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REVIEW

Curcumin and endometrial carcinoma: an old spice as a novel agent

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Abstract: One of the clinically major gynecological cancers is endometrial carcinoma that develops from the lining of the uterus. During the past years, different approaches have been developed to treat endometrial carcinoma, among which natural herbal medicine has recently faired as an effective method. The yellow Indian spice known as curcumin has been extolled for its healing powers and has recently been adopted for investigation by the scientific community as a potent anti-cancerous agent. This review focuses on the effect of curcumin on endometrial cancer (EC) and its role in specific pathways involved in carcinogenesis.

Keywords: herbal medicine, cancer, anti-cancerous, carcinogenesis

Introduction

Cancer is the second leading cause of death globally and accounts for an estimated 9.6 million deaths in 2018.[1] It consists of a group of diseases characterized by the development of abnormal cells that grow uncontrollably in tissues and eventually spread throughout the body.[2] This unrestrained growth is the consequence of the cells' capacity to evade apoptosis, avoid growth suppressors, and initiate invasion leading to maintained proliferation and eventually metastasis.[3] The reproductive organs are among the most common sites of cancer occurrence in females; these constitute gynecological cancers in which uterine cancer is the most commonly diagnosed type. In the US alone, uterine cancer is the fourth most diagnosed type of cancer in women.[4]

Uterine cancers are split into two distinct categories: the first is endometrial cancer (EC) and accounts for 92% of uterine cancer cases and the second is uterine sarcoma, accounting for only 8%.[5]

Both of these types primarily differ in the tissue of origin: EC develops in the tissue lining of the uterus known as the endometrium, while uterine sarcoma originates in the tissues that support the uterine glands, or in the uterine muscle known as the myometrium.

EC is very common in females from developed countries.[6] It is diagnosed more frequently in women who have passed the menopausal state; nonetheless, a fair percentage (15%–25%) of cases also occur in females who have not yet reached menopause.[7] The etiology of EC remains unclear; however, scientists have reported that imbalances in progesterone and estrogen levels may possibly be the main reason behind its development and progression.[8] Some studies report that fluctuations in the levels of these two female sex hormones may induce the thickening of the endometrium and thus increase the risk of this cancer.[9,10] However, others associate the occurrence of EC to genetic mutation(s) that give rise to abnormal cells within the endometrium.[11,12] Subsequently, these cells multiply in an uncontrollable and rapid

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manner, often leading to the formation of a tumor; in some cases, the tumor remains benign; however, malignant tumors proceed to become cancerous.

The typical symptoms of EC are unusual vaginal bleeding (mainly postmenopausal bleeding), unusual vaginal discharge, painful urination, pain during intercourse, pain in the pelvic area, and unintentional weight loss.[5] Some of the identified risk factors that may contribute to the direct or indirect development of EC include family history; obesity, diabetes, diet, and exercise; intrauterine device uses; previous cancers (breast, ovarian, etc); polycystic ovarian syndrome; hormone therapies; birth control pills; and endometrial hyperplasia.[6] Intrusive interventions are the usual approach for the treatment of ECs such as surgery (mainly hysterectomy and salpingo-oophorectomy) and other alternatives or complimentary treatments include radiation therapy (brachytherapy or external beam radiation therapy), chemotherapy, and hormone therapy.[13] With the exponential advancement of science, new promising therapies are being developed to treat different types of cancers, and among these remedies herbal medicine is being taken into serious consideration.[14]

Herbal medicine has long been a subject of discussion, sometimes dismissively,[15] and throughout history different cultures have integrated various herbs to treat a wide variety of illnesses.[16] This form of medicine has never ceased to flourish, and among the most promising spices that has and is still being investigated is curcumin (turmeric).[17]

Curcumin is a bright yellow-colored Indian spice derived from the herbaceous ginger plant turmeric, also known as *Curcuma longa*.[18] This spice has been used for centuries to treat numerous diseases such as diabetes, atherosclerosis as well as liver, rheumatoid, and infectious diseases.[18,19]

Recent advances in molecular biology have allowed a more microscopic inspection into the active properties of this pleiotropic chemical (diferuloylmethane), which has proven to effectively interact with numerous signaling molecules within the body. Curcumin seems to show antibacterial,[20] anti-inflammatory,[21] antioxidant,[22] and antimicrobial activities.[23]

In addition to all its benefits, curcumin also possesses anti-cancerous effects by targeting several important players in cell signaling pathways such as p53,[24] MAPKs, ERK, Ras,[25] Wnt-β,[26] PI3K, and Akt,[27] all of which play major roles in tumor progression. Furthermore, this herb, in combination with other agents, is capable of disrupting the cell cycle through its effect on cellular apoptosis by activating caspases as well as downregulating anti-apoptotic gene products (Bcl-X).[28] Curcumin can also interact with several molecules involved in proliferation (EGFR and AP-1),[29,30] metastasis and invasion (MMP-9),[31] angiogenesis (VEGF),[32] and inflammation (NF-κB, COX-2, TNF, IL-1, IL-6, IL-2, IL-8, and IL-12, 5-LOX).[33–35] Because of its multivalent potential to target several molecules, this spice can be used on various types of cancers including colorectal, leukemia, lymphoma, breast, pancreatic, ovarian, head and neck, lung, prostate, and melanoma.[34] An investigation into the available literature concerning curcumin as a potential therapy for cancers of the female reproductive system turned up with no paper studying the effect of curcumin on endometrial carcinoma. Therefore, this review is written to shed light and summarize any available data on the effect of curcumin as a promising therapeutic agent on this specific gynecological cancer.

