Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-3 Issue-5 || October 2024 || PP. 26-31

https://doi.org/10.55544/jrasb.3.5.5

Therapeutic Potential of Quercetin and their Compound Against Ovarian Cancer: New Approaches & Application

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www.jrasb.com || Vol. 3 No. 5 (2024): October Issue

Received: 13-09-2024	**Revised:** 16-09-2024	**Accepted:** 02-10-2024

ABSTRACT

Ovarian cancer is an exceptionally perilous form of cancer as it develops within the female reproductive system. Finding effective therapy platforms for ovarian cancer has been difficult because to the diverse array of molecular pathways and genetic alterations involved in its development. Therefore, it is imperative to discover novel therapeutic methodologies and advance their development. Medicinal herbs possess the capacity to independently or in combination with other pharmaceuticals, effectively treat malignancies such as ovarian cancer. Quercetin possesses remarkable anti-inflammatory and anti-cancer properties, making it one among numerous natural compounds with such qualities. Quercetin has demonstrated cytotoxicity against ovarian cancer cells in both laboratory experiments (in vitro) and live animal tests (in vivo). The potential anti-cancer effects of quercetin, particularly in relation to ovarian cancer, have not been extensively studied in human trials, despite encouraging findings from laboratory and animal experiments. Hence, it seems that quercetin could potentially be utilized in clinical trials as a therapeutic agent, either on its own or in conjunction with other chemotherapeutic drugs. This article will outline the primary aspects of quercetin's anti-cancer characteristics and thereafter concentrate on its application in the treatment of ovarian cancer.

Keywords- Ovarian cancer, Quercetin, Therapeutic potential.

I. INTRODUCTION

Among the many cancers that affect Indonesian women, ovarian cancer stands out as a leading cause of cancer-related deaths. The difficulty in quickly diagnosing the illness is one possible explanation for the high fatality rate. The observed 5-year survival rate for patients diagnosed at a more advanced stage (stage III/IV) is less than 30% [1][2]. The development of effective strategies for prevention and early diagnosis of ovarian cancer has been impeded by its substantial variability. Epidemiological studies have shown that oral contraceptives were the mainstay of prevention strategies for ovarian cancer in the past. Ovarian cancer

ISSN: 2583-4053

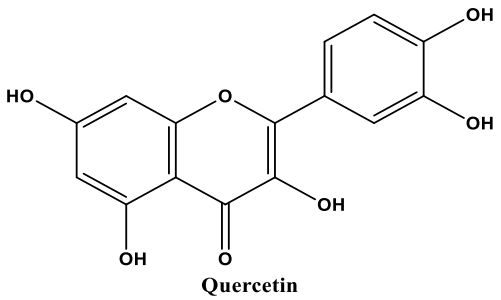
Volume-3 Issue-5 || October 2024 || PP. 26-31

https://doi.org/10.55544/jrasb.3.5.5

rates have not dropped noticeably despite these adjustments [3]. New strategies to prevent ovarian cancer are being discussed at the moment. The gold standard for ovarian cancer prevention is prophylactic salpingectomy [4][5]. Hysterectomy and female sterilization treatments should include prophylactic salpingectomy, according to a campaign started in 2010 by the British Columbia Ovarian Cancer Research Group (OVCARE) [6]. Incidence rates of ovarian cancer could fall by 20–40% over the next 20 years if this strategy pans out [7][8].

II. QUERCETIN AND ITS BIOLOGICAL ACTION

Quercetin is a flavonoid that is found in many different plants and is used in many different recipes [9]. The most common flavonoids in the body are quercetin glycosides, which are abundant in propolis and other nutrient-rich foods including apples, onions, broccoli, tea, and red wine. It has been designated as 3,3′,4′,5,7-pentahydroxyflavone by the International Union of Pure and Applied Chemistry (IUPAC) [10]. Because there are five hydroxyl groups on the flavonoid at positions 3, 5, 7, 3′, and 4′, the medicine is called 3,3′,4′,5,7-pentahydroxy-2-phenylchromen-4-one. The health benefits of quercetin, a dietary supplement, are encouraging. It is thought that quercetin helps protect the cardiovascular system, lower inflammation, and even prevent cancer, among its many positive impacts on human health [11]. This compound has many positive effects, including reducing the risk of cancer, tumors, ulcers, allergies, infections, inflammation, and diabetes. Further benefits include gastrointestinal protection, reduced blood pressure, immune system modulation, and anti-infective properties [12].



