

## Phytochemicals in the treatment of ovarian cancer

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### 1. ABSTRACT

Ovarian cancer ranks 5<sup>th</sup> among the most common gynecologic cancers and causes the highest mortality in females. Here, we discuss the role of a group of natural products that are being used in treatment and prevention of a host of cancers including ovarian cancer. Some plants and nutraceuticals and their polyphenolic constituents such as flavones, flavonoids, and antioxidants have shown cytotoxic effects on cancer cells both *in vitro* and *in vivo*. While phytochemicals do not harm normal cells, they have been found to be cytotoxic to cancer cells by virtue of inhibition of proliferation and/or induction of apoptosis, making them ideal in cancer therapeutics or as adjunct to conventional treatment regimens.

### 2. INTRODUCTION

Ovarian cancer is the most common and 5<sup>th</sup> most lethal malignant neoplasm of female reproductive tract (1). Such a high rate of death is due to late detection with diagnosed cases being in the late stage of the disease due to lack of symptoms and detectable biomarkers (2). According to World Health Organization, ovarian cancer is characterized as a heterogeneous group of diseases

which includes serous, mucinous, clear cell, squamous and endometrioid carcinoma (3, 4). The distinct molecular and genetic profiles of these cancer types and their varied response to treatment makes it difficult to design a common therapeutic regimen (3). The tumor microenvironment of ovarian carcinoma is comprised of fibroblasts, immune cells, and endothelial cells of the host as well as non-cellular components including the extracellular matrix (ECM), ECM remodeling enzymes [e.g., matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases (TIMPs), and lysyl oxidases (LOXs)], and growth factors (e.g., VEGF, TGF- $\beta$ , and PDGF). This microenvironment is permissive to tumor cell growth, migration, and invasion. Despite the advances in therapies available for initial staged ovarian carcinoma patients, So far, treatment of ovarian cancers that are diagnosed in the early stage of the disease only modestly increased survival rate (5). The survival is even lower in carcinomas that are diagnosed at late stage of disease with cytoreductive surgery and combination therapy being the only available treatment (6). A wide spectrum of cytokines, growth factors, adhesion molecules, proteases, hormones, coagulation factors, acute phase

