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Journal of Cancer Biology & Research

Mini Review

Cervical Cancer: The Case in Indonesia and Natural Product-Based Therapy

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Abstract

This short review is a glance at information about cervix cancer, mainly the situation in Indonesia. Research-based studies, current chemotherapy and possible future chemotherapy, including the mechanisms of action, for cervix cancer will be briefly discussed. The main purpose of this short review is to provide, in short form, information on how far the incidence of cervix cancer is currently emerging and why new treatment needs to be continuously developed, mainly from natural product-based cytotoxic drugs. This can serve as a warning, then hopefully leading to an improvement in cervix cancer treatment and also prevention, especially in developing countries such as those in South-East Asia, where the development of socioeconomic and education has steadily risen and remains impressive to sustain cancer control program.

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Submitted: 05 February 2016

Accepted: 29 February 2016

Published: 01 March 2016

Keywords

- Human Papilloma Virus (HPV)
- Chemotherapy
- Natural product
- Drug combination
- Multi-drug resistance

INTRODUCTION

Social and demographic status, risk factors, and the prevalence of cervix cancer in Indonesia

The number of cancer incidences is increasing and becoming a cause of death worldwide. Even though the disease can be prevented and cured at certain stages, increasing incidence is observed annually. Due to the increase in lifestyles associated with economic development, the cancer prevalence has spread not only in developed countries, but also the developing countries, such as countries in the region of South-East Asia, like Indonesia. WHO reports that cervix cancer is the second most dominant cancer after breast cancer in Indonesian women, with prevalence in woman aged 15 to 44 years [1]. Among the gynaecological cancers, cervix cancer is the most common cancer, followed by cancer of the ovary, the uterus, the vulva, the vagina, and Fallopian tube cancer [2]. A comprehensive statistic estimated in 2012, reports that about 20,928 new cervical cancer cases are diagnosed annually in Indonesia. The incidence rate of cervical cancer is 17 per 100,000 women per year, while in South-East Asia otherwise, and worldwide, the incidence rate is at 16.6 and 15.1, respectively [3]. Indonesia is the 4th ranking country in South-East Asia, with the highest cervical cancer incidence after Cambodia, Myanmar, and Thailand. Mortality caused by cervix cancer in Indonesia is about 28% lower as compared to the average deaths occurring in the world and 2.5% lower as compared to the average deaths occurring in South-East Asia [3]. An insignificant increase in cervical cancer incidence has been reported in Indonesia through the years from 2000 to 2012. Cancer prevention, early detection, accurate treatment, and appropriate diet are vital factors in achieving cures. Socioeconomic status and knowledge support, beyond any doubt, the success of prevention and therapy.

Cancer control in Indonesia was initiated by the Dutch Colonial Government from 1920 [4]. Several cancer control foundations were then established in Jakarta and in several other big cities in Indonesia. In 1974, a research centre for cancer and radiology was established under the National Health Research Institute of the Ministry of Health, followed by the establishment of the Cancer Centre Hospital in 1993 that facilitates teaching and training for medical doctors and research on oncology.

In order to provide direct check-ups and preventive steps for society and for patients at risk of cancer, the Ministry of Health initiated a comprehensive program involving prevention, early detection, early diagnosis, prompt treatment, follow-up, rehabilitation, cancer registration, and cancer research [4], with the hope that the program would cover lower- and middle-class society in the geographical area of Indonesia from east to west. The program is certainly inspired by WHO guides for effective programs for cancer control, which provide practical advice for program managers and policy-makers on how to advocate and implement effective cancer control. There are four basic implementations, consisting of prevention, early detection, diagnosis and treatment, and palliative care.

