



Review

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

Anchala I. Kuruppu^{a,c,*}, Priyani Paranagama^{a,b}, Charitha L. Goonasekara^{c,*}^a Department of Chemistry, Faculty of Science, University of Kelaniya, Sri Lanka^b Institute of Indigenous Medicine, University of Colombo, Sri Lanka^c Department of Preclinical Sciences, Faculty of Medicine, General Sir John Kotelawala Defence University, Sri Lanka

ARTICLE INFO

Article history:

Received 11 August 2018

Accepted 4 February 2019

Available online 7 February 2019

Keywords:

Plants with anti-cancer properties

Traditional medicine

Cancer

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.

© 2019 The Authors. Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Contents

1. Introduction	566
2. Plant-derived anti-cancer agents in clinical use	566
3. Sri Lankan plants that have anti-cancer properties	566
3.1. Zingiber officinale	568
3.2. Curcuma longa	568
3.3. Hemidesmus indicus	568
3.4. Munronia pinnata	569
3.5. Smilax zeylanica	569
3.6. Tinospora cordifolia	569
3.7. Adenantha pavonina	570
3.8. Thespesia populnea	570
3.9. Phyllanthus emblica	570
3.10. Boerhavia diffusa	571
4. Conclusions	571
Conflicts of interest	571
Acknowledgments	571
References	571

* Corresponding authors at: Department of Chemistry, Faculty of Science, University of Kelaniya, Sri Lanka, Department of Preclinical Sciences, Faculty of Medicine, General Sir John Kotelawala Defence University, Sri Lanka (A.I. Kuruppu) and Department of Preclinical Sciences, Faculty of Medicine, General Sir John Kotelawala Defence University, Sri Lanka (C. L. Goonasekara).

E-mail addresses: anchala_k@yahoo.com (A.I. Kuruppu), charithalg@kdu.ac.lk (C.L. Goonasekara).

Peer review under responsibility of King Saud University.



1. 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 (Organization, 2018). 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 an aging population, and exposure to certain chemicals, metals and infectious agents (Jemal et al., 2011; Iqbal et al., 2017). 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 (Pan et al., 2013). Excavations in Sri Lanka have shown that the Balangoda man used plants for medicinal purposes, about 30,000 years ago (Perera, 2004). 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 (Graham et al., 2000). 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 (Khan, 2014; Cragg and Newman, 2005). 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 (Dixon, 2001; Prajapati et al., 2007). Examples of secondary metabolites in plants 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 (Verpoorte, 1998).

2. 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 (Cragg and Newman, 2005; Mann, 2002). The two main vinca alkaloids are vincristine and vinblastine and a few structural analogues such as vinorelbine, vindesine and vinflunine (Fig. 1) have been developed (Iqbal et al., 2017; Mann, 2002). 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 (Moudi et al., 2013).

Another important class of anti-cancer agents are the taxanes. Paclitaxel (Taxol) (Fig. 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 (Fig. 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 (Fu et al., 2009). 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 (Fig. 1), was approved in 2010 for the treatment of metastatic prostate cancer. Further, larotaxel, milataxel, ortataxel, and tesetaxel (Fig. 1) are currently under clinical evaluation (Iqbal et al., 2017; Yared and Tkaczuk, 2012; Ojima et al., 2016).

Camptothecin (Fig. 1) a quinoline alkaloid, was obtained in 1966 from the stem of *Camptotheca acuminata*, 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 (Fig. 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 (Cragg and Newman, 2005; Liu et al., 2006).

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 (Montecucco et al., 2015; Hande, 1998). A number of novel etoposide derivatives are undergoing clinical evaluation (Zhang et al., 2017; Gentry et al., 2011). Teniposide, another semisynthetic derivative of *Podophyllum peltatum*, has a similar mechanism of action to etoposide but is insoluble in water (Clark and Slevin, 1987).

Harringtonine and Homoharringtonine (Fig. 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 in USA for the treatment of chronic myeloid leukaemia (Cragg and Newman, 2005; Moirangthem et al., 2014; Lü and Wang, 2014).

