Journal of Medicinal Plants Studies
www.PlantsJournal.com

ISSN (E): 2320-3862
ISSN (P): 2394-0530
NAAS Rating: 3.53
JMPS 2018; 6(4): 83-93

Received: 05-05-2018
Accepted: 10-06-2018

Mohammed Shafi Sofi
Molecular Diagnostics and Nanobiotechnology Laboratories, Department of Microbiology and Biotechnology, Bangalore University, J.B. Campus, Bangalore, Karnataka, India

Shabnum Nabi
Interdisciplinary Brain Research Centre, Aligarh Muslim University, Uttar Pradesh, India

Correspondence
Mohammed Shafi Sofi
Molecular Diagnostics and Nanobiotechnology Laboratories, Department of Microbiology and Biotechnology, Bangalore University, J.B. Campus, Bangalore, Karnataka, India

The role of phytocompounds in cancer treatment: A current review

Mohammed Shafi Sofi and Shabnum Nabi

Abstract
Plant-derived products are considered excellent sources for the discovery and development of novel cancer chemo-protective and chemotherapeutic agents. Throughout medical history, plant products have been shown to be valuable sources of novel anti-cancer drugs. Several plant-derived compounds are currently successfully employed in cancer treatment, and many natural products have been tested against cancer and still there has been a long standing interest in the identification of medicinal plants and derived natural products for developing novel cancer therapeutics. There are more than 270,000 higher plants existing on this planet. But only a small portion has been explored phytochemically. So, it is anticipated that plants can provide potential bioactive compounds for the development of new 'leads' to combat cancer diseases. The activities of phytoconstituents from plant and the synergistic action shown by them with other drugs make them ideal in alternative cancer therapies. It was also known that nature is able to produce a wide variety of chemical entities of novel structure. Many of the new and novel compounds isolated from natural sources might otherwise have never been discovered, especially those of considerable complexity requiring the development of methods for the creation of new ring systems. On the basis of ethnobotanical knowledge, researchers are screening natural bioactive phytoconstituents from plant to identify bioactive compounds for the development of new therapeutic agents for the treatment of cancer this includes studies on secondary metabolites with chemopreventive, antiproliferative and cytotoxic activities. In this review, complete outlines of the natural bioactive anticancer phytoconstituents from plant are described. Further pharmaceutical developmental challenges and opportunities in bringing the phytochemicals into the market are also explored.

Keywords: anticancer bioactive phytoconstituents, cytotoxicity, cancer treatment

Introduction
Cancer is one of the most dreaded diseases of the 20th century and spreading further with continuance and increasing incidence in 21st century, an estimated 12.4 million people will be diagnosed with some form of cancer and around 7.6 million people will die [1]. As part of this global effort, many natural products have been tested against cancer cell lines [2] and still there has been a long standing interest in the identification of medicinal plants and derived natural products for developing cancer therapeutics [3]. Plants have been used as sources of medicinal agents since the beginning of mankind. As the age of modern medicine and single pure drugs emerged, plant-derived active principles and their semi-synthetic and synthetic analogs have served as a major route to new pharmaceuticals [4]. Human beings have relied on natural products as a resource of drugs for thousands of years. Plant-based drugs have formed the basis of traditional medicine systems that have been used for centuries in many countries such as Egypt, China and India [5]. Today plant-based drugs continue to play an essential role in health care. It has been estimated by the World Health Organization that 80% of the population of the world rely mainly on traditional medicines for their primary health care [6].

Natural anticancer phytoconstituents and their applications
Currently, over 50% of anticancer drugs approved by the US FDA are nature-derived [7] and over 60% of all drugs in clinical trials for cancers are nature related [8]. Epidemiological studies suggest that a reduced risk of cancer is associated with the consumption of a phytochemical-rich diet that includes fruits and vegetables [9]. Fresh and processed fruits and food products contain high levels of a diverse range of phytochemicals of which polyphenols including hydrolysable tannins (ellagitannins andgallotannins) and condensed tannins (proanthocyanidins) and anthocyanins and other flavonoids make up a large proportion [10]. Suggested mechanisms of anticancer effects of polyphenols include antioxidant,

anti-inflammatory and antiproliferative activities as well as their effects on subcellular signaling pathways, induction of cell-cycle arrestand apoptosis [11]. These phytochemicals generate much scientific interest, because they fulfill basic requirements of an ideal chemopreventive agent, such as selective toxicity to cancerous or precancerous cells, efficacy against most types of cancers, oral route of administration, and acceptance by target human population and have a known mechanism of action [12]. In 25 years, the National Cancer Institute (NCI) screened more than 120,000 plant extracts from 35,000 species for novel anticancer agents. Some promising discoveries are: taxol, indicine-n-oxide, phyllanthoside, and homoharringtonine, isolated from *Taxus brevifolia* Nutt., *Heliotropium indicum* L., *Phyllanthus acurnznatus* Vahl. And *Cephalotaxus harringtonia* Koch. etc. Natural products include: (1) an entire organism, (2) part of an organism, (3) an extract of an organism or part of an organism and exudates and (4) pure compounds (e.g. alkaloids, coumarins, flavonoids, glycosides, xanthones, lignans, phenylpropanoids, isoprenoids, sugars, etc, as illustrated in table- I) isolated from plants. Many of these compounds show a variety of biological and pharmacological activities and some of these compounds are essential for everyday life, both for humans and animals [13]. These agents have been found in fruits, vegetables, raisins, nuts, herbal extracts, and commonly consumed beverages such as wine, tea, and coffee [14].

1. Alkaloids and their potential anticancer activities

The term 'alkaloid', is generally limited to organic bases formed in plants. By definition alkaloids contain nitrogen which is usually derived from amino acids. Because of the presence of a nitrogen atom, alkaloids react mostly alkaline and are able to form soluble salts in aqueous environments. In plants however they can occur in the free state, as a salt or as an N-oxide and they are accumulated in the plant vacuole as reservoir or often coupled to phenolic acids such aschlorogenic acid or caffeic acid. In plants over 12,000 alkaloids are known and several are used medicinally with a world market volume of US$ 4 billion [15]. Alkaloids are usually divided into five major groups dependent on the amino acid of origin in the biosynthesis (amino acid in brackets):

I. tropane-, pyrrolidine- and pyrrolizide-alkaloids (ornithine),
II. benzylisoquinoline (tyrosine),
III. indolequinoline (tryptophane),
IV. pyridine (pyridine), and
V. quinolizidine- and piperidine-alkaloids (lysine).

On the whole, alkaloids are very poisonous, but are used medicinally in very small quantity. More members of this class of compounds have come out of the plant fractionation program than of any other class. They are widely distributed in the plant kingdom and many are active against various types of cancers. Combinatorial biosynthesis of alkaloids is known for a few examples like vincristine, vinblastine, morphine and ajmaline [16] from plants and rebeccamycin and staurosporine from *Streptomyces albus* [17]. Of the wide variety of structural types isolated from plants, the alkaloids are undoubtedly the most interesting. Two dimeric benzylisoquinoline alkaloids, thalicarpine and tetrandrine, are of substantial interest as antitumor agents [18]. Thalicarpine [19] isolated from *Thalictrum dasycarpum Fisch.* (Ranunculaceae) and tetrandrine from *Cyclea peltata Diels* (Menispermaceae), both exhibit marked activity against walker carcinosarcoma-256 (WM) in rats and were selected for preclinical evaluation on this basis. Emetine, an isoquinoline alkaloid isolated from *Cephaelis acuminata* (Rubiaceae), exhibits activity in both the P-388 and L-1210 leukemia systems. Emetine is an older drug, widely used as an amoebicide. Clinical trials demonstrated some activity against lung carcinoma at high dose levels, but no beneficial results were observed against several other malignancies [20]. Investigation of a Chinese tree, *Camptotheca acuminata Decne.* (Nyssaceae) by Wall and coworkers revealed another important series of alkaloids. These include Camptothecin [21] and its 10-hydroxy and 10-methoxy derivatives [22]. Camptothecin is exceptionally active in the L-12l0 and P-388 leukemia systems and shows considerable activity against a variety of other animal tumors, including Walker 256 carcinoma, Lewis lung carcinoma, and 8-16 melanotic-melanoma. Ellipticine, 9-methoxyellipticine, and olivacine, obtained from several Ochrosia and Aspidosperma species (Apocynaceae), are of considerable interest due to their activity against L-1210 and a variety of other tumors. The more important of these is probably 9-methoxyellipticine, first isolated from *Ochrosia maculata.* [23]. Pyrrolizidine alkaloids occur most frequently in the families-Compositae, Boraginaceae and Leguminosae. As a group, they are considered teratogenic and strongly hepatotoxic; furthermore, they are high on the list of suspected or proven carcinogens. Paradoxically, several of this group, including monocrotaline and indicine N-oxide, are noted for their significant antitumor activity. Alkaloid sinococuline, isolated from *Stephania sutchuenensis*, has been found effective in inducing cell-growth inhibition in mouse fibroblast cell line (L-929), HL-60 and a rat alveolar macrophage culture in a dose-dependent manner [24]. Exposure to sinococuline *in vitro* also altered the macrophage function by reducing the production of Tumor necrosis factors (TNF) and reactive nitrogen intermediates. Apoptosis seems to be the mode of death induced by sinococuline [24]. The great diversity of chemical types in this group of compounds is illustrated in table 1 which lists the various alkaloids with their classes, their plant origin, and their scientific report.

