Chapter

Plant-Based Drugs as an Adjuvant to Cancer Chemotherapy

Lakshmi Mohan

Abstract

Humans have turned to natural products, obtained from plants, animals and aquatic life for treating diseases since time immemorial. Modern medicine is based on ancient wisdom transferred over generations. Drug development relies mainly on natural sources. Herbal medicines are making a comeback due to lower side effects, and positive results in the long term when compared to synthetic drugs. The current drug discovery process relies on identifying traditional medicines followed by Bioactivity-guided fractionation to isolate significant lead molecules. Plants have a history of long-term use by humans and hence it can be presumed that the bioactive compounds obtained from plants will have low human toxicity. There exists a huge potential for discovering new antitumor drug leads by screening natural products either in the form of crude extracts purified phytochemicals which have already been described in the literature. The fact that phytochemicals like paclitaxel, vinblastine, vincristine and camptothecin are being successfully used in clinical practice and several others like combretastatin and noscapine are in different stages of clinical trials implies the importance of plants in cancer chemotherapy.

Keywords: plant, medicinal plants, cancer, alternative therapy, synergy

1. Introduction

> *"Until man duplicates a blade of grass, nature can laugh at his so-called scientific knowledge. Remedies from chemicals will never stand in favourable comparison with the products of nature, the living cell of the plant, the final result of the rays of the sun, the mother of all life." - Thomas Alva Edison.*

The global cancer burden has escalated to 9.6 million deaths and 18.1 million new cases in 2018. It is a fact that one in 5 men and one in 6 women around the world develop cancer during their lifetime, and it kills one in 8 men and one in 11 women [1]. Cancer continues to be the second leading cause of death globally, the first being cardiovascular diseases. Patients with cancer normally have a poor prognosis in low and middle-income countries such as India, due to a lack of awareness about the disease, delayed diagnosis, and inadequate or no access to affordable therapeutic services when compared with patients in high-income countries. The number of incident cancer cases in India is estimated to be 1 069 000 in 2016. Access to critical cancer treatment is also very low in the country. It is the need of the day to find a natural, affordable treatment strategy for cancer [2].

The conventional modality for cancer treatment involves the use of surgery, radiation and chemotherapy either alone or in combination with the others. Each of the treatment modality offers its risks and benefits. Although chemotherapeutic medicines are toxic and have a very narrow therapeutic index, they offer a transient relief from symptoms and help prolong life especially in the case of cancers where surgery and radiation is not a feasible mode of treatment like leukaemia and lymphomas. Chemotherapy is a systemic treatment because it can be used to treat cancer anywhere in the body when compared to local treatment approaches. The chemotherapeutic agents that are currently used in clinical practice lack specificity to the cancer cells and could damage the healthy cells causing adverse side effects. Toxicity and severe side effects continue to be significant setbacks involved in chemotherapeutic approaches to the treatment of cancer. To overcome the limitations, scientists across the globe are searching for new anticancer agents with more specificity and fewer side effects. Many recent studies have found that an extensive array of natural substances exert selective toxicity against cancer cells by selectively eliminating them causing less harm to the normal cells [3].

Cragg and Newman et al. have identified that nearly 5% out of the 1031 new chemical entities approved for use as drug between 1981 and 2002, by the US FDA (Food and Drug Administration) were natural products and 23% were derived from natural products [4]. Some well-known plant secondary metabolites used as medicine are paclitaxel, vinblastine, vincristine, artemisinin, atropine, inulin, digoxin, morphine and codeine, and quinine [5, 6]. Normal metabolism in plants produces a variety of chemical compounds. The primary metabolites are found ubiquitously like fats and sugars whereas the secondary metabolites are more specific to a particular genus or species. An advantage of plant metabolites is that apart from serving as functional drugs, they can be used as lead molecules for the synthesis of derivatives or synthetic molecules with the active pharmacophore.

2. Cancer and metastasis

The term 'cancer' refers to a range of diseases in which abnormal cells proliferate and spread uncontrollably in the body [7]. Under normal conditions, cells grow and multiply systematically to form organs and tissues that have a specific function. Occasionally, however, they multiply in an uncontrolled manner after developing a random genetic mutation or due to the influence of a carcinogen and form a mass known as a tumour or neoplasm that has no physiological function. It was Hippocrates (460–370 B.C.), the Greek physician who used the names 'carcinos' and 'carcinoma' to define non-ulcer forming and ulcer-forming tumours. In Greek, carcinos and carcinoma mean 'crab'; and the disease was named so because the finger-like projections extending from cancer resemble a crab in shape. Carcinomas, a type of cancer which arises from epithelial cells, is the most common type of cancer affecting people today. The first abnormality concerning cell maturation to be evident microscopically is known as dysplasia. This, in turn, leads to architectural chaos, irregularity in the nucleus, augmented and abnormal mitoses, and an increase in the number of apoptotic cells.

