Therapeutic role of curcumin and its novel formulations in gynecological cancers

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Abstract

Gynecological cancers are among the leading causes of cancer-associated mortality worldwide. While the number of cases are rising, current therapeutic approaches are not efficient enough. There are considerable side-effects as well as treatment resistant types. In addition, which all make the treatment complicated for afflicted cases. Therefore, in order to improve efficacy of the treatment process and patients’ quality of life, searching for novel adjuvant treatments is highly warranted. Curcumin, a promising natural compound, is endowed with numerous therapeutic potentials including significant anticancer effects. Recently, various investigations have demonstrated the anticancer effects of curcumin and its novel analogues on gynecological cancers. Moreover, novel formulations of curcumin have resulted in further propitious effects. This review discusses these studies and highlights the possible underlying mechanisms of the observed effects.

Keywords: Curcumin, Nanocurcumin, Endometrial cancer, Ovarian cancer, Cervical cancer, Curcumin derivatives, Natural compound

Background

Natural compounds like curcumin, epigallocatechin gallate (EGCG), quersetin, and resveratrol, have been shown to modulate some genetic and epigenetic mechanisms, which may increase sensitivity of cancer cells to conventional agents and thus inhibit tumor growth [1, 2]. Curcumin, the main bioactive ingredient of turmeric, has been revealed to possess various therapeutic potentials, such as anti-tumor [3, 4], anti-atherosclerotic [5, 6], anti-microbial [7], anti-oxidant [8], and anti-inflammatory [9–11]. A wide variety of molecular targets have been reported for curcumin, including some transcription factors, gene modulators, kinases, growth factors, and cell membrane receptors [12–16]. Due to its various and pleiotropic functions, increasing number of studies has been focused on curcumin, specifically in malignancies.

Numerous investigations have shown that curcumin acts as a beneficial adjuvant and chemopreventive agent for cancer [17]. Notably, human studies have demonstrated the tolerability, safety and anti-carcinogenic ability of this compound for humans [13, 14]. The promising outcome of these studies has helped to raise the hope for a brighter future in cancer treatment.

Gynecologic cancers include an unlimited and abnormal cell growth, developing in female reproductive system, such as endometrial, ovarian, cervical, primary peritoneal, vulvar and vaginal malignancies. According to reports, more than 1 million patients were newly diagnosed, and more than 580 000 mortalities occurred because of endometrial, cervical, and ovary cancers in...
2018 [15]. While endometrial and cervical cancers are diagnosed in early stages, ovarian cancer is usually diagnosed in more advanced stages, when treatment is more challenging [16, 18]. Despite all the developments in cancer therapy and emergence of novel treatments, these cancers still have considerable mortality rates. Therefore, introducing novel agents which can potentially improve the therapeutic outcome for these affected patients is highly needed. Here, in this review we focus on current evidence for the efficacy of curcumin and its novel formulations in gynecological cancers.

The role of curcumin in gynecological cancers

In terms of gynecological cancers, curcumin has been shown to modify the effects of risk factors during the course of cancer progression and since the very beginning. Some of those well-known risk factors are obesity, smoking, estrogen and human papillomavirus (HPV) infections [19, 20]. Interestingly, curcumin has been shown to reduce estrogen synthesis, estrogen-derived DNA damage, inflammation in the adipose tissue, and inhibit E6 and E7 onco-protein expression in HPV [19].

According to in vitro studies, curcumin can prevent invasion and migration of endometrial carcinoma (EC) cell and plays an anti-metastatic role due to a reduction in the production and fuction of matrix metalloproteinases-2 and -9 (MMP-2 and MMP-9). Degradation of tumor extracellular matrix by these enzymes is a possible cause of metastasis and invasion of myometrial cancer to lymph node in type II EC. curcumin has been shown to suppress the ERK signaling pathway and decrease the expression of these enzymes [21].

Curcumin has been reported to induce apoptosis in ovarian cancer cells, through P53-independent pathway, but similar to wild-type P53 cells. Curcumin-treated HEY cells showed poly (ADP-ribose)polymerase-1 cleavage, DNA fragmentation, nuclear fragmentation and condensation, indicating the induction of cell apoptosis. Moreover, curcumin is able to induce apoptosis through both intrinsic and extrinsic mechanisms. The expression of antiapoptotic regulators, survivin and Bcl-2, was decreased following an increase in the activity of p38 protein, mitogen-activated protein kinases (MAPK). The anticancer cell death caused by curcumin was reported to also occur through suppressing the prosurvival Akt signaling in different ovarian cancer cells [22]. The expression of urokinase-type plasminogen activator (uPA) was reportedly blocked by curcumin in highly invasive human ovarian cancer cell line, HRA, which has a role in cancer metastasis. uPA is a serine protease expressed via Src-MAPK/ERK-AP-1 and Src-MAPK/ERK-P13K/ Akt-NF-kB pathways in response to TGF-B1, where curcumin inhibits the AP-1 complex formation [22]. Accordingly, curcumin can potentially improve the outcome in advanced gynecological cancers impeding cancer invasion and progression [23]. In the following sections, we discuss recent investigations on curcumin therapy for endometrial, cervical and ovarian cancer.