Table 1: Natural anticancer Phytocompounds with their class, plant source and family.

Sl.no.	Anticancer compound	Class	Plant Source	Family
1.	*Indicine N-oxide*	Pyrroliaidines	*Heliotropium indicum* L.	*Boraginaceae*
2.	*Thalicarpine*	Aporphines	*Thalictrum dasycarpum* Fisch.	*Ranunculaceae*
3.	*Catnptothecin*	Camptothecin group	*Camptotheca acuminata* Decne.	*Nyssaceae*
4.	*Taxol*	Taxaes	*Taxus brevifoLia* Nutt.	*Taxaceae*
5.	*Ellipticine*	Alkaloid	*Ochrosia elliptica* Labill.	*Apocynaceae*
6.	*Nitidine and fagaronine*	Benzophenso-thridines	*Fagara macrophylla*Lam.	*Rutaceae*
7.	*3-Esmethylcolchicine*	Colchicine group	*Colchicum speciosum* Steven.	*Colchicaceae*
8.	*Harringtonine and homoharringtonine*	Cephalotaxus alkaloids	*Cephalotaxus harringtonia* Koch.	*Drupaceae*
9.	*Tylocrebrine*	Phenenthroq- uicolizidines and Phenanthroin-dolizidines	*Tylophora crebriflora* Blake	*Asclepiadaceae*
10.	*Emetine*	Ecetine group	*Cephaelis acuminate* Karst**.**	*Rubiaceae*

11.	*Vinblastine/Vincristine*	Indole alkaloid	*Catharanthus roseus* L.	*Apocynaceae*
12.	*Maquiroside A*	Cardiac glycoside	*Maquira calophylla* (Poepp. & Endl.)	*Moraceae*
13.	*Kamebanin*	Diterpenoid	*Rabdosia umbrosa* var.	*Lamiaceae*
14.	*Lariciresinol*	Lignan	*Wikstroemia elliptica* Merr.	*Thymelaeaceae*
15.	*3',4'-Deoxypsorospermin*	Xanthone	*Psorospermum febrifugum* Spach.	*Guttiferae*
16.	*Larreantin*	Quinone	*Larrea tridentate* Coville.	*Zygophyllaceae*
17.	*Allamandin*	Monoterpenoid	*Allamanda cathartica* L.	*Apocynaceae*
18.	*Cudraisoflavone*	Lignans	*Cudrania cochinchinensis* Lour.	*Moraceae*
19.	*Helenalin*	Sesquiterpenoid	*Heliotropium indicum* L.	*Boraginaceae*
20	*Cucurcubitacin*	Triterpenoid	*Marah oreganus* (Torr. S. Watson)	*Cucurbitaceae*
21	*Colchicine*	Alkaloid	*Colchicum speciosum* Steven.	*Colchicaceae*
22.	*Umbelliferone*	Coumarin	*Wilkstroemia elliptica* Merr.	*Thymelaeaceae*
23.	*Epipodophyllotoxin (etoposide and teniposide)*	Alkaloids	*Podophyllum species* L.	*Berberidaceae*
24.	*Acer saponin. p*	Saponins	*Acer negundo* L.	*Aceraceae*
25.	*Acobioside A*	Steriods lactones	*A. oblongifoliav* var.	*Apocyneceae*
26.	*Adynerin*	Steriods lactones	*Nerium oleander* L.	*Apocyneceae*
27.	*Alkannin*	Quinones	*Arnebia nobilis* Reich.	*Boraginaceae*
28.	*α-amyrin*	Triterpenes	*Bursera schlechtendalii* Engl.	*Burseraceae*
29.	*Anacardic acid*	Polyphenols	*Anacardium occidentale* L.	*Anacardiaceae*
30.	*Aristolochic acid*	Alkaloids	*Aristolochia indica* L.	*Aristolochiaceae*
31.	*Bersaldegenin 3-acetate*	Steriods lactones	*Bersama Abyssinica* Fresen.	*Melianthaceae*
32.	*Betulin*	Triterpenes	*Alnus firmifolia* Nutt.	*Betulaceae*
33.	*Bruceantin*	Quassinoids	*Brucea antidysenterica* Mill.	*Simaroubaceae*
34.	*Calotropin*	Steriods lactones	*Asclepiascurassavica* L.	*Asclepiadaceae*
35.	*Camptothecin*	Alkaloids	*Camptotheca acuminata Decne.*	*Nyssaceae*
36	*Celsioside C*	Saponins	*Centaurea melitensis* L.	*Asteraceae*
37.	*Cerberin*	Steriods lactones	*Thevetia peruviana* Pers.	*Apocynaceae*
38.	*Cesalin*	Proteins	*Caesalpinia gilliesii* Wall.	*Fabaceae*
39.	*Colubrinol*	Ansa macrolides	*Colubrina texensis* Torr.&Gray	*Rhamnaceae*
40.	*Coptasine chloride*	Alkaloids	*Chelidonium majus* L.	*Papaveraceae*
41.	*Flavopiridol*	Flavonoid	*Dysoxylum binectariferum* Hook.	*Meliaceae*
42.	*Costunolide*	Sesquiterpenes	*Liriodendron tulipifera* L.	*Magnoliaceae*
43.	*Crinamide*	Alkaloids	*Crinum macrantherium* Engl.	*Amaryllidaceae*
44.	*Cryptopleurine*	Alkaloids	*Boehmeria-cylindrical* L.	*Urticeaceae*
45.	*Cucurbitacin B.*	Cucurbitacins	*Cucurbita digitata* Gray	*Cucurbitaceae*
46.	*Cucurbitacin glycos*	Cucurbitacins	*Datiscaglomerata* Presl.	*Datiscaceae*
47.	*Cycleadrine*	Alkaloids	*Cyclea peicata* L.	*Menispermaceae*
48.	*Cymarin*	Steriods lactones	*Apocynum cannabinum* L.	*Apocynaceae*
49	*Damsin*	Sesquiterpenes	*Ambrosia Ambrosioides* Cav.	*Asteraceae*
50	*Demecolcine*	Alkaloids	*Colchicumspeciosum* Steven	*Liliaceae*
51.	*3-Demethylpodophyllotoxin*	Lignans	*Linum album Kotschy ex* Boiss.	*Linaceae*
52.	*Deoxypodophyllotoxin*	Lignans	*Burserafagaroides*var.	*Burseraceae*
53.	*Digitoxin*	Steriods lactones	*Digitalis purpurea* L.	*Scrophulariaceae*
54.	*Elephantopin*	Sesquiterpenes	*Elephantopuselatus* Bertol.	*Asteraceae*
55.	*Ellipticine*	Alkaloids	*Ochrosia moorei* Muell. Benth.	*Apocyneceae*
56.	*Emodin(aloe-emodin)*	Quinones	*Rhamnus frangula* L.	*Rhamnaceae*
57.	*Erioflorin*	Sesquiterpenes	*Eriophyllumlanatum* (Pursh) Forbes var.	*Asteraceae*
58.	*Eupatofolin*	Sesquiterpenes	*Eupatorium cuneifolium* Willd.	*Asteraceae*
59.	*Eupatoroxin*	Sesquiterpenes	*Eupatorium rotundifolium* L.	*Asteraceae*
60.	*Fagaronine*	Alkaloids	*Fagara zanthoxyloides* Lam.	*Rutaceae*
61.	*Fastiligin B.*	Sesquiterpenes	*Baileyamultiradiata* Harv. & Gray	*Asteraceae*
62.	*Gaillardin*	Sesquiterpenes	*Gaillardia pulchella* Foug.	*Asteraceae*
63.	*Gallic acid*	Polyphenols	*Oenothera caespitosa* Nutt.	*Onagraceae*
64.	*Glaucarubolone*	Quassinoids	*Pierreodendron kerstingii*, Engl.	*Simaroubaceae*
65.	*Gossypol*	Terpenoid	*Gossypium hirsutum* L.	*Malvaceae*
66.	*Harringtonine*	Alkaloids	*Cephalotaxus harringtonia* Koch	*Cephalotaxaceae*
66.	*Helenalin*	Sesquiterpenes	*Helenium autumcale* L.	*Asteraceae*
67.	*Hyrcanoside*	Steriods lactones	*Coronilla varia* L.	*Fabaceae*
68.	*Indicine N-oxide*	Alkaloids	*Heliotropium indicum* L.	*Boraginaceae*
69.	*Isobruceine B.*	Quassinoids	*Brucea antidysenterica* Lam.	*Simaroubaceae*
70.	*Jatropham*	Diterpene	*Jatrophamacrorhiza* Benth.	*Euphorbiaceae*
71.	*Jatrophone*	Diterpenes	*Jacaranda caucana* Pittier	*Bignonieceae*
72.	*Lignin*	Polyphenols	*Elephantopus scaber* Linn.	*Asteraceae*
73.	*Maysine*	Ansa-macrolides	*Maytenus buchananii* Loes.	*Celastraceae*
74.	*Myrsine saponin*	Saponins	*Myrsine africana* L.	*Myrsinaceae*
75	*Nitidine chloride*	Alkaloids	*Fagara chalybea* Engl.	*Rutaceae*

