Journal of Pharmacognosy and Phytochemistry

Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
JPP 2019; 8(3): 3633-3641
Received: 16-03-2019
Accepted: 18-04-2019

Subhankari Prasad Chakraborty
Department of Physiology, Ramananda College, Bishnupur, Bankura, West Bengal, India

Correspondence
Subhankari Prasad Chakraborty
Department of Physiology, Ramananda College, Bishnupur, Bankura, West Bengal, India

Medicinal plants and cervical cancer therapy: An overview

Subhankari Prasad Chakraborty

Abstract
Human papilloma virus, the major risk factor of cervical cancer, the most common gynecologic malignancy worldwide, accounts for 8.5% deaths per year. Conventional treatments have side effects like nausea, vomiting, loss of appetite and hair, early bruising and bleeding, anemia, renal problems, etc. Hence, there is a need for finding new anti-cancer agents which is to be safe, cost effective, easily available and free from side effects. Medicinal plants have been on the forefront where research on the anti-cancer agent is planned. Keeping this purpose in mind, an attempt has been made in this review to provide evidence based analysis of plant extracts, phytochemical and phytomolecules which exhibit anti-tumorigenic activity or exert cytotoxic effect in human cervical carcinoma cells. This review mainly focuses on several medicinal plants such as *Rosmarinus officinalis*, *Solanum nigrum*, Kaffir lime, and *Garcinia nujiangensis* used in the treatment of cervical cancer and the secondary metabolites derived from different plant sources. Plant molecules such as cisplatin, curcumin, epigallocatechin-3-gallate, EGC, and other catechins that have a wide range of biological properties and the molecular mechanism were reviewed. This review will promote the research on the development of a plant-derived anti-cancer drug with lesser or no side effects and aid in understanding the mechanism of action of several plant-derived molecules. However, efficacy needs to be further investigated in various cervical cancer cell lines and more importantly, in *in vivo* cervical cancer models for possible use as an alternative and safe anticancer drug.

Keywords: Cervical cancer, medicinal plants, phytoconstituents, phytomolecules, herbal medicine

1. Introduction
Cancer is characterized by uncontrolled growth of cells which can invade and spread to distant parts of the body. There are over 100 different types of cancer and each is classified by the type of cell which is affected. Although it is a preventable disease, but it can have severe health consequences, and is a leading cause of death worldwide (Fahad and Shameem, 2018) [16]. Cervical cancer, the second most common gynecologic malignancy in females after breast cancer throughout the world, is continuing a serious health problem globally. It is one of the major causes of mortality in both developed and developing countries (Hosseini and Ghorbani, 2015) [20]. The scenario is worst in developing countries or wealthy country with low income groups. It has high mortality rate which accounts for more than 5,00,000 new cases and approximately 2,75,000 deaths occur (Medina-Alarcon *et al*., 2017; Viswanathan *et al*., 2016) [37, 66]. India beats about one fifth of the world's burden of cervical cancer (Naik *et al*., 2012). About 8.2 million patients died from cancer in 2012 (Fahad and Shameem, 2018) [16].
Persistent or chronic infection with one or more of the "high-risk" types of human papilloma virus (HPV) is the primary cause of cervical pre-cancerous lesion. During sexual relations, especially with early sexual exposure, HPV infection is most common. In most men and women who become infected with HPV, this infection will resolve spontaneously. Persistence of HPV infection if remain untreated it may lead the women to cervical pre-cancer stage which may progress to cancer within 10 to 20 years. Nowadays a large number of patients suffer from poor prognosis in spite of large number of available interventions. Majority of death due to cervical cancer can be prevented through cervical cancer prevention and control programme. For the prevention of cervical cancer, improvement in screening of cervical cancer, treatment of adult women and successful vaccination to girls against HPV is the priority basis criteria (Fahad and Shameem, 2018) [16]. Treatment of cervical cancer includes chemotherapy, radiotherapy, and surgery. Surgical treatment is recommended for patients at an early stage and fertile women. The effectiveness of chemotherapy and radiotherapy is specific for cancer cells, and it may destroy the normal cells. Patients treated with radiation or surgery develops recurrent metastatic disease. For treating advanced and refractory cervical cancer, effective therapies and innovations are required (Vooren *et al*., 2014) [67].

Several phytochemicals and plant extracts have been investigated against cervical cancer cells. Therefore, the effort for finding new anti-cancer agents with better efficacy and minimum side effects has been continued (Hosseini and Ghorbani, 2015) [20]. Researchers believed that the chemotherapy treatment is influenced by dietary phytochemical and help to cure patients from cancer (Kashafi *et al*., 2017) [27]. So, medicinal plants continue to play a significant medical and economical role (Booth *et al*., 2012) [9]. Several anti-cervical cancer drugs are derived from spices, herbs, vegetables and a variety of plants are used in folk medicine. Keeping in mind to consider natural products, about 25% of prescriptions contain active phytochemicals in the modern system of medicine. The efficacy of plants and their active constituent are being clinically tested for the treatment of cervical cancer which has to go hand-in-hand with the early lesions of cervical cancer screening program. The onset for the hunt of natural drugs for cervical cancer treatment was largely due to the very poor prognosis of synthetic drugs. Camptothecin, taxol, combretastatin and topotecan, plant derived drugs, play dominant roles in the treatment of cervical cancer (Wang *et al*., 2013) [68, 69, 70]. Topotecan was reported to be a promising anti-tumor agent for cervical cancer as it inhibits *topoisomerase* (Yakushiji *et al*., 1997) [71]. Recognition of potentially active plant-based product against cervical cancer cells will go long way for possible therapeutic usage. Keeping this in mind, attempt has been made in this review to explore the potential of phytochemicals and plant extracts known to exhibit anti-tumorigenic activity or exhibit cytotoxic effect against cervical carcinoma cells.

2. Herbal Extracts as Anti-Cervical Cancer Agent

About 65-80% population of developing countries are still using traditional medicine as a potent source of primary health care due to their affordability, accessibility, and cultural beliefs. Traditional medicinal plants may be a promising source of novel therapeutic agents, especially for cancer. It has been estimated that out of 2,50,000 medicinal plants on earth, almost 1000 species have anti-cancer potential. Thousands of species have been screened through bioassays for the search of novel plant based anti-cancer drugs (Rajendran *et al*., 2014) [47].

2.1 Aqueous extracts

The aqueous extracts of cactus pear, the fruit of *Arizona cactus* exhibit cytotoxic effect against human cervical cancer cells (HeLa). 1% cactus pear solution reduced 40-60% growth of HeLa cells whereas 5% of the solution kills almost 100% of cells within 5days with IC_{50} value of 1.8%. Cactus pear extract, at a concentration of 25% it induced apoptosis in HeLa cells by more than 50% and affected the cell cycle starting at 5% concentration by increasing cells in G1 and decreasing in S phase (Zou *et al*., 2005) [76]. *Portulaca oleracea*, a garden weed, traditionally has been used as anti-diabetic and anti-inflammation agent, has high anti-oxidant property, vitamins, dietary minerals, and iron. Aqueous extracts of *P. Oleracea* exhibited anti-proliferative and apoptotic effects against human cervical cancer cell line in a dose and time-dependent manner (Azarifar *et al*., 2015) [6]. Violet plant, an *herbaceous* plant has anti-oxidant, anti-inflammatory, anti-microbial, sedative, and anti-cancer activities. Aqueous extract of this plant has a strong inhibitory effect on proliferation of HeLa cells and cervical cancer cells which is mediated by the presence of active ingredient in the plant i.e., ethyl acetate (Kooti *et al*., 2017) [29].

