langauge, is regularly used as a spice and flavouring agent in Sri Lankan cuisine [29] [30]. Its major active chemical constituent is curcumin. Scientific evidence demonstrates that this plant is able to inhibit variety of cancers such as colon, hepatocellular, breast, renal, prostate cancers, T cell leukaemia, and B cell lymphoma [35]. For instance, one

study showed that curcumin is able to inhibit, colo 205 adenocarcinoma (colon cancer) cells and induce apoptosis via caspase-3 activity [36]. The same study showed that curcumin was able to increase the levels of reactive oxygen species and Ca^{2+}, leading to apoptosis of cells. Another study found that a mixture of *Curcuma longa, Zingiber officinale* and *Allium sativum* together with tamoxifen induced apoptosis in oestrogen receptor positive MCF-7 and ZR-75 breast cancer cell lines [37]. Garcea et al. investigated curcumin levels in the colon and rectum in 12 patients with colorectal cancer at different stages, where patients had been assigned to varying doses with the highest being 3.6 grams of curcumin per day for 7 days prior to surgery. Administration of capsules containing 3.6 grams of curcumin decreased M_1G levels from 4.8±2.9 adducts per 107 nucleotides in malignant colorectal tissue to 2.0±1.8 adducts per 107 nucleotides; thus, M_1G levels were 2.5-fold higher in malignant tissue compared with normal tissue [38] [39]. DNA damage is important in the aetiology of many cancers and damage may be reflected by exocyclic DNA adducts such as M_1G [40]. Further, *Curcuma longa* has been clinically evaluated as a chemo-preventive agent, especially for colorectal cancer, and this effect may be due to its ability to compete with aryl hydrocarbons for both AhR and CYP1A1 sites [35]. In one study, histological improvement of premalignant lesions of various cancers such as intestinal metaplasia of the stomach, bladder carcinoma, was observed when 1–8 grams of curcumin were given daily for 3 months [38]. Other than its anti-cancer uses, *Curcuma longa* is commonly used as an antibacterial agent and for diabetes mellitus, wounds and skin diseases [30].

3.3 *Hemidesmus indicus*

Hemidesmus indicus (Apocynaceae), commonly known as Indian sarsaparilla or "iramusu", is used in poly-herbal preparations aimed against cancer; the root is mostly used in traditional medicine preparations [41]. The leaves are used to make gruel or herbal drinks in Sri Lanka. This plant is mostly given for liver, uterine and breast cancers and leukaemia. The root of this plant contains ledol, nerolidol, caryophyllene, camphor, borneol, dehydrolupanyl-3 acetate, dehydrolupeol acetate, lupeol, dodecanoic acid, hexadecanoic acid, hemidesminin, hemidesmin-1 and 2 compounds; out of the above compounds, caryophyllene has shown to have anti-cancer properties in literature and this could be one of the compounds responsible for the cytotoxic properties of Hemidesmus indicus [42] [43] [44] [45]. Decoctions of *Hemidesmus indicus* have demonstrated a cytotoxic effect in HepG2 hepatocellular carcinoma cells while a hydroalcoholic extract has shown activity against HepG2, LoVo (colon cancer), MCF-7 (breast cancer), K562 (leukaemia) and Jurkat (leukaemia) cell lines

[46]. A decoction of *Hemidesmus indicus* was shown to induce an immunogenic type of cell death in DLD1 (colon cancer) cells, stimulating an upregulation of CD83 that caused dendritic cell maturation. Thus, this plant has the potential to act as an adjuvant agent by enhancing an immunogenic response in cancer [41]. In other studies, a poly-herbal formulation of *Nigella sativa* seeds, *Hemidesmus indicus* roots and *Smilax glabra* rhizomes induced apoptosis in HepG2 cells through activation of caspases 3 and 9 [47] [48]. The authors reported that long-term treatment (around 16 months) with this poly-herbal decoction inhibited diethylnitrosamine-induced glutathione S-transferase P expression in rat liver. Further, the same decoction inhibited carcinogen-mediated development of overt tumours along with histopathological changes leading to tumour development, possibly be due to a significant reduction of angiogenesis that was observed [49]. Galhena et al, demonstrated that the above decoction can protect against the cytogenetic damage mediated by bleomycin in human peripheral blood lymphocytes compared with cells that were treated only with bleomycin. Bleomycin is an anti-cancer drug which is shown to mediate DNA double-strand breaks in both cancer cells and normal cells. Thus, this decoction of *Hemidesmus indicus* could be used in cancer management [50].