76.	*Normaysine*	Ansa-macrolides	*Maytenus buchananii* Loes.	*Celastraceae*
77.	*Oleandrin*	Steriods lactones	*Nerium oleander* L.	*Apocynaceae*
78.	*Oxyacanthine*	Alkaloids	*Berberis asiatica* Roxb.	*Berberidaceae*
79.	*Parthenolide*	Sesquiterpenes	*Magnolia grandiflora* L.	*Magnoliaceae*
80.	*Paucin*	Sesquiterpenes	*Baileya pauciradiata* Harvey & Gray	*Asteraceae*
81.	*Podolide*	Diterpenes	*Podocarpus gracilior*Pilg.	*Podocarpaceae*
82.	*Podophyllotoxin*	Lignans	*Juniperus chinensia* L.	*Cupressaceae*
83.	*Rhodexin B*	Steriods lactones	*Cryptocarya laevigata* Blume	*Lauraceae*
84.	*Rotenone*	Isoflavones	*Derris trifoliata* Lour.	*Fabaceae*
85.	*β-sitosterol*	Sterols	*Bursera microphylla* Gray	*Eurseraceae*
86.	*β-solamarine*	Alkaloids	*Solanum dulcamara* L.	*Solanaceae*
87.	*Somalin*	Steriods lactones	*Acokanthera longiflora* Stapf.	*Apocyanaceae*
88.	*Steganol*	Lignans	*Steganotaenia araliacea* Hochest.	*Apiaceae*
89.	*Taxodione*	Quinones : Diterpenes	*Taxodium distichum* L.	*Taxodiaceae*
90.	*Thalicarpine*	Alkaloids	*Thalictrum dasycarpum* Fisch.	*Ranuculaceae*
91.	*Tubulosine*	Alkaloids	*Alangium salvifolium* Wang.	*Alangiaceae*
92.	*Urosolic acid*	Flavonoids	*Adinandra dumosa* jack	*Theaceae*
93.	*Withacnistin*	Steriods lactones	*Dunalia arborescens* L.	*Solanaceae*
94.	*Withaferin A*	Steriods lactones	*Physalis virginiana* Mill.	*Solanaceae*
95.	*Tylophorinine*	Alkaloids	*Tylophora crebriflora* Blake	*Asclepiadaceae*
96.	*Strophanthidin*	Steriods lactones	*Parquetina nigrescens* Afzel.	*Asclepiadaceae*
97.	*3' 5, 7-Trihydroxy-3, 4' dimethoxyflavone*	Flavonoids	*Baccharis sarothroides* Gray	*Asteraceae*
98.	*Tulipinolide*	Sterols	*Liriodendron tulipifera* L.	*Magnoliaceae*
99.	*Voacamine*	Alkaloids	*Tabernaemontana arborea* Sap.	*Apocynaceae*
100.	*Epistephanine*	Alkaloids	*Stephania japonica* Miers.	*Menispermaceae*

2. Phenolics and their potential anticancer activities

Recently, attention has been given to the chemopreventive and therapeutic effects of naturally occurring phenolic phytochemicals due to their anticancer potential. Phenolics are compounds possessing one or more aromatic rings with one or more hydroxyl groups. They are broadly distributed in the plant kingdom and are the most abundant secondary metabolites of plants, with more than 8,000 phenolic structures currently known, ranging from simple molecules such as phenolic acids to highly polymerized substances and may inhibit the formation and growth of tumors by induction of cell cycle arrest and apoptosis [25]. Many plant-derived, dietary polyphenols have been studied for their chemopreventive and chemotherapeutic properties against human cancers, including green tea polyphenols, genistein (found in soy), apigenin (celery, parsley), luteolin (broccoli), quercetin (onions), kaempferol (broccoli, grapefruits), curcumin (turmeric) [26]. The more we understand their involved molecular mechanisms and cellular targets, the better we could utilize these "natural gifts" for the prevention and treatment of human cancer. Furthermore, better understanding of their structure-activity relationships will guide synthesis of analog compounds with improved bio-availability, stability, potency and specificity. Phenolic extracts or isolated polyphenols from different plant food have been studied in a number of cancer cell lines representing different evolutionary stages of cancer. For example, berry extracts prepared from blackberry, raspberry, blueberry, cranberry, strawberry and the isolated polyphenols from strawberry including anthocyanins, kaempferol, quercetin, esters of coumaric acid and ellagic acid, were shown to inhibit the growth of human oral (KB, CAL-27), breast (MCF-7), colon (HT-29, HCT-116), and prostate (LNCaP, DU-145) tumor cell lines in a dose-dependent manner with different sensitivity between cell lines [27]. The key component that related to the inhibition of cancer cell growth could be ellagitannins from the *Rubus* family (raspberry, arctic bramble, and cloudberry) and strawberry, whereas the antiproliferative activity of lingonberry was caused predominantly by procyanidins [28]. Similar results have also been reported in several cell system with wine extracts and isolated polyphenols (resveratrol, quercetin, catechin, and epicatechin) [29], tea extract and major green tea polyphenols (epicatechin, epigallocatechin, epicatechin-3-gallate, and epigallocatechin-gallate) [30], although the effective concentrations depend on the system and the tested substances.

It is becoming apparent from tests in cell cultures, animal models, and human trials that certain plant derived phenolic compounds, such as Green tea polyphenols (GTPs),found in the tea plant (*Camellia sinensis*), are able to induce the desirable differential effect of killing cancer cells and promoting normal cell survival [31]. Thus, these compounds have a strong potential for clinical applications. Polyphenols and phenolic extracts from grape wine have been found to exert anticarcinogenic activity by decreasing growth, inducing apoptosis, altering cell cycle kinetics, and interfering with intracellular signal transduction events in cancer cells [32; 33]. The presence of ellagic acid and ellagic acid derivatives in muscadine grapes is unique among *Vitis* varieties, whereas it is a major compound in fruits such as blueberries, blackberries, raspberries, and cranberries [34]. The anticancer properties of free ellagic acid and polyphenolic extracts that contain ellagic acid was demonstrated in several studies [35] and also enhanced the anticancer activity of other polyphenolic compounds [33]. The great diversity of chemical types in this group of compounds are illustrated in table1, which lists the various phenolics with their classes, their plant origin, and their scientific report. Other phenolic extracts or compounds intensely studies are from olives, legumes, citrus, apples, and also curcumin from spice turmeric. For example, soy isoflavone genistein can inhibit the growth of various cancer cell lines including leukemia, lymphoma, prostate, breast, lung, head and neck cancer cells [36].

3. Flavonoids and their potential anticancer activities

Flavonoids constitute one of the most ubiquitous groups of all plant phenolics. So far, over 8,000 varieties of flavonoids

