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Curcumin's Potential as a Therapeutic Agent for Hpv-Induced Cancer

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Abstract

Curcumin, the main active compound of turmeric (Curcuma longa), shows potential as a therapeutic agent for Human Papillomavirus (HPV)-induced cancer. This study examines the mechanism of action of curcumin in inhibiting the proliferation of HPV-infected cervical cancer cells, including its anti-inflammatory, anti-cancer, and anti-viral properties reviewed from several references. Curcumin works by suppressing the expression of E6 and E7 oncoproteins, induction of apoptosis, and modulation of signaling pathways that support tumor growth, such as NF-κB. Although curcumin has great potential, the challenges of low bioavailability and rapid metabolism in the body still need to be overcome. Further research is needed to optimize the formulation and delivery method of curcumin as a cancer therapy.

Keywords: *Anti-inflammatory; Apoptosis; Cervical Cancer; Curcumin; Human Papillomavirus (HPV).*

Abstrak

Kurkumin, senyawa aktif utama kunyit (Curcuma longa), menunjukkan potensi sebagai agen terapeutik untuk kanker yang diinduksi oleh Human Papillomavirus (HPV). Penelitian ini mengkaji mekanisme kerja kurkumin dalam menghambat proliferasi sel kanker serviks yang terinfeksi HPV, termasuk sifat antiinflamasi, anti kanker, dan anti virus yang ditinjau dari beberapa referensi. Kurkumin bekerja dengan cara menekan ekspresi onkoprotein E6 dan E7, induksi apoptosis, dan modulasi jalur sinyal yang mendukung pertumbuhan tumor, seperti NF-κB. Meskipun kurkumin memiliki potensi yang besar, tantangan ketersediaan hayati yang rendah dan metabolisme yang cepat di dalam tubuh masih perlu diatasi. Penelitian lebih lanjut diperlukan untuk mengoptimalkan formulasi dan metode penghantaran kurkumin sebagai terapi kanker.

Kata Kunci: Antiinflamasi; Apoptosis; Human Papillomavirus (HPV); Kanker serviks; Kurkumin.

INTRODUCTION

Human Papilloma Virus (HPV) is a double-stranded DNA virus measuring 55 nm. Its genomic material consists of three functional coding regions: E (the gene that encodes the virus's initial function), L (the gene that encodes the virus's final function), and the LCR (Long Control Region) which lies in between. The virus exhibits structural homology with papilloma viruses and consists of about 72 capsomers [1]. *Human Papilloma Virus* (HPV) has been identified as the leading cause of cervical carcinoma or cervical cancer. In 1976, the involvement of HPV in the development of cervical tumors began to be seen and since then, various epidemiological and statistical studies have further strengthened this observation. HPV is one of the most common viruses transmitted through sexual intercourse and can be found in both men and women. HPV infection rates are reported to be higher in western countries compared to other regions of the world [2].

HPV infection induces increased proliferation of infected cells and lateral expansion. The development of cervical carcinoma is a multi-stage process characterized by a long latency period. The early stages of cervical carcinogenesis are characterized by *a premalignant* phase characterized by various gradations of *Cervical Intraepithelial Neoplasia* (CIN), ranging from CIN I, CIN II, to CIN III, which are histologically characterized by the presence of abnormalities [3]. Of the many types *of Human Papillomavirus* (HPV) that exist, types 16 and 18 are the two types that most often develop into cervical cancer [4]. Both types are detected in nearly 70% of cervical cancer cases found. HPV 16, a small virus without a sheath, has double-stranded DNA as its genetic material. The *human papillomavirus* (HPV) genome consists of seven functional coding regions. The E1/E2 region regulates the function of the E6 and E7 genes. The E4 region encodes proteins with functions that have not yet been fully characterized, but are thought to be involved in the regulation of viral release from cells. The E5 region encodes hydrophobic proteins that potentiates cellular immortalization. The E6 region produces proteins that inhibit negative regulators of the cell cycle and further suppress the activity of p53, a transcription factor that plays a role in apoptosis. The E7 region encodes viral proteins that interact with retinoblastoma tumor suppressor proteins, thus allowing cells to proliferate in the absence of external mitogenic stimulation. The L1/L2 region encodes structural proteins that are essential for late-stage viral function and the formation of infectious viral particles. Finally, the LCR (Long Control Region) region is located between regions E and L and plays an important role in the regulation of viral transcription and replication [5].