Curcumin and endometrial cancer

Endometrial cancer (EC), the most frequent malignant tumor of the genital tract in females, occurs in peri- and postmenopausal women [24, 25]. It is estimated that more than 50,000 new cases were diagnosed, and about 8,500 cases were expired due to this malignancy in the US in 2014. Recently, due to the life style changes, gynecological cancers are causing increasing mortalities [26]. The majority of affected individuals are diagnosed early and usually cured with surgery alone or in combination with radiotherapy [27]. However, mortality rate of this cancer has experienced a sharper rise than its incidence over the last decades [28–31]. Despite all the development in therapeutic strategies for this malignancy, end-stage patients face poor prognoses, and the 5-year survival rate is as low as 25–45% [26]. Additionally, the current therapeutic approaches are not effective for 15% of patients who show aggressive phenotype [27].

It was reported that in a 30-day in vivo investigation, daily intraperitoneal administration of 50 mg/kg curcumin decreased the volume of tumor five-fold in comparison with that in vehicle-treated animals [32]. Sirohi and his colleagues also carried out in vitro experiments utilizing both HEC-1B and Ishikawa cells and indicated that curcumin exhibits its anti-migratory impacts via increasing the Slit2 expression [32]. Slit2 induction downregulated the expression of migratory proteins, including the matrix metalloproteases MMP2/9, stromal cell-derived factor-1 (SDF-1), and CXCR4 (chemokine receptor 4) in EC cells [32]. This study indicated that curcumin suppresses tumor growth and inhibits proliferation of EC cells [32]. It also mediates ROS-induced apoptosis and shows inhibitory effects on migration of Hec-1B and Ishikawa cells through Slit-2-induced downregulation of MMP-2 and -9, SDF-1, and CXCR4 [32].

Androgen receptors (ARs) are ligand-dependent nuclear transcription factors which have been related to various tumors types, including endometrial, liver, bladder, and prostate tumors [33]. It has been demonstrated that curcumin dose- and time-dependently increases apoptosis and blocks proliferation of EC cell line RL-952 [34]. Curcumin also targeted Wnt pathway, which plays a crucial role in tumor proliferation and progression, and subsequently declined the expression of AR in cancer cells [34]. In a research carried out by Chen et al. [21], it was shown that curcumin inhibits the invasion and migration of endometrial carcinoma cells. Additionally, it decreased the proteinase activity and matrix metalloproteinase (MMP)-2 and -9 expression [21].
Curcumin in combination with ERK inhibitor U0126 synergistically reduced the expression of MMP-2/-9, leading to inhibit the cancer cells invasion [35]. Sun et al. illustrated that, in addition to suppression of EC cell invasion via downregulating MMP-2, curcumin inhibits their proliferation as well [35]. Feng et al. revealed that curcumin suppresses the apoptosis and proliferation of human endometrial carcinoma cells through downregulating the expression of AR via Wnt pathway [34]. Table 1 shows the available data about the effects of curcumin in EC therapy.

**Curcumin and cervical cancer**
Cervical cancer is the third most prevalent malignancy and the fourth leading cause of cancer-related mortality in women [44]. Nowadays, its incidence is triggering the younger females [45]. Patients who are still at early stages have good prognosis and successfully respond to conventional treatments, including chemoradiation and/or surgery [46]. While these standard therapies could cause serious damages to vaginal and ovarian functions [47], patients with extrapelvic engagement have 5-year survival rate of 17%, and in women with recurrent disease this rate is less than 5% [48]. Human papilloma virus (HPV) infection is the initial step in most of the cervical cancer cases [49]. In addition to chronic infection with HPV, smoke carcinogen (benzo[a]pyrene) and cigarette smoking are considered as major risk factors related to cervical cancer [50, 51].

Curcumin has revealed concentration-dependent chemotherapeutic and chemopreventive impacts in a number of investigations [52]. Curcumin exerts cytotoxic effects in cervical cancer cells in a time- and dose-dependent approach, especially in HPV-infected cells [53]. It has been confirmed that, via selectively suppressing activator protein 1 (AP-1) activity, curcumin

| **Table 1** Performed studies on curcumin and EC therapy |
|----------------------------------------------------------|
| **Type of curcumin** | **Dose** | **Target(s)** | **Effect(s)** | **Type of cell line** |
| Curcumin | 6 μM | CTGF, MMP-2, -9 Slit-2, CXCR4, SDF-1, MMP9 | Induction of apoptosis | Ishikawa |
| | 6 μM for 48h | - | Inhibition of tumor proliferation, migration, invasion, and growth | Ishikawa Hec-1B |
| | 50 mg/kg | - | Induction of ROS production | Ishikawa cell |
| | 30 μmol/L | MMP-2 | Curcumin can suppress invasion and proliferation of endometrial cancer cell | Ishikawa |
| | 50 μM | STAT-3 PIAS-3 | Curcumin can inhibit JAK-STAT signaling through PIAS-3 activation | RL95-2 Ishikawa OVCA cell |
| | 30 μM for 120h | TREK1 | Curcumin has an antiproliferative effect on endometrial cells. | Ishikawa |
| | 30 μM | MMP-2, -9 ERK | Curcumin can suppress invasion and proliferation of endometrial cancer cells through inhibition of MMP-2 and MMP-9 and the ERK signaling pathway | HEC-1B |
| | 300 mg/kg.d | Bcl-2 | Curcumin inhibits the Bcl-2 expression | - |
| | 40 to 60 μM for 3h | Ets-1 Bcl-2 | Curcumin can decrease the Bcl-2 and Ets-1 expression and induces apoptosis. | HEC-1A |
| | 100 μM/L | Androgen receptor (AR) | Curcumin can suppress apoptosis and proliferation of endometrial cancer cells through decreasing expression of androgen receptor | NA |
| | 112.5 μM | - | Curcumin has an antiproliferative effect on MCF-7, MG-63 and MDA-MB-231 cells | MDA-MB-231 MCF-7 MG-63 |
| Curcumin loaded amphiphilic mixed micelles | 10 μM | Survivin Bcl-2 PARP | Inhibition of tumor growth, Apoptosis induction | Ishikawa |
| Liposomal Curcumin | NA | NF-κB | Inhibition of tumor growth | Ishikawa |
| Curcumin Phytosome | 2 g/day | - | Immunomodulatory effects | - |
downregulates HPV18 transcription, which reverses the fra-1 and c-fos expression dynamics in cervical cancer cells [53]. Higher suppressive function of curcumin against cervical cancer is because of the inhibition of the mitochondrial pathway, iNOS, COX-2, and cyclin D1 activity, and ERK and Ras signaling pathways as well as telomerase action [54, 55]. Remarkably, curcumin acts through targeting several signaling pathways, making the proliferation of cervical cancer cells revert to normal. It also mediates important alterations in tumor-associated proteins correlated with cell metabolism, cell cycle, and carcinogenicity in HeLa cells [56].

