Phytochemicals as Complementary and Alternative Therapeutic Formulations with Potential pro-Apoptotic Effects on Various Cancerous Cell Lines: A Literature Survey

Muhammad Danish Mund 1, Samina Alam 2, Umair Hassan Khan 1, Uruj Tahir 3, *, Muhammad Saad Zubair 4, Tayyaba Younas 5, Bahare-Mustafa 1

1 Department of Poultry Sciences, University of Agriculture Faisalabad, Sub-Campus Toba Tek Singh, Pakistan
2 Department of Cellular and Molecular Physiology, College of Medicine, The Pennsylvania State University, Pennsylvania, USA
3 Department of Environmental Sciences, Fatima Jinnah Women University, Rawalpindi, Pakistan
4 Department of Microbiology, Government College University Faisalabad, Faisalabad, Pakistan
5 Department of Microbiology, University of Agriculture, Faisalabad, Pakistan

* Corresponding author: Uruj Tahir, Department of Environmental Sciences, Fatima Jinnah Women University, Rawalpindi, Pakistan. E-mail: urujtahirjavaid@gmail.com

Abstract
Cancer is characterized as one of the deadliest diseases and claims millions of lives every year with higher proportion of causalities in developing countries as compared to the developed ones. Though there exist a number of treatment technologies against cancer including chemotherapies, radiotherapies, surgeries etc. But people are now turning towards plant derived herbal therapies for treatment of cancerous diseases due to ill-effects associated with allopathic treatments. These plant derived bioactive compounds may target fast dividing cells by impairing mitosis or cause target cells to undergo apoptosis without affecting normal cells. This manuscript is concerned about current scenario of epidemiological prevalence of various cancer lines, the pharmacological applications of various plant derived bioactive compounds with potential competency as anticancer therapeutic agents and delineation of probable effects of these compounds on cellular targets and their mechanisms of action.

INTRODUCTION
Cancer is specified as a broad group of various infections usually characterized by persistently uncontrolled and abnormal cell production, where cell proliferation occurs via mitotic deregulations and thus leads to overgrowth of cancerous cells. These cells in malignance may migrate to other body parts in form of tumors and metastasize in blood stream and lymphatic system [1-3]. There are different forms of cancer diseases which may affect lungs, esophagus, prostate tissues, blood, colon [4], pancreas [5, 6] and cervices [7]. Cancer can be evident in any age group. However, the disease becomes invasive mainly at or above the age of 65 years [8]. Prevalence of cancer epidemics, despite of lack of clear elucidations in diagnosis, within human societies dates back to ancient Egyptian and classical world Era [9]. The disease incidences became more frequent in many countries since 1990s. Now cancer has turned into an overwhelming and a devastating public health hazard worldwide. It has been recognized as second largest cause of mortality and morbidity in developed countries (claiming about six million lives each year) while third in developing and low-income countries [10, 11]. Cancer globally claims around 7.6-7.9 million (13%) lives every year with mortality rates of 1.4 million due to lung cancer, 740,000 due to stomach cancers, 700,000 due to liver/hepatic cancers, 610,000 because of colorectal cancers and 460,000 because of breast cancer [1, 2, 12]. The developing countries contribute approximately 53% of disease incidences with 56% mortalities due to these illnesses, while percentage proportion of new cases is expected to rise by 73% as compared to developed ones (29%) in 2020. Additionally the estimated global mortality rate due to cancer is expected to rise to 104%
by 2020 with almost 5-times greater death rate in developing world [13]. Likewise, worldwide deaths due to cancer incidences have been projected to rise up to 11 million by 2030 [12]. According to 15th annual report of cancer incidence and epidemiology, cancer incidences in 2010 in Jordan occurred more frequently with male to female ratio of about 0.92:1 compared to that of 0.90:1 in 2009. Most commonly reported forms of cancers among Jordanians included breast (19.6%), colorectal (11.5%), lymphoma (7.9%), lung (7.8%) and prostate (4.5%) [10]. Similarly, Soleimani et al. [14] reported registration of approximately 75,644 new cancer cases in year 2015 in Iran, among those 18,019 cases (23.8%) were with high prevalence of esophagus, gastric, colorectal and liver cancers. Furthermore, WHO [15] has estimated mortality rate of 8% (including both sexes) due to cancer incidences in Pakistan. Such speedy growth trends of cancer incidences are actually threatening the residents of developing and low-income countries with insufficient and ill-equipped health systems to deal with complex and expensive cancer treatments [10]. This review describes current scenario of epidemiology of various cancer lines along with pharmacological applications of some plant derived bioactive compounds tested at laboratory scale which may have the therapeutic competency for treatment of cancer lines. The probable effects on cellular targets and mechanisms of action of these plant derived products have also been delineated.

CURRENT TREATMENT REGIMES FOR CANCER LINES

Being the global cause of mortality and morbidity these cancer diseases need to be dealt and/or treated in an effective way. Hence, these diseases are being treated with various approaches (either alone or in combinations) since long and still are in continuous use. Some of these treatment regimens include chemotherapies, radiotherapies, immunotherapies and surgeries [1, 2]. These therapies, individually as well as in combination, have proved to be significantly effective (e.g. chemotherapy plus surgery) against various cancer lines. However, survival percentage greatly varies depending upon the form, stage and site of the disease in addition to age of patient. Moreover, many difficulties and deficiencies including probable toxicity and damage to other non-targeted tissues and multidrug resistance acquisition during cancer therapy limit and/or compromise the effectiveness of some of these therapeutic processes (like chemotherapy). Additionally the rising prevalence of cancer and health care costs are among the most important factors that fascinated researchers and public for the search of plant based systems which exert health benefits towards reduction of cancer risks and modification of tumor behavior [16]. Therefore, scientific community is now searching and investigating plant-derived bioactive compounds as complementary and alternative therapeutic medicines against cancer [1, 17, 18].

PLANTS AS THERAPEUTIC AGENTS AGAINST CANCER

Use of plants and plant-derived products in disease management is not a new concept, as it has been practiced traditionally all over the world prior to the advent of allopathic medicines. These natural products not only possess broad spectrum effects but also ease patients from possible side-effects. Such supposed advantages of herbal medicinal products have surged the industrialized societies towards discovery of drugs with natural origin for cancer treatment [5, 11, 19].

To date many plants have been reported as useful in managing cancer and cancer related infections. For instance, habitual utilization of Toddrall asiatica (belonging to Rutaceae family) and its extracts as anti-HIV and anti-cancerous agent as well as for treating fever, neuralgia, epilepsy, malaria, sprains, cough and dyspepsia has been ascertained by Krishna et al. [18]. Likewise, Sowemimo et al. [20] also have reported significant cytotoxic activities of Sapium ellipticum leaves against MCF-7 cancer cell lines. Furthermore, applications of various plant species including Taxus baccata, Campotheca acuminata, Podophyllum peltatum and Vinca rosea within clinical settings have been proved to be very effective against breast cancer lines [21]. Similarly, Jatropha curcas, Jatropha gossypifolia, Picralima nitida and Pyrenacantha staudtii have efficiently been applied for treatment of various cancer cell lines [22].