have been identified [37]. Flavonoids occur as aglycones, glycosides and methylated derivatives [38]. In plants, flavonoids aglycones (i.e., flavonoids without attached sugar) occur in a variety of structural forms. All contain fifteen carbon atoms in their basic nucleus: two six-membered rings linked with a three carbon unit which may or may not be parts of a third ring [39]. Flavonoidic derivatives have a wide range of biological actions such as antibacterial, antiviral, anti-inflammatory, anticancer, and anti-allergic activities. Some of these benefits are attributed to the potent antioxidant effects of flavonoids, which include metal chelation and free-radical scavenging activities [40]. Flavopiridol the most active of approximately 100 analogs when assayed against Cdks and showed about 100-fold more selectivity compared to its activity vs tyrosine kinases. It showed roughly comparable activity in the 100–400 n*M* range for IC50 values, depending upon the specific Cdk. It was the first compound at NCI identified as a potential antitumor agent that subsequently was proven to be a relatively specific Cdk inhibitor [41]. The initial report [42] on its Cdk 2 inhibitory activity was made in 1994, followed by data demonstrating antitumor activity in 1995 [43]. Flavopiridol is currently in phase III clinical trials as an inhibitor of cyclin-dependent kinase 2 (Cdk2), both as a single agent and as a modulator in combination with other agents, particularly paclitaxel and cis-platinum. It has been reported to lead to partial and/or complete remissions in a number of phase I patients, leading to phase II studies in patients with paclitaxel-resistant tumors [44]. There have been a number of relatively recent reports of this agent and the various combinations with other drugs and drug candidates, a significant number of which are either natural products or derived from natural products [45]. Flavonoids are reported to inhibit specific enzymes, which include hydrolases, oxidoreductase, DNA synthases, RNA polymerases, lipoxygenase and gluthation s-transferase. They also block several digestive enzymes, including a-amylase, trypsin and lipase [46]. Many studies have shown that flavonoids inhibit PI3- kinase, protein kinase C, protein tyrosine kinase, and some transcriptional factors, and that such inhibition leads to cell growth arrest and tumor cell death [47; 48].As a result, a rising number of authorized physicians are prescribing pure flavonoids to treat many important common diseases. It has been stated that flavonoids, as antioxidants, can inhibit carcinogenesis [49]. Some flavonoids—such as fisetin, apigenin, and luteolin—are stated to be potent inhibitors of cell proliferation. Furthermore, it has been speculated that flavonoids can inhibit angiogenesis [50]. Angiogenesis is normally a strictly controlled process in the human body. The process of angiogenesis is regulated by a variety of endogenous angiogenic and angiostatic factors. It is switched on, for example, during wound healing. Pathologic, unregulated angiogenesis occurs in cancer [51]. Angiogenesis inhibitors can interfere with various steps in angiogenesis, such as the proliferation and migration of endothelial cells and lumen formation. Among the known angiogenesis inhibitors, flavonoids seem to play an important role [52]. However, the mechanism behind the antiangiogenetic effect of flavonoids is unclear. A possible mechanism could be inhibition of protein kinases. These enzymes are implicated to play an important role in signal transduction and are known for their effects on angiogenesis.

Flavonoids found in litchi fruit pericarp (LFP) tissues extract exhibited potential *in vitro* and *in vivo* anticancer activity against hepatocellular carcinoma [53]. Furthermore, the LFP extract demonstrated a dose- and time-dependent inhibitory effect on cancer cell growth [54]. Anticancer activity of LFP extract on both positive and negative breast cancers could be attributed, in part, to its DNA damaging effect, proliferating inhibition and apoptosis induction of cancer cells through up-regulation and down-regulation of multiple genes involved in cell cycle regulation and cell proliferation, apoptosis, signal transduction and transcriptional regulation, motility and invasiveness of cancer cells [53]. The anticancer activity of the flavanols found in LFP tissues is similar to that of the anthocyanins. The anti-breast cancer activities of epicatechin, procyanidin B2, procyanidin B4 and the ethyl acetate fraction from LFP were examined. Procyanidin B4 and ethyl acetate fraction showed a stronger inhibitory effect on HELF than MCF-7 while epicatechin and procyanidin B2 had lower cytotoxicities towards MCF-7 and HELF than paclitaxel. It was suggested that epicatechin and procyanidin B2 can be employed as components of anti-breast cancer drugs [55]. Flavonoids varied significantly in their Antiproliferative potency depending on the structural features. Flavonoids of the flavone, flavonol, flavanone and isoflavone classes possess antiproliferative effects in different cancer cell lines. These natural compounds like flavonoids have several great advantages over other therapeutic agents. The natural, hemi-synthetic and synthetic flavonoids alone or in combination with other preventive and/or therapeutic strategies will become effective future drugs against the most common degenerative diseases such as cancer, diabetes and cardiovascular complications [56].

4. Terpenoids and their potential anticancer activities

Terpenoids also referred to as terpenes, are the largest class of natural products constitute over 30,000 members [57; 58]. The classes of terpene compounds found in plants are monoterpenes, diterpenes, sesquiterpenes, triterpenes, tetraterpenes, and polyterpenes. Terpenoid biosynthesis involves mostly head to tail addition of isopentenyl diphosphate (IPP, the active C5 isoprene unit), to its isomer dimethylallyl diphosphate (DMAPP) synthesizing geranyl diphosphate (GPP, C10) [59]. These compounds are typically found in all parts (i.e. seed, flowers, foliage, roots and wood) of higher plants and also occur in mosses, liverworts, algae and lichens. Some are of insect or microbial origin. A number of dietary monoterpenes have antitumor activity, exhibiting not only the ability to prevent the formation or progression of cancer, but the ability to regress existing malignant tumors. Monoterpenes such as D-limonene and perillyl alcohol (POH) derived from orange peels and lavender, respectively, have been shown to possess chemopreventive properties against mammary, liver and lung carcinogenesis. It was reported, that the colon tumours of animals fed with POH exhibited increased apoptosis compared to those fed with control diet [60]. The cytotoxicity of diterpene taxol from *Taxus brevifolia* Nutt. (Taxaceae) represents both inhibition of cell proliferation and cell death. Over 100 different taxanes have been characterized from various *Taxus* species. The drug block cells in the G2/M phase of the cell cycle and induced apoptosis [61]. In lower concentration range, taxol stabilized the spindle during mitosis and this mitotic block led to the inhibition of cell proliferation and induction of apoptosis. In higher concentration range, taxol mainly increased the polymerization of microtubule and stimulated the formation of microtubule bundles which blocked entry into S phase and this led to the inhibition of cell proliferation and induction of necrosis [62]. Cell death induced by paclitaxel, on the other hand, occurs via a signalling pathway independent of

microtubules and G2/M arrest [63]. Paclitaxel is currently used to treat ovarian, lung, and breast cancers, head and neck carcinoma, and melanoma. It has been hailed as the perhaps most important addition to the chemotherapeutic armamentarium against cancer over the past several decades [64]. Limonene is a well-established chemopreventive and therapeutic agent against many tumor cells [65]. Carvone, a major monoterpene in caraway seed oil, has been shown to prevent chemically induced lung and forestomach carcinoma development [66]. In addition, carveol has chemopreventive activity against rat mammary cancer during the initiation phase [67]. The mechanism of action of monoterpenes against tumor cells is the induction of apoptosis and interference of the protein prenylation of key regulatory proteins [68]. Among other halogenated acyclic monoterpenes, halomin, isolated from the red alga *Portieria hornemnnii* [69], is very effective against renal, brain, colon, and non-small cell lung cancer cell lines through a unique mode of action [70]. Illudins are a family of natural toxic sesquiterpene compounds with anti-tumoractivity, isolated from the basidiomycete *Omphalotus illudens* (*O. olearius* and *Clitocybe illudens*). These compounds are believed to be responsible for the poisoningthat occurs when *Omphalutus* is mistaken for an edible mushroom [71]. Illudins S andM are extremely cytotoxic and exhibit antitumor activity [72]. Illudins are effectiveagainst various types of tumor cells at picomolar to nanomolar concentrations. Avariety of multidrug-resistant tumor cell lines remain sensitive to the illudins [73]. Irofulven (hydroxymethylacylfulvene), a derivative of illudin S, has been extensivelyinvestigated and is currently in phase II clinical trials. In particular, irofulven exhibits. efficacy against pancreatic carcinoma, a malignancy that is resistant to all other forms of chemotherapy. Irofulven rapidly enters cancer cells, where it binds to cellular macromoleculesand inhibits DNA synthesis [74]. The most unique aspect ofirofulven's anticancer activity seems to be its ability to act as a selective inducer of apoptosis in human cancer cell lines, and, in contrast to conventional antitumor agents, this activity of irofulven is effective against tumor cell lines regardless of their p53 orp21 expression [75]. In addition, the DNA lesion induced by illudins and irofulvenis largely ignored by global repair pathways. Therefore, the irofulven and other illudinsare considered a new and promising class of tumor-therapeutic agents [76]. Terpenoid-derived drugs have contributed significantly to human disease therapy and prevention. Some terpenoid drugs have provided tremendous benefits for patients and for the pharmaceutical industry. Artemisinin and its derivatives comprise a multimillion-dollar market worldwide. Taxol alone is estimated to have annual sales of over$1.8 billion. Terpenoids indisputably continue to be important compounds for drug discovery.