Tumours in the body can be benign or malignant. Benign tumours are those which do not invade other tissues or spread to other parts of the body. Malignant tumours, however, can grow in an uncontrolled way and by a process known as metastasis, can spread within the body. Even though all tumours are diverse and heterogeneous, they share the capacity to proliferate beyond the constraints that limit the growth of healthy tissue [7]. They can spread by direct local invasion,

vascular spread, cerebrospinal fluid (CSF) spread, transcoelomic (peritoneal or pleural) spread or lymphatic spread.

Modifications in the regulation of some crucial pathways that control cell proliferation (cell cycle) and survival (apoptosis) are responsible for creating all tumours [8]. The modifications include the loss of function of the tumour suppressor gene, oncogenic transformations, as well as modifications in the signal transduction pathways which leads to an augmented proliferation in response to external/mitogenic signals. As such, tumour-associated mutations in many of these pathways result in the alteration of the necessary regulatory mechanisms that control the mammalian cell cycle.

3. Cancer therapy

Surgery remains one of the foremost treatments for cancer. It has been mentioned by Roman doctor Gallien as a means of treating cancer as early as the 2nd century. It was followed by radiation therapy using radium and other diagnostic machines using relatively less voltage. Although the present methodology and the equipment for delivery of radiation therapy have improved allowing the obliteration of malignant tumours with great precision, this mode of therapy is limited by severe side effects and a restricted capacity to distinguish between healthy and tumour cells. Furthermore, both radiation and surgery are not beneficial in cases of advanced metastatic cancers.

Traditional treatments for cancer such as chemotherapy (e.g. anti-metabolites, alkylating agents, topoisomerase inhibitors) and radiation therapy were developed based upon the observation that transformed cells multiply at a higher rate when compared to normal cells. For example, ionising radiation results in DNA damage which, after multiple cell divisions, leads to errors in transcription and translation, eventually resulting in cell death [9]. In the same way, cytotoxic chemotherapy interferes with microtubule organisation, which is essential for mitosis and in due course, affects cell survival [10]. The same is true for various haematopoietic malignancies, however, as little as 5% of some solid tumours consist of rapidly proliferating, and therefore, susceptible cells. Hence, only a small subset of cancers such as Hodgkin's lymphoma, testicular cancer, acute lymphoid leukaemia and non-Hodgkin's lymphoma are routinely cured using these agents [11]. This is largely because therapies that are targeted against rapidly proliferating cells cause the death of normal tissues which also show enhanced proliferation rates, such as the gastrointestinal (GI) tract, bone marrow and the hair follicles [12].

4. Drug resistance

The development of drug resistance is also a major obstacle in patients receiving prolonged chemotherapeutic treatment. Clinical resistance to anticancer agents can occur at the time of drug introduction, as well as during treatment and following relapse [13]. Although various resistance mechanisms have been described, such as insufficient activation of the drug, utilisation of alternate metabolic pathways, mutations in the p53 gene and overexpression of the Bcl-2 gene family, the most intensely studied has been the decreased accumulation of drugs in cells, which is the leading cause of multi-drug resistance [14]. Such resistance is indicated by a failure to respond to a range of chemotherapeutic agents, many of which are structurally dissimilar and do not share a common intracellular target. The

mechanism responsible for Multidrug resistance in mammalian cells involves the overexpression of a 170 kDa cell surface, energy-dependent plasma membrane glycoprotein (P-gp) encoded on the MDR1 gene [15]. The physiological role of P-gp is the protection of cells against environmental toxins and works by exporting drugs outside of mammalian cells, thereby lowering the intracellular drug concentration less than the toxic threshold [16]. However, the chemotherapy of cancer, as compared with that of bacterial disease, poses a critical problem. Microorganisms are quantitatively and qualitatively different from human cells, while, cancer cells and normal cells are so similar that it has proved difficult to find general, exploitable biochemical differences between them. This is exemplified by the number of drugs selected for preclinical or clinical testing, based on their activity in experimental animal systems, which do not become clinically useful agents due to their severe or unpredictable toxicity towards normal cells, or because they lack any therapeutic advantage. The prevalence of MDR and systemic toxicity associated with currently administered cancer chemotherapies therefore suggest the need for alternative possibilities to be investigated to find new and worthy therapeutic agents.

5. Apoptosis and the need for apoptotic inducers

The process of homeostasis in multicellular organisms is strongly regulated by a process known as PCD (programmed cell death) or apoptosis. When cells obtain diverse indications for growth they generally die. This happens when certain developmental processes call for cell division but there are no external growth signals when a growth-related gene, e.g. c-myc gets highly expressed but the cellular environment lacks nutrient content, and in the presence of a toxic xenobiotic and the cell dies by a process termed apoptosis. The term 'apoptosis' was used for the first time in 1972 in literature, to describe a structurally-distinctive method of cell death which caused the loss of cells within live tissues [17].

