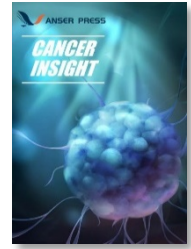




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Therapeutic Effects of Natural Products Isolated from Different Microorganisms in Treating Cervical Cancer: A Review

Dipro Mukherjee ^a, Dibyajit Lahiri ^{a*}, Moupriya Nag ^{b*}

^a Department of Biotechnology, University of Engineering & Management, Kolkata 700160, West Bengal, India

ABSTRACT

Cervical cancer is defined as a cancer arising in the cells of cervix that causes unusual vaginal bleeding, discharges, pain in the pelvic region, or pain during sexual activity. Cervical cancer is currently reported to be the fourth most prevalent malignancy among women globally. Surgery includes pelvic lymphadenectomy as well as radical hysterectomy, radiotherapy, as well as chemotherapy are the most common therapies for treating cervical cancer. Another approach includes targeted medication which affects the epidermal growth factor receptor (EGFR) and cyclooxygenase-2 (COX-2) for the curing cervical cancer. However, these therapies have the potential for risks and complications: surgery can result in bleeding and may cause organ damage surrounding the surgery, and clots may also start to form in the deep veins of the legs; radiotherapy can result in menopause, infertility, discomfort, or pain during intercourse; and chemotherapy can actually impact rapidly dividing cells along with cancer cells in the human body system. In this review, we will discuss about the use of several Randomised controlled trials (RCTs) for treating malnutrition in various oncology patients.

*Corresponding authors: Dibyajit Lahiri, Moupriya Nag.

E-mail addresses: moupriya.nag@uem.edu.in; dibyajit2011@gmail.com

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In this review, we will discuss about the various therapeutic effects of natural products isolated from different microorganisms in treating cervical cancer.

KEYWORDS: Cyclooxygenase-2 (COX-2); Epidermal growth factor receptor (EGFR); Pelvic lymphadenectomy; Radical hysterectomy; Radiotherapy; Chemotherapy

1 Introduction

These medications commonly recommended for treating cervical cancer revealed a range of side effects as well as causing treatment resistance [1-10]. Cisplatin, which is one of the most efficient anticancer medications, includes a self-defense mechanism that enables it to develop resistance [11-13]. When patients suffering from cervical cancer are considered, 5-fluorouracil (5-FU) has also showed resistance and adverse effects [12-14].

Natural compounds derived from living species, such as plants and animals, contain a number of active components that have been claimed to be interesting alternatives to chemotherapy medications or to be effective for application in combination with chemotherapeutic treatments [15-17]. For instance, purified flaxseed hydrolysate (PFH), isolated from Lignan, causes apoptosis in HeLa cells and prevents angiogenesis as well as metastasis [18]. In SiHa as well as CaSki cells, thymoquinone obtained from *Nigella sativa* had an apoptotic as well as anti-proliferative property. Some of the examples of natural compounds recognized so far are ethanolic extracts of *Bauhinia variegata* candida known as Praeruptorin-B and a quite famous tea. MicroRNA that includes miRNA as well as miR also play an important role in pathological growth of cancer as well as in cancer metastasis [19-23]. Numerous natural compounds have been shown to have anti-cancer properties by modulating cancer-related miRNAs. An experiment demonstrated that extracts of *Spatholobus suberectus* Dunn can be employed to promote apoptosis when miR-657 or activating transcription factor 2 (ATF2) was regulated in the cells of U266, U937 [24]. Another recognized natural substance, *Salvia miltiorrhiza* has the ability to inhibit cancer growth through regulating miR-216b [25-27]. Another natural compound, 10S-10-acetoxychavicol acetate (ACA) obtained from *Alpinia conchigera* was found to be inducing apoptosis on the cells of SiHa and CaSki. The technique of targeting miRNAs employing natural products have a promising future for treating cervical cancer [28]. Numerous publications in the last 5 years showed no studies that primarily focuses on the principles, effectiveness as well as the concentration of natural compounds responsible for treating cervical cancer.