**Table 1.** Popular Botanical dietary supplements, their potential active components and functions (28)

Dietary Supplements	Latin Name	Potential Active Components	Major Potential Health Benefit
Astragalus	<i>Astragalus membranaceus</i>	Polysaccharides, saponins (astragalosides)	Immunomodulatory, hepatoprotective
Black cohosh	<i>Cimicifuga racemosa</i>	Fukinolic acid	Relief of menopausal symptoms
Cranberry	<i>Vaccinium macrocarpon</i>	Proanthocyanidins	Prevention and treatment of urinary tract infections
Dang Gui	<i>Angelica sinensis</i>	Ligustilide	Treatment of gynecological conditions
Echinacea	<i>Echinacea purpurea</i> , <i>E. pallida</i> , <i>E. angustifolia</i>	Polysaccharides and glycoproteins, cichoric acid, Alkamides	Treatment of common cold, cough, and upper respiratory infections
Feverfew	<i>Tanacetum parthenium</i>	Parthenolide and other sesquiterpene lactones	Alleviation of fever, headache, and women's ailments
Garlic	<i>Allium sativum</i>	Allyl sulfur compounds	Antibacterial, anticarcinogenic, antithrombotic, hypolipidemic
Ginger	<i>Zingiber officinale</i> Roscoe	Gingerols	Antiemetic, anti-inflammatory, digestive aid
Ginkgo biloba	<i>Ginkgo biloba</i>	Ginkgolids, flavonoids	Treatment of cerebral dysfunction and circulatory disorders
American ginseng	<i>Panax quinquefolium</i>	Ginsenosides	Therapeutic effects on immune function, cardiovascular diseases, cancer, sexual function
Asian ginseng	<i>Panax ginseng</i>	Ginsenosides	Combat psychophysical tiredness and asthenia
Goldenseal	<i>Hydrastis canadensis</i>	Alkaloid berberine and $\beta$ -hydrastine	Soothing irritated skin and mucous membranes, easing dyspepsia
Grape seed extract	<i>Vitis vinifera</i>	Proanthocyanidins	Antioxidant, anti-inflammatory, immunostimulatory, antiviral, and Anticancer
Green tea polyphenols	<i>Camellia sinensis</i>	Epigallocatechin gallate and catechins	Preventive effects on heart diseases, cancer, neurodegenerative disorders, and diabetes
Kava	<i>Piper methysticum</i>	Kava lactones	Effects on relaxing and mood calming
Licorice	<i>Glycyrrhiza glabra</i>	Triterpene saponins, flavonoids and other phenolics	Possess soothing, anti-inflammatory, and antitussive properties
Maca	<i>Lepidium meyenii</i>	Aromatic isothiocyanates	Use for aphrodisiac purpose
Milk thistle	<i>Silybum marianum</i>	Silymarin	Treatment of liver disorders
Pycnogenol	<i>Pinus pinaster</i> ssp. <i>Atlantica</i>	Procyanidins	Use for protection of circulation, and to restore capillary healing
Red clover	<i>Trifolium pratense</i>	Isoflavones	Treatment for menopausal symptoms
Reishi mushroom	<i>Ganoderma lucidum</i>	Triterpenoids, polysaccharides	Antitumor and immunomodulating effects
Saw Palmetto	<i>Serenoa repens</i>	Unknown	Use for prostate health
Soy isoflavones	<i>Glycine max</i>	Genistein, daidzein	Prevention of menopausal symptoms, osteoporosis, coronary heart disease, and cancer
St John's wort	<i>Hypericum perforatum</i>	Hyperforin, hypericin	Treatment of mild depression
Valerian	<i>Valeriana officinalis</i> L.	Valepotriates (iridoids)	Use for mild sedative and sleep disturbance
Yohimbe	<i>Pausinystalia johimbe</i>	Yohimbine	Use for aphrodisiac purpose

reactants, apoptotic factors have been investigated in search of effective cancer treatment.

The history of therapeutic use of plants can be traced back to the Sumerian and Akkadian civilizations.

Extensive *in vitro* and *in vivo* studies have shown that phytochemicals with bioactive properties including nutraceuticals and their polyphenolic constituents such as flavones, flavonoids, antioxidants etc provide considerable protection against many cancer types (Table 1). A number

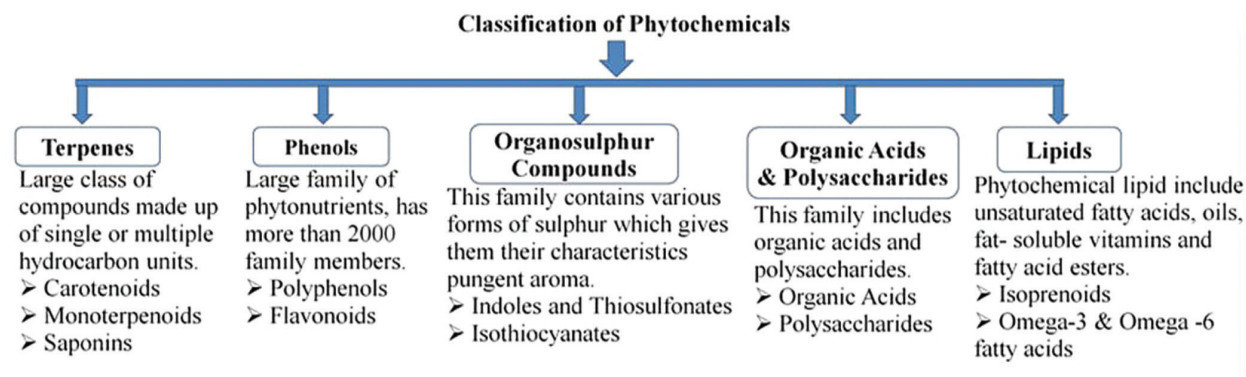


Figure 1. Classification of phytochemicals.

of studies have also revealed also have shown a great potential of phytochemicals in enhancing the effects of conventional therapy or used alone for treating several types of cancer (7). Some phytochemicals influence multiple targets through a common oncogenic signaling pathway (8).

