



A REVIEW ON HERBAL TREATMENT FOR OVARIAN CANCER

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ABSTRACT

According to the Centers for Disease Control and Prevention, ovarian cancer is the top cause of mortality among women diagnosed with gynecological cancers, as well as the second most frequent gynecologic malignancy in the US. Ovarian cancer is the third most frequent type of gynecological cancer worldwide. There are two types of ovarian cancer: epithelial and non-epithelial. Epithelial ovarian cancer is the most common kind, accounting for more than 95%, while roughly 5% are non-epithelial ovarian cancers (e.g., germ cell, sex-cord stromal, and small cell ovarian cancers). Its history has been scientifically documented for over 150 years; during this time, the fatality rate has remained constant, but the incidence has increased—despite the fact that therapies are extremely costly and advanced. This review examines nanoscale drug delivery techniques for ovarian cancer treatment and detection. Nanocarrier systems such as dendrimers, nanoparticles, liposomes, nano capsules, and nanomicelles were reviewed. Herbal medicine has an important role in the prevention and treatment of ovarian cancer. Plants have been utilized to treat diseases from time immemorial. Cancer control planning is difficult and multifaceted. Awareness and understanding are critical for lowering the risk of ovarian cancer.

KEYWORDS: Ovarian cancer, Nanocarrier, Herbal medicine, Liposomes.

INTRODUCTION

Ovarian Cancer

Ovarian cancers comprise epithelial and non-epithelial ovarian malignancies. Epithelial ovarian cancer is the most prevalent type, accounting for more than 95%, while approximately 5% are non-epithelial ovarian cancers (e.g., germ cell, sex-cord stromal and small cell ovarian cancers).

(Lheureux *et al.*, 2019) Ovarian cancer is the leading cause of death in women diagnosed with gynecological cancers and the second most common gynecologic malignancy in the United States, according to the Centers for Disease Control and Prevention. Worldwide, ovarian malignancy ranks as the third most common gynecologic cancer. (Huang *et al.*, 2022) Ovarian cancer is also the fifth most frequent cause of death from any cancer in women in the United States and the eighth worldwide. (Phung *et al.*, 2023) The most significant risk factor for ovarian cancer is advanced age, occurring most frequently in women who are postmenopausal. Globally and each year, 240,000 women are diagnosed with ovarian cancer, and epithelial carcinomas account for about 90% of all cases. Due to its clinical presentation often and unfortunately in advanced stages, ovarian cancer is classified as a malignancy of the peritoneal surface. (Webb *et al.*, 2017).

History of Ovarian Cancer

Ovarian cancer is the sixth most common tumor in women. More than 200,000 new cases are diagnosed each year worldwide. Each year, it constitutes 4% of all cancers diagnosed in women, and there are 6.6 new cases per 100,000 women per year. Its history has been known scientifically for over 150 years; during this time, its mortality rate has not changed but its incidence has—the former despite treatments, which are highly expensive and sophisticated. (Ferlay *et al.*, 2013) In Europe, more than a third of women with ovarian cancer live for five years after diagnosis. Despite complete remission (CR) with first-line chemotherapy (CT), ovarian epithelial cancer recurs in over 50% of women. (Sant *et al.*, 2003) Russia and the United Kingdom have the highest rates of ovarian cancer, whereas China has the lowest rates. In the United States, approximately 22,280 new cases occur annually and the projected number of deaths for 2016 is 14,240. Interestingly, the annual incidence of ovarian cancer reduced by 1.09% for women <65 years of age and by 0.95% for women ≥65 years of age between 1998 and 2008. (Yang *et al.*, 2013).

Pathophysiology of Ovarian Cancer

Ovarian cancer is a growth of cells that form in the ovaries. The cells multiply quickly and can invade and destroy healthy body tissue. The female reproductive

system contains two ovaries, one each side of the uterus. The ovaries--each about the size of an almond – produce eggs (ova) as well as the hormones estrogen and progesterone. When ovarian cancer moves beyond your ovaries of fallopian tube, cancer cells may reach your liver, lungs, or other places in your body. The majorities of ovarian cancer are of epithelial origin, whereas fewer ovarian cancers develop from the remaining cell types, such as sex-cord stromal germ cell, or mixed cell type tumor. (Wicha *et al*, 2006).