He and co-workers reported that both curcumin-photodynamic therapy (PDT) and dual antiplatelet therapy (DAPT), a Notch receptor blocker, are capable of inducing apoptosis and blocking the proliferation of cervical cancer Me180 cells [57]. Moreover, DAPT has synergistic effects on curcumin-PDT in cervical cancer treatment, which is primarily associated with NF-κB and Notch-1 down-regulation [57]. Ghasemi et al. recently performed an in vitro study to evaluate the probable mechanisms related to anticancer effects of curcumin on cervical cancer cell line [58]. They revealed that curcumin suppresses proliferation and invasion of cervical cancer cells through Wnt/β-catenin and NF-κB pathways impairment [58]. Shang and colleagues reported that, 13 μM curcumin induces cell death in HeLa cells via induction of DNA damage and chromatin condensation [59]. It has been demonstrated that curcumin in combination with ultrasound exerts more beneficial effects against cervical cancer cells [60]. Carr et al. indicated that this combination enhanced apoptosis in SiHa or HeLa cells [60]. Curcumin alone caused less necrosis compared to the combination therapy. They showed the ultrasound capacity to elevate curcumin effectiveness [60]. Recently, it has been reported that curcumin elevates intracellular ROS levels in cervical cancer cells, but not in healthy epithelial cells [61]. This effect leads to inhibition of ER stress and partly restoration of the viability in cancer cells treated with curcumin [61]. Collectively, these observations show that curcumin promotes ER stress-mediated apoptosis in cervical cancer cells through increasing the cell type-specific ROS generation [61]. According to Yoysungnoen-Chintana’s report, curcumin at high doses (1,000 and 1,500 mg/kg) inhibits angiogenesis as well as tumor growth in CaSkii-implanted mice possibly induced via downregulating the EGFR, COX-2 and VEGF expression [62]. Table 2 shows the available findings on curcumin therapy for cervical cancer in vivo and in vitro.

Curcumin and ovarian cancer
In the western world, ovarian cancer leads to the greatest mortality rate among all the gynecologic cancers. Affected individuals are usually diagnosed too late at advanced stages, when the cancer has spread to the peritoneal surfaces [96–98]. Surgery is the most efficient therapy for advanced stages, and is proceeded by chemotherapy with paclitaxel and carboplatin. After three chemotherapy cycles, interval cytoreductive surgery is alternatively done [96–98].

Curcumin reduces the needed dose of radiation and cisplatin in growth suppression of cisplatin-resistant ovarian cancer cells [99]. Curcumin, in combination with low amounts of cisplatin, also promotes apoptosis [99]. The decrease of cisplatin resistance in ovarian cancer cells by curcumin is probably through regulating extracellular vesicle-induced transfer of miR-214 and maternally expressed 3 (MEG3) [100]. This polyphenol has cytotoxic effects against platinum-resistant OVCAR-3 cells, which can be significantly enhanced by the compound Y15 (1, 2, 4, 5-benzene tetra amine tetrahydrochloride) [101]. Moreover, it decreases the number and size of ovarian tumors through inhibiting STAT3 and NF-κB signaling and inducing nuclear factor erythroid 2/heme oxygenase1 (Nrf2/HO-1) pathway [102]. In addition, curcumin induces G2/M cell-cycle arrest in cisplatin-resistant ovarian cancer cells via increasing apoptosis and phosphorylation of p53 by caspase-3 activation followed by poly (ADP-ribose) polymerase-1 (PARP) degradation [103].