3. 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" ayurveda

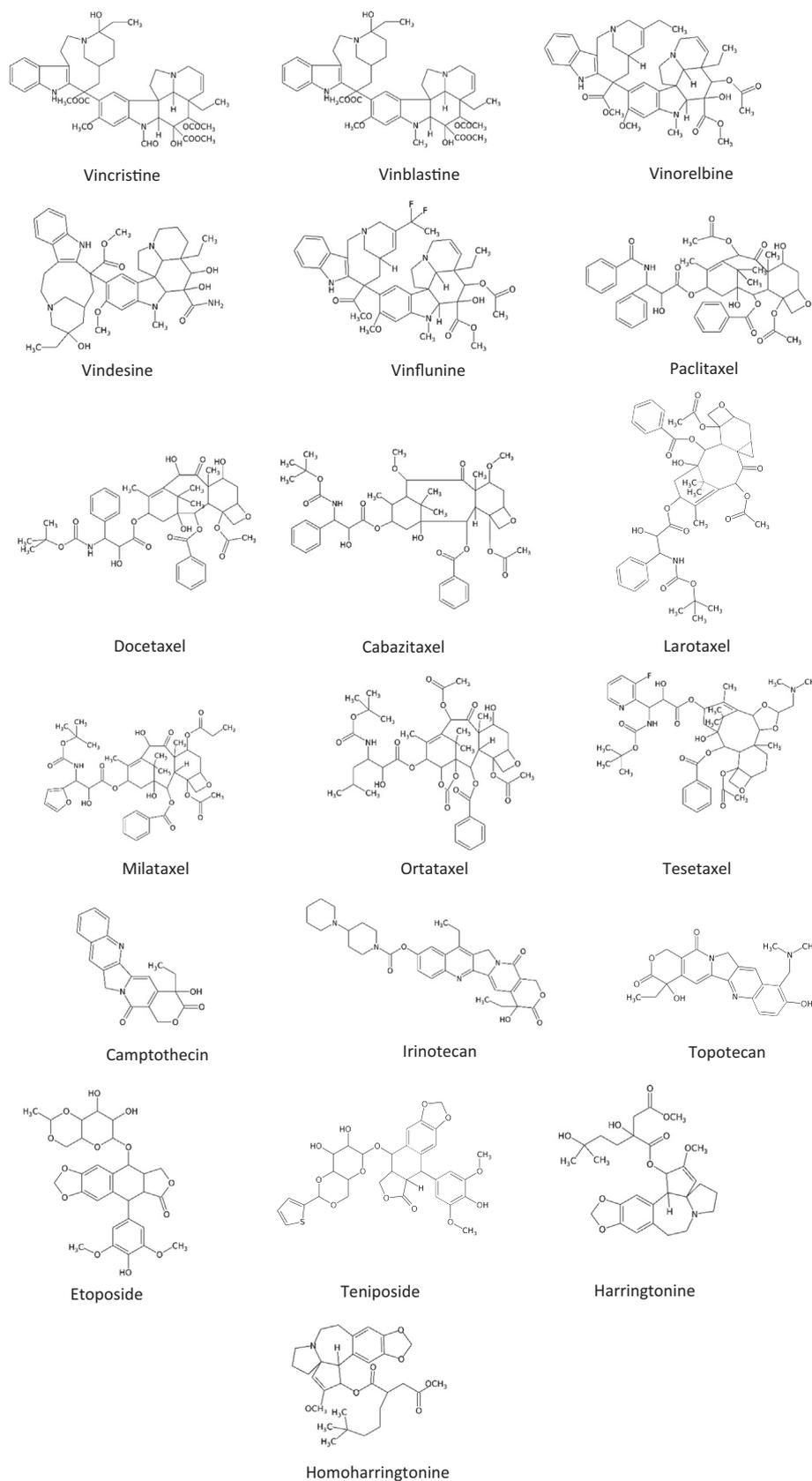


Fig. 1. Chemical structures of anti-cancer drugs derived from plants that are in clinical use.

and siddha systems, introduced by India, and the unani system that originated in Greece and introduced by the Arabs to Sri Lanka. Currently, around 70% of the population of the country uses this

traditional medicine system (Jayasinghe et al., 2017), 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 plant species; very rarely is an extract of just a single plant is 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 (Russell-Smith et al., 2006), 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 (Dharmadasa et al., 2012). 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), or "ingi" (in Tamil), is widely used in anti-cancer traditional medicine preparations for gastrointestinal, liver and oesophageal cancers (Singh, 2007). 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 (Williamson, 2002; Resorts, 2017). Many active ingredients are present in this plant, including gingerols, which are converted to shogaols, paradols and zingerone (Rahmani et al., 2014). *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 NF κ B through suppression of proinflammatory TNF α in liver cancer induced rats (Habib et al., 2008). NF κ B is a transcription factor that plays a role in biological processes such as inflammation, cell growth and survival, and TNF α is a cytokine which exerts its biological functions through activating NF κ B (Lin, 2008). 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 (Singh, 2007). Research has suggested that gingerol in ginger could be an effective chemo-preventive and/or chemotherapeutic agent for colorectal cancers. For example, ginger showed significant efficacy in mice when they were fed with ginger before and after tumour cells were injected, and also when ginger was fed after tumours had grown to a particular size (Singh, 2007). Gingerol, has demonstrated anti-angiogenic activity *in vitro* and *in vivo*, suggesting that it might have a possible role in preventing metastasis as well (Kim et al., 2005). 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 (Resorts, 2017).

3.2. *Curcuma longa*

The rhizome of *Curcuma longa* (Zingiberaceae) is commonly used in poly-herbal preparations, and is used to treat a wide range of cancers. This plant, known as turmeric or "kaha" in the Sinhalese language and "manchal" in Tamil. It is regularly used as a spice and flavouring agent in Sri Lankan cuisine (Williamson, 2002; Resorts, 2017). 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 (Aggarwal et al.,

2003). According to reports the mechanisms by which curcumin exerts its bioactivity are anti-oxidation, downregulation of the COX-2 enzyme and by decreasing levels of DNA adducts. One study showed that curcumin is able to inhibit, colo 205 adenocarcinoma (colon cancer) cells and induce apoptosis via caspase-3 activity (Chin-Cheng et al., 2006). The same study showed that curcumin was able to increase the levels of reactive oxygen species and Ca²⁺; 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; tamoxifen is an oestrogen antagonist in breast cancer (Vemuri et al., 2017). 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 g of curcumin per day for 7 days prior to surgery. Administration of capsules containing 3.6 g of curcumin decreased M₁G levels from 4.8 \pm 2.9 adducts per 107 nucleotides in malignant colorectal tissue to 2.0 \pm 1.8 adducts per 107 nucleotides (Bar-Sela et al., 2010; Garcea et al., 2005). DNA damage is important in the aetiology of many cancers and damage may be reflected by exocyclic DNA adducts such as M₁G (Sharma et al., 2001). 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. Activation of AhR results in the induction of CYP1A1 gene, which encodes for enzymes that metabolizes human carcinogens which results in cancer initiation (Aggarwal et al., 2003). In another study, histological improvement of premalignant lesions of various cancers such as intestinal metaplasia of the stomach, superficial bladder carcinoma, uterine cervical intraepithelial neoplasia was observed when 1–8 g of curcumin were given daily to patients for 3 months (Bar-Sela et al., 2010). Other than its anti-cancer uses, *Curcuma longa* is commonly used as an antibacterial agent and for diabetes mellitus, wounds and skin diseases (Resorts, 2017).