There are inherent cellular programs that direct a cell into self-destruction. Several occurrences helped establish this; e.g. in the nematode, *Caenorhabditis elegans*, it has been discovered observed that a set of 113 cells is destined for programmed cell death in the hermaphrodite form of the worm during embryogenesis, and a different set of 18 cells later in life, forming a total of 131 cells [18].

The key features include blebbing and shrinkage of the cytoplasm, conservation of cellular organelle structure, involving the mitochondria and the condensation and margination of chromatin, although all cell types do not show all of these characteristics. These changes are a consequence of a developmental program for cell death which is activated by the deficiency of a growth factor, or by the presence of a xenobiotic compound such as a therapeutic anticancer drug. The morphological criteria are still the most important when complex cell populations, such as tissues, are examined, and overall cell shrinkage and nuclear condensation are the easiest to recognise [19].

The discovery of about 30 novel molecules whose functions are completely related to the initiation or control of apoptosis has been made over the last decade. Another 20 molecules, associated with essential roles in cell signalling and DNA transcription, replication or repair, have been established as effectors of apoptosis regulation. The rate of apoptosis influences the lifespan of cells in the human body, both healthy and cancer cells. Thus, the modulation of apoptosis is useful in the deterrence, management and therapy of cancer. Synthesis of novel compounds based on existing templates continues to be an indispensable aspect of research. Natural products are capable of providing such templates. Latest studies on tumour inhibitory compounds originating from plants have given rise to a remarkable group

of unique structures. Moreover, epidemiological findings confirm the theory that following a diet containing plenty of fruits and vegetables which are key sources of micronutrients and phytochemicals, reduces the risk of acquiring cancer [20]. It has also been reported that some products from plants bring about apoptosis in neoplastic cells alone and not in normal cells [21].

There have been reports confirming the role of apoptosis as an essential mode of action for several anti-tumour agents, such as alkylating agents including the widely used cisplatin and 1,3- bis (2-chloroethyl)-1-nitrosourea (BCNU) [22], ionising radiation [23], topoisomerase inhibitor etoposide, taxol [24], the tumour necrosis factor (TNF) [25], and N-substituted benzamides like 3-chloroprocainamide and metoclopramide [26].

6. Plant secondary metabolites used IN conventional medicine

The WHO (World Health Organisation) defines a medicinal plant as a plant whose one or more parts, has constituents which can be applied for therapeutic purposes, or can act as precursors for chemical or pharmacological semi-synthesis. The parts of these medicinal plants such as the roots, tubers, barks, stems, leaves, flowers, seeds and fruits/grains, contains metabolites that are therapeutically active and are used to control or treat a disease condition.

Such non-nutritional chemical compounds or bioactive components in plants are called phytochemicals, the word –'phyto'- from Greek, meaning 'plant'. These phytoconstituents are responsible for protecting the plant against pest infestation or microbial infections [27]. A large variety of phytochemicals have been isolated and characterised from familiar sources including vegetables such as onion and broccoli, fruits like apples and grapes, spices such as nutmeg, pepper and turmeric, brews such as green tea, oolong tea and red wine [28], which possess strong antioxidant properties. These antioxidants in chemoprevention and treatment of cancer and many more diseases by defending cells from damage by highly reactive oxygen compounds called 'free radicals'. The common classes of plant secondary metabolites which have found their way into traditional and modern medicine include.

Quercetin, quercitrin and kaempferol are common flavonoids present in approximately seventy per cent of all plants. Flavonoids vary notably in their anti-proliferative effectiveness depending on their structure. Kuntz et al. discovered that baicalein and myricetin induced apoptosis in Caco-2 and HT-29 cells [29]. Flavone, flavanone, flavonol, and isoflavone classes of flavonoids possess anti-proliferative effects in various cancer cell lines. Tangeretin found in the peel of tangerine is used extensively in Kampo medicines in Japan for treating cancer [21].

Solamargine, derived from a Chinese herb, *Solanum incanum*, has been noted to bring about apoptosis in human hepatocyte (Hep-3B) cells and normal skin fibroblast cells [30]. The alkaloids isolated from *Tiliacora racemosa* root with several bis-benzylisoquinoline alkaloids induced apoptosis in K-562 cells. Camptothecin (CPT), extracted from the stem wood of a Chinese tree, *Camptotheca acuminata Decsne, Nyssaceae*, works as a topoisomerase I inhibitor and induces apoptosis in PLB-985 (a human leukaemia cell line) cells [31]. The widely popular alkaloids Vinblastine and vincristine are obtained from the Madagascar periwinkle, *Catharanthus roseus* (previously called *Vinca rosea*).

