Chapter

# Pharmacology Evaluation of Bioactive Compounds that Regulate Cervical Cancer Cells

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## Abstract

Cancer has been a public health problem that has gained a lot of death. However, in spite of the advances in the diagnosis and treatment of cervical cancer, women follow the struggle versus this disease. Also, those patients suffer from limited efficacy and specificity, undesirable effects, drug resistance, and a high cost of treatments. Currently, several studies have demonstrated the efficiency of natural products, called bioactive compounds, against cervical cancer cell lines. Bioactive compounds, including polyphenols and phenolic acids or flavonoids, etc., have antioxidant and pro-oxidant properties. These compounds are efficacy and show high specificity because probably they act as anti-oxidant and pro-oxidant. The pro-oxidant activity obstructs growth factors related to different signalling pathways that trigger cancer. Although, usually this kind of compounds helps for dispatching the apoptosis in cervical cancer cell. The aim of this chapter is reviewing how bioactive compounds affect the signalling pathways.

**Keywords:** HeLa, cervical cancer, bioactive compounds, signalling pathway, polyphenols

## 1. Introduction

Cancer is a term for diseases in which abnormal cells divide without control and can invade nearby tissues. Typically, cells in healthy tissues only share if they receive growth stimulatory signals known as growth factors, those that together with the cytokines regulate the progression of the cell cycle [1]. The progressive transformation of normal cells into malignant derivatives implies the accumulation of some genetic changes, which can be carried in the germ line, by the development of somatic mutation throughout the life of the individual, or by the incorporation of viruses, which eventually produce alterations in the cell cycle and DNA repair mechanisms [2, 3]. That triggers several oncogenic signalling pathways, leading to a series of drastic phenotypic and biochemical changes in the cell. These alterations refer to various areas, such as growth factor signalling, cell-cell adhesion, gene expression, motility or cell shape [4].

Cancer rates continue to rise, particularly in the developed world, becoming one of the leading public health problems in many countries [5]. Many cancers are associated with longevity, and the possibility of their appearance increases as the life expectancy of individuals lengthens [6]. On the other hand, cancers of high prevalence are related to environmental factors and lifestyles, which involve a series of modifiable risk factors for their development such as smoking, drinking, diet, sun exposure and others [7]. Currently, many anticancer agents are available, including alkylating agents, antimetabolites, antitumor antibiotics, natural products and hormones [8]. However, treatments available for cervical cancer show low efficacy and specificity, undesirable effects, a high cost of treatment, relapsed among patients who had improved, drug resistance and a decreased quality of life [9–11].

The bioactive compounds present in plants, fruits and vegetables, are antioxidant or stopping different signalling pathways including apoptosis and Wnt (Wingless/Integrates) [9–12]. Also, this kind of biocompounds has a selective cytotoxic effect, attacking only to the cancer cells [9, 10]. But, before its use, it is necessary to evaluate the activity of these therapies through in vitro antiproliferation assays, using cultures containing both tumour and non-tumour cells and different cell models [7]. Also, only few of these compounds have the potential to be therapeutic against cancer. This work describes the advance rise regarding the capacity of biocompounds to trigger or re-establish the antioxidant capacity or blocking oncogenes that participate in HeLa cancer cells.

## 2. Cervical cancer generalities

Cervical cancer (CC) is a principal cause of death in women in the whole world [9, 11, 13]. Prior reports indicated this cancer contributed with approximately 500,000 new cases and produced between 270,000 and 300,000 deaths in 2015 [9, 11, 13–15]. However, is clear that Hispanic women have a high incidence of cervical cancer and a significant death rate than other women in the world [16, 17]. The described above probably is due to the interaction between genetic factors of the population, geographic locations and environment exposures [18, 19]. In general, the susceptibility to the pathogens as human papillomaviruses (HPV), lifestyle and cultural factors and inadequate medical system contribute to the development of cervical cancer [17–19].