Understanding the risk factor of cervix cancer can presumably assist in controlling the emergence of cervix cancer, for example, in the prevention and early detection stages. Human Papilloma Virus (HPV) is the strongest epidemiological risk factor for cervix cancer, mainly when the cofactor is present. There are several types of HPV, with the most common found in most biopsy

specimens from Indonesian cervix cancer patients, these being HPV 16 and 18 [2]. Tobacco smoking is reported to possess a relevant association with cervical intraepithelial neoplasia and invasive cervix cancer, and can interfere with other factors such as the immune system, contraception, and nutrition [5,6]. Thus smoking habits, a common habit of Indonesians, should be taken into consideration as a high risk factor for cervix cancer. Women, with their current expanding lifestyle, are taking up smoking, and this can certainly increase the incidence of cervix cancer. Alcohol consumption, physical inactivity, obesity, and household solid fuel use are also well-known risk factors for cancer which can also contribute to cervix cancer in Indonesia.

Well-known cytotoxic therapy for cervix cancer

Treatment for cervix cancer involves a broad variety of options based on the stage of the cancer that includes surgery, radiation, and chemotherapy. Cryosurgery, laser surgery, the loop electrosurgical excision procedure (LEEP/LEETZ), and cold knife conisation are famous to treat squamous cell carcinoma in situ (Stage 0). Advanced stages of cancer are treated with chemo- and radiation therapy. Table 1 tabulates common cytotoxic therapies based on diverse group as DNA-targeting drugs, antimetabolites, and mitotic inhibitor which are used to treat cervix cancer in several stages.

Why do we need to continuously develop new approaches for cervix cancer therapy?

Besides the toxicity and side effects from most chemotherapy, the mechanism of drug resistance in chemotherapy is a persistent issue in cancer therapy. A short description of how cancer cells can be resistant to chemotherapy is given in the following paragraphs.

The absorption and metabolism of anticancer drugs in the target tissue can differ among cancer patients. In some cases, anticancer drugs show complete failure or partly incomplete. This fact has been observed as a result of genetic alteration, factors related to the tumour environment and alteration in the drug metabolism, and that can be summarized as one main issue of cancer drug resistance [15]. Apart from the non-cellular resistance mechanism as outlined above, there are three main mechanisms proposed as cellular factors causing drug resistance: first, the reduction of water-soluble drug uptake, probably due to changes in lipid membrane composition; second, various alterations in cells, such as those of enhanced DNA repair, alteration of the cell cycle, reduced apoptosis and changed drug metabolism (e.g. cytochrome P450); and third, enhancement of hydrophobic drug efflux [15,16].

As an instance, ATP-binding cassette (ABC) transporters are a family of transporter proteins that mostly relate to drug resistance through ATP-dependent drug efflux pumps. The mechanism of enhanced drug efflux is probably the best-studied for the drug resistance mechanism, because many cases show the expression of the transporter protein in cancer cells [16,17]. This protein family is present in normal cells and cancer cells, in most cells and organisms. In normal cells, the transporter functions as

Table 1: Well-known cytotoxic agents for cervix cancer therapy.

No.	Agent	Mode of Action	Stage of Cancer	Example of Use for Cervical Cancer (Singe or in Combination)	Reference
1.	Cisplatin	Cisplatin binds to DNA, forms the cross-link to form DNA adducts, activates several signalling transduction pathways, such as ATR, p53, p73 and MAPK, and culminates in the activation of apoptosis.	IA, IB, IIA, IIB, III, IVA, IVB	Combination cisplatin with paclitaxel increases efficiency and cost effectiveness of treatment.	[7]
2.	Carboplatin	Platinum-based cytotoxic generates DNA adducts, as in cisplatin, thus inhibiting replication and transcription and leading to cell death.	IVB	Combination of carboplatin with radiation therapy results in a high response rate and survivals in advanced cervical cancer.	[8]
				Combination of carboplatin and paclitaxel results in activity and tolerable toxicity in advanced cervical carcinoma.	[9]
3.	5-Fluoruracil	5-FU is an antimetabolite, a pyrimidine analogue that inhibits thymidylate synthase, the enzyme that catalyzes the conversion of deoxyuridine monophosphate, resulting in the inhibition of DNA synthesis.	IB, IIA, IIB, III, IVA	Oral administration of 5-FU after radical hysterectomy with radiotherapy yields useful results for patients at low-stage cervical cancer, but not for patients with pelvic node metastases.	[10]
4.	Paclitaxel (Taxol®)	Paclitaxel is a microtubule-stabilizing agent that interferes with the stability of mitotic spindle assembly, leading to the inhibition of the mitosis process.	IVB	Combination of paclitaxel and carboplatin results in activity and acceptable toxicity in advanced cervical carcinoma.	[9]
5.	Topotecan	1. Inhibition of DNA topoisomerase I results in inhibition of RNA transcription and apoptosis. 2. Inhibition of the hypoxia-inducible factor (HIF), mainly interesting in cervix cancer, since tumour tends to be either bulky or in radiated fields; results in tumour hypoxia.	IVB	Single use and in combination with cisplatin and radiation.	[11]