Cinnamon, a known anti-inflammatory, anti-oxidant, anti-microbial, anti-diabetic, and anti-tumor agent has enormous role for growth retardation of cervical cancer cells. The aqueous extract of cinnamon obtain from the bark of *Cinnamomum cassia* L. has potent anti-cancer activity against human cervical cancer cell (SiHa) by significantly affecting the growth rate of SiHa cells in a dose-dependent manner and also by inducing apoptosis through loss of mitochondrial membrane potential (Koppikar *et al*., 2010) [30]. *Solanum nigrum*, used as traditional folk medicine due to its diuretic and anti-pyretic effects, contains steroidal glycosides, steroidal alkaloids, steroidal oligoglycosides, solamargine, and solasonine. Aqueous extract of *S. nigrum* inhibits the uterine cervical carcinoma through multiple functions by stimulating the host immune system which resulted in massive necrosis in tumor tissues. It also inhibiting PCNA gene expression, arrested the cell cycle and triggered apoptosis in tumor cells (Li *et al*., 2008) [34].

2.2 Methanolic extracts

Polar methanol/water fractions of leaves, stems and branches of *Atriplex confertifolia* cause 90% death of human cervical cancer cells (HeLa) after 8-10 hours of incubation, but don't affect monocyte control cells (Capua *et al*., 2010) [10]. Bullet wood tree, also known as Spanish cherry (*Mimusops elengi* L.) are widely used for treatment of different diseases. Methanolic extract of leaf and bark of *M. elengi* has cytotoxic potential against human cervical cancer cell line (SiHa) by inducing apoptosis. These findings suggested that extracts and compounds of this plant may be useful for preventing and treating human gynecologic cancer diseases especially cervical cancer (Ganesh *et al*., 2014) [17]. *Cassia tora* Linn, a well known ayurvedic medicinal plant, acts as a laxative, anti-periodic and is used to treat leprosy, ringworm, bronchitis and cardiac disorders. Methanolic extract of *C. tora* leaf has concentration-dependent anti-proliferative activity against human cervical cancer cells by reducing DNA content and apoptosis in cells (Rejiya *et al*., 2009) [48].

Cordia dichotoma, a medicinal plant belonging to the family *Boraginaceae* has anti-oxidant, juvenomimetic, anti-fertility, anti-inflammatory, and various pharmacological activities. The methanolic extract of *C. dichotomous* has anti-cancer activity against human cervical cancer cells (HeLa) by inducing apoptosis through either by DNA fragmentations or by mitochondrial depolarization or accumulation of reactive oxygen species (ROS). Due to anti-cancerous activity it could be a new potent cancer chemopreventive or chemotherapeutic agent for human cervical cancer cells (Rehman and Hussain, 2015). Methanolic extracts *Inula viscosa* (L.), *Retama monosperma* (L.), and *Ormeniseriolepis* Coss have significant growth inhibitory effects against human cervical carcinoma cells lines (SiHa and HeLa) due to the presence of active compounds (Merghoub *et al*., 2009) [38].

Ganoderma applanatum, belongs to the species of *Basidiomycete*, is also known as "*Elfvingia applanata*", has been used as folk medicine for the treatment of various diseases including cancer. The methanolic extract of *G. applanatum* exhibited dose-dependent cell death against breast cancer and cervical cancer cell (HEp-2 cells), with IC_{50} value of 43.2µg/ml due to the presence of γ-terpinene, D-limonene, cis-2- methyl-4-pentylthianes, s-dioxide, β-cymene, and α-terpinolene which play a major role in inducing apoptosis (Hakkim *et al*., 2016) [19]. The crude methanolic extract of the leaves of *Leea indica* significantly decreased tumor weight at a dose of 40 mg/kg/day and inhibited the

growth of human cervical cancer cells (Ca^{2+} Ski) with IC_{50} value of 19.21μM due to presence of glycosides, mollic acid arabinoside and mollic acid xyloside through either activation and release of mitochondrial pro-apoptotic proteins known as caspases under the control of Bcl-2 family of proteins or upregulating the expression of pro-apoptotic receptors (Jain *et al*., 2016) [22].

Polygonum aviculare, belongs to *Polygonaceae-Dock* family, has astringent properties that can be a natural potent chemopreventive and chemotherapeutic plant for cervical cancer patients. Methanolic extract of *P. aviculare* has a potent anti-growth effect and showed cytotoxic and apoptotic effect on human cervical cell line (Hela-S) and may be exploited as a potential source for developing novel anti-cervical cancer drugs (Mohammad *et al*., 2011) [40]. *Xylopia aethiopica*, also known as African guinea pepper, belongs to the family *Annonaceae* and has great nutritional and medicinal values such as anti-bacterial, anti-fungal, anti-plasmodial, anti-oxidant, hypotensive, and diuretic effects. Methanolic extract of *X. aethiopica* fruit has potential anti-proliferative activity against human cervical cancer cells (C-33A cells) either by arresting cell cycle at G0/G1 and G2/M phases or by increasing p53 and p21 gene expression and induces apoptosis (Adaramoye *et al*., 2011) [1].

2.3 Ethanolic extracts

Neolignans, isolated from ethanolic extracts of the aerial parts of *Saururus chinensis* has anti-proliferative property against human cervical cancer cell line (C33a). The IC50 was found to be within 0.01 μM-2.80 μM as indicated by cell proliferation assay without any remarkable cytotoxic effects on human normal lung cells as a control (Lee *et al*., 2012) [2]. Ethanolic extracts of *Coscinium fenestratum* (stems) and *Kalanchoe pinnata* (leaves) have high *in vitro* cytotoxic activity and growth inhibition against human papilloma virus infected cells (KB3-1) by regulating some viral proteins which control cell division (Kaewpiboon *et al*., 2012) [24]. Crude ethanolic extract of dried ripened *Vitex agnus-castus* fruits have anti-tumor and cytotoxicity activities against human cervical carcinoma that attributed to the cell growth, and cell death occurs through apoptosis, and this apoptotic cell death may be attributed to increased intracellular oxidation (Bachrach, 2012) [7].

Rubus occidentalis, also known as black raspberries is a rich natural source of chemopreventive phytochemicals and contains a wide range of biological active phytochemicals. Ethanolic extract of *R. occidentalis* induce apoptosis and exhibit a significant growth inhibitory effect on cervical cancer cell lines (HeLa, SiHa, C-33A) in a dose and time-dependent manner (Zhang *et al*., 2011) [74]. *Boerhaavia diffusa* L., known as "punarnava", is used for the treatment of various diseases due to its diuretic, anti-fibrinolytic, anti-convulsant, anti-bacterial, anti-inflammatory, hepatoprotective, immunomodulatory and anti-proliferative properties. The ethanolic crude root extract of *B. diffusa* exhibits cytotoxic effect and causes 30% cell death of human cervical cancer cell line (HeLa) at a concentration of 300μg/mL. Methanol: chloroform fraction can inhibit the cell proliferation through the inhibition of cell cycle at S-phase, inhibition of DNA synthesis and induction of apoptosis (Srivastava *et al*., 2011) [57].

