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Review article

Curcumin in the treatment of urological cancers: Therapeutic targets, challenges and prospects

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ABSTRACT

Urological cancers include bladder, prostate and renal cancers that can cause death in males and females. Patients with urological cancers are mainly diagnosed at an advanced disease stage when they also develop resistance to therapy or poor response. The use of natural products in the treatment of urological cancers has shown a significant increase. Curcumin has been widely used in cancer treatment due to its ability to trigger cell death and suppress metastasis. The beneficial effects of curcumin in the treatment of urological cancers is the focus of current review. Curcumin can induce apoptosis in the three types of urological cancers limiting their proliferative potential. Furthermore, curcumin can suppress invasion of urological cancers through EMT inhibition. Notably, curcumin decreases the expression of MMPs, therefore interfering with urological cancer metastasis. When used in combination with chemotherapy agents, curcumin displays synergistic effects in suppressing cancer progression. It can also be used as a chemosensitizer. Based on pre-clinical studies, curcumin administration is beneficial in the treatment of urological cancers and future clinical applications might be considered upon solving problems related to the poor bioavailability of the compound. To improve the bioavailability of curcumin and increase its therapeutic index in urological cancer suppression, nanostructures have been developed to favor targeted delivery.

1. Introduction

Cancer is a devastating disease characterized by high morbidity and mortality. Cancer currently causes 7.6 million deaths annually and this is expected to increase to 13.1 million by 2030 [1]. There are different types of cancers and each has distinct malignancy features. However, breast, lung, colorectal, prostate and pancreatic cancers along with bladder and renal cancers are the most common. For this reason, a wealth of studies has focused on developing new therapeutics for these malignancies [1–6]. Cancer can develop at any time, although the incidence rate usually increases with age. Early diagnosis of cancer greatly helps in improving patients' survival and currently, there are

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three major forms of treatment for cancer and these include surgery, chemotherapy, and radiotherapy. However, tumor cells are prone to recurrence and migration in the presence of conventional therapies and this represents a challenge for physicians. Chemotherapeutic agents eliminate both cancer and normal cells, this representing a drawback of this form of treatment, which is also associated with some debilitating side effects [7]. Furthermore, drug resistance in cancer is responsible for chemotherapy failure [8–14].

Because of low efficacy of conventional therapeutics, new types of anti-cancer agents have been considered in recent years [7]. Phytochemicals are plant-based chemicals derived from nature and they might be relevant for cancer therapy [15–19] . There are several reasons for using natural products in disease treatment to achieve cancer suppression and these include low price, multi-targeting ability and safety profile [20–27]. Vegetables, fruits, spices and grains are rich in phytochemicals and their health promoting effects have been known from ancient times [28–32]. The use of natural products in cancer treatment has undergone a significant increase since tumor cells cannot develop resistance to phytochemicals with anti-cancer activity [33–35] Furthermore, co-administration of natural products and conventional chemotherapeutic agents has considerable synergistic effect [36,37]. Natural products can also increase sensitivity of tumor cells to chemotherapy by regulating cell death mechanisms and different signaling cascades [38–42]. In the current review, we emphasize the role of curcumin as a naturally occurring compound for the treatment of urological cancers, with a focus on the molecular pathways modulated by this compound. Although some reviews have been previously published, this is an updated review with aim to shed light on new findings about role of curcumin in treatment of urological cancers. The outline of current review is different from previously published studies and due to high incidence rate of urological cancers (for instance, prostate cancer is now the most common cancer in men), this review article can provide new insight about role of curcumin in cancer therapy.

2. Search strategy

The databases like “Google scholar”, “PubMed” and “Science direct” have been used for literature review. We used words like “curcumin”, “urological cancers”, “prostate cancer”, “bladder cancer” and “renal cancer” to conduct our search.

3. Curcumin and cancer suppression: a brief review

Turmeric is a spice derived from *Curcuma longa* and it is a natural source of curcuminoids. Turmeric has three distinct bioactive compounds that include curcumin, demethoxycurcumin and bisdemethoxycurcumin. The main component of turmeric is curcumin that is also known as diferulomethane and has a molecular weight of 368.38 kDa [43]. Curcumin is present as a crystalline powder with orange-yellow color. This polyphenolic phytochemical has been extensively deployed for medicinal purposes. Its pharmacological activities are linked to its antioxidant, anti-inflammatory, analgesic, anti-cancer, and anti-diabetic properties [44–46]. Curcumin is a potent immunomodulatory agent and can interact with various cells such as dendritic cells, macrophages, natural killer cells, B and T cells to regulate inflammation and cell proliferation [47].

In recent years curcumin use has been considered in cancer treatment due to the impacts on cell death mechanism and ability to regulate tumor microenvironment components [20,44,48,49]. Curcumin is an inducer of cell death *via* down-regulation of ZAKα and subsequent suppression of JNK and NF-κB pathways [50]. In cervical cancer cells, curcumin administration impairs migration and invasion tumor cells. In this regard, curcumin has been found to reduce the expression levels of pirin to inhibit EMT [51]. By down-regulating NADPH oxidase 5, curcumin inhibits Akt signaling and increases cisplatin sensitivity of human epithelial cancer [52]. Bis-chalcones of curcumin can induce endoplasmic reticulum stress to reduce survival rate of glioblastoma [53]. HMGB1 is key to VEGF-D upregulation with subsequent angiogenesis in the context of gastric cancer. Curcumin administration decreases HMGB1 expression to down-regulate VEGF-D and therefore impair lymphangiogensis of gastric cancer cells [54]. Curcumin induces apoptosis and cell cycle arrest and increases sensitivity of tumor cells to cisplatin chemotherapy. Furthermore, it suppresses oncogenic molecular pathways like STAT3 and NF-κB, this resulting in impairment of tumor progression and enhancement of cisplatin sensitivity [20]. When reducing the growth rate of glioblastoma cells, curcumin promotes expression of PTEN that suppresses Akt/mTOR axis [55]. An important aspect to consider is that not only curcumin mediates chemo-sensitivity, but it also alleviates the adverse effects of chemotherapy, which can therefore improve quality of life of affected patients [56]. Curcumin suppresses EMT by downregulating N-cadherin, and through upregulation of E-cadherin; these events are associated with increase in colon cancer cells' sensitivity to irinotecan [57]. Furthermore, curcumin increases the levels of miRNA-34a to trigger cell cycle arrest (G0/G1 phase) in gastric tumor cells [58]. GO-Y030, an analog of curcumin, can reduce the generation of IL-10 from Th17 cells, this enhancing immunotherapy effects in cancer [59].

Despite the substantial use of curcumin in cancer treatment and the promising results that have been obtained, there are still challenges that should be addressed. The most important drawback of curcumin relates to its poor bioavailability and rapid metabolism that contributes to decrease in its anti-cancer potential *in vivo*. Therefore, it is highly recommended to use nano-scale delivery systems to improve curcumin health-promoting impacts [49]. In a recent study, curcumin-loaded superparamagnetic iron oxide nanostructures were reported to increase the sensitivity of pancreatic cancer cells to gemcitabine chemotherapy evidenced by further suppression of proliferation and invasion of the tumor cells [60]. Biodegradable polymeric nanostructures have been deployed for the co-delivery of curcumin and paclitaxel to synergistically suppress breast cancer progression; their effectiveness has been also supported *in vivo* studies in animal models [61]. These delivery systems increase the efficacy of curcumin and suggest that targeted delivery of curcumin by nanoparticles could represent a promising strategy to achieve tumor suppression [62–66].