3.3. *Hemidesmus indicus*

Hemidesmus indicus (Apocynaceae), commonly known as Indian sarsaparilla or "iramusu" in Sinhalese and "nannari" in Tamil, is used in poly-herbal preparations aimed against cancer; the root is mostly used in traditional medicine preparations (Turrini et al., 2018). 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* (Rajan et al., 2011; Nagat et al., 2016; Das and Singh Bisht, 2013; Gao et al., 2018). Decoctions of *Hemidesmus indicus* have demonstrated a cytotoxic effect in HepG2 hepatocellular carcinoma cells (IC₅₀ 33.52 \pm 0.13 μ g/ml) while a hydroalcoholic extract has shown activity against HepG2 (IC₅₀ 34.50 \pm 0.14 μ g/ml), LoVo (colon cancer) (IC₅₀ 29.84 \pm 0.24 μ g/ml), and Jurkat (leukaemia) (IC₅₀ 63.79 \pm 7.97 μ g/ml) cell lines (Statti et al., 2015). 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 (Turrini et al., 2018). 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 (Ira Thabrew et al., 2005; Samarakoon et al., 2012). A group of researchers 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 that were leading to tumour development, possibly be due to a significant reduction of angiogenesis that was observed (Iddamaldeniya et al., 2006). 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 (Galhena et al., 2017). *Hemidesmus indicus* is also used as a blood purifier and for skin diseases and gastric ailments (Resorts, 2017; Statti et al., 2015).

3.4. *Munronia pinnata*

Munronia pinnata, a member of the Meliaceae 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" in Sinhalese (Dharmadasa et al., 2012), 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 (Napagoda et al., 2014). 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 (Napagoda et al., 2014). 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 (Gao et al., 2006). 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 (Fidyt et al., 2016). 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 by about 10-fold, and the most potent results were observed in DLD-1 cells: paclitaxel IC_{50} 0.43 ± 0.09 μ g/ml, and β -caryophyllene + paclitaxel IC_{50} 0.04 ± 0.01 μ g/ml (Fidyt et al., 2016). This plant is also used to treat inflammation, malaria and haemorrhoids (Dharmadasa et al., 2012; Resorts, 2017).

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 (Resorts, 2017). 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 (Murali et al., 2011). 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 (Rajesh and Perumal, 2013). In another study, a petroleum ether extract of the stem demonstrated an IC_{50} value of 15.49 ± 1.18 μ g/ml, close to the IC_{50} of the positive control tamoxifen (IC_{50} 5.31 ± 0.38 μ g/ml), in MCF-7 cancer cells illustrating strong cytotoxic potential (Uddin et al., 2015). 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 (Sethi et al., 2018). 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. It has been shown that antioxidants are able to protect living cells from DNA damage and lipid peroxidation caused by reactive oxygen species which could initiate cancer (Uddin et al., 2015). As an illustration, a methanol extract of the root had an IC_{50} of 3.00 ± 0.03 μ g/ml, which was better than the anti-oxidant activity of ascorbic acid (standard) IC_{50} 4.25 ± 0.29 μ g/ml (Murali et al., 2011). However, more research is warranted to elucidate the actual mechanism of action of this plant (Murali et al., 2011; Uddin et al., 2015). *Smilax zeylanica* is also used to treat abscesses, wounds, inflammation, epilepsy and skin disorders (Rajesh and Perumal, 2013).

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) / "chintil" (in Tamil) (Resorts, 2017). It is mostly used in poly-herbal formulations and is frequently given to leukaemia patients in Sri Lanka. 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 (Saha and Ghosh, 2012; Sinha et al., 2004; Patel et al., 2013). A 50% ethanolic extract of *Tinospora cordifolia* stem was found to reduce cell proliferation in C6 rat glioma cells (at 350 μ g/ml), accompanied by senescence. The extract also showed anti-migratory and anti-invasive potential, with downregulation of the neural cell adhesion molecule. Further, the extract was able to inhibit cell cycle progression in C6 cells in gap1 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 (Mishra and Kaur, 2013). 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 (Patel et al., 2013). Rao et al, demonstrated that treatment of Hela cancer cells with ~ 1 μ g/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 (Rao and Rao, 2010). *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 (Dhanasekaran et al., 2009). 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 (Resorts, 2017; Saha and Ghosh, 2012).

3.7. *Adenanthera pavonina*

Adenanthera pavonina, is known as red lucky seed in English or "madatiya" in Sinhalese / "anaikuntumani" in Tamil (Resorts, 2017). 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 (Mujahid et al., 2016; Bhadran et al., 2017). 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 (inhibition of cell survival: 78.54% at 160 μ g/ml of decoction); with the induction of apoptosis in HEP-2 cells (cervical cancer), and that the same combination showed high anti-oxidant activity as well (Lindamulage and Soysa, 2016; Silva and Soysa, 2011). 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 (Ferreira et al., 2011). Further studies have shown that a methanol stem extract of *Adenanthera pavonina* caused cytotoxic activity in Hela cells (IC_{50} 39.89 \pm 0.11 μ g/ml) and HCT-116 cells (IC_{50} 25.86 \pm 0.21 μ g/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 (Silva and Soysa, 2011; Bhadran et al., 2017). 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 a reduction of viable cancer cells compared to control; certain chemotherapy drugs do reduce blood cell count levels, and herbal preparations of this plant may help as an additive in such conditions (Arihara Siva Kumar et al., 2017). Other than for cancer, this plant is used to treat inflammation, bacterial infections, diarrhoea and depression (Resorts, 2017; Mujahid et al., 2016).