Methods

Our search for relevant studies was conducted using the following databases: Pubmed, Science Direct, and Google Scholar. A Boolean search of titles and abstracts for three groups of terms was conducted: "Reproductive Cancer" AND "Curcumin"; "Gynecological cancer" AND "Curcumin"; "Endometrial Carcinoma" AND "Curcumin" to make sure that no study involving endometrial carcinoma and curcumin would be left out. The search was restricted to those publications available in English. Identified titles and abstracts were screened for relevance. Studies discussing other gynecological cancers (such as ovarian or vulvar cancer) as well as statistical studies with an assessment of dietary intake of curcumin with no clear data about curcumin origin or dosage were excluded.

After this initial screening of titles and abstracts, full texts were further reviewed for relevance, applying the same inclusion criteria. Search restrictions were based on the type of publication set to journal and keywords set to "Curcumin" and "Endometrial Carcinoma". No date restriction was implemented, and all relevant papers were considered.

At this point, all full-text articles were read and any questions about article inclusion were resolved through discussion among the authors. Only 14 research papers met our selection criteria; these articles clearly discuss the direct action of curcumin on EC cells. All papers illustrate research conducted either in vitro on human EC cells or in vivo in zebrafish or rodent models.

Results

A study conducted on human EC cells (Ishikawa cell line) revealed that curcumin inhibits the proliferation and invasion of these cells. Curcumin was found to downregulate

(MMP-2) mRNA levels which presumably led to decreased expression of MMP-2 proteins capable of cleaving components of the extracellular matrix. The downregulation of MMP-2 caused a reduction in optical cell density and inhibition of cell invasion.[36] Treatment with curcumin also led to an increase in the expression of E-cadherin proteins which possess a significant role in preventing tumor cell invasion and proliferation.[36]

Another study, where curcumin-loaded mixed micelles (CUR-M) were prepared by encapsulating curcumin, revealed the effect of these CUR-M on EC cells in vitro (EC cell lines Ishikawa).[37] Curcumin caused inhibition of proliferation, suppression of motility, and induction of apoptosis in these cell lines in a dose-dependent manner. The CUR-M, prepared with two nonionic amphiphilic surfactants, showed an enhanced intracellular uptake. These micelles were found to inhibit the survival of Ishikawa cells in vitro through the downregulation of inhibitors of apoptosis proteins (IAPs; among them, survivin is a major culprit offering resistance development in EC) that are typically overexpressed in epithelial EC, hence leading to the induction of apoptosis. These mixed micelles were able to downregulate PARP which is a commonly used biomarker for the detection of apoptosis in EC cells. Curcumin and its micellar formulation also reduced IL-6 and TNF-α level that are involved in angiogenesis development in EC. Furthermore, the levels of IL-10 were enhanced,[37] corresponding to earlier findings which demonstrated that IL-10 has the ability to inhibit tumor growth and metastasis in several types of cancer.[38] The in vivo pharmacokinetics of CUR-M was evaluated as promising (in Wistar rodent model) after intravenous administration.[37] In a similar study on Ishikawa and HEC-1 cells, liposomal curcumin (LC), prepared by encapsulating curcumin in a liposomal delivery system, downregulated the expression of NF-κB proteins (nuclear factor kappa light chain enhancer of activated B cells),[39] which control DNA transcription and cytokine production,[40] hence leading to the decrease in the levels of various core molecules such as pro-apoptotic caspase-3[41] and extracellular matrix degrader MMP-9.[42] These in vitro experiments revealed that the treatment of EC cells with LC leads to the inhibition of proliferation, induction of apoptosis, and suppression of cell motility.[39]

An in vivo experiment conducted via a tumor model assay in zebrafish embryos confirmed that LC, injected into the perivitelline cavities of these embryos, delayed cancer growth by inhibiting the NF-κB pathway.[39]

