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REVIEW

Targeting Major Signaling Pathways of Bladder Cancer with Phytochemicals: A Review

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ABSTRACT

Bladder cancer is the 9th most prevalent cancer worldwide and carries a protracted treatment course with significant patient expense, morbidity, and mortality. Over 95% of bladder cancers arise from the urothelium and invade into the underlying muscle layer before metastasizing. Trans-urethral resection and BCG therapy is the current first-line treatment for non-muscle invasive bladder cancer but carries a high rate of tumor recurrence and progression. The poor outcomes associated with advanced disease indicate the urgent need for new and improved treatment strategies. There is increasing investigation into the molecular signaling pathways involved in bladder cancer pathogenesis with the goal of uncovering potential therapeutic targets. This article reviews the major signaling pathways implicated in bladder cancer, including PI3K/AKT/mTOR, Ras/Raf/MEK/MAPK, NF-κB, Wnt/β-catenin, Notch, Hedgehog, Hippo, JAK/STAT, and TGF-β as well as major cellular receptors central to cancer pathophysiology, including EGFR, Her2, FGFR, and VEGF. We also discuss various naturally occurring phytochemicals that show evidence of targeting these molecular pathways including curcumin, resveratrol, green tea polyphenols, sulforaphane, erucin, genistein, genipin, baicalein, quercetin, isoquercitin, vitamin E, parthenolide, dioscin, triptolide, kaempferol, pterostilbene, isoliquiritigenin, and escin. This review highlights the potential use of these compounds in treatment of bladder cancer.

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Introduction

Bladder cancer (BC) is the 9th most common cancer worldwide, and the 5th most common cancer in the United States (1,2). Incidence of BC increases with age until peaking in the 7th decade and prevalence is four times greater in men (2,3). With a 74% 10-year recurrence rate, BC requires lifetime surveillance and treatments (2). In fact, BC carries the highest cumulative cost per patient per lifetime of all cancers from diagnosis to death, and is estimated to reach annual total healthcare expenditure of five billion US dollars by the year 2020 (4,5).

BC arises from the transitional epithelium, or urothelial layer, of the bladder in approximately 95% of cases (6). Tumors are thought to originate as noninvasive transitional cell carcinomas that progress to invasion of the underlying detrusor muscle (6). Tumors that have not progressed to muscle invasion are classified as non-muscle-invasive bladder cancer (NMIBC) and become classified as muscle-invasive bladder cancer (MIBC) upon tumor penetration of the muscle layer (7). Current standard of care therapy for low and intermediate risk non-muscle-invasive bladder cancer (NMIBC) is trans-urethral resection of tumor followed by intravesical instillations of Bacillus Calmette-Guerin for up to 1-3 years post-diagnosis (8). Unfortunately, even this regimen shows a 40% 5-year recurrence (9,10). 20% of NMIBC cases will progress to MIBC, at which point 5-year disease-specific survival drops from 85% to 42% (7). Management of MIBC often includes radical cystectomy with cisplatin-based chemotherapy in the neoadjuvant or adjuvant setting (11,12). It is notable that this treatment carries significant morbidity and adverse effects on quality of life.

Multiple signaling pathways have been investigated in pathogenesis of BC. Studies have demonstrated

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MAPK activation via mutation in tyrosine kinase signaling pathways or Ras pathway in 85% of low-grade NMIBC cases (13,14). Activation of the PI3K/AKT/mTOR, Wnt/β-catenin, and NF-κB signaling pathways have been implicated in both NMIBC and MIBC, while VEGFR and EGFR pathways have been associated with risk of invasion and metastasis (15). Investigating the molecular targets of bladder cancer pathogenesis is essential to the development of novel strategies for prevention and treatment.

The treatment of malignancy remains the greatest challenge of modern medical science. While the advent of conventional chemotherapy has greatly improved our ability to treat cancer, the immense morbidity associated with cytotoxic agents poses a significant barrier. To circumvent this pitfall of conventional therapies, cancer biologists are increasingly investigating the hidden cures that lie in the natural world. Investigation of phytochemicals for the treatment and prevention of cancer is on the rise, ranging from In Vitro and In Vivo investigations to epidemiological studies and full clinical trials (16).