5. Tannins and their potential anticancer activities

Tannins, phenolic phytochemicals, which are natural constituents of green tea, are considered to have cancer preventive properties [77; 78]. Condensed tannins, isolated from black beans, did not affect the growth of normal cells, but induced cell death in cancer cells in a dose-dependent manner. This cell death was associated with a concentration-dependent decrease of ATP and a deterioration of cellular gross morphology [79]. Tannins are types of plant polyphenols widely distributed in the plant kingdom that have been recently found to possess remarkable antitumor-promoting effects in various animal models and tumor systems [80]. Some tannin-related compounds, e.g. tellimagrandin II, remurin B, nobotanin A, nobotanin F, rugosin D, oenothein A, woodfordin D, nobotanin C, woodfordin F and nobotanin K from different plant sources induced cytotoxicity and inter-nucleosomal DNA cleavage in HL-60 cells. Their activity increased with polymerization when their concentration was expressed on a molar basis [81]. Classically, tannins are divided into two chemically and biologically distinct groups: the condensed tannins (CTs) also referred to as proanthocyanidins, and the hydrolyzable tannins (HTs**)** [82]. There is interest in proanthocyanidins because of their potential health benefits. Recent interest in these food polyphenols has emerged because of their antioxidant, free radical-scavenging, and metal-chelating activities, which may lead to their possible role in the treatment and prevention of cancer and other pathologies [83]. Several hydrolyzable tannins (HTs**)** and condensed tannins (CTs) have been found to block the activities of many mutagens and to have anticarcinogenic effects. When applied topically, injected, or added to the diet or drinking water, tannins were found to inhibit tumor initiation and carcinogenesis in the skin and the mammary gland [84]. The protective effects of tannins against many types of cancers lead us to postulate that these polyphenols are universal antitumor agents [85].

6. Phytosterols and their potential anticancer activities

Phytosterols are specific phytochemicals that resemble cholesterol in structure but are found exclusively in plants. Phytosterols have been studied both for their cholesterol lowering effects and their anticancer properties [86]. The most common phytosterols in the human diet are b-sitosterol, campesterol, and stigmasterol. Phytosterols are derivatives of the parent molecule 4-desmethyl sterol [87]. Phytosterols exist within plants in both esterified and free alcohol forms, more than 200 phytosterols exist naturally in the plant kingdom and many are found in edible foodstuffs [88]. Phytosterols in the diet are associated with a reduction in common cancers including cancers of the colon, breast, and prostate [89]. It was also showed that a 2% b-sitosterol mixture (95% b-sitosterol, 4% campesterol, and 1% stigmasterol) in the diet reduced to one-third the incidence of observable colon tumors induced by intracolonic administration of N-methyl-N-nitrosourea (MNU). Reduction in both the size of the proliferative compartment as well as the colonocyte labeling index within crypt columns in MNU-treated rats that were maintained on a diet containing 0.2% b-sitosterol [90]. Similarly in mice fed diets supplemented with phytosterols (0.3–2%), there was observed a dose-dependent reduction in cholic acid-induced colonic cell proliferation [91]. In similar experiments, using ovariectomized athymic mice that were injected with the MCF-7 estrogen receptor positive human breast cancer cells, a 32–42% reduction in tumor size was observed in mice fed diets enriched in b-sitosterol [92]. Potential protective effect of phytosterols against proliferation and metastasis of PC-3 human prostate cancer cells in male SCID mice was examined [93]. At the end of the 8 wk feeding period, there was a 40–43% reduction in tumor size in animals fed the phytosterol diet versus the cholesterol diet and a 50% reduction in the rate of tumor metastasis to the lung, liver, and lymph nodes compared to those fed the cholesterol diet [86]. Phytosterols also affect cell cycle kinetics. In tissue culture studies of MDA-MB-231 human breast carcinoma cells, b-sitosterol induced cell cycle arrest at the G2/M transition [94]. Significant induction of cellular apoptosis following b-sitosterol supplementation has been observed in MDA-MB-231 hormone-insensitive human breast adeno-carcinoma cells,

in metastatic LNCaP hormone- sensitive human prostate adenocarcinoma cells, in HT-29 human colon adenocarcinoma, and in PC-3 hormone-insensitive human prostate adenocarcinima cells [95]. Other phytosterols including diosgenin and solamargine are potent inducers of apoptosis in human erythroleukemia HEL and K562 cell lines and human hepatocytic Hep3B cells [96].

7. Lignans and their potential anticancer activities

Lignans are a large group of phenolic compounds defined as dimers of phenylpropane (C6C3) units. This widely spread group of natural products possess a long and remarkable history of medicinal use in the ancient cultures of many people's [97]. The first unifying definition of lignans was made by R. D. Howarth in 1936, who described them as a group of plant phenols with a structure, determined by the union oftwocinnamic acid residues or their biogenetic equivalents [98]. According to IUPAC nomenclature, lignans are 8, 8'-coupled dimmers of coniferyl alcohol or other cinnamyl alcohols. Lignans have a long history of medicinal use as the first records date back over 1000 years. Lignans may protect against certain cancers, particularly hormone-sensitive cancers such as those of the breast, endometrium and prostate, by interfering with sex hormone metabolism. Lignans have been shown to stimulate hepatic synthesis of sex hormone binding globulin (SHBG), thus enhancing the clearance of circulating estrogen [99] and to bind to estrogen receptors on SHBG in a dose-dependent manner, thereby inhibiting estrogen and testosterone binding [100]. Among the lignin-related compounds, natural lignified materials isolated from *Pinus parviflora* Sieb. Induced DNA fragmentation whereas alkali lignin and lignin-sulphonate were inactive. A variety of tannins and lignin-related compounds induce DNA fragmentation in different human myelogenous leukaemia cell lines and HL-60 cells [100; 101].

8. Saponins and their potential anticancer activities

Saponins are glycosides with a distinctive foaming characteristic. They are found in many plants, but get their name from the soapwort plant (*Saponaria*), the root of which was used historically as soap (Latin *sapo* → soap). According to the structure of the aglycone or sapogenin, two kinds of saponins are recognised – the steroidal and the pentacyclic triterpenoid types. They consist of a polycyclic aglycone that is either a choline steroid or triterpenoid attached through C3 and an ether bond to a sugar side chain. Saponins exhibited many different biological and pharmacological actions such as immunomodulatory, antitumor, antiinflammatory, molluscicidal, antiviral, antifungal, hypoglycemic, hypocholesterolemic [102]. Saponins have a diverse range of properties, which include sweetness, bitterness foaming, emulsifying and haemolytic properties. Saponins have wide applications in beverages and confectionery, as well as in cosmetics and pharmaceutical products. They are believed to form the main constituents of many plant drugs and folk medicines, and are considered responsible for numerous pharmacological properties [103]. Notably, saponins can activate the mammalian immune system, which has led to significant interest in their potential as vaccine adjuvants [104]. Five saponins (diosgenin, hecogenin, tigogenin, sarsasapogenin, smilagenin) have been tested for their biological activities on human 1547 osteosarcoma cells. All examined saponins have shown a significant role on tested cell line in term of proliferation rate, cell cycle distribution and apoptosis induction [105]. Many saponins have shown cytotoxic and antitumor activity. Recent research showed that PD (Polyphyllin- D) is a diosgenyl saponin originally found in PPY (*Paris polyphylla)* is a potent apoptosis inducer through mitochondrial dysfunction in drug-resistant HepG2 cells [106] and has inhibitory effects on the growth of human breast cancer cells and in xenograft [107]. The proteomic and transcriptomic analyses revealed that PD induced the cytotoxic effect through a mechanism initiated by ER stress followed by mitochondrial apoptotic pathway [108]. However, the antimetastasis activity has not been discussed. Although the potential of soybean saponins as anticarcinogens has been studied in recent years, animal studies are rather limited and most of the evidence comes from cell culture studies [109]. Anticancer activities of saponin containing plants such as ginseng and licorice are also being investigated [110; 111]. While the cancer preventive effects of ginseng have been demonstrated in experimental models and in epidemiological studies, the evidence on its effect on humans is not conclusive [111].

9. Quassinoids and their potential anticancer activities

Quassinoids possess a wide spectrum of biological activities, some of which have been well researched and documented. According to their basic skeleton, quassinoids are categorized into five distinct groups, C-18, C-19, C-20, C-22 and C-25 types [112]. Many of these quassinoids display a wide range of biological activities *in vitro* and/or *in vivo,* including antitumor, antimalarial, antiviral, anti-inflammatory, antifeedant, insecticidal, amoebicidal, antiulcer and herbicidal activities [113]. At the present, quassinoids are found solely in various species of the *Simaroubaceae* family, such as *Brucea antidysenterica*, *Brucea javanica*, *Simaba amara*, *Picrasma ailanthoides*, *Pierreodendron kerstingii*, and *Ailantluts grandis*. All of these species belong to the *Simarouboidaea* subfamily of *Simaroubaceae*, and some, in particular, have been used clinically for centuries. Originally, the collective bitter substances contained in such plants were termed quassin, after a man by the name of Quassi, who treated fever with the bark of these plants [113]. The research and application of quassinoids continued to extend through the 1990's with the isolation and structure elucidation of many new compounds. Today, over 150 quassinoids have been isolated and fully characterized, and dozens of them have been found that do not fall into any of the basic quassinoid skeletal configurations the antitumor activity is one of the most impressive medicinal properties of quassinoids and has been well researched [114]. Many quassinoids display antitumor activity in different potencies. Bruceantin, bruceantinol, glaucarubinone and simalikalacton D are among the most potent. The mechanism of the action is believed to be that quassinoids can inhibit the protein synthesis by inhibition of the ribosomal peptidyl transferase activity leading to the termination of the chain elongation [115]. Bruceantin, a quassinoid isolated from *Brucea antidysenteria* (Simaroubaceae), is a potent anticancer compound that decreased the growth of LLC cells. Its primary mechanism of action is the inhibition of protein synthesis [116].

