



Apoptosis Caused by Natural Compounds in Cervical Cancer Cell Line



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Submission: June 24, 2019; Published: July 10, 2019

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Abstract

Cancer is a life-threatening disease involving out-of-control of cell growth in a mammalian body, these are of many types like (liver cancer, cervical cancer, skin cancer, breast cancer) There are many types of therapies available those are effective against cancer like (chemotherapy, radiotherapy). But these therapies are very painful and also cause some effect on healthy cells. Cervical cancer is one of the leading cancers caused by HPV (human papilloma virus) which mainly occur in women and after the age of 22 year the chance of cervical cancer increase. It is obtained from the cells of cervix. It can be detected through the regular Pap smear. But now days natural compounds are one of the best treatments to fight from the cancer because in natural compound many types of compounds are available those have capability to kill approximately 80% of the cancerous cells. Natural compounds include Quercetin, Eugenol, Green Tea, Genistein etc. which are known to be very effective against cervical cancer.

Keywords: Cervical cancer; Human papilloma virus; Apoptosis; Quercetin; Eugenol

Introduction

Cancer is a type of disease that spreads due to uncontrolled of cell growth due to the collection of defects or variation in their DNA and with imminence to attack or distribute to other parts of the body. Cancer is specified as a wide group of several infections normally characterized by persistently uncontrolled and unnatural at usual cell yield, where cell proliferation comes via mitotic deregulations and thus contributes to overgrowth of cancerous cells. In the case of malignancy, these cells may transmigrate from one body parts to other in the form of tumors and metastasis in blood stream sand lymphatic system (Ochwang et al., 2015 and Srivatava et al., 2015). Various studies have demonstrated that the cancer danger at the level of particular organs is due to exposure to particular environmental chemicals, biological factors (as Human Papilloma virus, Helicobacter hepticus, HIV1, HBV) or physical factors (such as X-radiation, gamma radiation) (Zulkipli et al., 2015). Research proposes that most malignancies are caused by a dysfunction of multiple genes coding for macromolecules like as growth factors, growth factor receptors, anti-apoptotic proteins, transcription factors, and tumor suppressors, all of which establish the aim for disease treatment (Cogliano et al., 2011 and Vogelstein et al., 2004).

Cervix cancer is one of the numbers of cancer, which are second main origin of cancer deaths in women worldwide. At least 500,000 patients are diseased yearly those are

suffering from cervical cancer in the developing world (North et al., 2007). In 2006 there were generally 9710 new diseases and approximately 3700 deaths in United States (Atlanta et al., 2008). A persevering human papilloma virus (HPV) infection is a requirement for the growth of precursor lesions and invasive cervical carcinoma. Invasive cervical malignancy has a long premalignant phase termed cervical intraepithelial neoplasia (CIN). The preserve development from HPV infection to CIN and invasive disease generate CIN an excellent aspirant for chemo prevention (Alvarez et al., 2003). Cervical carcinoma is a disease that development quite slowly and starts with the precancerous condition called as dysplasia. Dysplasia is readily identified in a regular Pap smear and is absolutely treatable. Cervical carcinoma is a lethal malignancy obtains from the cells of the cervix. Due to programmed cell death, in a day approximately 50 and 70 billion cells lose in average adult human (Mitchell et al., 1995). Infection with the common human papillomavirus (HPV) is a cause of approximately 90% of all cervical carcinoma. About half of the sexually transmitted HPVs are companion with cervical carcinoma.

Many reports have been summarized epidemiologically and experimentally on natural compound and its relation to prevention of cancer (Johnson et al., 2005), especially in relation to tea Compound and its effect on cervical carcinogenesis (Ahn et

al., 2003) and Yokoyama et al., 2004). Luteolin, is one of the most powerful flavonoids, can stop the development of tumor cells in vitro and in vivo via suppression of tumor cell proliferation, initiation of cell cycle arrest and apoptosis by inhibiting enzymes required in cell activation such as phosphodiesterase's kinases and DNA topoisomerases. All recent approaches, in relation to the prognosis of patients and metastatic cervical cancer remains inadequate (Yang et al., 1998).

Programmed cell Death

Programmed cell Death refers to controlled regulation of cycle and removal of undesirable cells at right times without inducing surrounding tissue impairment (Millimouno et al., 2014 and Gerschenson et al., 1992). Programmed cell death occurs generally during maturation and aging and as a homeostatic mechanism to keep cell populations in tissues and as a defense mechanism such as in immune reactions or when cells are damaged by disease or noxious factor. Programmed cell death is a form of apoptosis characterized by stereotypic structural changes executed by cysteine-aspartate proteases (caspases) and regulated by the Bcl-2 family of proteins (Allen et al., 1993 and Wei et al., 2001). Numerous reports have described the mechanism by which p53 induces programmed cell death. As p53 functions principally as a transcription factor, it is important to explore the genes regulated by p53 that lead to the regulation of programmed cell death. Early studies showed that wild type p53 can bind the bax gene promoter region and regulate bax gene transcription (Miyashita et al., 1995).