3.8. *Thespesia populnea*

Thespesia populnea (Malvaceae), commonly known as tulip tree or "gansuriya" (Sinhalese) / "kavarachu" (Tamil) (Resorts, 2017), is used as a single agent and in combination with other plants as a ploy herbal formulation in the Sri Lankan traditional medicine practice. 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 (Phanse et al., 2013; Boonsri et al., 2008). 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 \pm 1.19 mm³) significantly compared with con-

trol (2.31 \pm 1.26 mm³) treatment (Mika and Guruvayoorappan, 2012). Further, the extract reduced glutathione levels in tumour cells (15.6 \pm 0.6 nmol/mg protein to 9.2 \pm 0.2 nmol/mg protein) as well as serum γ -glutamyltransferase (γ -glutamyl transpeptidase) levels (142.8 \pm 2.3 nmol p-nitroaniline/ml to 52.9 \pm 1.2 nmol p-nitroaniline/ml) in tumour-bearing mice, resulting in apoptosis induction. γ -glutamyltransferase is a membrane-bound enzyme involved in the metabolism of glutathione and plays an active role in neoplastic transformation. Glutathione 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 (Mika and Guruvayoorappan, 2012; Jose et al., 2006; Corti et al., 2010). 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 μ g/ml; chloroform: 41.32 μ g/ml) and Dalton's lymphoma ascites (IC_{50} hexane: 32.85 μ g/ml; chloroform: 18.55 μ g/ml) cells (Chandran et al., 2016). 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 μ g/ml), Hela (IC_{50} 0.55 μ g/ml) and HT-29 (IC_{50} 0.18 μ g/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 (Boonsri et al., 2008). 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 (Silva and Soysa, 2011). This plant is also used for inflammation, piles, boils, ulcers, bacterial infections and diarrhoea (Resorts, 2017; Phanse et al., 2013).

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 in English. It is called "nelli" in Sinhalese or "topu-nelli" in Tamil (Resorts, 2017). 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, coriagin, pyrogallol, quercetin, quercetin 3- β -D-glucopyranoside, kaempferol, and kaempferol 3- β -D-glucopyranoside (Zhao et al., 2014; Liu et al., 2012; De et al., 2013). An aqueous decoction of *Phyllanthus emblica* fruit has demonstrated inhibitory activity in A549 (lung), HepG2, Hela, MDA-MB 231, SKOV-3 (ovarian) and SW620 (colon) cancer cell lines, and the most potent activity was observed against the Hela cell line (GI_{50} 46.30 \pm 6.30 μ g/ml). However, the extract was not toxic to MRC-5 (non-transformed lung fibroblast) cells (GI_{50} > 400 μ g/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 NF κ B (Ngamkitidechakul et al., 2010). 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 enhancing anti-cancer activity (Ngamkitidechakul et al., 2010). An aqueous solution of *Phyllanthus emblica* (400 µg/ml) was found to inhibit the growth of OVCAR3 cells (ovarian); the same solution (100 mg/kg daily) inhibited mouse ovarian xenograft tumours significantly reducing the expression of angiogenic gene hypoxia-inducible factor 1 α and by autophagy. Further, 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 (De et al., 2013). This plant is also given for diabetes mellitus, mental disorders, abdominal diseases and skin diseases (Resorts, 2017).

3.10. *Boerhavia diffusa*

The root of *Boerhavia diffusa* (Nyctaginaceae), commonly known as hog weed or “pita sudu sarana” in Sinhalese / “karichcharani” in Tamil (Resorts, 2017), 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 (Mishra et al., 2014). 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 (Srivastava et al., 2009). 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; indicating potential anti-oestrogenic activity of *Boerhavia diffusa* against human breast cancer cells (Sreeja, 2009). Administration of an aqueous methanol (3:7) extract of *Boerhavia diffusa* whole plant was found to be effective in hindering 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. However, 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 (Leyon et al., 2004). This plant is also used for liver disorders, asthma, skin diseases, snake bites, inflammation and heart diseases (Resorts, 2017; Mishra et al., 2014).

4. Conclusions

The plants described in this review have a diverse range of medicinal properties including anti-cancer properties. In the Sri Lankan traditional medicine practice, these plants are often used in combination with other plant sources as poly herbal formulae 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 the plants in Sri Lanka 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/poly herbal formulae are evaluated in preclinical and clinical studies. Further, utilization of modern biotechnological approaches such as nanotechnology-based drug delivery systems will support the progression of medicinal plant research to its full potential and help to minimize side effects of the drugs developed from these plants. (Wang et al., 2012). Medicinal plants could also 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 these medicinal plants in such treatment, since there could be positive as well as negative outcomes via pharmacodynamic and pharmacokinetic herb-drug interactions. 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, which includes vegetables, fresh fruits, beans, seeds, and whole grains. These foods or nutraceuticals construct a health-promoting, disease-preventing diet with protective substances (Pandey et al., 2013). 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 interest

None.

Acknowledgments

The authors would like to thank Dr. Nimal Jayathilaka, Ayurveda cancer specialist, Bandaranayaka Memorial Ayurvedic Research Institute, Navinna, Maharagama, Sri Lanka, and Dr. Nishan Jayasundara, Ayurveda physician, Institute of Indigenous Medicine, University of Colombo, Sri Lanka, for the information provided on plants used in the traditional medicine practice in Sri Lanka. The authors also thank Dr. E. J. Laughton for editorial support of the manuscript.

References

- Aggarwal, Bharat B., Kumar, A., Bharti, A.C., 2003. Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Res.* 23, 363–398.
- Arihara Siva Kumar, G., Javvadi, R.K., Vinay Kumar, K., Manohar Reddy, E., Veera Reddy, Y., Harshavardhan, G., Akbar, M.D., 2017. Effect of methanolic extract of *Adenanthera pavonina* Linn on Dalton's ascitic lymphoma. *Indian J. Res. Pharm. Biotechnol.* 1, 138–141.
- Bar-Sela, G., Epelbaum, R., Schaffer, M., 2010. Curcumin as an anti-cancer agent: review of the gap between basic and clinical applications. *Curr. Med. Chem.* 17, 190–197.
- Bhadran, Shubha, George, S.A., Sudhakar Malla, Harini Bp., 2017. Screening of bioprotective properties of various plant extracts and gas chromatography-mass spectrometry profiling of *Adenanthera pavonina* stem extract. *Asian J. Pharm. Clin. Res.* 10, 1–8.
- Boonsri, Sompong, Karalai, Chatchanok, Ponglimanont, Chanita, Chantrapromma, Suchada, Kanjana-opas, Akkharawit, 2008. Cytotoxic and Antibacterial Sesquiterpenes from *Thespesia populnea*. *J. Nat. Prod.* 71, 1173–1177.