Quercetin

Figure 1: Chemical structure of Quercetin

III. OVARIAN CANCER CARCINOGENESIS AND PROGRESSION: MOLECULAR MECHANISMS

The processes that lead to ovarian cancer have been the subject of numerous theories. Women may be more vulnerable to DNA damage and cancer due to the ovarian epithelium's frequent cycles of breakdown and repair during ovulation, according to one theory [13] Women who ovulate more frequently are at increased risk for developing ovarian cancer. Ovarian cancer is much more common in rats that exhibit hyper-ovulation [14]. According to some studies, ovulation can set in motion a chain reaction of biological events that leads to cancer. Therefore, the increased risk of mutagenicity associated with excessive ovulation may be due to inflammation [15]. An increase in prostaglandins, leukotrienes, and vasoactive molecules like bradykinin, among others, is caused by ovulation. Ovulation is characterized by an inflammatory response upon follicle rupture. Oxidative stress, prostaglandins, and cytokines are more likely to reach the epithelium that surrounds the ovulation site. One competing theory proposes that elevated gonadotrophin levels promote inclusion cyst epithelial proliferation by direct or indirect activation of steroidogenesis, hence causing the inclusion cyst epithelium to proliferate [16]. Neoplastic transformation develops as a result of this. In addition, research has linked reproductive hormones to an increased risk of ovarian cancer. In particular, research has shown that oestrogen promotes cancer cell proliferation and that progestins have anti-cancer effects via increasing cell death [17]. In addition, ovarian cancer may have a role in persistent inflammation. Epithelial ovarian cancer cells having the power to diffuse to the peritoneal cavity and generate the buildup of ascites, resulting in an immunosuppressive environment that exacerbates tumour advancement [18]. Ascetic fluid activates protein kinase B (Akt) in order to counteract cell death mediated by tumour necrosis factor receptor apoptosis-inducing ligand (TRAIL). Ascites and plasma samples taken from patients with advanced epithelial ovarian cancer showed significant changes in inflammatory chemicals and cytokines, according to a recent study. All signs point to a dynamic remodeling of these cytokines, according to these results. On top of that, there is a correlation between ovarian cancer and increased levels of certain inflammatory molecules, such as Akt, lysophosphatidyl acid (LPA), and protein kinase C (PKC) [19]. New evidence suggests that LPA, via the Akt/NF-kB signaling pathway, increases IL-6, IL-8, and VEFG production in ovarian cancer cells. In addition, PKC is an essential component of other signal transduction pathways that are involved in cancer. The progression of ovarian cancer and its resistance to treatment are both linked to impaired PKC function. Ovarian cancer associated with inflammation is significantly worsened by the aforementioned medications and processes when taken together. Damage to DNA, proteins, and lipids is a direct result of inflammation's production of harmful oxidising chemicals, which in turn accelerate cancer progression. Increased cell replication and chronic inflammation are also associated. Mutagenesis is more likely to occur when cell division is both rapid and excessive because more DNA is repaired as a result of

ISSN: 2583-4053

Volume-3 Issue-5 || October 2024 || PP. 26-31

https://doi.org/10.55544/jrasb.3.5.5

replication errors. Many inflammatory mediators, including cytokines and interleukins, are released by ovarian cancer cells [20]. One example is the difference in prostaglandin levels between healthy cells and ovarian tumors. When prostaglandin levels are high, cancer cells proliferate more quickly. An important factor in the development and progression of ovarian cancer is the induction of substantial oxidative stress. Oxidative stress is higher and antioxidant amounts are lower in ovarian cancer patients compared to healthy women, according to studies. From what we can tell so far, ovarian cancer-affected epithelial tissues are in a pro-oxidant condition, with reduced levels of antioxidant enzymes and higher expression of pro-oxidant ones [21]. Tissues from ovarian cancer exhibit increased amounts of nitric oxide synthase (iNOS), myeloperoxidase (MPO), nitric oxide (NO), and NADPH oxidase, and lower levels of apoptosis. Also, caspase-3 activity was significantly reduced in ovarian tumors due to an increase in caspase-3 nitrosylation [22]. Nitric oxide (NO) can be enhanced from inducible nitric oxide synthase (iNOS) by the oxidation enzyme monophosphoethanolamine (MPO). There has been consistent evidence in recent datasets that ovarian cancer cells have elevated MPO levels. MPO controls cell death, immune response, inflammation, and 3-nitrotyrosine production. Furthermore, oxidative stress is increased due to the presence of free iron in MPO, which helps generate reactive oxygen species (ROS). When iron and hydrogen peroxide (H2O2) interact, oxidative stress increases the generation of reactive oxygen species (ROS). The development and progression of ovarian cancer may be influenced by oxidative stress [23].