It has been hypothesized that plant extracts either may target fast dividing cells and impair the process of mitosis, or may cause target cells to undergo process of apoptosis [23]. For instance, Vernonia amygdalina (woody shrub) has been reported to inhibit the proliferation of human breast cancer cell lines MCF-7 and MDA-MB-231 via apoptosis or arresting the cell cycle [24]. Similarly, acetone and ethanolic formulations of T. procumbens leaf extracts exhibited considerably higher anti-cancerous potential against Hep G2 and A549 cell lines [25]. Additionally, these plant-based cancer chemotherapies have been speculated to offer anti-proliferative and anti-cancerous effects by altering the expressions of proteins Bcl-2, Bax, caspases-3 and TpS3 genes in cancer cells as evident in case of walnut green husk [26]. The willow bark extract BNO1455 successfully inhibited cell growth and encouraged apoptosis in human colon and lung cancer cell lines regardless of their cycloxygenase (COX) selectivity, thus suggested its potential as cancer preventive compound [27]. Moreover, use of various standardized extracts or fractions of single or mixed herbs with anticancer effects as dietary supplements has also been reported [28].

PHYTOCHEMICALS AND/OR PLANT DERIVED BIOACTIVE COMPOUNDS AS ANTI-CANCER AGENTS

Screening and evaluation of numerous plant extracts and their bioactive compounds for anti-cancerous and antitumor activities has been reported by Agarwal et al. [16]. Studies have shown that such phytochemicals extracted from various plant roots, leaves, stems, bark, bulbs and others parts do possess anticancer activities, thus can potentially be utilized in synthesis of new drugs [17]. Hitherto thousands of plant derivatives including camptothecin, flavopiridol, paclitaxel, combretastatin, betulinic acid, vincristine and vinblastine have been screened and modified synthetically to eliminate the complications and to increase their anticancer selectivity and efficacy [28]. Similarly, teniposide, etoposide, irinotecan, topotecan, vincristine, vinblastin and taxol (plant derived drugs) showed a good affinity for fighting against neoplastic cancers [29]. Flavopiridol, was found to possess tyrosine kinase activity and potent growth inhibitory effects against a
series of breast and lung carcinoma cell lines [30]. Likewise, methanolic extracts of *Mentha longifolia* revealed presence of phenols and flavonoids in remarkable quantities. Moreover, these extracts also showed antioxidant and anti-mutagenic activities [31]. *Azadirachta indica* has been reported to contain gallic acid, ellagic acid, quercetin and quercetin-3-O-glucoside with significant antioxidant and cytotoxic activities, consequently it could be considered as a great potential source for natural health products [32]. Additionally *F. gummosa* ethanolic extracts besides containing highest amounts of total phenolic and flavonoid contents have also been reported to contain some effective compounds which can be used as chemotherapeutic agents [33]. Similarly, taxol and vincas pyrrolizidines obtained from medicinal plants are counted among the best anticancer drugs. According to one estimate, more than 700 mono and poly-herbal preparations are available in the form of decoctions, tinctures, tablets and capsules from more than 100 plants and are in clinical use [34]. It has been estimated that around 25% new chemical entities and 42% anticancer drugs obtained from natural products and their derivatives are marketed worldwide during 1981-2006 [35]. Furthermore, Chinembi et al. [17] and Newman and Cragg [36] reported that naturally derived products with anticancer activities covered about 70% of new chemicals during a period of 1981-2010.

**Epidemiological Prevalence of Various Cancer Lines and Chemo-Therapeutic Applications of Phytochemicals for their treatment**

Based upon the origin there exists variety of cancer diseases namely e.g. breast cancer, melanoma, liver cancer, leukemia, oral cancer, thyroid, lung, pancreatic, prostate, kidney, bladder and colorectal cancers [37]. However, in order to treat such deadliest diseases a number of different bioactive compounds have been extracted from plants and marketed as therapeutic agents with many new species still under the investigation process for their effectiveness against various cancer cell lines including:

**Breast Cancer**

Breast cancer, one of the most common neoplasms diagnosed in women, is the fifth leading cause of death in women. It internationally constitutes 10-10.4% of all the newly registered cancer cases and accounts for more than 1.6% of mortality among women worldwide [11, 38, 39]. Omogbadegun [40] reported that breast cancer globally affects about 12.5% of women during their lifetime and results in approximately 400,000 deaths per year in addition to around 4.4 million women diagnosed with this disease. Studies also have shown that a great proportion of women get affected with variable forms of breast cancers. For instance, **7111** of female population in USA, Canada and Australia has been reported as affected with primary breast cancer and **538 females** were found to be suffering with secondary breast cancer while only **124 male members** got affected with breast cancer in 2003 [41]. Conversely, breast cancer has diverse epidemiology in Middle East, Asian and rest of the developing world [39]. According to Shulman et al. [42], reported death rate due to breast cancer incidences was **48%** in countries with low-income, **40%** in low to middle income and **38%** in high-middle income and **24%** in high-income countries. Among Asian countries Pakistan experiences **2.5 times** higher proportions of breast cancer incidences with **34.6%** affected females as compared Iran and India [39]. Likewise, reported cancer cases from Iran encompassed about **77%** of patients with breast cancer who had a tumor larger than 2 cm and **65%** of patients were diagnosed with positive lymph nodes. In addition to these facts women population diagnosed with breast cancer in Iran, Turkey and Pakistan is almost **10 years** younger than those diagnosed in western countries [38]. Moreover, data based on registered cases of breast cancer at Sansthan in 2011 showed that approximately **38%** patients suffering from breast cancer live in age group of 40-50 years, a period in life of a female which is most strongly related to major hormonal changes and time coinciding with setting in of the menopause [43]. It has been estimated that new cases of breast cancer on yearly basis will be raised to about 15 million by 2020, with approximately **10.5 million** expected to occur in developing countries. This annual figure in African countries is likely to increase by 1 million cases, while in Nigeria it is expected to be **500,000** by 2020 [40].

