Medicinal Plants in the Treatment of Ovarian Cancer- An Insight

Dr. Vandna Kalsi¹, Simranjeet Kaur²*, Barinderjit Kaur³, Abhay Kumar⁴, Twinkle⁵

¹,²,⁴,⁵ Department of Pharmacognosy, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India

³Department of Pharmacology, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India

ABSTRACT

Background: Ovarian cancer is eleventh common type of fatal cancers of the reproductive system. It occurs in ovary after menopause and causes abnormal growth of cells. Globally, more than one million cases are treated or diagnosed every year. Among all the gynaecologic malignancies, epithelial ovarian cancer is the most popular in women. It is the most common cancer in women. Medicinal plants are very helpful to treat ovarian cancer. Some plants or plant components which are commonly used to treat ovarian cancer are amla, blueberries, ginger, ginseng, quercetin, paclitaxel, and curcumin.

Main body: This review has focused on ovarian cancer and medicinal plants which are used in the treatment of ovarian cancer. According to traditional system of medicines, chief chemical constituents and pharmacological actions of medicinal plants are very helpful in the treatment of ovarian cancer. These plants are reported to have activities like anticancer, antiinflammatory, antipyretic, and also reported to have nutritional value.

Conclusion: Although there are different therapies to treat ovarian cancer but now days, the use of medicinal products is being considered as a novel approach. According to traditional systems, various medicinal herbs are used to treat ovarian cancer. Some natural products or medicinal plants constituents which we use in our daily life include amla, ginger, curcumin, tea, blueberries, quercetin are very useful in treatment of ovarian cancer. These types of agents can be used for positive results like inhibiting cancer cells, apoptosis, proliferation and induction of apoptosis.
Keywords: Ovarian cancer, medicinal plants, apoptosis, *Emblica officinalis*, *Zingiber officinale*, quercetin

**Background**

Throughout the world, ovarian cancer is one of the many causes of death from gynecological malignant cancer or tumors [1]. Ovarian cancer is eleventh common type of fatal reproductive system disease [2]. In 2018, the ovarian cancer was at seventh position among other cancers in females [3]. Ovarian cancer occurs in ovary and causes abnormal growth of cells after menopause [4]. In US, in 2016, more than twenty thousand women were diagnosed with ovarian cancer and about fourteen thousand died due to ovarian cancer [5]. Study from the evidences give us information that mostly ovarian tumors are immunogenic that consist tumor infiltrating lymphocytes that specify the interaction between the host immune system and tumor cell [6]. Till now, the cause for the ovarian cancer is not properly known. The risk is the strongest if there is a positive family history of having breast or ovarian carcinoma [7]. It is the most common disease that is leading cause of gynecologic deaths in United States and European Union [8]. Survival rate for patients with ovarian cancer is approximately 40%, but gets reduced in the advanced stage of the disease [6]. It has also been observed that women having more chances of ovarian carcinoma are those who are undergoing infertility treatment. This is due to increase in the levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) [9]. Medicinal plants are those plants which are used to treat various types of diseases and have medicinal properties. For example, ginseng has anticarcinogenic effects. It includes antimetastasis and inhibition of angiogenesis, cell cytotoxicity and differentiation, has synergistic effect on chemical therapeutic agents, promotes antitumor activity related to inflammation and also leads to reduced MDR [10]. Other uses of ginseng are sedative and hypnotic, aphrodisiac, antidepressant, diuretic, immunomodulatory functions, nervous system-simulating effects, beneficial in the prevention of postprandial hypoglycemia [11].