- Chandran, R.P., Manju, S., Shaji, P.K., Nair, G.A., Sukumar, B., 2016. In vitro cytotoxic activities of leaf extracts of *Thespesia Populnea* and *Hygrophilla Schulli* against Dalton's lymphoma ascites and ehrlich ascites carcinoma cell lines. *Austin J. Lung Cancer Res.* 1, 1007.
- Chin-Cheng, Su, Lin, J.-G., Li, Te-Mao, Chung, Jing-Gung, Yang, Jai-Sing, Ip, Siu-Wan, Lin, Wen-Chuan, Chen, Guang-Wei, 2006. Curcumin-induced apoptosis of human colon cancer colo 205 cells through the production of ROS, Ca²⁺ and the activation of caspase-3. *Anticancer Res.* 26, 4379–4390.
- Corti, Alessandro, Franzini, Maria, Paolicchi, Aldo, Pompella, Alfonso, 2010. Gamma-glutamyltransferase of cancer cells at the crossroads of tumor progression, drug resistance and drug targeting. *Anticancer Res.* 30, 1169–1181.
- Das, S., Singh Bisht, S., 2013. The bioactive and therapeutic potential of hemidesmus indicus r. br. (indian sarsaparilla) root. *Phytother. Res.* 6, 791–801.
- De, Alok, De, A., Papisian, Chris, Hentges, Shane, Banerjee, Snigdha, Haque, Inamul, Banerjee, Sushanta K., 2013. *Embllica officinalis* extract induces autophagy and inhibits human ovarian cancer cell proliferation, angiogenesis, growth of mouse xenograft tumors. *PLoS ONE* 8, 1–16.
- Dhanasekaran, Muniyappan, Baskar, Arul-Albert, Ignacimuthu, Savarimuthu, Agastian, Paul, Duraipandiyar, Veeramuthu, 2009. Chemopreventive potential of Epoxy clerodane diterpene from *Tinospora cordifolia* against diethylnitrosamine-induced hepatocellular carcinoma. *Invest. New Drugs* 27, 347–355.
- Dharmadasa, R.M., Premakumara, G.A.S., Hettiarachchi, P.L., Ratnasooriya, W.D., 2012. Cytotoxicity and in vivo antimalarial activity of aqueous whole plant extract of *Munronia pinnata* (Wall.) Theob. (Meliaceae) in mice. *Res. J. Med. Plants* 6, 267–273.
- Dixon, R.A., 2001. Natural products and plant disease resistance. *Nature* 411, 843–847.
- Ferreira, Paulo Michel P., Farias, D.F., Viana, Martônio P., Souza, Terezinha M., Vasconcelos, Ilka M., Soares, Bruno M., Pessoa, Cláudia, Costa-lotuf, Leticia V., Moraes, Manoel O., Carvalho, Ana.F.U., 2011. Study of the antiproliferative potential of seed extracts from Northeastern Brazilian plants. *Ann. Brazilian Acad. Sci.* 83, 1045–1058.
- Fidy, Klaudyna, Fiedorowicz, Anna, Strzadala, Leon, Szumny, Antoni, 2016. β -caryophyllene and β -caryophyllene oxide—natural compounds of anticancer and analgesic properties. *Cancer Med.* 5, 3007–3010.
- Fu, Y., Li, S., Zu, Y., Yang, G., Yang, Z., Luo, M., Jiang, S., Wink, M., Efferth, T., 2009. Medicinal chemistry of paclitaxel and its analogues. *Curr. Med. Chem.* 16, 3966–3985.
- Galhena, Bandula Prasanna, Samarakoon, S.S.R., Thabrew, Myrtle Ira, Paul, Solomon, F.D., Perumal, Venkatchalam, Mani, Chinnadurai, 2017. Protective effect of a polyherbal aqueous extract comprised of *nigella sativa* (seeds), *hemidesmus indicus* (roots), and *Smilax glabra* (rhizome) on bleomycin induced cytogenetic damage in human lymphocytes. *Biomed Res. Int.*, 1–7.
- Gao, Jiang-Jing, Hirakawa, A., Min, Byung Sun, Nakamura, Norio, Hattori, Masao, 2006. In vivo antitumor effects of bitter principles from the antlered form of fruiting bodies of *Ganoderma lucidum*. *J. Nat. Med.* 60, 42–48.
- Gao, Xiaoxu, Wei, J., Hong, Lina, Fan, Sanpeng, Gaosheng, Hu, Jia, Jingming, 2018. Comparative analysis of chemical composition, anti-inflammatory activity and antitumor activity in essential oils from *siegesbeckia orientalis*, *S. glabrescens* and *S. pubescens* with an ITS sequence analysis. *Molecules* 23, 2185.
- Garcea, Giuseppe, Berry, D.P., Jones, Donald J.L., Singh, Raj, Dennison, Ashley R., Farmer, Peter B., Sharma, Ricky A., Steward, William P., Gescher, Andreas J., 2005. Consumption of the putative chemopreventive agent curcumin by cancer patients: assessment of curcumin levels in the colorectum and their pharmacodynamic consequences. *Cancer Epidemiol. Biomark. Prev.* 14, 120–125.