Our research groups investigate signaling pathways key to the development, proliferation, and survival of bladder cancer, as well as phytochemicals that target these pathways. The purpose of this review is to summarize our current understanding of the signaling pathways that have been implicated in bladder cancer pathogenesis and the naturally occurring phytochemicals that have shown promise in targeting these pathways.

Bladder Cancer Signaling Pathways

PI3K/AKT/mTOR Signaling

The phosphoinositide 3-kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling pathway is central to the regulation of multiple cellular metabolic processes, cell growth, proliferation, and survival. The cascade initiates upon phosphorylation of PI3K by one a multitude of receptor tyrosine kinases, including endothelial growth factor receptor, insulin-like growth factor receptor, and fibroblast growth factor receptor (17). PI3K-induced signal transduction is mediated by the generation of the second messenger phosphatidylinositol (3–5)-trisphosphate (PIP3) through phosphorylation of the membrane-bound phospholipid component PIP2 (18). PIP3 works to recruit and activate the serine/threonine kinase AKT, which is brought to the plasma membrane. Once situated in the plasma membrane, AKT activates several signaling cascades involved in cellular proliferation (19). Included in these proliferative pathways is the inhibition of proapoptotic factor Bax, ubiquitination and degradation of the tumor-suppressor FOXO, and activation of mTOR (20). The activated mTOR complexes 1 and 2 phosphorylate numerous effectors of proliferation, most notably p70-S6K and 4E-BP (21).

The PI3K/AKT/mTOR pathway is controlled by several key regulatory mechanisms. mTORC1 and p70-S6K are involved in a negative feedback loop with PI3K and AKT, which contributes to the poor therapeutic efficacy of targeted inhibition of mTOR: as mTOR levels decline, PI3K and AKT levels increase and cross-talk with other growth pathways (22). A second inhibitory pathway involves the tumor suppressor phosphatase and tensin homolog (PTEN). PTEN works in the cytoplasm to dephosphorylate PIP3 and thus prevents recruitment and activation of AKT (23). PTEN has also been shown to induce cell cycle arrest through decreasing expression of cyclin D1 and inhibiting phosphorylation of MAPK (24).

Several alterations in the PI3K/AKT/mTOR pathway have been seen in bladder cancer. Loss of PTEN pathway suppression is associated with increased mortality, metastasis, and invasiveness (25). It is estimated that as high as 30% of MIBC have either mutated PTEN or loss of PTEN heterozygosity (26). Mutation of the PIK3CA gene has been reported to be present in 25% of bladder cancer cases (27). PIK3CA encodes for the catalytic domain of PI3K, and mutation is associated with low-grade superficial disease (28). Increased mTOR activity is seen in 55% MIBC and is thought to increase VEGF expression, thereby aiding tumor growth and survival through angiogenesis (29,30). Other mutations include TSC1, a downstream effector of AKT, which has been reported to occur in 11.7% of bladder cancers, and AKT mutations, which have been implicated in resistance to the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) pathway (31,32).

Ras/Raf/MEK/MAPK Pathway

The Ras/Raf/MEK/mitogen activated protein kinase (MAPK) cascade is an evolutionarily conserved pathway involved in cellular growth, differentiation, survival, and apoptosis (33). While there are six known groups of MAPKs, the prototypical MAPK pathway is mediated by extracellular signal-regulated kinases 1 and 2 (ERK1/2) (34). This cascade initiates with activation of Ras by a receptor tyrosine kinase (35). GTP-bound Ras then activates the kinase Raf, which phosphorylates and activates MEK (35). MEK activates

transcription factors Jun and Fos to enter the nucleus and increase expression of genes central to cell proliferation and survival (35). Two distinct MAPK pathways are those mediated by JNK and p38, which work to inhibit cellular proliferation and induce apoptosis (36,37).