2.4 Hydroalcoholic extracts

Boswellia serrata, a medicinal plant, belongs to *Burseraceae* family has anti-inflammatory, anti-microbial, and anti-tumor activity. Hydroalcoholic extract of *B. serrata* causes the death of human cervical cancer cells (HeLa) by inducing apoptosis (Kooti *et al*., 2017) [29]. *Satureja bachtiarica* Bunge belongs to the family *Lamiaceae*. The hydroalcoholic extract of *S. bachtiarica* Bunge has dose and time dependent growth inhibitory and anti-cancer effect against human cervical cancer cells (HeLa) due to the presence of bioactive components such as tannins, fatty substances like terpenoids and phenolics compounds (Shoushtar *et al*., 2017) [52].

2.5 Dichloromethane extracts

Dichloromethane extract of *Goniothalamus macrophyllus* root have cytotoxic effect against human cervical cancer cell (HeLa) with a IC_{50} values of 3.2μl/ml via induction of apoptosis and causes cell cycle arrest and cell death at S phase (Alabsi *et al*., 2012) [4]. Biologically active secondary metabolites from the dichloromethane extract of stem bark of *Mesua beccariana* such as stigmasterol has *in vitro* cytotoxicity, growth inhibition and anti-proliferative activity against human cervical cancer cell (HeLa) (Teh *et al*., 2012) [60]. *Bauhinia strychnifolia*, a medicinal plant of Thailand has *in vitro* cytotoxic activity against human cervical cancer cell (KB3-1) with IC_{50} value of 1.86μg/ml (Kaewpiboon *et al*., 2012) [24].

2.6 Hexane extracts

Biologically active secondary metabolites from the hexane extract of stem bark of *Mesua beccariana* such as beccamarin has *in vitro* cytotoxicity, growth inhibition and anti-proliferative activity against human cervical cancer cell (HeLa) (Teh *et al*., 2012) [60]. The crude hexane extract of *Bauhinia strychnifolia* has also high cytotoxic effect against human cervical cancer cell (KB3-1) with IC_{50} value of 1.86 μg/ml (Kaewpiboon *et al*., 2012) [24]. *Anisomeles malabarica*, belongs to the family of *Lamiaceae*, possess anti-spasmodic, diaphoretic, anti-pyretic and anti-periodic properties. The n-hexane extract of *A. malabarica* inhibit cell proliferation and induce cell death in HPV infected cervical cancer cells by apoptosis and necrosis due to the presence of secondary metabolites such as anisomelic acid, ovatodiolide, geranic acid, citral, betulinic acid, and beta-sitosterol (Preethy *et al*., 2012) [45].

2.7 Chloroform extracts

Paulownia coreana is used as health food and medicine for the treatment of cancer as well as other major infectious diseases. Chloroform soluble fraction of the leaves of *Paulownia coreana* exhibited cell growth inhibition and anti-proliferation activity in cervical cancer cell lines at a relatively low concentration (<10 μg/mL) and induces apoptosis at a high concentration (>50 μg/mL) in a time dependent manner by inducing cell cycle arrest in the S/G2 phase and caspase-dependent apoptosis through activating caspase-8, -9, and -3, the main regulators of apoptotic cell death (Jung *et al*., 2012) [23]. *Anisomeles malabarica*, belongs to the family of *Lamiaceae*, possess anti-spasmodic, diaphoretic, anti-pyretic, and anti-periodic properties. The chloroform extract of *A. malabarica* inhibit cell proliferation and induce cell death in HPV infected cervical cancer cells by apoptosis and necrosis due to the presence of secondary metabolites such as anisomelic acid, ovatodiolide, geranic acid, citral, betulinic acid, and beta-sitosterol (Preethy *et al*., 2012) [45]. Chloroform extract of Kaffir lime leaves and fruits have effective potential to reduce human cervical cancer cells (HeLa) viability in micromolar concentrations as these

extracts have anti-oxidant activity, free radical scavenging ability, anti-microbial activity, and anti-inflammatory activity due to the presence of alkaloid, flavonoid, terpenoid, tannin, and saponin compounds (Tunjung *et al*., 2015) [63].

2.8 Acetone extracts

Acetone extracts of *Origanum vulgare* (Oregano) and *Laurus nobilis* (Bay leaf) have strong *in vitro* anti-proliferation and cytotoxicity activity against human cervical cancer cell line (HeLa) by causing the hyper-condensation of chromatin and the degradation of DNA (Berrington and Lall, 2012) [8]. Acetone extract of *S. discolor* inhibited the growth and survival of human cervical cancer cell lines (HeLa) through arresting cell cycle at G2 phase and inducing apoptosis by increasing mitochondrial membrane depolarization, expression of Bax, caspase-9, caspase-3, and cleaved-poly ADP-ribose polymerase due to the presence of chrysin, a major phytochemical constituent (Kumar *et al*., 2014) [32].

3. Phytochemicals as Anti-Cervical Cancer Agent

Plant derived phytochemicals are defined as bioactive non-nutrient compounds which reduces the risk of major chronic diseases risk (Doughari *et al*., 2009) [15]. Phytochemicals are able to impede initiation or repeal the promotion step of multistep carcinogenesis (Russo *et al*., 2012) [49]. They can also stop or postpone the development of pre-cancerous cells into the malignant ones (Shen *et al*., 2014) [51].

3.1 Alkaloids

Alkaloids isolated from *Cynanchum vincetoxicum* and *Tylophora tanakae* has cytotoxic property against human cervical carcinoma cells with a IC_{50} value of 7-17nM through induction of apoptosis due to the presence of a rigid phenanthrene structure which is a prerequisite for a high cytotoxicity of the free bases, reiterating earlier findings for the *N*-oxide alkaloids (Staerk *et al*., 2002) [58]. Two isomeric indole alkaloids, naucleaorals A and B, isolated from the roots of *Nauclea orientalis* have cytotoxicity against human cervical carcinoma cell line (HeLa) with IC_{50} value of 4.0 and 7.8μg/mL, respectively (Sichaem *et al*., 2010) [53]. Another alkaloid, (6aR)-normecambroline, isolated from the bark of *Neolitsea dealbata* also inhibit human cervical carcinoma cell line (HeLa) through cell cycle arrest at G0/G1 phase and eventual apoptosis with IC_{50} of 4.0μM (Tran *et al*., 2010) [62].

3.2 Phenolic

Boerhaavia diffusa L., known as "punarnava", is a perennial creeping herb that is used for the treatment of various ailments. Pharmacological studies have demonstrated that it exhibits a range of properties such as diuretic, analgesic, anti-fibrinolytic, anti-convulsant, anti-bacterial, anti-inflammatory, hepatoprotective, immunomodulatory and anti-proliferative due to presence of phenolic compounds, namely alkaloids and amino acids (Venkatajothi, 2017) [65]. *Satureja bachtiarica* Bunge has dose and time-dependent anti-cancer effect against human cervical cancer cell (Hela) which can inhibit the growth of cells due to presence of bioactive components such as tannins, fatty substances like terpenoids and phenolics (Shoushtar *et al*., 2017) [52].