IV. QUERCETIN ROLE IN OVARIAN CANCER

The two most deadly gynaecologic malignancies are ovarian and cervical cancers. Both of these cancers rank high among female-specific cancers. While pregnancy and nursing can reduce the incidence of some illnesses, other factors that increase the risk include age, nulliparity, early menstruation onset, late menopause start, and a family history of the condition [24]. To combat drug resistance and create new cancer chemotherapeutic treatments, Nessa and her colleagues performed a study to investigate the feasibility of combining drugs [25]. The researchers mixed two plant-based chemicals with recognized anticancer properties quercetin and thymoquinone with two platinum-based drugs cisplatin and oxaliplatin that are frequently used to treat ovarian cancer and other cancers. Two human epithelial ovarian cancer cell lines that were tested with this combination were A2780 and its cisplatin-resistant variant, A2780 [26]. The results show that a 2-hour delay between the two doses of the phytochemical and platinum medication is optimal. The opposite was true when the two drugs were administered as a bolus, leading to the least amount of synergy [27]. Adding the phytochemical two hours prior to platinum treatment was thought to increase cancer cells' sensitivity to platinum, which could provide a remedy to medicine resistance. Improving quercetin's solubility in water was one of the goals of the research team aiming to make the compound more effective in treating ovarian cancer. In order to do this, micelles made of biodegradable monomethoxy poly(ethylene glycol)-poly (ε-caprolactone) were used to encapsulate quercetin. In reaction to the quercetin nano-formulation, the A2780S ovarian cancer cells showed no signs of being able to divide [28]. The amount of the formulation needed to achieve this observed absence of proliferation. In addition, A2780S cells were brought to death by quercetin injection, which led to the activation of caspase-3 and caspase-9. It also altered the mitochondrial transmembrane potential, decreased MCL-1 and Bcl-2 levels, and increased Bax levels. According to these results, quercetin can cause A2780S cells to die via activating the mitochondrial apoptotic pathway [29]. The effect of trace levels of quercetin on the sensitivity to cisplatin and paclitaxel in the human ovarian cancer cell lines SKOV-3, EFO27, OVCAR-3, and A278OP was investigated in a study by Maciejczyk and Surowiak. These scientists discovered that ovarian cancer cells can be made more sensitive to cisplatin and paclitaxel by giving them small doses of quercetin. In human ovarian cancer cell lines A2780s and A2780cp, which are both sensitive to and resistant to cisplatin, the combination of liposomal and quercetin significantly slowed tumor progression compared to cell lines treated with free liposomes or quercetin alone [30]. In addition, it stimulated programmed cell death in both cell types studied, reduced the number of tiny blood vessels, and prevented tumor growth. Furthermore, quercetin may strengthen DR5 expression and make human ovarian cancer cells more vulnerable to TRAIL. When JNK was activated and CHOP expression was upregulated, DR5 was activated as well. The up-regulation of DR5 was also facilitated by ROS production. These results point to apoptosis and caspase-3, CHOP, and DR5 activation as mechanisms by which quercetin enhances the effectiveness of TRAIL-induced suppression of tumor development in human SKOV-3 xenograft cells [31][32]. At doses ranging from 40 to 100 μM, quercetin induced cell death in human ovarian cancer C13* and SKOV3 cells. In addition, it protected cells from reactive oxygen species (ROS) damage, increased synthesis of antioxidant enzymes that occur naturally in the body, and decreased cellular ROS levels [33]. Based on these results, reactive oxygen species (ROS) likely play a role in the reduction of antineoplastic medications. In addition, quercetin significantly diminished the therapeutic efficacy of cisplatin and the ROS-induced damage in xenograft cancer tissue [34]. The growth of SKOV-3 cells was successfully reduced and cell death was caused by quercetin in a dose- and time-dependent

ISSN: 2583-4053

Volume-3 Issue-5 || October 2024 || PP. 26-31

https://doi.org/10.55544/jrasb.3.5.5

manner. On top of that, it arrested the ovarian cancer SKOV-3 cells in the G0/G1 phase of the cell cycle and drastically decreased their number in the G2/M phase. Furthermore, ovarian cancer cells SKOV-3 and OVCAR-8 experienced cell death, caspase-3 activation, enhanced cisplatin sensitivity, and decreased EGFR expression and activation upon quercetin treatment [35][36]. Furthermore, via deactivating the MAPK-ERK pathway, quercetin halted cell cycle progression. This led to an increase in p21 expression and a decrease in cyclin D1, DNA-PK, and phospho-histone H3. In SKOV-3 and A2780 ovarian cancer cells, quercetin increased miR-145 expression and cleaved caspase-3 expression levels significantly [37]. Moreover, quercetin significantly amplified cisplatin's toxicity and triggered the endoplasmic reticulum's three-fold stress response when given to ovarian cancer patients before treatment. Additionally, it mitigated STAT3 phosphorylation and inhibited the BCL-2 gene, which is situated downstream of STAT3, and enhanced the anti-cancer activity of cisplatin in a mouse model with ovarian cancer grafts [38].

V. CONCLUSION

A number of molecular mechanisms contribute to the intricate progression of ovarian cancer, including inflammation, oxidative stress, and DNA damage. Researchers have found that quercetin can prevent ovarian cancer by reducing inflammation, enhancing antioxidant defenses, suppressing cell growth, causing cell cycle arrest, and promoting apoptosis. However, further research is needed to fully comprehend its efficacy in combating ovarian cancer. Quercetin is a promising option for the treatment of ovarian cancer because of its possible synergistic effects with other chemo-preventive medications.

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