In human ovarian cancer cell lines A2780 and SK-OV-3, curcumin is able to induce apoptosis as well as protective autophagy via suppression of AKT/mTOR/p70S6K pathway, demonstrating the synergistic impacts of curcumin and autophagy suppression [104]. Curcumin inhibits the activity of Sarco/endoplasmic reticulum calcium ATPase (SERCA) leading to dysregulation in Ca²⁺ homeostasis; and hence, contributes to apoptosis in ovarian cancer cells [105]. As discussed before, curcumin has anti-proliferative effects and can restrict tumor growth by this potential. Shi and colleagues demonstrated, in addition to apoptosis induction, 40 μM curcumin suppressed the growth of ovarian cancer cells [106]. Lin et al. showed that, in addition to apoptosis induction and anti-proliferative effects, curcumin suppresses angiogenesis in ovarian cancer in vivo and in vitro [107]. Furthermore, curcumin is capable of suppressing endothelial growth factor (EGF)-mediated Aquaporin 3 up-regulation and cell migration in CaOV3 ovarian cancer cells through its inhibitory impacts on EGFR and AKT/ERK activation [108]. In an in vitro investigation, Xiaoling et al. reported that curcumin inhibits the metastasis and invasion of the human ovarian cancer cells SKOV3 through suppressing CXCR4 and CXCL-12 expression [109]. Wahl and his colleagues illustrated that combined treatment of Apo2 ligand (Apo2L)/TNF-related apoptosis-inducing ligand and curcumin (5-15 μM) leads to
| Type of curcumin | Dose | Main target(s) | Main effect(s) | Model (in vivo/in vitro/human) | Cell line | Ref |
|-----------------|------|---------------|---------------|-------------------------------|----------|-----|
| Curcumin        | 20 μM for 72h | N-cadherin, Vimentin, Slug, PIR, Pirin | Inhibition of cancer cell growth, migration, invasion Inhibition of angiogenesis Induction of apoptosis and necrosis Induction of cell cycle arrest Increased radiosensitization of cancer cells | In vitro | SiHa | [63] |
| 2.5, 5 μmol/L in vivo (150-200 μL) | 5x IC50 (34.23 μM/ml) | Notch-1, NF-κB, VEGF | | In vivo | Me180 | [57] |
| 13 μM | ROS, p21, Bax, p53, ROS, p21, Bax | TGF-β activates Wnt/β-catenin signaling pathway | Curcumin improves the paclitaxel-induced apoptosis of cervical cancer cell lines infected with HPV. | In vitro | HeLa | [66] |
| 10 μM | NF-κB-p53-caspase-3 pathway | Curcumin improves the paclitaxel-induced apoptosis of cervical cancer cell lines infected with HPV. | | In vitro | CaSki | [68] |
| 5 μM | Akt, MAPK, and AP-1 pathways | Curcumin can act as an anti-proliferative and anti-inflammatory agent for Ca Ski, HeLa, and SiHa cells | | In vitro | HeLa | [73] |
| 1000 and 1500 mg/kg for 30 days | Curcumin sensitizes cervical cancer cells to cisplatin-based chemotherapy through inhibition of Pgp1 and MRP1. | | | In vitro | SiHa, SiHaR | [70] |
| 20μM | Curcumin induced ER stress-mediated apoptosis via increasing of ROS generation and by activation of CHOP | | | In vitro | C33A, CaSki, HeLa | [61] |
| IC50, 17 μM (HeLa), 12 μM (ME-180), 51 μM (SiHa), 21 μM (SW756) Dose: 50 μM for 48h | Curcumin-based vaginal cream effectively eradicates HPV positive cervical cancer cells. | | | In vitro | HeLa, ME-180, SiHa, SW756 | [71] |
| 10 and 25 μM | Akt, MAPK, and AP-1 pathways | Curcumin mediates apoptosis in SiHa and HeLa cell lines. Curcumin can act as an anti-proliferative and anti-inflammatory agent for Ca Ski, HeLa, and SiHa cells | | In vitro | HeLa, SiHa, CaSki | [73] |
| 25 and 50 μM | Apoptosis and inflammatory pathways | Curcumin mediates apoptosis in SiHa and HeLa cell lines. Curcumin can act as an anti-proliferative and anti-inflammatory agent for Ca Ski, HeLa, and SiHa cells | | In vitro | HeLa, SiHa, CaSki | [73] |
| 50 and 100 μM for 24h | Curcumin can induce apoptosis by inhibition of PCNA, Cyclin D1, telomerase, and p16 and by activation of p53 and p73 in HPV-negative cancer cells pretreated with estradiol. | | | In vivo | HeLa | [54] |