MAPK activation through either Ras or FGFR3 mutation was shown to be present in 85% of NMIBC cases, highlighting the importance of this pathway to the pathogenesis of bladder cancer (38). It is notable that, while mutation of Ras and FGFR3 are mutually exclusive events, both lead to downstream activation of MAPK (39).

Wnt/β-Catenin Pathway

The Wnt/β-catenin pathway is highly conserved and critical to both embryological development and carcinogenesis of several cancers (40). Wnt signaling regulates a multitude of cellular processes, including motility, polarity, and stem cell renewal (40). This pathway is initiated by Wnt binding to the membrane receptor Frizzled, which phosphorylates and activates the membrane-bound effector LRP. During the inactive state, β-catenin is bound by a complex of intracellular proteins called the destruction complex, which mediate β-catenin ubiquitination and proteasomal degradation (41). Activated LRP induces translocation of the destruction complex to the membrane, where the destruction complex component Disheveled (Dvl) prevents ubiquitination of β-catenin (41). Rising levels of β-catenin enter the nucleus and lead to transcription of genes involved in growth and proliferation (41,42).

The Wnt/β-catenin pathway was first implicated in cancer with the discovery of the *APC* gene mutation in Familial Adenomatous Polyposis(43). This pathway has gained increased attention for BC, and may have prognostic significance for MIBC (44). Moreover, alteration of Wnt family molecules is observed in up to 73% of chemotherapy naïve MIBC and high-grade NMIBC (45). Silencing Wnt Inhibitory Factor 1 through CpG hypermethylation has been shown to contribute to BC pathogenesis, and loss of certain Wnt pathway inhibitors has been studied as an independent predictor of MIBC (46). Recent studies have shown Wnt signaling to be activated in approximately one third of clinical samples, and that Wnt cross-talks with the PI3K and MAPK pathways to promote tumorigenesis (47–49).

Notch Pathway

The Notch pathway is a highly conserved signaling pathway involved in embryonic developmental processes ranging from embryo polarity to cardiac development (50). The Notch family includes four single-pass transmembrane receptors referred to as NOTCH 1-4 (51). Binding of the NOTCH receptor induces cleavage of the Notch intracellular domain (NCID) followed by translocation to the nucleus to bind the transcription repressor CSL. Notch/CSL signaling has been shown to regulate several cellular proliferation pathways, including cyclinD1, c-Myc, p21, Survivin, and NF-κB (50). Oddly, both activation and inactivation of the Notch pathway have been implicated in the pathogenesis of different cancer lines (50).

The significance of the Notch pathway in BC in controversial. The pathway has been shown to be a tumor suppressor in BC, with one study reporting 60% of sampled bladder cancer lines possessing a loss-of-function mutation in the Notch pathway, specifically NOTCH 1 and 2 (52). Alternatively, low Notch signaling activity has been observed to predict increased aggressiveness of bladder cancer and worsened prognosis, which is theorized to result from increased transcription of mediators involved in epithelial-mesenchymal transition (EMT) (53,54). Indeed, suppression of Notch signaling was seen to upregulate SNAIL, SLUG, ZEB2 and Vimentin while downregulating E-cadherin. However, recent research has suggested Notch signaling to have paradoxical effects in BC. While NOTCH1 may be tumor-suppressive, NOTCH2 may promote tumorigenesis (55). Evidence found that NOTCH1 inhibits EMT, while NOTCH2 promotes EMT (55). In addition, NOTCH3 was recently shown to be upregulated in BC and to be associated with poor clinical outcomes (56). Given this complexity, further studies are warranted to dissect the individual Notch pathways.

Hedgehog Pathway

Hedgehog signaling plays a central role in embryogenesis and post-natal stem cell function (57). This pathway includes the ligands Sonic Hedgehog (SHH), Desert Hedgehog (DHH), and Indian Hedgehog (IHH), all of which bind the transmembrane receptor Patched (PTCH) (57). When bound, PTCH releases its inhibition of the protein Smoothened (SMO) which activates the GLI transcription factors to modulate transcription of hedgehog target genes in the nucleus (57). Shin et al showed In Vivo that cellular damage induced SHH expression in basal stem cells of the

urothelium (58). This event was associated with increased Wnt signaling in stromal cells and proliferation of both urothelial and stromal cells (58). Increased SHH expression has been observed in 96% of NMIBC and 52% of MIBC samples (59).

