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Exploring the Role of Curcumin in Benign Ovarian Tumor Therapy: Molecular and Clinical Insights

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ABSTRACT

Recent advancements in understanding the molecular mechanisms underlying ovarian tumor development and progression have opened new avenues for targeted anticancer therapies. These novel treatments aim to influence specific metabolic pathways while minimizing the systemic toxicity associated with conventional therapies. Among the emerging strategies for cancer prevention, curcumin active polyphenolic compound derived from the rhizome of Curcuma longa L, has gained significant attention due to its broad-spectrum pharmacological properties, including antioxidant, anti-inflammatory, and anticancer effects. In particular, curcumin's potential to combat ovarian cancer (OC) has been extensively studied, demonstrating its ability to enhance chemotherapy sensitivity and slow tumor progression. Research indicates that curcumin exerts its anticancer effects through multiple mechanisms, such as inducing apoptosis, inhibiting cell cycle progression, promoting autophagy, preventing tumor metastasis, and modulating enzyme activity. As investigations into curcumin's mechanisms against OC continue, its potential clinical applications are expected to expand. This review compiles recent findings on curcumin's anti-OC effects and explores its molecular pathways, aiming to provide insights for future research and therapeutic development.

Keywords: curcumin; benign ovarian tumor; molecular mechanism; anti-tumor.

INTRODUCTION

The ovaries have an important function in reproduction and menstruation. Disorders in the ovaries can impede the growth, development, and maturation of ovarian cells to be impeded. One of the abnormalities found in the ovaries is an ovarian tumor.[1] A tumor is a group of abnormal cells that form due to excessive and uncoordinated cell division. Tumors are divided into two major groups, namely benign tumors and malignant tumors or cancer.[2] Ovarian tumors are new masses or abnormal tissues that form in the ovaries, having characteristics different from the original tissue cells due to the proliferation and differentiation of abnormal ovarian cells caused by gene mutations that regulate the proliferation of these cells.[1]

The most common ovarian tumor in women is a benign ovarian tumor, with an incidence of 80%, mostly with cystic lesions, and the rest are malignant ovarian tumors.[3] The incidence of benign ovarian tumors in the form of cysts in Indonesia in 2015 was 23,400 people, with 13,900 of them dying. The high mortality rate is caused by the fact that this disease initially does not show symptoms and only presents complaints when it has already metastasized. 60-70% of patients come at an advanced stage.[4] The Indonesian Demographic Health Survey (SDKI) states that the incidence rate of ovarian cysts in Indonesia reaches 37.2% and is most commonly found in women aged between 20-40 years. This disease rarely affects women of pubertal age or under 20 years old, so there is a possibility that women in this age group do not experience benign ovarian tumors.[5] The current standard of care includes primary surgical cytoreduction followed by cytotoxic chemotherapy. The very high recurrence rate remains a significant issue. Therefore, effective therapeutic strategies and targets while minimizing unwanted side effects should be the focus of future scientific studies.

Turmeric (*Curcuma Longa*) is a herbal plant from the Zingiberaceae family, easily found throughout tropical Asia, including India, Southern China, Southeast Asia, Papua, and northern Australia. In Asian countries, turmeric is often used in food and medicine, as well as a natural dye and flavor enhancer in concentrations ranging from 5-500 mg/kg. Turmeric has been described as an anti-inflammatory agent because the active component of turmeric, namely *diefuroluoylmethane*, has been proven to have antiviral, antibacterial, antioxidant, anti-inflammatory, antiproliferative, and antiangiogenic activities. Curcumin has also been proven to inhibit the activation and reduce the expression of cyclooxygenase-2 (COX-2), 5-lipoxygenase, vascular endothelial growth factor (VEGF), phosphorylated signal transducer and activator of transcription 3 (STAT3), all of which are associated with tumorigenesis.

