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Curcumin in Advancing Treatment for Gynecological Cancers with Developed Drug- and Radiotherapy-Associated Resistance

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Abstract The development of resistance toward current cancer therapy modalities is an ongoing challenge in gynecological cancers, especially ovarian and cervical malignancies that require further investigations in the context of drug- and irradiation-induced resistance. In this regard, curcumin has demonstrated beneficial and highly pleiotropic actions and increased the therapeutic efficiency of radiochemotherapy. The antiproliferative, anti-metastatic, anti-angiogenic, and anti-inflammatory effects of curcumin have been extensively reported in the literature, and it could also act as a chemopreventive agent which mitigates the out-of-target harmful impact of chemotherapeutics on surrounding normal tissues. The current review discussed the modulating influences of curcumin on some cell and molecular features, including the cell signaling and molecular pathways altered upon curcumin treatment, the expression of target genes involved in the progression of gynecological cancers, as well as the expression of genes accountable for the development of resistance toward common chemotherapeutics and radiotherapy. The cell molecular targets implicated in curcumin's resensitizing effect, when used together with cisplatin, paclitaxel, and irradiation in gynecological cancers, are also addressed. Finally, rational approaches for improving the therapeutic benefits of curcumin, including curcumin derivatives with enhanced therapeutic efficacy, using nanoformulations to advance curcumin stability in physiological media and improve bioavailability have been elucidated.

Keywords Cervical cancer · Cisplatin · Curcumin · Nanoformulation · Ovarian cancer · Paclitaxel

Abbreviations

CDK	Cyclin-dependent kinase
COX-2	Cyclooxygenase-2
Cur	Curcumin
DNMTs	DNA methyltransferases
GSTs	Glutathione S-transferases
HDAC	Histone deacetylases
IAPs	Inhibitor of apoptosis family of proteins
ICAM-1	Intercellular adhesion molecule 1
IKK	IκB kinase

iNOS	Inducible nitric oxide synthase
MT	Metallothionein
P-gp	P-glycoprotein
PI3K	Phosphatidylinositide 3-kinase
VEGF	Vascular endothelial growth factor

1 Introduction

Cancer is defined as the uncontrolled growth of particular cells inside an organism, where the outgrowth of cells eventually causes serious complications (Peng et al. 2003). Considering that cancer cells are derived from a normal cell or tissue following the accumulation of mutations imparting aggressive features, there is almost as many kinds of cancer cells as there are normal tissues (Abouzeid et al. 2014; Chen et al. 2015a; Ganta and Amiji 2009; Montopoli et al. 2009; Nessa et al. 2012; Peng et al. 2003). The prominent types of cancers are derived from tissues with high rate of cell division or great exposure to potential mitogenic compounds. According to the Global Burden of Disease Study (GBD), gynecological cancers and breast cancer are ranked among the top kinds of cancers causing death, together, both accounted for 4.29% mortality among women worldwide in 2017 (https://vizhub.healthdata.org/gbd). Although the targeted treatment of cancer cells has remained a difficult task, thanks to the numerous attempts of scientists, the treatment modalities have greatly improved. In this regard, combined-therapy modalities have been shown to give superior successful results compared to single-treatment modalities in controlling different types of cancers, including gynecological cancers (Abouzeid et al. 2014; Aqil et al. 2017; Ganta and Amiji 2009; Huq et al. 2014; Punfa et al. 2012; Saengkrit et al. 2014; Sarisozen et al. 2014).

The sequential mode of therapy in gynecological cancers begins with the surgical removal of tumors followed with radiotherapy and chemotherapy, to eliminate any remaining cancer cells. However, the management of cancer therapy faces difficulties upon relapse with more refractory tumors (Watson et al. 2010; Zaman et al. 2016; Zhang et al. 2017). For example, in ovarian cancer, more than 70% of the first diagnosed patients are found resistant to taxane treatment, and finally all of them are left resistant upon relapse (Watson et al. 2010). Although combination chemoradiotherapy improves the survival rate, it also increases the chance of dose-limiting toxicities (Watson et al. 2010). In this regard, curcumin, a polyphenol derived from *Curcuma longa* plant, has shown beneficial anti-inflammatory (Abdollahi et al. 2018; Aggarwal and Harikumar 2009; Momtazi-Borojeni et al. 2017), antitumor (Kuttan et al. 2007; Momtazi et al. 2016), anti-metastatic, anti-angiogenic (Kuttan et al. 2007), antioxidant (Ak and Gülçin 2008), and chemopreventive (Duvoix et al. 2005; Kawamori et al. 1999; Rezaee et al. 2016) properties, when added to the current regimens. The molecular targets of curcumin are reportedly very diverse, including various kinases, gene modulators, transcription factors,

varying growth factors, and cell membrane receptors (Hajavi et al. 2017; Kasinski et al. 2008; Pan et al. 2008; Soflaei et al. 2017; Watson et al. 2010; Zhang et al. 2017). Curcumin with very wide pleiotropic functions holds the key to modifying the trend of cancer therapy and advanced development of current cancer therapy modalities. Regarding gynecological cancers, curcumin has demonstrated opposing typical cervical cancer risk factors in advancing molecular alterations toward cancer incidence or progression, including human papilloma virus infections (typically HPV16 and 18), estrogen, smoking, and obesity (Maruthur et al. 2009; Zaman et al. 2016). For instance, it has been shown that curcumin could inhibit the expression of E6 and E7 oncoprotein, reduce estrogen-induced DNA damage, and mitigate adipose-related inflammation and estrogen production (Zaman et al. 2016).

The current review presents an assortment of studies on curcumin ameliorating functions in gynecological cancer progression and metastasis. The sensitizing influence of curcumin treatment, when combined with routine chemotherapeutic agents like cisplatin and paclitaxel as well as irradiation, has been addressed, together with the molecular pathways associated with the drug-induced resistance which curcumin counteracts. Moreover, the approaches adopted to advance curcumin anticancer potential, stability, and bioavailability have also been discussed thoroughly in terms of effectiveness, which includes various curcumin formulations and curcumin derivatives.