Conclusion

Natural products discovered from medicinal plants have played an important role in the treatment of cancer. From the approximately 250000–300000 plants all over the world, only a small portion has been systematically investigated for the presence of bioactive phytochemicals. So, it is anticipated that plants can provide potential bioactive compounds for the

development of new 'leads' to combat cancer diseases. In this literature review, all the natural products experimentally studied showed some kind of pharmacological activity which could explain their capacity to act against cancer development. Also in this review, the data on 100 ethnomedical plants have been listed which are enumerated in table-I. These plants are still used traditionally as herbal drugs against various tumors such as sarcoma, lymphoma, carcinoma, and leukemia. Although these studies tend to support the use of these plant products on an experimental basis carried out *in vitro* and *in vivo*, in animals, in humans and in human cancer cell lines, their use will require clinical evaluation. In this literature review, all the natural products experimentally studied showed some kind of pharmacological activity which could explain their capacity to act against cancer development. The introduction of active agents derived from nature into the cancer armamentarium has changed the natural history of many types of human cancer. Experimental agents derived from natural products are offering us a great opportunity to evaluate not only totally new chemical classes of anticancer agents, but also novel and potentially relevant mechanisms of action. To conclude, it must be accepted that medicinal herbs have rich anticancer potential. They have shown anticancer activity in animal models of leukemia, skin cancer and sarcomas. Selected plants has been explored for biological activity and further investigations into anticancer activity of the plants, must be undertaken. The introduction of active agents derived from nature into the cancer armamentarium has changed the natural history of many types of human cancer. Experimental agents derived from natural products are offering us a great opportunity to evaluate not only totally new chemical classes of anticancer agents, but also novel and potentially relevant mechanisms of action.

References

1. World Health Organization. World Health Report. Geneva, Switzerland, 2010.
2. Capua CJ, Hopson NP, Stewart CMM, Johnston GR, Neill KLO, Schaalje GB, Lee CM,Booth GM. Cytotoxicity of Atriplex confertifolia. Journal of Toxicology. 2010; 1155:1-7.
3. George S, Bhalerao SV, Lidstone EA, Ahmad IS, Abbasi A, Cunningham BT, Watkin KL. Cytotoxicity screening of Bangladeshi medicinal plant extracts on pancreatic cancer cells. BMC Complementary and Alternative Medicine. 2010; 10:1472-6882.
4. Patel B, Das S, Prakash R, Yasir M. Natural bioactive compound with anticancer potential. International Journal of Advances in Pharmaceutical Sciences. 2010; 1:32-41.
5. Balandrin NF, Kinghorn AD, Farnsworth NR. Human Medicinal Agents from Plants. American Chemical Society (ACS) Symposium Series. 1993; 534: 2-12.
6. Farnsworth NR, Akerele O, Bingel AS, Soejarto DD, Guo Z. Medicinal plants in therapy. Bulletin of the World Health Organization.1985; 63:965-81.
7. Kim J. and Park, EJ. Cytotoxic anticancer candidates from natural resources. Current Medicinal Chemistry - Anti-Cancer Agents. 2002; 2:485-537.
8. Cragg GM, Newman DJ. Antineoplastic agents from natural sources: achievements and future directions. Expert Opinion on Investigational Drugs. 2000; 9:2783-97.
9. Block G, Patterson B, Subar A. Fruit, vegetables and cancer prevention: a review of the epidemiological evidence. Nutrition and Cancer. 1992; 18:1-29.
10. Santos-Buelga C, Scalbert A. Proanthocyandins and tannin-like compounds-nature, occurrence, dietary intake and effects on nutrition and health. Journal of the Science of Food and Agriculture. 2000; 80:1094-117.
11. Yang CS, Landau JM, Huang MT, Newmark HL. Inhibition of carcinogenesis by dietary polyphenolic compounds. Annual Review of Nutrition. 2001; 21:381-406.
12. Galati G, O-Brien PJ. Potential toxicity of flavonoids and other dietary phenolics: significance for their chemopreventive and anticancer properties. Free Radical Biology & Medicine. 2004; 37:287-303.
13. Satyajit DS, Zahid L, Alexander IG. Natural products isolation. Journal of Pharmacy and Pharmacology. 2006; 49: 1045-1049.
14. Hertog MG, Hollman PC, Katan MB, Kromhout D. Intake of potentially anticarcinogenic flavonoids and their determinants in adults in the Netherlands. Nutrition and Cancer. 1993; 20:21-9.
15. Julsing MK, Koulman A, Woerdenbag HJ, Quax WJ, Kayser O. Combinatorial biosynthesis of medicinal plant secondary metabolites. Biomolecular Engineering. 2006; 23:265-279.
16. Warzecha H, Gerasimenko I, Kutchan TM, Stockigt J. Molecular cloning and functional bacterial expression of a plant glucosidase specifically involved in alkaloid biosynthesis. Phytochemistry. 2000; 54:657-666.
17. Sanchez C, Zhu L, Brana AF, Salas AP, Rohr J, Mendez C,Salas JA. Combinatorial biosynthesis of antitumor indolocarbazole compounds. Proceedings of the National Academy of Sciences. 2005; 102:461-466.
18. Kupchan SM, Yokoyama N, Thyagarajan BS. Menispermaceae alkaloids. II. The alkaloids of Cyclea peltata Diels. Journal of Pharmaceutical Sciences. 1961; 50:164-167.
19. Tomita M, Furukawa H, Lu ST, Kupchan SM. The constitution of thalicarpine. Tetrahedron Letters. 1965; 6: 4309-4316.
20. Siddiqui S, Firat D, Olshin S. Phase II study of emetine (NSC 33669) in the treatment of solid tumors. Cancer Chemotherapy Reports. 1973; 57:423-428.
21. Wall ME, Wani MC, Cook CE, Palmer KH, McPhail AT, Sim GA. Plant antitumor agents. I. The isolation and structure of camptothecin, a novel alkaloidal leukemia and tumor inhibitor from Camptotheca acuminata. Journal of the American Chemical Society. 1966; 88:3888-3890.
22. Wani MC, Wall ME. Plant antitumor agents. II. The structure of two new alkaloids from Camptotheca acuminata. Organic chemistry. 1969; 34:1364-1367.
23. Svoboda GH, Poore GA, Montfort ML. Alkaloids of Ochrosia maculata Jacq. (Ochrosia borbonica Grnel. Journal of Pharmaceutical Sciences. 1968; 57:1720-1725.
24. Liu WK, Wang XK, Che CT. Cytotoxic effects of sinococculine. Cancer Letters. 1996; 99:217–224.
25. Dai J, Mumper RJ. Plant phenolics: extraction, analysis and their antioxidant and anticancer properties. Molecules. 2010; 15:7313-7352.
26. Chen D,Dou Q. Tea polyphenols and their roles in cancer prevention and chemotherapy. International Journal of Molecular Sciences. 2008; 9:1196-1206.
27. Seeram NP, Adams LS, Zhang Y, Lee R, Sand D, Scheuller HS, Heber D. Blackberry, black raspberry, blueberry, cranberry, red raspberry, and strawberry extracts inhibit growth and stimulate apoptosis of human