Interestingly, increased expression of PTCH2 in MIBC cell lines may reduce SHH activity (60). While high SHH expression is a hallmark of BC stem cells, loss of SHH may coincide with progression to invasive disease (60). Indeed, genetic ablation of SHH in mice demonstrated accelerated BC carcinogenesis (60). This phenomenon was thought to result from decreased expression BMPs, a prominent SHH target gene family that regulates urothelial differentiation (60).

Other Signaling Pathways

Hippo Pathway

The Hippo, or MST/WW45/LATS signaling pathway is involved in cell growth, apoptosis, and homeostasis, and has been most studied for its role in controlling organ size during embryonic development (61). This pathway is composed of a core phosphorylation cascade involving the protein kinases MST1/2, WW45, and LATS1/2, and the upstream transmembrane receptor Fat (61). The end result of this cascade is the phosphorylation and inactivation of the anti-apoptotic and pro-growth transcription factors yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) (62). Increasing evidence suggests deregulation of the Hippo pathway to be involved in BC pathogenesis. Decreased expression of MST1/2 and LATS1 has was observed in localized BC cell lines, while increased expression of YAP and TAZ was observed in high-grade and metastatic samples (61,63). It is notable that YAP1 has been implicated as a biomarker which indicates worsened prognosis and chemoresistance of BC to cisplatin (64).

JAK2/STAT3 Pathway

The Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway stimulates cell proliferation, migration, apoptosis. This pathway is initiated by the binding of ligands including cytokines, interferons, and interleukins to respective cellular receptors (65). Binding induces receptor dimerization and subsequent transphosphorylation of associated JAKs, which recruit STATs to the cell membrane (65). STATs are then phosphorylated, leading to formation of homo and heterodimers which translocate to the nucleus (65). The JAK/STAT pathway has been shown to interact with other cellular pathways, including the PI3K/AKT/mTOR pathway and MAPK/ERK pathway: activated JAKs are able to phosphorylate PI3K as well the Grb2 effector of MAPK signaling (66).

JAK2/STAT3 activation through overexpression of upstream Musashi-2 has been observed in 34% of BC samples (67). Additionally, JAK2/STAT3 activity was observed to increase migration and invasion of cancer cells (67). STAT3 activation is suggested to be an essential step in expression of MMP-1 following EGF stimulation and resultant bladder tumor migration and proliferation (68). Furthermore, a study of transgenic mice overexpressing STAT3 were seen to develop invasive disease directly from *carcinoma-in-situ*, suggesting STAT3's role in tumor invasion (69).

TGF-β Signaling

Transforming growth factor-β (TGF-β) is a cytokine that primarily functions in immunity and tissue repair (70). While TGF-β typically serves as a tumor suppressor, evidence suggests that TGF-β signaling can undergo aberrations in cancer cells to enhance proliferation, survival, and adhesion (70). TGF-β was observed to active the mTOR pathway in BC, and increased expression TGF-β receptors is associated with high-grade and muscle-invasive specimens (71). Mouse studies found ablation of TGF-β signaling to inhibit progression and invasion, as well as reduce EMT in bladder tumors (72).

Important Receptors of Bladder Cancer Signaling

Epidermal Growth Factor Receptor (EGFR) and Human Epidermal Growth Factor Receptor 2 (Her2)

EGFR and Her2 are type 1 tyrosine kinases known to be involved in the pathogenesis of several tumor types (73,74). Targeting these receptors has proven effective in lung and breast cancers, but resistance is known to develop through mutation of Ras and other downstream effectors (74). Analysis of clinical samples found EGFR expression to be present in 71% of localized BC and 69% of metastases, while HER2 expression was present in 83% of primary tumors and 74% of metastasis (75). Co-expression of these receptors was seen in more than half of all cases (75). Expression of EGFR is an independent prognostic indicator of high-grade BC and mortality (76,77). Her2/neu has been observed to be associated with

increased lymph node invasion and tumor stage, as well as poor disease-specific survival (78).