4. Urological cancers: an overview

4.1. Bladder cancer

Bladder, prostate and renal cancers are among the most common urological malignancies that cause high mortality and morbidity worldwide. The ninth most common malignancy around the world is bladder cancer and it also represents the most common tumor of urinary tract. Up to 83,730 new cases were diagnosed in 2021 mainly in men [67–69]. There are important aspects to consider in bladder cancer, which accounts for 5–10 % of all cancer cases, and these relate to its recurrence and high treatment costs [70–73]. Urothelial carcinoma is the most common type of bladder cancer and it derives from stratified epithelium-urothelium [74]. 70–75 % of bladder malignancies consist of superficial non-muscle invasive bladder cancers (NMIBC) at the time of diagnosis [70,75–77]. The prognosis of patients with NMIBC is favorable and 5-year overall survival is 80 %. In the case of muscle-invasive bladder cancer (MIBC), 5-year survival rate is 17–57 %, and 50 % during invasion of bladder wall by tumor cells [78]. Although there are different types of therapy available for bladder cancer like surgery, chemotherapy and radiotherapy, bladder cancer is still responsible for high death rate and genetic mutations have been implicated in its progression [4,79]. Plant-derived natural products have been extensively used in the treatment of bladder cancer. As an example, resveratrol decreases the expression of miRNA-21 to suppress Akt/Bcl-2 axis and trigger apoptosis in bladder tumor [80]. Resveratrol prevents the phosphorylation of Akt, while it induces phosphorylation of MAPK,

therefore impairing cancer progression [81]. Quercetin, another phytochemical with anti-cancer activity, stimulates AMPK signaling and triggers apoptosis in bladder tumor cells [82]. Quercetin suppresses the proliferation of bladder tumor cells by increasing the activity of Ca-activated K channels [83]. Kaempferol can reduce the levels of DNMT3B *via* methylation, with consequent inhibition of protein synthesis and limitation of tumor progression [84]. Kaempferol triggers apoptosis and suppresses the proliferative potential of bladder tumor cells through inhibition of the c-Met/p38 axis [85]. Based on these studies, use of natural products might be beneficial in the treatment of bladder cancer.

4.2. Prostate cancer

Prostate cancer is the most common non-cutaneous tumor among American men [86]. Androgen-deprivation therapy (ADT) is deployed in the treatment of prostate cancer sensitive to castration; ADT, however, does not represent an effective treatment in castration-resistant prostate cancer. Targeting of androgen receptor (AR) has been considered a promising strategy to achieve prostate cancer suppression although it might also lead prostate tumor cells to proliferate in an AR-independent manner [87]. 1.3 million patients are diagnosed annually with prostate cancer and the death rate is 360,000 [88]. Surgery and radiotherapy have been beneficial in improving the survival of prostate cancer patients although advanced and metastatic prostate cancers have unfavorable prognosis, as indicated by the substantial decrease in their survival rate [89–92]. Gene therapy is a new emerging therapeutic strategy that enables targeting oncogenic pathways in prostate cancer [93]. Besides, activation of pro-survival autophagy can promote progression of prostate tumor cells [5]. As for bladder cancer, phytochemicals have been applied for the treatment of prostate cancer [94–97]. Resveratrol suppresses cancer stem cell features and EMT to increase radio-sensitivity of prostate cancer cells [98]. Resveratrol-loaded PLGA nanostructures induce apoptosis and cell cycle arrest at G1/S phase [99]. Further, resveratrol promotes the expression of E-cadherin and reduces HGF secretion to inhibit prostate cancer progression [100]. Quercetin is known to promote ROS generation and inhibit Akt signaling to limit prostate cancer progression [101]. Furthermore, quercetin induces ROS generation and mediates endoplasmic reticulum stress to increase paclitaxel sensitivity in prostate tumor cells [102]. Ginsenoside Rh2 reduces the expression of CNNM1 that suppresses angiogenesis in prostate cancer [103]. Overall, these studies highlight potential of plant derived-natural products in suppressing prostate cancer progression [104–107].

4.3. Renal cancer

One of the most common renal neoplasia is renal cancer, of which clear cell renal cell carcinoma (ccRCC) is a common subtype [108,109]. Although significant advances have been made to dissect renal cancer pathogenesis and management, its incidence rate is still increasing [110]. Patients with renal cancer may undergo recurrence or metastasis and its incidence rate is higher in men than in women. The incidence rate of renal cancer might differ based on geographical locations and the highest incidence rates have been observed in North America, Europe and Australia. The highest mortality rate for renal cancer is present in USA, Chile, Argentina and Uruguay [111]. In addition to ccRCC that represents 75 % of total renal cancer cases, papillary renal cell carcinoma, and chromophobe renal cell carcinoma are other types of renal malignancies, accounting for 1 % of all cases [112,113]. Despite different strategies having been used for renal cancer treatment, its mortality and morbidity remain high, this prompting the development of novel therapeutics to improve patients' survival [114,115]. Plant derived-natural products with anti-cancer activity have been extensively used in the treatment of renal cancer. Resveratrol can decrease the size and number of spheres in renal cancer and it suppresses Sonic Hedgehog signaling to impair stemness [116]. Resveratrol decreases the expression of VEGF and suppresses the growth of renal cancer cells [117]. A combination of quercetin and hyperoside reduces the levels of miRNA-27a as a tumor-promoting factor, to ultimately impair renal cancer progression [118]. Kaempferol can inhibit both Akt and FAK molecular pathways, therefore suppressing the invasion and metastasis of renal cancer cells [119]. Overall, these studies provide evidence that natural products could limit renal cancer progression [120,121]. In the following section, we will review the role of curcumin in the treatment of urological cancers with a focus on molecular interactions modulated by this phytochemical.

5. Curcumin and bladder cancer

Overall, curcumin is a beneficial agent in suppressing the development of bladder cancer and in increasing the sensitivity of tumor cells to therapy [122,123]. Both clinical and pre-clinical studies have confirmed the role of curcumin as a drug sensitizer that also limits progression of bladder cancer cells [124]. One of the new emerging targets in bladder cancer therapy is the Wnt/β-catenin axis. Inhibition of Wnt/β-catenin signaling by TMEM88 is important to achieve reduction in the proliferation and metastasis of bladder tumor cells [125]. Mitofusin 2 is downregulated in bladder cancer and is negatively associated with cancer stage and lymph node metastasis. Down-regulation of mitofusin 2 favors bladder tumor cells in growth and invasion. It has been reported that mitofusin 2 suppresses Wnt/β-catenin signaling, therefore exerting anti-cancer activity [126] EFEMP2 reverses EMT in bladder cancer through inhibition of the Wnt/β-catenin signaling [127]. As the Wnt/β-catenin signaling has an oncogenic role in bladder cancer [128,129] its blockade might represent a new avenue for this tumor treatment. Some studies have shown heightened expression of β-catenin in bladder cancer cells. Curcumin administration has been shown to reduce the proliferation and invasion of bladder tumor cells through inhibition of β-catenin signaling [130]. β-catenin is associated with the metastasis of cancer cells *via* EMT induction. It has been found that RNF128 down-regulation activates β-catenin signaling, this promoting EMT [131]. Increasing evidence demonstrates β-catenin as an upstream mediator of EMT, being involved in EMT induction and increased cancer metastasis [65,132,133]. Curcumin suppresses EMT *via* β-catenin down-regulation to impair bladder cancer migration [130]. In addition to EMT that mediates the metastasis of bladder cancer cells, heightened expression of matrix metalloproteinases (MMPs) increases the detachment of bladder tumor cells from the basement membrane, therefore increasing their motility. By reducing the levels and activity of MMPs, curcumin suppresses the metastatic potential of bladder cancer [74]. The oncogenic molecular pathways responsible for bladder cancer progression like mTOR, PI3K/Akt and VEGF among others, undergo inhibition by curcumin [134].

