Phytochemicals in Cancer with Special Emphasis on Ovarian Cancer

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Abstract

Ovarian cancer is one of the most prevalent malignancies and is the deadliest among all gynecologic cancers. Although tremendous progress has been made on cancer biology and tumour treatment, knowledge on the mechanisms of cancer development including that for ovarian cancer remains incomplete. Thus, in addition to cancer prevention it is urgent to develop effective therapeutic modalities even for the advanced stage and drug-resistant forms of the disease with ovarian cancer being no exception. Multistep tumourigenesis is activated by various environmental carcinogens, inflammatory agents and tumour promoters. Carcinogens modulate the transcription factors, anti-apoptotic and pro-apoptotic proteins, protein kinases, cell cycle proteins, cell adhesion molecules and growth factor signaling pathways and thus produce malignancies. Phytochemicals exert their antitumour effects by numerous signaling pathways which in turn affect multiple steps in the various cellular pathways leading to tumourigenesis. Antitumour active phytochemicals have cytotoxic action in all ovarian cancer cell lines with comparable or greater activity in the resistant cell lines than in the parent cell line. As phytochemicals have been a part of human diet without toxic effects, they are likely to protect normal cells and tissues caused by the direct and bystander effects of platinum drugs. Therefore, it is quite logical to assume that phytochemicals possessing both cancer preventive and therapeutic attributes, can be ideal candidates in cancer prevention and synergistic outcomes from their combination with targeted therapy.

Key Words: Ovarian cancer, Phytochemicals, Cell signaling pathways, Chemoprevention, Targeted therapy

Significance | Reviews current literature on use of phytochemicals in prevention and therapy of ovarian cancer including mechanism of action.

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Introduction

Cancer is one of the most dreaded diseases of our time that invokes death sentence in many minds. Ovarian cancer is one of the most prevalent malignancies and is the fifth leading cause of cancer-related death among women, being the deadliest of all gynecologic cancers (Anon, 2019). The treatment of ovarian cancer remains a major challenge. Despite much research effort, improvement in surgical techniques, and development of an ever expanding number of chemotherapeutic agents, it is still the most lethal gynaecological tumour and the cause of considerable morbidity for the suffers (Marsden *et al.*, 2000). Like other cancer, various treatments available for ovarian cancer often face two main problems namely development of resistance associated with prolonged use and presence of severe side effects. Although tremendous progress has been made on cancer biology and tumour treatment, knowledge on the mechanisms of cancer development remains incomplete. This is the reason why the means of treatment against cancer are far from being ideal and are often met with failure. Thus, in addition to cancer prevention there is

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an urgent need for the development of effective therapeutic modalities even for advanced stage and the drug-resistant forms. Recently, there has been a growing interest in the use of dietary chemopreventive agents (such as phytochemicals) which can prevent cancer initiation, suppress proliferation and induce apoptosis in tumour cells. In this review the mechanism of cancer development and actions of antitumour active phytochemicals will be discussed briefly.

Materials and Methods

For this review relevant literatures were collected from the major scientific databases including Pubmed, Science direct, Medline and Google scholar to find out mechanisms and development of cancer, molecular mechanisms of anti tumour activities of phytochemicals. Some articles were cited through cross citations from other publications or by directly accessing the journals' web-site. More emphasis was given to the literatures published in recent years. The keyword combinations for the search included: causes, mechanisms and development of ovarian cancer as well as other cancers, tumour active phytochemicals and their mechanisms of actions, drug resistance and phytochemicals. Additional information was assimilated by using some other keywords such as cancer development and cell cycle control, cell proliferation, apoptosis, oxidative stress, cancer stem cell. A total of 182 research articles reporting on the development of cancer, drug resistance, use of phytochemicals in prevention and treatment of cancer are recovered and presented in this review. Cytotoxic action of phytochemicals on various ovarian cancer cells are collected from the laboratory results of the Cancer Research Team, Discipline of Biomedical Science, The university of Sydney, Australia.

Ovarian Cancer: A short overview

Among ovarian cancer, the most common (90% of cases) is epithelial type which arises from the cells on the outside of the ovary; about 4% of cases are the germ cell type that arises from the cells which produce eggs; and the rests are stromal type arising from supporting tissues within the ovary (Council, 2020). The World Health Organization has categorized epithelial ovarian carcinoma according to the predominant epithelial cell type, which are serous carcinoma, endometrioid carcinoma, mucinous carcinoma and clear-cell carcinoma of the ovary. Number of genetic and epigenetic changes lead to ovarian carcinoma cell transformation (Lengyel, 2010). Various studies confirmed that genes expressed in different ovarian carcinomas are concordantly expressed in the normal tissues they resemble histologically (Marquez *et al.*, 2005). It is also evident that ovarian tumorigenesis can progress either along a stepwise mutation process from a slow growing borderline tumor to a well-differentiated carcinoma known as type I or encompasses as a genetically unstable high-grade serous carcinoma that metastasizes rapidly known as type II (Lengyel, 2010).

Mechanisms of Cancer Development:

Causes of Cancer: Cancer development is believed to be a multiple step process including initiation, promotion and progression (Surh, 2003). Very recent and convincing hypothesis is that inflammation contributes to every step of carcinogenesis, including tumour initiation, promotion and progression (Grivennikov *et al.*, 2010). Components of the inflammatory pathway, including free radicals, cytokines, NF-κB, STAT-3, iNOS, COX-2, prostaglandins and VEGF have been shown to contribute to the development of various malignancies including ovarian cancer (Seo *et al.*, 2004). Aberrant expression of microRNAs (miRNAs/miRs) are involved in the development and progression of ovarian cancer supported by the observation that downregulation of miR-183 markedly inhibited cell proliferation, migration and invasion, and promoted apoptosis in ovarian cancer cells (Zhou *et al.*, 2019).

One strong risk factor found in epidemiologic studies is a positive family history (Amos and Struewing, 1993, Schuijer *et al.*, 2003). This might be the results of homeostatic imbalances that can happen due to factors such as genetic mutation and if not corrected by genes such as tumour suppressor genes, will lead to the development of cancerous cells. For example, a woman who carries the mutated tumour suppressor genes BRCA1 and BRCA2 is at a higher risk of developing ovarian and breast cancers especially having the history of either breast or ovarian cancer (Ford *et al.*, 1998, Narod, 2002).