Globally, cervical cancer has become a serious public health problem, especially threatening the lives of young women. Although the prevalence varies across countries, cervical cancer mortality rates tend to be higher in Western countries. The data show a stark inequality, with minority groups such as Native Americans, Hispanics, and African-Americans experiencing a heavier burden of disease [6]. Based on WHO data, HPV infects about 500,000 new individuals each year, resulting in 250,000 deaths. These alarming numbers have prompted molecular virologist to conduct in-depth research into the mechanisms of HPV infection (pathogenesis) and develop effective therapies to fight the disease [7]. Based on recent data, the prevalence of HPV infection in women globally, especially in the United States, is much higher than in men. The overall prevalence of HPV infection is higher in women than in men, with rates of 17.9% and 8%, respectively. In addition, there is a difference in prevalence by race. African-Americans have a 20-29% higher risk of HPV infection than Caucasians. Another significant risk factor is the number of sexual partners. Individuals with multiple sexual partners had a much higher risk of HPV infection (20.1%) than those with only one lifetime partner 7% [8].

So the purpose of this literature review is to determine the potential of curcumin as a therapeutic agent for HPV-induced cancer, accompanied by the mechanism of action of curcumin that inhibits carcinogens, and equipped with study tests from several literature

RESEARCH METHODS

The writing in this journal is by using the systematic literature review method to examine the antiviral activity of turmeric (Curcuma longa L.) as a therapeutic agent of the Human Papillomavirus (HPV). Literature searches are conducted on indexed electronic databases such as PubMed, Science Direct, Google Scholar, and Scopus. With the limitations of the literature explored, namely the antiviral activity of turmeric as a therapeutic agent of the HPV virus.

RESULTS AND DISCUSSION

Turmeric (*Curcuma longa*) is an herbal plant that has been used in traditional medicine for thousands of years. Its main active component is curcumin, which is known to have a wide range of therapeutic benefits, such as anti-inflammatory, antiviral, and anticancer properties. This compound has been extensively researched primarily for its potential in treating cancer and viral infections, including *Human Papillomavirus* (HPV) [9]. Curcumin, the main polyphenol compound in turmeric, has been the focus of research due to its anticancer potential. In vitro studies have shown that curcumin can significantly inhibit the proliferation of HPV-infected cervical cancer cells through the induction of apoptosis and cell cycle arrest. This cytotoxic effect of curcumin is stronger in HPV-infected cells compared to normal cells, which suggests the synergistic potential between curcumin and HPV infection in inducing cell death [10].

Anti-Inflammatory Properties

Curcumin has long been known as a powerful anti-inflammatory agent. This ability is supported by research that reveals that curcumin works by inhibiting the production of various inflammatory mediators in the body. These inflammatory mediators include cytokines, which are molecules that play a role in communication between cells, and enzymes involved in the inflammatory process. For example, studies have found that curcumin is effective in lowering levels of TNF-α (*Tumor Necrosis Factor alpha*) and IL-6 (*Interleukin-6*). These two cytokines are known as pro-inflammatory because they trigger and amplify the inflammatory response in the body, and are often involved in a variety of chronic inflammatory diseases. In addition to its ability to inhibit other inflammatory mediators, curcumin is also effective in suppressing the NF-kB pathway. NF-kB is a major transcription factor that controls the expression of genes involved in the inflammatory response. By inhibiting this pathway, curcumin can effectively modulate inflammation [10]

Anti-cancer properties

Curcumin has pleiotropic anticancer properties, which means this compound works through a variety of mechanisms. One of the main mechanisms is the induction of apoptosis in cancer cells, which is very important in controlling tumor growth. Curcumin is effective in inducing apoptosis in cancers associated with inflammation and viral infections through modulation of oncoproteins and apoptotic signaling pathways. In addition to its widely researched anticancer effects, curcumin also shows chemopreventive potential through inhibition of cell proliferation and suppression of angiogenesis. Further, studies have revealed that curcumin may inhibit the growth of HPV-infected cervical cancer cells. This effect is associated with decreased expression of E6 and E7 oncoproteins, which are potential targets in the prevention and treatment of cervical cancer [11]

Anti-Viral Properties

In addition to anticancer properties, curcumin also has potential as an antiviral agent. Curcumin's mechanism of action in inhibiting viral replication involves interference with various stages of the viral life cycle, including penetration, translation, and assembly. For example, in the case of HPV infection, curcumin has been shown to decrease the expression of the L1 gene, which is important for the production of viral capsids. In vitro and in vivo studies have shown that curcumin effectively inhibits viral infections through modulation of virus-host cell interactions and suppression of viral induced inflammatory responses. Curcumin can interfere with the attachment of the virus to the host cell or inhibit the penetration of the virus into the cell. In addition, curcumin

can also modulate inflammatory signaling pathways and reduce the production of pro-inflammatory cytokines that play a role in the pathogenesis of viral infections [12].