Hemidesmus indicus is also used as a blood purifier and for skin diseases and gastric aliments [30] [46].

3.4 *Munronia pinnata*

Munronia pinnata, a member of the Meliacea family, is used in poly-herbal formulations and is also given as a single extract to cancer patients. In Sri Lanka this plant is commonly known as “bin kohomba” [27] and is mostly given for lung and brain cancers. Leaves, roots or the whole plant are used for medicinal purposes. The demand for this herb is very high in Sri Lanka and as a result it is very expensive to obtain. There is also a threat of extinction of *Munronia pinnata* due to insufficient supply to meet the high demand. Thus, conservation of this rare and valuable plant is important [51]. A study has revealed that this plant contains β-caryophyllene, caryophyllene oxide and ganoderiol F as active compounds. There is limited research conducted on the anti-cancer properties of *Munronia pinnata*. However, the compounds found in this plant have demonstrated cytotoxic activity in various studies and might be responsible for the plant’s anti-cancer properties [51]. For instance, ganoderiol F has shown remarkable inhibitory effects against LLC (mouse Lewis lung cancer), T47D (breast cancer), S-180 and Meth-A (mouse sarcoma) cell lines. The same compound

demonstrated remarkable inhibitory effect on the growth of Lewis lung carcinoma tumours in mice [52]. Further, β-caryophyllene, has been shown to inhibit HCT-116 and HT-29 (colon cancer) cell lines and PANC-1 (pancreatic cancer) cells. Caryophyllene oxide has been shown to inhibit SNU-1, SNU-16 (stomach cancer) cell lines and Hela (cervical cancer) cells. These compounds may exert their action by inhibiting PI3K/AKT/mTOR and STAT3 signalling pathways which are responsible in cell survival and proliferation of cancer cells [53]. Further studies have shown that these compounds are able to enhance the efficacy of paclitaxel and doxorubicin. For instance, researchers have found that β-caryophyllene enhanced the activity of paclitaxel in MCF-7, DLD-1 and L-929 (murine fibroblast) cells [53]. This plant is also used to treat inflammation, malaria and haemorrhoids [27] [30].

3.5 *Smilax zeylanica*

Smilax zeylanica (Smilacaceae), commonly known as kumarika in English and 'kabarossa" in Sinhalese, is used as a single agent and also as an ingredient of poly-herbal formulations [30]. It is used to treat a wide variety of cancers in Sri Lanka and mainly the root is used for medicinal purposes. *Smilax zeylanica* root contains diosgenin, smilagenin and β-sitosterol as active compounds [54]. A study performed in male swiss albino mice showed that *Smilax zeylanica* leaf extract (400 mg/kg daily) suppressed benzo[a]pyrene-induced lung carcinoma by decreasing the number of nodules in the lung (1.33±0.22 nodules in treated mice compared with 12.50±1.23 in untreated animals; $p<0.001$), accompanied by significant weight gain during the experimental period [55]. In another study, a petroleum ether extract of the stem demonstrated an IC_{50} value of 15.49±1.18 μg/ml, close to the IC_{50} of the positive control tamoxifen ((an oestrogen antagonist in breast cancer) (IC_{50} 5.31±0.38 μg/ml)), in MCF-7 cancer cells illustrating strong cytotoxic potential that was depicted by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay [56]. Interestingly reports have illustrated that diosgenin which is a compound of this plant has a unique structural similarity to oestrogen and is able to inhibit proliferation of MCF-7 and MDA-MB 231 (breast cancer) cells by upregulation of p53 tumour suppressor gene and down regulation of Bcl2 which promotes cell survival [57]. Furthermore, the cytotoxicity of this plant could also be due to its high anti-oxidant activity as it contains a good amount of phenolics, flavonoids and tannins [56]. As an illustration, a methanol extract of the root had an IC_{50} of 3.0±0.033 μg/ml, which was better than that of ascorbic acid (standard; IC_{50} 4.25±0.29 μg/ml) in a 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid (ABTS) assay [54]. However, more research is warranted to elucidate the actual mechanism of action of this plant