- Gentry, Amanda C., Pitts, S.L., Jablonsky, Michael J., Bailly, Christian, Graves, David E., Osheroff, Neil, 2011. Interactions between the etoposide derivative F14512 and human type II topoisomerases: implications for the C4 spermine moiety in promoting enzyme-mediated DNA cleavage. *Biochemistry* 50, 3240–3249.
- Graham, J.G., Fabricant, M.L.Q.D.S., Farnsworth, N.R., 2000. Plants used against cancer – an extension of the work of Jonathan Hartwell. *J. Ethnopharmacol.* 73, 347–377.
- Habib, Shafina Hanim Mohd, Makpol, S., Hamid, Noor Aini Abdul, Das, Srijit, Ngah, Wan Zurinah Wan, Yusof, Yasmin-Anum-Mohd, 2008. Ginger extract (*Zingiber officinale*) has anti-cancer and anti-inflammatory effects on ethionine-induced hepatoma rats. *Clinics* 63, 807–813.
- Hande, K.R., 1998. Etoposide: four decades of development of a topoisomerase II inhibitor. *Eur. J. Cancer* 34, 1514–1521.
- Iddamadeniya, S.S., Thabrew, M.L., Wickramasinghe, S.M.D.N., Ratnatunge, N., Thammityagodage, M.G., 2006. A long-term investigation of the anti-hepatocarcinogenic potential of an indigenous medicine comprised of *Nigella sativa*, *Hemidesmus indicus* and *Smilax glabra*. *J. Carcinogenesis* 5, 11.
- Iqbal, Javed, Abbasi, B.A., Mahmood, Tariq, Kanwal, Sobia, Ali, Barkat, Shah, Sayed Afzal, Khalil, Ali Talha, 2017. Plant-derived anticancer agents: a green anticancer approach. *Asian Pacific J. Trop. Biomed.* 7, 1129–1150.
- Ira Thabrew, M., Mistry, R.R., Morsy, Mohammed A., Hughes, Robin D., 2005. Cytotoxic effects of a decoction of *Nigella sativa*, *Hemidesmus indicus* and *Smilax glabra* on human hepatoma HepG2 cells. *Life Sci.* 77, 1319–1330.
- Jayasinghe, Susanthi, Bandara, B.M.R., Wickramasinghe, A., Karunaratne, D.N., Wijesundara, D.S.A., Karunaratne, Veranja, 2017. The importance of harnessing the rich diversity of Sri Lankan flora for their. *Ceylon J. Sci.* 46, 3–13.
- Jemal, Ahmedin, Bray, Freddie, Center, Melissa M., Ferlay, Jacques, Ward, Elizabeth, Forman, David, 2011. Global cancer statistics. *CA Cancer J. Clin.* 61, 69–90.
- Jose, Jose M., Ortega, Angel, Obrador, Elena, 2006. Glutathione in cancer biology and therapy. *Crit. Rev. Clin. Lab. Sci.* 43, 143–181.
- Khan, H., 2014. Medicinal plants in light of history: recognized therapeutic modality. *Evid.-Based Complement. Alternat. Med.* 19, 216–219.
- Kim, Eok-Cheon, Min, J.-K., Kim, Tae-Yoon, Lee, Shin-Jeong, Yang, Hyun-Ok, Han, Sanghwa, Kim, Young-Myeong, Kwon, Young-Guen, 2005. [6]-Gingerol, a pungent ingredient of ginger, inhibits angiogenesis in vitro and in vivo. *Biochem. Biophys. Res. Commun.* 335, 300–308.
- Leyon, P.V., Lini, C.C., Kuttan, G., 2004. Inhibitory effect of *Boerhaavia diffusa* on experimental metastasis by B16F10 melanoma in C57BL/6 mice. *Life Sci.* 76, 1339–1349.
- Lin, X.W.A.Y., 2008. Tumor necrosis factor and cancer, buddies or foes? *Acta Pharmacol. Sin.* 29, 1275–1288.
- Lindamulage, I.K.S., Soysa, P., 2016. Evaluation of anticancer properties of a decoction containing *Adenanthera pavonina* L. and *Thespesia populnea* L. *BMC Complement. Alternat. Med.* 16, 1–8.
- Liu, Leroy, Desai, S.D., Li, Tsai-Kun, Mao, Yong, Sun, Mei, Sim, Sai-Peng, 2006. Mechanism of action of camptothecin. *Ann. N. Y. Acad. Sci.* 922, 1–10.
- Liu, Xiaoli, Zhao, M., Kegang, Wu, Chai, Xianghua, Hongpeng, Yu, Tao, Zhihua, Wang, Jinshui, 2012. Immunomodulatory and anticancer activities of phenolics from *embllica fruit* (*Phyllanthus emblica* L.). *Food Chem.* 131, 685–690.
- Lü, S., Wang, J., 2014. Homoharringtonine and omacetaxine for myeloid hematological malignancies. *J. Hematol. Oncol.* 7, 2.
- Mann, J., 2002. Natural products in cancer chemotherapy: past, present and future. *Nature* 2, 143–148.
- Mika, D., Guruvayoorappan, C., 2012. Experimental study on anti-tumor and anti-inflammatory effect of *Thespesia populnea* phytochemical extract in mice models. *Immunopharmacol. Immunotoxicol.* 35, 157–163.