| 15 μM for 48h | Curcumin exhibits antitumor activity against cervical cancer cells. Curcumin downregulates PGE2 expression. | | | In vitro | HeLa | [56] |
| 10 μM for 8h | MAP kinase | Curcumin is a potent radiosensitizer | | In vitro | HeLa | [74] |
| Type of curcumin | Dose | Main target (s) | Main effect (s) | Model (in vivo/in vitro/human) | Cell line | Ref |
|------------------|------|----------------|----------------|-------------------------------|-----------|-----|
| Combined curcumin with ultrasound (8 s of 5-7.5 MHz) | 10 μM | - | Curcumin can lead to necrosis in cervical cancer cell lines. Combined curcumin ultrasound enhances necrosis in cervical cancer cell lines. | In vitro | SiHa C33A | [60] |
| ST06-AgNPs | IC50: 1 μM Dose: 1-2 μM Dose: 5 mg/kg body weight for 30 days (In vivo) | - | Inhibited cancer cell growth | In vivo | HeLa | [75] |
| Folic acid-modified liposomal curcumin | IC50: 1.47 μg/mL for free curcumin IC50: 0.45 μg/mL for (DSPE)-PEG2000-FA-LPU/CUR Dose: 25 mg/kg for 51 days (In vivo) | - | Anti-proliferative effects | In vitro | HeLa | [76] |
| 4-Bromo-4’-chloro pyrazoline | IC50: 8.7 μg/mL for Chloro bromo analog | - | Apoptosis induction | In vitro | HeLa | [77] |
| Chloro and bromo-pyrazole-curcumin | IC50: 14.2 and 18.6 μg/mL for Chloro derivative and bromo analog, respectively. IC50: 42.4 μg/mL for curcumin | - | Apoptosis induction | In vitro | HeLa | [78] |
| Curcumin-loaded microbubble | 1.25–40 μM | - | Decreased cancer cell viability | In vitro | HeLa | [79] |
| Bisdemethoxycurcumin | 5 μM for 24 and 48h NF-κB, MMP-2 and -9 Pathways | - | Anti-migration and anti-invasion effects | In vitro | HeLa | [80] |
| Curcumin-PDT | - | Notch signaling pathway | Necrosis induction | In vivo | Me180 | [81] |
| Curcumin-loaded micells | 50 μg/mL | - | Increased cytotoxicity against cancer cells. Apoptosis induction | In vitro | HeLa HepG2 NIH-3T3 | [82] |
| Demethoxycurcumin | 15 μM IC50: 7.5 μM NF-κB Pathways | - | Anti-migration and anti-invasion effects | In vitro | HeLa | [83] |
| Curcumin-loaded chitosan nanoparticles | 24 μM | - | Apoptosis induction Anti-proliferative effects Showed better chemopreventive and chemotherapeutic effects than curcumin | In vitro | SiHa | [84] |
| Difluorinated curcumin Folate decorated bovine serum albumin (FA-BSA) nanoparticles loaded with Difluorinated curcumin (CDF) (FA-BSA-CDF) | Dose: 2 μM (Difluorinated curcumin and FA-BSA-CDF) Dose: 0.5 μM (Combination) | - | Synergistic anticancer effects Apoptosis induction | In vitro | HeLa SKOV3 | [85] |
| Curcumin-nanoemulsion | 20 to 40 μM | - | Apoptosis induction | In vitro | CaSkI SiHa HaCaT | [86] |
| Curcumin-Loaded TPGS/F127/P123 Mixed Polymeric | Dose: 8 μg/mL Dose: 25 mg/kg for 11 | - | Increased cytotoxicity against cancer cells Induction of apoptosis and cell death | In vitro | HeLa | [87] |
increased apoptotic cell death induction [110]. They also stated that, because the mentioned combination are able to activate both the intrinsic and extrinsic apoptosis pathways, they may overcome chemoresistance to conventional chemotherapeutic drugs [110]. Epithelial ovarian cancer (EOC) spheroids have a key role in chemoresistance development [111]. A research was conducted to evaluate curcumin effects on chemoresistance and antiperitoneal metastasis in EOC spheroids [112]. It was indicated that high invasive EOC cells that form spheroids express a high level of aldehyde dehydrogenase 1 family member A1, a cancer stem cell marker, which was markedly downregulated by curcumin [112]. Curcumin significantly increased EOC spheroids’ sensitivity to cisplatin and abolished their sphere-forming ability [112]. Furthermore, curcumin inhibited pre-existing EOC spheroids’ growth and also suppressed their invasion to the mesothelial monolayers and their adhesion to extracellular matrix [112]. Table 3 summarizes the current data on the therapeutic effects of curcumin on ovarian cancer in vivo and in vitro.