2 Curcumin in the Treatment of Gynecological Cancers

It has been shown that curcumin could act as an anti-metastatic agent and inhibit endometrial carcinoma (EC) cell migration and invasion in vitro through decreasing the expression and activity of the matrix metalloproteinases (MMP)-2 and MMP-9. These enzymes that degrade the extracellular matrix in tumors make the metastasis of cancer cells possible and are believed to drive deep myometrial cancer invasion and metastasis in lymph node in type II EC. The reduced expression of these enzymes by curcumin was also found to occur through suppression of the ERK signaling pathway (Chen et al. 2015b). Curcumin-induced apoptosis in ovarian cancer cells was found to be independent of p35, as it displayed the same cytotoxic activity in cells with reduced or knockdown p53 expression, as shown in the wild-type p53 cells. Nuclear condensation and fragmentation, DNA fragmentation, and poly(ADP-ribose) polymerase-1 cleavage were the cell features in HEY cells treated with curcumin which denoted cell apoptosis. Furthermore, it was found that both the intrinsic and extrinsic pathways of apoptosis could be activated by curcumin. The enhanced activity of p38 mitogen-activated protein kinases (MAPK) reduced the expression of antiapoptotic regulators of survivin and Bcl-2, and the suppression of prosurvival Akt signaling was also found to be involved in curcumin-mediated anticancer cell death in various ovarian cancer cells (Watson et al. 2010).

It has been shown that curcumin could partially suppress urokinase-type plasminogen activator (uPA) expression in the highly invasive human ovarian cancer cell line, HRA, which is involved in cancer cell metastasis. The expression of the

serine protease uPA has been determined to be fed through Src-MAPK/ERK-PI3K/Akt-NF-kB and the Src-MAPK/ERK-AP-1 pathways in response to TGF-B1, where curcumin is reported to only abrogate the formation of the AP-1 complex (Tanaka et al. 2004). Given the beneficial influences of curcumin in limiting invasive cancer cell progression, the use of curcumin in the commonly used therapy regimen for advanced gynecological cancer types could help to improve the outcome of therapy. This paper presents studies on gynecological cancerous tumors, in which curcumin addition has been demonstrated to improve the therapeutic window and oppose drug-resistant cancer cell types.

3 Curcumin in Restoring Platinum Drug-Induced Resistance

Platinum drugs such as cisplatin and oxaliplatin are the first-line chemotherapeutics against ovarian, bladder, and testicular cancers, and their administrations are frequently faced with the development of resistant tumors (Montopoli et al. 2009). The loss of platinum uptake by cells through gated channel-facilitated diffusion, p53 gene implication in DNA damage repair, and enhanced intracellular level of glutathione, responsible for platinum inactivation and removal, are among the underlying mechanisms for the drug resistance. To evade the platinum drug-induced resistance, extensive studies have been conducted, in which a combination therapy with phytochemicals has been shown to be highly effective. In this regard, curcumin has been utilized in combination with platinum drugs like cisplatin and oxaliplatin to enhance their anticancer properties.

It has been shown that curcumin could resensitize cisplatin-resistant ovarian cancer cells, and it suppresses DNA damage responses against these DNA cross-linking agents. It has been found that curcumin treatment downregulates the Fanconi anemia (FA)/BRCA pathway-related DNA damage repair responses, such as FANCD2 protein mono-ubiquitination, which is the prerequisite step for the DNA damage repair complex to form and relocate into chromatin of the DNA lesion sites (Chen et al. 2015a). Therefore, curcumin could reverse the acquired resistance in cancer cells, which lies in the enhanced activation of the FA/BRCA pathway, in response to DNA cross-linking agents in long-term administration (Fig. 1).

Moreover, curcumin could suppress cisplatin resistance development through extracellular vesicle-mediated cell-cell communication. It is believed that the extracellular vesicles, known as exosome, transfer some proteins, mRNAs, and noncoding RNAs from donor cells to recipient cells, and this communication leads to the development of a drug-resistant cell population in various cancers (Zhang et al. 2017). Curcumin could limit such exosome-mediated chemoresistance by changing their contents. For instance, curcumin treatment has been shown to be accompanied with the restoration of MEG3 long noncoding (lnc) RNA levels (Fig. 1), upregulation of miR-29a and miR-185, and downregulation of miR-124

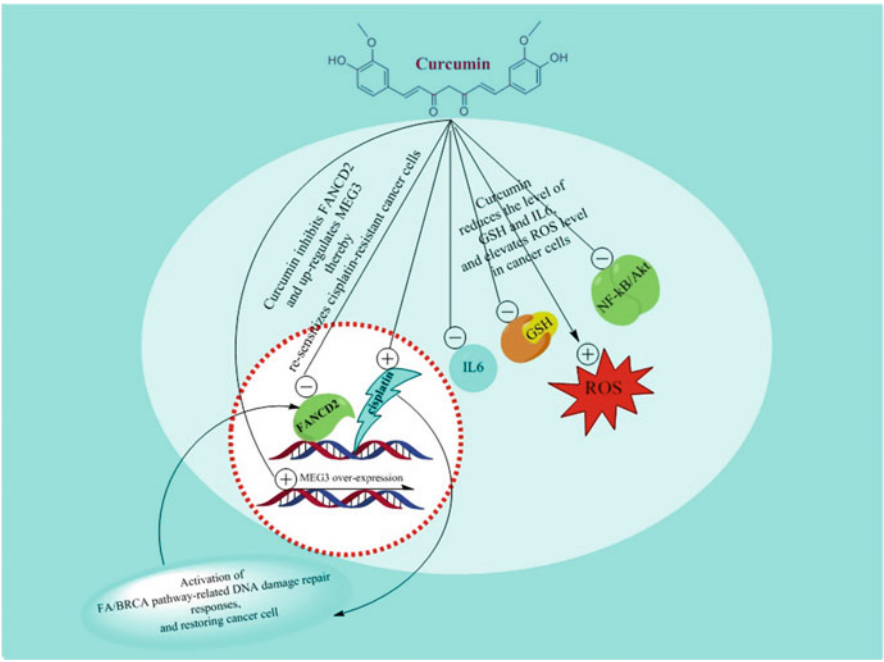

Fig. 1 A conclusive view of main mediators in curcumin-mediated resensitizing platinum-resistant ovarian cancer cells. Curcumin has been found to restore platinum drug-induced resistance through suppressing the Fanconi anemia (FA)/BRCA pathway-related DNA damage repair responses, such as FANCD2 protein. Curcumin can also exert resensitizing effect through upregulation of MEG3 lncRNAs levels that inhibit drug resistance. Furthermore, curcumin enhances the ROS production via reduction of cellular levels of IL-6, NF-Kb, and GSH

and DNA methyl transferases (DNMTs) in cisplatin-resistant cells and exosomes, resulting in chemo-sensitization in A2780cp ovarian cancer cells. In this regard, curcumin-mediated overexpression of miR-29a and miR-185 has been shown to reduce DNMT1, 3A, and 3B levels and downregulate miR-124 expression, which is an mRNA regulator acting through the PTEN/Akt pathway and the P53/Nanog axis, and could reduce the survival of ovarian cancer cells, cisplatin resistance, and stem cell development (Zhang et al. 2017).