Genetic mutations are associated with cancer progression and their role has been examined and confirmed in different studies [135–137]. Based on these investigations, curcumin affects gene expression in bladder cancer therapy. An interesting aspect to consider is the involvement of epigenetic factors in tumor progression [138–141], as well as their regulation by curcumin [142]. microRNAs (miRNAs) are short non-coding RNAs consisting of up to 24 nucleotides in length that can regulate expression of other genes and play an importance role in cancer [4,143–145]. miR-7641 is an oncogenic factor that increases the invasion of breast tumor cells and confers poor prognosis [146]. Exosomes derived from cancer-associated fibroblasts promote the expression of miR-7641 to induce glycolysis and cancer stemness *via* HIF-1α upregulation [147]. Overall, down-regulation of miR-7641 impairs tumor progression and represents a potential target for effective cancer therapy [148,149]. Another study revealed the ability of curcumin in regulating miRNA-7641 to obtain bladder cancer suppression. Overexpression of miR-7641 occurs in bladder cancer and is known to promote migration of tumor cells. Furthermore, miR-7641 upregulation

was found to prevent apoptosis in bladder cancer. Curcumin administration reduces miR-7641 expression, which ultimately leads to increased levels of p16; this event triggers apoptosis and interferes with the invasion of bladder tumor cells [142]. *In vitro* data have confirmed the role of curcumin in suppressing bladder cancer progression. Curcumin exerts its anti-cancer activity in a time- and concentration-dependent manner. Curcumin at 10–40 μM promotes the expression of caspase 3/7 in triggering apoptosis; and reduces the levels of MMP-2 and MMP-9, therefore suppressing the invasion of bladder tumor cells [150].

Cancer stem cells (CSCs) are a rare population present in tumors that because of their self-renewal capacity develop new colonies for tumor progression [151,152]. LncRNA LBCS mediates SOX2 down-regulation to prevent self-renewal ability of CSCs and suppress drug resistance in bladder cancer [153]. Reduced expression of Mettl3 in CSCs impairs the progression of bladder tumor cells and inhibits angiogenesis [154]. Various molecular pathways are involved in the regulation of CSCs and stemness of bladder tumor cells. It has been reported that stimulation of Sonic hedgehog signaling is of importance for stemness and for preserving CSC features in bladder cancer [155–157]. Curcumin modulates Sonic Hedgehog signaling, therefore inhibiting cancer progression. Curcumin administration at 10, 30 and 50 μM decreases the expression of CSC markers like CD44, CD133, ALDH1-A1, Oct-4 and Nanog to suppress bladder tumor stemness. Curcumin administration prevents colony formation, impairs growth and induces apoptosis of bladder cancer cells by suppressing the Sonic Hedgehog signaling [158]. Increasing evidence has revealed a role for TROP2 in tumor progression and its association with unfavorable prognosis [159]. High levels of TROP2 promote growth and metastasis of tumor cells [160,161]. Previous work has shown that TROP2 down-regulation induces apoptosis *via* Akt/β-catenin signaling inhibition [162] TROP2 is a potential target of curcumin in cancer therapy. It has been reported and that curcumin limits the growth and invasion of bladder tumor cells and interferes with invasion *via* TROP2 down-regulation. Upon inhibition of TROP2 by curcumin, a significant reduction in the expression of downstream targets like cyclin E1 occurs; whereas the expression of p27 increases to impede bladder cancer progression [163].

PI3K/Akt signaling is an oncogenic factor in bladder cancer. Demethoxycurcumin suppresses PI3K/Akt signaling in triggering apoptosis in bladder cancer cells [164]. The down-regulation of PI3K/Akt by flaccidoxide leads to induction of apoptosis in bladder tumor [165]. CTHRC1 activates the PI3K/Akt axis to enhance growth and metastasis of bladder tumor cells [166]. Therefore, inhibition of PI3K/Akt could limit bladder cancer progression [167,168]. Curcumin administration at 0–45 μM inhibits PI3K/Akt axis, while it promotes c-Myc expression in a time-dependent manner; this triggers apoptosis and reduces viability of bladder tumor cells [169]. Noteworthy, *in vivo* studies have also confirmed the potential of curcumin in triggering apoptosis and reducing bladder tumor progression [170].

One of the hallmarks of cancer cells is their cell cycle progression [171]. Aurora A is a new emerging target in cancer as it can promote growth and invasion of tumor cells. Aurora A overexpression is responsible for cell cycle progression and mediates drug resistance [172–175]. Additional studies have indicated that curcumin decreases the expression of aurora A and histone H3, the Aurora A downstream target, to prevent the generation of monopolar spindle, induce cell cycle arrest (G2/M phase) and decrease cell division [176]. Curcumin ability in impeding cancer progression, including bladder cancer is attributed to EMT inhibition [177]. Specificity protein (Sp) transcription factors undergo upregulation in bladder tumor. Curcumin exerts anti-cancer activities by reducing the levels of Sp1, Sp3 and Sp4 [178]. Upon inhibition of YAP/TAZ axis, curcumin induces the degradation of KLF5 *via* proteasomal pathway to impair progression of bladder tumor cells [179].

Two important strategies in the treatment of bladder cancer include radiotherapy and chemotherapy. In addition to the fact that radiotherapy and chemotherapy are associated with adverse effects, bladder tumor cells develop resistance to these therapeutic modalities and different underlying mechanisms are involved in these processes [180–186]. Proliferation and survival of bladder tumor cells exposed to radiotherapy increase due to activation of DNA repair mechanism. Radiotherapy exerts lethal impact by triggering DNA damage. Curcumin decreases the volume of bladder tumor cells and interferes with their migration and invasion. Furthermore, curcumin prevents DNA damage repair to prevent radio-resistance in cancer cells [187]. Most studies have focused on the ability of curcumin to act in synergy with chemotherapy and in reversing drug resistance [188–190]. A combination of curcumin and resveratrol might help in regulating factors involved in chemoresistance. Further, this combination was shown to suppress metastasis of bladder cancer cells [191] through PARP upregulation [192]. Notably, a combination of curcumin and light is of importance in impairing progression of bladder tumor cells and promotes efficacy of curcumin in this case [191].

Although cisplatin is a potent anti-cancer agent used in the treatment of bladder cancer, it has limitations due to development of resistance.

Table 1
Curcumin as an inhibitor of bladder cancer progression.