**Limitation of curcumin**
The clinical anti-cancer effects of curcumin have not yet been fully documented despite its potential effects. Poor solubility in water is one of the main restrictions in curcumin application (only about 11 ng / ml), thereby possibly limiting its beneficial effects [150]. Other drawbacks are instability in alkaline and neutral environments, and low bioavailability because of rapid metabolism and elimination [151, 152].

Intravenous, peritoneal and oral administration of curcumin leads to the formation of glucuronide metabolites in the liver and excretion through the bile into the gastrointestinal tract [153, 154]. In a study, daily administration of curcumin (3600 mg) in patients with metastatic colorectal cancer, the circulatory curcumin content was in nanomolar level [155]. Similarly, other findings showed minor changes in the peripheral blood of patients at high risk following daily administration of curcumin (8000 mg) [156]. After the administration of curcumin at the doses of 500-8000 mg, there was no measurable level in the blood and only a small amount of its metabolites was measured in research units taking 10,000-12,000 mg [157, 158]. It can be concluded that the therapeutic potentials of curcumin may be enhanced by improving its bioavailability and solubility.

**Novel formulations of curcumin in the treatment of gynecological cancers**
As mentioned before, curcumin has low absorption and poor bioavailability [159]; thus, several investigators have

### Table 2: Conducted investigations on the treatment of cervical cancer with curcumin (Continued)

| Type of curcumin | Dose | Main target(s) | Main effect(s) | Model (in vivo/in vitro/human) | Cell line | Ref |
|------------------|------|----------------|----------------|------------------------------|----------|-----|
| Micelles         | times in 2 days (In vivo) | cycle arrest cells | - | - | - | - |
| Curcumin-loaded chitosan-alginate-sodium tripolyphosphate nanoparticles | 50 μg/mL | Bax , Bcl-2 | Anti-proliferative effects Apoptosis induction | In vitro | HeLa | [88] |
| Folic acid conjugated polymeric micelles loaded with a curcuminidifluorinated | 0.47 ± 0.14 μM | PTEN, NF-κB | Apoptosis induction | In vitro | HeLa | [89] |
| Curcumin-loaded chitosan Nanoparticles | 108 μM | Bax , Bcl-2 | Apoptosis induction | In vitro | SiHa, Caski C33a | [90] |
| Tetrahydrocurcumin | 100, 300, or 500 mg/kg body weight for 30 days | COX-2, EGFR, p-ERK1&2, p-AKT, PI-67 | Apoptosis induction Antitumor Effect | In vivo | CaSkI | [91] |
| Nano-Curcumin | 20 and 25 μM for 48h | Anti-survival pathways | Inhibited cancer cell growth Induction of apoptosis and cycle cell arrest | In vitro | SiHa, Caski | [19] |
| Tetrahydrocurcumin | 50, 100 mg/kg | - | Inhibited cancer cell growth Anti-angiogenesis effects | In vivo | CaSkI | [92, 93] |
| Curcumin (CCM)-loaded nanoscale zeolitic imidazolate framework-8 (CCM@NZIF-8) nanoparticles | Dose: 1-10 μg/mL, Dose: 25 mg/kg body weight for 6 times in 2 days (In vivo) | - | Anti-proliferative effects Showed higher efficacy than free curcumin | In vivo | HeLa | [94] |
| Curcumin-loaded cationic liposome | IC50: 16, 21 μM | - | Apoptosis induction | In vitro | HeLa | [95] |
| Type of curcumin | Dose | Main target (s) | Main effect (s) | Model (in vivo/in vitro/human) | Cell line | Ref |
|------------------|------|----------------|----------------|-------------------------------|-----------|-----|
| Curcumin         | 20 μM for 96 hours | Wnt/β-catenin | Inhibition of tumor growth, migration, and invasion | In vitro | SKOV3 | [113] |
|                  | 20 μM for 48 hours | -              | Inhibition of epithelial-mesenchymal transition | In vitro | ES2, OVCAR3 | [114] |
|                  | 30, 40 μM for 48 hours | AKT/mTOR/p70S6K | Induction of apoptosis | In vitro | SK-OV-3, A2780 | [104] |
|                  | 400 μM | NQO1, c-Myc, Cyclin B1, Cyclin D1 | Increased the sensitivity of cancer cells | In vitro | OVCAR3, OVCAR5, SKOV3 | [115] |
|                  | 20 μM | FAK | Induction of apoptosis | In vitro | SKOV3, OVCAR3, PA-1 | [116] |
|                  | 25.8, 53.0 mg/day | NF-κB | Antioxidant and anti-proliferative effects | In vivo | - | [117] |
|                  | Dose: 20 mg/kg (in vivo) | miR-124 | | In vitro | SKOV3 | [118] |
|                  | Dose: 10 μM for 48 hours | miR-214, MEG3 | | In vitro | A2780, OVCAR3, SKOV3 | [100] |
|                  | 1 μM for 36 hours | - | | In vitro | SKOV3 | [119] |
|                  | 60 μM for 72 hours | - | | In vitro | SKOV3 | [120] |
|                  | 50 μM | MMP-9, CD44, osteopontin | | In vitro | SKOV3 | [121] |
|                  | 10 μM for 2 and 3 hours | STAT3, IL-6, IL-8 | | In vitro | PA-1, OVCAR-3 | [122] |
|                  | 80 μM for 24 hours | Caspase-3, PARP-1, Bcl-2, P13K/Akt, P38 MAPK | | In vitro | HEY, OVCAR-49, OCC1, SKOV3 | [22] |
|                  | 50 μM for 240 min | Caspase-3, IL-6, STAT-3, p-JAK-1 and p-JAK-2, PIAS-3, SOCS-3 | | In vitro | OVCAR420, OVCAR429 | [36] |
|                  | 40 μM for 24 hours | AQP-3 | | In vitro | CaOV3 | [108] |
|                  | 0.5 μM for 48 hours | ROS, glutathione | | In vitro | C13, 2008 | [122] |
|                  | 50μM for 24 hours | AMPK, p38, p53 | | In vitro | CaOV3 | [123] |
|                  | 40μM for 72 hours | P13K/Akt | | In vitro | SKOV3 | [124] |
|                  | 60μM | ALDH1A1 | | In vitro | SKOV3, OVCAR3 | [112] |
|                  | 15μM for 24 hours | SERCA | | In vitro | MDAH 2774, SKOV3, PA1 | [105] |
|                  | 41.6μmol/L for 12 hours | Bcl-2, pS3, MDM2, NFκB, caspase-3 | | In vitro | A2780 | [125] |
|                  | 3 μM for 12 hours | Rho A/Rho-kinase | | In vitro | SKOV3 | [126] |
|                  | 40μM for 48 hours | Bcl-2, Bcl-xL, caspase-3, p53, Bax | | In vitro | HO-8910 | [106] |
| Curcumin-loaded biodegradable | 0.1 mg/mL | - | CUR-NP exhibited better | In vitro | SK-OV-3 | [127] |
Table 3  Recent studies on curcumin treatment for ovarian cancer (Continued)