Endometriosis is another risk factor for ovarian cancer. Some epidemiological studies and some historical pathological observations show that both clear cell ovarian and endometrioid ovarian carcinomas may arise from endometriosis. Other neoplasms such as seromucinous borderline, low-grade serous ovarian carcinomas, adenosarcomas and endometrial stromal sarcomas may also arise from endometriosis (Dawson *et al.*, 2018).

Ageing is also a major risk factor for the development of cancer. This is most likely due to the inevitable time-dependent decline in physiological organ function and the decline of cellular repair mechanisms (Aunan *et al.*, 2017).

One very prominent hypothesis for ovarian carcinogenesis is ovulation hypothesis, which relates ovarian cancer risk to continual ovulation (Fathalla, 1971). In support of the hypothesis it can be cited that extensive epidemiologic evidence indicates that oral contraceptive use, multiple pregnancies, and prolonged breast-feeding can decrease the cancer risk (Fathalla, 1971, Kim *et al.*, 2011).

Cancer development: Cancer is a disease in which cells divide without control and invade other tissues. Cancer cells can spread to other parts of the body through the blood and lymph systems. Autonomy in growth signals, insensitivity to growth inhibitory signals, avoidance of apoptosis, unlimited replicative potential, persistent angiogenesis, tissue invasion and metastasis make cancer cells distinct from normal

cells (Hanahan and Weinberg, 2000). For understanding the underlying mechanisms of cancer development and to plan for proper treatment method, a brief discussion on cell proliferation and cell death and other important characteristics for the management and progression of cancer are considered further.

Cell proliferation and cell death: Cell proliferation and cell death are two diametrically opposed cellular fates that are coupled at various levels through individual molecular players (Evan and Vousden, 2001, Lowe *et al.*, 2004). In normal cells growth stimulating and growth limiting signals are finely controlled and very well balanced, such that cell proliferation occurs only when it is required. Whereas in tumour cells this balance gets disrupted and continued cell propagation takes place (Hahn and Weinberg, 2002). As apoptosis is the major cause of cell death, agents that trigger apoptosis/cell death, could be the most promising candidates as therapeutics for cancer (Ravindran *et al.*, 2009). In addition to angiogenesis, metastasis and suppression of apoptosis, uncontrolled proliferation of cancer cells also lies at the heart of the disease. Therefore, clear knowledge on cell proliferation and its control is a must to find out the therapeutic targets of successful tumour regression.

Cell cycle control points: Advances in understanding of the cell cycle machinery during the last few years have demonstrated that disruption of normal cell cycle control is a hallmark of human cancer (Sa and Das, 2008). Cyclin dependent kinases (CDKs) are highly regulated family of enzymes that remain at the heart of the regulatory apparatus during the cell cycle progression (Norbury and Nurse, 1992, Hartwell and Kastan, 1994, Nurse *et al.*, 1998, Park and Lee, 2003). CDKs (CDK4, CDK6, CDK2, and CDC2) and cyclins associates (cyclin D, E, A, and B) are positive regulators that induce cell cycle progression from G1 to mitosis whereas important negative regulators such as cyclin dependent kinase inhibitors (CKIs) act as brakes to stop the cell cycle progression in response to regulatory signals. By direct association with CDK, CKIs can negatively regulate CDK activity (Park and Lee, 2003). Two families of CKIs have been characterized according to their structures and CDK targets are INK and CIP/KIP family. The four members of the INK family, INK4A (p16), INK4B (p15), INK4C (p18), and INK4D (p19), exclusively bind to CDK4 and CDK6, preventing their association with D-type cyclins. The three members of the CIP/KIP family, CIP1 (p21), KIP1 (p27), and KIP2 (p57), form heterotrimeric complexes with the G1/S CDKs i.e. bind to both cyclin and CDK subunits, inhibit cyclin E- and A-dependent kinases but act as positive regulators of cyclin D-dependent kinases. CKIs come into play in response to different cellular processes (Sherr and Roberts, 1999, Sherr, 2000). For instance, the KIP1 levels are generally high in quiescent cells. CIP1 is one of the effectors of tumour suppressor p53 that is important in checkpoint associated with DNA damage (Park and Lee, 2003).

As applied to cell cycle control, the critical event remains the restriction point. After passing this point, the cell is irreversibly committed to the next phase of the cell cycle. The primary substrates of CDK4/6 and CDK2 in G1 progression are members of the retinoblastoma protein family pRB, p107, and p130, and are the as negative regulators at the restriction point (Morgan, 1997, Adams, 2001). In mammalian cell, E2F family of transcription factors plays key roles in regulation of cell cycle and DNA synthesis. E2F1, 2 and E2F3a act as the activators while and E2F3b, E2F4-8 act as suppressors (Harbour and Dean, 2000, Sozzani *et al.*, 2006).

Possible targets for therapeutic intervention have been revealed from loss of cell cycle regulation in cancer. It is thought that restoration of proper restriction point control would allow cancer cells to return to the state of quiescence. As phytochemicals have specific cellular targets even in cell cycle component, the use of phytochemicals could be a promising strategy for the treatment of cancer.

Apoptosis: The ability of cancer cells to evade apoptosis (programmed cell death) is a major characteristic that enables them to undergo uncontrolled growth. The efficiency of treatment depends on the successful stimulation of apoptosis in cancer cells (Melet *et al.*, 2008). For example, activation of the JNK signaling pathway is frequently observed in apoptosis. A number of apoptotic molecules including p53, c-Myc, Bcl-2 and Bcl-xL are prime targets for JNK-mediated phosphorylation which are involved in regulation of cytochrome c release, the key event in caspases activation (Fuchs *et al.*, 1998, Fuchs *et al.*, 1998, Noguchi *et al.*, 1999, Yamamoto *et al.*, 1999, Tournier *et al.*, 2000). Another very important pathway is Akt pathway. Akt-mediated phosphorylation can impact on the transcriptional regulation of apoptosis. For example, Akt-mediated phosphorylation and inactivation of forkhead (FKHRL1) serve to limit transcription of its target genes including FasL, IGF-BP1 and Bim, all of which function to promote apoptosis (Kasibhatla and Tseng, 2003). In contrast, Akt is able to accelerate the degradation of IκB, and thus potentiate the activity of NF-κB, which in turn accelerates the expression of its target genes the anti-apoptotic Bcl-2 protein A1, TNF receptor-associated factors and the caspase inhibitors (Kane *et al.*, 1999, Zong *et al.*, 1999, Kasibhatla and Tseng, 2003). Thus, successful treatment also depends on the suppression of this pro-survival Akt pathway.