However, one of the pathways is suspected to be the main target in case of malignancy that can be inhibited by turmeric is NF-κB.[6]

Due to the numerous therapeutic potentials of this plant, various curcumin products have circulated in the market in the form of tablets, drinks, ointments, and cosmetics. The widespread use of curcumin in India, Japan, Thailand, China, Korea, Malaysia, Pakistan, and America has increased the level of safety for curcumin consumption globally. As a result, the US Food and Drug Administration (US FDA) has labeled curcumin as a product that is "Generally Recognized as Safe". Moreover, the Joint United Nations and World Health Organization Expert Committee on Food Additives (JECFA) and the European Food Safety Authority (EFSA) recommend a daily intake of 0-3 mg/kg body weight of curcumin.[7,8]

In an experimental study conducted, it was shown that curcumin can inhibit NF-κB inactivation and suppress in vitro proliferation. It is stated that an oral dose of 500 mg/kg is the optimal dose required to suppress NF-κB. Tumor growth also experienced a reduction, especially when consumed with the anti-mitosis chemotherapy drug docetaxel, which can reduce tumor growth by up to 77% compared to the control group.[9]

BENIGN OVARIAN TUMOR

Definition

Benign ovarian tumors are abnormal solid masses that grow slowly in a woman's ovaries. Usually, ovarian tumors are benign and remain benign, but some types may develop into cancer if not treated. The main issue that often arises with ovarian tumors is recurrence, which can occur even after chemotherapy. This is suspected to be due to the presence of a residual population of cancer cells that were not affected by the therapy and reappear after the treatment is completed.[10]

Benign epithelial tumors are the most commonly found type of ovarian tumor. They originate from the cells located on the outer surface of the ovary. If cystic (*cystadenoma*), usually solid (*adenofibroma*) or mixed (*cystadenofibroma*). Benign epithelial ovarian tumors encompass various subtypes, notably serous, mucinous, and cystadenofibroma.[11]

Benign germ cell tumors originate from cells that produce eggs (ova). They are also commonly referred to as mature teratoma cysts or dermoid cysts. Most germ cell tumors appear when women are in their reproductive years (teenagers to 40 years old).[11] Benign ovarian tumors develop slowly and rarely become malignant. Some common types include *benign cystic* teratomas, also known as dermoid cysts, which originate from all three germ cell layers but primarily contain ectodermal tissue. Fibromas are connective tissue tumors that typically grow gradually and usually measure less than 7 cm in diameter. Cystadenomas, another type of benign ovarian tumor, are classified as either serous or mucinous, depending on the type of fluid they contain.[12]

Etiology

There are many risk factors associated with ovarian tumors. Some appear in postmenopausal women, where increasing age is often associated with a higher incidence, more advanced stages of the disease, and lower survival rates. Parity has a protective role according to several case-control studies, where most women with parity have a reduced risk of ovarian tumors.[10] The strongest risk factor currently is a family history of breast or ovarian cancer, where if someone has a history of breast cancer, the risk of developing ovarian cancer also significantly increases. Several studies show that there is an increased risk caused by smoking, especially the risk of mucinous epithelial cell tumors.[11]

Pathophysiology

The NF-κB signaling pathway is the master, commander, and regulator in ovarian tumors that drives chemoresistance formation, maintenance of cancer stem cells, metastasis, and immune evasion. Many signaling pathways are dysregulated in ovarian tumors that can activate NF-κB. The activation of NF-κB functions as an anti-apoptosis and immunomodulatory response to tumor formation. The activity of NF-κB in ovarian tumors helps create an environment safe from the body's immune cells and attracts immune cells with phenotypes that aid tumor formation, ultimately supporting the life and survival of the tumor until metastasis. Therefore, NF-κB is an interesting target to study in ovarian tumors, but current strategies are still limited, especially in stopping this signaling process.[13]

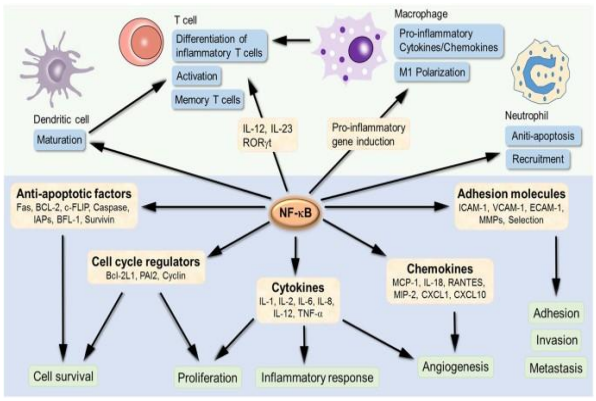

FIGURE 1: The Role of NF-κB in Tumor Survival.[13]