Relevant experimental data reported during the last few years were gathered using Google Scholar database and PUBMED (containing Medline). These studies explained the anticancer properties of natural products

when used for treating cervical cancer. The NCBI PubChem website was referred to identify the chemical structures of substances obtained from natural compounds [29-32].

2 Apoptosis

Apoptosis is defined as a distinct type of cell death and also considered as an essential process responsible for regulating the cell survival homeostasis [33]. It can also be defined as a process that destroys potential cancerous cells and is triggered by cell atrophy, novel protein production, and cell suicide genes; it also has a significant impact on the malignant phenotype [34-37]. As a result, apoptosis is utilized in cancer research in the form of an anticancer mechanism. In HeLa as well as in SiHa cells, several researches were conducted to understand the anti-cancer mechanism of natural compounds that are mediated by apoptosis.

3 Various Natural Compounds

A group of researchers surprisingly found 4w to be more effective when compared to its parent compounds and thus can be utilized for triggering anti-cancer potential in HeLa cells [38]. A study also reported that purple root tubers as well as Ipomoea batatas leaves contain anthocyanins that can induce CFP or YFP activity in HeLa cells [39-41]. The therapy caused apoptosis, cell cycle arrest, and modification in cell architecture. Furthermore, the leaf anthocyanins had a much stronger anti-cervical cancer cell potential. Glycosmis parva contain Arborinine which possess the ability to downregulate Bcl2-L1 when incubated for 24 hours in HeLa cells [42]. Arborinine also has the ability to trigger apoptosis and to inhibit the migration of cancer and thus it acts as an effective anti-cancer compound. It can also inhibit the growth of tumor spheroid more efficiently when compared to several other chemotherapeutic drugs that include bleomycin, gemcitabine, and cisplatin.

β -elemene, a sesquiterpene compound isolated from the herb Curcuma zedoaria when introduced in SiHa cells were found to increase the expression of p53, p15 and Bax while on the other hand it decreased the expression of cyclin D1, MMP-2, Bcl-2, β -catenin, TCF7, and c-Myc [43-45]. The result also stated that the compound exhibits the potential to stop cell cycle along with that I can also inhibit migration. Along with that, I can also inhibit cell proliferation as well as cell invasion and can trigger apoptosis by blocking the Wnt/-catenin signalling cascade in cervical cancer cells. Nanoparticles of copper oxide that are usually produced from Azadirachta indica, Murraya koenigii, Tamarindus indica, Hibiscus rosasinensis and Moringa oleifera. These

nanoparticles when introduced in HeLa cells showed various anti-cancer properties that include triggering apoptosis and inhibiting oxidant [46-48]. When HeLa cells are treated with a cocktail of polymeric micelles and TPGS/F127/P123 coupled with curcumin extracted from *Curcuma longa* [49]. Apoptosis, apoptosis mediated apoptosis, and stopping cell cycle were all produced as a result of the processes. Emodin, a chemical compound when introduced in SiHa and C33A cells was found to be able to reduce the activity of HOCl/OCl⁻ as well as p-Akt and was also able to inhibit NO⁻ and O₂⁻ [51]. Studies also stated that emodin was able to induce cytotoxicity in cells, DNA damage and also oxidative stress. Epifriedelinol that can be obtained easily from *Aster tataricus* as well as from *Vitex peduncularis* when introduced to HeLa cells showed increment of level of caspase-3, -8, and -9 level while on the other hand the level of Bcl-2, -xL, survivin, as well as of actin was reduced [52]. Using the methods, it lowered cell viability and promoted apoptosis when anti-apoptotic protein expression is inhibited, while pro-apoptotic protein expression is increased. Furthermore, the ratio of pro-apoptotic to anti-apoptotic proteins was adjusted. When Eugenol isolated from *Syzygium aromaticum* was introduced into HeLa as well as SiHa cells, it was able to upregulate caspase-3, Bax, PARP, and ROS and also downregulate XIAP as well as Bcl-2 [53]. The compound was also able to change the cell viability depending on time or dose with a steady morphological variation and thus exhibit an effective inhibitory potential. Another study also stated about introducing icaritin isolated from *Epimedium* into both HeLa as well as SiHa cells upregulated ROS, c-caspase-3, Bax and c-caspase-9 while it downregulated both Bcl-2 as well as XIAP [54-57]. Icaritin when administered in the cells of SiHa and HeLa showed increased cell death when severe oxidative DNA damage was induced, resulting in breaking of significant amount of DNA strand and activating the intrinsic apoptotic pathway. A group of researchers also studied the efficiency of juncusol isolated from *Juncus inflexu* by introducing them in the cells of HeLa, CaSki as well as SiHa cells and found that the compound exhibited the potential of inducing apoptosis and inhibiting cell proliferation [33]. By analysing the cell cycle it was also concluded that G₂/M as well as sub G₁ cell populations were increased when treated with juncusol [58-65]. Moreover, this compound when added to HeLa cells was able to increase the activity of caspase-3, -8, as well as -9 which further suggest that it can also induce apoptosis. Additionally, this compound was able to inhibit tubulin polymerization as well as cause activation of EGFR which further propose that the compound can effectively stop G₂/M-phase cell cycle and inhibit the migration of cells. Methyl protodioscin derived from *Polygonatum sibiricum* was studied for its anti-cancer efficiency. It was found to cause apoptosis of cells when