A new cytotoxic proteoglycan, which is related to the family of arabinogalactan proteins, isolated from the saffron plant (*Crocus sativus L.*) exhibited induction of apoptosis in cultured macrophages with a lesser non-cytotoxic concentration increasing the DNA laddering effect in apoptotic cells [32].

A phytopreparation made from *Viscum album L.*, is currently being used as an adjuvant in cancer therapy and is found to stimulate the immune system by improving the number and activity of neutrophils and NK cells [33]. The formulation has various toxic proteins including viscotoxins (VT) and mistletoe lectins (ML); induces the synthesis of cytokines such as IFN-g,TNF-a, IL-6 and 1 L-1 and exhibits cytostatic and cytotoxic effects on human lymphocytes and cultured tumour cells alike.

7. Why use plant-based drugs?

Plants are an important part of nature's reservoir of medicinal agents and it is safe to say that they are nearly devoid of the side effects generally caused by synthetic drugs and chemical agents [34]. The WHO (World Health Organisation) reports that traditional medicine remains the chief mode of the treatment availed by 75–80% of the world's total population for primary health care, particularly in developing countries. This can be attributed to improved compatibility with the human body, better cultural acceptability, and reduced or practically no side-effects [35, 36].

Although several compounds isolated from plants are in the process of being thoroughly tested for their anticancer properties, it is becoming acknowledged that the medicinal effects of plants are due to a complex interaction of the combination of compounds present in the whole plant (additive/synergistic and/or antagonistic) rather than the single constituents [27].

The review of the literature reveals that phytochemicals present in normal fruit and vegetables have harmonising and overlapping mechanisms of action, such as the modulation of detoxification enzymes, stimulation of the immune system, scavenging of free radicals, regulation of gene expression, hormone metabolism, antibacterial and antiviral properties. Bioactive plant extracts are valuable resources which aid in the development of less toxic, more efficient drugs to manage the progression of cancer.

A major problem concerning cancer chemotherapy is the development of resistance to cytotoxic agents. Overcoming multidrug resistance requires research into new antineoplastic agents. In this regard, natural products acquired from plants have shown to have high potential as drug reservoirs [37]. According to the WHO, around 80% of the population in developing countries rely on traditional medicines, mostly derived from plants for primary health care. The modern pharmacopoeia contains a minimum of 25% drugs which are derived from plants and several others which are synthetic analogues [38]. Hence, fighting cancers with natural compounds derived from plants present a very favourable alternative.

Phytochemicals display structural diversity and contain scaffolds tailored to bind and inhibit the functions of several key proteins. They have more chiral centres and varied ring systems when compared to synthetic drugs. This complexity is responsible for increasing its target selectivity thereby reducing non-specific binding and adverse side effects [39].

8. Drug combinations and synergy

Drug combinations are widely used to treat deadly diseases such as AIDS and cancer. The main intention is to accomplish a reduction in dose and toxicity, synergistic therapeutic effect and lessen or delay the induction of drug resistance.

Plant secondary metabolite	Synergy with anti-cancer agents	Experimental models	References
Apigenin	TRAIL	HeLa cervical cancer cell line	[42]
		Human acute lymphoblastic leukemic cell line Jurkat, human prostate cancer cell line DU145, human colon cancer cell line DLD-1	[43]
	Tamoxifen	MCF7 human breast cancer cells	[44]
	Fulvestrant		
Berberine	Cisplatin	Ovarian cancer cell line VCAR3	[45]
	Doxorubicin	Murine melanoma B16F10 cells	[46]
	Epirubicin	T24 bladder cancer cells	[47]
	Evodiamine	Human breast cancer MCF-7 cells	[48]
	Tamoxifen	Human breast cancer MCF-7 cells	[49]
Curcumin	Cisplatin, etoposide, camptothecin, doxorubicin	Human and rat glioblastoma cell lines	[50]
	Cisplatin, oxaliplatin	Human ovarian carcinoma cell lines (2008 and C13)	[51]
	5-fluorouracil, a combination of 5-fluorouracil and oxaliplatin	Human colon cancer cell line (HT-29)	[52]
Genistein	Cisplatin	Human pancreatic carcinoma cell line (BxPC-3), murine xenograft model of BxPC-3 cells	[53]
		Human pancreatic carcinoma cell lines (COLO-357 and L3.6pl)	[54]
	Camptothecin	Human cervical cancer cell line (HeLa), human ovarian carcinoma line (OAW-42)	[55]
	Doxorubicin	Hormone-independent human breast cancer cell line (MDA-MB-231)	[56]
(-)-epigallocatechin 3-gallate (EGCG)	Cisplatin	Human ovarian cancer cell lines (SKOV3, CAOV3, and C200)	[57]
	doxorubicin	Murine xenografts of human carcinoma DOX-resistant cells (KB-A-1)	[58]