Abnormalities in apoptotic pathways are believed to be associated with reduced activity of pro-apoptotic or tumour suppressor genes or proteins or increased expressions of oncogenes or anti-apoptotic proteins. As the development of tumours arises as a consequence of dysregulated proliferation and suppression of apoptosis, each primary defects provides an obvious opportunity for clinical intervention (Kasibhatla and Tseng, 2003). It is hoped that greater insights into the

field of apoptosis and cancer will uncover new and effective strategies to tackle the complexity of tumour chemoresistance.

Oxidative Stress: Although cancer cells have many adaptive mechanisms to minimize the effect of oxidative damage and baseline or even a controlled reactive oxygen species (ROS) levels can produce a pro-survival effect, excessive levels of ROS can disrupt redox homeostasis and hence can affect cell death or survival which ultimately cause cellular harm. It does so either by irreversibly damaging cellular macromolecules including DNA, carbohydrates, protein, and lipids (Dalle-Donne *et al.*, 2003) or by modulating redox-sensitive signaling proteins at the levels of transduction or transcriptional regulation (or both), thus trigger apoptotic cell death (Trachootham *et al.*, 2008). Moreover, modifications induced by ROS would target several other proteins such as NF-κB, AP-1, HRas, MAPK, IP3 kinase, PKC-ε, Ras, p53, HIF-1, ASK-1, Bcl-2, caspases, JNK, and p38 MAPK that play key roles in cell death and survival (England and Cotter, 2005).

The overall redox status is the net result of ROS generation and elimination. This means compounds that heighten ROS generation or suppress its elimination can favour ROS accumulation and hence induce damage to cancer cells or cause its death (Trachootham *et al.*, 2009). Compounds that promote ROS generation, *i.e.*, mitochondrial electron transport chain modulators, redox-cycling compounds, or that disrupt antioxidant defenses, *i.e.*, GSH depleting agents, and inhibitors of super oxide dismutase (SOD), and catalase could selectively sensitize cancer cells to overbalanced ROS so as to cause cell death (Barbieri *et al.*, 1994, Trachootham *et al.*, 2009, Gibellini *et al.*, 2010).

Drug resistance is a major problem in cancer chemotherapy affecting the clinical outcome. Among the various mechanisms of resistance, phase II detoxification system involving glutathione is a major factor. Besides high concentration of GSH and increased expression of GSTs, GSH-transporters are a common feature of transformed cells that, in turn, are associated with high resistance to chemotherapeutic agents (Yang *et al.*, 2006, Singh *et al.*, 2012). Manipulation of intracellular GSH level using compounds that stimulate ROS synthesis or compounds that inhibit synthesis of GSH can be used to increase the sensitivity of different tumour cell lines to therapy and thus selective differential chemotherapy responses of normal versus tumour cells is possible (Williamson *et al.*, 1982). Although different cells respond differently to oxidative stress inducing therapies (Mattson David *et al.*, 2009), it is found that manipulation of intracellular oxidant status of tumour cells can be clinically useful. Increasing ROS or decreasing free radical scavengers such as GSH thus can be a therapeutic strategy for overcoming resistance.

Drug resistance: Considering that the cytotoxic outcome of chemotherapy is a multifaceted process, relating to drug entry into cells to the final stages of apoptosis, it follows that intracellular events interfering with any of these processes will inhibit apoptosis and lead to drug resistance. Resistance mechanisms, therefore, arise as a consequence of ample intracellular modifications including changes in cellular uptake, drug efflux, increased detoxification, inhibition of apoptosis and increased DNA repair (Siddik, 2003).

Cisplatin is a platinum based anticancer drug commonly used to treat various cancers including ovarian, testicular and head and neck cancers (Crul *et al.*, 2002, Boulikas and Vougiouka, 2004). However, acquired resistance remains one of the problems associated with the use of cisplatin (Binju *et al.*, 2019). Of the various mechanisms of platinum resistance, one is associated with reduced cellular accumulation (Garmann *et al.*, 2008). Since reduced accumulation can be shown over a wide range of cisplatin concentrations, it is logical to think that resistance occurs as a result of changes in passive drug diffusion (Kelland, 2000), reduction of energy-dependent active transport involving Na^+K^+-ATPase or a gated ion channel (Kishimoto *et al.*, 2006), overexpression of Enhancer of zeste homolog 2 (EZH2) (Binju *et al.*, 2019) and repression of high-affinity copper transporter CTR1 located at the plasma membrane. In addition to reduced cellular accumulation of cisplatin, an active efflux pump for cisplatin in some cases also associates with cisplatin resistance (Komatsu *et al.*, 2000). Overexpression of adenosine triphosphate (ATP7A and ATP7B)(Holzer and Howell, 2006, Holzer *et al.*, 2006) and ATP-binding cassette, sub-family C2 (ABCC2) (Surowiak *et al.*, 2006) is found to cause reduced accumulation of cisplatin due to increased efflux of the drug out of the cell. Among the various mechanisms, phase II detoxification system involving glutathione is believed to a major factor of resistance which is supported by increased level of glutathione (GSH) and glutathione-S-transferases (GSTs)(Singh *et al.*, 2012). Over-expression of the *MRP/GS-X* pump for excretion of GSH conjugates is also observed in cisplatin-resistant human leukemia HL-60 cells (Ishikawa *et al.*, 1996). Other efflux proteins such as MDR1 and MRP1 have also been found to couple with sequestration of cisplatin and other platinum drugs (Samimi *et al.*, 2004).