added to HeLa cells since it increases ROS and well as G2/M phase [66-69]. An experiment using methyl protodioscin showed that the compound can be effectively used to alter cell morphology, to stop cell cycle and also to inhibit cell proliferation. A study also revealed that when mitomycin C (MMC) present in ginger (Gi) was co administered with frankincense (Fr) oil and introduced to HeLa cells, both cytotoxicity as well as apoptosis was increased [70-73]. In HeLa cells, Fr-MMC miraculously survived nuclear apoptosis when administered at lower dosage compared to Gi-MMC. A cocktail of MMC with Gi-NE and Fr-NE tested on HeLa cells, significantly increase the cytotoxicity of MMC. Researchers also studied the antitumor properties of both naringenin oxime as well as oxime ether derivatives [74-77]. Furthermore, analysing cell cycle also proposed that compound 6 was able to extend the subG1 phase and also to induce apoptosis when administered to HeLa as well as SiHa cells. Nitensidine B, a guanidine alkaloid derived from *Pterogyne nitens* Tul leaves when introduced in HPV16 as well as SiHa cells were observed to induce caspase-3 and -7 and to inhibit aldolase A, pyruvate kinase, alpha-enolase and also glyceraldehyde 3-p-dehydrogenase [78-81]. An experiment was conducted using nitensidine B that further established the fact that this compound can effectively be used to induce apoptosis as well as to inhibit glycolysis. Notoginsenoside R7, a triterpenoid saponin derived from *Panax notoginseng* was observed to possess the ability to upregulate Bax, p-PTEN, and Akt and to downregulate Bcl-2, -XL, caspase-3, -9, and raptor when added to HeLa cells [82-84]. This compound was even found to reduce the tumour weight. Finally, notoginsenoside R7 may be employed for treating cervical cancer as well as numerous tumours associated with PI3K/PTEN/Akt/mTOR signalling pathway.

HeLa, SiHa, C-33A, and CaSki cells when experimented with osthole produced from *Cnidium monnieri* (L.) Cusson, significantly elevated the amounts of Bax, H2AX, E-cadherin, and c-caspase-3, -9 proteins. [85-87]. On the other hand, osthole was responsible for downregulating Bcl-2, β -catenin, N-cadherin, p-IKK α , p-p65, NF- κ B, MMP-2, -9, vimentin, IKK α , p65 and p50. Studies also stated that osthole can efficiently induce apoptosis and inhibit cell viability, cell invasion, cell proliferation and cell migration. The research revealed that physcion was linked to cell cytotoxicity, oxidative stress, apoptosis and inducing DNA damage. In HeLa cells, when silver nanoparticles (AgNPs) derived from garlic, turmeric and green tea undergo the process of phyto-synthesis can lower cell viability, trigger apoptosis and inhibit oxidizing agent [88]. The two compounds, paclitaxel and piperine isolated from the plant *Piper nigrum* when combined together can be used to increase the level of Bax, c-PARP, Bcl-2 and caspase-3 on the other hand the level of both p-Akt and Mcl-1 is decreased when