Plant secondary metabolite	Synergy with anti-cancer agents	Experimental models	References
Eupatin	Mitoxantrone	NCI-H460 human lung non-small-cell carcinoma cells	[59]
Indirubin	Arylidene derivatives	Human non-small cell lung carcinoma cells	[60]
	TRAIL	Breast cancer and bladder carcinoma cell lines	[61]
	Vinblastine	HeLa cells	[62]
Kaempferol	TRAIL	Human glioblastoma cell lines U87, U251, and U373	[63]
	Vinblastine	Cervical carcinoma cell lines (KB-V1, KB-3-1)	[64]
	Paclitaxel		
	Mitoxantrone	K562, LLC, K562, and KB Cell Lines	[65]
Luteolin	Cisplatin	Human liver cancer cells HepG2and Hep3B and human colorectal cancer cells HT29 and HCT116	[66]
	Doxorubicin	4T1 and MCF-7 cells	[67]
	Rapamycin	Human breast and ovarian cancer cell lines MDA-MB-453, AU565, SKOV3.ip1, HBL100, and MCF-7. MCF-7 and AU56	[68]
Quercetin	Cisplatin	Human laryngeal carcinoma cell line (Hep-2)	[69]
	Doxorubicin	Neuroblastoma and Ewing's sarcoma cell lines	[70]
	Vinblastine Paclitaxel	Cervical carcinoma cell lines (KB-V1, KB-3-1)	[64]
	Gemcitabine Topotecan	Murine fibrosarcoma cell lines	[71]
Resveratrol	Cisplatin	Wistar rats	[72, 73]
	Doxorubicin	Human acute myeloid leukemia cell lines (ML-2/DX30, AML-2/DX100, and AML-2/DX300)	[74]
Silybin	Cisplatin Carboplatin	Human prostate carcinoma cell line DU145	[75]
	SN-38 Mitoxantrone	K562, LLC, K562, and KB Cell Lines	[65]
	Paclitaxel TRIAL	Human ovarian carcinoma line A2780	[76]

Table 1.
Combinations studies with anti-cancer drugs in clinical practice.

Synergistic interactions are essential in phytomedicine and explain the effectiveness of extremely low doses of active constituents in herbal formulations. Traditional medicine works on the idea that a whole or partly purified plant extract offers improvements over a single isolated ingredient. Synergism also leads to toxicity reduction and minimization of resistance. Though vinblastine is successful clinically by itself [40, 41], its use in combination with other anticancer agents is now under evaluation, mostly for the management of recurrent or advanced cancers that are resistant to conventional chemotherapy. The occurrence of clinical drug resistance has emphasised the need to search for novel chemotherapeutic drugs and better combinations among these agents. Typically, synergy is considered to be greater than additive therapeutic effects when compared with the efficacy of each drug by itself. Recently, combination therapies being tested make use of drugs with different mechanisms of action, under the rationale that targeting two separate pathways will result in improved cytotoxicity, whether additive or synergistic.

Several researchers have tried to enhance the potential of known anti-cancer agents like vinblastine and paclitaxel by the virtue of combination therapy with cisplatin, etoposide and doxorubicin. **Table 1** gives a list of the combination studies performed on plant secondary metabolites with anti-cancer drugs in clinical practice which showed synergistic activity.

9. Future perspectives

Cancer cells have evolved multiple mechanisms to evade apoptosis and escape to other sites. Phytomedicine and ethnopharmacology have proved to be very effective in the prevention and treatment of human ailments. Plant extracts have several components with diverse possible intracellular targets. From literature, it is evident that plants have a long history of oral use in traditional medicine and hence, are considered safe and non-toxic and there lies a huge potential in developing crude whole plant extracts for the treatment of cancer, alone or in a combination with other drugs in clinical practice. It is also advisable to explore the potential of these plants as chemopreventive agents because of their antioxidant and free radical scavenging activity. However, before these plant metabolites can be used for cancer prevention or therapy, they must be subject to further testing which should include in vivo studies in animal models and clinical trials (randomised double-blind) in human subjects.

Author details

Lakshmi Mohan
Department of Food Technology, Saintgits College of Engineering, Kerala, India

*Address all correspondence to: lakshmi.mohan@saintgits.org

References

[1] Bray, F., et al., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 2018.

[2] Cragg, G.M., D.G. Kingston, and D.J. Newman, Anticancer agents from natural products. 2011: CRC press.

[3] Cragg, G.M. and D.J. Newman, Plants as a source of anti-cancer agents. Journal of ethnopharmacology, 2005. 100(1-2): p. 72-79.

[4] Laurence, L., et al., Goodman and Gilman's manual of pharmacology and therapeutics. 2008, The McGraw-Hill Publication, New Delhi.

[5] Evans, W.C., Trease and Evans' Pharmacognosy E-Book. 2009: Elsevier Health Sciences.