The bulky DNA adducts generated by platinum drugs are mainly repaired by the nucleotide excision repair (NER) pathway composed of at least 17 different proteins. Upregulation of only a few rate-limiting proteins is necessary to increase the excision repair capacity in resistant tumour cells (Siddik, 2003, Rocha *et al.*, 2018). Increases in the excision repair cross-complementing ERCC1 or ERCC1/XPF complexes and over-expression of the NER-related XPA gene contributing to enhanced repair, are also observed in resistant cells (Wang *et al.*, 2011, McNeil and Melton, 2012). In addition, mismatch repair (MMR) complex maintains the integrity of the genome through repair of DNA mismatch lesions, but when it fails to do so would activate the apoptotic signal (Galluzzi *et al.*, 2011). Downregulation or mutations in MMR genes hMLH1, hMSH2 and hMSH6 are observed

consistently in resistant cells thus fail to activate the apoptotic signal (Rosell *et al.*, 2003, Siddik, 2003, McNeil and Melton, 2012).

Cancer stem cells: In recent times, it has been anticipated that cancer stem cells (CSCs) are responsible for the cellular heterogeneity of the tumour, resistance to therapy, self-restoration and unrestricted spread of the disease (Solomon *et al.*, 2008, Chan *et al.*, 2018). CSCs possess characteristics associated with normal stem cells, specifically the ability to give rise to all cell types found in a particular cancer sample. They may generate tumours through the stem cell processes of self-renewal and differentiation into multiple cell types (Zhan *et al.*, 2013). Although chemotherapy can reduce tumour mass, an aggressive population of CSCs within the tumour may be capable of resisting chemotherapeutic drugs and are believed to be an underlying cause for tumour recurrence and metastasis (Brian T. Kawasaki and Farrar, 2008). Development of specific therapies targeted at CSCs holds hope for improvement of survival and quality of life of cancer patients, especially for sufferers of metastatic disease. Elimination of ovarian CSCs has been challenging in part due to heterogeneity of tumour. CSCs are resistant to conventional anti-proliferative drugs. It has been suggested that conventional chemotherapies may only kill differentiated or differentiating cells (which form the bulk of the tumour) but not the CSCs (Chan *et al.*, 2018). In order to be cured, it is imperative that CSCs must be eliminated by the cancer therapy. Combination treatments or phytochemicals alone due to their multiple specific actions can target both differentiated and un-differentiated cells thus providing a new direction to cancer treatment in the future (Valent *et al.*, 2012, Zhan *et al.*, 2013).

Mechanisms of anti-tumour action of phytochemicals:

From the above discussion, it is clear that tumourigenesis is a multistep process that can be activated by any of various environmental carcinogens, inflammatory agents and tumour promoters. These carcinogens bring about changes in transcription factors, anti-apoptotic proteins, pro-apoptotic proteins, protein kinases, cell cycle proteins, cell adhesion molecules and growth factor signaling pathways and thus lead to malignancies.

Despite significant innovations in cancer therapy over the past several decades, the global burden of cancer continues to increase so that cancer has become one of the most devastating diseases worldwide. Therefore, cancer prevention has become an important avenue through which the fight against cancer could be feasible (Sarkar and Li, 2007). Since tumour active plant compounds often exert their anti-tumour activity through the regulation of cell signaling pathways different from those of platinum drugs, it is logical to think that phytochemicals in combination with the platinum drugs or alone may exert enhanced anti-tumour activity through synergistic action and/or compensation of the adverse effects (Chan and Fong, 2007). The combination therapy or treatment with phytochemicals alone may also decrease the systemic toxicity caused by chemotherapies or radiotherapies because of lower doses required.

Thus, based on mode of action number of phytochemicals were chosen to test their activity against ovarian cancer cell lines (both parent and resistant) to justify the use of phytochemicals towards improvement in cancer treatment and to overcome resistance. Specific molecular mechanisms and cytotoxic action of the selected phytochemicals are discussed below to find out the specific logical way to fight against cancer.

Anethole: Anethole (1-methoxy-4-(prop-1-enyl) benzene), the chief component of anise oil, fennel oil and camphor, and its derivative anethole ditholethione (ADT) have been shown to block carcinogenesis. They act as antioxidants (Park *et al.*, 2003), increase intracellular levels of GSH and GST (Bouthillier *et al.*, 1996, Drukarch *et al.*, 1997, Chen and deGraffenried, 2012), suppress TNF-induced lipid peroxidation and ROI generation and reduce oxidative levels by scavenging hydroxyl radicals (Chainy *et al.*, 2000, Chen and deGraffenried, 2012). Anethole suppresses JNK and MAPK- kinase and NF-⍰B activation process (Aggarwal and Shishodia, 2006). Anethole also suppresses TNF induced activation of AP-1, which is involved in carcinogenesis (Karin, 1996, Chainy *et al.*, 2000). AP-1 activation requires the activation of c-Jun N-terminal kinase (JNK) and mitogen-activated protein kinase (MAPK) kinase (MAPKK or MEK) (Karin, 1996).

Betulinic acid: Betulinic acid (3β, hydroxy-lup-20(29)-en-28-oic acid) is a naturally occurring pentacyclic triterpenoid available in the outer bark of a variety of tree species, e.g. white-barked birch trees (Tan *et al.*, 2003, Fulda, 2008). It has potent antitumour properties and can be used as an effective alternative when certain chemotherapy drugs fail. Non-malignant cells and normal tissues are not affected by BA as it exerts its effects directly on the mitochondrion to trigger death of cancerous cells (Ali-Seyed *et al.*, 2016). It also has been shown to exert their effect through mechanisms that involve modulation of NF-κB. Without activating ERK, BA activates p38 and SAP/JNK early in the programmed cell death process and thus induction of apoptosis (Fulda *et al.*, 1999, Tan *et al.*, 2003). Further, betulinic acid exhibits anti-angiogenic activity due to activation of selective proteasome-dependent degradation of the transcription factors specificity protein 1 (Sp1), Sp3, and Sp4, which regulate vascular endothelial growth (VEGF) expression (Chintharlapalli *et al.*, 2007).