Types and Characteristics Ovarian cancer

Ovarian cancer typically develops from three types of tissue: around 85 to 95 percent epithelial cells, 5 to 8

percent stromal cells, and 3 to 5 percent germ cells. The kind of ovarian tumor changes with age (Table 1.1). Epithelial cell cancers most commonly affect women over the age of 50. Stromal cell tumors can occur in women of any age, however some tumors, such as androblastomas, may be more common in adolescence. Germ cell cancers typically affect patients under the age of one year and those aged 15 to 19. (Young *et al*, 1994).

Table 1: Types and Characteristics (CRUM *et al.*, 2005).

| S. No | Cancer Type | %age Ovarian Cancer | Characteristics |
|-------|---|---------------------|---|
| 1. | Epithelial cell | 85 to 95 | Most common in patients older than 50 years; 15 percent of epithelial cell ovarian cancers are borderline or have low malignant potential, with a 10-year survival rate up to 99 percent for stage. |
| 2. | Serous | NA | 40 percent of all ovarian cancers; most common ovarian cancer. |
| 3. | Endometrioid | NA | 20 percent of all ovarian cancers; 15 percent of endometrioid carcinomas coexist with endometriosis; 40 percent bilateral. |
| 4. | Mucinous | NA | 25 percent of all ovarian cancers; origin unclear; may occur in association with endometriosis; associated with pseudomyxoma peritonei. |
| 5. | Stromal cell | 5 to 8 | Derived from the sex cord of embryonic gonads. |
| 6. | Granulosa-theca | NA | Wide age range; may produce precocious sexual development in prepubertal girls; may be associated with endometrial hyperplasia, cystic disease of the breast, and endometrial carcinoma in adults; ascites in 40 percent of fibromathecoma tumors; may be associated with ascites and hydrothorax. (Meigs syndrome) |
| 7. | Sertoli-Leydig (androblastomas) | NA | Common in adolescence; may be masculinizing; may block normal female sexual development. |
| 8. | Germ cell | 3 to 5 | Found mostly in children and young adults 20 to 30 years of age; highly malignant; usually unilateral. |
| 9. | Endodermal sinus tumor | NA | Most common germ cell ovarian cancer in children; usually larger than 15 cm; median age of patients is 18 years, one third of patients are premenarcha. |
| 10. | Embryonal (multipotential) | NA | Extraembryonic yolk sac carcinoma. Primitive: embryonal carcinoma (highly malignant), precocious puberty. Somatic: immature teratoma. Trophoblast choriocarcinomas. Undifferentiated: dysgerminomas (most common malignant germ cell ovarian cancer), 10 to 20 percent bilateral, radiosensitive. |
| 11. | Mature Metastasis to ovaries (Krukenberg tumor) | 5 | Typically from breast or gastrointestinal primary sites. |

Herbal treatment for ovarian cancer

1. Quercetin

Quercetin is one of the phytochemicals that is widely found in foods consumed daily (nuts, teas, vegetables).

Consumption of fruits contain quercetin such as apples and citrus fruit juices reduce the incidence of ovarian cancer. Several studies have investigated cytotoxic effects of quercetin on ovarian cancer cell both in-vitro

and in-vivo. Quercetin inhibits ovarian cancer cell growth by blocking cell cycle progression, programmed cell death, inhibiting vascular endothelial growth factor expression and it also suppress the phosphatidylinositol-3-kinase signaling pathway. Typical dietary intake 5-50mg/day. (Schulz *et al.*; 2005)