*Pandanus amaryllifolius* commonly known as pandan wangi belongs to screw pine family and has been used for treatment of fever, sore throat, toothache and headache, and also to cure thyroid issues, epilepsy and leprosy as well as anti-spasmodic [44]. Chong et al. [44] analyzed the mechanism of action of ethanolic extracts of *P. amaryllifolius* on human MDA-MB-231 cells and observed that the plant extract exerted growth inhibitory effects on cell proliferation due to arrest of DNA replication of cell cycle in G0/G1 phase via caspase induction and protein level alterations. It has been reported that *P. amaryllifolius* extract abundantly contained various bioactive phytochemicals and phytosterol (stigma sterols) that permitted cytotoxicity and induced apoptosis via regulating apoptotic markers. The treatment of breast cancer cell lines with *P. amaryllifolius* and its bioactive constituents resulted in PS-externalization, activation of 3/7 and 9 caspase enzymes and induced mitochondrial cytochrome c mediated apoptosis by up-regulating tumor suppressor protein p53 and down-regulating XIAP (anti-apoptotic) protein, respectively. *Commiphora mukul*, locally known as guggal, belongs to *Burseraceae* family and has traditionally been used in ayurvedic treatment of ulcer, epilepsy, obesity, rheumatoid arthritis, arthrosis and lipid disorders [45, 46]. Jiang et al. [46] reported that Gugulipid (GL) extracts of *C. mukul* effectively inhibited the growth of MCF-7 and MDA-MB-231 cells with an *IC*<sub>50</sub> concentration of 2 µM. GL inhibited Wnt/β-Catenin-TCF4 signaling pathway, which is an important contributor in carcinogenesis and metastasis, hence its inhibition has great significance for cancer chemoprevention and chemotherapy. GL treatment inhibited the growth of cancer cells and brought about apoptotic cell death by triggering cytoplasmic histone-associated DNA fragmentation, inducing caspase 3 activities, down-regulating β-Catenin pathway of cancer affected cells, significantly reducing expression of Wnt/β-Catenin targeting genes (cyclin D1, C-Myc, survivin) and inhibiting transcription factors. However, RNA interferences of β-Catenin and TCF-4 were found to enhance the cell death at significant levels. Similarly, *Ferulago angulate* previously known for its anti-inflammatory and anti-ulcerative activities has been evaluated by Karimian et al. [47] for apop-
toxic activity against MCF-7 cell lines. The treatment with hexane extracts of *F. angulate* revealed significant induction of apoptotic activity in MCF-7 cells with IC₅₀ value of 5.3 µg mL⁻¹ via caspase enzyme activation, following up-regulation of pro-apoptotic and down-regulation of anti-apoptotic proteins. *F. angulate* leaves hexane extract (FALHE) treatment resulted in up-regulation of p21, p27 and Bax proteins, and down-regulation of Bc1-2 which suppressed the proliferation of cancerous cells by arresting cell cycle, thereby induced mitochondria-mediated apoptosis by reducing mitochondrial membrane potential through releasing cytochrome c from mitochondria in to cytosol which in turn activated caspase 9 enzymatic pathway and eventually led to cell death. Thymol (3, C₆H₆O₃) and carvacrol (4, C₁₀H₁₄O), contained in FALHE are known to have great anti-proliferative and apoptotic potential against various cancer cell lines without affecting the normal cells [48].

Flavokawain B (FKB) is a naturally existing chalcone that is extracted from the roots of Kava-Kava (*Piper methysticum*). *P. methysticum* root extracts have been applied for treatment of anxiety [48, 49]. Regarding the treatment of breast cancer, Abu et al. [49] described that Flavokawain B (FKB) extracts of Kava-Kava plant induced apoptosis via DNA fragmentation in 4T1 tumors in vivo and also inhibited metastasis along with efficient regulation of immune system. In-vitro incubation of cells with FKB for 24 hours caused reduction in cell motility and metastasis and thereby impeded the invasion as well as proliferation of 4T1 cells from 100% to 54.26% with a dose concentration of 9 µg mL⁻¹, to 43.6% with 13.5 µg mL⁻¹ and to 33.72% with 28 µg mL⁻¹ of respective doses. FKB also resulted in decrease in tumor volume from 700 mm³ to 462.5 mm³ in addition to tumor weight loss from 0.617 g to 0.44 g just within 28 days of treatment. Furthermore, FKB led to enhancement in amount of CD4/CD3 T-cell, natural killer (NK) cells, IFN-γ and IL-2, respectively. However a decline in c-MYC (c-Myc is a regulator gene that codes for a transcription factor) level and nitric oxide which may participate in development of inflammation, metastasis and angiogenesis was observed following FKB treatment. Likewise, Tor et al. [50] while investigating the effects of ethylacetate extract of *Dillenia suffruticosa* (EAD) on cancer cells reported that EAD treatment was found to activate caspase enzymatic pathway which halted the cancer cell cycle and induced 50% inhibition of liver tumor cells through apoptosis. Likewise, *S. birrea* root hexane extract (FALHE) treatment resulted in activation of AMPK which led to suppression of fatty acid synthase activities. The treatment of Hep3B cells resulted in activation of AMPK which led to suppression of fatty acid synthase (FASN) responsible for promoting tumor-genesis and actively mediated death of carcinoma cells along with facilitating the proliferation of normal cells without affecting them negatively. Another plant species *Leucaena leucocephala* has been reported to possess anti-bacterial, anti-helminthic and analgesic functions. Haggag et al. [58] studied antioxidant and cytotoxic effects of multiple phenolic compounds extracted from leaves of *L. leucocephala* and found that out of these polyphenols only two, myricetin 3-O-[2',3',4'-tri-O-galloyl]-α-L-rhamnopyranoside and 1,3,6-tri-O-galloyl-β-D-glucopyranoside possessed significant antioxidant potentials and induced apoptosis in HepG2 cancer cells. Additionally, Convertini et al. [59] reported cytotoxic effects of *Permylulated Anigopreissin A* (PAA) against different human cancer cell lines including liver cancer. PAA treatment was found to activate caspase enzymatic pathway which halted the cancer cell cycle and induced 50% inhibition of liver tumor cells through apoptosis. Likewise, *S. birrea* methanolic root extracts (MRE) can potentially induce apoptosis in HepG2 cancer cell lines. The polyphenols, flavonoids and tannins contained in MRE together with antioxidant activity also triggered apoptosis via morphological changes (like mitochondrial membrane permeabilization and release of soluble proteins enclosed by mitochondria) within the cancer affected cells [60]. Similarly, ethanolic extracts of *C. kanehirai* Hayata (CKHE-E) persuaded intrinsic pathway of apoptosis and inhibited the cellular viability, especially via caspase-3 cascade and proteolytic activity in human hepatoma HA22T/VGH and HepG2 cell lines. The phytochemical analysis of CKHE-E revealed that Sesamin and methyl (21R)-phorophorbide acted as more remarkable chemotherapeutic agents or adjuvants. The microscopic inspection showed apoptotic and sound morphological changes in cancer cell with 0.5 and 1.0 mg mL⁻¹ of CKHE-E after 24 and 48 hours. The treatment led to increased percentage of apoptosis via sub-G1 cells and cleavage of caspase 3 in human HA22T/VGH and HepG2 cells in a dose and time-dependent manner. *C. kanehirai* is also famous for its role in curing dermatological diseases, nervous depression and dispel apathy [61].
SKIN CANCER