### 3. CLASSIFICATION OF PHYTOCHEMICALS

Many phytochemicals derived from fruits and vegetables have shown health promoting properties. These phytochemicals can be classified as terpenes, carotenoids, monoterpenes including perillyl alcohol and limonene, Saponins, phenols (polyphenols and flavonoids), organo-sulphur compounds (indoles, isothiocyanates and thiosulfonates), organic acid and polysaccharides (organic acids, polysaccharides), lipids (isoprenoids and omega-3 and omega-6 fatty acid).

#### 3.1. Terpenes

Terpenes, the most widespread class of phytochemicals, contain flammable unsaturated hydrocarbons and exist mainly in a liquid form (9). They have general formula  $(C_5H_8)_n$  and depending upon the carbon number they are classified as mono-, di-, tri- and sesquiterpenoids. The 3 major classes of terpenes are shown in Figure 1.

##### 3.1.1. Carotenoids

Carotenoids are natural fat soluble pigments which provide bright coloration to plants. A 40-carbon polyene chain, which is derived from isoprene, forms the backbone of carotenoids. The polyene backbone consists of conjugated double bonds which allow the carotenoids to take up excess energy from other molecules through a non radiative energy transfer mechanism (10). These characteristics make carotenoids an efficient antioxidant compound. Carotenoids scavenge reactive oxygen and free radicals and their antioxidative properties enhance immune function, protect from sunburn and inhibit the development of certain types of cancers (11).

Source: Apricots, carrot, pumpkins and sweet potato are sources of  $\beta$ -carotene. Tomatoes and watermelon are sources of lycopene. Mango, papaya, peaches, prunes, oranges are the sources of lutein and zeaxanthin (12).

Mechanism of action: Mechanism of action of carotenoids remains uncertain but possibilities include antioxidative property, modulation of lipoxygenase activity, activation of certain gene responsible cell to cell communication and provitamin A activity (12).

##### 3.1.2. Monoterpenes

Monoterpenes include perillyl alcohol and limonene (13).

###### 3.1.2.1. Perillyl alcohol

Source: Essential oils of lavender, peppermint, spearmint cherries, celery seeds and several other plants (14).

Mechanism of action: Perillyl alcohol is active in inducing apoptosis in tumour cells without affecting normal cells and can cause the tumor cells to differentiate. Perillyl alcohol increases mannose-6-phosphate, induces phase 1 and phase 2 detoxification system and decreases ubiquinone synthesis (14).

###### 3.1.2.2. Limonene

Limonene is a colorless liquid hydrocarbon classified as cyclic terpenes. Limonene possesses a strong smell of orange (15).

Source: Mandarins, oranges (15).

Mechanism of action: Limonene induces apoptosis and has anti-proliferative activity (15).

##### 3.1.3. Saponins

Saponins are derived from *Saponaria Vaccaria* (*Quillaja saponaria*). Saponins are comprised of a Sugar (glycone) backbone plus sapogenin (aglycone). Saponins

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have a high molecular weight as they possess sugar molecule combined with triterpene or steroid aglycone. Saponins are usually soluble in water and insoluble in ether and are hydrolyzed to aglycone also known as sapogenin. Saponin glycosides are divided into two types based on the chemical structure of their aglycones (sapogenins) (16).

Source: Legumes, soybeans (16).

Mechanism of action: Saponins lower cholesterol, and have anti-cancer and immune stimulatory properties. Anti-cancer properties of saponins appear to be the result of antioxidative effect, immune modulation and regulation of cell proliferation (16).