In vitro/ in vivo	Cell line/ Animal model	Study design	Remarks	Refs
In vitro	RT112, UMUC3, and TCCSUP cells	0.2 μg/ml	Preventing migration A combination of curcumin and visible light is important in suppressing bladder cancer progression	[191]
In vitro	EJ bladder cancer cells	0–45 μM	Apoptosis induction Inhibition of PI3K/Akt signaling c-Myc overexpression	[169]
In vitro	5637 and WH bladder cancer cells	10 and 20 μM	Inhibition of YAP/TAZ axis to increase degradation of KLF5	[179]
In vitro	253 J-Bv and T24 cells	5–20 μM	ROS generation Activation of ERK1/2 signaling Increasing cisplatin sensitivity of bladder cancer cells	[197]
In vitro	T24, J82 and TCCSUP cells	10 μM	miRNA-203 overexpression by curcumin to suppress Src/Akt axis in bladder cancer therapy	[201]
In vitro	T24 cells	0–30 μM	Cell cycle arrest Triggering mitotic spindle defect Down-regulation of Aurora A	[176]
In vitro	T24 cells	0–20 μM	Inhibition of ERK1/2 signaling to repress tumor growth	[205]
In vitro *In vivo*	Immune deficient mice	–	Synergistic co-delivery of siRNA and curcumin Tumor proliferation suppression	[206]
In vitro *In vivo*	MBT-2 cell line C3H female mice	10 μmol/L	Curcumin improves anti-cancer activity of Bacillus Calmette-Guerin Upregulation of TRAIL receptors Inhibition of NF-kB signaling	[207]
In vivo	Mice	100 mg/kg	MAPK down-regulation EMT inhibition Preventing bladder cancer progression caused by tobacco smoke	[208]
In vitro	KU-7 cells	0–100 μM	Down-regulation of NF-kB by curcumin Apoptosis induction Reducing generation of cytokines	[209]
In vitro	T24 cells	–	COX-2 down-regulation G2/M arrest by curcumin in bladder tumor cells	[210]
In vitro	5637 cells and BFTC 905 cells	10 μM	HO-1 is induced by curcumin; using HO-1 inhibitors promotes curcumin anti-cancer activity	[211]

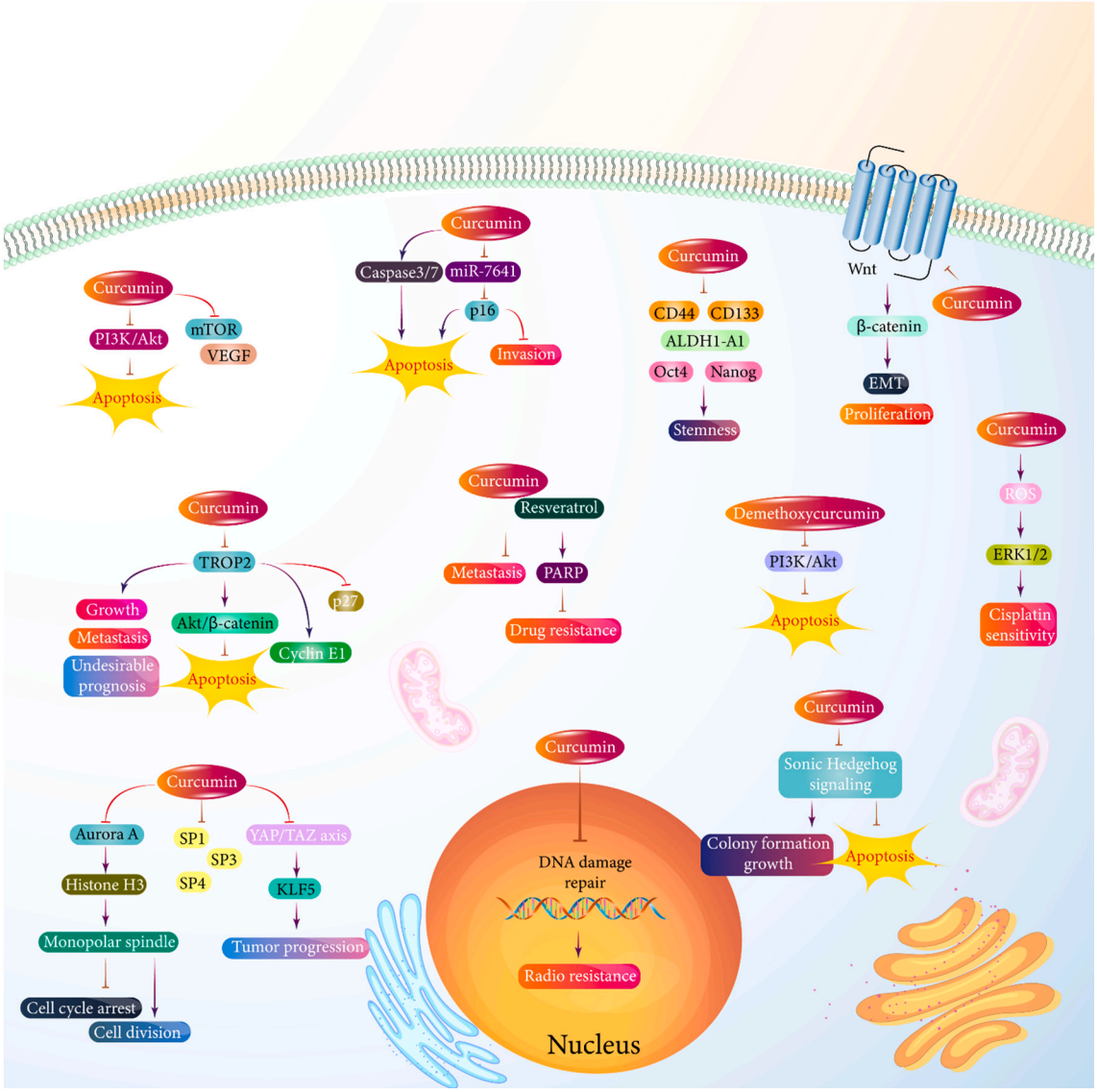

Fig. 1. Curcumin in bladder cancer treatment. Apoptosis induction and cell cycle arrest are the mechanisms through which curcumin suppresses bladder cancer. The combination with other agents such as resveratrol can potentiate anti-tumor activity of curcumin. Furthermore, curcumin promotes DNA damage to limit bladder tumor progression.

Circ0008399 cooperates with WTAP to increase methyltransferase activity and expression, this being a key step in triggering cisplatin resistance in bladder cancer [193]. Down-regulation of HNRNPU prevents DNA damage repair and promotes sensitivity of bladder tumor cells to cisplatin chemotherapy [194]. STAT3 and FOXO1 are additional regulators modulating drug sensitivity/resistance in bladder cancer [195,196]. There is evidence that curcumin not only prevents cisplatin resistance, but also boosts the anti-cancer properties of this agent. It has also been reported that curcumin mediates ROS generation; this induces ERK1/2 signaling that, in turn, potentiates the effect of cisplatin in suppressing bladder cancer [197]. To increase curcumin efficacy, nanoscale delivery systems have been developed and subsequently tested *in vitro* and *in vivo* [198,199]. The potential of curcumin and associated regulatory effects on the various molecular pathways in suppressing bladder cancer progression have been discussed in various studies [200–211] and summarized in Table 1. Fig. 1 shows the role of curcumin in bladder cancer inhibition.