HPV (*Human Papillomavirus*) is a small DNA tumor virus (8 kb) that has been shown to play a role in about 90% of cervical cancer cases, 90% of anal cancer, 50% of penile cancer, 40% of vulvar cancer, 70% of vaginal cancer, and 20-60% of oropharyngeal cancer [13]. High-risk HPV (HR) types such as 16 and 18 are specifically involved in 80-90% of cervical cancer cases and 30-70% in other anatomical locations. Interestingly, oropharyngeal and/or head and neck cancers associated with HPV show alarming increases among men and women in developing countries [14]. To date, there is no specific therapy that is effective for the treatment of HPV. However, two recently developed HPV L1 virion protein-based prophylactic vaccines, namely *quadrivalent Gardasil* (HPV 16/18/6/11) and *bivalent Cervarix* (HPV 16/18), have been commercialized worldwide. In 2014, the US FDA approved nonavalent vaccines for nine types of HPV (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58) [15], although these vaccines are still not widely available in other developing countries [16].

Host cell-derived Al factor 1 (V) suggests that the transactivation and DNA-binding activity of the cellular transcription factor AP-1 as well as the proinflammatory transcription factor NF-kB can be modulated by intracellular redox status changes influenced by the synthetic antioxidant agent pyrrolidine dithiocarbamate. This leads to the selective suppression of HPV transcription in cervical cancer cells [17]. Therefore, it is of great interest to investigate the role of a powerful natural antioxidant in cervical and oral cancer, namely cumin, which has been used in traditional medicine systems for various effects and treatments since ancient times [18]. Curcumin (*diferulolylmethane*, 1,7(4-OH-3 *methoxy phenyl*)1-6, *heptadene* 3,5-dion) is an active ingredient of a spice derived from the turmeric plant (*Curcuma longa*) of the *Zingiberaceae* family (ginger) and is widely used in cuisine in the Southeast Asian region [19] [20]. Curcumin contains compounds known as curcuminoids, consisting of curcumin (77%), demethoxycurcumin (17%), and bisdemethoxycurcumin (3%). Curcumin is the main component that makes up about 2-5% of turmeric powder [21]. In addition to being used as a spice, turmeric has many health effects and exhibits pleiotropic roles as an antiviral, anticancer, anti-inflammatory, and wound-healing agent [22]. As a dietary supplement, turmeric has been shown to be pharmacologically safe with very low or no toxicity levels, even doses as high as 8 g/day have been administered orally to humans without side effects [23].

Curcumin inhibits many regulatory molecules and enhanced signaling pathways in cancer and other diseases, making it a highly effective chemopreventive as well as chemosensitizing agent [24]. Curcumin suppresses cell growth and tumor formation by lowering the regulation of important kinases such as PKC, JNK, EGFR, and MAPK. In addition, curcumin also inhibits the NF-kB pathway, which includes cyclin D1 as well as inflammatory cytokines and chemokin. Curcumin induces the expression of phase II methanolizing enzymes and antiangiogenic effects by inhibiting CYP450, VEGF receptors, and angiopoietin [25]. Curcumin is known to induce apoptosis through activation of mitochondrial pathways, leading to the activation of caspase 3 and 9, as well as PARP cleavage, as well as inhibiting the Bcl-2 and Bcl-xL antiapoptosis genes [26]. In in vitro studies on cervical and oral cancer cells, curcumin has been shown to have a strong anti-HPV effect [27]. Based on a preclinical study followed by a randomized, placebo-controlled Phase II clinical trial of curcumin and other formulations [28].