Anti- Cancer activity of Quercetin

Quercetin is a lipophilic substance that can cross cell membranes and activate various intracellular signaling pathways involved in chemoprevention. One of the remarkable properties of quercetin is its dual action as a pro-oxidant or antioxidant. Quercetin can lower ROS by giving electrons, which decreases ROS-mediated DNA damage. This is the major antioxidant mechanism of quercetin, as shown at cellular amounts received by food. In contrast, at greater concentrations, quercetin causes oxidative stress and cytotoxicity in tumor cells by increasing damage and triggering apoptotic pathways. Quercetin is also regarded as a powerful apoptosis inducer at high dosages. (Awad *et al.*, 2000) It has been proven that the mitochondrial-mediated route is the primary mechanism by which quercetin induces apoptosis. Quercetin causes apoptosis by activating p53, increasing pro-apoptotic molecules such as Bax, caspase-3, and caspase-9, and decreasing anti-apoptotic agents including survivin and Bcl-2. Several experimental studies indicated that greater doses of quercetin can cause apoptosis via death-domain pathways in several cancer cells. Quercetin's anti-cancer and pro-apoptotic actions are dependent on p53. (Tanigawa *et al.*, 2008) Quercetin suppresses the development of metastatic ovarian cancer cells via inducing mitochondrial-mediated apoptosis. Nano-formulated quercetin caused apoptosis by activating caspase-3, caspase-9, and Bax while decreasing MCL-1 and Bcl-2. (Gao *et al.*, 2012)

2. Curcumin

Curcumin is a natural hydrophobic polyphenols compound isolated from the rhizome of *Curcuma longa* (turmeric). This natural compound act as an anti-inflammatory, anti-aging, or a broad-spectrum anticancer drug. Curcumin has been reported to selectively kill cancer cell through various biological pathways without toxic side effect on normal cell. These biological pathways include the induction of apoptosis, cell cycles arrest, inhibition of tumor cell metastasis. Clinical trials have shown that curcumin does not have toxic effect at dose of 8g per day. (Saydmohammed *et al.*; 2010).

Anti-Cancer effect of Curcumin

Curcumin's anti-inflammation, anti-apoptosis, and antioxidant capabilities may help to treat ovarian cancer. Curcumin has been proven to reduce d-galactose-induced oxidative stress, apoptosis, and ovarian damage. Curcumin treatment resulted in increased SOD and decreased MDA levels, as well as reduced SOD2 and CAT mRNA expression levels. Furthermore, this study found that curcumin raises the expression levels of the

proteins NF-E2-related factor-2 (Nrf2) and HO-1, which are implicated in the ROS elimination mechanism. Nrf2 binds to antioxidant response elements (AREs) in the promoter region of Nrf2 target genes, which use HO-1 sequential enzymatic pathways to remove. (Gozzelino *et al.*, 2010).

3. Ginger

Ginger (*Zingiber officinale*) is a natural dietary component with antioxidant and anticarcinogenic properties. The ginger component gingerol has been shown to exert anti-inflammatory effects. It inhibits NF- κ B activation induced by a variety of agent, and has been shown to down regulate NF- κ B regulated gene product involved in cellular proliferation and angiogenesis. These factors have also been shown to promote tumor cell proliferation, angiogenesis, and affect apoptotic response in ovarian cancer. Ginger treatment resulted in a profound inhibition of cell proliferation and growth at doses of 50 μ g/ μ l and higher. (kim *et al.*; 2005)

Anti- Cancer activity of ginger

Apoptosis, or programmed cell death, originated as a quick and irreversible method for eliminating defective cells. Apoptosis is often carried out in two ways: the mitochondrial-mediated internal pathway and the death receptor-mediated extrinsic route. This mechanism involves cysteine-aspartate proteases (caspases) and Bcl-2 family proteins. Furthermore, it is widely recognized that in pathological circumstances like as cancer, alterations/mutations in the p53 gene are one of the primary reasons of apoptotic modifications. (Fridman *et al.*, 2003) Treatment of Ovarian Cancer Cell Line SKOV-3 with ginger extract for 48 hours caused a reduction in Bcl-2 gene expression and the subsequent p53-induced apoptosis. (Fridman *et al.*, 2003)