Fibroblast Growth Factor Receptor (FGFR)

FGFR is a highly conserved receptor tyrosine kinase family with four isotypes that mediated cellular proliferation, differentiation, and apoptosis (79). FGFR1 and three are the most common isotypes to be mutated in BC, with FGFR1 amplification occurring in 3% of all tumors and FGFR3 mutation occurring in 50-60% NMIBC and 10-15% of MIBC (80,81). FGFR mutation indicates better BC prognosis, with increased survival and lower risk of recurrence and progression (82,83). Interestingly, FGFR-mutant bladder cancer cells are unlikely to become invasive in the absence of co-existing deletion of CDKN2A (84). A recent phase two clinical trial found 40% response rate of non-resectable FGFR-positive bladder cancer tumors treated with an FGFR inhibitor, highlighting the potential importance of this receptor as a therapeutic target (85).

Vascular Endothelial Growth Factor Receptor (VEGF)

VEGF expression is a well-described mechanism of tumor angiogenesis in BC (86). Expression of VEGF correlates with higher grade, stage, and vascular invasion of BC, as well as worsened prognosis (87,88). VEGF has multiple functions, including inducing proliferation of cancer cells in addition to its role in angiogenesis (86). VEGF remains a potential target for BC therapy.

Transcription Factors

NF-κB Transcription Factor

Nuclear factor-kappa B (NF-κB) is a transcription factor that has been identified in almost all cell types since its discovery as a regulator of the κB light chain in B lymphocytes (89). NF-κB plays a central role in innate and adaptive immunity, and is a key pathway induced during inflammation and hypoxia (90,91). Inactive NF-κB exists in the cytosol as a complex with IκB inhibitory proteins and is most often activated by either a classical or alternative pathway (92). Classical activation begins with stimulation of inhibitor of κB kinase (IKK) which phosphorylates inhibitor of IκB (IκB), causing IκB's subsequent ubiquitin-mediated degradation (92). This frees NF-κB to translocate to the nucleus (92). The alternative pathway initiates with NF-κB inducing kinase (NIK) phosphorylating IKK and activating p100 to polyubiquitinate inhibitor molecules (91,92). Once in the nucleus, NF-κB dimers activate expression of target genes through direct binding of promoter and enhancer regions (92).

The role of NF-κB in BC remains an area of active research. BC is most often a result of chronic toxin exposure, such as cigarette smoke and aromatic amines (89). These exposures are thought to persistently induce NF-κB and other inflammatory pathways, thereby predisposing to cancerogenic aberrations (89). NF-κB induces expression of several inflammatory mediators that are linked with MIBC, such as IL-8, IL-5, and IL-20 (89,93). NF-κB is known to increase transcription of Major Metalloproteinases (MMP) 2 and 9, which are thought to aid metastasis and invasion of bladder tumors though remodeling of the extracellular matrix (94). MMPs are central to EMT in cancer cells, which is characterized by the loss of cell-cell adhesions and cell polarity of the transitional epithelium (95). EMT has been implicated as a required event immediately preceding bladder tumor invasion (95). Indeed, MMP detection in the urine, blood, and tissue is associated with high-grade, high-risk bladder cancer (96–98).

NF-κB has was shown to increase expression of anti-apoptotic genes after exposure to toxins, including survivin, cIAP-1/2, and XIAP (99,100). Additional investigation implicates NF-κB in cyclo-oxygenase-2 (COX-2) overexpression in normal bladder cells and tumor cells, an event associated with increased invasion, recurrence, and poorer prognosis (101–103).

Phytochemicals as Novel Compounds Targeting Bladder Cancer

Phytochemical have been studied for use in various pathologies and have garnered investigation for the treatment of cancer. The chemical structures and natural sources of major phytochemicals that have shown potential for the treatment of BC are presented in Figures 1 and 2, and their targets are listed in Figure 3 and Table 1.