[54] [56]. *Smilax zeylanica* is also used to treat abscesses, wounds, inflammation, epilepsy and skin disorders [55].

3.6 *Tinospora cordifolia*

The stem of *Tinospora cordifolia* which belongs to the family Menispermaceae is used in medicinal preparations for cancer. Commonly known as heart-leaved moonseed (in English) or "rasakinda" (in Sinhalese) [30], it is mostly used in poly-herbal formulations and is frequently given to leukaemia patients. The active compounds of this plant are berberine, choline, tembetarine, tetrahydropalmatine, β-sitosterol, giloinsterol, furanolactone, 18-norclerodane glucoside, tinosporin, palmatine, magnoflorine, tinocordiside and cordifolioside A [58] [59] [60]. A 50% ethanolic extract of *Tinospora cordifolia* stem was found to reduce cell proliferation in C6 rat glioma cells (at 350 μg/ml), accompanied by senescence. The extract also showed anti-migratory and anti-invasive potential, with downregulation of neural cell adhesion molecule. Further, the extract was able to inhibit cell cycle progression in C6 cells in gap0/1 and gap2/mitosis phases of the cell cycle, probably due to suppression of cyclin D1, and induce apoptosis in treated cells by reducing expression of anti-apoptotic protein Bcl-xL [61]. Another study has shown that this plant has a radioprotective role, which could be due to cordifolioside A, a compound found in this plant that has shown in vivo radioprotective effects [60]. Rao et, at demonstrated that treatment of Hela cancer cells with ~ 1 μg/ml *Tinospora cordifolia* dichloromethane extract before exposure to 2 Gy γ-radiation caused a significant decline in cell viability compared with irradiation of Hela cells with different doses of γ-radiation only. Further, treatment of Hela cells with various concentrations of the plant extract caused a significant decline in cell viability after exposure to 1–4 Gy γ-radiation, demonstrating that the cytotoxicity effect of γ-radiation was increased [62]. *Tinospora cordifolia* has subdued diethylnitrosamine-induced hepatocellular carcinoma in male Wistar albino rats by increasing anti-oxidant activity via superoxide dismutase and catalase enzymes; the activity of hepatic markers such as serum glutamic oxaloacetic transaminase and serum glutamic pyruvate transaminase enzymes reverted to normal levels, confirming the plant's hepatoprotective properties [63]. Other than in cancer, this plant is used in Sri Lankan traditional medicine practice in a variety of diseases such as jaundice, skin diseases, fever, malaria, chronic diarrhoea, diabetes mellitus, snake bites, inflammation and dysentery [30] [58].