Capsaicin: Capsaicin (*trans*-8-methyl-N-Vanilyl-6-nonenamide) is the pungent ingredient of red pepper and hot chili pepper is a cancer-suppressing agent. It is capable of inhibiting, retarding or reversing the multi-stage carcinogenesis and also angiogenesis and it does so by blocking translocation of NF-κB, and by inhibiting AP-1 and STAT3 signaling pathway (Oyagbemi *et al.*, 2010). By upregulating tribbles-

related protein 3 (TRIB3) expression it also promotes apoptotic cell death in cancer cells (Lin *et al.*, 2018). Capsaicin inhibits constitutive activation of STAT3 and thus down-regulates the expression of the STAT3-regulated gene products, such as cyclin D1, Bcl-2, Bcl-xL, survivin and VEGF (Bhutani *et al.*, 2007). Capsaicin also induces the accumulation of cells in G1 phase, inhibits proliferation, and induces apoptosis by ROS generation, alteration of the mitochondrial inner transmembrane potential, JNK activation, activation of caspase 3, ceramide accumulation and extracellular signal-regulated protein kinase (ERK) activation (Sánchez *et al.*, 2007, Sánchez *et al.*, 2008, Oyagbemi *et al.*, 2010). In addition, generation of ROS in cells with the resultant induction of apoptosis and cell cycle arrest are beneficial for cancer chemoprevention.

Cholecalciferol: Mammalian skin produces cholecalciferol (vitamin D_3) in the presence of sunlight (Norman, 2008). Though the major function of cholecalciferol is sustaining plasma calcium concentration and bone health (Chang *et al.*, 2015), it has the ability to decrease interferon-gamma and NF-κB expression towards inducing autophagy (Wu and Sun, 2011). It is associated with reducing anti-apoptotic proteins expression such as cyclin D1, Bcl-2 and it also increases pro-apoptotic BAX protein expression (Yang *et al.*, 2008). In addition, it inhibits cancer multiplication, progression and triggers apoptosis (Tokar and Webber, 2005, Fleet *et al.*, 2012, Giammanco *et al.*, 2015).

Curcumin: Curcumin (diferuloylmethane) is a key component of turmeric governs a number of intracellular targets, including proteins involved in antioxidant response, immune response, apoptosis, cell cycle regulation and tumor progression (Kumar *et al.*, 2016). Curcumin suppresses the expression of TNFα and NF-κB, thus decreases the expression of inflammatory enzymes cyclooxygenase (COX2) and inducible nitric oxide synthase (iNOS) and ultimately sensitizes resistant cancer cells towards apoptosis by cisplatin and taxol (HemaIswarya and Doble, 2006, Sarkar *et al.*, 2006). Curcumin also down-regulates the expression of IL1, IL6, TNFα (II), and angiogenic factors such as vascular endothelial growth factor (VEGF) (Lin *et al.*, 2007, Tan *et al.*, 2010). Curcumin modulates CKis, CDK-cyclin and Rb-E2F complexes to render G1-arrest and alters CDK/cyclin B complex formation to block G2/M transition (Sablina Anna *et al.*, 2005). Curcumin promotes caspase-3-mediated cleavage of β-catenin, decreases β-catenin/Tcf-Lef transactivation capacity for c-Myc and cyclin D1 (Jaiswal *et al.*, 2002).

Genistein: Genistein is a major component of soybean isoflavone and has multiple functions associated with anti-tumour effects (Suzuki *et al.*, 2002). Genistein upregulates pro-apoptotic proteins (Bad and Bax) and miRNA-218 expression and also induces activation of cleaved caspase-3. It also reduces the activated NF-κB signalling and overproduction of pro-inflammatory cytokines (TNF-alpha, IL-1beta and IL-6), nuclear translocation of p65 and subsequent gene expression in cancer cells (Zheng *et al.*, 2017). Genistein also inhibits AKT pathway and thus can enhance necrotic-like cancer cell death (Satoh *et al.*, 2003). Moreover, genistein antagonizes estrogen- and androgen-mediated signaling pathways in the processes of carcinogenesis (Mathieson and Kitts, 1980). It also inhibits topoisomerase II (Okura *et al.*, 1988), 17β-hydroxysteroid dehydrogenase and 5α-reductase (Evans *et al.*, 1995). Genistein has also been found to have antioxidant properties, and thus acts as a potent inhibitor of angiogenesis and metastasis (Banerjee *et al.*, 2008). It is believed to have the ability to increase the expression of gene for glutathione peroxidase, without any significant change in the expression of gene for other antioxidant enzymes such as superoxide dismutase and catalase (Suzuki *et al.*, 2002). Finally, inhibition of proteasome activity by genistein might contribute to its cancer-preventive properties (Kazi *et al.*, 2003).

Honokiol: Honokiol is derived from seed/leaf/bark of *Magnolia virginia* magnolia tree (Fried and Arbiser, 2009). Honokiol is reported to suppress NF-κB, EFGR, STAT3 and mTOR transduction pathways (Arora *et al.*, 2012) and induce caspase-dependent apoptosis and blocks VEGF expression to prevent new blood vessel formation (Fried and Arbiser, 2009). Honokiol inhibits tumour cell proliferation and decreases human epidermal growth receptor 2 expressions (Liu *et al.*, 2008). Honokiol also inhibits G_1 cell cycle phase progression and increases pro-apoptotic BAX expression (Arora *et al.*, 2011). Honokiol has the ability to induce apoptosis via both p53 dependent and p53 independent pathways (Wang *et al.*, 2004, Guo *et al.*, 2015).

Kaempferol: Kaempferol is isolated from different plants and fruits, i.e. green tea, broccoli, apple, grapes and tomato (Kim and Choi, 2013). Kaempferol significantly decreases VEGF biomarker expression towards preventing formation of the new blood vessel. It inhibits cell cycle G_2/M phase transition by preventing cyclin-dependent kinase 1 and cyclin B. It blocks AP-1 and ERKp38- JNK signaling pathways to prevent the tumour cell invasion. It dampens the NF-κB expression as well as Bcl-2 and Bcl-xL anti-apoptotic proteins. Kaempferol greatly induces pro-apoptotic p53, BAX and BAD proteins expression (Kim and Choi, 2013).