Curcumin has been found to enhance the cell killing potential of chemotherapeutics by increasing the generation of reactive oxygen species (ROS) in cancer cells. It has been reported that curcumin could reduce the level of intracellular thiol of GSH, which is known to be involved in cisplatin deactivation (Yunos et al. 2011) (Fig. 1). It has been shown that pretreatment with cisplatin for 4 h before curcumin addition results in a synergistic cytotoxicity in some ovarian cancer cells, where curcumin could potentiate the ROS-mediated cell death triggered by cisplatin. The curcumin efficiency in suppression of cancer cell growth was found to be positively correlated with the basal levels of ROS in cancer cells. Interestingly, curcumin exhibited chemopreventive effect on normal tissues by activating the NF-kB

pathway where the ROS intracellular level is decreased, whereas high curcumin concentrations (>15 μM) were found to enhance ROS levels in these tissues. Conversely, in cancer cells with previously high ROS concentrations, curcumin was shown to enhance ROS levels by inactivating the NF-kB pathway (Sreekanth et al. 2011; Yunos et al. 2011). Moreover, it appears that the reduced ROS and the increased GSH basal levels are the main hallmark of the development of resistance to cisplatin in cisplatin-resistant ovarian cancer cells, which could be linked to the more active NF-kB pathway in these cells. In summary, it is plausible for curcumin to contribute much greater to induce ROS generation in cisplatin-treated cancer cells than in non-treated ones, indicating that curcumin could act as a modifier in chemotherapy (Yunos et al. 2011) (Fig. 1).

In addition to the NF-kB transcription factor discussed above, it was found that the expression of many other proteins was altered upon curcumin treatment (Nessa et al. 2012). A total of 59 proteins were found to be associated with platinum resistance in ovarian cancer cells, juxtaposing 2D gel electrophoresis from A2780 tumor model with that of resistant tumor cells (Huq et al. 2014). These included cytoskeletal proteins involved in cell invasion and metastasis, stress-related proteins and molecular chaperones, proteins involved in detoxification and metabolic processes, as well as a set of mRNA processing proteins (for a complete list, refer to Huq et al. 2014). The inhibition of inflammatory cytokines (e.g., TNF-α, IL-1, IL-6) and enzymes (e.g., cyclooxygenase or COX-2 and inducible nitric oxide synthase or iNOS), suppression of angiogenic factors (e.g., vascular endothelial growth factor or VEGF), and modulation of other signaling proteins [e.g., the upregulation of serine/threonine-specific protein kinase (AKT)] have also been reported in curcumin-treated cancer cells (Nessa et al. 2012).

It has also been shown that curcumin-mediated sensitization to cisplatin is associated with its anti-inflammatory activities in resistant cancer cells. It has been revealed that IL-6 reduction in curcumin-treated CAOV3 and SKOV3 ovarian cancer cell lines is accompanied by increased sensitivity to cisplatin, where it is believed that the overproduction of pro-inflammatory cytokines as such by the tumor cells drives drug resistance and tumor invasion (Chan et al. 2003). The production of IL-6 could also induce drug resistance in other cancer cells, including myeloma, lung, breast, prostate, and colon cancer cells. It has been found that multiple molecular targets are affected in IL-6-induced platinum resistance in various tumor cells. Mechanistically, IL-6 could reduce cisplatin accumulation in tumor cells through induction of multidrug-resistant proteins (MRPs) and P-glycoprotein (Pgp) in human hepatoma and renal carcinoma cells, induce the expression of glutathione S-transferase involved in ROS scavenging in breast cancer cells, and enhance the expression of metal-detoxifying protein of metallothionein in ovarian cancer cells. It has also been proposed to be involved in enhancing the invasiveness of ovarian cancer cells, where the induced transcription factor NF-kB results to the expression of additional inflammatory cytokines (Chan et al. 2003).

The modulation of epigenetic regulators could lead to the emergence of cancer cells, where curcumin has also been shown to counteract them (Roy and Mukherjee 2014). In cervical cancer cases, the human papilloma virus is putatively known as

the causative agent of cancer emergence and development, in which curcumin has been effective in suppressing the expression of viral oncoproteins of HPV-E6 and HPV-E7. Curcumin treatment has also been reported to mitigate cell molecular modulations derived from the activity of HPV-E6 and HPV-E7 proteins. Curcumin could inhibit p53 ubiquitin-dependent proteasomal degradation driven by HPV-E6 and act against HPV-E7-reduced pRb functionality. Curcumin could result in cell cycle arrest at the G1/S phase through the modification of regulatory proteins involved in cell cycle. It could inhibit the histone deacetylases (HDACs) that are activated by HPV. The acetylation and upregulation of p53 proteins; increased pRb, p21, and p27; and the corresponding suppression of cylin D1 and CDK4 have also been shown in both cisplatin-sensitive and cisplatin-resistant cancer cell line SiHa upon curcumin treatment, which are known to occur during cancer cell apoptosis (Roy and Mukherjee 2014).

Figure 2 depicts the summary of the abovementioned multiple pathways and molecular targets where curcumin exerts opposing influence over cisplatin-induced resistance. In summary, it appears that curcumin is a modifier of multiple cellular pathways deregulated during cancer cell progression and, therefore, it could contribute to the advanced antiproliferative responses of other chemoagents applied for cervical and ovarian cancers. Such an improvement might hinder the development of resistance toward these agents. Paclitaxel is another chemotherapeutic agent that is administered for different sorts of gynecological cancers, and it has been shown that co-treatment with curcumin and paclitaxel could promote antitumor responses in comparison with paclitaxel alone. In this context, curcumin formulations could alter the expression of multiple cellular proteins and provide resistance to paclitaxel, which are discussed in the following two sections.