experimented with both HeLa as well as PTX cells. The combination was also able to induce cell apoptosis [89-91]. When HeLa cells are treated with the two compounds prenylflavonoid C1 as well as C5, obtained from *Mallotus conspurcatus* have the potential to upregulate EGFP, Bcl-2, Apaf-1, cytochrome c, ROS, caspase-3, and -9 while on the other hand they downregulate c-Myc and hTERT [92]. The compounds also induce mitochondrial dysfunction, apoptosis as well as cytotoxicity and inhibit the activity of telomerase. Another compound obtained from *Dioscoreae rhizome* when treated with both HeLa as well as C33A cells are able to upregulate JNK, PERK, Bax, PARP, p38, ATF4, caspase-3, -8, -9 while it downregulates the level of Bcl-2 [93-95]. It also initiates induction of ROS and the ER stress pathway. The two polyphenols, resveratrol present in red grapes and red wines and pterostilbene found in blueberries and grapes when experimented with HeLa cells showed upregulation of caspase-3 and downregulation of both PCNA and VEGF [96]. Experimenting these compounds with both PC1 as well as HPV E6 cells stated that are also able to suppress the growth of tumour especially in the cervical cancer cell lines and can also induce cell cycle arrest. Tf-CT-ME isolated from *Tripterygium wilfordii*, exhibit the potential to elevate the level of c-caspase-3, downregulate Bcl-2/Bax, trigger cell cycle arrest and also possesses anti-proliferative property when tested against HeLa cells [97]. Thymoquinone, a phytochemical compound obtained from *Nigella sativa* when added to both SiHa as well as CaSki cells showed upregulation of Bax and E-cadherin while downregulation of Bcl-2, Twist1, and vimentin [98-99]. The fruity parts of *Terminalia bellerica* Roxb., *Terminalia chebula* Retz., and *Phyllanthus emblica* Linn. when combined together resulted in the formation of Triphala, an efficient polyherbal Ayurvedic drug. This drug when tested against HeLa cells showed inhibition of cell proliferation and induction of apoptosis [100]. Thus, triphala showed remarkable potential in the treatment of cervical cancer. *Alpinia conchigera* produces 10'-acetoxychavicol acetate (ACA) that can upregulate the level of both RSU1 and GAPDH and downregulate miR-629 when treated against CaSki and SiHa cells [101]. It can also induce apoptosis and reduce cell viability. Thus, ACA emerged to be a potential anti-cancer agent. 3,5,40-trimethoxystilbene with 5,6,7-trimethoxyflavone constitute 4f that further exhibit the ability to activate cytotoxic as well as the apoptotic potential when experimented with HeLa cells [102]. It not only modifies the nuclei existing in HeLa cells morphologically but also can induce cell death via inducing apoptosis. 5'-epi-SPA-6952A isolated from *Streptomyces diastatochromogenes* can upregulate the level of Bax/Bcl-2, caspase-3, -9, p53, cytochrome c and c-PARP, downregulate MMP, induce apoptosis, stop cell cycle, alter cellular morphology and inhibit

cellular migration as well as proliferation. All these includes all the natural extracts derived so far that were able to trigger cell death in cervical cancer [103].

4 Conclusions

Thus, the review focused on the naturally derived compounds exhibiting anti-tumor potential against cervical cancer. They also modulated multi-drug resistance as well as miRNAs, possess antiangiogenesis, and anti-metastasis properties and can induce apoptosis. Naturally derived compounds like emodin, *Penicillium sclerotiorum* and curcumin were found to be the best inducers of apoptosis. Lignan and *Pistacia vera* L., exhibited the most anti-angiogenic. Besides EGCG there are 5 other natural compounds that can inhibit metastasis of cervical cancer. In cervical cancer pine rosin along with numerous natural compounds were found to sensitise drug resistance. Few researchers also revealed that naturally derived compounds can efficiently regulate miRNA The non-clinical outcomes of this study are expected to pave the way for the development of new cervical cancer therapies having significantly fewer adverse consequences that can be utilised in clinic.

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