| Type of curcumin                                                                 | Dose                        | Main target (s)                                                                 | Main effect (s)                                                                 | Model (in vivo/in vitro/human) | Cell line                  | Ref     |
|--------------------------------------------------------------------------------|-----------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------------------------------|----------------------------|---------|
| PLGA nanoparticles (CUR-NP)                                                    | 50 μM                       |                                                                               | physicochemical properties compared to free curcumin                         | In vitro                      | A2780                      | [128]   |
| Curcumin-coated silver nanoparticles (cAgNPs)                                 | 2 μg/mL for 48 hours        | Caspase 3/9, p53, MPP-9                                                      | Apoptosis induction                                                          | In vitro                      | ES2-Luc, A2780ADR          | [129]   |
| Combinational polymeric micelles for co-delivery of quercetin/resveratrol/curcumin | 1 mg/ml                     | Caspase-3                                                                     | Apoptosis induction                                                          | In vitro                      | ES2-Luc, A2780ADR          | [129]   |
| DNC                                                                            | 55 μM for 48 hours           | LSINCT5, CCAT2, ABO73614, ANRIL, PAL1, BC200, MALAT1                          | Apoptosis induction, Inhibited tumor growth                                   | In vitro                      | OVCAR3, SKOV3              | [130]   |
| Curcumin-loaded PLGA MPs                                                       | Dose: 20 and 40 μM for 48 and 72 hours Dose: 100 mg/kg (In vivo) |                                                                               | CPMs formulation was more effective than free curcumin in suppressing proliferation of ovarian cancer cells | In vitro                      | SKOV-3                    | [131]   |
| Curcumin nanoparticle                                                          | 50 μg/ml, 6.62 μg/mL         | P-gp                                                                          | Decreased chemotherapy resistance, Induced cell cycle arrest, Apoptosis induction, Antioxidant effects | In vitro                      | A2780, SKOV3               | [132]   |
| Difluorinated curcumin Folate decorated bovine serum albumin (FA-BSA) nanoparticles loaded with Difluorinated curcumin (CDF) (FA-BSA-CDF) | 162.8 nM                     |                                                                               | Apoptosis induction                                                          | In vitro                      | SKOV3                      | [85]    |
| FA-SMA-CDF nanomicelles                                                        | 1.55 ± 0.23 μM for 72 hours | PTEN, NFKB                                                                     | Apoptosis induction                                                          | In vitro                      | SKOV3                      | [89]    |
| Demethoxycurcumin                                                             | 20, 40 μM for 48 hours       | IRS2/PI3K/Akt, miR-551a                                                       | Anti-proliferative effects, Apoptosis induction                               | In vitro                      | ES2, HO8640, HO8640PM, SKOV3 | [134]   |
| Doxorubicin/curcumin co-loaded alginate-shelled nanodroplets                   | -                           |                                                                               | Inhibited tumor growth                                                        | In vitro                      | A2780                      | [135]   |
| Boron-curcumin complex                                                         | 6 mg                        |                                                                               | Enhancement of anticancer effects of curcumin                                 | In vivo                       | IGROV-1                    | [136]   |
| Curcumin-loaded NLC                                                            | 30 μM for 24 hours           | PARP, caspase-3                                                               | Apoptosis induction                                                          | In vitro                      | A2780                      | [137]   |
| Curcumin-loaded δ-T3 nanoemulsion                                             | 1.96 ± 0.37 mg/ml           | NF-kB                                                                         | Anti-proliferative effects, Apoptosis induction                               | In vitro                      | OVCAR-8                    | [138]   |
| Bisdemethoxycurcumin                                                          | 15 μM for 24 hours           | MMP-2, -9, CD147, uPA, ICAM-1, VCAM-1, TIMP-1, NF-kB p65, VEGF                | Inhibited growth, adhesion and motility of tumor cells, Arrested cell cycle, Anti-migration and anti-invasion effects, Antioxidant effects | In vitro                      | SKOV-3                    | [139]   |
| Monofunctional platinum (II) tris (quinoline) chloroplatimium (II)           | 60 to 200 μM for 72 hours    |                                                                               | Greater toxicity on resistant tumor cells compared to cisplatin               | In vitro                      | A2780                      | [140]   |
| ASA/Cur-coloaded mPEG-PLGA nanoparticles                                       | 5 μg/mL                      | Caspase-3, -9 Bcl-2, Bax                                                      | Apoptosis induction, The co-delivery of curcumin enhanced its antitumor activity | In vitro                      | ES-2, SKOV3                | [141]   |
| Curcumin and platinum-loaded micelles                                         | 1 mg                        |                                                                               | The co-delivery of curcumin enhanced its antitumor activity                   | In vitro                      | A2780                      | [142]   |
| MPEG-PCL curcumin micelles                                                   | 5 μg/mL                      |                                                                               | Induced cell cycle arrest                                                      | In vitro                      | A2780                      | [143]   |
been attempting to improve its therapeutic effectiveness and pharmacokinetic profile by approaches such as development of new analogs [150, 160, 161]. Structural alterations in curcumin molecule leads to numerous beneficial properties for treating different diseases, including neurodegenerative diseases, diabetes, and cardiovascular diseases [159]. Curcumin and its analogs are extensively utilized as antioxidants, antimicrobial, anti-inflammatory, and anticancer agents. Successful attempts for synthesizing new analogues of curcumin with enhanced bioactivity have been reported [3, 162, 163]. It has been indicated that curcumin has anticancer functions due to its impact on various biological pathways implicated in metastasis, apoptosis, cell cycle regulation, tumorigenesis, oncogene expression, and mutagenesis [164, 165]. Recently, it has been revealed that some of these analogs display considerably stronger anticancer property than curcumin [50–53]. Hence, to overcome the restrictions of curcumin, researchers are developing and evaluating increasing number of curcumin novel analogs [166–168]. These analogs have shown a wide-spectrum of anticancer features in different cancer cells, such as colon [169], breast [170], and prostate [171].