Skin cancer, most common human malignancy, is known to affect 30% and 70% individuals at any age worldwide [62]. Changes in outdoor activities and contact to sunlight are thought to be significant predisposing factors for increased incidences of melanoma [63]. Each year around more than 400,000 individuals are diagnosed with skin cancer depending upon the skin type, age and exposure to sun [64]. Cutaneous melanoma is known as one of the most rapidly increasing cancers among Caucasians in comparison with Africans, Asians, Latin Americans and American-Indians [63, 65]. According to Hay et al. [62] skin diseases are the 4th leading cause of nonfatal diseases at global level with more enormous burden in low and high income countries. The incidence of skin cancer registered in Iran during 2004-2008 included 43,694 cases including 27,364 males. The highest incidence rate (9964 cases) was reported in 2008, but lowest rate (7320 cases) was recorded in 2004 [66]. Moreover, skin cancer incidences have also been reported to increase continuously in many regions of Pakistan [65, 67]. Leiter and Garbe [63] reported increase in disease incidence rates of up to 5 folds in Europe, which are expected to increase further to 40-50/100,000 inhabitants per year in next few decades. According to CDC [68] reports white people are more likely to die of skin melanoma followed by Hispanics, Asian/Pacific Islander and black men and women. Leaf extracts of *Olea europaea* (olive tree) have previously been applied for anticipation of chronic diseases and cardiovascular disorders and as antimicrobial, antioxidant, anti-inflammatory and anticancer agents. Due to these health benefits olive leaves have gained much of the scientific interest especially in pharmacological field [69, 70]. Mijatovic et al. [69] described significant inhibitory effects of dry olive leaf extract (DOLE) against highly malignant, immuno- and chemo-resistant type of melanoma through altering the cell membrane integrity and proteins. Application of DOLE has significantly reduced solid mass and colonization of skin cancer cell lines with 40 mg kg⁻¹ and 1.25 mg mL⁻¹ in dose and time dependent manner. DOLE treatment diminished the expression of Bim and P53 while up-regulated the expression of EndoG (this protein primarily participates in caspase-independent apoptosis via DNA degradation) and thus successfully promoted cell death by disrupting the integrity of cell membranes followed by DNA fragmentation. Flower extracts from *Rafflesia kerrii* Meijer (RM) have also been reported to possess anti-cancerous and anti-proliferative effects on skin cancer cell lines A431 [71]. Various concentrations of RM induced up-regulation of apoptotic markers, brought about morphological changes and chromatin condensation, which eventually led to the induction of apoptosis in skin cancer cell lines. The IC₅₀ value of RM was projected to be 0.3 μg mL⁻¹. In the same manner Centipede grass extract (CGE) exerted apoptotic and anti-proliferative effects on B16F1 (mouse skin cancer cell line) and SKMEL-5 (human skin cell lines) by inhibiting phosphoinositide 3-kinase (PI3K)/AKT/p-glycogen synthase kinase-3β (GSK-3β) signaling pathways and triggering caspase enzymes. SKMEL-5 cell lines appeared more sensitive to CGE treatment in contrast to B16F1. CGE resulted in disruption of mitochondrial membrane and thus induced apoptosis in cancerous cells. The IC₅₀ values of CGE were recorded as 19.18 and 43.41 μg mL⁻¹ for SKMEL-5 and B16F1 cells, respectively [72].

LEUKEMIA

Acute myeloid (AM) and acute lymphoblastic leukemia (ALL) accounted for 22% and 56% of leukemia cases in Songkhla during 1989-2011, respectively. It has been estimated that ALL incidences are increasing persistently by 1.3% per year while AML at a rate of 4.0% per year [73]. In Songkhla, ALL and AML incidences have significantly increased during 1990-2011 which differed significantly from that of US. However, the survival rate has significantly improved by at least 2% per year from 1990-2011 in Songkhla for leukemia, ALL and AML [74].

Rocaglamide (Roc) extracted from *Aglaia* have been reported to be utilized as insecticidal and anti-inflammatory agents. This phytochemical has also been reported to possess anti-cancer activities [75, 76]. Hence, the anti-neoplastic effects of rocaglamide along with regulation of protein and gene expressions on various human leukemia cell lines and acute lymphoblastic leukemia, chronic myeloid leukemia and acute myeloid leukemia cells have been demonstrated by Zhu et al. [75]. The bioactive compound preferentially induced apoptosis in leukemia cells by modulation of mitogen-activated protein kinase activities. The rapid P38 and c-Jun N-terminal kinases (JNK) phosphorylation activated respective proteins and led to long term inhibition and reduction of phosphorylated extracellular signal-regulated kinases (ERK) upon Roc treatment. P38 participated in mitochondrial arbitrated apoptosis by stimulating mitochondrial translocation of pro-apoptotic Bcl2 family protein Bax via bringing Bid cleavage. The dose of Roc up to 2.5 μM was found to have cytotoxic effects against human acute T cell leukemia Hut78 and Jurkat cell lines. *Viscum album* is famous as most widely used complimentary therapy for treating cancer patients. The extracts are applied subcutaneously and reported to have fewer side effects during chemotherapy [77]. Seifert et al. [78] described anti-neoplastic effects and molecular mechanisms of aqueous mistletoe extracts (MT) from pine (MT-P) and fir (MT-A) trees against lymphoblastic leukemia. They transplanted mice with NALM-6 cell lines and then treated them with variable doses of MTs. Significant losses at a rate of 62.1% and 32.8% in mitochondrial membrane potential of NALM-6 cells were detected upon in-vitro treatment with 250 μg mL⁻¹ of MT-P and MT-A after 48 hours. Mistletoe from pine tree extracts (containing higher ML-III content) was found to be the most effective even in lower amounts against human acute lymphoblastic leukemia cell lines (NALM-6) without having any side effects and induced apoptosis via loss of mitochondrial membrane potential and DNA fragmentation in dose-dependent manner. Similarly, wagnonin was reported as active form of flavones having anti-cancerous activities especially in malignant lymphocytes without effecting normal cells. Wagnonin treatment resulted in down-regulation of anti-apoptotic protein myeloid cell leukemia 1 (Mcl-1) or cyclin dependent kinase (CDK9) expression and is known to trigger prolonged intracellular Ca⁺ mobilization and inhibit CDK9-mediated phosphorylation of RANPII via binding to its ATP- pockets, which is a basal transcription factor [79].