[6] Bertram, J.S., The molecular biology of cancer. Molecular aspects of medicine, 2000. 21(6): p. 167-223.

[7] Evan, G.I. and K.H. Vousden, Proliferation, cell cycle and apoptosis in cancer. Nature, 2001. 411(6835): p. 342.

[8] Rydberg, B., Radiation-induced DNA damage and chromatin structure. Acta oncologica, 2001. 40(6): p. 682-685.

[9] Marchetti, P., et al., Weekly administration of paclitaxel: theoretical and clinical basis. Critical reviews in oncology/hematology, 2002. 44: p. 3-13.

[10] Abeloff, M., et al., Review of Clinical Oncology. 2004.

[11] Kaelin Jr, W.G., The concept of synthetic lethality in the context of anticancer therapy. Nature reviews cancer, 2005. 5(9): p. 689.

[12] Le, T., et al., First aid for the USMLE step 1 2015. 2015: McGraw-Hill Medical.

[13] Quesada, A., M.G. Grávalos, and J.F. Puentes, Polyaromatic alkaloids from marine invertebrates as cytotoxic compounds and inhibitors of multidrug resistance caused by P-glycoprotein. British journal of cancer, 1996. 74(5): p. 677.

[14] Gottesman, M.M., Mechanisms of cancer drug resistance. Annual review of medicine, 2002. 53(1): p. 615-627.

[15] Bellamy, W.T., P-glycoproteins and multidrug resistance. Annual review of pharmacology and toxicology, 1996. 36(1): p. 161-183.

[16] Gottesman, M.M. and I. Pastan, Biochemistry of multidrug resistance mediated by the multidrug transporter. Annual review of biochemistry, 1993. 62(1): p. 385-427.

[17] Kerr, J., A. Wyllie, and A. Currie, Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. British journal of cancer, 1972. 26(4): p. 239.

[18] Chalfie, M., et al., The neural circuit for touch sensitivity in *Caenorhabditis elegans*. Journal of Neuroscience, 1985. 5(4): p. 956-964.

[19] Studzinski, G.P., Apoptosis: a practical approach. 1999: Oxford University Press, USA.

[20] Reddy, B.S., Studies with the azoxymethane–rat preclinical model for assessing colon tumor development and chemoprevention. Environmental and molecular mutagenesis, 2004. 44(1): p. 26-35.

[21] Hirano, T., et al., Citrus flavone tangeretin inhibits leukaemic HL-60 cell growth partially through induction of apoptosis with less cytotoxicity on normal lymphocytes. British journal of cancer, 1995. 72(6): p. 1380.

[22] D'Amico, A. and W. Gillies McKenna, Apoptosis and a re-investigation of the biologic basis for cancer therapy. Radiotherapy and Oncology, 1994. 33(1): p. 3-10.

[23] Radford, I., et al., Radiation response of mouse lymphoid and myeloid cell lines. Part II. Apoptotic death is shown by all lines examined. International Journal of Radiation Biology, 1994. 65(2): p. 217-227.

[24] Gibb, R., et al., Apoptosis as a Measure of Chemosensitivity to Cisplatin and Taxol Therapy in Ovarian Cancer Cell Lines* 1. Gynecologic oncology, 1997. 65(1): p. 13-22.

[25] Shih, S. and O. Stutman, Cell cycle-dependent tumor necrosis factor apoptosis. Cancer research, 1996. 56(7): p. 1591.

[26] Pero, R., et al., Newly discovered anti-inflammatory properties of the benzamides and nicotinamides. Molecular and cellular biochemistry, 1999. 193(1): p. 119-125.

[27] Liu, R.H., Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals. The American journal of clinical nutrition, 2003. 78(3): p. 517S–520S.

[28] Doughari, J.H., Phytochemicals: extraction methods, basic structures and mode of action as potential chemotherapeutic agents, in Phytochemicals-A global perspective of their role in nutrition and health. 2012, InTech.

[29] Kuntz, S., U. Wenzel, and H. Daniel, Comparative analysis of the effects of flavonoids on proliferation, cytotoxicity, and apoptosis in human colon cancer cell lines. European journal of nutrition, 1999. 38(3): p. 133-142.

[30] Hsu, S.-H., et al., Solamargine Purified From*solanum incanum* Chinese Herb Triggers Gene Expression of Human TNFR I Which May Lead to Cell Apoptosis. Biochemical and biophysical research communications, 1996. 229(1): p. 1-5.

[31] Hiraoka, W., et al., Role of oxygen radicals generated by NADPH oxidase in apoptosis induced in human leukemia cells. The Journal of clinical investigation, 1998. 102(11): p. 1961-1968.

[32] Escribano, J., et al., In vitro activation of macrophages by a novel proteoglycan isolated from corms of *Crocus sativus* L. Cancer letters, 1999. 144(1): p. 107-114.