3.7 *Adenanthera pavonina*

Adenanthera pavonina, is known as red lucky seed in English or "madatiya" in Sinhalese [30]. This plant is used as a single agent and also in poly-herbal formulations and the bark is used mainly in medicinal preparations. This member of the Leguminosae family is mostly given for leukaemia and lymphoma. A number of active compounds have been isolated from this plant, including arginine, cysteine, arachidonic acid, β-sitosterol, dulcitol, echinocystic acid, glutamic acid, lignoceric acid, oxalic acid, malonic acid and octacosanol [64] [65]. Researchers have reported that a combination of equal proportions of *Adenanthera pavonina* and *Thespesia populnea* bark in the form of a decoction showed anti-proliferative effects (cell survival inhibition of 78.54% at 160 µg/ml of decoction); with the induction of apoptosis in HEp-2 cells (cervical cancer), and that the same combination showed high anti-oxidant activity [66] [67]. Another study showed that an ethanolic extract of *Adenanthera pavonina* seeds inhibited cell growth in HCT-8 (colon cancer) and HL-60 (leukaemia) cell lines [68]. Further studies have shown that a methanol stem extract of *Adenanthera pavonina* caused cytotoxic activity in Hela cells (IC_{50} 39.89±0.11 µg/ml) and HCT-116 cells (IC_{50} 25.86±0.21 µg/ml). These investigations have shown that this plant has high anti-oxidant activity and acts as a free radical scavenger. Studies have also shown that this plant is able to arrest the gap2/mitosis phase in the cell cycle in cancer cells along with apoptotic induction [67] [65]. Moreover, Kumar et al, revealed that when male Swiss albino mice were induced with Dalton's ascitic lymphoma, *Adenanthera pavonina* stem extract (250 mg/kg daily) restored the haemoglobin and red blood cell content to near normal levels, along with decrease of viable cancer cells compared to control; certain chemotherapy drugs do reduces blood cell count levels, and herbal preparations of this plant may help as an additive in such conditions [69]. Other than for cancer, this plant is used to treat inflammation, bacterial infections, diarrhoea and depression [30] [64].

3.8 *Thespesia populnea*

Thespesia populnea (Malvaceae), commonly known as tulip tree or "gansuriya" (Sinhalese) [30], is used as a both as a single agent and in combination with other plants as a ploy herbal forumaltion in Sri Lankan traditional medicine formulae. It is often given to patients with leukaemia and lymphoma. Some of the active chemical compounds isolated from this plant are mansonone C, D, E, G, H and S, populene A-H, kaempferol, kaempferol 3-glucoside, quercetin, quercetin 3-glucoside, rutin, nonacosane, lupenone, myricyl alcohol, lupeol, β-sitosterol, gossypol and thespone [70] [71]. A methanol leaf extract of this plant was found to inhibit B16-F10 melanoma solid tumour development in mice; the tumour volume was

reduced (1.46±1.19 mm^3) significantly compared with control (2.31±1.26 mm^3) treatment [72]. Further, the extract reduced glutathione levels in tumour cells (15.6±0.6 nmol/mg protein to 9.2 ± 0.2 nmol/mg protein) as well as serum γ-glutamyltransferase (γ-glutamyl transpeptidase) levels (142.8 ± 2.3 nmol p-nitroaniline/ml to 52.9 ± 1.2 nmol p-nitroaniline/ml) in the tumour-bearing mice, resulting in apoptosis induction ($p<0.01$). γ-glutamyltransferase is a membrane-bound enzyme involved in the metabolism of glutathione and plays an active role in neoplastic transformation. Glutathione is protects cancer cells against free radicals and regulates the sensitivity of cells to radiation and drug-induced cytotoxicity. The same study also showed that treatment with *Thespesia populnea* considerably increased blood count levels such as white blood cell count and haemoglobin content compared to control animals [72] [73] [74]. Another study showed that hexane and chloroform leaf extracts of *Thespesia populnea* demonstrated anti-proliferative activity against murine lymphoid cancer cells such as Ehrlich ascites (IC_{50} hexane: 38.94 µg/ml; chloroform: 41.32 µg/ml) and Dalton's lymphoma ascites (IC_{50} hexane: 32.85 µg/ml; chloroform:18.55µg/ml) cells [75]. Further, compounds isolated from a dichloromethane stem extract of *Thespesia populnea* have shown inhibitory activity in cancer cell lines and the highest inhibitory effects were shown by the compound, mansonone E; MCF-7 (IC_{50} 0.05 µg/ml) , Hela (IC_{50} 0.55 µg/ml) and HT-29 (IC_{50} 0.18 µg/ml). Further, mansonone D and populene D possessed strong inhibitory activity against MCF-7 and Hela cells respectively, whereas populene C exhibited moderate inhibitory activity against all cell lines tested [71]. Some of the cytotoxic activity of this plant might be due to its high anti-oxidant activity in quenching free radicals, but more research is needed to determine the actual mechanism of action [67]. This plant is also used for inflammation, piles, boils, ulcers, bacterial infections and diarrhoea [30] [70].