Use of *Achras sapota* as anti-inflammatory, analgesic and anti-microbial agent, and for treating pulmonary diseases has been documented in Indian context. Being rich in proteins, sugars, minerals, carotenoids, ascorbic acid and phenolic compounds as well as having multifunctional properties Sapota juices can
also be used as health promoting beverages. Moreover, studies have indicated this plant species as suitable candidate for treatment of various cancer types because of wide-ranging chemical diversity of dietary substances derived from the plant [80, 81]. Srivastava et al. [81] considered the effects of methanolic extract of Sapota fruit (MESF) on NALM6 (pre-B cell leukemia) and K562 (chronic myelogenous leukemia) tumor cells and mice tumor. This compound was found to induce cytotoxicity by activating pro-apoptotic and down-regulating mitochondrial protective proteins. MESF induced depolarization and trans-membrane potential in mitochondria and translocation of phosphatidyl serine from inner to outer leaflet of cell membrane and significantly up-regulated pro-apoptotic proteins and apoptotic markers which hallmarked apoptosis initiation. MESF treatment led to cell death of approximately 80% at 2 mg mL\(^{-1}\) and induced cytotoxicity in NALM6 and K562 cells with IC\(_{50}\) value of 0.9 mg mL\(^{-1}\) and 2.5 mg mL\(^{-1}\), respectively, after 72 hours of treatment. Moreover tumor progression inhibition resulted in 3 folds increase in lifespan in 50% of mice, thus suggesting its potential role in preventing genesis and progression of cancer cells.

Curcumin is the most potent polyphenolic bioactive compound that is derived from turmeric. Studies have elucidated anticancer activities of curcumin against different cancer types including pancreatic cancer [82, 83]. Keeping in view the anticancer effects Sharma et al. [84] reported that curcumin induces up-regulation of p15 gene and down-regulation of DNA methyltransferase 1 in acute lymphoid leukemia (ALL) and acute myeloid leukemia (AML) cells and also initiated apoptosis which eventually led to genomic instabilities. Curcumin treatment also led to genomic instabilities. Curcumin significantly increased cytotoxicity due to ROS (reactive oxygen species) formation which had a destructive effect on DNA and protein content of Raji cell lines at 10 and 20 μM in a dose-dependent manner, whereas IC\(_{50}\) dose of curcumin was 20 μM, where nuclear changes and apoptotic body formations ascertained DNA fragmentations along with genomic abnormalities (like breakage of chromosomal arms, aberrant metaphases etc.). Moreover, curcumin treatment also led to cell-cycle arrest in G1 phase and depletion in S-phase fraction with approximately 15 folds up-regulation of P15 mRNA and DNA methyltransferase (DNMT1) inhibition. These findings suggest that curcumin do possess anti-cancerous effects and brings about apoptosis via ROS mediation and structural abnormalities in chromosomes (i.e. by causing genomic instabilities). In another study Aguínaga-Sánchez et al. [85] evaluated crude extract from chayote hybrid for anti-cancerous activities. It strongly inhibited proliferation of P388, J774 and WEHI-3 leukemic cell lines with an IC\(_{50}\) below 1.3 μg mL\(^{-1}\) and had minimal effects on normal bone marrow mononuclear cells lines. The treatment with crude extract caused translocation of phosphatidylserine to cytoplasmic membranes of the leukemic cell lines which marked early apoptotic events followed by DNA fragmentation.

C. zeylanicum (from Lauraceae family) is known for its role in the treatment of gynecological, digestive and respiratory disorders. Assadollahi et al. [86] evaluated anti-oxidant effects of C. zeylanicum aqueous extracts on cell development of human myelocytic leukemia cell line (THP-1). Incubation of THP-1 cells in 0.1 mg mL\(^{-1}\) of C. zeylanicum solution showed significant induction of apoptosis just within 24 hours. Bejarano et al. [87] reported that Quercus suber cork extract (QSE) contains a diversity of phenolic compounds which induce apoptosis in human promyelocytic leukaemia cells through caspase activation and mitochondrial disintegration pathway. QSE induced significant apoptosis at 30 μg phenol mL\(^{-1}\); the compounds present in QSE induced alterations in cell cycle kinetics through physiological and damaging pathways.

**LUNG CANCER**

The incidence of lung cancer is still very high and is increasing among women and men in many countries. However, there are still very poor or inadequate techniques for prognosis of this illness. It is one of the leading causes of mortality among all cancer deaths [88]. In 2013 about 14.9 million cancer cases were registered with 8.2 million deaths and there were approximately 196.3 million incidences of disability-adjusted life years (DALYs). Tracheal, bronchus and lung (TBL) cancers were expressed as the leading cause for death among men and women, with around 1.6 million deaths worldwide [89]. *Excoecaria agallocha* (belonging to Euphorbiaceae family) has been applied as an anti-inflammatory, anti-viral and anti-bacterial agent, and also for curing epilepsy. Patil et al. [90] have reported remarkable cytotoxic activities of ethanolic extracts of stem of *E. agallocha* against human lung cancer cells. The extract caused apoptotic cell death in p53\(^{+/+}\) cancer cells (A549 and H460) and halted G1 phase in p53\(^{-/-}\) cells (H358 and H1299). *E. agallocha* exhibited the strongest cytotoxic effects at a dose of 100 μg mL\(^{-1}\) with 81% reduction in cell viability of A549 and that of 58% for H1299 cell lines. The initiation of cell death was arbitrated via p53, Bcl-2, Bax-dependent pathways. Similarly, another plant *Abutilon indicum* from Malvaceae family, usually applied in treatment of gonorrhea, diarrhea, fevers and bronchitis etc., has recently been evaluated for anti-inflammatory and anti-proliferative activities against lung cancer cell lines by Kaladhar et al. [91]. The ethanolic leaf extract of *A. indicum* modulated Apaf-1 gene expression and proteins thereby proved to be an effective chemo-preventive agent against A549 cell line. Incubation of A549 cell line with ethanolic leaf extract of *A. indicum* showed anti-inflammation by 5-LOX and cyclooxygenase (COX) inhibition at IC\(_{50}\) of 8.89 μg mL\(^{-1}\) and anti-proliferative effect through Apaf-1 gene that activated cytochrome c-driven caspase by means of MAP Kinase pathway. The percentage of cell inhibition was progressively increased to 72.1% at 200 μg mL\(^{-1}\) as compared to cisplatin that showed percentage cell inhibition of 91.1% μg mL\(^{-1}\).