Research, also conducted on Ishikawa cells, showed the anti-proliferative role of curcumin through its ability to inhibit the anti-apoptotic molecule TREK-1.[43] In vivo studies on non-obese diabetic severe combined immunodeficient (NOD-SCID) mice showed that curcumin also suppresses tumor growth; it was noted that a daily dose of 50 mg/kg body weight intraperitoneally per day for 30 days was sufficient in reducing tumor volume by fivefold as compared to that in vehicle-treated animals, without apparent toxicity.[44] This group also conducted in vitro experiments using both Ishikawa cells and HEC-1B cell lines and showed the anti-migratory effects of curcumin by enhancing the expression of the signaling molecule Slit2. The induction of Slit2 caused the downregulation of migratory protein expression such as CXCR4 (chemokine receptor 4), SDF-1 (stromal cell-derived factor-1), and the matrix metalloproteases MMP2/9 in endometrial carcinoma cells.[44] Another study also showed the inhibitory effect of curcumin on MMP2/9 expression by obstructing the ERK signaling pathway.[45] This pathway is known to control many cellular processes by transmitting extracellular signals into the nuclei via phosphorylated ERK proteins.[46] Curcumin was found to inhibit ERK phosphorylation and hence block the metastatic effect of cancer.[45]

Curcumin may also affect endometrial carcinoma through the downregulation of androgen receptors (ARs), which are ligand-dependent nuclear transcription factors.[47] These receptors have been associated with different types of tumors such as prostate, bladder, liver, endometrial, and others.[47] An experiment showed that treating human endometrial carcinoma cells, RL-952 cells, with curcumin inhibited cellular proliferation and enhanced the apoptosis of these cells. These changes occurred in a time- and-dose-dependent fashion. Curcumin targeted the Wnt signaling pathway, which plays an important role in tumor progression and proliferation, and consequently reduced AR expression in the carcinoma cells.[26] As a result, the proliferation of EC cells was inhibited and apoptosis was induced.[26]

Other research also revealed how curcumin enhanced the role of an aromatase inhibitor, letrozole, used to treat estrogen-sensitive cancers such as endometrial carcinoma. Nude mice were transplanted with EC cells, RL-952, and then treated with letrozole, curcumin, or both simultaneously. Mice that were treated with either letrozole or curcumin alone experienced induction of apoptosis in tumor cells. However, the group treated with both letrozole and curcumin exhibited an increased rate of apoptosis through the inhibition of Bcl-2 proteins.[48,49]

Alternative studies used a curcumin analog referred to as HO-3867 to demonstrate the effect of this isolated compound on different human EC cell lines: Ishikawa, HEC1B, RL-95-2, and SK-UT-1B.[50] This analog targeted STAT-3 in

cancer cells; STAT-3 is a protein associated with different types of cancers. In its phosphorylated active state, STAT-3 modulates the expression of various genes involved in cancer function. When HO-3867 caused the decrease in pSTAT3 levels, EC cells underwent apoptosis.[50] These results were ascertained by using an in vivo model of BALB/c nude mice whose diet was supplemented with HO-3867.[50] Furthermore, curcumin-treated human EC cell lines (RL95-2 and Ishikawa) were shown to inhibit IL-6 expression, overexpress PIAS-3 (protein inhibitor of activated STAT-3), and downregulate SOCS-3 (suppressor of cytokine signaling 3).[51] These changes led to the suppression of the JAK-STAT pathway that controls gene expression through extracellular factors.[52] As a result, the phosphorylation of the proto-oncogenic STAT-3 protein was attenuated and the tumor cell growth was inhibited.[51]

Curcumin's antitumor effect also works by interfering with the expression of Ets-1 (a proto-oncogene) and Bcl-2 (anti-apoptotic molecule). Tumor formation can result from the overexpression of the Ets-1 proto-oncogene that induces an increase in Bcl-2 levels. However, treatment of HEC-1-A cells with curcumin attenuated both molecules and caused the apoptosis of the cancer cells.[53,54] To further ascertain curcumin's anti-proliferative role, an experiment that combined curcumin and three synthetic aminoanthraquinone derivatives (Rau 008, Rau 010, and Rau 018) was carried out.[55] The anti-proliferative role of curcumin was revealed through its ability to reduce ALP enzyme activity in HEC-1A cells.[56]

Discussion

Advanced EC has high mortality and poor prognosis,[57] with first-line or emerging chemotherapy drugs having limited effectiveness and causing severe side effects and toxicity.[58] To find safer therapeutic drugs for EC, especially for long-term use, researchers are turning to "old-age" herbal medicine, inspecting them for natural antitumor drugs in active plant ingredients. Curcumin (turmeric), a lipid-soluble active ingredient of *Curcuma* used in traditional Chinese medicine, has diverse reported effects against inflammation, oxidation, infection, and tumors.[17,59] Because of its abundance, cost-effectiveness, and accessibility, curcumin is considered as a promising antitumor drug for further exploitation and application and it has been widely applied to antitumor experiments worldwide, which have shown significant outcomes in preventing the onset, development, and metastasis of tumors.[17,59]

In our paper, we shed the light on the studies that measured the effect(s) of curcumin on endometrial carcinoma (Table 1). The old spice revealed its ability to modulate multiple molecular targets involved in carcinogenesis via the regulation

Table 1 Summary of the studies, ordered by date and listing the dose, administration mode, and the effects of curcumin against different endometrial carcinoma cell lines, zebrafish, and rodent models