[33] Büssing, A., et al., Induction of apoptosis in human lymphocytes treated with *Viscum album* L. is mediated by the mistletoe lectins. Cancer letters, 1996. 99(1): p. 59-72.

[34] Fennell, C., et al., Assessing African medicinal plants for efficacy and safety: pharmacological screening and toxicology. Journal of ethnopharmacology, 2004. 94(2-3): p. 205-217.

[35] Kamboj, V.P., Herbal medicine. Current science, 2000. 78(1): p. 35-39.

[36] Yadav, N. and V. Dixit, Recent approaches in herbal drug standardization. Int J Integr Biol, 2008. 2(3): p. 195-203.

[37] Kuete, V. and T. Efferth, Pharmacogenomics of Cameroonian traditional herbal medicine for cancer therapy. Journal of ethnopharmacology, 2011. 137(1): p. 752-766.

[38] Health, G.I.f.T.S.o., Medicinal plants for forest conservation and health care. Vol. 11. 1997: Food & Agriculture Org.

[39] Wang, H., et al., Plants vs. cancer: a review on natural phytochemicals in preventing and treating cancers and

their druggability. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents), 2012. 12(10): p. 1281-1305.

[40] Johnson, I.S., et al., The vinca alkaloids: a new class of oncolytic agents. 1963, AACR.

[41] Noble, R.L., The discovery of the vinca alkaloids—chemotherapeutic agents against cancer. Biochemistry and cell biology, 1990. 68(12): p. 1344-1351.

[42] Szliszka, E., et al., Dietary flavonoids sensitize HeLa cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). International Journal of Molecular Sciences, 2008. 9(1): p. 56-64.

[43] Horinaka, M., et al., The dietary flavonoid apigenin sensitizes malignant tumor cells to tumor necrosis factor–related apoptosis-inducing ligand. Molecular Cancer Therapeutics, 2006. 5(4): p. 945-951.

[44] Long, X., et al., Apigenin inhibits antiestrogen-resistant breast cancer cell growth through estrogen receptor-α-dependent and estrogen receptor-α-independent mechanisms. Molecular cancer therapeutics, 2008. 7(7): p. 2096-2108.

[45] Liu, L., et al., Berberine in combination with cisplatin induces necroptosis and apoptosis in ovarian cancer cells. Biological research, 2019. 52(1): p. 37.

[46] Mittal, A., S. Tabasum, and R.P. Singh, Berberine in combination with doxorubicin suppresses growth of murine melanoma B16F10 cells in culture and xenograft. Phytomedicine, 2014. 21(3): p. 340-347.

[47] Zhuo, Y., et al., Berberine promotes antiproliferative effects of epirubicin in T24 bladder cancer cells by enhancing apoptosis and cell cycle arrest. International journal of clinical pharmacology and therapeutics, 2017. 55(1): p. 32.

[48] Du, J., et al., Berberine and evodiamine act synergistically against human breast cancer MCF-7 cells by inducing cell cycle arrest and apoptosis. Anticancer Research, 2017. 37(11): p. 6141-6151.

[49] Wen, C., et al., Berberine enhances the anti-tumor activity of tamoxifen in drug-sensitive MCF-7 and drug-resistant MCF-7/TAM cells. Molecular medicine reports, 2016. 14(3): p. 2250-2256.

[50] Dhandapani, K.M., V.B. Mahesh, and D.W. Brann, Curcumin suppresses growth and chemoresistance of human glioblastoma cells via AP-1 and NFκB transcription factors. Journal of neurochemistry, 2007. 102(2): p. 522-538.

[51] Montopoli, M., et al., Cell-cycle inhibition and apoptosis induced by curcumin and cisplatin or oxaliplatin in human ovarian carcinoma cells. Cell proliferation, 2009. 42(2): p. 195-206.

[52] Du, B., et al., Synergistic inhibitory effects of curcumin and 5-fluorouracil on the growth of the human colon cancer cell line HT-29. Chemotherapy, 2006. 52(1): p. 23-28.

[53] Sharma, V., C.D. Hupp, and J.J. Tepe, Enhancement of Chemotherapeutic Efficacy by Small Molecule Inhibition of NF-κ B and Checkpoint Kinases. Current medicinal chemistry, 2007. 14(10): p. 1061-1074.

[54] Banerjee, S., et al., Retracted: In vitro and in vivo molecular evidence of genistein action in augmenting the efficacy of cisplatin in pancreatic cancer. International journal of cancer, 2007. 120(4): p. 906-917.

[55] Ortega, N.d., et al., Obtention and characterization of phenolic extracts from different cocoa sources. Journal of agricultural and food chemistry, 2008. 56(20): p. 9621-9627.

[56] Lim, H.A., et al., Genistein induces glucose-regulated protein 78 in mammary tumor cells. Journal of medicinal food, 2006. 9(1): p. 28-32.