**PROSTATE CANCER**

Prostate cancer is the second most common non-cutaneous cancer and 6th leading cause of death in men at global level. Prostate has been recognized as second leading site of cancer among males [92, 93]. According to reports one out of every eighth males is diagnosed with prostate cancer during their lives. The associated risk factors are not fully known, but age and genetic history are usually considered as the main predisposing factors. Prostate cancer poses no threat to survival but may lead to pain, urinary symptoms and general malaise of prostatitis [92]. Nearly 14% (122,000) of all prostate cancers diagnosed globally in 2008 were within the Asian-Pacific region (10 per 100,000 individuals) and the disease accounted for approximately 42,000 deaths. Moreover, worldwide bur-
den of prostate cancer is expected to rise to 1.7 million new cases with around 499,000 mortalities by 2030 [93, 94]. *Epilobium* species have been applied as medicines due to various beneficial attributes towards human health. *Epilobium* infusions have traditionally been applied for treatment of skin infections, stomach ulcers, sleeping disorders, prostatic hyperplasia, gastritis etc. Recently the studies on the extracts of *Epilobium* species have verified their anti-proliferative activities against different cancer cell lines [95, 96]. Regarding the anti-proliferative activities Stolarczyk et al. [95] assessed the effects of standardized aqueous extracts from *Epilobium* sp. on LNCaP human prostate cancer cells. The extracts were found to induce apoptosis in LNCaP prostate cancer cells through activating caspase 3 enzyme and by disrupting the mitochondrial membrane potential, where apoptotic activity totally relied upon activation of mitochondrial pathway.

Moreover, the extracts contained oenothein B, flavonoids and polyphenols which were found to be biologically active against LNCaP cancer cells. Treatment of human prostate cancer cell line with different *Epilobium* sp. revealed that the extracts from *E. parviflorum* and *E. hirsutum* were the most active with IC$_{50}$ values of 32.2 µg mL$^{-1}$ and 37.3 µg mL$^{-1}$, respectively. In-vitro cell treatment triggered mitochondrial disruption and resulted in liberation of cytochrome c from mitochondria into the cytosol, and also activated the caspases which led to apoptosis of cancerous cells. According to Pollock et al. [97] strigolactone analogues (SL) were promising candidates for prostate cancer cell therapy, due to their ability of activating stress inducing gene expression and apoptosis with minimal effects on growth and survival of normal cells. SLs were found to arrest the cell cycle by inducing cellular stress responses and triggering apoptosis in cancerous cells. Among all SL analogues (EG5, EG9c, ST357, ST362 and MEB55) tested ST362 and MEB55 appeared as most potent inhibitors. The IC$_{50}$ of ST362 and MEB55 after 3 consecutive days of treatment ranged from 2.8 ppm to 12.8 ppm respectively, while for other SL analogues observed IC$_{50}$ was above 1ppm. In same way berberine and butanol fraction of bark extract from *Phellodendron amurense* was found to be responsible for inducing apoptosis in prostate cancer cells by targeting critical cell survival signaling pathways both in vitro and in vivo [98]. Incubation of human PCA cell lines and androgen-independent PC-3 cells with Nexrutine and its fractions (F1, F2 and F3) showed that F3 was most potent in its efficacy against cancer cells. The dose concentration of 2.5 µg mL$^{-1}$ of nexrutine or butanal fraction (F3) adequately inhibited the proliferation of androgen independent PC-3 cells by 50% just within 24 hours. The butanal fraction (F3) inhibited proliferation of PC3 cells, induced apoptosis, modulated the transcriptional activity of NFkB promoters, NFkB (nuclear factor kappa-β) DNA binding and protein expression of pAkt, p65 and pIkBα (Phospho-Inhibitory Subunit Of NF Kappa B Alpha) in prostate cancer cells in similar pattern as nexrutine did [98], thereby provided an insight about the potential effects of berberine on prostate cancer cell lines. Gupta et al. [99] reported that LNCaPsh53 and LNCaPsh53 human prostate cancer cells after treatment with 20-80 µg mL$^{-1}$ of GTP (green tea polyphenol) for 24 hours exhibited dose-dependent inhibition in cell viability from 100% to 33.98% and 100% to 66%, respectively. GTP effectively stimulated the apoptosis process in cancer cells regardless of presence or absence of P53 function by disrupting the signaling pathways and activating pro-apoptotic proteins along with down-regulation of anti-apoptotic proteins, all these events executed the apoptosis of cancerous cells by losing mitochondrial transmembrane potential, releasing cytochrome c and activating terminal caspases thus resulted in PARP-cleavage [99].

Additionally, herbal therapies usually sold as nutritional supplements can be used for the effective treatment of prostate cancer. Celastrol, is a quinone methide triterpene extracted from Chinese vine *Tripterygium wilfordii*. Celastrol has been reported as a potent inhibitor of the proteasomal chymotrypsin activity with an IC$_{50}$ value of 2.5 µmol L$^{-1}$, both in vitro in cultured prostate tumor cells and animals. Inhibition of this activity in prostate cancer cells is associated with induction of apoptosis and/or antitumor activity of Celastrol. The conjugated ketone carbons C2 and C6 in Celastrol have been speculated to contribute towards its proteasome-inhibitory effects [100]. Similarly, Genistein, an isoflavone found in soybeans, has been shown to inhibit the growth of many types of cancer cells in vitro and in vivo without affecting normal cells. Genistein can potentially be used in treatment of different types of cancers including prostate, breast, lung and pancreatic cancers. Genistein pretreatment inactivates nuclear factor NF-xB and Akt. NF-xB mediates inhibition of apoptosis and promotes cancer cell growth. Inactivation of NF-xB sensitizes cancer cell to growth inhibition [101].

### COLORECTAL CANCER

Colorectal cancer (CRC) is the 3rd most common form of cancer in men (10% with 746,000 cases) and 2nd most common in women (9.2% with 614,000 cases) in the world [102]. The colorectal cancer infections are known to account for almost 9% among all the fatal cancer incidences [4]. The prevalence rate of CRC is also persistently increasing in Asian countries. Despite of higher age-standardized rates (ASR) in some countries, several studies have revealed a male predominance difference along with increased disease risk in elder population [103]. Moreover, cumulative risk (at an age of 0-74 years) of incident colorectal cancer for Croatia was reported to be 5.25% for males and that of 2.86% for females [102]. Tragulpakseerojn et al. [104] reported that *M. oleifera* leaves contain flavonoid kaempferol and new substances that inhibited cell proliferation and induced apoptosis in HCT116 cells in a dose dependent manner. Procaspases were converted into caspases and activated proteases which resulted in proteolytic cleavage. *M. oleifera* contained major proportion of pf1-pf3 compounds with pf2 and pf3 having more inhibitory and cytotoxic activities as compared to pf1. pf2 and pf3 inhibited cell viability up to 75% while pf1 25% following treatment with dose of 0.25 µg mL$^{-1}$. Quassinti et al. [105] reported the ability of wild celery oil and isofuranodiene to persuade apoptosis in colon cancer cells in time and concentration-dependent manner. The wild celery induced oxidative stress, generated ROS for facilitating cell death by apoptosis (i.e. DNA fragmentation, phosphatidyserine externalization and elevated caspase-3 activation) and necrosis. Additionally, Omoyeni et al. [106] reported significant induction of apoptosis in colorectal adenocarcinoma cancer cells after being treated with *Pleiocarpa pyrcanthua* leaves extract and its isolated compounds. *P. pyrcanthua* compounds, 27-p-E-coumarolxyursolic acid and 27-p-z-coumarolxy-
ursolic acid, were found to have good anti-cancerous and anti-proliferative abilities with IC₅₀ values of more than 100, 40.9 and 36.3 μg mL⁻¹, respectively against Caca-2 cells. These compounds activated caspases and brought about apoptosis through phosphatidylserine externalization and morphological changes such as cell shrinkage and detachment. Similarly, Tan et al. [107] analyzed apoptosis in HT-29 cells with water extract of brewer’s rice (WBR) and observed that it inhibited Wnt signaling activity through up-regulation of the cassein kinase 1 (CK1) and adenomatous polyposis coli (APC) mRNA levels and down-regulation of glycogen synthase kinase 3β (GSK3β). Vadde et al. [108] evaluated the effects of methanolic extract of Tribhala (MET) against human colon HCT116 and HCCSCs cancer cell lines and concluded that MET induces suppression as well as apoptosis via decreasing the expression of c-Myc and cyclin D in cell nucleus and by modulating BAX and Bcl-2 levels without concerning P53 expression.