Overall, these studies clearly support the role of curcumin in regulating molecular pathways and in suppressing bladder cancer progression. It has been shown that curcumin regulates the levels of miRNAs and circRNAs in bladder cancer. Future studies should focus on the role of curcumin in regulating lncRNA expression and in the inhibition of bladder cancer progression. Furthermore, additional important pathways regulated by curcumin and governed by STAT3 and PTEN, should be also investigated in future studies. Although nanostructures have been designed for curcumin delivery, studies focusing on nanotheranostics would be preferable to achieve both delivery of curcumin and bioimaging of bladder cancer.

6. Curcumin and prostate cancer

The best-known mechanism through which curcumin reduces prostate cancer progression is related to induction of apoptosis [212]. Increasing evidence demonstrates that curcumin regulates autophagy in various diseases, including cancer [213–217]. Additional data have indicated that curcumin induces both apoptosis and autophagy in prostate cancer therapy. Curcumin induces these cell death mechanisms *via* iron chelation and by enhancing the expression of TfR1 and IRP1. The use of 3-MA, an autophagy inhibitor, promotes curcumin ability to induce apoptosis in prostate cancer, supporting the notion that

autophagy exerts a pro-survival function [212]. It is important noting that autophagy may promote prostate cancer progression; for this reason, it is crucial adding an autophagy inhibitor along with curcumin in cancer therapy. miRNAs are key players involved in prostate cancer progression, as they affect proliferation, invasion, and therapy response of tumor cells [218–220]. When considering the modulatory impact of curcumin on miRNAs [221–224], it is known that it can suppress prostate cancer progression by regulating miRNAs and downstream targets. It has been reported that curcumin increases the expression of miRNA-30a-5p. This miRNA decreases PCLAF, which, in turn, reduces the growth and invasion of prostate tumor cells. Curcumin also induces apoptosis in a concentration- and time-dependent manner [225]. Further, miRNA-143 is upregulated by curcumin and this event is key in mediating suppression of proliferation and metastasis of cancer cells. Following miR-143 upregulation by curcumin, levels of PGK1 decrease, with consequent increase in FOXD3 expression. These events limit the growth and metastasis of prostate tumor cells [226]. Furthermore, cadmium is known as one of the important risk factors for prostate carcinogenesis and tissue levels of cadmium in prostate have been linked with the malignant disease. [227–229]. Future studies should focus on the role of curcumin in reversing cadmium-mediated prostate cancer development. Besides, zinc-curcumin complexes have shown high anti-cancer activity [230] and their function in regulating prostate cancer progression should be also evaluated in the near future.

miR-34a is a new emerging target in cancer therapy. This onco-suppressor miRNA decreases the levels of CDC25A to suppress cervical cancer progression [231]. In addition to reducing the growth and invasion of tumor cells [232], miR-34a inhibits drug resistance in cancer [233]. Therefore, overexpression of miR-34a is pivotal in cancer therapy. Curcumin administration induces miR-34a; this is followed by reduced expression of c-Myc and β-catenin, with consequent inhibition of tumor cells growth [234]. The high viability and survival rate of prostate tumor cells represent challenges for the treatment. Curcumin is beneficial in triggering both apoptosis and necroptosis and in decreasing viability of prostate tumor cells. It has been reported that curcumin mediates ATP depletion and induces mitochondrial dysfunction to ultimately trigger apoptosis and necroptosis [235]. Notably, the efficacy of curcumin in prostate cancer treatment can be enhanced by combination with light. A recent study has shown that low dose curcumin and light irradiation can reduce the expression of CDK1, cyclin A and B to suppress the growth and invasion of prostate tumor cells [236]. Prostate tumor cells grow in both androgen-dependent and independent manners, and this is the reason for their resistance to therapies such as ADT. The advantage of curcumin relates to the fact that this phytochemical suppresses the progression of prostate tumor cells that are both dependent and independent of androgen [237].

The factors responsible for prostate cancer progression are suppressed by curcumin. Activation of Notch-1 signaling promotes the progression of prostate cancer. Overexpression of Notch-1 ensures the survival of prostate tumor cells and enhances their migratory ability. Curcumin administration suppresses the growth and invasion of prostate tumor cells in a time- and concentration-dependent manner. It has been reported that curcumin blocks the DNA-binding activity of NICD, the active product of Notch-1. It also reduces the expression of MMP-2 and MT1-MMP, in this way interfering with prostate cancer invasion [238]. Curcumin analogs can also affect prostate cancer progression. As an example, Dehydrozingerone (DZG), a bioactive compound of curcumin, suppresses progression of prostate tumor cells *in vitro* and *in vivo* by limiting growth and angiogenesis. DZG has higher serum concentration when compared to curcumin. After intraperitoneal administration, it remains in the blood for 3 h, having a longer half-life and better a biodistribution profile than curcumin [239].

Development of castration-resistant prostate cancer depends on intratumoral androgen biosynthesis and curcumin might be considered as an ideal agent in this context. Curcumin oral administration at 200 mg/kg/day prevents androgen generation in prostate cancer and

Table 2
Curcumin administration and prostate cancer therapy.

In vitro/In vivo	Cell line/Animal model	Study design	Remark	Refs
In vitro	PC3 cells	–	Co-delivery of curcumin and doxorubicin with functionalized graphene oxide nanoparticles Cargo release in response to pH Cancer suppression	[279]
In vitro *In vivo*	PC3 cells Mice	–	Delivery of curcumin by single-walled carbon nanotubes in prostate cancer therapy Suppression of tumor growth Providing photothermal ablation	[280]
In vitro	PC3 cells	–	Using scorpion venom-conjugated phytosomes for the delivery of curcumin Particle size of 137.5–298.4 nm Zeta potential of 2.9–26.9 mV Apoptosis and necrosis induction Cell cycle arrest	[281]
In vitro	PC3 cells	–	Application of PLGA nanoparticles for the delivery of curcumin More cytotoxicity against cancer cells than curcumin alone Apoptosis and autophagy induction	[282]
In vitro	LNCaP and PC3 cells	15 μM	Combination of curcumin and As_2O_3 suppresses prostate cancer progression Growth inhibition Apoptosis induction Angiogenesis inhibition	[283]
In vitro	DU145 cells	–	Curcumin-loaded nanoliposomes suppress tumor progression	[284]
In vitro	TRAMP C1 cells	1000 nM	Hypomethylation of Nrf2 promoter Activation of Nrf2 signaling	[285]
In vitro	DU145 cells	–	Co-delivery of curcumin and resveratrol by alginate nanoparticles Particle size of 60.23 nm Up to 70.99 % encapsulation efficiency High cellular uptake Suppression of tumor progression	[286]
In vitro *In vivo*	LNCaP cells Mice	30 mg/kg	Inhibition of JNK pathway Apoptosis induction Suppression of cancer cell proliferation	[287]
In vitro	PC3 cells	25 μM	Preventing ROS generation EMT inhibition Decrease in tumor cell metastasis Down-regulation of CXCR4 and IL-6	[288]
In vitro *In vivo*	PC3 cells Immunodeficient mice	15 μM	Down-regulation of CXCL1 and CXCL2 Apoptosis induction Proliferation inhibition Preventing metastasis *via* COX-2, SPARC and EFEMP down-regulation	[289]