Caffeic acid (CA), a dietary phenolic phytochemical present in coffee, possess a wide variety of biological activities such as anti-oxidant, anti-thrombosis, anti-hypertensive, anti-fibrosis, anti-viral, and anti-tumor properties. The inhibitory effect of caffeic acid on human cervical cancer cells (HeLa and ME-180) proliferation by an oxidative mechanism has been reported (Kanimozhi and Prasad, 2015) [26]. Gallic acid (GA), a polyhydroxy phenolic compound, widely distributed in gallnuts, sumac, grape, green tea, oak bark, strawberry, lemon, banana, pineapple, witch hazel, and apple peel, possess inhibitory effect on HPV containing cells by inducing apoptosis and kills the cells containing HPV genome; suggesting the potential application of GA for the development of anti-HPV agents (Shi *et al*., 2016) [50].

3.3 Flavonoids

Apigenin, a plant flavonoid, inhibit the growth of human cervical cancer cells (HeLa) and was reported as a potential anti-tumor agent. Apigenin reduces the viability of HeLa cells at a concentration of 37-74μM with IC_{50} value of 35.89μM by triggering the apoptotic pathway, characterized by induction of cell cycle arrest at G1 phase, DNA fragmentation, increased expression of p21/WAF1, caspase-3, and some other mediators of apoptosis and also decreased the protein expression of anti-apoptotic factor-the Bcl-2 protein (Zheng *et al*., 2005) [75]. Hesperetin, a flavonoid, obtained from citrus fruits, have anti-atherogenic, anti-inflammatory, and anti-hypertensive effects. Concentration and time-dependent inhibition and proliferation of human cervical cancer cells (SiHa cells) by hesperetin through cell arrest at G2/M phase and increased expression of caspase-3, caspase-8, caspase-9, p53, Bax, and Fas death receptor due to the attenuation of the mitochondrial membrane has been reported (Alshatwi *et al*., 2013) [5]. Isoliquiritigenin, a flavonoid, found in licorice (legume) and shallot (Liliaceae), has potent anti-oxidant, anti-inflammatory, anti-platelet aggregation and cancer preventing properties. Growth inhibition of human cervical cancer cells (HeLa) by isoliquiritigenin through blocking of cell cycle progression at G2/M phase, inducing apoptotic cell death, changes in the expression of mitochondrial proteins and subsequently triggering of mitochondrial apoptotic pathway has been reported (Hsu *et al*., 2009) [21].

Kaempferol, a flavonoids, has anti-oxidant and anti-tumor properties and also shown to induce apoptosis in cancer cells. Cytotoxic activity of kaempferol against human cervical cancer cells (HeLa) with IC_{50} value of 10.48μM through the induction of cellular apoptosis and aging, by regulating the p13k/AKT and hTERT pathways has been reported (Kashafi *et al*., 2017) [27]. Protoapigenone, a flavonoid, isolated from *Thelypteris torresiana*, has *in vitro* cytotoxic activity against human cervical cancer cells (C33A, HeLa, and SiHa). Suppression of cervical cancer cells both *in vivo* and *in vitro* by protoapigenone through the inhibition of PIK3 signaling pathway, AKT1/MTOR activity, activation of caspases-9, -8, and -3, also PARP cleavage and promotion of apoptosis has been reported (Chen *et al*., 2013) [13]. Silymarin, a flavonoid, is the active component of *Silybum marianum* (milk thistle) which has anti-cancer potential in preclinical trials through growth inhibition of cancer cells including cervical cancer cells (Post-White *et al*., 2007) [44]. Genistein, the most abundant isoflavone in soybeans, possesses a dose-dependent inhibition effect on human cervical cell lines (CaSki and ME180) through cell cycle arrest at G2/M phase and augmentation of cellular apoptosis (Moga *et al*., 2016) [39].

3.4 Polyphenols

The polyphenol-rich fractions obtained from the extracts of rowan berries, raspberry, lingonberry, cloudberry, arctic bramble, and strawberry have potent growth inhibitory and anti-proliferative activity against human cervical cancer cell (HeLa) due to presence of high content of ellagitannins which

release ellagic acid, a potent anti-proliferative compound under physiological conditions (McDougall *et al*., 2008) [36]. Other polyphenolic compound such as ethyl gallate, isolated from ethanol extract of *Acacia nilotica* leaves has cytotoxic and anti-proliferative effect on human cervical cancer cells (HeLa) with IC_{50} value of 72µg/mL (Kalaivani *et al*., 2011) [25]. Compounds such as 6-Methoxygossypol and 6, 6'-dimethoxygossypol, isolated from the root tissue of cotton plant, also belongs to the polyphenolic group, and have dose-dependent growth inhibitory effect against human cervical cancer cell line (SiHa) with IC_{50} value of 10ppm for both the compounds (Wang *et al*., 2008) [68, 69, 70].

The root of *C*urcumin *longa* contains curcumin, a natural compound; and the fruits of strawberries, raspberries, and walnuts contain ellagic acid, a polyphenol. Curcumin has been used in food additive, cosmetic, and as a traditional herbal medicine for its various biological activities such as anti-inflammatory, anti-oxidant, anti-carcinogenic, thrombo suppressive, cardioprotective, anti-arthritic, and anti-infectious properties. The combination of curcumin and ellagic acid at various concentrations exhibits anticancer properties than either of the drugs when used alone by restoring p53 and inducing ROS generation and DNA damage. The mechanistic study indicated that curcumin and ellagic acid show anti-HPV activity as evidenced by a decrease in HPV E6 oncoprotein on HeLa cells and provides an important lead for anticancer therapeutics (Kumar *et al*., 2016) [31]. Suppresion of human cervical cancer at all three stages of carcinogenesis i.e., initiation, promotion, and progression by curcumin and its product (ferulic acid) has been reported (Di Domenico *et al*., 2012) [14].

Epigallocatechin-3-gallate (EGCG), a polyphenols found in green tea, has anti-tumor activity against various types of cancers both *in vitro* and *in vivo*. *In vitro* suppression of cervical cancer cell growth by EGCG through the induction of apoptosis and cell cycle arrests at the G1 phase has been reported (Ahn *et al*., 2003) [2]. Iridomyrmecin, a plant iridoid compound, belongs to polyphenolic group, has anti-oxidant activity that exhibits potent cytotoxic and anti-tumor activity against human cervical cancer cells (HeLa) through cell cycle arrest at G1 phase, loss of mitochondrial membrane potential, inducing early and late apoptosis, down-regulation of PI3K/Akt protein expressions, and up-regulation of lncRNA CCAT2 expression (Lin *et al*., 2016) [35]. Resveratrol, a polyphenol, found in the seeds and skins of grapes, red wine, mulberries, and peanuts inhibit proliferation and induce autophagy and apoptotic death in cervical cancer cells through the inhibition of NF-kB and AP-1 trans-activation and suppression of the transcription of MMP-9 (Moga *et al*., 2016) [39].