GASTRIC CANCER

Gastric cancer is the 2nd leading cause of mortalities in the world. Out of 90% cases, adenocarcinomas comprise the major gastric cancers, which mostly rise from glands of most superficial layer or mucosa of stomach. Each year around 990,000 people are diagnosed with gastric cancer internationally including about 738,000 deaths from this disease [109]. According to WHO 2002 database most of the countries in East Asia (including Japan, Korea and China) have more incidence of gastric cancers i.e. > 40 cases per 100,000 men. Conversely, most of other countries in West and South Asia have a comparatively lowered cancer incidence registry with approximately <10 cases per 100,000 men [110]. Ulmus davidiana has traditionally been used in Japanese medicine as anti-glycation, anti-angiogenic and anti-inflammatory agent. Ahn et al. [111] reported higher efficiency of ultrafine particles of U. davidiana var. japonica (uf UJ) against human gastric cancer cell lines SNU-1, SNU-216 and SNU-484. uf UJ ethanolic extracts induced morphological changes in cancer cells with stronger apoptotic effect through loss of plasma membrane integrity, ER stress, up- and down-regulation of biochemical markers etc. Moreover the herbal extract also induced apoptosis through proteolytic activation of caspase enzymatic pathway. Therefore, the gastric cancer cells were unable to exhibit any anchorage-independent growth in presence of ufUJ. IC₅₀ of AM1 and AM2 in SNU-1 cells was observed at 75 and 37 μg mL⁻¹ , that in SNU-216 cells was at 370 and 320 μg mL⁻¹ , and for SNU-484 cells was at 280 and 25 μg mL⁻¹ , respectively. Likewise Ferulago angulata Boiss extract was found to possess significant antioxidant ability against human adenocarcinoma gastric cell line (AGS) such as Rhus verniciflua Stokes (RVS) and Scutellaria litwinowii [112]. The essential oil of F. angulata induced apoptosis in malignant cells with characteristic DNA fragmentation. A significant increase in number of apoptotic cells was observed in concentration-dependent manner. The leaf and flower extract were found to have cytotoxic effects at ≥ 20 μg mL⁻¹ and 40 μg mL⁻¹ after the treatment period of 24 and 48 hours, respectively. However AGS cells showed 49.13% late apoptosis and 26% early, and 45.8% late apoptosis and 24.15% early apoptosis when treated with 160 μg mL⁻¹ of leaf and flower extracts [112].

CERVICAL CANCER

Worldwide, cervical cancer is the third most common cancer in women, and is 1st/2nd most common in developing countries. It has been reported as the top most cause of mortality in Colombia with second most leading cause of cancer incidence between women during the last 3 decades [113]. In Iran, the age-standardized incidence (ASIR) was estimated as 2.5 per 100,000 in pathology-based cancer registries during the year 2007. However, it has been increased to double in population-based cancer registry with mean age-standardized cervical cancer mortality (ASMR) of 1.04 per 100,000 and mortality to incidence ratio of 42%. Moreover, the prevalence of human papilloma virus (HPV) infection was found to be 76% in patients suffering from cervical cancer [114]. Sreedevi et al. [115] reported widespread patterns of cervical cancer and HPV types among cervical cancer patients and between women especially including high-risk groups e.g. commercial sex workers and HIV (human immunodeficiency virus) positive women. Furthermore, cervical cancer is recognized as globally important cause of women mortality with higher prevalence in sub-Saharan Africa [11]. The age-standardized incidence rates (ASIRs) per 100,000 and age-standardized death rates (ASDRs) per 100,000 in 2013 were recorded to be higher in developing countries as compared to developed ones [90]. Tulbaghia violacea known as wild garlic is used in the treatment of many ailments like cold, fever, tuberculosis and asthma etc. Bungu et al. [116] described anticancer activities of bulb and leave extracts of T. violacea. The bulb extract was found to be more effective against HeLa cells. The bulb and leaf extract of T. violacea inhibited growth of cells up to 54.7% and 37.5% in HeLa cells, respectively. Moreover this treatment caused nuclear damage and PARP cleavage through caspase 3 activation and alterations of metabolic events that are not tissue specific. The anti-cancer effects of Limoniasstrum guyniannum aqueous gall extract (G extract) and luteolin on HeLa cancer cell lines were evaluated and assessed by Krifa et al. [117]. They concluded that G extract up-regulated the tumor suppressor gene p16 INK4A and down-regulated anti-apoptotic factors UHRF1 and DNMT1. G extract and luteolin caused a decline in expression of epigenetic integrator UHRF1 and its partner DNMT1 and led to a reduced genomic DNA methylation which refers to re-expression of p16INK4A tumor suppressor gene. Moreover, GE arrested the cancer cell cycle at G2/M phase and inhibited HeLa cells up to 79.6% and 59.7% with 300 μg mL⁻¹, respectively. Another plant species Annona muricata possessing anti-viral activities has been documented to offer a promising chemoprevention measure against HeLa (cervical) cancer cells induced by human papilloma virus (HPV) by Astirin and colleagues [118]. They observed that A. muricata leaf extracts with chloroform lowered ATP levels through disrupting the circulation of cancerous cells and revealed highest percentage proportion of cell death (i.e. 91.86% at a dose of 2000 μg mL⁻¹). It is evident from the above mentioned facts that cancer epidemics are presenting major havocs equally among male and female populations with variable demographical trends all over the globe. The plant extracts and plant-derived bioactive compounds do possess the potential to be utilized as therapeutic agents against different cancer lines. The plant derived bioactive compounds summarized in (Table 1) appear to induce apop-
tosis in affected cell lines via arresting the cell cycle, disrupting the mitochondrial membranes and affecting the expressions of cancer promoting genes etc. Since all these plant-derived bioactive compounds have elucidated significant efficiencies against different types of cancers, however, the molecular and cellular aspects as well as toxicological effects of these bioactive compounds also need to be evaluated. Therefore, extensive research keeping all these aspects in mind as well as clinical experimentation and evaluation need to be conducted prior to their applications and marketing for human consumption.