Clinical trials on curcumin have shown significant potential as a chemopreventive and chemosensitizing agent due to its ability to suppress various regulatory molecules

and signaling pathways commonly involved in cancer development [27]. The mechanism of action of curcumin in suppressing cell growth and tumor formation involves a decrease in the regulation of important kinases such as *Protein Kinase C* (PKC), *c-Jun N-terminal Kinase* (JNK), *Epidermal Growth Factor Receptor* (EGFR), and *Mitogen-Activated Protein Kinase* (MAPK) [27]. In addition, curcumin also inhibits *the Nuclear Factor kappa B* (NF-κB) pathway and *the Activator Protein* 1 (AP-1) pathway, including cyclin D1 as well as inflammatory cytokines and chemokines [29]. Curcumin plays a role in inducing the expression of phase II metabolic enzymes and provides antiangiogenic effects through inhibition of CYP450, *Vascular Endothelial Growth Factor* (VEGF) receptors, and angi-opoietin. Curcumin is also known to trigger apoptosis, which is a programmed cell death process, by activating mitochondrial pathways that lead to the activation of caspases 3, 7, and 9, as well as the cleavage *of Poly*(ADP- ribose) *polymerase* (PARP). On the other hand, curcumin also inhibits anti-apoptosis genes such as *B-cell lymphoma* 2 (Bcl2) and *B-cell extra-large lymphoma* (Bcl-xL) [30]. Other clinical trials regarding intravaginal application of curcumin-based capsules or vaginal creams at night for 4 weeks have shown significant clearance of the virus (-80%) [31]. Some authors also report curcumin's role as an anti-HPV agent. Treatment with curcumin has been shown to inhibit the transcription of HPV 16 E6/E7 within six hours of treatment, as well as restore the expression of tumor-suppressor proteins p55, Rb, and PTPN13 [32]. Curcumin also has the ability to enhance paclitaxel-induced apoptosis in HPV-positive human cervical cancer cell lines via the NF-kB and p53-caspase 3 pathways [33]. In addition, curcumin promotes histone deacetylation, chromatin overhaul, and proapoptotic transactivation mediated by p53. Protein ligand-based analysis showed that curcumin interacts with the p53 binding sac on the E6 protein residue [34].

113-122 (CQK PLCPEEK) facilitates the restoration of p53 function. Curcumin has been reported to improve radiation sensitivity in head and neck cancer cells through inhibition of thiodoxine reductase 1 [35]. Therefore, this herbal antioxidant is able to suppress HPV oncoproteins, restore the p53 protein, and inhibit the increase in HPV E7 regulation induced by the tobacco carcinogen benzo[a]pyrene. In addition, curcumin is known to decrease the regulation of increased miRNA-21 expression in cervical cancer through AP-1 binding to its promoter [36].

Although curcumin shows potential to lower HPV oncogene expression and serves as a therapeutic agent for HPV-induced cancers [37], there are several key issues such as hydrophobicity, rapid metabolism, improper targeting, and poor bioavailability. To address this problem, many derivatives of curcumin, nanocurcumin, or certain chemical groups have been added to curcumin [38]. A low-molecular-weight curcumin-2 conjugate (cur-2FA) has been developed for targeted curcumin delivery to cancer cells or cancer stem cells that selectively express high-affinity folate receptors on cell surfaces [39]. Studies show increased cellular uptake of Cur-2FA as well as increased bioavailability. Conjugated chemistry is used in a manner designed to improve delivery effectiveness [40].

CONCLUSION

Curcumin is the main active compound in turmeric (Curcuma longa), showing potential as a therapeutic agent in treating cancer induced by Human Papillomavirus (HPV). Various studies have shown that curcumin has anti-inflammatory, anticancer, and antiviral properties that contribute to inhibiting the proliferation of cervical cancer cells that infect HPV. The mechanism of action of curcumin involves suppression of HPV oncoprotein expression (E6 and E7), induction of apoptosis, and inhibition of signaling

pathways that support tumor growth, such as NF-κB and Cell A. However, the clinical effectiveness of curcumin still faces major challenges, namely low bioavailability due to its hydrophobicity and rapid metabolism in the body. To overcome these constraints, various strategies have been developed, such as the use of curcumin derivatives, nanocurcumin, and conjugation with other molecules to improve stability and absorption. Therefore, although curcumin has great potential as an agent for HPV-related cancer prevention and therapy, further research is needed to optimize formulations and delivery methods for its clinical effectiveness to be maximized.

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