4 Molecular Evidences of Synergistic Anticancer Features of Curcumin and Paclitaxel In Vivo

In a study conducted by Sreekanth et al. (Sreekanth et al. 2011), a comprehensive picture of the molecular evidences pertaining to the chemosensitizing effectiveness of liposomal curcumin in paclitaxel therapy has been presented, in which a curcumin liposomal formulation, consisting of phosphatidylcholine and cholesterol, was injected intraperitoneally every other day at a dose of 25 mg/kg to tumor-burden mice treated with paclitaxel (i.p. dose of 10 mg/kg, twice weekly). The tumors were mouse squamous cervical carcinoma model induced by 3-methylcholanthrene (3-MC), a carcinogen, and a xenograft model of a human cervical cancer (HeLa cells) in nonobese diabetic mice having severe combined immunodeficiency (NOD-SCID). It was found that the co-treatment with curcumin and paclitaxel resulted in a synergistic reduction in tumor emergence and tumor volume as compared to the single treatments. To determine the underlying cell and molecular mechanisms, a large collection of molecular targets were examined, including

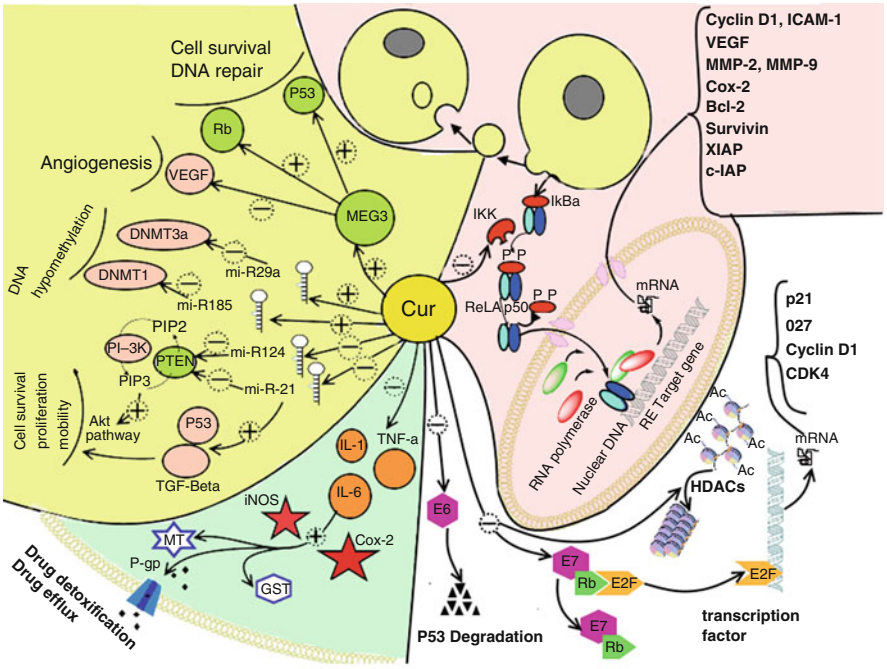

Fig. 2 A summary of the molecular pathways by which curcumin treatment could lead to the sanitization of cancer cells in the cisplatin-induced resistant cancer cells. Curcumin could modulate the content of exosomes that contain molecular messengers driving the development of resistance toward cisplatin in the recipient cells (yellow sect). By inactivating the NF-kB pathway, curcumin could modify many molecular targets that are involved in cancer progression and metastasis (pink sect). Curcumin could reduce inflammatory cytokine secretion and the enzymes producing inflammatory compounds. Through IL-6 downregulation, moreover, curcumin could reduce the expression of metallothionein, glutathione S-transferase and P-glycoproteins, involved in the scavenging of superoxide radicals, drug detoxification, and drug efflux from cells, respectively (Green section). Finally, by counteracting HPV-E6 and HPV-E7 oncoprotein, curcumin could restore the level of antiapoptotic protein p53, inactivate histone deacetylase involved in chromatin condensation, and limit E2F transcription factor translocation to the nucleus, where the expression of target genes drives cell division and growth

the NF-kB activation status and the expression of NF-kB target genes involved in inflammation and tumor aggressiveness (such as Cox-2, ICAM-1, cyclin D1, VEGF, MMP-2, and MMP-9); the expression of antiapoptotic proteins that are transactivated by NF-kB (Bcl-2, c-IA P1, survivin, and XIAP); the expression and activation of three vital MAP kinases – i.e., c-Jun-NH2 kinase (JNK), extracellular signal-regulated protein kinase (ERK), and p38; as well as the cleavage and activity of procaspases 9, 8, 7, and 3. All these molecular evidences indicated that curcumin could tackle cancerous tumors by modulating various cell signaling pathways and kinases (Sreekanth et al. 2011), which could promote the efficiency of treatment in combination with paclitaxel. Similarly, it has been reported that the combination of curcumin (5 μM) and paclitaxel (5 nM) could augment anticancer responses more

efficiently than paclitaxel alone in HeLa cells, without any synergistic effect on normal cervical cells, the 293 cell line (Bava et al. 2005). It has been proposed that the curcumin-induced sensitization to paclitaxel could be related to the opposite effect of curcumin on the NF-kB activation status. It was identified that curcumin could suppress NF-kB and Akt pathways, augment the activation of caspases and cytochrome c release. Moreover, it was discovered that curcumin opposed the NF-kB activation induced by paclitaxel and reduced the phosphorylation of Akt, which is a survival signal regulated by NF-kB (Bava et al. 2005). However, at low concentrations (5 μM), curcumin could not interfere with the tubulin-polymerization action of paclitaxel and could not further augment the cell cycle protein Cdc2, which increased during paclitaxel-induced mitotic arrest. This indicates that paclitaxel-induced resensitization by curcumin is independent of the classic function of taxols (or paclitaxel).

To exert the abovementioned influences in cancer cells in vivo, it is required to improve the efficiency of drug delivery to these cells through the application of various drug delivery systems. Curcumin and paclitaxel have been shown to have poor pharmacokinetic profiles, which necessitates the use of appropriate formulations to help in attaining the required dose of the drug at tumor sites.

5 Curcumin and Paclitaxel in the Form of Nanoformulations

According to the recent version of the National Comprehensive Cancer Network (NCCN) guidelines for cervical cancer, cisplatin and paclitaxel are recommended as the first-line combination therapy for cervical cancer metastasis (Li et al. 2017). However, the drug-related side effects (nephrotoxicity and hepatotoxicity) and development of resistance to the therapy have raised serious concerns in clinics (Li et al. 2017). As mentioned for cisplatin, some similar mechanisms are also accountable for the development of paclitaxel-induced resistance, including the upregulation of transmembrane-associated multidrug resistance proteins (P-gp, MRP-1, and ABCG2) and activation of major cell signaling pathways, most importantly, the NF-kB upregulation at the heart of many cellular responses related to cancer cell evasion. The upregulation of cytoprotective pathways like Akt and mitogen-activated protein kinase (MAPK), changes in the frequency of b-tubulin isotypes (Giannakakou et al. 1997; Yusuf et al. 2003), and changes in topoisomerase II (Topo IIa) activity and GST activities have also been reported for paclitaxel-induced resistance. Under these conditions, finding a chemopreventive agent like curcumin that could concomitantly confer cancer cell's drug resensitization is the rational approach in dealing with invasive tumors. It has been shown that not only can curcumin reverse the multidrug resistance of cancer cells, it also could

reduce the nephrotoxicity of paclitaxel, thereby enhancing the chemotherapeutic window. Similar findings have also been presumed for the paclitaxel and curcumin combination therapy, especially in the forms of various nanoformulations to enhance their stability and tumor delivery of these hydrophobic agents.