3.5 Naphthoquinone esters

Rhinacanthins-C, -N and -Q isolated from dried roots of *Rhinacanthus nasutus*, a plant traditionally used in Thai folk medicine for treating various cancers including cervical and hepatocellular cancers, suppressed HeLa cells by arresting the cell cycle at G2/M phase that helps to prevent further damage and give the cell time to repair the defect, or undergoes apoptosis by activation of caspase-3 pathway (Siripong *et al*., 2006) [55]. Rhinacanthone, one of the main bioactive naphthoquinones, isolated from *Rhinacanthus nasutus*, possess dose-dependent cytotoxic and anti-proliferative activity against human cervical cancer cells (HeLa) by arresting cell cycle at G2/M phase, modulation of Bcl-2 family, down regulation of surviving and up-regulation of apoptosis inducing factor (AIF protein) as well as activations of mitochondria mediated caspase-dependent and caspase-independent signalling pathways (Siripong *et al*., 2009) [54]. Azaanthraquinone compound such as laoticuzanone A, isolated from the stems of *Goniothalamus laoticus* has cytotoxic activiity against human cervical cancer cells (HeLa) with IC_{50} values of 0.50µg/ml (Tip-Pyang *et al*., 2010) [61]. Diospyrin, a bisnaphthoquinonoid natural product has similar result of apotosis induction, chromatin condensation and nuclear fragmentation of HeLa cells and the apoptosis was believed to be mediated via activation of caspase-3 and caspase-8 (Chakrabarty *et al*., 2002) [11].

3.6 Phorbol esters

Phorbol esters, isolated from meal prepared from the kernel of *Jatropha curcas*, has dose-dependent cytotoxic and anti-proliferation effects on human cervical cancer cells (HeLa) with IC_{50} of 133.0±1.96µg through morphological changes, DNA fragmentation and finally apoptosis. Phorbol esters isolated from Jatropha meal activates the *phosphokinase-C delta* (*PKC-δ*) and down-regulates the proto-oncogenes (*c-Myc*, *c-Fos* and *c-Jun*), suggesting that these changes probably lead to the activation of caspase-3 protein, results of apoptosis in HeLa cell. Hence, Jatropha meal is promising as an alternative to replace the chemotherapeutic drugs for cancer therapy (Oskoueian *et al*., 2012) [43].

4. Phyto-molecules as Anti-Cervical Cancer Agent

To avoid undesirable side effects of commercial anti-cancer drug, several classes of anti-cancer drugs have been developed from natural products. Searching of potent, safe, and selective anti-cancer compounds is crucial for new drug development in cancer research. 60% of currently used anti-cancer agents are derived from natural sources (Kumar *et al*., 2014) [32]. Many chemical compounds of herbal plants have been explored for their potential anti-tumor activity and safety (Su *et al*., 2014). Most medicinal herbs contain anti-oxidant and number of phytochemicals that prevent cancer or potentiate chemotherapy, and decrease cell proliferation, metastasis, angiogenesis and induce apoptosis (Kashafi *et al*., 2017) [27].

Amoora rohituka is used as herbal medicine for cancer, tumor, liver, and spleen diseases. Amooranin, a triterpene acid, isolated from *A. rohituka*, possesses significant anti-cancer potential that inhibits the growth and spread of cervical cancer cells (HeLa) by arresting cell cycle at G2/M phase and by inducing apoptosis (Umadevi *et al*., 2013) [64]. Carnosic acid (CA), one of the major bioactive compound of *Rosmarinus officinalis* L., possess *in vitro* anti-inflammatory and anti-cancer activities in cervical cancer cells by upregulation of apoptosis and ROS production that leads to the phosphorylation of *c-Jun N-terminal kinase* and activation of endoplasmic reticulum stress, promoting the progression of apoptosis through stimulating caspase-3 expression (Su *et al*., 2016). Isoatriplicolide tiglate, isolated from medicinal plants *Paulownia coreana*, act as anti-proliferation agents against cervical cancer cell lines by inducing cell cycle arrest at S/G2 phase and caspase-dependent apoptosis, particularly by activating caspase-8, -9, and -3 has been reported (Kma, 2013) [28].

Cisplatin, the cell cycle non-specific agent, is the most effective common drug extensively used in chemotherapy, inhibits the division of tumor cells by triggering obstacles in DNA replication. Matrine, isolated from *Sophora flavescens*, belongs to tetracyclic thiazides, possess traditional medicinal

functions such as protecting the cardiovascular system, improving patients' immunologic function, and protecting liver along with anti-viral and anti-tumor roles. The combined treatment of matrine and cisplatin, with a synergistic effect, can notably inhibit the growth of tumor in U14 rats with cervical cancer, by significantly improve the immunologic function of rats and decrease the toxic reaction in the process of treatment (Zhang *et al*., 2015) [72]. Nujiangexanthone A, isolated from the leaves of Chinese endemic species *Garcinia nujiangensis*, exhibits cytotoxicity against an array of human tumor cell lines. It acts as a crucial agent in treating cervical cancer. Nujiangexanthone A exhibited selective cytotoxicity against cervical cancer cells (HeLa and SiHa) by inducing cell cycle arrest at G0/G1 phase and down-regulating the cyclins A, B1, and E1, as well as cyclin-dependent kinases 2,4, and 6, during the selective restoration of p27 (Zhang *et al*., 2016) [59]. Oleanolic acid, belongs to oleanane triterpene group of natural products, possesses a range of promising biological and medicinal effects. In a concentration and time dependent manner, oleanolic acid methyl vanillate ester exhibits anticancer activity on HeLa cervical cancer cells by inducing both early and late apoptosis, and ROS generation (Song *et al*., 2015) [56]. Withaferin A, an active component of the medicinal plant *Withania somnifera*, possesses anti-inflammatory, anti-tumor, anti-stress, anti-oxidant, immunomodulatory, hemopoietic and rejuvenating properties. Withaferin A exhibit inhibitory effects against human cervical cancer cells through inducing p53- dependent apoptosis by repression of HPV oncogenes and upregulation of tumor suppressor proteins (Munagala *et al*., 2011) [41]. Ceratodictyols A and B and mixtures of ceratodictyols C and D and ceratodictyols E and F, isolated from the red alga-sponge assemblage Ceratodictyon spongiosum/Haliclona cymaeformis have cytotoxic activity against HeLa cells with IC_{50} value of 67μM for each (Akiyama *et al*., 2009) [3].

Yuk-Hap Tang *(Angellicae gigantis, Cnidii rhizome, Paeoniae lactiflorae, Rehmanniae rhizoma)* has effective cytotoxic and killing property against cervical cancer cells (HeLa) by activating caspase-3, -6 and -9; increasing pro-apoptotic protein, Bax; decreasing anti-apoptotic protein, Bcl-2; and also decreasing the expression of Mn-SOD protein in HeLa cells (Chae *et al*., 2004) [12]. RCE-4, isolated from Reineckia carnea, exhibit dose-dependent potent cytotoxicity against cervical cancer cells (CaSki) with IC_{50} value of 3.37μM, by inducing mitochondrial mediated apoptosis through nuclear shrinkage, condensation, fragmentation and decreasing the mitochondrial membrane potential which release of *cytochrome c* from the mitochondria into the cytoplasm; suggesting its application as an anti-cancer agent (Wang *et al*., 2013) [68, 69, 70]. It was reported that the cytotoxicity of commercially available anti-cancer drug i.e., cisplatin, in combination with Noni was enhanced significantly against cervical cancer cell line (HeLa and SiHa) by decreasing the cellular survival and inducing the apoptosis through increasing the expression of pro-apoptotic (Bax) protein and decreasing the expression of anti-apoptotic (Bcl-2) protein (Gupta *et al*., 2013) [18].