cancer cells in vitro. Journal of Agricultural and Food Chemistry. 2006; 54:9329-9339.
28. McDougall GJ, Ross HA, Ikeji M, Stewart D. Berry Extracts Exert Different antiproliferative effects against cervical and colon cancer cells grown in vitro. Journal of Agricultural and Food Chemistry. 2008; 56:3016-3023.
29. Damianaki A, Bakogeorgou E, Kampa M, Notas G, Hatzoglou A, Panagiotou S, Gemetzi C, Kouroumalis E, Martin PM, Castanas E. Potent inhibitory action of red wine polyphenols on human breast cancer cells. Journal of Cellular Biochemistry. 2000; 78:429-441.
30. Weisburg JH, Weissman DB, Sedaghat T, Babich H. In vitro cytotoxicity of epigallocatechin gallate and tea extracts to cancerous and normal cells from the human oral cavity. Basic & Clinical Pharmacology & Toxicology. 2004; 95:191-200.
31. Hsu S, Yu FS, Lewis J, Singh B, Borke J, Osaki T, Athar M, Schuster G. Induction of p57 is required for cell survival when exposed to green tea polyphenols. Anticancer Research. 2002; 22:4115–4120.
32. Hou DX. Potential mechanisms of cancer chemoprevention by anthocyanins. Current Molecular Medicine. 2003; 3(2):149-159.
33. Susanne U, Salcott M, Lee JH, Percival SS, Talcott STInduction of Cell Death in Caco-2 Human Colon Carcinoma Cells by Ellagic Acid Rich Fractions from Muscadine Grapes (Vitis rotundifolia). Journal of Agricultural and Food Chemistry. 2006; 54:5336-5343.
34. Talcott ST, Lee JH. Ellagic acid and flavonoid antioxidant content of muscadine wine and juice. Journal of Agricultural and Food Chemistry. 2002; 50:3186-3192.
35. Losso JN, Bansode RR, Trappey A, Bawadi HA, TruaxR. In vitro anti-proliferative activities of ellagic acid. Journal of Nutritional Biochemistry. 2004; 15:672-678.
36. Sarkar FH, Li Y. Mechanisms of cancer chemoprevention by soy isoflavone genistein. Cancer and Metastasis Reviews. 2002; 21:265-280.
37. Groot DH, Raven U. Tissue injury by reactive oxygen species and the Protective effects of flavonoids. Fundamental & Clinical Pharmacology. 1998; 12:249-255.
38. Harbome JB, Grayer RJ. "The Flavonoids - Advances in Research since 1980". (Harbome. J.B.Ed) Chapman and Hall, Lonon. 1988, 1.
39. Middleton E. The flavonoids. Trends in Pharmacological Sciences. 1984; 5:335-338.
40. Amin A, Buratovich M. The Anti-cancer Charm of Flavonoids: A cup-of-tea will do. Recent Patents on Anti-Cancer Drug Discovery. 2007; 2:109-117.
41. Sielecki T, Boylan JF, Benfield PA, Trainor GL. Cyclin-dependent kinase inhibitors: useful targets in cell cycle regulation. Journal of Medicinal Chemistry. 2000; 43:1-18.
42. Losiewicz MD, Carlson BA, Kaur G, Sausville EA, Worland PJ. Potent inhibition of cdc2 kinase activity by the flavanoid, Biochemical and Biophysical Research Communications. 1994; 201:589-595.
43. Czech J, Hoffman D, Naik R, Sedlacek H. Anti-tumoral activity of flavones. International Journal of Oncology. 1995; 6:31-36.
44. Kaubisch A, Schwartz GK. Cyclin-dependent kinase and protein kinase C inhibitors: a novel class of antineoplastic agents in clinical development. Cancer Journal. 2000; 6:192–212.
45. Senderowicz AM. Small-molecule cyclin-dependent kinase modulators. Oncogene. 2003; 22:6609-6620.
46. Sadik CD, Sies H, Schewe T. Inhibition of 15-lipoxygenases by flavonoids: structure-activity relations and mode of action. Biochemical Pharmacology. 2003; 65:773-81.
47. Gamet-Payrastre L, Manenti S, Gratacap MP, Tulliez J, Chap H, Payrastre B. Flavonoids and the inhibition of PKC and PI3-kinase. General Pharmacology. 1999; 32:279-286.
48. Miranda CL, Stevens JF, Helmrich A, Henderson MC, Rodriguez RJ, Yang YH. Antiproliferative and cytotoxic effects of prenylated flavonoids from hops (Humulus lupulus) in human cancer cell lines. Food Chemical Toxicology. 1999; 37:271-285.
49. Stefani ED, Boffetta P, Deneo-Pellegrini H. Dietary antioxidants and lung cancer risk: a case-control study in Uruguay. Nutrition and Cancer. 1999; 34:100-10.
50. Fotsis T, Pepper MS, Aktas E. Flavonoids, dietary-derived inhibitors of cell proliferation and in vitro angiogenesis. Cancer Research. 1997; 57:2916-21.
51. Fan TP, Jaggar R, Bicknell R. Controlling the vasculature: angiogenesis, anti-angiogenesis and vascular targeting of gene therapy. Trends in Pharmacological Sciences. 1995; 16:57-66.
52. Paper DH. Natural products as angiogenesis inhibitors. Planta Medica. 1998; 64:686-95.
53. Wang X, Yuan S, Wang J, Lin P, Liu G, Lu Y, Zhang J, Wang W, Wei Y. Anticancer activity of litchi fruit pericarp extract against human breast cancer in vitro and in vivo. Toxicology and Applied Pharmacology. 2006; 215:168-178.
54. Zhao M, Yang B, Wang J, Liu Y, Yu L, Jiang YM. Immunomodulatory and anticancer activities of flavonoids extracted from litchi Litchi chinensis Sonn. pericarp. International Immunopharmacology. 2007; 7:162-166.
55. Li J, Jiang Y. Litchi Flavonoids: Isolation, Identification and Biological Activity. Molecules. 2007; 12:745-758.
56. Tapas AR, Sakarkar DM, Kakde RB. Flavonoids as Nutraceuticals: A Review. Tropical Journal of Pharmaceutical Research. 2008; 7(3):1089-1099.
57. Sacchettini JC, Poulter CD. Creating isoprenoid diversity. Science. 1997; 277:1788-1789.
58. Dewick PM. The biosynthesis of C5-C25 terpenoid compounds. Natural Product Reports. 2002; 19:181-222.
59. Mann J, Davidson RS, Hobbs JB, Banthorpe DV, Harnorne JB. Natural products: their chemistry and biological significance. Longman Scientific & Technical, Esse. 1994; 289.
60. Reddy BS, Wang CX, Samaha H, Lubet R, Steele VE, Kelloff GJ, Rao, CV. Chemoprevention of colon carcinogenesis by dietary perillyl alcohol. Cancer Research. 1997; 57:420-425.
61. Gibb RK, Taylor DD, Wan T, O-Connor DM, Doering DL, Gercel-Taylor C. Apoptosis as a measure of chemosensitivity to cisplatin and taxol therapy in ovarian cancer cell lines. Gynecologic Oncology. 1997; 65:13-22.
62. Yeung TK, Germond C, Chen X, Wang Z. The Mode of Action of Taxol: Apoptosis at Low Concentration and Necrosis at High Concentration. Biochemical and Biophysical Research Communications. 1999; 263:398-404.
63. Fan W. Possible mechanisms of paclitaxel-induced