Paclitaxelis is commonly prescribed against a wide spectrum of epithelial cancers (Sreekanth et al. 2011), where the hydrophobic nature of the drug promotes drug assimilation into tissues. However, when the drug is intended to reach a local tumor far from the injection site, hydrophobic chemoagents are required to be loaded in a vehicle with a hydrophilic outer layer to prevent the drug from rapid elimination and uptake by neighboring cells. The same strategy is also needed for the hydrophobic curcumin, where it is assumed to impart chemoprevention and chemo-sensitization in normal tissues and tumors, respectively (Ganta and Amiji 2009).

Apart from cellular mechanisms of drug resistance and in vivo poor drug distribution, the high interstitial fluid pressure prevents the drug from moving toward cancer cells, where the presentation of the drug in the form of nanoformulation could overcome it (Abouzeid et al. 2014). Moreover, many researchers have attempted to apply various formulations, sometimes with excipients that impart some cellular modulating effect resulting to facilitated cell apoptosis (Ganta and Amiji 2009). For instance, it was reported that poly (ethylene oxide)-modified poly-(epsilon-caprolactone) (PEO-PCL) nanoparticles encapsulating paclitaxel (PTX) and C6-ceramide, a lipid potentiating the apoptotic signal responses, could enhance both the efficiency of paclitaxel transfer to tumor and anticancer responses in SKOV3 human ovarian cancer cells in xenograft tumors, inoculated to female nu/nu mice. Through the encapsulation of curcumin along with paclitaxel in flaxseed oil containing nano-emulsion, it was found that curcumin could block NF-kB pathways and ABC transporter expression in both the wild-type and paclitaxel-resistant SKOV3 cells and enhance the death of cancer cells (Ganta and Amiji 2009). Furthermore, it has also been shown that the nano-emulsion, rich in omega-3 and omega-6 unsaturated fatty acids, promotes the cellular delivery of curcumin and paclitaxel. Although the author did not present any data regarding the residence time of curcumin and paclitaxel in the serum or blood and only focused on the mitigation of MDR features and cellular apoptosis, it was found that the nanoformulation was physically stable in size (~150 nm in diameter), and it could entrap large concentrations of paclitaxel and curcumin. Since both curcumin and paclitaxel are hydrophobic in nature, it was proposed that the inner oil phase could solubilize them and the outer hydrophilic shell of the droplets due to the presence of dense PEG chains, could enhance their physical stability, and apparently would promote drug delivery to tumor, if they are injected in vivo through the circulatory system (Ganta and Amiji 2009).

The improved solubility and stability of paclitaxel and curcumin together with the slow drug release feature have also been reported for other types of nanoformulations, where the entrapment of drug in nanoparticles bypasses the drug efflux course regulated by MDR proteins and curcumin downregulates MDR proteins such as P-gp. For instance, Liu et al. developed a complex system of PLGA-phospholipid-PEG nanoparticles (PLGA stands for poly-[lactic-co-glycolic]-acid polymer) from paclitaxel and curcumin, where nanoparticles comprised a PLGA core containing the

drug and curcumin, the thin phospholipid interfacial layer, and the PEG hydrophilic outer layer. It has been found out that this system was more effective in controlling drug release compared to simple PLGA systems and could retain paclitaxel up to 72 h in PBS. Moreover, it has also been shown that the PLGA nanoparticles containing curcumin and paclitaxel are more efficacious in decreasing the expression of P-gp compared to free curcumin (Liu et al. 2016). Polyethylene glycol-phosphatidylethanolamine (PEG-PE) micelles targeted with transferrin (TF) are another example of nanoparticles that have been used to promote paclitaxel and curcumin delivery to tumor sites and enhance the efficacy of tumor therapy. These micelles were evaluated against resistant ovarian cancers in a cancer cell culture grown in multicellular three-dimensional spheroids and in vivo tumors. When paclitaxel was co-delivered with curcumin in the form of micelles, an increase was recorded in the cytotoxicity of paclitaxel. In addition, transferrin modification of the micelles could assist in significantly deeper micelle penetration into the spheroids and tumors (Sarisozen et al. 2014).

These studies all stated that curcumin could significantly enhance the antitumor potential of paclitaxel against resistant cancer cells, when curcumin is added into the chemotherapy regimen. Radiotherapy is also applied along with platinum-based agents in the treatment of advanced ovarian and cervical cancers. As previously discussed, curcumin could overcome these drug-induced resistances, and it has been shown to overcome radiotherapy-induced resistance as well.

6 The Radiosensitizing Function of Curcumin in Gynecological Cancers

Radiation therapy is an efficient intervention to control cancer cell growth evasion and metastasis, especially when they are combined with chemotherapeutic agents capable of inducing radiosensitization such as carboplatin, cisplatin, 5-fluorouracil, ifosfamide, etoposide, and most taxanes. For instance, chemotherapy involving cisplatin and 5-fluorouracil is the present chemotherapy regimen for patients suffering stage IIA to IVA cervical cancer, which are administered together with radiotherapy. Although the combined chemoradiotherapy improves survival rate, such combination also increases the probability of chemotherapy-related toxicities including gastrointestinal and hematological toxicities. In this regard, the introduction of a safe agent like curcumin that is capable of inducing radiosensitization without a significant toxicity on normal tissues could enhance the therapeutic window and bring benefits for patients with advanced cervical cancers. Phase I clinical trials proved that the oral administration of curcumin is totally safe up to 12,000 mg/day (Javvadi et al. 2008; Lao et al. 2006) and could reduce histological lesions related to cancer evasion in some patients (Cheng et al. 2001).

It has been shown that pretreatment with curcumin could enhance the cell growth-inhibiting impact of radiotherapy in cervical carcinoma cells (HeLa and SiHa cells) and spare the normal fibroblast the trouble of increased radiation toxicity through a

modulating intracellular ROS level (Javvadi et al. 2008). This is of importance as it has been shown that curcumin could act differently on normal and cancer cells, encouraging ROS generation in cancer cells while acting as antioxidant in normal cells. The elevated ROS in cancer cells could lead to the long-term activation of extracellular signal-regulated kinases (ERK1/ERK2) which encourage radiosensitization (Javvadi et al. 2008). Conversely, no evidence of NF-kB and Akt involvement in improving the irradiation therapy of cervical cancer cells was found on curcumin treatment, although curcumin has been shown to reduce the activity of NF-kB and Akt in prostate and colorectal cancers (Javvadi et al. 2008). Moreover, as explained above, curcumin has been shown to resensitize paclitaxel-induced resistant cells through the downregulation of NF-kB and Akt signaling pathways. These studies revealed that apparently, the downregulating effect of curcumin on these pathways is either dependent on cell type or therapy regime, although the implication of NF-kB and Akt activation in cancer cell survival has been firmly established. What is consistent is that the curcumin prooxidant activity could promote the anticancer effect of irradiation by contributing to induced ROS generation in cancer cells, regardless of cancer cell type or therapy regimen.