5. Conclusion

In spite of several treatment strategies, the mortality rate due to cancer has been increasing. Plant-derived molecules or drugs could be an effective alternative for the treatment of different types of cancer. Present review focuses on experimental studies conducted on animals has confirmed the anti-cancerous activity of herbal drugs along with other pharmacological actions like anti-oxidant, analgesic, anti-inflammatory, anti-metastatic, etc. due to the presence of flavonoids, phenols, lignans, polysaccharides, etc but clinical studies are lacking behind. Plant extracts or its constituents that kill human cervical carcinoma cells *in vitro*, their efficacies needed to be further investigated in various cervical cell lines and more importantly, in *in vivo* experimental animal systems. However, more *in vivo* research investigations will probably generate better understanding on the role of the plant extracts or its constituents with an aim at their possible use as an alternative and safe anti-cancer drug. It will even be desirable if plant-based drug itself is not so effective but in combination with known commercially used anti-cancer drug, it is able to enhance the effectiveness of the drug, then this can result into reduction in the drug dose and the resultant side effects can be minimized.

However, there are many limitations and ethical issues regarding the safety and efficacy of these drugs to be used in human beings. Hence, there is need for further clinical studies to establish the efficacy and safety of these drugs. Therefore, phase II trials in patients with precancerous lesion on cervix are needed to explore.

6. Acknowledgement

Author express gratefulness to Ramananda College, Bishnupur for providing the facilities to execute this review work. Author of this review paper is highly obliged to the Principal, Ramananda College, Bishnupur, Bankura for constant help and encouragement.

7. Declaration of interest

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

8. References

1. Adaramoye OA, Sarkar J, Singh N, Meena S, Changkija B, Yadav PP *et al*. Antiproliferative action of *Xylopia aethiopica* fruit extract on human cervical cancer cells. Phytother. Res., 2011; 25(10):1558-1563.
2. Ahn WS, Huh SW, Bae SM, Lee IP, Lee JM, Namkoong SE *et al*. A major constituent of green tea, EGCG, inhibits the growth of a human cervical cancer cell line, CaSki cells, through apoptosis, G1 arrest, and regulation of gene expression. DNA Cell. Biol. 2003; 22(3):217-224.
3. Akiyama T, Ueoka R, van Soest RWM, Matsunaga S. Ceratodictyols, 1-glyceryl ethers from the red alga-sponge association *Ceratodictyon spongiosum/Haliclona cymaeformis*. J Nat. Prod. 2009; 72(8):1552-1554.
4. Alabsi AM, Ali R, Ali AM, Al-Dubai SA, Harun H, Abu Kasim NH *et al*. Apoptosis induction, cell cycle arrest and *in vitro* anticancer activity of gonothalamin in a cancer cell lines. Asian Pac. Cancer Prev. 2012; 13(10):5131-5136.
5. Alshatwi AA, Ramesh E, Periasamy VS, Subash-Babu P. The apoptotic effect of hesperetin on human cervical cancer cells is mediated through cell cycle arrest, death receptor, and mitochondrial pathways. Fundam. Clin. Pharmacol. 2013; 27(6):581-592.
6. Azarifar Z, Mortazavi M, Farhadian R, Parvari S, Roushnadeh AM. Cytotoxicity effects of aqueous extract of *Purtulaca oleracea* on HeLa cell line. Pharm. Sci. 2015; 21:41-45.