Some medicinal plants are rich sources of ingredients which are used for synthesis of drug and drug developments. More than 80% populace uses Ayurveda, Unani, Siddha, and some other traditional medicines to treat various diseases [12]. A variety of synthetic drugs are prepared from medicinal plants like amla, *Emblica officinalis*, quercetin from red onions or other substances like nuts, apples., blueberries from *Vaccinium ssp* [13].
Introduction

Cancer is primarily a broader term and a second cause of death across the world. Cancer destroys the cellular function of the cells and cause genes dysfunction [14]; more than 1 million cases are treated or diagnosed every year [15, 16]. There are more than 277 different types of cancer [17]. It is the uncontrolled growth of cells in the body. This uncommon growth of cells is called as malignant cells or cancer cells. Ovarian cancer is one of the main causes of death from gynaecological malignant cancer or tumours [1]. Ovarian cancer is eleventh common type of fatal reproductive system disease [2]. In 2018, the ovarian cancer was on seventh position among other cancers in females [3]. Ovarian cancer occurs in ovary and cause abnormal growth of cells after menopause [4]. Cancer is of two types i.e. benign and malignant. When unrepaired cells are undying; it leads to uncontrolled growth and mass of cancer cells. Among all the gynaecological malignancies, epithelial ovarian cancer is the most popular one. It results in death of women [18]. In US, in 2016, more than twenty thousand women were diagnosed with ovarian cancer and about fourteen thousand died due to ovarian cancer [5]. Study from the evidences give us information that mostly ovarian tumours are immunogenic that consist tumour infiltrating lymphocytes that specify the interaction between the host immune system and tumour cell [6].

Stages of ovarian cancer

Four stages of ovarian cancer are:

1. Early ovarian cancer (FIGO Federation of Gynecology and Obstetrics Stages I to IIA)
2. Advanced ovarian cancer (IIB to IV)
3. Stage III
4. Stage IV (IV A and IV B)

A number of patients (50-85%) dealing with ovarian cancer have residual tumor and the size of tumor is less than 1 cm and it is operated by specialist of gynecology [19]. There are no specific symptoms of ovarian cancer but common symptoms include change in colon pattern, swelling of stomach etc. It is very difficult to diagnose in the early stages [20]. A study carried out in Germany has shown that an improvement in the five year relative survival might have
stopped in early 21st century for ovarian cancer [21]. Ovarian cancer can be detected in early stage when both the ovaries are having the tumor for which cure rate using conventional therapies (cytoreductive surgery and chemotherapy) is quite high approximately 90%. Then, the disease spreads into other pelvic organs like uterus and bladder (stage 2), the abdomen (stage 3), or beyond the peritoneal cavity (stage 4). Then the cure rate decreases. For a well and successful management it is required to understand the pathogenesis of the ovarian cancer and the mechanism how it undergoes metastasis. Mostly the cases of ovarian cancer (70%) are usually diagnosed at the later stage of the disease. Approximately 80% of females are diagnosed in advance stage of ovarian cancer only [22].

Based on the tissue study, ovarian carcinoma have been classified into three main categories (Figure 1).

![Figure 1: Types of ovarian carcinoma](image)

Ovarian carcinoma occurring in the epithelial cells is having the maximum frequency of occurrence, about 85% [9, 23].
Etiology

Till now, the causes for the ovarian cancer are not properly known. The strongest risk is in the patients who are having a positive family history of breast or ovarian carcinoma. Factors that result in the poor prognosis of the patients having ovarian carcinoma include:

- Localization within the peritoneal cavity
- Absence of early symptoms
- The disease is not eradicated properly with surgery
- Patients get resistant to the chemotherapy [9]

It is believed that ovarian cancer seems to have family phenotype mutation of the germ line in BRCA genes (BRCA1 and BRCA2) that finally lead to the generation of ovarian cancer in women having up to 70 years age. So BRCA genes mutation alteration can reduce the occurrence of ovarian cancer [9]. Figure 2 shows the etiology of this disease.
**Figure 2: Etiology of ovarian cancer**

**Signs and symptoms**

In initial stage, it does not show any sign or symptoms. But in advanced stages, may show few signs and symptoms like: abdominal or pelvic pain, difficulty in eating, bloating, frequent urination, anorexia, lower abdominal pain. Less common signs are changes in periods, fatigue, constipation, back pain, pain during intercourse [9]. Some of the females may have edema of varicose veins or legs, weakness or weight loss, abdominal distension, pelvic pain, bladder, liver, abdominal swelling [4,24].

**Risk factors**

Factors that cause high risk of ovarian cancer are family history, age, infertility and other like breast feeding [7]; use of oral contraceptives, tubal ligation which are used to have protective effects [25, 26]. All the factors are listed in figure 3.