KURKUMIN

Definition

Turmeric (*Curcuma Longa*) is a herbal plant from the Zingiberaceae family, and it is easily found throughout tropical Asia, including India, Southern China, Southeast Asia, Papua, and northern Australia. In Asian countries, turmeric is often used in food and medicine, as well as a natural dye and flavor enhancer in concentrations ranging from 5-500 mg/kg. Turmeric has been described as an anti-inflammatory agent because the active component of turmeric, namely, *diefuroluoylmethane*, has been

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Curcumin significantly inhibits the antioxidant process by breaking the chains of free radicals. The ability of curcumin to capture hydrogen peroxide is also much higher than that of commercial antioxidants at the same concentrations, such as BHA, BHT, and even vitamin E. A meta-analysis study conducted further research on curcumin and found that it can also significantly reduce oxidative stress markers. Additionally, curcumin also reduces the protein response involved in the inflammatory process, such as *tumor necrosis factor alpha* (TNF-α), interleukin-1 (IL-1), IL-2, IL-6, IL-8, and IL-12. TNF-alpha is a significant inflammatory mediator that ultimately leads to chronic diseases. The presence of TNF alpha activates NF-κB and ultimately accelerates the inflammatory response process. Curcumin has the benefit of inhibiting TNF-alpha activation in the NF-κB pathway and neutralizing ROS that cause oxidative stress.[8,13]

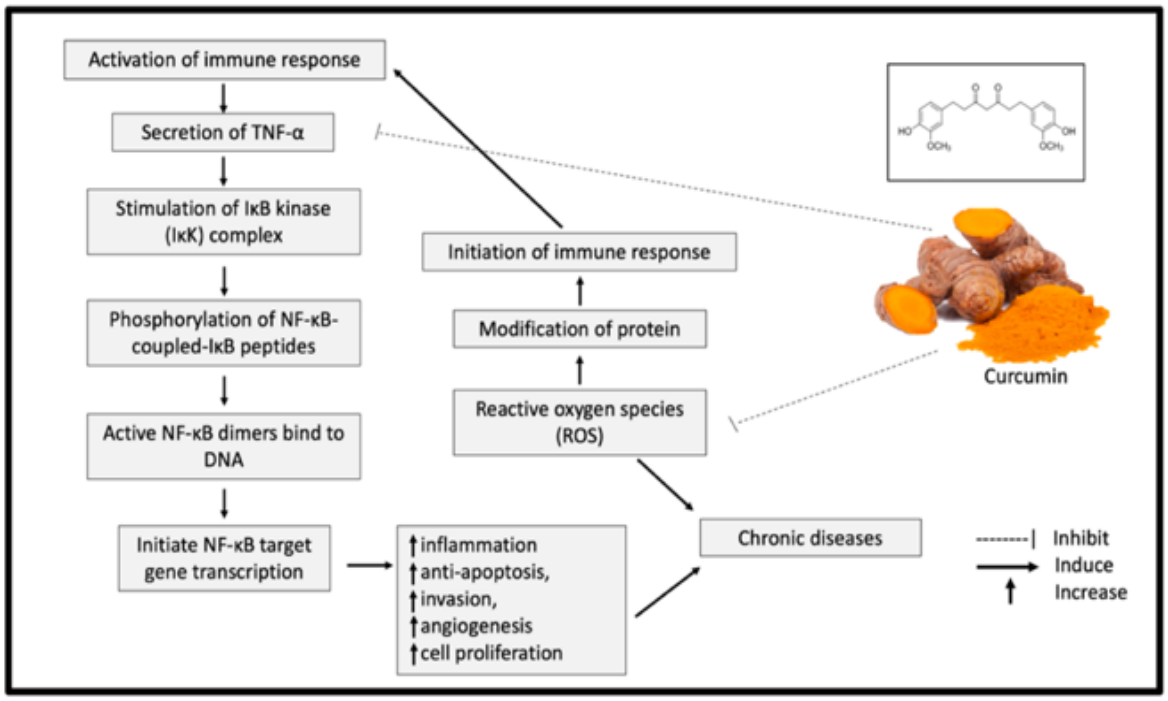

FIGURE 2: The Role of Curcumin in Inhibiting NF-κB Signaling Pathway.[13]