3.9 *Phyllanthus emblica*

The fruit of *Phyllanthus emblica* (Phyllanthaceae) is used in medicinal preparations, usually in combination with other herbs. This plant, commonly known as gooseberry or "nelli" [30]. This plant is mostly given for throat and lung cancers in Sri Lanka, and is often consumed as a fruit or as fruit juice. Active compounds found in the fruit of this plant include geraniin, isocorilagin, ellagic acid, tannic acid, ascorbic acid, chebulagic acid, gallic acid, corilagin, pyrogallol, quercetin, quercetin 3-β-D-glucopyranoside, kaempferol, and kaempferol 3-β-D-glucopyranoside [76] [77] [78]. An aqueous decoction of *Phyllanthus emblica* fruit has demonstrated inhibitory activity in A549 (lung) (GI_{50} 54.6±11.0 µg/ml), HepG2 (GI_{50}

99.9±18.0 µg/ml), Hela (GI_{50} 46.3±6.3 µg/ml), MDA-MB 231 (GI_{50} 80.6±11.1 µg/ml), SKOV-3 (ovarian) (GI_{50} 105.5±10.0 µg/ml) and SW620 (colon) (GI_{50} 79.8±19.4 µg/ml) cancer cell lines; where the most potent activity was observed against the Hela cell line. However, the extract was not toxic to MRC-5 (non-transformed lung fibroblast) cells (GI_{50} >400 µg/ml). This extract caused induction of caspase 3/7 and caspase 8 and upregulation of Fas protein in Hela cells, resulting in apoptosis by activating the death receptor Fas/caspase-8-dependent apoptosis pathway that may lead to inhibiting the biological activity of NFκB [79]. The anti-tumour promoting activity of the fruit extract was evaluated by a 7,12-dimethylbenz[a]anthracene (DMBA)/12-Otetradecanoylphorbol-13-acetate (TPA)-induced skin tumourigenesis mouse model. When mice were treated with DMBA, TPA and the extract (4 mg), both tumour numbers and volumes had significantly reduced to > 50% over a 20 week period ($p<0.01$). This plant has shown to have high levels of anti-oxidant activity by compounds, such as ellagic acid, gallic acid and tannic acid. These compounds have demonstrated to protect against skin tumour promotion by TPA via inhibition of ornithine decarboxylase activity and hydrogen peroxide production, thus enhance anti-cancer activity [79]. An aqueous solution of *Phyllanthus emblica* (400 µg/ml) was found to inhibit the growth of OVCAR3 cells (ovarian) ($p<0.007$); the same solution (100 mg/kg daily) inhibited mouse ovarian xenograft tumours significantly ($p=0.005$) reducing the expression of angiogenic gene hypoxia-inducible factor 1α and by autophagy. The *Phyllanthus emblica* solution (300 µg/ml) has acted synergistically with cisplatin (1-10 µg/ml) (a first-line chemotherapeutic drug given for ovarian cancer) to reduce OVCAR3 cell proliferation [78]. This plant is also given for diabetes mellitus, mental disorders, abdominal diseases and skin diseases [30].