### 2.1 Cancer cervical and human papilloma virus (HPV)

Current information noticed that almost 100 serotypes of HPV exist. But, 2 of these, 16 and 18 serotypes, are related to the development of cervical cancer in Latin women [14, 17]. During cervical carcinogenesis, a viral protein E6 sequesters to p53 protein. Also, another viral protein called E7 participates in the same process, sequestering Rb protein. In consequence, the arrest of both proteins p53 and Rb induces deregulation in the cell cycle. However, possibly the HPV is not an exclusive aetiology agent that produces this disease. Further information noticed that sex steroid hormone participates in the early stages of cervical carcinogenesis [14]. Previous report evidenced the possible relationship between E7 viral and $E_2$ (17β, also spelled oestradiol), but this is poorly understood [14]. Perhaps, our knowledge about the risk factors that derive from the developed cancer will be increasing but also is necessary to improve our awareness of the prevention and treatment of disease.

### 2.2 Current therapies against cervical cancer

In this context, in Mexico 15% of women are detected with precancerous lesions of cervical cancer, and they could be potentially prevented. Currently, chemotherapy, radiotherapy, hormonal therapy, biological therapy and surgery are the treatments majority employed in the early stages of CC [10, 20, 21]. But, the treatments above mentioned often are associated with certain disadvantages, such as toxicity of chemical agent or drug resistance [22]. For example, *cisplatin* in combination with *bevacizumab* can increase the expectations of survival, but they are scarce to the population. In another case, *paclitaxel* is a chemotherapeutic agent used against ovarian carcinoma, but there is evidence of the resistance for this agent [11]. Also, the use of chemotherapy represents other drawbacks, the undesirable effects, the high cost of treatment and recurrence among patients who had improved [10, 20]. All of these adverse effects are due to the lack of a specific target cancer cell, because chemotherapeutics do not have a cancer-specific receptor, protein or DNA [20]. Another limit, in Mexico, there is one radiotherapy machine available for 2 million Mexican. But, reducing the doses of the chemical agent or employing natural compounds can overcome this significant barrier that exists to eliminate CC [11]. Natural or bioactive compounds are used against multiple illnesses including rheumatic, anthelmintic, diuretic, hypoglycaemia and cancer [23].

### 2.3 Relationship between ROS and cervical cancer

The diseases above mentioned, including CC, could produce free radicals that induce damage to the cells, tissues and organs [12]. However, the proper function of cells depends on the mitochondria's ability to regulate metabolic processes and produce molecules, including free radicals as reactive oxygen species (ROS) [11, 24, 25]. ROS controls both physiological and pathological process related to cell proliferation, invasion cell, and tumour hypoxia and drug resistance [11, 12, 26, 27]. Also, in the cell, a defence system against ROS includes several enzymes such as superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and glutathione S-transferase [28]. However, when the cellular antioxidant systems are damaged, antioxidants are insufficient to neutralise ROS, and then oxidative stress occurs [27, 29]. Moreover, in a pathological process, ROS are responsible for damaging proteins, lipids and nucleic acids [29, 30]. Nonetheless, bioactive compounds are strongly linked to the radical scavenging capacity and protect the cell against oxidative DNA damage [12, 25, 31].

### 2.4 Alternative therapy among cervical cancer

The plants, fruits and vegetable contain large amounts of bioactive compounds that act as antioxidant, and they can be used with therapeutic purpose [27, 32, 33]. Among antioxidants, different subclasses are described, (a) flavonoids, (b) phenolic acids and polyphenols, (c) stilbenoids, (d) catechins and (e) tannins, and they are abundant and available in natural products previously mentioned [20, 31, 34]. Other compounds related with their oxidant capacity and ROS productions are listed in **Table 1**. The antioxidants that are most well-known, curcumin, resveratrol and gallic acid, have activity against cancer cell line in vitro [15, 24, 28, 35]. For example, galangin is a flavonoid with various biological effects in different cancer cells [25]. Also, the green tea has cancer-preventive effects due to containing catechins known as EGCG (−)-epicatechin-3-gallate, (−)-epigallocatechin and (−)-epicatechin. Also, CTS extract possesses chlorogenic acid, (+)-catechin, caffeic acid, phloretic acid, veratric acid, hesperidin, quercetin and naringenin. Additionally, fucoidan is a major bioactive