THE ROLE OF CURCUMIN IN BENIGN OVARIAN TUMORS

Curcumin, which is a component found in turmeric, has been proven to significantly suppress inflammation and angiogenesis by inhibiting transcription factors in nuclear factor-κB. The presence of reactive oxygen species (ROS), which are free radicals, leads to protein modifications that will activate the immune response. One form of the immune response in the body is the secretion of TNF-α, which subsequently stimulates the IkB kinase complex and activates NF-κB that binds to DNA. Genetic transcription caused by NF-κB leads to the increase of the following: inflammation, anti-apoptosis, invasion, angiogenesis, and cell proliferation. These factors are contributors to tumorigenesis and also the main causes of chronic diseases.[7]

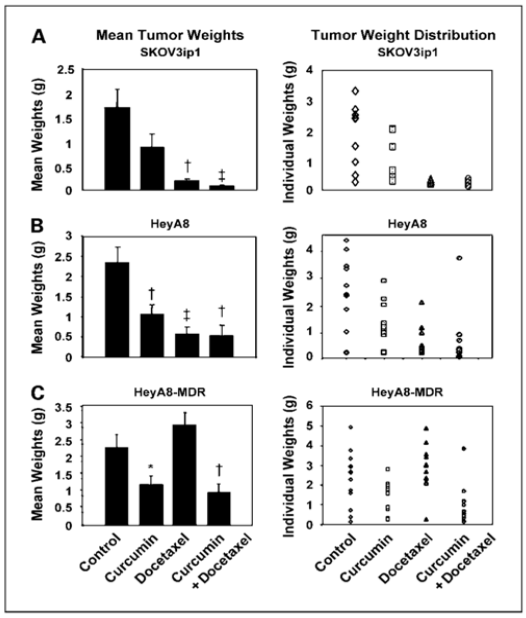

FIGURE 3: Comparison of Tumor Growth between Control, Curcumin, and Chemotherapy.[14]

Yvonne et al. conducted research on 3 types of cells, namely: SKOV3ip1, HeyA8, and HeyA8-MDR. From the results of this study, it was found that monotherapy with curcumin significantly reduced the tumor weight by 49% in the SKOV3ip1 cell model and by 55% in the HeyA8 model. The combination of docetaxel (an anti-mitosis chemotherapy drug) with curcumin resulted in a 96% reduction in the SKOV3ip1 tumor model and a 77% reduction in the HeyA8 model.[9,13]

From the results of this study, it can be concluded that curcumin has effects on ovarian tumors through antitumorigenic and antiangiogenic mechanisms. Curcumin-based therapy has good efficacy in cases of patients who are sensitive to chemotherapy as well as those who are resistant to chemotherapy. Furthermore, there is strong suspicion that these therapeutic effects arise due to the inhibition of the NF-κB pathway and other transcription factors, as well as angiogenic growth factors, including the phosphorylation of STAT3, COX-2, IL-8, MMP-9, and VEGF. In vitro studies show that NF-κB plays an important role in tumor growth, apoptosis, and tumor chemoresistance.[7,9,14]

On the other hand, the biggest disadvantage of taking curcumin supplements is that they are not easily absorbed by the body. This is due to the fact that they are quickly broken down and eliminated. When curcumin is taken orally, 40% of it is excreted in feces. As a result, there are a number of curcumin formulations that have been developed to improve its bioavailability. These include nanoparticles, encapsulation, phospholipid complexes, structural analogs, subcutaneous injections, topical applications, and hydrophilic carriers, all of which have been shown to increase the bioavailability of curcumin.[7]

CONCLUSION

Ovarian tumors continue to be a major issue and burden in the healthcare field. This is not only because they are still very hard to diagnose in the early stages, but also because they have a high risk of recurrence. There are many instances in which patients have finished their chemotherapy but still have a recurrence. One of the probable causes of this is the activation of the NF-κB pathway. The NF-κB pathway is responsible for angiogenesis and tumor growth, and it eventually contributes to the development of tumors. It all begins with oxidative stress and free radicals, which eventually lead to the activation of NF-κB. Curcumin is one of the natural and beneficial antioxidants that play a key role in the growth of ovarian tumors. When curcumin (the molecule contained in turmeric) is coupled with chemotherapy medications, it can limit tumor development by as much as 96% by preventing the NF-κB factor from being activated. Research on curcumin has begun to pick up speed, and the results that have been gained so far have been very promising. However, further research is still needed to determine how effective it is in humans and how well it is absorbed by the body.

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