Morphology of Programmed Cell Death

Electron and light microscopy have identified the various structural changes that occur during programmed cell death. During the early process of programmed cell death, cell shrinkage and pyknosis is visible by light microscopy (Oltvai et al., 1993). With cell shrinkage, the cells are smaller in size, the cytoplasm is thick, and the organelles are more tightly packed. Pyknosis is the result of chromatin contraction and this is the almost characteristic feature of programmed cell death. The apoptotic cell seems as a round or oval mass with dark eosinophilic cytoplasm and thick purple nuclear chromatin break up.

Programmed Cell Death Mechanism

The mechanisms of programmed cell death are extremely complicated and sophisticated, requiring an energy-dependent cascade of molecular events. Research shows that there are two most important programmed cell death pathways: the extrinsic or death receptor pathway and the intrinsic or mitochondrial pathway. Still, this is now demonstrated that the two pathways are associated and that molecules in one pathway can persuade the other (Igney et al., 2002). It has been found that granzyme A-induced apoptosis is a caspase-independent pathway through single stranded DNA damage. All the three (intrinsic, extrinsic and granzyme B-induced) pathways of apoptosis arrive together on the same point putting to cell death by the activation of caspase-3/7 followed by cell shrinkage, chromatin contraction

and fragmentation of chromosomal DNA, degradation of nuclear as well as cytoskeleton proteins etc.

The Extrinsic Death Receptor Pathway

The extrinsic signaling pathways that begin programmed cell death include trans membrane receptor-mediated interactions. These include death receptors that are members of the tumor necrosis factor (TNF) receptor gene superfamily members of the TNF receptor family share similar cyteine-rich extracellular domains and have a living substance domain of concerning eighty amino acids referred to as the "death domain. This death domain plays an essential role in transmittal the death signal from the cell surface to the intracellular signaling pathways. The best-characterized ligands and corresponding death receptors involve FasL/FasR, TNF- α /TNFR1, Apo3L/DR3, Apo2L/DR4 and Apo2L/DR5.

The Intrinsic Death Receptor Pathway

Following polymer injury, enlarged level of Bax and/or faded level of Bcl2 could permeabilize the mitochondria to unleash pro apoptotic factors, like cytochrome c, that trigger resultant activation of procaspase-9, followed by downstream apoptotic effectors. Recently it has been found that in response to polymer injury, activation of caspase-2 is needed before mitochondrial permeabilization and unleash of cytochrome-c (Guo et al., 2014). Activation of caspase-2 would possibly occur while not process of the precursor molecule but, oligomerization is a crucial step for caspase-2 activation.

Current treatment for Cancer Cell Line

Being the global cause of mortality and morbidity, these cancer diseases need to be dealt and/or treated in an effective way (Islam et al., 2013).). Hence, these diseases are being treated with various approaches (either alone or synergistically) since long and still are in continuous use. Some of these treatment regimens include chemotherapies, radiotherapies, immune therapies and surgeries.

Involvement of Natural Compounds in Cervical Cancer Treatment

Natural products have long been used as the important sources of cervical cancer treatment which is estimated to become the major cause of death in the current century. There are more than one thousand species that have been found to possess significant anticancer properties (Mukherjee et al., 2001). Natural compounds are obtained from plants, marine and micro-organism's life forms have gained a significant interest among cancer researchers for the potential to influence multiple cancer hallmarks. Drugs derived from natural products with anti-bacterial, anti-coagulant, anti-parasitic, immune suppressive and anticancer activity are capable of treating 87% of categorized human diseases. Among the 128 anticancer drugs released on the market between 1981 and 2010 were natural products and 32 were derived from natural products (Mukherjee et al., 2001).

Sulforaphane

The another bioactive phytochemical sulforaphane (SFN), highly present in broccoli, sprouts, cabbage and kale, has been broadly studied for its anticancer activity. SFN has been observed to enhance xenobiotic metabolism and promote cell cycle arrest and apoptosis in several human cancer cells (Clarke et al., 2008). Like many other plant polyphenols SFN can also change epigenetic events in cancer cells. Overall, SFN is an effective tool to fight from the cancer and safe chemo preventive molecule.

Indole-3-Carbinol [I3C] and Diindolylmethane [DIM]

Indole-3-carbinol (I3C) is a hydrolyzed compound of the phytochemical glucosinolate, existing in cruciferous vegetables, along with broccoli, cabbage, cauliflower, mustard, and radish. Conversion of glucosinolate to I3C is catalyzed by an accelerate gift within these plants known as myrosinase; acidic pH in the abdomen converts I3C to di indolyl methane (DIM). Each I3C and DIM are reported to induce programmed cell death in several neoplastic cell lines from solid tumors of various organs by poignant variety of kinases and nuclear receptor mediated signaling (Banerjee et al., 2011). A study with human colon cancer HT-29, SW620, RKO, LS174T, and HCT-116 cell lines and in tumor xenografts showed that DIM evoked proteosomal mediated degradation of class I HDACs (1–3,8) with no impact on class II HDAC proteins.