Mycophenolic acid: Mycophenolic acid is a secondary metabolite produced by marine fungi *Penicillium brevicompactum* (Rovirosa *et al.*, 2006). Mycophenolic acid is a potent inhibitor of inosine monophosphate dehydrogenase enzyme in the de-novo guanosine nucleotides synthesis (Allison and Eugui, 2000), which prevents T cells synthesis namely TNF-α, IL-17 and Interferon-γ (He *et al.*, 2011). Therefore, it could inhibit replication of DNA. It increases pro-apoptotic p53 protein activity towards facilitating apoptosis (Sun *et al.*, 2008) and blocks vascular VEGF-α secretion towards preventing

new blood vessel formation (Monguilhott Dalmarco *et al.*, 2011). It also inhibits AKT/mTOR and NF-κB pathways (Morales *et al.*, 2008, He *et al.*, 2011, Zheng *et al.*, 2011) towards promoting anticancer activity.

Paclitaxel: Paclitaxel (Taxol), was first discovered in the bark of the western yew tree, Taxus brevifolia (Kaye, 1996). The combined treatment of paclitaxel with cisplatin in first-line therapy marked the next major advance in the treatment efficacy for advanced ovarian cancer. It is a mitotic inhibitor that arrests cells at G_2/M phase. It interferes with the normal breakdown of microtubules during cell division by stabilizing microtubules, and thus it destroys cell's ability to use its cytoskeleton in a flexible manner. In addition paclitaxel also acts as a molecular mop by sequestering free tubulin effectively depleting the cells supply of tubulin monomers and/or dimers and thus trigger apoptosis (Foss *et al.*, 2008). Paclitaxel also induces apoptosis in cancer cells by binding to anti-apoptotic protein Bcl-2 (Haldar *et al.*, 1995). Recently, numerous preclinical studies have suggested that the combination of paclitaxel and curcumin may be an ideal strategy to reverse multi drug resistance and synergistically improve therapeutic efficacy in cancer therapy (Wei *et al.*, 2017).

Quercetin: Quercetin (3,3',4',5,7-pentahydroxyflavone) is an important dietary flavonoid, present in different vegetables, fruits, seeds, nuts and tea It strongly increases intracellular ROS levels, by producing quercetin radicals (Quercetin-O•) (Jeong *et al.*, 2008), and thus causes free radical-induced apoptosis through the ROS/AMPKα1/ASK1/p38 and the AMPKα1/COX2 signaling pathways (Lee *et al.*, 2010). In addition, quercetin radicals also lowers the intracellular pool of GSH and thus triggers apoptosis through mitochondrial depolarization (Lugli *et al.*, 2005, Gibellini *et al.*, 2010). Quercetin reduces drug-induced up-regulation of p53, p21 and Bax and reduces the levels of cyclin B1 and survivin proteins (Samuel *et al.*, 2012). These events go along with the cleavage of procaspase 9 and poly (ADP-ribose) polymerase (PARP) (Granado-Serrano *et al.*, 2006, Lee *et al.*, 2006, Yang *et al.*, 2006). Quercetin also inhibits the activation of NF-κB and PI3K/AKT pathway (Aggarwal and Shishodia, 2006, Granado-Serrano *et al.*, 2006, Gibellini *et al.*, 2010) and upregulates the death receptor (DR)-5, which is activated by TNF-related apoptosis-inducing ligand (TRAIL) (Kim *et al.*, 2008, Jung *et al.*, 2010).

Resveratrol: Resveratrol (3,5,4'-trihydroxystilben) present in red grapes, mulberries and some nuts induces apoptosis and overcomes chemo-resistance through the down-regulation of NF-κB activation and signal transducer and activator transcription factor 3 (STAT3), anti-apoptotic and cell survival gene products such as Bcl-2, and also by regulating the cyclooxygenase (COX) expression (Sexton *et al.*, 2006, Hu *et al.*, 2007, Singh *et al.*, 2009). Resveratrol also up-regulates the tumour suppressor p53 and cytokine (MIC-1) that possesses anti-tumourigenic activity (Golkar *et al.*, 2007). It also increases the expression of glutathione S-transferase (GST) and glutathione peroxidase (GPx) or their activity resulting in lowered glutathione level (Hu *et al.*, 2007). In the absence of oxygen, resveratrol also acts as a protector against radiation (Bader and Getoff, 2006). Resveratrol downregulates expression of related Wnt/beta-catenin signaling pathway target genes, such as β-catenin, c-myc, cyclin D1, MMP-2 and MMP-9, and upregulates E-cadherin level as well. Resveratrol also suppresses the activity of Wnt/ β-catenin signaling pathway (Xie *et al.*, 2017).

Thymoquinone: Thymoquinone (2-Isopropyl-5-methylbenzo-1,4-quinone) is a plant compound present in the Nigella sativa has potent anti-proliferative, pro-apoptotic, anti-oxidant, cytotoxic, anti-metastatic, and NK-dependent cytotoxic effects. The most significant pathways through which thymoquinone mediates its anti-cancer activity are p53, NF- κB, PPARgamma, STAT3, MAPK, and PI3K/AKT signaling pathways (Majdalawieh *et al.*, 2017). Apoptosis induction by thymoquinone is associated with an increase in mRNA expression of p53 and the downstream p53 target gene p21WAF1 and a significant inhibition of anti-apoptotic Bcl-2 protein (Gali-Muhtasib *et al.*, 2004). Thymoquinone suppresses activation of AKT and ERK, TNF, NF-κB and the NF-κB-dependent reporter gene expression (Aggarwal *et al.*, 2008). It also has been found to down-regulate the expression of antiapoptotic (IAP1, IAP2, XIAP Bcl-2, Bcl-xL, and survivin), proliferative (cyclin D1, COX-2, and c-myc), and angiogenic (MMP-9 and VEGF) gene products (El-Dakhakhny *et al.*, 2002, El-Mahmoudy *et al.*, 2002, Gali-Muhtasib *et al.*, 2004, El-Mahmoudy *et al.*, 2005, El Mezayen *et al.*, 2006, Roepke *et al.*, 2007).