Curcumin

Curcumin is the primary curcuminoid of turmeric and has been investigated for treatment of various medical conditions (104,105). Curcumin is a polyphenol and contains a β-diketone moiety that is subject to keto − enol tautomerization, causing immense

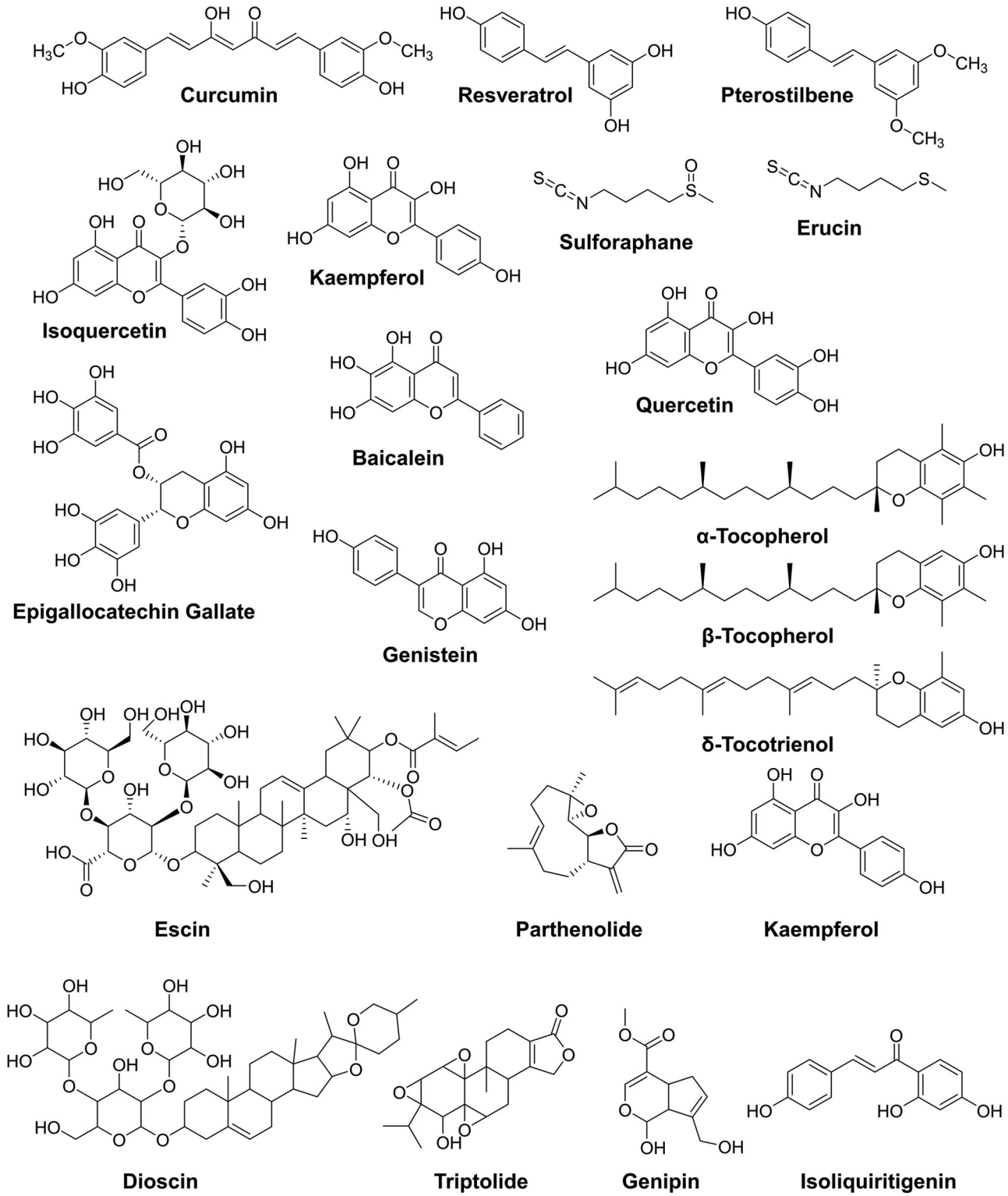

Figure 1. Chemical structures of phytochemicals.