---

**Figure 3: Risk factors**
Types of epithelial ovarian carcinoma

**Type I:** Low grade serous carcinoma, mucinous carcinoma, clear cell carcinoma, endometrioid

Adenocarcinoma

**Type II:** High grade carcinoma (Table 1)

Table 1- Types of epithelial ovarian carcinoma

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow growing indolent neoplasms</td>
<td>High grade clinically with more aggressive neoplasms</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>Typical hyperplasia</td>
</tr>
<tr>
<td>Stable genome</td>
<td>Genetically highly unstable</td>
</tr>
<tr>
<td>Do not show TP53 mutations</td>
<td>Exhibiting TP53 mutations and diagnosed at an</td>
</tr>
<tr>
<td></td>
<td>advanced stage.</td>
</tr>
</tbody>
</table>

**Diagnosis**

Diagnosis of the ovarian carcinoma at the initial state is not possible much as there are not enough symptoms in the patient [9]. Most of the patients having the ovarian cancer are diagnosed at later stage of the disease. The most effective and best parameter for checking the extent and location of the disease spreading is imaging. This is also used to get the proper management as per the International Federation of Gynecologists and Obstetricians (FIGO). For doing the imaging, some tools are used on daily base that include CT (computed tomography) scan, MRI (magnetic resonance imaging) and ultrasound. Some other parameters include physical examination and transvaginal ultrasonography. Exploratory laparotomy is used to get the cause of the ovarian cysts. In this screening, one can also use a combination of Symptom Index (SI) along with a serum HE4 test or CA125 test.
Treatment

Current treatment of ovarian cancer is surgery that is further followed by platinum based chemotherapy. Initially, response for the chemotherapy is very high, but it may also lead to recurrence of chemo resistant illness that could increase the contribution in the prognosis of ovarian cancer [6, 27] Some common treatments include radiation therapy, surgery, and chemotherapy, immune checkpoint inhibitors, antibody therapy, combinatorial immunotherapy, adoptive cell therapy, use of medicinal plants and their products and, vaccines [9]. Surgery is done basically when residual lesions size is greater than 1 cm. The main aim of surgery is to decrease the cancer cells [28].

Medicinal plants and products

Medicinal plants are those plants which are used to treat various types of diseases and have medicinal properties. Some medicinal plants are rich sources of ingredients which are used for synthesis of drug and drug developments. Throughout the world, more than 80% of populace uses Ayurveda, Unani, Siddha, and some other traditional systems of medicines to treat and cure various diseases [12].

Amla: It is fresh or dried fruit of Emblica officinalis belonging to family Euphorbiaceae [29]. It is also known as gooseberry plant and Amalki in traditional system of medicines, Ayurveda. It is one of the important plants, all parts of the plant are used like fruit, bark, roots and leaves but mostly fruits of plant are used to treat ovarian cancer. In Middle Eastern and Ayurvedic Pharmacopoeia, amla preparations are used for treatment of ovarian cancer. It is the rich source of vitamin C [30]. It is one of the richest sources of vitamin C [29].

The fruits of amla contain different types of components viz. ascorbic acid, gallic acid, chebulinic acid, ellagic acid, quercetin, 1-O-galloyl-beta-D-glucose. It is also rich in minerals like iron, phosphorus etc. The branches of amla plant contain different types of bioactive compounds like phyllanemblinins E and C, (2)-Epigallacatechin 3-o-gallate, geraniin, etc. Amla extract is very useful remedy to treat ovarian cancer as it helps to inhibit proliferation in ovarian cancer as well as other types of cancers. It has shown antitumour effects in in- vivo studies [31]. Mechanism of anticancer effect is not known but the extract of amla inhibits the substance that produces cancerous cells of ovarian cancer along with other cancers in case of tumor growth in
vivo as well as in vitro. miR375 is also called miRs it is basically a class of short, non coding ribonucleic acid RNAs.