Pan and colleagues indicated that, in plasma of curcumin-treated animals, 99% of the administered curcumin is glucuronide-conjugated [172]. It was also revealed that reduced curcumin metabolites, including curcumin glucuronosides, dihydrocurcumin and tetrahydrocurcumin are the main curcumin metabolites [172]. It has been shown that these metabolites have a crucial role in multiple therapeutic effects, including anticancer [173], anti-inflammatory [174], and antioxidation [175]. However, numerous investigation have demonstrated that anticancer activity of curcumin metabolites is weaker in comparison to the parent molecule [176, 177]. Thus, several approaches, such as structural modification and improving carrier molecules have been tested to compensate the curcumin’s bioavailability limitations [176]. For increasing the therapeutic potential and bioavailability, different delivery systems including phospholipid complexes, micelles, nanoparticles, and liposomes have been recently recommended for curcumin treatment in cancer [176]. For instance, phospholipid complexes and micelles improve curcumin’s gastrointestinal absorption, leading to greater plasma concentrations [176]. It has been revealed that curcumin-loaded amphiphilic mixed micelles has better bioavailability, causes remarkable accumulation of rhodamine, and modulates the expression levels of IL-6, IL-10 and TNF-α [41]. It also induced apoptosis and enhanced the intracellular uptake leading to inhibition of Ishikawa EC cells’ growth [41]. Xu et al. conducted a research to evaluate the efficacy of liposomal curcumin as a treatment for endometrial cancer [178]. Liposomal curcumin dose-dependently suppressed the motility, induced apoptosis and inhibited the proliferation of HEC-1 and Ishikawa cells [178]. It also blocked the expression of MMP-9, caspase-3, and NF-κB. Importantly, no toxicity was seen in the zebrafish model [178]. Demethoxycurcumin, a novel derivative of curcumin, induced apoptosis in cervical cancer cells in vitro and decreased tumor volume in an in vivo model [91]. In an investigation, curcumin-loaded chitosan nanoparticles were used for cervical cancer cells and it was shown that this delivery system enhanced the anti-proliferative effects of the drug against cancer cells and was not toxic to normal cells.
[90]. Du et al. reported that demethoxycurcumin, a curcumin analog, inhibited insulin receptor substrate–2 (IRS2) through miR-551a upregulation leading to hindering of ovarian cancer cells growth [134]. Compared to free curcumin, curcumin-loaded nanostructured lipid carriers (NLCs) showed better anticancer results, and more effectively reduced cell colony survival. These findings suggest that the curcumin entrapment into NLCs enhances the efficacy of curcumin in vitro [137]. Hossein et al. have recently demonstrated that dendrosomal nanocurcumin (DNC) leads to greater cell death when combined with oxaliplatin. DNC also induced apoptosis in ovarian cancer cells [179]. De Matos et al. indicated that curcumin-nanoemulsion acts as a photosensitizing agent in PDT, demonstrating potential alternative capacity for cervical lesions [86]. Making novel formulations such as effective derivatives, as well as utilizing novel drug delivery systems can significantly increase the anticancer potential of curcumin. More experimental studies and human trials are needed to confirm the efficacy of curcumin and its novel formulations for the treatment of gynecological cancers.

**Conclusion and future perspectives**

Gynecologic cancers represent a wide variety of cancers such as ovarian, uterine/endometrial, cervical, gestational trophoblastic, primary peritoneal, vaginal and vulvar cancers. Some of these cancers are known as “silent killer”, since the patient is usually unaware of tumor presence, until it is too late to cure. On the other hand, current therapeutic approaches carry serious limitations. Hence, developing new therapeutic platforms could optimize the treatment outcome for these cancers.

Curcumin is a well-known natural compound, which possesses a wide range of biologic effects such as anti-inflammatory, anti-cancer, and anti-oxidant activities. Several studies have proved the potential benefit of curcumin treatment both with monotherapy and in combination with standard chemotherapy drugs. The anticancer effects of curcumin in gynecologic cancers is shown to be linked to activation of autophagic and apoptotic pathways and inhibition of invasion and metastasis in various tumors. Curcumin suppresses major regulatory genes such as NF-κB and its downstream gene targets, which play significant roles in controlling invasion and metastasis of cancer cells. Interestingly, curcumin has been shown to improve the efficacy of current therapies by sensitizing resistance cancer cells to chemoradiotherapy, which has been a big obstacle in cancer treatment. Importantly, the safety and well-tolerability of curcumin has been demonstrated in clinical trials.

Along with different beneficial effects, curcumin treatment faces some limitations such as low bioavailability. However, several studies have proposed new formulations of curcumin to overcome this problem. Also utilization of different analogues and novel delivery systems such as nanoparticles, liposomes and micelles may further improve the anti-cancer effects of curcumin and open a new horizon in the treatment of gynecologic cancers.

**Acknowledgements**

Not applicable.

**Authors’ contributions**

HM involved in conception, design, statistical analysis and drafting of the manuscript. MD, MH-P, RM, MR, JT, MJ, MIA and AS contributed in data collection and manuscript drafting. All authors approved the final version for submission.

**Funding**

Not applicable.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

The authors have no conflict of interest to disclose.

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**Received**: 28 January 2020 **Accepted**: 23 October 2020

**Published online**: 04 November 2020

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