apoptosis. Biochemical Pharmacology. 1999; 57:1215-1221.
64. Rowinsky EK. The development and clinical utility of the taxane class of antimicrotubule chemotherapy agents. Annual Review of Medicine. 1997; 48:353-374.
65. Kris-Etherton PM, Hecker KD, BonanomeA. Bioactive compounds in foods: their role in the prevention of cardiovascular disease and cancer. American Journal of the Medical Sciences. 2002; 113:71-88.
66. Wattenberg LW, SparninsV L, Barany G. Inhibition of N nitrosodiethylamine carcinogenesis in mice by naturally occurring organosulfur compounds and monoterpenes. Cancer Research. 1989; 49:2689-2692.
67. Crowell PL, Kennan WS, Vedejs E, Gould MN. Chemoprevention of mammary carcinogenesis by hydroxylated metabolites of limonene. Procedings of American Association for Cancer Research Annual Meet, 1990.
68. Crowell PL. Prevention and therapy of cancer by dietary monoterpenes. Journal of Nutrition. 1999; 129:775-778.
69. Fuller RW, Cardellina JH, Jurek J. Isolation and structure activity features of halomonrelated antitumor monoterpenes from the red alga Portieria hornemannii. Journal of Medicinal Chemistry. 1994; 37:4407-4411.
70. Egorin MJ, Rosen DM, Benjamin SE, Callery PS, Sentz DL, Eiseman JL. In vitro metabolism by mouse and human liver preparations of halomon, an antitumor halogenated monoterpene. Cancer Chemotherapy and Pharmacology. 1997; 41:9-14.
71. McMorris TC, Yu J, Lira R. Structure-activity studies of antitumor agent irofulven (hydroxymethylacylfulvene) and analogues. Journal of Organic Chemistry. 2001; 66:6158-6163.
72. McMorris TC, Kashinatham A, Lira R. Sesquiterpenes from Omphalotus illudens. Phytochemistry. 2002; 61:395-398.
73. Kelner MJ, McMorris TC, Montoya MA. Characterization of cellular accumulation and toxicity of illudin S. in sensitive and nonsensitive tumor cells. Cancer Chemotherapy and Pharmacology. 1997; 40:65-71.
74. Herzog MCS, Arnett B, MacDonald JR, Woynarowski JM. Drug uptake and cellular targets of hydroxymethylacylfulvene (HMAF). Biochemical Pharmacology. 1999; 58:217-225.
75. Woynarowska BA, Woynarowski JM, Herzig MCS, Roberts K, Higdon AL, MacDonald JR. Differential cytotoxicity and induction of apoptosis in tumor and normal cells by hydroxymethylacylfulvene (HMAF). Biochemical Pharmacology. 2000; 59:1217-1226.
76. Jaspers NGJ, Raams A, Kelner MJ. Anti-tumour compounds illudin S and Irofulven induce DNA lesions ignored by global repair and exclusively processed by transcription- and replication-coupled repair pathways. DNA Repair. 2002; 1:1027-1038.
77. Lambert JD, Yang CS. Cancer chemopreventive activity and bioavailability of tea and tea polyphenols. Mutation Research. 2003; 523&524:201-208.
78. Keil C, Petermann E, Oei SL. Tannins elevate the level of poly (ADP-ribose) in HeLa cell extracts. Archives of Biochemistry and Biophysics. 2004; 425:115-121.
79. Bawadi HA, Bansode RR, Trappey A, Truax RE, Losso JN. Inhibition of Caco-2 colon, MCF-7 and Hs578T breast and DU 145 prostatic cancer cell proliferation by water-soluble black bean condensed tannins. Cancer Letters. 2005; 218:153-162.
80. Mukhtar H, Das M, Khan W, Wang Z, Bik D. Exceptional activity of tannic acid among naturally occurring plant phenols in protecting against 7:12-dimethylbenz[a] anthracene, benzo[a]pyrene, 3-methylcholanthrene- and N-methyl-N-nitrosourea-induced skin tumorigenesis in mice. Cancer Research. 1988; 48:2361-2365.
81. Sakagami H, Sakagami T, Yoshida H, Omata T, Shiota F, Takahashi H, Kawazoe Y, Takeda M. Hypochlorite scavenging activity of polyphenols. Anticancer Research. 1995; 15:917-922.
82. Gali MH, Perchellet J, Khatib S. Inhibitory effects of plant tannins on ultraviolet light-induced epidermal DNA synthesis in hairless mice. Journal of Photochemistry and Photobiology. 1998; 67:663-668.
83. Gali MH, Perchellet E, Klish D, Johnson J, Perchellet J. Antitumor-promoting activities of hydrolyzable tannins in mouse skin. Carcinogenesis. 1992; 13:715-718.
84. Das M, Bickers D, Mukhtar H. Protection against chemically induced skin tumorigenesis in SENCAR mice by tannic acid. International Journal of Cancer. 1989; 43:468-470.
85. Gali MH, Yamut S, Sidani M. Plant tannins as inhibitors of hydroperoxide production and tumor promotion induced by ultraviolet B radiation in mouse skin in vivo. Oncology Reports. 1999; 6:847-853.
86. Bradford PG, Awad AB. Phytosterols as anticancer compounds. Molecular Nutrition & Food Research. 2007; 51:161-170.
87. Darnet S, Rahier A. Plant sterol biosynthesis: identification of two distinct families of sterol 4a-methyl oxidases. Biochemical Journal. 2004; 378:889-898.
88. Piironen V, Lindsay DG, Miettinen TA, Toivo J, Lampi AM. Plant sterols: biosynthesis, biological function and their importance to human nutrition.Journal of the Science of Food and Agriculture. 2000; 80:939-966.
89. Raicht RF, Cohen BI, Fazzini E, Sarwal A, Takehashi M. Protective effect of plant sterols against chemically induced colon tumors in rats, Cancer Research. 1980; 40:403-405.
90. Deschner EE, Cohen BI, Raicht RF. The kinetics of the protective effect of b-sitosterol against MNU-induced colon neoplasia. Journal of Cancer Research and Clinical Oncology. 1982; 103:49-54.
91. Janezic SA, Rao AV. Dose-dependent effects of dietary phytosterols on epithelial cell proliferation of the murine colon. Food and Chemical Toxicology. 1992; 30:611-616.
92. Ju YH, Clausen LM, Allred KF, Almada AL, Helferich WG. Beta-sitosterol, beta-sitosterol glucoside and a mixture of beta-sitosterol and beta-sitosterol glucoside modulate the growth of estrogen-responsive breast cancer cells in vitro and in ovariectomized athymic mice, Journal of Nutrition. 2004; 134:1145-1151.
93. Awad AB, Fink CS, Williams H, Kim U. In vitro and in vivo (SCID mice) effect of phytosterols on the growth and dissemination of human prostate cancer PC-3 cells. European Journal of Cancer Preview. 2001; 10:507-513.
94. Awad AB, Williams H, Fink CS. Phytosterols reduce in vitro metastatic ability of MDA-MB-231 human breast cancer cells. Nutrition and Cancer. 2001; 40:157-164.
95. Awad AB, Chinnam M, Fink CS, Bradford PG. Targeting ceramide by dietary means to stimulate apoptosis in tumor cells. Current Topics in Nutraceutical Research.

2004; 2:93-100.
96. Liagre B, Bertrand J, Leger DY, Beneytout JL. Diosgenin, a plant steroid, induces apoptosis in COX-2 deficient K562 cells with activation of the p38 MAP kinase signaling and inhibition of NF-kappaB binding. International Journal of Molecular Medicine. 2005; 16:1095-1101.
97. Ionkova I. Biotechnological Approaches for the Production of Lignans. Pharmacognosy Reviews. 2007; 1:57-68.
98. Howarth RD. Natural resins. Annual Reports on the Progress of Chemistry. 1936; 33:266-279.
99. Hargraves DF, Potten CS, Harding C. Two-week dietary soy supplementation has an estrogenic effect on normal premenopausal breast. Journal of Clinical Endocrinology and Metabolism. 1999; 84:4017-4024.
100. Hilakivi-Clarke L, Onojafe I, Raygada M. Prepubertal exposure to zearalenone or genistein reduces mammary tumorigenesis. British Journal of Cancer. 1999; 80:1682-1688.
101. Taraphdar AK, Roy M, Bhattacharya RK. Natural products as inducers of apoptosis: Implication for cancer therapy and prevention. Current Science. 2001; 80:1387-1396.
102. Sparg SG, Light ME, Staden VJ. Biological activities and distribution of plant saponins. Journal of Ethnopharmacology. 2004; 94:219-243.
103. Liu J, Henkel T. Traditional Chinese medicine (TCM) are polyphenols and saponins the key ingredients triggering biological activities. Current Medicinal Chemistry. 2002; 9:1483-5.
104. Sun HX, Xie Y, Ye YP. Advances in saponin-based adjuvants. Vaccine. 2009; 27:1787-1796.
105. Swami S, Raghavachari N, Muller UR, Bao YP, Feldma D. Vitamin D growth inhibition of breast cancer cells: gene expression patterns assessed by cDNA microarray. Breast Cancer Research Treands. 2003; 80:49-62.
106. Cheung JY, Ong RC, Suen YK, Ooi V, Wong HN, Mak TC, *et al*. Polyphyllin D is a potent apoptosis inducer in drug-resistant HepG2 cells. Cancer Letters. 2005; 217:203-211.
107. Lee KH, Xiao Z. Podophyllotoxins and analogs. In: Cragg, GM, Kingston DGI, Newman DJ. (Eds.), Anticancer Agents from Natural Products. Brunner-Routledge Psychology. 2005; 5:71-88.
108. Siu FM, Ma DL, Cheung YW, Lok CN, Yan K, Yang Z, *et al*. Proteomic and transcriptomic study on the action of a cytotoxic saponin (Polyphyllin D): induction of endoplasmic reticulum stress and mitochondria-mediated apoptotic pathways. Proteomics. 2008; 8:3105-3117.
109. Kerwin SM. Soy saponins and the anticancer effects of soybeans and soy-based foods. Current Medicinal Chemistry - Anti-Cancer Agents. 2004; 4:263-272.
110. Wang ZY, Nixon DW. Licorice and cancer. Nutrition and Cancer. 2001; 39:1-11.
111. Shin HR, Kim JY, Yun TK, Morgan G, Vainio H. The cancer preventive potential of Panax ginseng: A review of human and experimental evidence. Cancer Cause Control. 2000; 11:565-576.
112. Polonsky J. Quassinoid bitter principles II. Forts. Chem. Org. Naturst. 1985; 47:221.
113. Guo Z, Vangapandu S, Sindelar RW, Walker LA, Sindelar RD. Biologically Active Quassinoids and Their Chemistry: Potential Leads for Drug Design. Current Medicinal Chemistry. 2005; 12:173-190.
114. Ohnishi S, Fukamiya N, Okano M, Bruceosides DEF. Three new cytotoxic quassinoid glucosides from Brucea javanica. Journal of Natural Products. 1995; 58:1032-1038.
115. Hall IH, Liou YF, Lee KH, Chaney, SG, Willingham JW. Antitumor agents LIX: effects of quassinoids on protein synthesis of a number of murine tumors and normal cells. Journal of Pharmaceutical Sciences. 1983; 72:626-630.
116. Alexandrova R, Alexandrov I, Velcheva M, VaradinovaT. Phytoproducts and cancer. Experimental Pathology and Parasitology. 2000; 4:15-26.