6.	Gemcitabine (Gemzar)	Gemcitabine (dFdC) is an antimetabolite, an analogue of deoxycytidine. The phosphorylated active form of gemcitabine (dFdCTP) inside the cell can inhibit processes required for DNA synthesis. Gemcitabine incorporates the nucleotide on the end of the elongating DNA strand, leading to the inhibition of DNA polymerases. Gemcitabine also interferes with the cellular regulatory processes, serves to enhance the overall inhibitory activities on cell growth, and finally leads to cell death.	IVB	In phase I/II clinical trials, combination of gemcitabine with cisplatin and/or radiotherapy shows a high response rate and prolonged survival. The combination of gemcitabine with cisplatin also exhibits a promising outcome as neoadjuvant therapy.	[12]
7.	Bevacizumab (Avastin)	Anti-angiogenesis and targeting the VEGF pathway, most likely attractive for cervical cancer.	IVB	A phase II trial examined bevacizumab in woman with persistent or recurrent squamous cell carcinoma of the cervix and exhibited a positive response in terms of haematology, renal, hepatic, and coagulation functions. This study suggested a comparable activity to cytotoxic chemotherapy drugs.	[13]
				Combination of bevacizumab with chemotherapy in patient with recurrent, persistent, or metastatic cervical exhibited an improvement of 3.7 months in median overall survival.	[14]

a host detoxification and protection against xenobiotics [18]. The proteins are mainly localized in the intestines, liver, kidneys, and blood-brain barrier [19,20]. In cancer cells, three major types of ABC transporters have been studied in detail to understand the mechanism leading toward drug resistance. These proteins have been reported in many human cancer cells, including leukaemia [21,22] and solid tumours [23-25]. They are P-glycoprotein (P-gp) or MDR1 protein (multiple-drug resistance protein), multiple-resistance associated protein 1 (MRP1) (encoded by the *ABCC1* gene), and breast cancer resistance protein (BCRP), a protein encoded by *ABCG2* gene and composed by one transmembrane domain and ATP-binding domain. The protein turns on the function only after dimerization [20].

Resistance to cisplatin and carboplatin have been reported in several cases in cancer therapy. In the cell treated with cisplatin, DNA-damage mediated apoptotic signals can, however, become resistant, due to an increase of DNA adduct repair. The mechanism of cisplatin resistance can be derived from the over-expression of XPA, a protein that plays an important role in both global genome and transcription-coupled repair pathways. XPA -4G>A polymorphism is identified in the 5' non-coding region and located four nucleotides upstream of the ATG start codon. This polymorphism may affect mRNA tertiary structure and stability, causing susceptibility to cancer [26]. Resistance to other platinum-based drugs, e.g. carboplatin, involves multifactorial aspects, such as enhanced drug detoxification, and an improved repair DNA mechanism, resulting in repression of apoptosis and reducing the accumulation of intracellular carboplatin [27].

Attempts to overcome resistance mainly involve combination drug therapy, using different classes of drugs with minimally overlapping toxicities to allow maximal dosages and with the narrowest cycle intervals. Anticancer agents with relatively modest toxicity are those drugs belonging to the group of anti-metabolites. The combination of anti-metabolite and DNA targeting drugs such as cisplatin may effect the inhibition of DNA repair or the formation of DNA adduct. As an example, recent findings suggest that L-canavanine, an analogue of arginine, acts as an antimetabolite and potentiates the DNA-targeting drugs, doxorubicin and cisplatin, and also the microtubule-targeting drugs, paclitaxel and vinblastine, in cervical cancer cell [28,29]. Further in vivo and a comprehensive clinical trial are clearly needed to find out whether L-canavanine is suitable as an alternative to the current well-known antimetabolites, 5-fluoruracil and methotrexate.