### Table 1: Summary of Pharmacological Effects of Some Plant Derived Bioactive Compounds and Extracts on Various Cancer Cell Lines

<table>
<thead>
<tr>
<th>Plant Species</th>
<th>Plant constituent/bioactive compound</th>
<th>Cancer cell line</th>
<th>Mechanism of action / effect on cellular targets</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pandanus amaryllifolius</strong></td>
<td>Leaf ethanol extract</td>
<td>MDA-MB-231</td>
<td>DNA fragmentation, mitochondrial mediated apoptosis pathway, caspase induction, p53 up-regulation, XIAP down-regulation</td>
<td>Chong et al. [23]</td>
</tr>
<tr>
<td><strong>Commiphora mukul</strong></td>
<td>Gugulipid extract</td>
<td>MDA-MB-231, MCF-7</td>
<td>DNA fragmentation, inhibited transcription factors, β-Catenin-TCF4 signaling pathway inhibition, caspase induction</td>
<td>Jiang et al. [47]</td>
</tr>
<tr>
<td><strong>Ferulago angulata</strong></td>
<td>Thymol and carvacrol from leaf hexane extract</td>
<td>MCF-7</td>
<td>Arrested cell progression in G1 phase, mitochondrial mediated apoptosis, activation of caspase enzyme, p21, p27 and Bax up-regulation, Bcl-2 down-regulation</td>
<td>Karimian et al. [48]</td>
</tr>
<tr>
<td><strong>Piper methysticum</strong></td>
<td>Flavokawain B from root extract</td>
<td>4T1</td>
<td>Inhibited proliferation and metastasis of tumor cells, Induced apoptosis, tumor reduction, boosted immune system</td>
<td>Abu et al. [50]</td>
</tr>
<tr>
<td><strong>Dillenia suffruticosa</strong></td>
<td>Ethyl acetate extract of root powder</td>
<td>MCF-7</td>
<td>Oxidative-stress related apoptosis mediated by AKT and ERK and Bcl-2 down-regulation, and up-regulation of p53 and P21 genes</td>
<td>Tor et al. [51]</td>
</tr>
<tr>
<td><strong>Morus alba</strong></td>
<td>Leaf polyphenol extract</td>
<td>Hep3B</td>
<td>Apoptosis induction via AMPK/P13K/AKT pathway, down-regulation of antiapoptotic proteins (Bcl-2, Bcl-xL), up-regulation of proapoptotic proteins (Bax, BID), activation of caspases</td>
<td>Yang et al. [58]</td>
</tr>
<tr>
<td><strong>Sclerocarya birrea</strong></td>
<td>Methanolic root extract</td>
<td>HepG2</td>
<td>Mitochondrial-dependent and ROS-induced apoptotic pathways</td>
<td>Armentano et al. [61]</td>
</tr>
<tr>
<td><strong>Cinnamomum kanchirai</strong></td>
<td>Ethanolic leaf extract</td>
<td>HepG2, HA22T/VGH</td>
<td>Apoptosis via caspase-3 cascade, DNA fragmentation, caspase 8 and 9 activation, up-regulated Bax, down-regulated Bcl-2</td>
<td>Liu et al. [62]</td>
</tr>
<tr>
<td><strong>Rafflesia kerrii Meijer</strong></td>
<td>Flower extract</td>
<td>A431</td>
<td>Apoptosis via caspase (3) dependent pathway, nuclear condensation and fragmentation, down-regulation of ERK and Akt signaling pathway, up-regulated JNK and p38 expression</td>
<td>Thuncharoen [72]</td>
</tr>
<tr>
<td><strong>Eremochloa ophiuroides</strong></td>
<td>Leaf extract</td>
<td>SKMEL-5, B16F1</td>
<td>Inhibited proliferation by cell cycle arrest at G2/M phase, mitochondrial membrane depolarization, enhancement of ADP-ribose polymerase degradation, Activation of caspase 3 and 7, down-regulated p-Akt, GSK-3β and P-BAD, inhibited P13K</td>
<td>Badaboina et al. [73]</td>
</tr>
<tr>
<td><strong>Viscum album</strong></td>
<td>Aqueous mistletoe extracts</td>
<td>NALM-6</td>
<td>Apoptosis via loss of mitochondrial membrane potential and DNA fragmentation</td>
<td>Seifert et al. [2008]</td>
</tr>
<tr>
<td><strong>Achras sapota</strong></td>
<td>Methanolic fruit extract</td>
<td>NALM6, K562</td>
<td>Apoptosis via mitochondrial pathway without arresting the cell cycle progression, upregulated proapoptotic proteins, activated MCL-1, PARP-1 and Caspase 9 enzymes</td>
<td>Srivastava et al. [79]</td>
</tr>
<tr>
<td><strong>Epilobium sp.</strong></td>
<td>Aqueous extracts</td>
<td>LNCaP</td>
<td>Induced apoptosis via mitochondrial pathway, decreased mitochondrial potential, activated caspase 3 protein</td>
<td>Stolarczyk et al. [96]</td>
</tr>
<tr>
<td><strong>Smyrnium olusatrum</strong></td>
<td>Flower oil</td>
<td>HCT116</td>
<td>Facilitated apoptosis via DNA fragmentation, phosphatidyserine externalization, elevation in caspase-3 level and necrosis</td>
<td>Quassinti et al. [106]</td>
</tr>
<tr>
<td><strong>Ulmus davidiana var. japonica</strong></td>
<td>ultrafine particles</td>
<td>SNU-1, SNU-216, SNU-484</td>
<td>Induced apoptosis through proteolytic activation of caspase-3, 6 and 9, and by poly (ADP-ribose) polymerase cleavage</td>
<td>Ahn et al. [112]</td>
</tr>
<tr>
<td><strong>Limoniastrum guyni- nium</strong></td>
<td>Aqueous gall Extract</td>
<td>HeLa</td>
<td>Arrested cell cycle at G2/M phase, growth inhibition via activation of p16INK4A-dependent cell cycle checkpoint signalling pathway and down-regulation of UHRF1 and DNMT1 expression</td>
<td>Knifa et al. [118]</td>
</tr>
</tbody>
</table>
CONFLICTS OF INTEREST
We declare no conflict of interest.

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REFERENCES


117. Yang H, Chen D, Cui QC, Yuan X, Dou QP. Celastrol, a triterpene extracted from the Chinese "Thunder of God Vine," is a potent protea-