6-shogaol: 6-shogaol is mainly isolated from Ginger *Zingiber officinale* Roscoe (Ok and Jeong, 2012). 6-shogaol inhibits cell proliferation and triggers autophagy by blocking mTOR/AKT pathway (Hung *et al.*, 2009, Ray *et al.*, 2015, Li and Chiang, 2017). It induces mitotic arrest and reduces the cancer cells viability (Ishiguro *et al.*, 2007) and inhibits cell cycle G_2/M phase transition (Li and Chiang, 2017). 6-shogaol exceedingly attenuates NF-κB genes such as MMP-9, survivin, c-MYC, and cyclin D1 (Ling *et al.*, 2010, Saha *et al.*, 2014). It increases PPAR-γ dependent apoptosis (Tan *et al.*, 2013) and also causes programmed cell death through caspase-dependent oxidative stress pathway (Chen *et al.*, 2007, Liu *et al.*, 2013) and initiates up-regulation of p27, interleukin-7 and BAX pro-apoptotic factors to assist apoptosis (Saha *et al.*, 2014).

Phytochemicals in cancer treatment:

From the above discussions it is clear that phytochemicals exert their anti-tumour effects by bringing into play numerous cellular proteins, signaling pathways (summarized in Table-1) which in turn affect

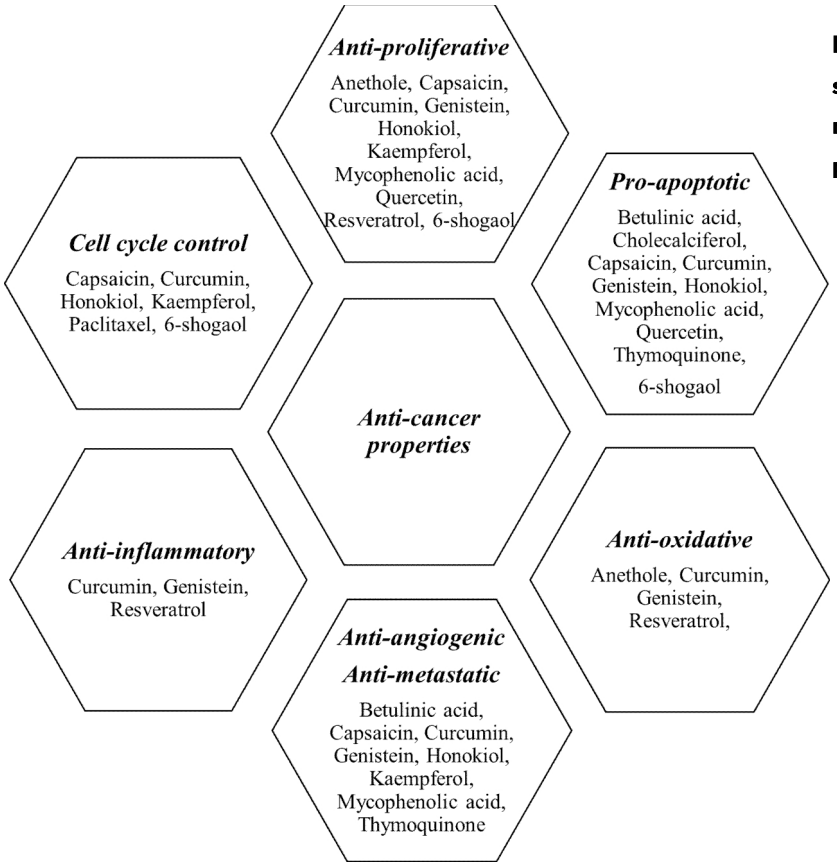

Figure 1 | Schematic classification of the selected phytochemicals that targets specific mechanisms in cancer treatment and prevention.

Table 1 | Molecular targets of phytochemicals upregulated (↑) or downregulated (↓) to induce apoptosis and thus treatment of cancer

Cell survival proteins	Apoptotic proteins	Growth factors	Transcription factors	Metastasis molecules	Cell adhesion molecules	Cell cycle proteins	Protein kinases	Others
Bcl-2 ↓	Caspase9↑	TNF↓	NF-κB↓	5-LOX↓	ICAM-1↓	CyclinD1↓	IKK↓	MDR↓
Bcl-XL↓	Caspase8↑	EGF↓	AP-1↓	COX2↓	VCAM↓	CyclinE↓	EGFR↓	FTPase↓
Survivin↓	Caspase7↑	PDGF↓	EGR-1↓	iNOS↓	ELAM↓	p21/WAF↑	HER2↓	ROS↑
TRAF1↓	Caspase3↑	FGF↓	STAT1↓	MMP9↓		p27Kip/Cip↑	AKT↓	GST↑
IAP1↓	PARP↑	TGFα/β↓	STAT3↓	IL-8↓		CDK1,2,4,6,7↓	Src↓	GSH↑
IAP2↓	Bax↑	Erythropoietin↓	STAT5↓	VEGF↓			JAK2↓	Hemeoxygenase↑
xIAP↓	Bak↑	IGF↓	EpRE↓				TYK2↓	Xanthine Oxidase↓
cFLIP↓	DR5↑	IL-1,2,6,8↓	CBP↓				JNK↓	Ubiquitin isopeptidase↓
Bfl1/A1↓	TRAIL↑	INF-γ↓	β-Catenin↓				PKA↓	uPA↓
	TRIB3↑	CSF↓	Nrf2↑				PKC↓	Topoisomerase II↓
			PPARγ↑				MAPKK↓	Tumour suppressor p53↑
			P53↑				ERK↓	c-MYC↓
			AR↓				SAP/JNK↑	MMP-9↓
			Sp1↑				mTOR↓	EZH2↓
			Sp3↑					miRNAs↓
			Sp4↑					

Table 2 | IC50 values (μM for all compounds except for Ane for which it is in mM) and resistant factors (RF) for phytochemicals as applied to the ovarian cancer cell lines A2780, A2780cisR A2780ZD0473R and SKOV-3. RF is defined as the ratio of the IC50 value of a compound in the resistant cell line over that in the parent cell line. Results are expressed as Mean ± SD where n = 5 and SD denotes 'standard deviation' (IC50 : Concentration required to inhibit cell growth by 50%).