Cell line/model	Dose/administration mode of curcumin	Molecular targets/effect(s)	Result(s)	Reference
Ishikawa cells	15–30 μmol/L	Downregulates MMP-2 mRNA	Inhibition of proliferation and invasion	Sun et al[36]
– Ishikawa cells – HEC-1 cells	– LC, IC_{50}=52.8 μM – LC IC_{50}=80.8 μM	– Downregulates NF-κB proteins – Decreases caspase-3 and MMP-9	– Inhibition of proliferation – Suppression of motility – Induction of apoptosis	Xu et al[39]
– Zebrafish (tumor model assay; injected with Ishikawa or HEC-1 cells)	– Injected with Ishikawa cells into perivitelline cavities, LC=15 μM – Injected with HEC-1 cells into perivitelline cavities, LC=30 μM	– Downregulates NF-κB proteins		
– Ishikawa cells	CUR-M 1–15 μM (IC_{50})	– Downregulates survivin and PARP – Downregulates TNF and IL-6 – Upregulates IL-10	– Induction of apoptosis – Reduction of inflammation – Reduction of angiogenesis	Kumar et al[37]
– Ishikawa cells – HEC-1B cells – Primary human endometrial adenocarcinoma cells	– 5.9 μM (IC_{50}) – 5.9 μM (IC_{50}) – 17.9 μM (IC_{50})	– Enhances expression of Slit-2 – Downregulates CXCR4, SDF-1, and MMP2/9	– Inhibition of migration – Inhibition of proliferation – Reduction in tumor volume by fivefold compared to control	Sirohi et al[44]
– Rodent model NOD-SCID mice (injected with Ishikawa cells)	– 50 mg/kg body weight per day (inter-peritoneal injection)			

(*Continued*)

Table 1 (*Continued*)

Cell line/model	Dose/administration mode of curcumin	Molecular targets/effect(s)	Result(s)	Reference
HEC-1A	– Curcumin (25 μM) and Rau 008 (120 μM) – Curcumin (25 μM) and Rau 010 (120 μM) – Curcumin (100 μM) and Rau 018 (30 μM) – Curcumin (75 μM) and tamoxifen (60 μM) – Curcumin (100 μM) and 17β-estradiol (30 μM)	Reduces ALP activity	Inhibition of proliferation	Pereira et al[55]
– Ishikawa cells – HEC-1B cells	10–30 μM	– Obstructs ERK signaling pathways – Inhibits MMP2/9 expression	Inhibition of migration and invasion	Chen et al[45]
– Ishikawa cells – HEC-1B cells – RL-95-2 cells – SK-UT-1B cells	– 1–20 μM HO-3867	– Decreases the phosphorylation of STAT-3 proteins	Induction of apoptosis	Tierney et al[50]
– BALB/c nude mice (injected with Ishikawa cells)	– 50 and 100 ppm of HO-3867 (mixed with animal feed)			
RL-952 cells	10–100 μmol/L	Reduces AR expression	– Inhibition of proliferation – Induction of apoptosis	Feng et al[26]
Ishikawa cell line	10–30 μM	Inhibits TREK-1	Inhibition of proliferation	Patel et al[43]
– Ishikawa cells – RL-95-2 cells	10–50 μM	– Inhibits IL-6 expression – Overexpresses PIAS-3 – Downregulates SOCS-3 – Suppresses JAK-STAT pathway	Inhibition of tumor cell growth	Saydmohammed et al[51]
Nude mice injected with RL-952 cells	– Curcumin 1 μg/day + letrozole 1 μg/day – Curcumin 50 mg/(kg·day) + letrozole 10 μg/day (injected subcutaneously on the cervicum and dorsum)	Inhibits Bcl-2 proteins	Induction of apoptosis	Liang et al[48,49]
HEC-1A cells	20–100 μM	Attenuates Ets-1 and Bcl-2 proteins	Induction of apoptosis	Yu and Shah[53]
HEC-1-A	50 and 100 μM	Causes an increase in the G2/M phases	– Inhibition of proliferation – Induction of apoptosis	Wei et al[54]

Abbreviations: AR, androgen receptor; CUR-M, curcumin-loaded mixed micelles; LC, liposomal curcumin.

of diverse transcription factors,[39] inflammatory cytokines,[37] growth factors, protein kinases,[45] and various other enzymes and signaling biomolecules (Figure 1).[26,36,43,44,50,51,53,54] In addition to modulating different cell signaling pathways in endometrial tumor cells, curcumin showed that it can be an effective chemosensitizer in the case of EC.[48,49,55] Previous research on other types of cancers has already described the potential of curcumin in cancer cell chemosensitization to chemotherapeutic agents such as 5-fluorouracil, doxorubicin, paclitaxel, cisplatin, and celecoxib in different malignancies.[60]

Nevertheless, curcumin has some serious limitations, it has low water solubility and absorption, high instability, and rapid degradability, which reduce its bioavailability and restrict its direct clinical application as an antitumor drug.[23] To improve the bioavailability of curcumin and benefit from its antitumor pharmacological effects in vivo, researchers have developed drug-loading systems in vivo. In particular, drug delivery was tested via colloid carrier systems, including liposomes and nanotechnology (nano-emulsions and nanoparticles).[61] In the case of endometrial carcinoma, LC