7. Bachrach ZY. Contribution of selected medicinal plants for cancer prevention and therapy. Sci. J Fac. Med. Nis. 2012; 29(3):117-123.
8. Berrington D, Lall N. Anticancer Activity of Certain Herbs and Spices on the Cervical Epithelial Carcinoma (HeLa) Cell Line. Evid. Based Complement Alternat. Med., 2012; 564927, 11.
9. Booth GM, Malmstrom RD, Kipp E, Paul A. Cytotoxicity of selected medicinal and nonmedicinal plant extracts to microbial and cervical cancer cells. J. Biomed. Biotechnol., 2012, 106746.
10. Capua CJ, Hopson NP, Stewart CMM, Johnston GR, Neill KLO, Schaalji GB *et al*. Cytotoxicity of *Atriplex confertifolia*. J Toxicol. 2010; 976548, 7.
11. Chakrabarty S, Roy M, Hazra B, Bhattacharya RK. Induction of apoptosis in human cancer cell lines by diospyrin, a plant-derived bisnaphthoquinonoid, and its synthetic derivatives. Cancer Lett. 2002; 188(1-2):85-93.
12. Chae HJ, Park JM, Lee GY, Park HR, Chae SW, Jeong GS *et al*. Yuk-Hap-Tang induces apoptosis by intervening mn-SOD in human cervical carcinoma HeLa cells. Am. J Chin. Med. 2004; 32(6):883-895.
13. Chen YJ, Kay N, Yang JM, Lin CT, Chang HL, Wu YC *et al*. Total synthetic protoapigenone WYC02 inhibits cervical cancer cell proliferation and tumour growth through PIK3 signalling pathway. Basic Clin. Pharmacol. Toxicol. 2013; 113(1):8-18.
14. Di Domenico F, Foppoli C, Coccia R, Perluigi M. Antioxidants in cervical cancer: Chemopreventive and chemotherapeutic effects of polyphenols. Biochem. Biophys. Acta. 2012; 1822(5):737-747.
15. Doughari JH, Human IS, Benade AJ, Ndakidemi PA. Phytochemicals as chemotherapeutic agents and antioxidants: Possible solution to the control of antibiotic resistant verocytotoxin producing bacteria. Planta medica., 2009; 3(11):839-848
16. Fahad T, Shameem I. An evidence based approach to the management of cervical cancer in unani system of medicine: A review. J of Pharmacogn. Phytochem. 2018; 7(2):2536-2544
17. Ganesh G, Abhishek T, Saurabh M, Sarada NC. Cytotoxic and apoptosis induction potential of *Mimusops elengi* L. in human cervical cancer (SiHa) cell line. J King Saud Univ. Sci. 2014; 26(4):333-337.
18. Gupta RK, Banerjee A, Pathak S, Sharma C, Singh N. Induction of mitochondrial-mediated apoptosis by *Morinda citrifolia* (Noni) in human cervical cancer cells. Asian Pac. J Cancer Prev. 2013; 14(1):237-242.
19. Hakkim FL, Al-Buloshi M, Achankunju J. Chemical composition and anti-proliferative effect of Oman's *Ganoderma applanatum* on breast cancer and cervical cancer cells. J Taibah. Univ. Med. Sci. 2016; 11(2):145-151.
20. Hosseini A, Ghorbani A. Cancer therapy with phytochemicals: evidence from clinical studies. Avicenna J Phytomed. 2015; 5(2):84-97.
21. Hsu YL, Chia CC, Chen PJ, Huang SE, Huang SC, Kuo PL. Shallot and licorice constituent isoliquiritigenin arrests cell cycle progression and induces apoptosis through the induction of ATM/p53 and initiation of the mitochondrial system in human cervical carcinoma HeLa cells. Mol. Nutr. Food Res. 2009; 53(7):826-835.
22. Jain S, Dwivedi J, Jain PK, Satpathy S, Patra A. Medicinal plants for treatment of cancer: A brief review. Pharmacog. J. 2016; 8(2):87-102.
23. Jung S, Moon HI, Ohk J, Lee S, Li C, Kim SK, Lee MS. Inhibitory effect and mechanism on antiproliferation of isoatriplicolide tiglate (PCAC) from *Paulownia coreana*. Molecules, 2012; 17(5):5945-5951.
24. Kaewpiboon C, Lirdprapamongkol K, Srisomsap C, Winayanuwattikun P, Yongvanich T, Puwaprisirisan P *et al*. Studies of the *in vitro* cytotoxic, antioxidant, lipase inhibitory and antimicrobial activities of selected Thai medicinal plants. BMC Comp. Altern. Med. 2012; 12:217-224.
25. Kalaivani T, Rajasekaran C, Mathew L. Free radical scavenging, cytotoxic, and hemolytic activities of an active antioxidant compound ethyl gallate from leaves of *Acacia nilotica* (L.) Wild. Ex. Delile subsp. indica (Benth.) Brenan. J Food Sci. 2011; 76(6):144-149.
26. Kanimozhi G, Prasad NR. Anticancer Effect of Caffeic Acid on Human Cervical Cancer Cells; In: Coffee in Health and Disease Prevention, 2015, 655-661.
27. Kashafi E, Moradzadeh M, Mohamadkhani A, Erfanian S. Kaempferol increases apoptosis in human cervical cancer HeLa cells via PI3K/AKT and telomerase pathways. Biomed. Pharmacother. 2017; 89:573-577.
28. Kma L. Roles of plant extracts and constituents in cervical cancer therapy. Asian Pac. J Cancer Prev. 2013; 14(6):3429-3436.
29. Kooti W, Servatyari K, Behzadifar M, Asadi-Samani M, Sadeghi F, Nouri B *et al*. Effective medicinal plant in cancer treatment, Part 2: Review study. J Evid. Based Complem. Altern. Med. 2017; 22(4):982-995.
30. Koppikar SJ, Choudhari AS, Suryavanshi SA, Kumari S, Chattopadhyay S, Kaul-Ghanekar R. Aqueous cinnamon extract (ACE-c) from the bark of *Cinnamomum cassia* causes apoptosis in human cervical cancer cell line (SiHa) through loss of mitochondrial membrane potential. BMC Cancer, 2010; 10:210.
31. Kumar D, Basu S, Parija L, Rout D, Manna S, Dandapat J, Debata PR. Curcumin and ellagic acid synergistically induce ROS generation, DNA damage, p53 accumulation and apoptosis in HeLa cervical carcinoma cells. Biomed. Pharmacother. 2016; 81:31-37.
32. Kumar A, Deepa B, Saravanan R, Hameed SA. Reactive oxygen and nitrogen species scavenging and anticancer potential of *Cissus quadrangularis* L. against EAC cell line. Int. J Pharm. Pharm. Sci. 2014; 6:269-274.
33. Lee YJ, Kim J, Yi JM, Oh SM, Kim NS, Kim H *et al*. Anti-proliferative neolignans from *Saururus chinensis* against human cancer cell lines. Biol. Pharm. Bull. 2012; 35(8):1361-1366.
34. Li J, Li Q, Feng T, Li K. Aqueous extract of *Solanum nigrum* inhibit growth of cervical carcinoma (U14) via modulating immune response of tumor bearing mice and inducing apoptosis of tumor cells. Fitoterapia, 2008; 79(7-8):548-556.
35. Lin L, Cheng XL, Li MZ, Wang T, Dong MH, Wang ZY *et al*. Antitumor effects of iridomyrmecin in HeLa cervical cancer cells are mediated via apoptosis induction, loss of mitochondrial membrane potential, cell cycle arrest and down-regulation of PI3K/Akt and up-regulation of lncRNA CCAT2 expression. Banglad. J. Pharmacol. 2016; 11(4):856-862.
36. McDougall GJ, Ross HA, Ikeji M, Stewart D. Berry extracts exert different antiproliferative effects against cervical and colon cancer cells grown *in vitro*. J Agric. Food Chem. 2008; 56(9):3016-3023.