Following their studies on the function of ROS in inducing cancer cell apoptosis (Javvadi et al. 2010; Javvadi et al. 2008), they pinpointed thioredoxin reductase-1 (TxnRd1), a cytosolic antioxidant enzyme scavenging IR-induced ROS, to mediate curcumin-sensitizing effect on irradiated cancer cells. They confirmed that the curcumin-mediated inhibition of TxnRd1 activity could result in increased radiosensitization in cancer cells, since TxnRd1 overexpression has been shown to terminate radiosensitization in cancer cells, in response to curcumin treatment (Fig. 3).

Taken together, the pleiotropic function of curcumin on cancer cells and its diverse utility to be introduced in the treating schedule of different types of gynecological tumors, where curcumin by affecting a wide variety of cell signaling modulators, could counteract the phenomena responsible for the development of chemotherapy and/or IR-induced resistance in cancer cells, which is very common in these cancers. However, as earlier mentioned, the cancer-targeted functions of curcumin occur at high concentrations which are often very difficult to reach in tumors in vivo; therefore, an alternative set of investigations has focused on enhancing the efficiency of curcumin in cancer cell treatment.

7 Approaches to Enhance Curcumin Anticancer Efficacy

Although curcumin's multi-therapeutic function has drawn many researchers to investigate this polyphenolic compound, the insufficient therapeutic benefits of curcumin have prompted many researchers to look for various approaches to promote the anticancer potential of curcumin (Table 1). These include a set of investigations to enhance the pharmacokinetic profile of curcumin using various formulations, examination of curcumin analogs with the hope to discover derivatives

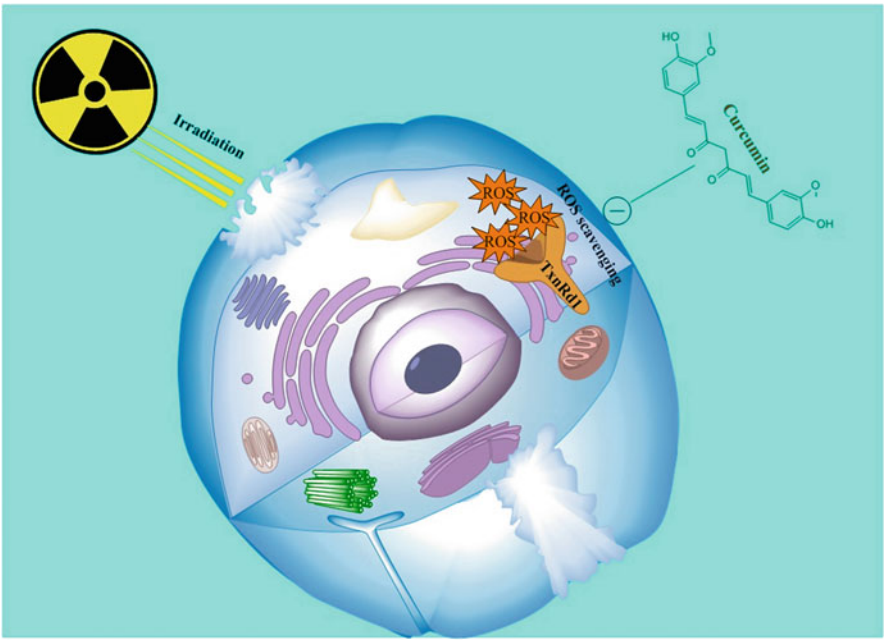

Fig. 3 Curcumin-mediated radiosensitization in gynecological cancers. Curcumin can sensitize gynecological cancers to radiation therapy through inhibiting thioredoxin reductase-1 (TxnRd1) that is a cytosolic antioxidant enzyme scavenging IR-induced ROS

with more anticancer potency, and basic studies to unravel the molecular pathways modulated with curcumin treatment in order to find a combination therapy capable of tackling various malignancies.

8 Exploitation of Molecular Pathways Modulated by Curcumin in Gynecological Cancers

It has been reported that the elevated levels of intracellular sphingosine/ceramides could promote curcumin-induced inhibition of cell growth and apoptosis in ovarian cancer cells (Yang et al. 2012). Sphingosine-1-phosphate, sphingosine, and ceramides are the metabolites of sphingolipids acting as messengers in cancer cell progression. While sphingosine/ceramides encourage cell apoptosis, sphingosine-1-phosphate potentiates cancer cell survival, and the balance between sphingosine/ceramides and sphingosine-1-phosphate determines the fate of cells. It has been shown that the curcumin-mediated cell apoptosis in ovarian cancer cells could be enhanced by the inhibition of sphingosine kinase-1 (SphK1) by the pharmacological inhibitor (SB 203580). Moreover, the inhibition of ceramide production by fumonisin B1 terminated the ShK1-induced cancer cell growth. As a result, the

Table 1 Rational approaches to overcome curcumin insufficient efficacy in cervical and ovarian cancer cells