Besides a rational therapeutic drug combination, the use of predictive biomarkers in patients is an effective approach in personalized medicine; thus, the therapy is also expected to be target-specific and controllable for possible drug resistance.

Targeted Therapy

Although surgery and chemoradiotherapy can cure 80 – 95% of women with early stage cancer, the recurrent and metastatic disease remains a major cause of cancer death. In some patients of a low or middle economic class, the disease is detected mostly at an advance stage. Besides drug resistance, much scientific evidence suggests that there is a high demand for new agents with novel mechanisms of action for this disease. The mechanism includes agents that modulate and vary signal transduction pathways, inhibiting angiogenesis, targeting epidermal growth factor receptor, cell cycle, histone deacetylases, cyclooxygenase-2 (COX-2), mammalian target of rapamycin (mTOR) [30], and oncogenes, such as HPV E6 and E7, expressed in most cervical cancers and inducted to malignant phenotypes [31].

From all the proposed therapy, genetic biomarkers associated with cytotoxic therapies and targeted therapies play important roles in diagnosis, prognosis and predicting. This approach can be clearly developed for pharmacogenomics and personalized medicine. Clinical development of those agents is urgently required. The screening for new agents for cervical cancer merits the virtual complex metabolism related to the therapeutic intervention and outcomes guided by genetic biomarkers from the patient.

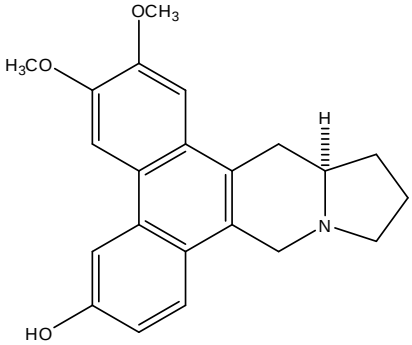
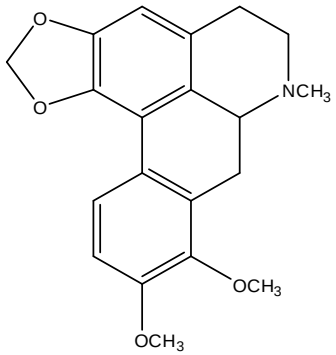
Plant-based cytotoxic drugs for cervix cancer