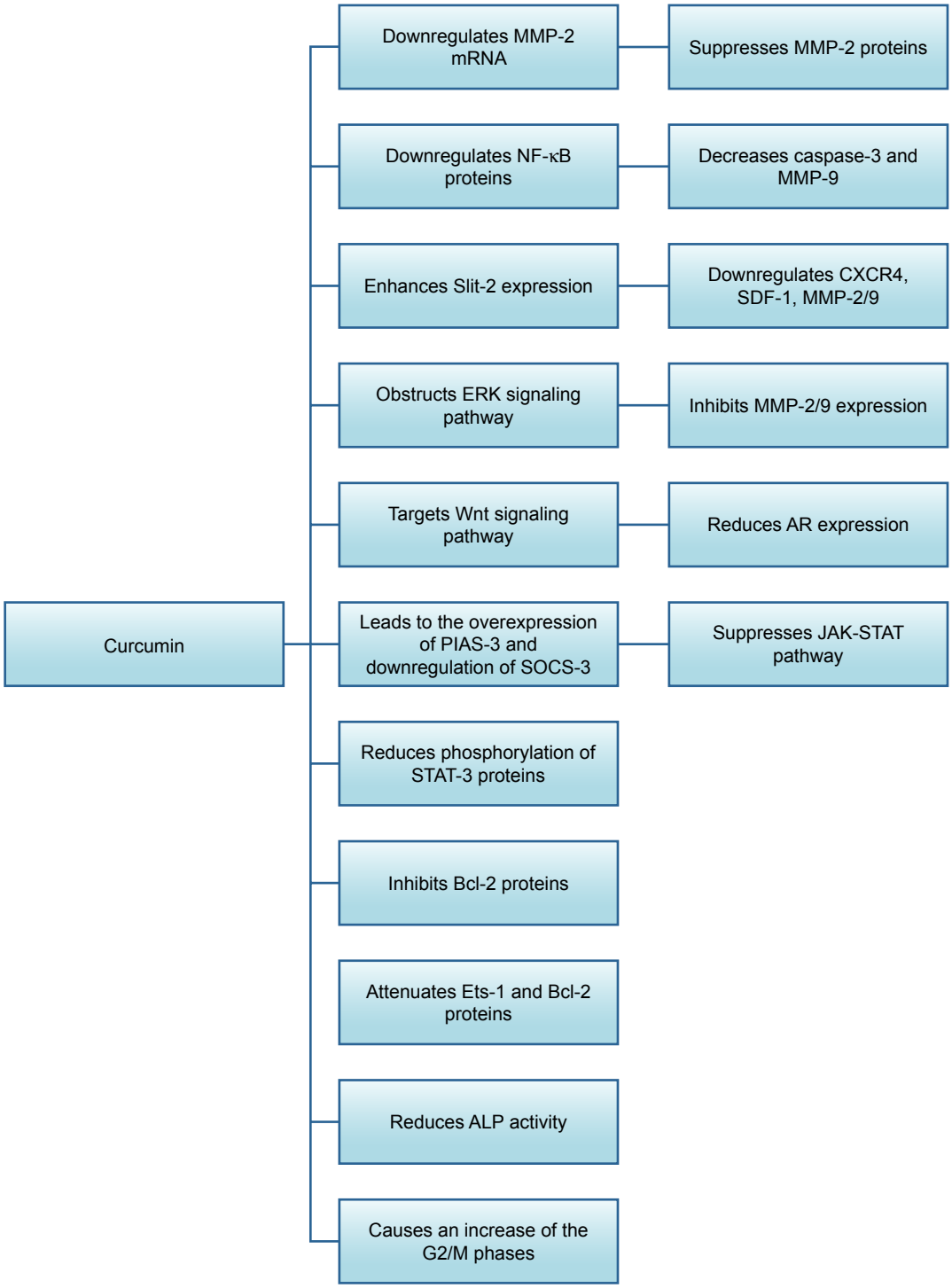

Figure 1 Effect of curcumin on different molecular targets in endometrial carcinoma.

and curcumin-loaded micelles (CUR-M) were assessed in vivo and have shown promising results.[37,39]