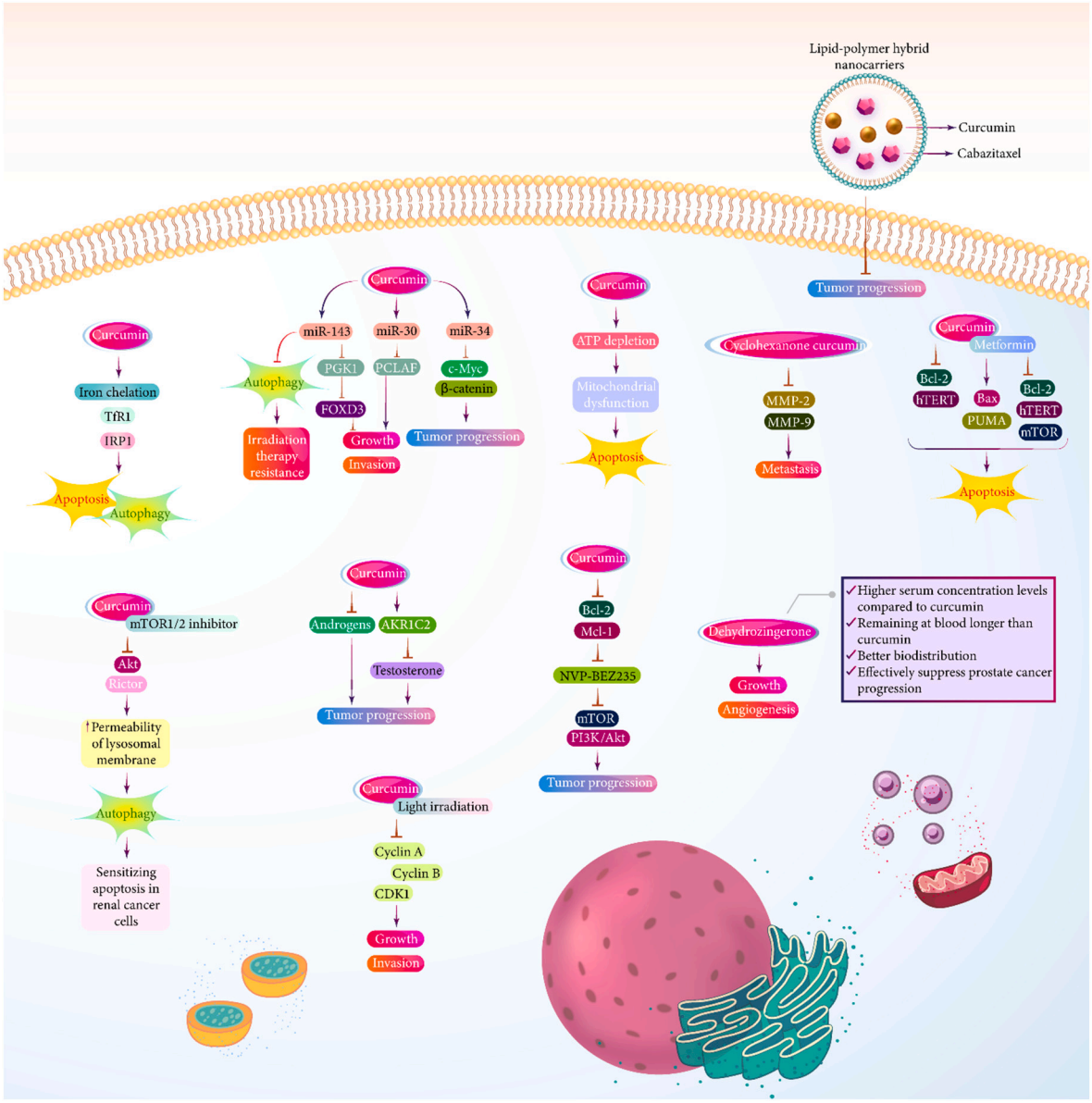

Fig. 2. Curcumin in prostate cancer treatment. Curcumin limits prostate cancer metastasis by downregulating MMPs and by inhibiting angiogenesis. Furthermore, curcumin decreases the expression of Bcl-2 and Mcl-1 to induce apoptosis and can affect autophagy.

inhibits testosterone production by upregulating AKR1C2, this impairing tumor progression [240]. Combination therapy has been of importance in impeding progression of cancer cells [241,242]. Increasing evidence has supported the role of metformin as a potent anti-prostate cancer agent [243–246]. A recent study has used a combination of curcumin and metformin to suppress the progression of prostate tumor cells. The authors have reported increased efficacy of curcumin and metformin combination in prostate cancer suppression. The synergistic effects depend on curcumin reduction of Bcl-2 and hTERT, metformin-induced upregulation of Bax and PUMA, and metformin downregulation of hTERT, mTOR, p53 and Bcl-2. These events trigger apoptosis and suppress the progression of prostate tumor cells [247].

Curcumin can also be used to sensitize prostate tumor cells to therapy. As prostate cancer cells depend on hormones for their progression, castration has been considered an ideal strategy in this context. However, the resistance of prostate cancer cells to castration would compromise efficacy of surgery. Curcumin has shown the ability to limit the progression of castration-resistant prostate cancer. Cyclohexanone curcumin analogs reduce the expression of MMP-2 and MMP-9 and suppress prostate cancer metastasis by preventing degradation of extracellular matrix. *In vivo* studies have also demonstrated the ability of curcumin analogs to suppress the growth and angiogenesis in mice [248]. Curcumin and its analogs were found to induce apoptosis and cell cycle arrest at G2/M phase in castration-resistance prostate cancer [249]. One of the molecular mechanisms involved in prostate cancer is autophagy, the modulation of which could be deployed in prostate cancer therapy [250–254]. Autophagy inhibition by curcumin increases the sensitivity of prostate tumor cells to radiation therapy. In this regard, curcumin promotes the expression of miR-143 to mediate autophagy inhibition and therefore re-sensitizes prostate tumor cells to radiation therapy [255].

Nanostructures have been used for the delivery of curcumin in prostate cancer therapy [256]. Curcumin-loaded nanostructures have been used to suppress the progression of docetaxel-resistant, castration-resistant prostate tumor cells. The lipid-based nanoparticles had curcumin encapsulated and they had a particle size of 150 nm or less. Their loading efficiency was 7.5 % and entrapment efficiency was 90 %. These curcumin-loaded nanoparticles demonstrated superior cytotoxicity

against prostate tumor cells and they effectively inhibited cancer progression [257]. In another study, curcumin- and cabazitaxel-*co*-loaded lipid-polymer hybrid nanostructures have been developed; these had particle size of 121.3 nm, zeta potential of 23.5 mV and effectively accumulated at the tumor [258]. Based on these investigations, the potential of curcumin in prostate cancer suppression has been validated in several prior studies [259–278]. Future studies should therefore evaluate the role of curcumin in the treatment of prostate cancer patients. Curcumin induces apoptosis and cell cycle arrest and its analogs have shown higher anti-prostate cancer activity. Curcumin anti-cancer activity enhances significantly when using nanostructures (Table 2 and Fig. 2), [279–289]. There are two important limitations associated with the use of curcumin in prostate cancer treatment. Curcumin regulates apoptosis and autophagy as programmed cell death mechanisms involved in prostate cancer suppression. More studies should be planned to assess the role of curcumin in affecting ferroptosis and mitophagy as additional important mechanisms. Furthermore, curcumin has been shown to regulate MMPs, therefore inhibiting prostate cancer metastasis. However, no studies have tested that how curcumin can actually regulate EMT in prostate cancer therapy. This should be therefore addressed in future studies.