Drug	A2780 (μM)	$A2780^{cisR}$ (μM)	RF	$A2780^{ZD0473R}$ (μM)	RF	SKOV-3 (μM)	Reference
Anethole	2.42 ± 0.97	1.72 ± 0.83	0.71	1.36 ± 0.62	0.56	-	(Nessa *et al.*, 2012)
Betulinic acid	5.36 ± 1.18	2.93 ± 0.77	0.55	3.86 ± 0.56	0.72	-	(Nessa, 2013)
Capsaicin	17.65 ± 3.51	22.34 ± 1.64	1.27	20.03 ± 2.78	1.14	-	(Nessa, 2013)
Cholecalciferol	17.57±0.88	13.24±0.27	0.75	13.24±0.26	0.75	34.73±3.40	(Anwar *et al.*, 2017, Anwar, 2018)
Colchicine	0.007 ± 0.03	0.009 ± 0.02	1.351	0.009 ± 0.03	1.454	-	(Alamro, 2015)
Curcumin	6.83 ± 1.63	9.65 ± 4.66	1.41	8.26 ± 2.84	1.21	-	(Nessa *et al.*, 2012)
Emetin	0.023 ± 0.0009	0.018 ± 0.0009	0.78	0.022 ± 0.001	0.95	-	(Alam, 2018)
Epigallocatechin gallate	6.87 ± 2.72	6.67 ± 3.61	0.97	9.63 ± 4.73	1.40	11.08 ± 1.21	(Mazumder *et al.*, 2012)
Genistein	14.15 ± 3.10	21.10 ± 6.24	1.49	15.07 ± 2.42	1.49	-	(Nessa, 2013)
Honokiol	22.10±1.77	18.21±1.82	0.82	29.51±4.42	1.33	39.16±5.09	(Anwar, 2018)
Kaempferol	24.14±2.41	13.65±1.91	0.56	79.10±3.95	3.27	58.36±5.84	(Anwar, 2018)
Mycophenolic acid	1.82±0.14	1.43±0.07	0.78	1.34±0.10	0.73	7.83±0.94	(Anwar *et al.*, 2016)
Paclitaxel	0.0057 ± 0.002	0.017 ± 0.002	2.98	0.0118 ± 0.002	2.07	-	(Nessa, 2013)
Patulin	1.47 ± 0.12	1.28 ± 0.08	0.87	1.44 ± 0.10	0.97	-	(Alam, 2018)
Quercetin	22.69 ± 3.86	25.95 ± 5.34	1.14	21.47 ± 8.39	0.95	-	(Nessa *et al.*, 2011)
Resveratrol	24.78 ± 5.87	26.65 ± 7.82	1.08	24.82 ± 7.79	1.00	-	(Nessa *et al.*, 2012)
Thymoquinone	5.70 ± 0.68	4.82 ± 1.56	0.85	4.66 ± 2.50	0.82	5.94 ± 2.93	(Nessa *et al.*, 2011, Mazumder, 2013)
Ursolic acid	12.38 ± 3.00	10.13 ± 2.66	0.82	11.48 ± 1.10	0.93	25.75 ± 2.52	(Mazumder, 2013)
6-shogaol	9.45±0.75	8.31±1.16	0.88	10.20±1.02	1.07	6.79±0.61	(Anwar *et al.*, 2016)
α-Mangostin	-	-	-	-	-	3.062 ± 0.349	(Ittiudomrak *et al.*, 2019)
Apigenin	-	-	-	-	-	18.197 ± 3.095	(Ittiudomrak *et al.*, 2019)
Doxorubicin	-	-	-	-	-	0.117 ± 0.008	(Ittiudomrak *et al.*, 2019)
Myricetin	~ 25	-	-	-	-	-	(Zheng *et al.*, 2017)

multiple steps in the pathways leading to tumourigenesis. In addition, based on the specific mode of action in cancer treatment and prevention, the selected phytochemicals are classified broadly in six major groups are shown in the Figure-1. This is also supported by the cytotoxic action of the selected phytochemicals by *in vitro* Cytotoxicity tests on ovarian cancer cell lines (summarized in Table-2).

From the IC_{50} values given in Table 2, it can be seen that all of the phytochemicals generally have cytotoxic action in all ovarian cancer cell lines and have either comparable or greater activity in the resistant cell lines than in the parent cell line. When the major factors involved in the development of cancer and platinum resistance in ovarian cancer are counter acted by phytochemicals, it is not unexpected to find that the phytochemicals have comparable or greater activity in the parent and the resistant cell lines.

As plant derived products are natural products, another aim of using the phytochemicals would be to prevent the damage to normal cells and tissues caused by the direct and bystander effects of platinum drugs. As the molecular mechanisms of action of platinum drugs and the phytochemicals are found to be different, it is logical to assume that phytochemicals possessing both cancer preventive and therapeutic attributes, can be ideal candidates for combination with targeted therapy towards synergistic outcome.

Conclusion

Cancer is the most dreaded disease of our time because of its ability to metastasize and develop resistance to drugs resulting in failure in treatment, and the lack of complete understanding of mechanisms of its development. Knowledge on mechanism of cytotoxic activity of phytochemicals in various cancer cell lines shows that phytochemicals bring antitumour effects by modulating numerous cellular proteins, signaling pathways which in turn affect multiple steps in the pathways leading to prevent tumourigenesis. Thus, it is logical to think that phytochemicals can be wonderful agent against cancer development and therapy especially related problems associated with conventional cancer therapies. Because of heterogeneity of ovarian cancer, relationships among histological group, stage of disease, tumour markers, patient characteristics and survival of different ovarian cancer patients are different, meaning one patient may benefit from one type of treatment whereas many others might fail to respond. Therefore, there should be continuous search for the new tumour active phytochemicals that will provide better patient care, efficacy and safety.

Future Directions: In depth in vivo studies involving the use of phytochemicals alone and in combination with targeted therapy against cancer are needed towards the development of less toxic and more affordable anticancer therapy including that for ovarian cancer.

Author Contributions

Nessa and Anwar reviewed the current literature and drafted the manuscript. Huq conceptualized the project, provided overall guidance and edited the manuscript.

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Competing financial interests

The author(s) declare no competing financial interests.

Supplementary Information

All standard and non-standard abbreviation in PDF file. Please download.

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