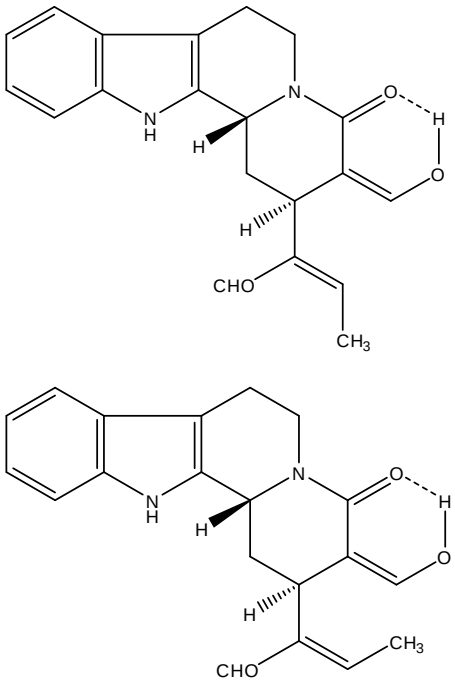
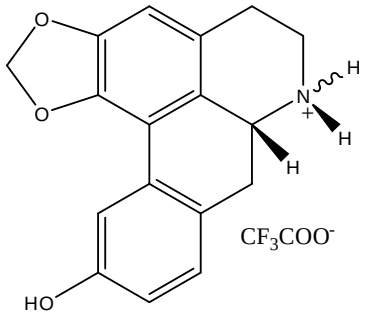
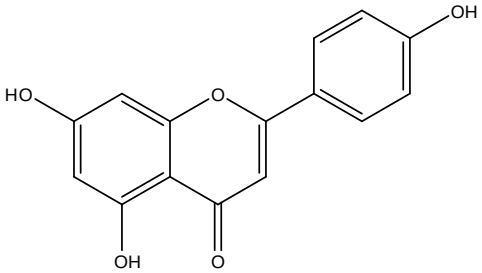
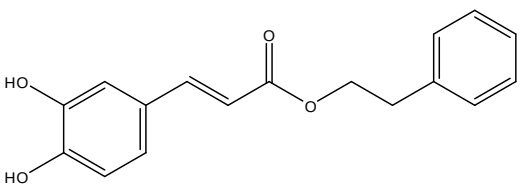
The lack of success of conventional chemotherapy in reducing mortality and its serious side effects indicates that natural products are ideal candidates for exerting synergism and enhancement effects on anticancer drugs. A single plant species contains various chemical substances that not only can act on a single target (mono-target), but also interfere with several targets (multi-target SM) in a pleiotropic manner. The pleiotropic effect can occur when a single substance has more than one active pharmacophoric group. The presence of more than one pleiotropic substance from different classes would most likely expand the spectrum of activity, resulting in the additive effect and also the synergistic effect. Thus, the mixture of several substances, such as in the plant extract, can contribute to such effective activity, additive and synergistic by promoting the uptake of the polar substance entering the biomembranes and inactivating activities or inhibiting the growth of cells [20]. The chemical components and mechanisms of action of many natural plants with anti-cervical cancer potential have been investigated, though many others remain unknown. Persistent investigation to find new substances, including their specific mechanism of action against cervical cancer, is urgently needed. Clinical trials are also obligatory to verify the use of these medical plants reasonably.

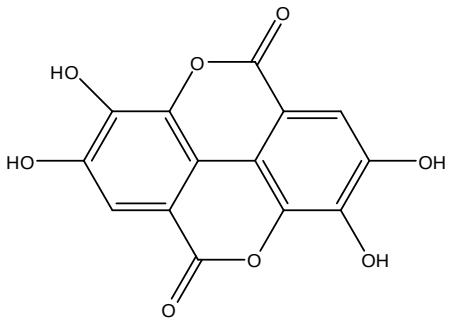
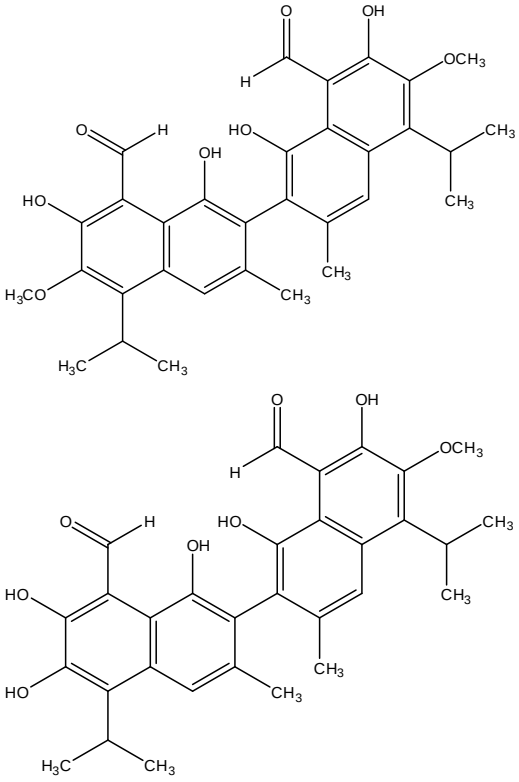
Several plant extracts and fractions have exhibited promising activity against cervical cancer, triggering several modulators of apoptotis, for instance the methanol:chloroform fraction of *Boerhaavia diffusa* (punarnava) roots. The fraction can reduce cell proliferation of HeLa cells and morphological changes of the cells can be detected. The inhibition of cell proliferation is proposed, because the fraction arrested cells at the S-phase, following apoptotic events identified via DNA fragmentation and caspase-9 [32]. In another instance, a promising candidate is noni, derived from *Morinda citrifolia*, showing synergism and enhancing therapeutic effects in combination with cisplatin in two human cervical carcinoma cells, HeLa and SiHa cell lines. Noni is a capable herbal-based anticancer drug. The apoptotic events suggest an involvement of the intrinsic mitochondrial pathway via up-regulation of p53 and pro-apoptotic Bax proteins, down- regulation of the anti-apoptotic Bcl-2, Bcl-XL proteins, and up-regulation of the activity of caspase-9 and -3 [33]. *M. citrifolia* can be found abundantly in tropical countries, like Indonesia.

