

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

This article was published in the following Dove Medical Press journal:
International Journal of Women's Health

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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 fared 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- κ B, 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- κ B 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-3⁴¹ 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- κ B 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 $\mu\text{mol/L}$	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	<ul style="list-style-type: none"> – 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
<ul style="list-style-type: none"> – Ishikawa cells – HEC-1B cells 	10–30 μ M	<ul style="list-style-type: none"> – Obstructs ERK signaling pathways – Inhibits MMP2/9 expression 	Inhibition of migration and invasion	Chen et al ⁴⁵
<ul style="list-style-type: none"> – Ishikawa cells – HEC-1B cells – RL-95-2 cells – SK-UT-1B cells 	– 1–20 μ M 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 μ mol/L	Reduces AR expression	<ul style="list-style-type: none"> – Inhibition of proliferation – Induction of apoptosis 	Feng et al ²⁶
Ishikawa cell line	10–30 μ M	Inhibits TREK-1	Inhibition of proliferation	Patel et al ⁴³
<ul style="list-style-type: none"> – Ishikawa cells – RL-95-2 cells 	10–50 μ M	<ul style="list-style-type: none"> – 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	<ul style="list-style-type: none"> – 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 μ M	Attenuates Ets-1 and Bcl-2 proteins	Induction of apoptosis	Yu and Shah ⁵³
HEC-1-A	50 and 100 μ M	Causes an increase in the G2/M phases	<ul style="list-style-type: none"> – 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

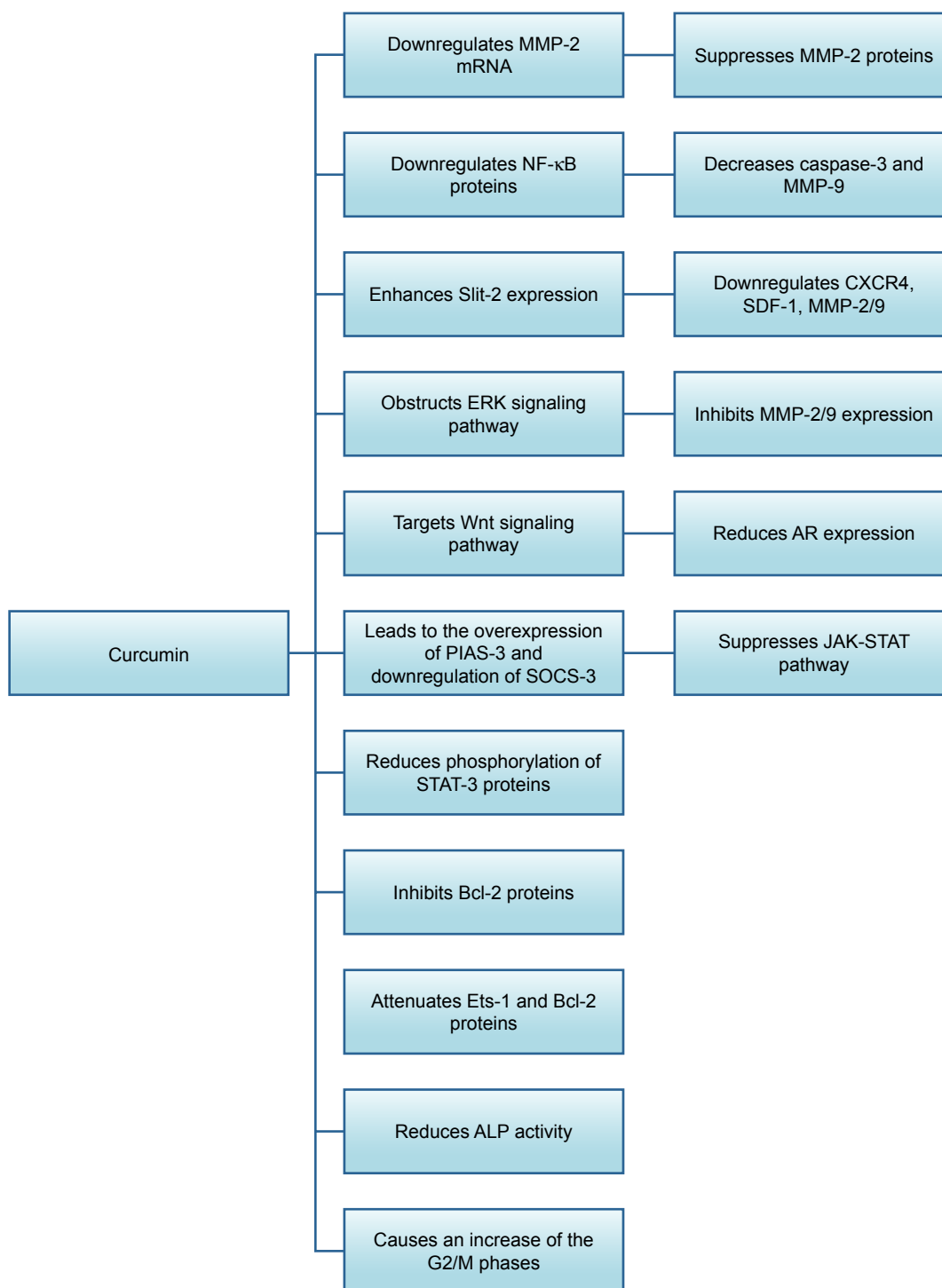


Figure 1 Effect of curcumin on different molecular targets in endometrial carcinoma.

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.

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