7. Curcumin and renal cell carcinoma

Curcumin has shown effectiveness in suppressing the progression of renal cancer cells [290–293]. Nuclear factor-kappaB (NF-κB) signaling has been implicated in tumor progression and therapy resistance [144,294–297]. Noteworthy, NF-κB can induce radio-resistance in various tumors [298,299]. In tumor cells exposed to radiotherapy, cancer-associated fibroblasts induce NF-κB signaling that increases tumor cell viability [300]. Inhibiting NF-κB signaling results in cancer cell radio-sensitivity [299]. LncRNA NKILA induces NF-κB signaling, which, in turn, increases progression of laryngeal cancer cells and triggers radio-resistance [301]. Interference with NF-κB signaling is key to induce radio-sensitivity [302] and this is the mechanism by which curcumin operates in renal cancer treatment. Curcumin administration impairs the proliferation of renal cancer cells and mediates DNA damage. Furthermore, curcumin induces apoptosis and G2/M arrest. Curcumin suppresses NF-κB signaling and related molecular pathways such as VEGF and COX2 to enhance radio-sensitivity of renal cancer cells [303]. Mammalian target of rapamycin (mTOR) signaling is an oncogenic pathway in renal cancer. Decreased phosphorylation of mTOR is associated with a decrease in growth of renal tumor cells [304]. Inhibition of mTOR signaling by simvastatin impairs the metastatic potential of renal cancer cells [305]. It has been reported that curcumin suppresses mTOR signaling and reduces the levels of MMP-2 and MMP-9, facilitating apoptosis and decreasing the invasion of renal tumor cells [306]. Activation of PI3K/Akt signaling promotes renal cancer progression. DUXAP9 can activate PI3K/Akt signaling to enhance growth and metastasis [307]. Nobiletin and eupatilin suppress the PI3K/Akt signaling, this resulting in apoptosis induction and reduction in renal cancer cell survival [308]. Eupatilin inhibits PI3K/Akt signaling in mediating apoptosis in renal cancer [309]. Akin to other anti-cancer agents, curcumin at 10–100 μM inhibits PI3K/Akt signaling and reduces the expression of cyclin B1. This results in cell cycle arrest, impaired proliferative ability and decreased viability of renal cancer cells [310].

Sunitinib is used for the treatment of renal cancer and its efficacy could be potentiated upon addition of curcumin. Curcumin prevents the phosphorylation of Rab to mediate down-regulation of cyclin D1, which, in turn, limits tumor progression while enhancing cancer cell sensitivity to sunitinib [311]. The invasion potential of renal cancer cells mainly depends on EMT induction. TRIM24 promotes the expression of N-cadherin and β-catenin that favor renal cancer cell metastasis by inducing EMT [312]. In contrast, RUNX3 decreases miR-6780a-5p expression to upregulate E-cadherin and reduce the progression of renal cancer cells through EMT inhibition [313]. miR-124 and miR-203 jointly reduce the levels of ZEB2, this also leading to EMT inhibition and limitation of renal cancer cell progression [314]. It has been reported that cigarette smoking is associated with EMT induction in enhancing renal cancer cell progression. Curcumin administration inhibits the ERK5/AP-1 axis to reverse EMT *via* E-cadherin upregulation, and through vimentin, N-cadherin and TWIST down-regulation [315].

Potassium bromate ($KBrO_3$) is an FDA approved additive that is still used in some countries as an oxidizing agent in food [316]. Pre-clinical studies have shown that $KBrO_3$ promotes oxidative stress and favors renal cancer development, this being reversed by curcumin [317–319]. Furthermore, $KBrO_3$ promotes inflammation and proliferation, while it inhibits apoptosis, all mechanisms being negated by curcumin [320]. One of the problems associated with the treatment of renal cancer is the ability of tumor cells to develop resistance to apoptosis. Curcumin administration appears to be beneficial because it sensitizes renal tumor cells to apoptosis. It has been reported that curcumin promotes the expression of death receptor 5 (DR5) *via* ROS generation and induces apoptosis of renal cancer cells by activating TRAIL pathway [321]. Furthermore, curcumin increases the levels of p53 *via* YAP upregulation. This enhances the ability of temsirolimus to trigger apoptosis of renal cancer cells [322]. It has also been reported that curcumin down-regulates Bcl-2 and Mcl-1 to increase renal cancer suppression by

Table 3
Curcumin in treatment of renal cancer.

In vitro/ *In vivo*	Cell line/ Animal model	Study design	Remark	Refs
In vitro	ACHN cells line	5–80 μmol/L	Proliferation inhibition DNA damage induction Cell cycle arrest at G2/M phase Increasing radio-sensitivity NF-κB signaling inhibition	[303]
In vitro	786-O cells	0–50 μmol/L	Inhibition of tumor cells growth Inhibition of mTOR signaling Decreasing levels of MMP-2 and MMP-9	[306]
In vitro	RCC-949 cells	20 and 100 μM	Decreasing viability of tumor cells Cell cycle arrest Inhibition of PI3K/Akt signaling	[310]
In vitro	786-O and ACHN cell lines	2 μM	Inhibition of ERK5/AP-1 signaling EMT inhibition	[315]
In vitro	ACHN cell lines	–	Exerting chemo-preventive activity Preventing inflammation Apoptosis induction Preventing tumorigenesis linked to $KBrO_3$	[320]
In vitro	Caki-1 and OS-RC-2 cells	–	Apoptosis induction Potentiating temsirolimus effects in renal cancer therapy YAP down-regulation to promote p53 expression	[322]
In vitro	ACHN cell lines	30 μM	Apoptosis induction Down-regulation of Bcl-2 and Mcl-1 p53 overexpression	[323]
In vitro *In vivo*	Caki cells Xenograft model	20 μM	A combination of curcumin and mTORC1/2 inhibitor induces apoptosis Tumor growth inhibition in xenografts Autophagy induction	[324]
In vitro	Caki cells	10–80 μM	Inducing apoptosis and decreasing viability of tumor cells ROS generation Cytochrome C release Caspase-3 overexpression	[329]