Curcumin derivatives	Description	Ref.
3,5-bis (2-flurobenzylidene) piperidin-4-one	Increased cytotoxicity, inhibition of NF-kB nuclear translocation, TNF-a-induced IkB phosphorylation and degradation, and IKK inactivation	Kasinski et al. (2008)
1,5-bis(22-hydroxyl)21,4-pentadiene	In silico study proposed improved interaction with HPV16-E6 protein active site and p53 restoration	Singh and Misra (2013)
1,5-bis(2-hydroxyphenyl)2 1,4-pentadiene-3-one	Increased cytotoxicity, DNA fragmentation, and decreased HPV16- and HPV18-associated E6 and E6 oncoproteins	Wang et al. (2011)
Dimethoxycurcumin	Increased cytotoxicity and downregulation of cyclin D1	Wang et al. (2011)
Curcumin conjugation		
Curcumin-piperic acid	In silico studies assumed increased toxicity in cervical cancers	Mishra et al. (2005b)
Dipiperoyl and diglycinoyl curcumin	Increased cytotoxicity and ROS generation in histiocytoma cells, but it may be efficient against cervical and ovarian cancer cells?	Mishra et al. (2005a)
Curcumin-chlorogenic acid	In silico study proposed increased cytotoxicity and HPV15-E6 downregulation	Singh and Misra (2013)
Curcumin nanoformulations		
Liposomal curcumin	Including DDAB, cholesterol, and a nonionic surfactant like Montanov82 increased cytotoxicity and cell penetration of curcumin	Saengkrit et al. (2014)
Niosomal curcumin	Including nonionic surfactants of Span80, Tween80, and Poloxamer 188 enhanced cytotoxicity and controlled curcumin release	Singh and Misra (2013)
Milk-derived exosome	Tumor growth inhibition following oral administration	Aqil et al. (2017)
PLGA nanoparticles conjugated to anti-Pgp proteins	Targeted delivery of curcumin to cervical cancer cell line of KB-V1, expressing highly P-gp	Punfa et al. (2012)
Naïve PLGA nanoparticles	Enhanced cell apoptosis, reduced tumor burden, and suppressed HPV-E6 and HPV-E7 oncoprotein expression	Zaman et al. (2016)
Fe_3O_4 nanoparticles coated layer by layer with dextran and polylysine films	Enhanced curcumin entrapment in the particles, increased cell penetration, and enhanced cytotoxicity	Kumar et al. (2014) and Mancarella et al. (2015)

balance was shifted toward ceramide accumulation which pushes cancer cells toward apoptosis and may be useful to cumulatively enhance antiproliferative response in combination with curcumin.

In addition to ceramide accumulation, curcumin has been shown to result in the modulations of other cell signaling molecules. It has been found that the activation of AMP-activated protein kinase (AMPK) could induce cell death and suppress cell progression in a variety of cancer cells, and CaOV3 ovarian cancer cell pretreatment with an AMPK inhibitor attenuates curcumin-induced cell death. Moreover, p38 activation and Akt inhibition are other changes which occur in apoptotic cancer cells treated with curcumin. Considering all the mentioned cell signaling effectors, every agent that could contribute to these modulations has been proven to enhance the anticancer potential of curcumin (Pan et al. 2008), and maybe their topical administration combined with curcumin as an ointment could exhibit therapeutic response in gynecological cancers that is worth being investigated.

9 Curcumin Derivatives

Molecular docking studies of curcumin analogs with various functional group substitutions were conducted on prospective targets like EGFR tyrosine kinases, where the potential analogs were tested on various cancer cells with the hope of unraveling the relationship between curcumin structure and its activity (Sharma et al. 2015). Sometimes, these studies culminate in the discovery of more potent analogs as compared to curcumin.

As discussed previously, the NF-kB signaling pathway plays a central role in governing cancer cell progression and metastasis, where curcumin has exhibited cancer-therapeutic values via NF-kB inactivation. In this regard, Kasinski et al. (2008) presented a synthetic monoketone analog of curcumin-termed 3,5-bis(2-flurobenzylidene) piperidin-4-one – with enhanced anticancer activity against a variety of cancer cells, including ovarian and cervical cancer cells. In comparison with curcumin, this analog exhibited enhanced cancer cell growth inhibition up to tenfold in comparison with curcumin. Likewise, the analog rapidly inhibited the nuclear translocation of NF-kB at a dose tenfold lower than that of curcumin. In mechanism, NF-kB inhibition was found to result from the strong analog-IKK interaction which resulted in cancer cell apoptosis.

1,5-bis(22-hydroxyl)21,4-pentadiene, as a curcumin derivative lacking a diketone site and methoxy functional groups, has been found to exert more antiproliferative effect than curcumin on different cervical cancer cells (Singh and Misra 2013). The curcumin analog 1,5-bis(2-hydroxyphenyl)2 1,4-pentadiene-3-one could induce apoptosis more efficiently than curcumin, and it downregulates the expression of oncogenes E6 and E7 in HPV16- and HPV18-infected cervical cancer cells, known as risk factors of cervical cancers (Paulraj et al. 2015). It has been shown that dimethoxycurcumin is a more stable analog of curcumin in physiological media and could exert improved anticancer effect on multiple cervical cancer cells

(Teymouri et al. 2018). These are shining examples of curcumin derivatives with enhanced efficacy, which begin with in silico studies on curcumin analogs with successful in vitro improved potency. However, the translation of such a potency to a real clinical setting is yet to be fully fulfilled. The low water stability and in vivo bioavailability of curcumin are the main setbacks of curcumin therapy. It has been shown that curcumin conjugation to hydrophilic molecules like amino acid, piperic acid, and chlorogenic acid could increase the stability of curcumin in physiological media (Singh and Misra 2013). Curcumin conjugation to piperic acid could enhance the cell penetrability of curcumin, and its administration with chlorogenic acid might fully restrict cancer cell proliferation in estrogen-responsive cervical cancer cells, where curcumin has been found to be partially effective in comparison (Mishra et al. 2005b; Singh and Misra 2013).

Apart from the conjugation of curcumin to small molecules, it has been shown that curcumin entrapment in various nanoparticulate systems could improve its efficacy and tissue distribution in cervical and ovarian cancer cells, as discussed in the following section.

10 Curcumin Nanoformulations

So far, a range of beneficial functions of curcumin has been presented, although much diverse biological actions remained unstated as they are out of scope in this review (Panahi et al. 2018; Teymouri et al. 2018; Teymouri et al. 2017). However, as already stated, there are some limitations associated with the therapeutic translation of curcumin in clinics such as low stability at physiological pH, hydrophobic nature, rapid elimination from circulation, hepatic metabolism, etc. (Aqil et al. 2017; Garcea et al. 2004). To overcome these limitations, there are numerous investigations, in which various lipid-based formulations and polymeric-based nanoparticles are utilized for curcumin delivery (Abouzeid et al. 2014; Aqil et al. 2017; Ganta and Amiji 2009; Kumar et al. 2014; Punfa et al. 2012; Saengkrit et al. 2014; Sarisozen et al. 2014; Xu et al. 2016). The list is very long, but as the scope of the current review is restricted to "curcumin in treating gynecological cancers," this paper presented curcumin-loaded nanoparticles that have been tested against these cancers.