| Compound | Anti-carcinogenic effects |
|---|---|
| Terpenes and steroids | Inhibit cancer cell proliferation and metastasis; cell cycle arrest, apoptosis, anti-angiogenesis, anti multidrug resistance |
| Alkaloids | Target DNA replication or protein synthesis, resulting in apoptosis of the neoplastic cells |
| *Phenolic compounds* | |
| Chalcones | Anticancer, anti-inflammatory, antioxidant; cytotoxic activities through multiple mechanisms which include cell cycle disruption, angiogenesis inhibition, tubulin polymerization inhibition, apoptosis induction and blockade of nuclear factor-kappa B (NF-B) signalling pathway |
| Coumarins | Antioxidants and anti-inflammatory; anti-proliferative activity may be due to inhibition of CDK2 activity |
| Flavonoids | Antioxidant and cytotoxic effect, cell growth and proliferation inhibition; modulate the metabolism of carcinogen, inhibition of multidrug resistance, anti-angiogenesis effect, induce apoptosis and cell cycle arrest |
| Hydroxybenzoic acids | Antioxidant capacity; inhibit cell proliferation and cell cycle progression; metalloproteinase inhibition |
| Hydroxycinammic acids | Anti-proliferative effect; suppressive effects of signalling pathways that are related to NF-κB, ERK, protein kinase C, calcium signalling, phosphatidylinositol 3-kinase (PI3K) and nuclear transcription activity |
| Lignins | Antioxidant and cytotoxic effect |
| Lignans | Cytotoxic potential; angiogenesis and metastasis inhibition induces apoptosis |
| Stilbenes | Antioxidant activity; inhibition of cancer cell proliferation, induces apoptosis and reduces angiogenesis |
| Xanthones | Antioxidant and pro-apoptotic effect; anti-proliferative, cell-cycle arrest |

*Antioxidant properties can be risen with phenolic compounds described here. However, possible signalling pathways, apoptotic or inflammation, can be affected by this kind of compounds.*

**Table 1.**
*List of phenolic compounds. Antioxidant properties can be risen with phenolic compounds described here. However, possible signalling pathways, apoptotic or inflammation, can be affected by this kind of compounds.*

compound in *Sargassum polycystum* and demonstrated anti-proliferation, antitumor and anticancer properties [13]. Moreover, pterostilbene can be found in berries and grapes and showed therapeutic effects in a variety of cancer types [36]. Other biocompounds such as triptolide, celastrol and tripchlorolide were isolated from *Tripterygium wilfordii*; these compounds are immunosuppressive and anticancer [37]. Gallic acid is a natural phenolic compound with the potential to act against different cancers or viruses [38]. Further information, extracts from *Annona muricata* leaves were shown to have the capacity to induce apoptosis in HeLa cells, suggesting that the extracts have the potential to be used as a treatment against virus-induced cancer cells [39]. Also, this compound can be used in combination with a chemotherapeutic agent to increase the efficiency of chemotherapy [11].

Also, the genus *Annona* has been shown to have promising compounds, called Annonaceous acetogenins (AGEs), that can be utilised in the treatment of cancer because they induce cell cytotoxicity by inhibiting the mitochondrial complex I, and their capacity of acetogenins to inhibit NADH oxidase was also shown to be important for their antitumour function [40, 41]. However, the biological activities of the compounds obtained from *Annona* species are diverse. For example, the crude extract of *A. crassiflora* significantly alters cell viability of cervical cancer cell lines as well as proliferation and migration and induces cell death [42]. Many studies have described, or continuous screening the anticancer bioactive compounds, and explained the potential of plants against illness [25]. Though,

the success of the prevention or treatment depends on the quality and quantity of bioactive compounds. But, the biological effects and mechanisms of action of flavonoids, phenolic acids, stilbenoids and tannins have been studied lightly.