Single compounds derived from plant extracts possessing cytotoxic activity against cervical cancer cells have been reviewed in several studies [34]. Table 2 displays a small number of selected compounds with their action in cervical cancer cells. This example can then be developed in that the search for related plant species which might possess a homologous group of active compounds is increased, or such related groups can be developed as synthetic compounds and their derivatives with profound and specific activity in cervical cancer.

Table 2: Selected compounds with activity in cervical cancer cells.

No.	Natural Product	Structure	Occurance	Activity	Reference
Alkaloids					
1.	Phenanthroindolizidine alkaloids		*Cynanchum vincetoxicum* and *Tylophora tanakae*	The IC_{50} value of the compounds is low in the nanomolar range, indicating activity comparable to that of clinically used cytotoxic drugs.	[35]
2.	Crebanine		*Stephania venosa*	Growth inhibition of KB cancer cell lines and cell cycle arrest in G0/G1 phase and eventual apoptosis via caspases activation	[36]

3.	Naucleaorals A Naucleaorals B		*Nauclea orientalis*	Cytotoxicity to HeLa cells with an IC_{50} value in the range of 4.0 - 7.8 µg/mL.	[37]
4.	(6aR)-normecambroline		*Neolitsea dealbata*	Cytotoxicity to HeLa cells with an IC_{50} value of 4.0 µM.	[38]
Flavonoids					
1.	Apigenin		Widely distributed plant flavonoid	Apigenin inhibits the growth of HeLa cells, arrests the cell at the G1 phase, increases expression of p21/WAF1, caspase-3, and some virtual mechanisms of apoptosis. Moreover, it decreases the protein expression of anti-apoptotic factor, the Bcl-2 protein.	[39]
Polyphenol					
1.	Caffeic acid phenyl ester		Propolis	Induction of S- and G2/M phase cell cycle arrest and initiation of apoptosis. The mechanism is associated with increased expression of E2F-1, upregulating the E2F-1 target genes cyclin A, cyclin E, and apoptotic protease activating of factor 1 (Apaf-1).	[32]

2.	Ellagic acid		Widely distributed plant polyphenol	The radio-sensitized activity of ellagic acid in HeLa cells is proposed by up-regulation of oxidative stress and membrane damage.	[40]
3.	6-Methoxygossypol 6,6'-dimethoxygossypol		Root tissue of cotton plant	The IC_{50} value of those compounds in cervical cancer cell line-SiHa is around 10 ppm.	[41]

CONCLUSION

Treatment for cervical cancer needs to be continuously developed due to the drug resistance issue, adverse side effects, and toxicity. New agents, most attractively derived from natural products, shall be taken into consideration in future, since these agents, in most cases, possess more than one active pharmacophoric group and are clearly able to expand the spectrum of activity. Genetic biomarkers and personalized therapy for positive outcomes shall be a target with high priority in research and medical treatment in oncology. The socialization of programmes to control cervical cancer should be able to reach all levels of society, particularly in developing countries in South-East Asia.

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Cite this article

Nurcahyanti ADR (2016) Cervical Cancer: The Case in Indonesia and Natural Product-Based Therapy. J Cancer Biol Res 4(1): 1078.