Conclusion

EC remains a very common gynecological malignancy in developed nations. In contrast to the progress observed with many other cancer types, the incidence of EC has increased over the past 30 years. Finding new agents to prevent its occurrence and/or its evolution is of high importance. Although we cautiously extrapolate results of experiments done in rodents or zebrafish to human beings and carefully relay conclusions from in vitro to in vivo studies, all the collected data show that curcumin has a significant effect on endometrial carcinoma where it exhibited pro-apoptotic, anti-proliferative, and

anti-migratory activities of endometrial tumor cells. Further studies are particularly needed in the case of endometrial carcinoma to determine the appropriate drug delivery system and the advised daily dose per kilogram of body weight. Compared to other traditional chemotherapeutic drugs and as evidenced by multiple clinical trials carried out, curcumin has high tolerability, almost no apparent toxicity or side effect, which makes this old spice a promising novel anticancer or at least an effective chemosensitizer agent against endometrial carcinoma.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2018;144(8):1941–1953. doi:10.1002/ijc.31937
2. Cooper G. *The Cell: A Molecular Approach*. 2nd ed. Sunderland, MA: Sinauer Associates; 2000.
3. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646–674. doi:10.1016/j.cell.2011.02.013
4. Saso S, Louis LS, Doctor F, et al. Does fertility treatment increase the risk of uterine cancer? A meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2015;195:52–60. doi:10.1016/j.ejogrb.2015.09.002
5. Saso S, Chatterjee J, Georgiou E, Ditri AM, Smith JR, Ghaem-Maghami S. Endometrial cancer. *BMJ*. 2011;343:d3954. doi:10.1136/bmj.d3954
6. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. *Ann Oncol*. 2015;27(1):16–41. doi:10.1093/annonc/mdv484
7. Suri V, Arora A. Management of endometrial cancer: A review. *Rev Recent Clin Trials*. 2015;10(4):309–316.
8. Kim JJ, Kurita T, Bulun SE. Progesterone action in endometrial cancer, endometriosis, uterine fibroids, and breast cancer. *Endocr Rev*. 2013;34(1):130–162.
9. Felix AS, Weissfeld JL, Pfeiffer RM, et al. Endometrial thickness and risk of breast and endometrial carcinomas in the prostate, lung, colorectal and ovarian cancer screening trial. *Int J Cancer*. 2014;134(4):954–960.
10. Emons G, Beckmann M, Schmidt D, Mallmann P; Group UcotGOW. New WHO classification of endometrial hyperplasias. *Geburtshilfe Frauenheilkd*. 2015;75(2):135. doi:10.1055/s-0034-1396256
11. Gayther SA, Pharoah PD. The inherited genetics of ovarian and endometrial cancer. *Curr Opin Genet Dev*. 2010;20(3):231–238. doi:10.1016/j.gde.2010.03.001
12. Banno K, Yanokura M, Iida M, Masuda K, Aoki D. Carcinogenic mechanisms of endometrial cancer: involvement of genetics and epigenetics. *J Obstet Gynaecol Res*. 2014;40(8):1957–1967. doi:10.1111/jog.12442
13. Lee W-L, Yen M-S, Chao K-C, et al. Hormone therapy for patients with advanced or recurrent endometrial cancer. *J Chin Med Assoc*. 2014;77(5):221–226. doi:10.1016/j.jcma.2014.02.007
14. Yin S-Y, Wei W-C, Jian F-Y, Yang N-S. Therapeutic applications of herbal medicines for cancer patients. *Evid Based Complementary Altern Med*. 2013;1–15.
15. Firenzuoli F, Gori L. Herbal medicine today: clinical and research issues. *Evid Based Complementary Altern Med*. 2007;4(S1):37–40. doi:10.1093/ecam/nem096
16. Petrovska BB. Historical review of medicinal plants' usage. *Pharmacogn Rev*. 2012;6(11):1. doi:10.4103/0973-7847.95849
17. Zheng J, Zhou Y, Li Y, Xu D-P, Li S, Li H-B. Spices for prevention and treatment of cancers. *Nutrients*. 2016;8(8):495. doi:10.3390/nu8080495
18. Noorafshan A, Ashkani-Esfahani S. A review of therapeutic effects of curcumin. *Curr Pharm Des*. 2013;19(11):2032–2046.