### 2.5 Antioxidant and ROS cancer prevention

Antioxidant capacities describe the biological mechanism of bioactive compounds and how consequence prevents the oxidative stress in normal cell [11, 31, 35, 43]. But these compounds also can act as pro-oxidant agent and increase the ROS production in cancer cell [11, 31, 35, 43]. However, Gu et al. mentioned that those compounds are antioxidants in lower concentration and can be a pro-oxidant at a high level [31]. Also, the intake of polyphenols and phenolic compounds has multiple protective functions against inflammation and tumorigenesis. However, the success of the prevention and treatment also depends on the quality and quantity of bioactive compounds. But, more critical is the fact that the consumption and bioavailability of polyphenols are insufficiently studied to determine the efficacy for disease prevention or disease treatment [15, 35]. From this, derive the relationship among bioactive compounds and the induction of apoptosis, anti-proliferation, antimetastasis and anti-angiogenesis [12]. Further information notices the interaction of the phenolic compound is involved with receptor or enzymes in signal transduction [31]. This interaction may downregulate or upregulate essential proteins in signalling pathways that control the biological process [35].

### 2.6 Signalling pathways blocked by polyphenols

In addition to the antioxidant effects above mentioned, these bioactive compounds can induce two phases during ROS activation. Phase I starts when polyphenols inhibit cytochrome P450 (CYPs) including CYP1A1 and CYP1B1, and the increase and excretion of polar metabolites and prevention of the formation of DNA adducts remark phase II [35, 44]. But, pro-oxidant activities mediated by polyphenols and phenolic compounds increase the ROS production. Lin et al. reported that resveratrol induced apoptosis in HeLa cell line [15]. The extract of *Cudrania tricuspidata* stem (CTS) on cell viability was investigated in HPV-positive cervical cancer cells. CTS induced apoptosis by downregulating the E6 and E7 viral oncogenes. Also, the mRNA expression levels of extrinsic pathway molecules such as Fas, death receptor 5 (DR5) and TNF-related apoptosis-inducing ligand (TRAIL) were increased by CTS. CTS induced apoptosis by activating the extrinsic pathway in SiHa cervical cancer cells. Chlorogenic acid has been reported to have anticancer, antioxidant and antidiabetic effects. Also, galangin increased ROS, which induced the activation of cell death via various mechanisms including apoptosis or arrest of cell cycle [15, 20, 25]. Bruges reported that pyrogallol induced mitochondrial apoptotic response. Mitochondrial pathway probably begins with the activation of BH3-only proteins. This protein causes the production of BAK1 and BAX, which promote a membrane permeabilisation. Last, in cytoplasm increasing cytochrome C level, this allows apoptosome formation and caspase-9 activations. In extrinsic apoptosis pathway, binding of the cell death ligands and cell death receptors activates caspase-8 and caspase-3 (**Figure 1**) [35, 45]. Similarly, *Terminalia sericea* enabled caspases-7 and -8 and poly (ADP-ribose) polymerase (PARP) in HeLa cancer cell line [31]. Also, pyrogallol induces superoxide anion, and this generates activation of caspase-3 and phosphatidylserine [45]. Silva et al. mentioned that the hexane partition derived from the crude extract presented cytotoxic effect in SiHa cells and initiates cell responses, such as DNA damage (H2AX activity), apoptosis via intrinsic pathway (cleavage of caspase-9, caspase-3, poly (ADP-ribose) polymerase (PARP) and mitochondrial

