Medicinal plants and cervical cancer therapy: An overview

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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 spieces, 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 (Yakushi 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 IC50 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].

Cinnamom, 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 cinnamom 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, steroidol oligoglycosides, solamargin, 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) [40].

*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 *Ormeniseriolopsis* 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 *Basidiomycete*, is also known as “Elvingia 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 IC50 value of 43.2μg/ml due to the presence of γ-terpine, D-limonene, cis-2- methyl-1-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 (Ca²⁺ Ski) with IC₅₀ value of 19.21µM due to presence of glycosides, mollic acid arabinoside and mollic acid xyliside through either activation and release of mitochondrial pro-apoptotic proteins known as caspasases under the control of Bcl-2 family of proteins or upregulating the expression of pro-apoptotic receptors (Jain et al., 2016) [25].

Polygonum aviculae, belongs to Polygonaceae-Dock family, has an astringent properties that can be a natural potent chemopreventive and chemotherapeutic plant for cervical cancer patients. Methanolic extract of P. aviculae 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) [26]. Xylophia 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 chinesis 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 IC₅₀ values of 3.2μl/ml via induction of apoptosis and causes cell cycle arrest and cell death at S phase (Alabi et al., 2012) [4]. Biologically active secondary metabolites from the dichloromethane extract of stem bark of Mesua beccariana such as stigmastanol 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 IC₅₀ 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 IC₅₀ value of 1.86 µg/ml (Kaewpiboon et al., 2012) [24]. Anisomeles malabarica, belongs to the family of Lamiaceae, possesses 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 anisomic 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, -3, the main regulators of apoptotic cell death (Jung et al., 2012) [123]. 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 anisomic 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 chrysosin, a major phytochemical constituent (Kumar et al., 2014) [52].

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 IC50 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, naucleorals A and B, isolated from the roots of Nauclea orientalis have cytotoxicity against human cervical carcinoma cell line (HeLa) with IC50 value of 4.0 and 7.8μg/mL, respectively (Sichaem et al., 2010) [53]. Another alkaloid, (6αR)-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 IC50 of 4.0μM (Tran et al., 2010) [62].

3.2 Phenolic
Boerhavia 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-fibrioinolytic, 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) [28]. 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) [59].

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 IC50 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 IC50 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 PI3K 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) [30]. 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) [66, 69, 70].

The root of *Curcumin 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]. Suppression 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 PTEN/Akt protein expressions, and up-regulation of IncRNA 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-κB 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]. Azaantheraquinone compound such as laoticuzanone A, isolated from the stems of *Goniothalamus laoticus* has cytotoxic activity against human cervical cancer cells (HeLa) with IC_{50} values of 0.50μg/mL (Tip-Pyang et al., 2010) [60]. Diospyrin, a bisnaphthoquinonoid natural product has similar result of apoptosis 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 (Oskouieian et al., 2012) [43].

### 4. Phytoregulates 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. Amooran, 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). Isoatricolicidine tiglate, isolated from medicinal plants *Pau dovinia 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 nuijjangensis, 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 sommifera, 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) [42]. Ceratodicytols A and B and mixtures of ceratodicytols C and D and ceratodicytols E and F, isolated from the red alga-sponge assemblage Ceratodicytton spongiosum/Haliclona cymaeformis have cytotoxic activity against HeLa cells with IC50 value of 67μM for each (Akiyama et al., 2009) [3].

Yuk-Hap Tang (Angelicca gigantis, Cnidii rhizome, Paemias lactiflorae, Rehmannia rhizoma) has effective cytotoxic and killing property against cervical cancer cells (HeLa) through increasing the expression of pro-apoptotic (Bax) protein; decreasing 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.

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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


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