19. Hewlings S, Kalman D. Curcumin: a review of its' effects on human health. *Foods*. 2017;6(10):92. doi:10.3390/foods6080062
20. Izui S, Sekine S, Maeda K, et al. Antibacterial activity of curcumin against periodontopathic bacteria. *J Periodontol*. 2016;87(1):83–90. doi:10.1902/jop.2015.150260
21. Farhood B, Mortezaee K, Goradel NH, et al. Curcumin as an anti-inflammatory agent: implications to radiotherapy and chemotherapy. *J Cell Physiol*. 2018;234(5):5728–5740.
22. Pulido-Moran M, Moreno-Fernandez J, Ramirez-Tortosa C, Ramirez-Tortosa M. Curcumin and health. *Molecules*. 2016;21(3):264. doi:10.3390/molecules21030264
23. Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. *Aaps J*. 2013;15(1):195–218. doi:10.1208/s12248-012-9432-8
24. Tyagi A, Prasad S. Targeting P53 Pathway by curcumin for cancer prevention and treatment. *Cell Dev Biol*. 2015;4:2.
25. Cao AL, Tang QF, Zhou WC, Qiu YY, Hu SJ, Yin PH. Ras/ERK signaling pathway is involved in curcumin-induced cell cycle arrest and apoptosis in human gastric carcinoma AGS cells. *Journal of Asian Natural Products Research*. 2015;17(1):56–63. doi:10.1080/10286020.2014.951923
26. Feng W, Yang CX, Zhang L, Fang Y, Yan M. Curcumin promotes the apoptosis of human endometrial carcinoma cells by downregulating the expression of androgen receptor through Wnt signal pathway. *Eur J Gynaecol Oncol*. 2014;35(6):718–723.
27. Hamzehzadeh L, Atkin SL, Majeed M, Butler AE, Sahebkar A. The versatile role of curcumin in cancer prevention and treatment: A focus on PI3K/AKT pathway. *J Cell Physiol*. 2018;233:6530–6537. doi:10.1002/jcp.v233.10
28. Rashmi R, Kumar S, Karunagaran D. Human colon cancer cells lacking Bax resist curcumin-induced apoptosis and Bax requirement is dispensable with ectopic expression of Smac or downregulation of Bcl-XL. *Carcinogenesis*. 2005;26(4):713–723. doi:10.1093/carcin/bgi025
29. Kim J-H, Xu C, Keum Y-S, Reddy B, Conney A, Kong A-NT. Inhibition of EGFR signaling in human prostate cancer PC-3 cells by combination treatment with β-phenylethyl isothiocyanate and curcumin. *Carcinogenesis*. 2005;27(3):475–482. doi:10.1093/carcin/bgi272
30. Dhandapani KM, Mahesh VB, Brann DW. Curcumin suppresses growth and chemoresistance of human glioblastoma cells via AP–1 and NFκB transcription factors. *J Neurochem*. 2007;102(2):522–538. doi:10.1111/j.1471-4159.2007.04633.x
31. Fan Z, Duan X, Cai H, et al. Curcumin inhibits the invasion of lung cancer cells by modulating the PKCα/Nox-2/ROS/ATF-2/MMP-9 signaling pathway. *Oncol Rep*. 2015;34(2):691–698. doi:10.3892/or.2015.4044
32. Fu Z, Chen X, Guan S, Yan Y, Lin H, Hua Z-C. Curcumin inhibits angiogenesis and improves defective hematopoiesis induced by tumor-derived VEGF in tumor model through modulating VEGF-VEGFR2 signaling pathway. *Oncotarget*. 2015;6(23):19469. doi:10.18632/oncotarget.v6i23
33. Sharma C, Kaur J, Shishodia S, Aggarwal BB, Ralhan R. Curcumin down regulates smokeless tobacco-induced NF-κB activation and COX-2 expression in human oral premalignant and cancer cells. *Toxicology*. 2006;228(1):1–15. doi:10.1016/j.tox.2006.07.027
34. Anand P, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB. Curcumin and cancer: an "old-age" disease with an "age-old" solution. *Cancer Lett*. 2008;267(1):133–164. doi:10.1016/j.canlet.2008.03.025
35. Basnet P, Skalko-Basnet N. Curcumin: an anti-inflammatory molecule from a curry spice on the path to cancer treatment. *Molecules*. 2011;16(6):4567–4598. doi:10.3390/molecules16064567
36. Sun M, Yu F, Gong M, Fan G, Liu C. Effects of curcumin on the role of MMP-2 in endometrial cancer cell proliferation and invasion. *Eur Rev Med Pharmacol Sci*. 2018;22(15):5033–5041. doi:10.26355/eurrev_201808_15646
37. Kumar A, Sirohi VK, Anum F, et al. Enhanced apoptosis, survivin down-regulation and assisted immunochemotherapy by curcumin loaded amphiphilic mixed micelles for subjugating endometrial cancer. *Nanomedicine*. 2017;13(6):1953–1963. doi:10.1016/j.nano.2017.04.014