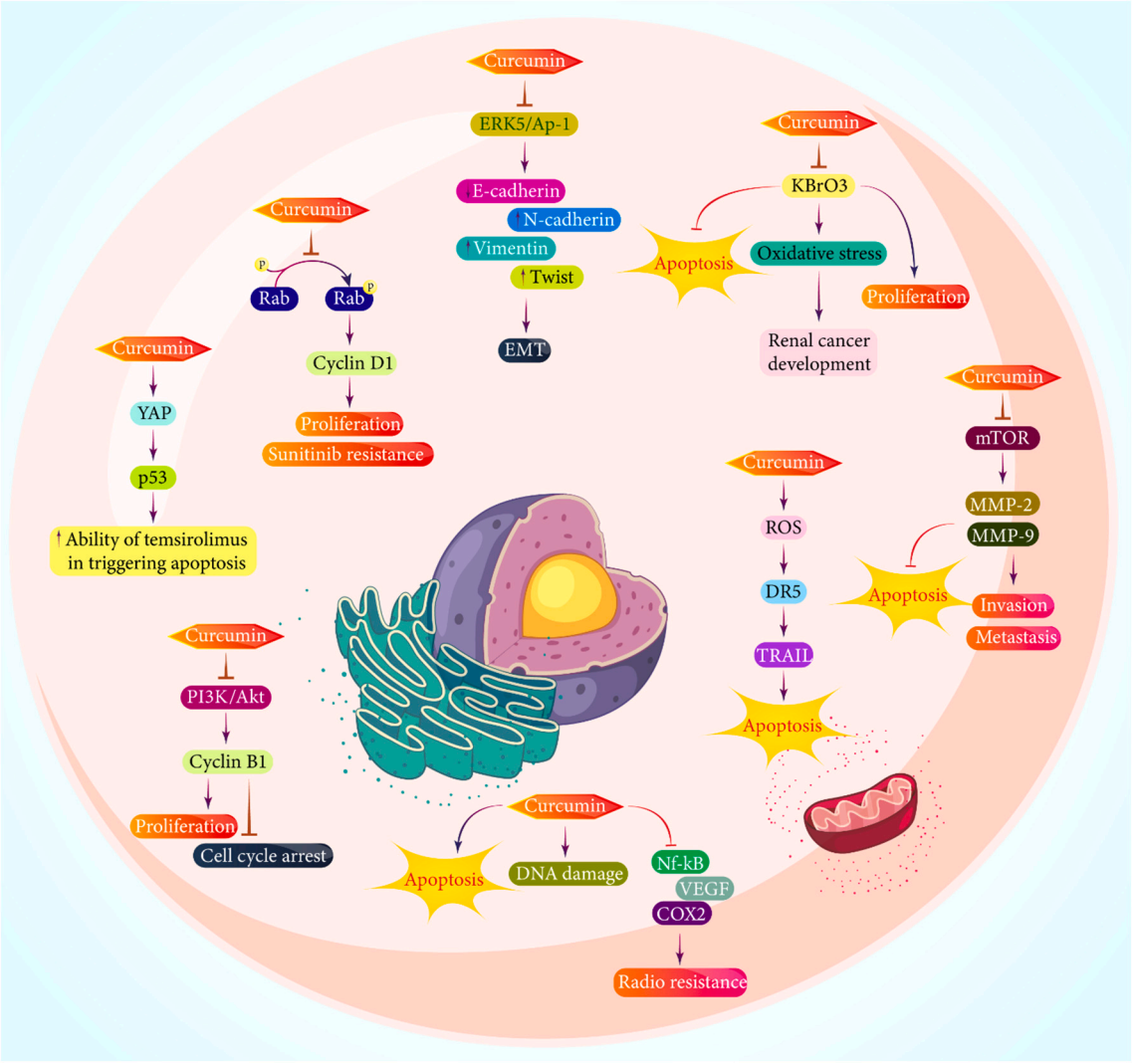

Fig. 3. Curcumin as a potent anti-cancer agent in renal cancer treatment. By inducing oxidative stress, curcumin promotes apoptosis and decreases the proliferation of renal cancer cells. Furthermore, curcumin down-regulates MMP-2 and MMP-9 levels and decreases renal cancer invasion. Finally, it can also induce DNA damage and is beneficial in increasing radio-therapy and drug sensitivity of renal cancer cells.

NVP-BEZ235 as mTOR and PI3K/Akt inhibitors [323]. By increasing the permeability of lyosomal membrane, mTORC1/2 inhibitors and curcumin induce autophagy to sensitize apoptosis in renal cancer cells. Curcumin and mTORC1/2 inhibitors induce autophagy by decreasing the levels of Akt and Rictor [324]. As autophagy may have a pro-survival role in cancer and its capacity in apoptosis inhibition [325–328], further studies should carefully focus on autophagy induction for promoting apoptosis in renal cancer The best known pathway through which curcumin and its analogs trigger apoptosis in renal cancer involves ROS generation, cytochrome C release and overexpression of caspase-3 [329]. Table 3 and Fig. 3 summarize the role of curcumin in renal cancer treatment. Overall, the studies highlighted above show that curcumin suppresses renal cancer metastasis by down-regulating MMPs and through inhibition of EMT. Future studies should evaluate how curcumin affects autophagy in regulating renal cancer progression. Furthermore, since different studies have focused on the ability of curcumin to regulate PI3K/Akt signaling, additional investigations should evaluate the impact of curcumin on PTEN signaling, an upstream regulator of this pathway. Future studies should also test the potential of nanostructures for the delivery of curcumin in renal cancer treatment.

8. Conclusion and remarks

As affordable and effective compounds in tumor cell suppression, plant derived-natural products have been extensively used in cancer treatment in recent years. Curcumin has been used in the treatment of various cancers including urological tumors. The potential of curcumin in cancer suppression is linked to the regulation of various biological mechanisms related to tumor progression. Furthermore, curcumin can affect different molecular pathways in cancer therapy. The present review has provided an updated discussion on the role of curcumin in suppressing urological cancers like bladder, prostate and renal cancers.

Curcumin has been found to affect several factors involved in bladder cancer, like Wnt/β-catenin, mTOR, PI3K/AKT and VEGF. By reducing the expression of these factors, curcumin limits bladder cancer progression. Curcumin has a role in the inhibition of EMT and MMP, with both promoting motility of bladder cancer cells. Epigenetic factors such as miRNAs are also affected by curcumin. Additional effects mediated by curcumin include stemness and CSC suppression; apoptosis induction and downregulation of Aurora A, thus resulting in cell cycle arrest in tumor cells.

In prostate cancer therapy, curcumin has been beneficial in triggering apoptosis and cell cycle arrest. Curcumin can impair progression

of castration-resistance prostate cancer cells and can prevent production of androgen. Curcumin increases the sensitivity of prostate cancer cells to chemotherapy and radiotherapy. Curcumin nanoparticles have been developed to improve the agent's anti-cancer activity. Interestingly, curcumin analogs demonstrate superior serum concentration and bio-distribution compared to curcumin and might be therefore considered as additional therapeutic options for prostate cancer.

Radio-resistance and chemoresistance are two major challenges in renal cancer treatment. Increasing evidence has shown the ability of curcumin in enhancing the sensitivity of renal tumor cells to radio-therapy and chemotherapy. Curcumin mediates DNA damage to induce apoptosis. Curcumin favors pro-death autophagy, thus sensitizing renal cancer cells to apoptosis. Curcumin mediates cell cycle arrest and limits cancer cell progression by inhibiting EMT. The most important molecular pathways regulated by curcumin in the treatment of renal cancer include VEGF, COX2, mTOR and PI3K/Akt.

Based on the literature presented above, curcumin can be extensively used in the treatment of patients with urological cancers. However, before testing curcumin in clinical trials, some of its limitations should be overcome, especially the poor bioavailability. *In vitro* studies indicate that curcumin inhibits the progression of urological cancers with high efficacy. Although *in vivo* studies support the role of curcumin in urological cancer therapy, efficacy is lower when compared to *in vitro* studies. Future studies should aim at developing nanostructures to favor curcumin-targeted delivery and enhance its therapeutic index.

Declaration of competing interest

The authors declare no conflict of interest.

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