- Mishra, Shikha, Aeri, V., Gaur, Praveen Kumar, Jachak, Sanjay M., . Phytochemical, therapeutic, and ethnopharmacological overview for a traditionally important herb: *boerhavia diffusa* linn. *Biomed Res. Int.*, 1–19.
- Mishra, R., Kaur, G., 2013. Aqueous ethanolic extract of *tinospora cordifolia* as a potential candidate for differentiation based therapy of glioblastomas. *PLoS ONE* 8, 1–13.
- Moirangthem, Dinesh Singh, Borah, J.C., Laishram, Surbala, Kalita, Mohan Chandra, Talukdar, Narayan Chandra, 2014. HPLC analysis of harringtonine and homoharringtonine in the needles of *cephalotaxus griffithii* alkaloid fraction and cytotoxic activity on chronic myelogenous leukaemia K562 cell. *Nat. Prod. Res.* 28, 1503–1506.
- Montecucco, Alessandra, Zanetta, Francesca, Biamonti, Giuseppe, 2015. Molecular mechanisms of etoposide. *Exp. Clin. Sci.* 14, 95–108.
- Moudi, Maryam, Go, R., Yien, Christina Yong Seok, Nazre, Mohd, 2013. *Vinca* alkaloids. *Int. J. Prevent. Med.* 4, 1231–1235.
- Mujahid, Md., Ansari, V.A., Sirbaila, Anup K., Kumar, Ranjan, Usmani, Afreen, 2016. An insight of pharmacognostic and phytopharmacology study of *Adenanthera pavonina* J. Chem. Pharmaceut. Res. 8, 586–596.
- Murali, Anita, Ashok, P., Madhavan, V., 2011. In vitro antioxidant activity and hptlc studies on the roots and rhizomes of *Smilax zeylanica* l. (*smilacaceae*). *Int. J. Pharm. Pharmaceut. Sci.* 3, 192–195.
- Nagat, M., Reena Lawrence, E.B., Saani, Mariya, 2016. Phytochemical screening, antioxidant and antibacterial activity of active compounds from *hemidesmus indicus*. *Int. J. Curr. Pharm. Res.* 8, 24–27.
- Napagoda, Mayuri, Gerstmeier, J., Koeberle, Andreas, Wesely, Sandra, Popella, Sven, Lorenz, Sybille, Scheubert, Kerstin, Böcker, Sebastian, Svatoš, Aleš, Wertz, Oliver, 2014. *Munroniapinnata* (Wall.)Theob.: unveiling phytochemistry and dualinhibitionof5-lipoxygenase and microsomal prostaglandin E2 synthase (mPGES)-1. *J. Ethnopharmacol.* 151, 882–890.
- Cragg, G.M., Newman, D.J., 2005. Plants as a source of anti-cancer agents. *J. Ethnopharmacol.* 100, 72–79.
- Ngamkitidechakul, C., Jaijoi, K., Hansakul, P., Soonthornchareonnon, N., Sireeratawang, S., 2010. Antitumor effects of *phyllanthus emblica* l.: induction of cancer cell apoptosis and inhibition of in vivo tumour promotion and in vitro invasion of human cancer cells. *Phytother. Res.* 24, 1405–1413.
- Ojima, Iwao, Lichtenthal, B., Lee, Siyeon, Wang, Changwei, Wang, Xin, 2016. Taxane anticancer agents: a patent perspective. *Expert Opin. Ther. Pat.* 26, 1–20.
- Organization, W.H., 2018. Cancer 2018 [cited 2018 05; 15]. Available from: <<http://www.who.int/news-room/fact-sheets/detail/cancer>>.
- Pan, Si-Yuan, Litscher, G., Gao, Si-Hua, Zhou, Shu-Feng, Zhi-Ling, Yu, Chen, Hou-Qi, Zhang, Shuo-Feng, Tang, Min-Ke, Sun, Jian-Ning, Ko, Kam-Ming, 2013. Historical perspective of traditional indigenous medical practices: the current renaissance and conservation of herbal resources. *Evid.-Based Complement. Alternat. Med.* 2014, 1–20.
- Pandey, M.M., Rastogi, S., Rawat, A.K.S., . Indian traditional ayurvedic system of medicine and nutritional supplementation. *Evid.-Based Complement. Alternat. Med.*, 1–12.
- Patel, Arti, Bigoniya, Papiya, Singh, Chandra Shekhar, Patel, Narayan Singh, 2013. Radioprotective and cytoprotective activity of *Tinospora cordifolia* stem enriched extract containing cordifolioside-A. *Indian J. Pharmacol.* 45, 237–243.
- Perera, D.L., 2004. Truth and Myth of Green Piracy.
- Phanse, Mohini A., Patil, M.J., Abbulu, Konde, 2013. Review on pharmacological studies of *Thespesia populnea* linn. *Int. J. Pharm. Pharmaceut. Sci.* 5, 1–5.
- Prajapati, Narayan Das, S.S.P., Sharma, Arun K., Kumar, Tarun, 2007. *A Handbook of Medicinal Plants: A Complete Source Book*.
- Rahmani, Arshad H., Al shabrimi, Fahad M., Aly, Salah M., 2014. Active ingredients of ginger as potential candidates in the prevention and treatment of diseases via