37. Medina-Alarcon KP, Voltan AR, Fonseca-Santos B, Moro IJ, de Oliveira Souza F, Chorilli M *et al*. Highlights in nanocarriers for the treatment against cervical cancer. Mater. Sci. Eng. C. Mater. Biol. Appl. 2017; 80:748-759.
38. Merghoub N, Benbacer L, Amzazi S, Morjani H, Mzibri ME. Cytotoxic effect of some Moroccan medicinal plant extracts on human cervical cell lines. J Med. Plants Res. 2009; 3(12):1045-1050.
39. Moga MA, Dimienescu OG, Arvatescu CA, Mironescu A, Dracea L, Ples L. The role of natural polyphenols in the prevention and treatment of cervical cancer-an overview. Molecules, 2016; 21(8):1-32.
40. Mohammad R, Hossein B, Davood F, Farnaz T, Ali F, Yusef R. The apoptotic and cytotoxic effects of *Polygonum avicular* extract on HeLa-S cervical cancer cell line. Afr. J Biochem. Res. 2011; 5:373-378.
41. Munagala R, Kausar H, Munjal C, Gupta RC. Withaferin A induces p53-dependent apoptosis by repression of HPV oncogenes and upregulation of tumor suppressor proteins in human cervical cancer cells. Carcinogenesis, 2011; 32(11):1697-1705.
42. Naik PR, Nagraj, Nirgude AS. Awareness of cervical cancer and effectiveness of educational intervention programme among students in a rural area of Andhra Pradesh. Healthline, 2012; 3(2):41-45.
43. Oskoueian E, Abdullah N, Ahmad S. Phorbol esters from *Jatropha* meal triggered apoptosis, activated PKC-δ, caspase-3 proteins and down-regulated the proto-oncogenes in MCF-7 and HeLa cancer cell lines. Molecules. 2012; 17(9):10816-10830.
44. Post-White J, Ladas EJ, Kelly KM. Advances in the use of milk thistle (*Silybum marianum*). Integr. Cancer Ther. 2007; 6(2):104-109.
45. Preethy CP, Padmapriya R, Periasamy VS, Riyasdeen A, Srinag S, Krishnamurthy H *et al*. Antiproliferative property of n-hexane and chloroform extracts of *Anisomeles malabarica* (L). R. Br. In HPV16- positive human cervical cancer cells. J Pharmacol. Pharmacother. 2012; 3(1):26-34.
46. Rahman A, Hussain A. Anti-cancer activity and apoptosis inducing effect of methanolic extract of *Cordia dichotoma* against human cancer cell line. J Bangladesh Pharm. Soc. 2015; 10(1):27-34.
47. Rajendran S, Saravanan R, Ramalingam S, Hameed SA. Antiproliferative and antioxidant activity of *Gynandropsis pentaphylla* Linn on MCF-7 cell line. Int. J Pharm. Pharm. Sci. 2014; 6(7):496-502.
48. Rejiya CS, Cibin TR, Abraham A. Leaves of *Cassia tora* as a novel cancer therapeutic-an *in vitro* study. Toxicol. in Vitro, 2009; 23(6):1034-1038.
49. Russo M, Spagnuolo C, Tedesco I, Bilotto S, Russo GL. The flavonoid quercetin in disease prevention and therapy: facts and fancies. Biochem. Pharmacol. 2012; 83(1):6-15.
50. Shi L, Lei Y, Srivastava R, Qin W, Chen JJ. Gallic acid induces apoptosis in human cervical epithelial cells containing human papilloma virus Type 16 episomes. J Med. Virol. 2016; 88(1):127-134.
51. Shen T, Khor SC, Zhou F, Duan T, Xu YY, Zheng YF *et al*. Chemoprevention by lipid-soluble tea polyphenols in diethylnitrosamine/Phenobarbital induced hepatic pre-cancerous lesions. Anticancer Res. 2014; 34(2):683-93.
52. Shoushtar AB, Sazgar H, Pirbaloti AG. Cytotoxic effect of hydroalcoholic extract from *Satureja bachtiarica* bunge on HeLa cancer cell line. J Herb. Drugs. 2017; 7:223-229.
53. Sichaem J, Surapinit S, Siripong P, Khumkratok S, Jong-aramruang J, Tip-pyang S. Two new cytotoxic isomeric indole alkaloids from the roots of *Nauclea orientalis*. Fitoterapia, 2010; 81(7):830-833.
54. Siripong P, Hahnvajanawong C, Yahuafai J, Piyaviriyakul S, Kanokmedakul K, Kongkathip N *et al*. Induction of apoptosis by rhinacanthone isolated from *Rhinacanthus nasutus* roots in human cervical carcinoma cells. Biol. Pharm. Bull. 2009; 32(7):1251-1260.
55. Siripong P, Yahuafai J, Shimizu K, Ichikawa K, Yonezawa S, Asai T *et al*. Induction of apoptosis in tumor cells by three naphthoquinone esters isolated from Thai medicinal plant: *Rhinacanthus nasutus* KURZ. Biol. Pharm. Bull. 2006; 29(10):2070-2076.
56. Song X, Liu CC, Hong YR, Zhu XC. Anticancer activity of novel oleanolic acid methyl ester derivative in HeLa cervical cancer cells is mediated through apoptosis induction and reactive oxygen species production. Bangladesh J Pharmacol. 2015; 10(4):896-902.
57. Srivastava R, Saluja D, Dwarakanath BS, Chopra M. Inhibition of human cervical cancer cell growth by ethanolic extract of *Boerhaavia diffusa* Linn. (Punarnava) root. Evid. Based Complement. Alternat. Med. 2011, 427031, 13.
58. Staerk D, Lykkeberg AK, Christensen J, Budnik BA, Abe F, Jaroszewski JW. *In vitro* cytotoxic activity of phenanthroindolizidine alkaloids from *Cynanchum vincetoxicum* and *Tylophora tanakae* against drug-sensitive and multidrug-resistant cancer cells. J Nat. Prod. 2002; 65(9):1299-1302.
59. Su K, Wang CF, Zhang Y, Cai YJ, Zhang YY, Zhao Q. The inhibitory effects of carnosic acid on cervical cancer cells growth by promoting apoptosis via ROS-regulated signaling pathway. Biomed. Pharmacother. 2016; 82:180-181.
60. Teh SS, Cheng Lian Ee G, Mah SH, Lim YM, Rahmani M. *Mesua beccariana* (Clusiaceae), a source of potential anti-cancer lead compounds in drug discovery. Molecules, 2012; 17(9):10791-10800.
61. Tip-pyang S, Limpipatwattana Y, Khumkratok S, Siripong P, Sichaem J. A new cytotoxic 1-azaanthraquinone from the stems of *Goniothalamus* laoticus. Fitoterapia, 2010; 81(7):894-896.
62. Tran TD, Pham NB, Fechner G, Quinn RJ. Chemical investigation of drug-like compounds from the Australian tree, Neolitseadealbata. Bioorg. Med. Chem. Lett., 2010; 20(19):5859-5863.
63. Tunjung WA, Cinatljr J, Michaelis M, Smales CM. Anti-cancer effect of kaffir lime (*Citrus hystrix* DC) leaf extract in cervical cancer and neuroblastoma cell lines. Procedia. Chem. 2015; 14:465-468.
64. Umadevi M, Kumar KPS, Bhowmik D, Duraive S. Traditionally used anticancer herbs in India. J. Med. Plants Stud. 2013; 1(3):56-74.
65. Venkatajothi R. *In-vitro* anticancer activity of *Boerhaavia diffusa* Linn. Int. J Curr. Res. Biol. Med. 2017; 2:20-24.
66. Viswanathan AN, Dizon DS, Gien LT, Koh WJ. Chapter 58-Cervical Cancer. Clinical Radiation Oncology. 4th ed. Philidelphia, PA: Elsevier, 2016, 1173-202.
67. Vooren KV, Curto A, Garattini L. Curing cervical cancer or preventing it: A case of opportunity cost in the long run? Vaccine, 2014; 32(51):6867-6869.

68. Wang G, Huang W, He H, Fu X, Wang J, Zou K *et al*. Growth inhibition and apoptosis-inducing effect on human cancer cells by RCE-4, a spirostanol saponin derivative from natural medicines. Int. J Mol. Med. 2013; 31:219-224.
69. Wang SJ, Zheng CJ, Peng C, Zhang H, Jiang YP, Han T *et al*. Plants and cervical cancer: An overview. Expert Opin. Investig. Drugs. 2013; 22(9):1133-1156.
70. Wang X, Beckham TH, Morris JC, Chen F, Gangemi JD. Bioactivities of gossypol, 6-methoxygossypol, and 6,6'-dimethoxygossypol. J Agric. Food Chem. 2008; 56:4393-4398.
71. Yakushiji M, Sugiyama T, Ushijima K. Promising new drugs for gynecological cancer. Gan to Kagaku Ryoho, 1997; 24(13):1932-1937.
72. Zhang GL, Jiang L, Yan Q, Liu RH, Zhang L. Anti-tumor effect of matrine combined with cisplatin on rat models of cervical cancer. Asian Pac. J Trop. Med., 2015; 8(12):1055-1059.
73. Zhang L, Feng J, Kong S, Wu M, Xi Z, Zhang B *et al*. Nujiangexathone A, a novel compound from *Garcinia nujiangensis*, suppresses cervical cancer growth by targeting hnRNPK. Cancer Lett. 2016; 380(2):447-456.
74. Zhang Z, Knobloch TJ, Seamon LG, Stoner GD, Cohn DE, Paskett ED *et al*. A black raspberry extract inhibits proliferation and regulates apoptosis in cervical cancer cells. Gynecol. Oncol. 2011; 123(2):401-406.
75. Zheng PW, Chiang LC, Lin CC. Apigenin induced apoptosis through p53-dependent pathway in human cervical carcinoma cells. Life Sci., 2005; 76(12):1367-1379.
76. Zou DM, Brewer M, Garcia F, Feugang JM, Wang J, Zang R *et al*. Cactus pear: a natural product in cancer chemoprevention. Nutr. J. 2005; 4:25-26.