chemical instability (106). It composes 6% of turmeric by weight and is a target for extensive phase I and II metabolism (106). Curcumin has shown efficacy in pre-clinical models of various cancer lines, including pancreatic, colon, breast, and lung cancer (107). Despite showing promising In Vitro results, In Vivo activity has been limited by poor oral bioavailability and water solubility (108). Multiple trials have attempted to increase the oral bioavailability of curcumin through improved delivery mechanisms, such as nanosuspensions, micelles, nanoparticles, and nanoemulsions, all with only modest success (109).

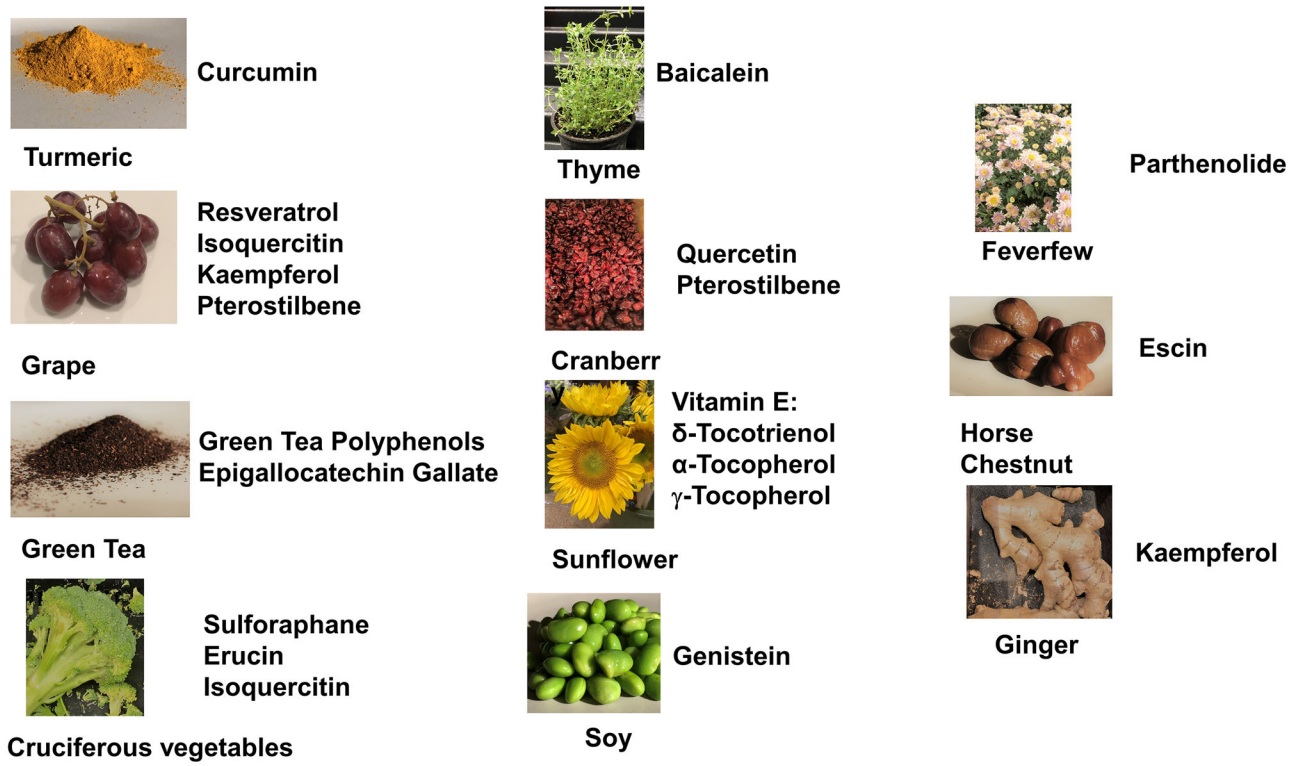

Figure 2. Phytochemicals and their natural sources.