3.10 *Boerhavia diffusa*

The root of *Boerhavia diffusa* (Nyctaginaceae), commonly known as hog weed or "pita sudu sarana" [30], is used in traditional Sri Lankan medicine preparations. It is used in poly-herbal formulae and is mainly given for gastric and liver cancers in Sri Lanka. The leaves of this plant are also consumed in Sri Lankan cuisine. Some of the active chemical compounds of this plant are borhaavone, boeravinone A-J, punarnavoside, quercetin, kaempferol, 3,4-dihydroxy-5-methoxycinnamoyl-rhamnoside, β-ecdysone, boeradiffusene, triacont-24-en-1-oic acid and eupalitin-3-O-β-D-galactopyranoside [80]. A methanol: chloroform fraction (300 µg/ml) of an ethanolic extract of *Boerhavia diffusa* root was found to have anti-proliferative effects on Hela cancer cells (85% cell death), with inhibition of the synthesis phase of the cell

cycle along with induction of apoptosis by triggering caspase 3/9 [81]. A methanol extract (320 μg/ml) of the whole plant demonstrated anti-proliferative effects in MCF-7 cells (inhibition of 46.8%) with an arrest in gap1 phase in the cell cycle; indication potential anti-oestrogenic activity of *Boerhaavia diffusa* against human breast cancer cells [82]. Administration of an aqueous methanol (3:7) extract of *Boerhavia diffusa* whole plant was found to be effective in inhibiting the formation of B16F10 melanoma-induced lung metastases in mice (95% inhibition compared to control), by inhibiting the expression of matrix metalloproteinases 2/9 which are associated with cell invasion and angiogenesis. The treated mice had showed much lower lung collagen hydroxyproline content indicating a reduced fibrosis and a smooth alveolar function. A reduction in the number of lung tumour nodules that are metastatic colonies of melanoma, correlated with the findings. Currently the principal compounds responsible in inhibiting the cascade of event of metastasis are not known. But the prevention of tumour cell proliferation, which is established from these experiments together with the angiostatic nature of the extract might be contributing to the anti-metastatic property shown by this plant [83]. This plant is also used for liver disorders, asthma, skin diseases, snake bites, inflammation and heart diseases [30] [80].

4.0 Conclusions

The plants described in this review have a diverse range of medicinal properties including anti-cancer properties. In Sri Lankan traditional medicine practice, these plants are often used in combination with other plant sources to treat cancer. The combinatorial approach increases the synergetic effect of all plants, improving the effectiveness of the treatment and lessening side effects. Combination therapy also decreases the likelihood of developing resistant cancer cells by targeting multiple signalling pathways often activated in a complex disease such as cancer. Supporting the above statement, some of these plants have also shown to have remarkable anti-cancer activity against currently incurable cancers. Therefore, traditional medicine knowledge should be used to discover novel drug leads for cancer. Even though many plants are being used for treatment purposes, there is a lack of scientific evidence to support such use for several of these species. Thus, it is very important that these plants are evaluated in preclinical and clinical studies, and that potent compounds can be isolated and identified. Utilization of modern biotechnological approaches such as nanotechnology-based drug delivery systems will support the progression of natural product research to its full potential and help to minimize side effects of the compounds developed. Further, co-administration of prescription medicines along with herbal supplements may have positive as

well as negative outcomes via pharmacodynamics and pharmacokinetic herb-drug interactions [84]. However, multiple constituents in plants may yield beneficial pharmacological activities as described above via synergistic activities. Medicinal plants could possess effective anticancer compounds that may be used as adjuvants to existing chemotherapy to improve efficacy and/or reduce drug-induced toxicity; such as chemotherapy-induced nausea and vomiting to improve patients' quality of life. Nevertheless, human clinical trials are warranted to verify the clinical utility of the medicinal plants in cancer treatment and in chemoprevention. Furthermore, research has suggested an inverse correlation between human cancers and various dietary constituents. The daily diet should be made up of nutrient rich plant foods, whose calories are accompanied by health-promoting phytochemicals, vegetables, fresh fruits, beans, seeds, and whole grains. These foods or nutraceuticals construct a health-promoting, disease-preventing diet with protective substances [85]. Sri Lankan cuisine often incorporates gruels, herbal drinks and spices made out of plants; these culinary preparations have enormous health benefits, including chemo-preventive properties, and are effective inhibitors of cancer. Prevention is certainly an attractive cancer management strategy. Thus it might be possible to reduce the process of carcinogenesis with regular use of these plants along with a healthy lifestyle.

Conflicts of interests

None

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