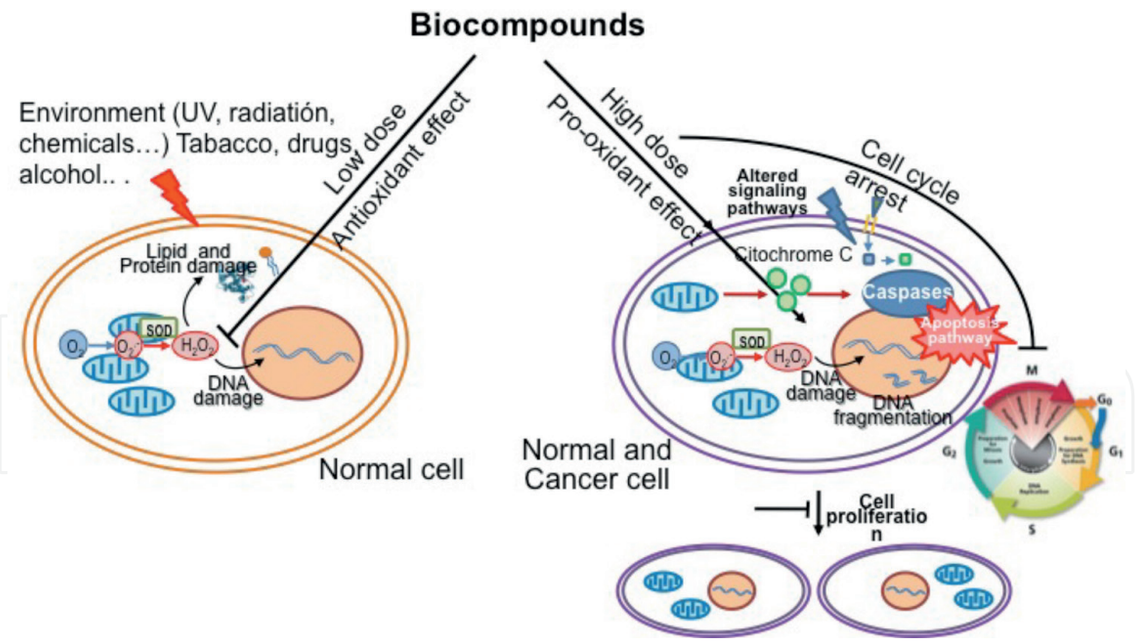


**Figure 1.**
*Effect of biocompounds in cellular processes. In the figure, it is observed that at low concentrations, biocompounds (left) can exert an antioxidant effect, whereby it acts by reducing reactive oxygen species. However, at high concentrations (right), biocompounds have pro-oxidant effects, which can affect both normal and carcinogenic cells and result in alteration of key pathways for homeostasis of the cell, causing cell cycle arrest and stop cell proliferation, damage to DNA and apoptosis, among others, cellular process.*

membrane depolarization) and decreased p21 expression by ubiquitin proteasome pathway [42]. Fusi et al. reported that the antioxidant activity of resveratrol, catechin, curcumin, etc. increases sirtuin 1 (SIRT1) expression and monophosphate-activated protein kinase (AMPK) activation in HeLa cell line [27, 44]. Prior reports indicated AMPK is an enzyme that inhibits anabolic process and increases catabolic activity. Perhaps, the relationship between SIRT1 and AMPK may protect against oxidative stress [27, 44]. On the other hand, pro-oxidant activities induced by polyphenols generate ROS and produce [1] cell cycle arrest, and [2] induction of apoptosis and DNA fragmentation. In HeLa cells, autophagy-signalling pathways are modulated by polyphenols, i.e. resveratrol, curcumin and genistein, and act on epidermal growth factor kinase B (EFGR)/AMPK, and this inhibits the mammalian target of rapamycin (mTORC1) via TSC1/2. Also, these three polyphenols inhibit nuclear factor kappa-light-enhancer of activated B cells (NF-κB), and these compounds plus quercetin stop phosphatidilinositide 3-kinases/protein kinase B (PI3K/Akt), and last, rottlerin breaks PKC5 [35, 44]. Last, safflower polysaccharide (SPS) is a major active component of *Carthamus tinctorius*. SPS inhibited proliferation and increased apoptosis of HeLa cells through downregulation of the phosphatidylinositol-3-kinase/AKT pathway [46].

## 3. Conclusions

The potential disadvantage that represents the strategies against cervical cancer or other cancers is the resistance, high cost, secondary effects and disposal of pharmaceuticals. However, extracts of plants, including phenolic acid and polyphenolic, flavonoids, etc., have gained remarkable interest such as new treatment or strategies versus cervical cancer. The antioxidant properties of plants were demonstrated with multiple investigations, some of which are pointed out in this chapter, especially for its antioxidant properties, influence on cellular apoptosis, ROS increase, etc.

Currently the efforts to discover new anticancer agents continue, and it is possible that plants containing compounds still unknown and that compounds could modulate the pathways that government cancer. Also, the signalling pathways regulated by these compounds have been superficially studied. Unfortunately, these foods are not always available to all people, and in the case of those who have them within reach, they do not consume them. Also, it is important that people change their hygienic dietary habits and improve the quality of their immune system and the level of cellular oxidative stress does not increase the risk for development of cancer.

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## Conflict of interest

Authors declare no conflict of interest.

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