4. Amla

Amla (*Embllica officinalis*) is a fruited plant that has been recognized for its therapeutic significance. It has been used since ancient times in the Indian traditional school of medicine 'Ayurveda' for treating numerous ailments, including cancer. Amla extracts have anti-inflammatory properties and may prevent inflammation-related malignancies. The decreased proliferation of ovarian cancer cells was related to the activation of the autophagy system, independent of apoptosis. antiproliferative action at doses less than 500 micrograms per milliliter. (Baliga *et al.*, 2011)

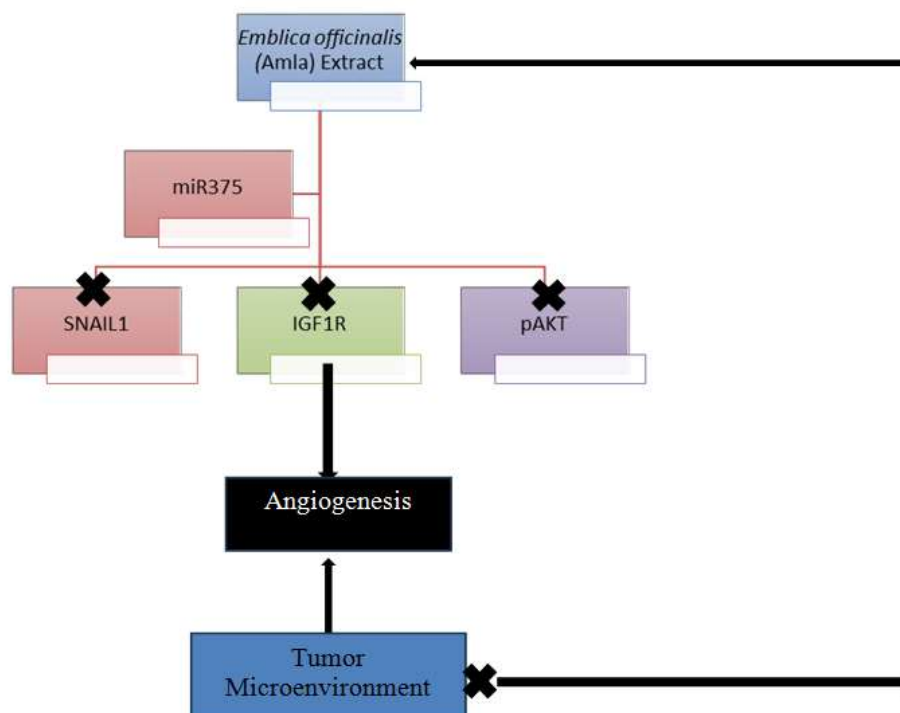
Anti- Cancer activity of Amla

Amla extract (AE) suppresses the proliferation of many cancer cells, including OC cells, in vitro and tumor formation in vivo. Recently, we found that AE inhibits cell proliferation, tumor development, and angiogenesis in OVCAR3 cells. The mechanism behind its anti-tumorigenic action is unknown. (Papasian *et al.*, 2013) The release of miR-375 in exosomes, as well as the downregulation of IGF1R and SNAIL1, and the overexpression of E-cadherin, indicate that AE may have

an effect on cancer cell-environment interactions. Angiogenesis is a continuous, parallel process necessary for tumor growth. We previously discovered that AE attenuates angiogenesis. A number of OC cell lines with well-defined anatomical origins are recognized. These include cells from high grade serous tumors (e.g., TOV2978G), high grade serous ascites (OV4453), adenocarcinomas (e.g., OVCAR3), serous adenocarcinomas (e.g., OVCAR4), low grade serous ascites (VOA1312_CL), and other particular cell lines

such as snu8 and UWB1.289 (BRCA1 null). Some of these lines are more aggressive, while others are less aggressive than SKOV3 cells. Confirmation of the cellular effects of AE using multiple cells lines will provide a basis for validating multiple targets of AE. Toward these goals, we propose that AE targets multiple sites that alter tumor microenvironment that inhibit angiogenesis leading to interference with tumor physiology and growth. (Saleem *et al.*, 2015).

Schematic depicting *E. officinalis*' potential method of action on angiogenesis in OC.



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