[57] Chan, M.M., et al., Epigallocatechin-3-gallate delivers hydrogen peroxide to induce death of ovarian cancer cells and enhances their cisplatin susceptibility. Journal of cellular physiology, 2006. 207(2): p. 389-396.

[58] Zhang, Q., D. Wei, and J. Liu, In vivo reversal of doxorubicin resistance by (−)-epigallocatechin gallate in a solid human carcinoma xenograft. Cancer letters, 2004. 208(2): p. 179-186.

[59] Henrich, C.J., et al., A high-throughput cell-based assay for inhibitors of ABCG2 activity. Journal of biomolecular screening, 2006. 11(2): p. 176-183.

[60] Rajagopalan, P., et al., Rational combinations of indirubin and arylidene derivatives exhibit synergism in human non-small cell lung carcinoma cells. Journal of food biochemistry, 2019. 43(7): p. e12861.

[61] Braig, S., et al., The pleiotropic profile of the indirubin derivative 6BIO overcomes TRAIL resistance in cancer. Biochemical pharmacology, 2014. 91(2): p. 157-167.

[62] Mohan, L., et al., Indirubin, a bis-indole alkaloid binds to tubulin and exhibits antimitotic activity against HeLa cells in synergism with vinblastine. Biomedicine & Pharmacotherapy, 2018. 105: p. 506-517.

[63] Siegelin, M.D., et al., The flavonoid kaempferol sensitizes human glioma cells to TRAIL-mediated apoptosis by proteasomal degradation of survivin. Molecular cancer therapeutics, 2008. 7(11): p. 3566-3574.

[64] Limtrakul, P., O. Khantamat, and K. Pintha, Inhibition of P-glycoprotein function and expression by kaempferol and quercetin. Journal of chemotherapy, 2005. 17(1): p. 86-95.

[65] Imai, Y., et al., Phytoestrogens/flavonoids reverse breast cancer resistance protein/ABCG2-mediated multidrug resistance. Cancer research, 2004. 64(12): p. 4346-4352.

[66] Shi, R., et al., Luteolin sensitizes the anticancer effect of cisplatin via c-Jun NH2-terminal kinase–mediated p53 phosphorylation and stabilization. Molecular cancer therapeutics, 2007. 6(4): p. 1338-1347.

[67] Du, G.-J., et al., Luteolin as a glycolysis inhibitor offers superior efficacy and lesser toxicity of doxorubicin in breast cancer cells. Biochemical and biophysical research communications, 2008. 372(3): p. 497-502.

[68] Chiang, C.-T., T.-D. Way, and J.-K. Lin, Sensitizing HER2-overexpressing cancer cells to luteolin-induced apoptosis through suppressing p21WAF1/CIP1 expression with rapamycin. Molecular cancer therapeutics, 2007. 6(7): p. 2127-2138.

[69] Kuhar, M., S. Imran, and N. Singh, Curcumin and quercetin combined with cisplatin to induce apoptosis in human laryngeal carcinoma Hep-2 cells through the mitochondrial pathway. J Cancer Mol, 2007. 3(4): p. 121-128.

[70] Zanini, C., et al., Inhibition of heat shock proteins (HSP) expression by quercetin and differential doxorubicin sensitization in neuroblastoma and Ewing's sarcoma cell lines. Journal

of neurochemistry, 2007. 103(4): p. 1344-1354.

[71] Sliutz, G., et al., Drug resistance against gemcitabine and topotecan mediated by constitutive hsp70 overexpression in vitro: implication of quercetin as sensitiser in chemotherapy. British journal of cancer, 1996. 74(2): p. 172-177.

[72] Do Amaral, C.L., et al., Resveratrol attenuates cisplatin-induced nephrotoxicity in rats. Archives of toxicology, 2008. 82(6): p. 363-370.

[73] Wang, J., et al., Resveratrol protects against cisplatin-induced cardiotoxicity by alleviating oxidative damage. Cancer Biotherapy and Radiopharmaceuticals, 2009. 24(6): p. 675-680.

[74] Kweon, S.H., J.H. Song, and T.S. Kim, Resveratrol-mediated reversal of doxorubicin resistance in acute myeloid leukemia cells via downregulation of MRP1 expression. Biochemical and biophysical research communications, 2010. 395(1): p. 104-110.

[75] Dhanalakshmi, S., et al., Silibinin sensitizes human prostate carcinoma DU145 cells to cisplatin-and carboplatin-induced growth inhibition and apoptotic death. International journal of cancer, 2003. 106(5): p. 699-705.

[76] Zhou, L., et al., Silibinin restores paclitaxel sensitivity to paclitaxel-resistant human ovarian carcinoma cells. Anticancer research, 2008. 28(2A): p. 1119-1127.