### 3.2. Phenols

Phenols are one of the largest families of phytonutrients with over 2000 members. They are responsible for the colour of fruits and plants and are mostly synthesized from phenylalanine by the action of phenylalanine ammonia lyase (PAL) (17). The simplest compounds have single phenolic units which is abundant in culinary herbs. Phenols are antioxidants with antimicrobial including antifungals property. They are broadly classified as shown in Figure 1 to polyphenols and flavonoids.

#### 3.2.1. Polyphenols

In fruits, vegetables and spices the existence of polyphenolic compounds are well marked. High dietary intake of polyphenols is associated with decreased cardiovascular disease, specific forms of cancer and neurodegenerative diseases (18).

Source: Tea, Red wine, Cocoa, fruit juices and olive oil (18).

Mechanism of action: Polyphenols involve two main mechanism of action:

- a) Mechanism-I (modulation of enzymatic activity) (19).
- b) Mechanism-II (modulation of cancer cell signaling) (19).

#### 3.2.2. Flavonoids

Flavonoids are synthesized in almost all plant tissues and there are at least 2000 naturally occurring flavonoids. They are grouped into seven classes: flavones, flavanones, flavonols, flavanonols, isoflavones, flavanols (catechins) and anthocyanidins (20).

Source: Edible fruits, leafy vegetables, roots, tubers, bulbs, herbs, spices, legumes, tea, coffee, and red wine (20).

Mechanism of action: Flavonoids have multiple effects on cells including (a) antioxidative property, (b) ability to scavenge active oxygen species and electrophiles, (c) inhibition of nitrosation, (d) ability to

chelate metals (such as Fe and Cu), (e) producing hydrogen peroxide in presence of certain metals and (f) the ability to modulate certain cellular enzyme activities (20).

### 3.3. Organosulphur compounds

Phytonutrients of this family possess various forms of sulfur, which give them their characteristic pungent aroma. The sulfur compounds in the following two groups (Figure 1) are slightly different and consequently each has specific health benefits (21).

#### 3.3.1. Indoles and Isothiocyanates

Indoles and Isothiocyanates are formed during the mastication of some cruciferous vegetables (22).

Source: Indoles and Isothiocyanates are released from mustard greens and seeds, horse-raddish, cabbage (a rich source of indole -3- carbinol), broccoli, and cauliflower (22).

Mechanism of action: Indole-3-carbinol is a bioactive compound and induces and activates cytochrome P450 (Phase I enzyme) and glutathione S-transferase (Phase II enzyme) and this accounts for the cancer-preventive properties exhibited by this class of compounds (21). These compounds bind to chemical carcinogens and also activate liver detoxification enzymes that generate products with anti cancer properties (21).

#### 3.3.2. Thiosulfonates

This group of phytonutrients generally contains sulphur (23).

Source: Garlic and onion (23).

Mechanism of action: Crushing the plants containing thiosulfonates leads to the release of sulfur compounds such as allicin, allyl sulfides, allyl mercaptocystein with strong antioxidative properties. Specific allyl sulfides block the activity of toxins produced by bacteria and viruses (23) Garlic has anti-microbial properties and inhibits a large number of bacteria such as *Helicobacter pylori*. Garlic has also been shown to increase immunity and to prevent the stomach cancer (23).

### 3.4. Organic acid and polysaccharides

Many of the phytonutrients are rich in organic acids and polysaccharides (Figure 1).

#### 3.4.1. Organic acids

Source: Oxalic acid (Tea, coffee, spinach), cinnamic acid (Aloe vera), ferulic (Oats, rice), gallic (tea), ellagic (guava), salicylic acid (peppermint) (24).

Mechanism of action: Organic acids have antioxidant, cancer preventive, liver protective effect and act as inflammatory mediators (24).

### 3.4.2. Polysaccharides

Source: Mushrooms (25).

Mechanism of action: Polysaccharides have anti-cancer effects and boost the immune system (25).