38. Wang Y, Liu XH, Li YH, Li O. The paradox of IL-10-mediated modulation in cervical cancer. *Biomed Rep*. 2013;1(3):347–351. doi:10.3892/br.2013.69
39. Xu H, Gong Z, Zhou S, et al. Liposomal curcumin targeting endometrial cancer through the NF-kappaB pathway. *Cell Physiol Biochem*. 2018;48(2):569–582. doi:10.1159/000491886
40. Lawrence T. The nuclear factor NF-κB pathway in inflammation. *Cold Spring Harb Perspect Biol*. 2009;1(6):1–10.
41. Porter AG, Jänicke RU. Emerging roles of caspase-3 in apoptosis. *Cell Death Differ*. 1999;6(2):99. doi:10.1038/sj.cdd.4400453
42. Yabluchanskiy A, Ma Y, Iyer RP, Hall ME, Lindsey ML. Matrix metalloproteinase-9: many shades of function in cardiovascular disease. *Physiology*. 2013;28(6):391–403. doi:10.1152/physiol.00029.2013
43. Patel SK, Jackson L, Warren AY, Arya P, Shaw RW, Khan RN. A role for two-pore potassium (K2P) channels in endometrial epithelial function. *J Cell Mol Med*. 2013;17(1):134–146. doi:10.1111/j.1582-4934.2012.01656.x
44. Sirohi VK, Popli P, Sankhwar P, et al. Curcumin exhibits anti-tumor effect and attenuates cellular migration via Slit-2 mediated down-regulation of SDF-1 and CXCR4 in endometrial adenocarcinoma cells. *J Nutr Biochem*. 2017;44:60–70. doi:10.1016/j.jnutbio.2016.12.021
45. Chen Q, Gao Q, Chen K, Wang Y, Chen L, Li XU. Curcumin suppresses migration and invasion of human endometrial carcinoma cells. *Oncol Lett*. 2015;10(3):1297–1302. doi:10.3892/ol.2015.3478
46. Arkun Y, Yasemi M. Dynamics and control of the ERK signaling pathway: sensitivity, bistability, and oscillations. *PLoS One*. 2018;13(4):e0195513. doi:10.1371/journal.pone.0195513
47. Davey RA, Grossmann M. Androgen receptor structure, function and biology: from bench to bedside. *Clin Biochem Rev*. 2016;37(1):3.
48. Liang Y, Zhang H, Wu Y, Hao Q, Wang J, Hu Y. Inhibiting effect of letrozole combined with curcumin on xenografted endometrial carcinoma growth in nude mice. *Chin J Cancer*. 2010;29(1):9–14.
49. Liang YJ, Hao Q, Wu YZ, Wang QL, Wang JD, Hu YL. Aromatase inhibitor letrozole in synergy with curcumin in the inhibition of xenografted endometrial carcinoma growth. *Int J Gynecol Cancer*. 2009;19(7):1248–1252. doi:10.1111/IGC.0b013e3181b33d76
50. Tierney BJ, McCann GA, Naidu S, et al. Aberrantly activated pSTAT3-Ser727 in human endometrial cancer is suppressed by HO-3867, a novel STAT3 inhibitor. *Gynecol Oncol*. 2014;135(1):133–141. doi:10.1016/j.ygyno.2014.07.087
51. Saydmohammed M, Joseph D, Syed V. Curcumin suppresses constitutive activation of STAT-3 by up-regulating protein inhibitor of activated STAT-3 (PIAS-3) in ovarian and endometrial cancer cells. *J Cell Biochem*. 2010;110(2):447–456. doi:10.1002/jcb.22558
52. O'Shea JJ, Schwartz DM, Villarino AV, Gadina M, McInnes IB, Laurence A. The JAK-STAT pathway: impact on human disease and therapeutic intervention. *Annu Rev Med*. 2015;66:311–328. doi:10.1146/annurev-med-051113-024537
53. Yu Z, Shah DM. Curcumin down-regulates Ets-1 and Bcl-2 expression in human endometrial carcinoma HEC-1-A cells. *Gynecol Oncol*. 2007;106(3):541–548. doi:10.1016/j.ygyno.2007.05.024
54. Wei SC, Lin YS, Tsao PN, Wu-Tsai JJ, Wu CH, Wong JM. Comparison of the anti-proliferation and apoptosis-induction activities of sulindac, celecoxib, curcumin, and nifedipine in mismatch repair-deficient cell lines. *J Formos Med Assoc*. 2004;103(8):599–606.
55. Pereira MC, Mohammed R, Van Otterlo WAL, De Koning CB, Davids H. Evaluation of the effects of aminonaphthoquinone derivatives in combination with curcumin against ER-positive breast cancer and related tumours. *Anticancer Res*. 2017;37(12):6749–6759. doi:10.21873/anticanres.12135
56. Sharma U, Pal D, Prasad R. Alkaline phosphatase: an overview. *Indian J Clin Biochem*. 2014;29(3):269–278. doi:10.1007/s12291-013-0408-y
57. Marshall AD, Bailey CG, Champ K, et al. CTCF genetic alterations in endometrial carcinoma are pro-tumorigenic. *Oncogene*. 2017;36(29):4100. doi:10.1038/onc.2017.25
58. Heudel P, Fabbro M, Roemer-Becuwe C, et al. Phase II study of the PI3K inhibitor BKM120 in patients with advanced or recurrent endometrial carcinoma: a stratified type I–type II study from the GINECO group. *Br J Cancer*. 2017;116(3):303. doi:10.1038/bjc.2016.430
59. Zhou Y, Zheng J, Li Y, et al. Natural polyphenols for prevention and treatment of cancer. *Nutrients*. 2016;8(8):515. doi:10.3390/nu8080515
60. Bordoloi D, Kunnumakkara AB. The potential of curcumin: a multitargeting agent in cancer cell chemosensitization. In: *Role of Nutraceuticals in Cancer Chemosensitization*. London: Elsevier; 2018:31–60.
61. Doello K, Ortiz R, Alvarez PJ, Melguizo C, Cabeza L, Prados J. Latest in vitro and in vivo assay, clinical trials and patents in cancer treatment using curcumin: a literature review. *Nutr Cancer*. 2018;70(4):569–578.