- modulation of biological activities. *Int. J. Physiol., Pathophysiol. Pharmacol.* 6, 125–136.
- Rajan, S., Shalini, R., Bharathi, C., Aruna, V., Elgin, A., Brindha, P., 2011. Pharmacognostical and phytochemical studies on *Hemidesmus indicus* root. *Int. J. Pharmacognosy Phytochem. Res.* 3, 74–79.
- Rajesh, V., Perumal, P., 2013. Cytoprotective effect of *Smilax zeylanica* Linn. leaves against Benzo[a]pyrene induced lung cancer with reference to lipid peroxidation and antioxidant system in Swiss albino mice. *Oriental Pharm. Exp. Med.* 13, 1–11.
- Rao, Shaival K., Rao, Priya S., 2010. Alteration in the radiosensitivity of HeLa cells by dichloromethane extract of *Guduchi* (*Tinospora cordifolia*). *Integrative Cancer Therapies* 9, 378–384.
- Resorts, 2017. *Ayurvedic Medicinal Plants of Sri Lanka*. 2017 [cited 2018 01-05]; Available from: <<http://www.instituteofayurveda.org/plants/>>.
- Russell-Smitha, Jeremy, Karunaratne, N.S., Mahindapala, Ranjith, 2006. Rapid inventory of wild medicinal plant populations in Sri Lanka. *Biol. Conserv.* 132, 22–32.
- Saha, S., Ghosh, S., 2012. *Tinospora cordifolia*: one plant, many roles. *Ancient Sci. Life* 31, 151–159.
- Samarakoon, Sameera R., Thabrew, I., Galhena, Prasanna B., Tennekoon, Kamani H., 2012. Modulation of apoptosis in human hepatocellular carcinoma (HepG2 cells) by a standardized herbal decoction of *Nigella sativa* seeds, *Hemidesmus indicus* roots and *Smilax glabra* rhizomes with anti-hepatocarcinogenic effects. *BMC Complement. Alternat. Med.* 12, 25.
- Sethi, Gautam, Shanmugam, Muthu, Warriar, Sudha, Merarchi, Myriam, Arfuso, Frank, Kumar, Alan, Bishayee, Anupam, 2018. Pro-apoptotic and anti-cancer properties of diosgenin: a comprehensive and critical review. *Nutrients* 10, 645.
- Sharma, Ricky A., Ireson, C.R., Verschoyle, Richard D., Hill, Kirsti A., Williams, Marion L., Leuratti, Chiara, Manson, Margaret M., Marnett, Lawrence J., Steward, William P., Gescher, Andreas, 2001. Effects of dietary curcumin on glutathione S-transferase and malondialdehyde-DNA adducts in rat liver and colon mucosa: relationship with drug levels. *Clin. Cancer Res.* 1, 1452–1458.
- Silva, I.K., Soysa, P., 2011. Evaluation of phytochemical composition and antioxidant capacity of a decoction containing *Adenanthera pavonina* L. and *Thespesia populnea* L. *Pharmacognosy Mag.* 7, 193–199.
- Singh, Y.S.A.M., 2007. Cancer preventive properties of ginger: a brief review. *Food Chem. Toxicol.* 45, 683–690.
- Sinha, K., Mishra, N.P., Singh, J., Khanuja, S.P.S., 2004. *Tinospora cordifolia* (*Guduchi*), a reservoir plant for therapeutic applications: a review. *Indian J. Tradit. Knowl.* 3, 257–270.
- Clark, P.I., Slevin, M.L., 1987. The clinical pharmacology of etoposide and teniposide. *Clin. Pharmacokinet.* 12, 223–252.
- Sreeja, S.S.A.S., 2009. An in vitro study on antiproliferative and antiestrogenic effects of *Boerhaavia diffusa* L. extracts. *J. Ethnopharmacol.* 126, 221–225.
- Srivastava, Rakhi, Saluja, D., Dwarakanath, Bilikere S., Chopra, Madhu, 2009. Inhibition of human cervical cancer cell growth by ethanolic extract of *boerhaavia diffusa* linn. (punarnava) root. *Evid.-Based Complement. Alternat. Med.*, 1–13.
- Statti, Giancarlo, Marrelli, M., Conforti, Filomena, Spagnoletti, Antonella, Tacchini, Massimo, Fimognari, Carmela, Brognara, Eleonora, Gambari, Roberto, Sacchetti, Gianni, Guerrini, Alessandra, 2015. Inhibition of cancer cell proliferation and antiradical effects of decoction, hydroalcoholic extract, and principal constituents of *Hemidesmus indicus* R Br. *Phytother. Res.* 29, 857–863.
- Turrini, Eleonora, Catanzaro, E., Muraro, Manuele G., Governa, Valeria, Trella, Emanuele, Mele, Valentina, Calcabrini, Cinzia, Morroni, Fabiana, Sita, Giulia, Hrelia, Patrizia, Tacchini, Massimo, Fimognari, Carmela, 2018. *Hemidesmus indicus* induces immunogenic death in human colorectal cancer cells. *Oncotarget* 9, 24443–24456.
- Uddin, Mohammad Nasir, Ahmed, T., Pathan, Sanzida, Mamun Al-Amin, Md., Sohel Rana, Md., 2015. Antioxidant and cytotoxic activity of stems of *Smilax zeylanica* in vitro. *J. Basic Clin. Physiol. Pharmacol.* 26, 453–463.
- Vemuri, Satish Kumar, Banala, R.R., Subbaiah, G.P.V., Srivastava, Saurabh Kumar, Gurava Reddy, A.V., Malarvili, Thekkumalai, 2017. Anti-cancer potential of a mix of natural extracts of turmeric, ginger and garlic: a cell-based study. *Egyptian Jo. Basic Appl. Sci.* 4, 332–344.
- Verpoorte, R., 1998. Exploration of nature's chemodiversity: the role of secondary metabolites as leads in drug development. *Drug Discovery Today* 3, 232–238.
- Wang, Chong-Zhi, Calway, T., Yuan, Chun-Su, 2012. Herbal medicines as adjuvants for cancer therapeutics. *Am. J. Chin. Med.* 40, 657–669.
- Williamson, E.M., 2002. *Major Herbs of Ayurveda*. Elsevier Science.
- Yared, J.A., Tkaczuk, K.H.R., 2012. Update on taxane development: new analogs and new formulations. *Drug Des., Develop. Therapy* 6, 371–384.
- Zhang, Xu, Rakesh, K.P., Shantharam, C.S., Manukumar, H.M., Asiri, A.M., Marwani, H.M., Qin, Hua-Li, 2017. Podophyllotoxin derivatives as an excellent anticancer aspirant for future chemotherapy: a key current imminent needs. *Bioorg. Med. Chem.* 26, 340–355.
- Zhao, Tiejun, Sun, Q., Marques, Maud, Witcher, Michael, 2014. Anticancer properties of *Phyllanthus emblica* (Indian Gooseberry). *Oxid. Med. Cell. Longevity* 2015, 1–7.