### 3.5. Lipids

Phytochemical lipid includes unsaturated fatty acids, oils, fat-soluble vitamins, and fatty acid esters. The group includes isoprenoids that includes multiple 5-carbon isoprene units and a long unsaturated side chain, omega-3 and omega -6- fatty acids (Figure 1).

#### 3.5.1. Isoprenoids

Isoprenoids consists of multiple 5-carbon isoprene units (26).

Source: Grains and palm oils (26).

Mechanism of action: Isoprenoids protect the phospholipid bi-layers in cell membranes from free radical damage. It also facilitates receptor function thus boosting the antioxidative power of individual cycle participants (26).

#### 3.5.2. Omega-3 and omega-6 fatty acid

Source: Dark green leafy vegetables, grains, legumes, nuts and seeds. ALA-Seed oil such as primrose, borage. EPA and DHA found in fish, especially salmon, herring, tuna and white fish (27).

Mechanism of action: Omega-3 and omega-6 fatty acid reduce inflammation, platelet aggregation and immune response. These activities protect against cardiovascular diseases, cancer and many other forms of chronic diseases. DHA reduces depression, attention deficits and anxiety and prevents breast, prostate and colon cancer (27).

## 4. MODE OF ACTION OF PHYTOCHEMICALS AGAINST OVARIAN CANCER

Ovarian carcinoma is the 5<sup>th</sup> most common and lethal gynecological cancer which causes deaths of approximately 60% of women who suffer from the disease. The mortality rate of this cancer has not changed significantly over the last three decades. Ovarian cancer cells have the tendency to develop resistance to conventional cancer treatments. Tumor growth is influenced and is enhanced by a microenvironment contributed by the host including endothelial cells, fibroblasts, and infiltrating inflammatory cells. These cells are recruited to the tumor microenvironment by cytokines and growth factors that are released by cancer cells (29). The type-1 and type-2 Epithelial Ovarian Cancer (EOC) cells release different cytokines including tumor necrosis factor-  $\alpha$  (TNF- $\alpha$ ) and IL-6 (29-36).

Phytochemicals including apigenin, baicalein, curcumin, genistein, luteolin, oridonin, quercetin, and wogonin have shown to deactivate NF- $\kappa$ B, a master switch in the inflammatory process within the tumor microenvironment either by preventing NF- $\kappa$ B nuclear transportation or by suppressing NF- $\kappa$ B protein activity (37-42).

One of the major challenges in the treatment of advanced EOC has been the development of resistance to treatment. Cancer cells can acquire drug-resistance by several mechanisms including mutation or deletion of the transcription factor *TP53* which normally activates DNA repair and initiate apoptosis and loss of TRAIL-induced apoptosis (43). NF- $\kappa$ B and p53, have an antagonistic relationship in cancer (43-46). It has been shown that the tumor suppressor activity of p53 is reduced by the activation of NF- $\kappa$ B, thereby leading to conditions conducive to a dominant ontogeny mediated transformation. Many *in vitro* studies show upregulation of wild-type p53 protein in ovarian cancer by baicalein, curcumin, genistein, luteolin, quercetin, oridonin, resveratrol, and wogonin (47-50). TRAIL-resistant cancer cells were found to undergo apoptosis by baicalein, curcumin, luteolin, procyanidins, quercetin, resveratrol, sulphoraphane and wogonin (51-56). In human EOC cells, hispidulin potentiated the TRAIL-induced apoptosis (57).

Type 2 aggressive EOC cells exhibit activated expression of VEGF and a high rate of vasculogenesis (58, 59). Phytochemicals have shown promising effect by virtue of their effects on VEGF (60-62). 5 flavonoids including apigenin, luteolin, quercetin, genistein, and kaempferol have reduced in a dose dependent manner the cell growth and VEGF production in ovarian cancer cell line OVCAR-3 (63). Several studies have shown that wogonin and kaempferol inhibit VEGF protein expression in various cancer cells (64-66).

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