It has been shown that lipid-based nanoparticles, including liposomes and niosomes, enhance curcumin stability in aqueous medium as they could accommodate hydrophobic curcumin in their membrane and prevent curcumin from degradation and precipitation (Saengkrit et al. 2014). In this regard, it has been shown that the nonionic surfactant (Montanov82®) could decrease liposomal curcumin agglomeration and restrict liposomal enlargement and precipitation in long-term storage. It could also enhance curcumin entrapment efficiency in liposomes. Likewise, the addition of cholesterol has also been reported to improve the entrapment efficiency of curcumin and limit the release of curcumin. Although introducing didecyldimethylammonium bromide (DDAB) imparts a positive charge to liposomes that increases cell uptake in vitro, positively charged liposomes have been

determined to be rapidly removed by the neighboring blood cells at the injection site when they are intravenously administered. As a result, special consideration should be given to the route intended for liposomal curcumin administration. If liposomal curcumin is administered intravenously, where the liposomes are required to travel a long distance before they reach tumor and accumulate there, negative-to-neutral-charged liposomes would be probably more successful in reaching the tumor (Teymouri et al. 2016; Teymouri et al. 2015). However, when the intention is to enhance curcumin delivery via topical application, for example, as cream or an ointment in cervical cancers, positively charged liposomal curcumin would promote curcumin delivery to tissues as well as the therapeutic outcome due to increasing cell internalization of liposomal curcumin (Debata et al. 2013; Song and Kim 2006). Another issue that should be taken carefully into account is that the DDAB-containing liposomes per se have been proven toxic to both cancerous and normal cells. DDAB together with DOPE at DDAB/DOPE at 40 μM have been found to be potentially harmful to CasKi cells. It is necessary to investigate whether these liposomal components will cause unwanted suffering before deciding about their application in clinics, so as to avoid the possible undesired side effects (Saengkrit et al. 2014).

The curcumin-niosome system has also been shown to possess high entrapment efficiency and lead to superior apoptotic rate in ovarian cancer A2780 cells compared with the free curcumin dispersed in dimethyl sulfoxide (Xu et al. 2016). The niosome system consisted of a nonionic surfactant of Span 80, Tween 80, and Poloxamer 80 plus additives of cholesterol was examined in terms of entrapment efficiency and curcumin delivery. It was found that the system is a highly superior version of liposomal curcumin in terms of curcumin entrapment efficiency. However, whether niosomal curcumin would be a safer and more successful delivery system, impart improved pharmacokinetic profiles, and result in higher tumor accumulation of curcumin than liposomal curcumin is an interesting contrastive study to be undertaken. Moreover, the surfactant-related hemolysis should be considered when optimizing these formulations of curcumin (Xu et al. 2016). Given such serious complications that liposome or noisome ingredients might carry for clinical application, searching for drug delivery systems that are perfectly safe is highly desirable.

Milk-derived exosomes loaded with curcumin have been demonstrated to surpass the low bioavailability of oral curcumin and resulted in three to five times increased delivery of curcumin to various organs, as compared to free curcumin (Aqil et al. 2017). The exosomal curcumin exhibited increased antiproliferative and anti-inflammatory activity against multiple cancer cell lines, including breast, lung, and cervical cancer cells. The underlying mechanism for the promoted efficacy of curcumin might lie in the fact that exosomes enter via endocytosis and go through the endosomal pathway, where curcumin activity would be preserved in the desirable acidic media of endosomes. Apart from this, exosomes alone have been shown to possess a moderate intrinsic antiproliferative and anti-inflammatory activity leading to tumor growth inhibition, which is hardly believed to be achieved by immune factors, miRNAs, and proteins derived from exosomes. Furthermore, high

contents of proteins would provide a vast area of hydrophobic domains on the surfaces of exosomes for the lipophilic curcumin to interact and trap in exosomes. These exosomes were shown to protect curcumin from degradation throughout the gastrointestinal tract and enhance curcumin intake, indicating that exosomal curcumins are highly successful oral formulations (Aqil et al. 2017).

Besides lipid-based nanoparticles, various polymer-based nanoparticles have been utilized to achieve the prolonged stability and enhanced efficacy of curcumin. For instance, PLGA-based curcumin nanoparticles have been reported to significantly decrease the tumor volume in an orthotopic mouse model of cervical cancer when it is injected intratumorally. The reduction of oncogenic miR-21, suppression of beta-catenin, and abrogation of E6/E7 HPV oncoproteins were found in tumor cells treated with curcumin-containing PLGA nanoparticles (Zaman et al. 2016). The surface modification of curcumin-containing PLGA nanoparticles like the attachment of anti-P-glycoproteins further enhanced curcumin delivery and cytotoxicity in the resistant cells overexpressing P-gp (Punfa et al. 2012). Poly(2-hydroxyethyl methacrylate) [PHEMA] with hydrophilic surface and Fe_3O_4 superparamagnetic nanoparticles (SPION) coated layer by layer with positively charged Poly(L-lysine) and negatively charged dextran is another example of polymer-based nanoparticles that has been applied for improving curcumin delivery to cervical cancer cells (Kumar et al. 2014; Mancarella et al. 2015). There are many other nanoparticulate systems and formulations that have been applied for improving curcumin delivery to various cancer cells, some tested in vitro and others in vivo (Teymouri et al. 2017). However, to determine which of these systems are fully applicable in clinic settings requires more in-depth investigation of curcumin nanoparticulate implications in cervical cancer tumors.

11 Conclusion

The current review attempted to present an appropriate assortment of reports on the therapeutic and adjuvant potential of curcumin for resistant cancer malignancies, by placing emphasis on the studies conducted on gynecological cancers. The current chemotherapy and radiotherapy have frequently been reported to face refractory tumors upon relapse in ovarian and cervical cancers with a minor chance of treatment. In this regard, multiple cell and molecular evidences imply that curcumin could indeed resensitize the cells to chemotherapeutics and irradiation as evidenced by the enhanced therapeutic index of these regimens, when they are administered in combination with curcumin. These include suppression of the pathways involved in DNA damage repair, the inactivation of major transcription factors capable of promoting cell survival like NF-kB, AP-1, intracellular ROS elevation, down-regulation of MDR-related proteins, and inhibition of inflammatory responses. Apart from these potential benefits of curcumin combination therapy, it was discussed that curcumin has the potential to act as an antitumor agent alone in these cancer types. Finally, various strategies of enhancing the therapeutic potency of curcumin ranging

from alterations of curcumin molecular structure and curcumin encapsulation in varying nanoformulations have been presented in a hope to discover a more target-directed approach to tumor eradication. Curcumin concentration in tissues and tumor is a defining factor with respect to the intrinsic ROS scavenging potency of cells. Therefore, it is highly important to investigate the therapeutic benefits of administering a given curcumin formulation combined with a chemodrug formulation followed by radiotherapy, to harness the cancer-treating potential of curcumin at most. Studies in this direction are highly necessary to translate the in vitro features of curcumin successfully into clinics, in managing the treatment of resistant cancer tumors of gynecological cancers.

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