The aqueous extract of amla basically prepared from its fruit, leaves, bark, and roots has been shown to have anticarcinogenic activity, and it is also used to reduce proliferation, growth of tumors and angiogenesis of ovarian carcinoma cell line OVCAR-3 cells. Other uses are antihypertensive, antiinflammatory, antioxidant, diuretic, laxative, jaundice, anemia [31].

The studies have indicated that a combination of insulin like growth factor- 1 receptor which is critically important for cell proliferation, growth and survival of the cells and a cytotoxic agent can be more effective in early stages of ovarian cancer [32]. There have been studies on the follicle stimulating hormone indicating that it can facilitate neovascularization of ovarian cancers. The exact mechanism is not known yet but it can increase vascular endothelial growth factor expression in cancer cells [33].

**Quercetin:** It is the phytochemical present in amla, geloy, teas, herbs, nuts and our daily food. It is also present in many types of vegetables and plants, and high amount of quercetin is present in red onions [34]. Quercetin is found in black grapes, apples, cabbage, red chillies, and red onions. It is used as commercial supplement [35]. Safe oral dose for quercetin per day is 1g which is able to inhibit many types of cancer like ovarian cancer, lung cancer, colorectal cancer, breast cancer, and pancreatic cancer [3, 36]. It is also used as antiinflammatory, and antioxidant agent [37]. The microenvironment in ovarian cancer consists of growth factors like vascular endothelial growth factor, platelets growth factor, immune cells, extracellular matrix, and some enzymes like matrix metalloproteinase [38].

For checking mechanism of action of quercetin on inhibition of ovarian cancer, several experiments have been performed. In these studies, it has been found that quercetin shows effect on apoptosis in mice dealing with ovarian cancer [39]. It was observed that quercetin causes apoptosis via caspase-dependent pathway and mitochondria intrinsic pathway. It also helps to stop endoplasmic reticulum stress and helps to induce authophagy that plays role in protect the ovarian cells. In case of metastatic ovarian cancer cells, quercetin helps to decrease viability and apoptosis [40].
In case of ovarian cancer, there are many proapoptotic and antiapoptotic molecules. Antiapoptotic molecules are Bcl-1 and Bcl-2 and quercetin helps to decrease these molecules [40]. Nano-formulations of quercetin were also prepared and examined in mice model. The study has shown that it can inhibit or stop the growth of ovarian cancer cells in vitro in ovarian cancer mice [41]. It has antitumor and antiinflammatory activities. It is used to reduce blood pressure. It is also used to induce apoptosis and inhibition of proliferation, inhibition of progression of cell cycle. It is also utilized as antioxidant agent and has other pharmacological actions also [40, 41].

**Ginger extract:** It is obtained from the rhizomes of *Zingiber officinale* Roscoe belonging to family Zingiberaceae [29]. *Zingiber officinale* is functional food in terms of nutritional and phytochemical parameters. It contains carbohydrates, fats, protein, dietary fiber, calcium, vitamin C, carotene and iron. It has presence of polyphenols, anthocyanidins, flavonoids and some organic acids mainly citric, malic, oxalic, tartaric and succinic acid. It has terpenes such as zingiberene, beta-besabolene and alpha curcumene. It has aromatic fragrance due to presence of zingiberene. Ginger has characteristic odor and pungent taste due to presence of bioactive compounds gingerols and shogaols [42]. Carcinogenic processes can be interfered in many cell types by some ginger components such as gingerol and paradol. Mechanism of action includes the inhibition of EGF-induced cell transformation and AP- activation. It also causes induction of apoptosis thereby acting as antineoplastic agent [43].

Biological profile of ginger include antioxidant, antiinflammatory, hypoglycaemic, antilipidemic, cardiovascular, immunosuppressive, hepatoprotective, gastrointestinal, and antimicrobial activities. It has been shown to have antiproliferative potential (anticancer), as well as cytoprotective properties (antiaging and chemopreventive) [42].