Resveratrol

Resveratrol is a phytoalexin mainly present in grapes. It absolutely was shown resveratrol causes programmed cell death in HL60 cells and T47D breast cancer cells (Wheat et al., 2008). It induces programmed cell death through CD95 signaling-dependent programmed cell death in HL60 and T47D cells. Resveratrol, a polyphenol found in red wine, peanuts, and some berries, possesses antioxidant and anti-inflammatory properties, and has been found to possess beneficial effects in cardiovascular disease and cancer (Savouret et al., 2002). Resveratrol exhibits weak DNMT restrictive activity in MCF7 breast carcinoma cells and was unable to reverse methylation of various tumor suppressor genes. Resveratrol activates SIRT1 chemical change (catalytic) core freelance of its terminal domains, indicating the existence of a resveratrol binding site at intervals the chemical change (catalytic) core of the enzyme (Tili et al., 2010). Topical application of resveratrol to the skin completely decreased tumorigenesis, still the impact was decreased in SIRT1-null mice, suggesting resveratrol needs SIRT1 encoded super molecule (protein) for its protection (Wang et al., 2008). Resveratrol has also been shown to supply protection from cancer by modifying miRNAs.

Green Tea

All over the world most widely consumed beverage is tea after water it has various styles of consumption like green, black

and oolong tea (Yang et al., 1993). Tea polyphenols, namely the catechins mainly found in green tea, have been observed to reduce the risk of numerous diseases, including cancer. Epicatechin (EC), Epicatechin-3-gallate (ECG), Epigallocatechin (EGC), and Epigallocatechin-3-gallate (EGCG) are four predominant catechins present in green tea, EGCG constitute over 50% of the total catechin extracted from green tea and has been broadly studied for its anticancer effects (Issa et al., 2007). The effects of green tea compounds on cell growth, apoptosis, cell cycle, and organic phenomenon were examined and characterized Yokoyama et al. [12]. Each epigallocatechingallate and polyphenols inhibit immortalized cervical tissue and neoplastic cell growth (Ahn et al., 2003). Cell death induction and cell cycle changes were determined during a dose-dependent manner. This study provides information on the potential mechanisms of action of tea compounds in suppression of HPV-related cervical cells, and it will change us to assess the feasibility of victimization these agent's (Li et al., 2005).

Genistein and Soy Isoflavones

Genistein is a phytosterols belonging to Flavonoids family. Programmed cell death induction by genistein in human promyelocytic HL-60 leukaemic cells has been confirmed by using flow cytometric analysis (Li et al., 2005). It inhibits tyrosine kinase, angiogenesis and arrests cell cycle in G2/M phase (Wheat et al., 2008).

Quercetin

Quercetin (Q), is a flavonoid compound which is occur in vegetables, fruits, tea and other plant-derived foods. Quercetin has a unique biological property which is used to improving mental/physical performance and reducing infection risk (Liu et al., 2013 & 2003), (Guo et al., 2014). Quercetin has been occurred to have pro-apoptotic and anti-proliferative effects on HeLa cells (Xiang et al., 2014). Quercetin is active in all the stages of carcinogenesis from initiation to invasion and metastasis and is able also to undermine the basis of the growth and maintenance of tumors. PI3K/Akt pathway in HeLa cells have been found to mainly mediate the anti-proliferative and apoptotic processes caused by Quercetin. Quercetin is an antioxidant in vitro because it can scavenge radicals, inhibit lipid peroxidation and chelate metals (Rice et al., 1996). Quercetin is also used in the prevention of cardiovascular disease. However, to induce this health affects in humans, quercetin must enter the systemic circulation. Quercetin in foods is bound to sugars, mainly as β -glycosides, and the bioavailability of these various quercetin glycosides is affected by their sugar moiety (Hollman et al., 1995).

Eugenol

Eugenol is a natural compound found in many plants like clove, cinnamon etc. It has been used as an antiseptic agent. Clove (*Syzygium aromaticum*) is a flower bud used as a spice in foods for enhancing the flavor. The aroma and flavor of the clove is due to the presence of eugenol (70-85%), unnecessary

oil. The other two major compounds in the clove extract are Eugenyl acetate (15%) and β -caryophyllene (5-12%). It is demonstrated that eugenol is used as analgesics in dental treatment and is also combined with zinc oxide to be used as dental fillings (Sonalker et al., 2014). They reveal anti-microbial against many foods borne pathogens. Additionally, it also exhibits strong anti-fungal property against *Candida aspergillus* and dermatophyte species (Singh et al., 2016). Eugenol together with 5-fluorouracil exhibited lot of toxicity against the cervical cancer cells (HeLa). Eugenol has ability in the prevention of diseases such as cancer, coronary heart, inflammatory disorder, and neurologic degeneration. It contained phenolic structure and natural antioxidant such as which plays an important role in protecting tissues toward free radical damages (Fujisawa et al., 2002) (Traka et al., 2005 & Mukhtar et al., 1999).

Conclusion

The natural compounds play an important role in cancer chemoprevention. They can help against cancers like cervical cancer, through apoptotic as well as other pathways. These compounds could be tested in clinical trials in cervical cancer patients. This would further validate the experimental studies and would translate the research findings from bench to bedside.

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DOI: [10.19080/CTOIJ.2019.14.555886](https://doi.org/10.19080/CTOIJ.2019.14.555886)

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