**Green tea:** Green tea is prepared from the leaves of the plant (*Camellia sinensis*) cultivated in East Asia. This plant grows as big as shrub or tree. The most important phytochemical constituent in green tea is polyphenols which are claimed to have the best antioxidant properties. These polyphenols are also responsible for bitter taste of the plant. Some polyphenols present in the plant are epicatechin, catechin, gallate, and epigallocatechin gallate (EGCG). EGCG is the most active component. Green tea also does have some alkaloids like caffeine, theobromine and theophylline. Leaves also contain other compounds such as purines, minerals, volatile oils, vitamins and polysaccharides [44]. Regarding the mechanism of action of polyphenols, many
theories have been given from time to time. One such theory is related to preventive activity of EGCG. It has anticarcinogenic effect due to activation of antipromotion processes such as it inhibits the tumor growth, invasion, and metastasis and cell transformation. EGCG has sealing effect that includes inhibition of interaction of tumor enhancers, growth factors or other hormones with their respective receptors [45]. Green tea can be utilized in many health problems such as atherosclerosis, high cholesterol, cancer, inflammatory bowel disease (IBD), diabetes, liver disease, weight loss [44].

**Turmeric:** It consists of dried or fresh rhizomes of *Curcuma longa* belonging to the family Zingiberaceae [29]. The main component in turmeric is curcumin (60%). It also contains components like starch grains, volatile oil, curcuminoids, and resins. De-methoxy and Bis-de-methoxy curcumin is also present. In India, turmeric has been used as traditional medicine since much longer period of time [46]. Ca\(^{2+}\) homeostasis is necessary for cell survival, and SERCA (sarco/ endoplasmic reticulum Ca\(^{2+}\)) regulates cellular Ca\(^{2+}\) flux from the cytosol to the endoplasmic reticulum for storage (20). It has been reported that curcumin inhibited SERCA activity and then disrupted Ca\(^{2+}\) homeostasis in ovarian cancer cells. Subsequently, a high concentration of Ca\(^{2+}\) in the cytoplasm promoted cell apoptosis [34]. Curcumin induces apoptotic cell death [47]. It is used to treat various types of cancer like ovarian cancer, and, colon cancer, etc. It is used as traditional medicine and as coloring agent and spice in food, and cuisines. It is a potent antiinflammatory and antioxidant agent. It is used in dietary supplements, allergy, arthritis, and, liver diseases.

**Resveratrol:** It is a natural polyphenolic compound which is obtained from plants like peanut, japonica, and red grapes [34]. It is also called as 3, 5, 4-Trihydroxystilbene [48]. It is a phytoalexin which is basically derived from grapes and other food products with antioxidant and chemopreventive activities. The compounds of resveratrol have been classified into four types that are flavonoids, lignans, isoflavaoids, and flavonoids. It is basically stilbenol resveratrol having two phenolic rings that link to each with ethylene bridge. In the chemical structure of resveratrol, two isomeric forms are present that are cis and Trans. [49, 50]. Resveratrol inhibits cell growth and glycolytic response and it also decreases glucose uptake [51]. Resveratrol helps to decrease cell growth and metabolism, it also decreases vascular endothelial growth factor (VEGF) secretion and cell growth. It has antimetastatic activity according to previous studies.
The high expression of vascular endothelial growth factor leads to metastasis of ovarian cancer [52]. It has antitumor effect. It inhibits proliferation of cells and stops the cell cycle in human cell cancer lines like pancreas, liver, colon, lungs etc. [53]. It is mostly used to treat heart disease and also in case of high level of cholesterol [54]. It is also used to decrease pain and swelling and in rheumatoid arthritis. It is used as nutritional supplement, and to treat diabetes type II. It is used as an antiinflammatory agent.

CONCLUSION

Cancer is second cause of death across the world. In 2016, more than 20,000 females were diagnosed with ovarian cancer in USA and every year death toll goes almost 14,000 in females. Although there are different drug therapies to treat ovarian cancer but now a day’s the use of medicinal products has been considered as a novel approach. According to traditional system of medicines, various medicinal herbs can be used to treat ovarian cancer. Some natural products or medicinal plants constituents which we use in our daily life include amla, ginger, curcumin, tea, blueberries, quercetin etc., which can be very useful in the treatment of ovarian cancer. These types of agents can be used for inhibiting cancer cells, proliferation and induction of apoptosis. At last medicinal plants are very useful to treat ovarian cancer.

ABBREVIATIONS


REFERENCES