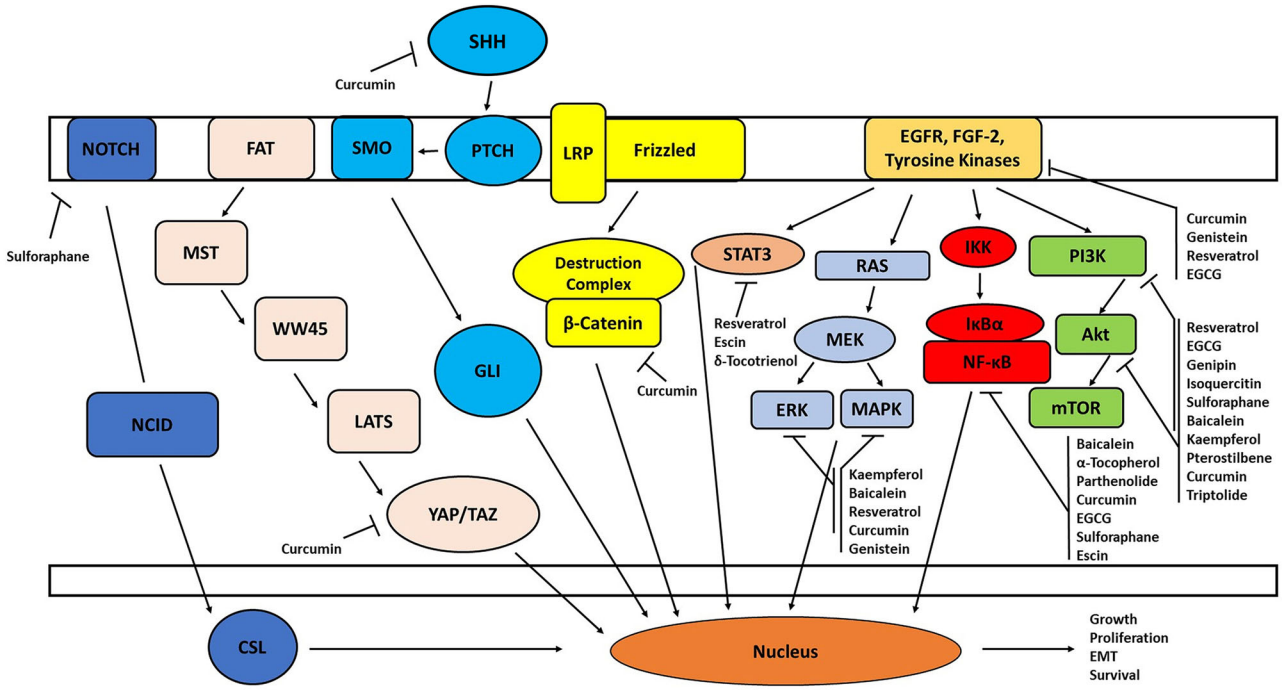

Figure 3. A pictorial representation of natural compounds targeting major bladder cancer signaling pathways.

Curcumin has been shown to suppress BC proliferation and induce apoptosis. In Vivo study observed this to arise from decreased activity of the cyclin D1 axis and downregulation of Hippo (110). Alternatively, In Vitro investigation showed inhibition of the PI3K/Akt/mTOR, upregulation of PTEN, reduction in Trop2 signaling, suppression of matrix metalloproteinases, and induction of G2/M phase arrest (111–115). Notably,

Table 1. A table summarizing phytochemicals and their targets in bladder cancer.

Compound	Source	Results	Study Type	Reference
Curcumin	Turmeric	↓Expression Trop2, Cyclin E1, ↑Expression p27	*In vitro*	(113) Zhang et al.
		↓Expression MMP-2, MMP-9, ↑Expression TIMP-2	*In vitro*	(114) Shi et al.
		↓Expression IGF2, ↓PI3K/AK/mTOR signaling	*In vivo*	(111) Tian et al.
		↑Expression PTEN, GSK-3B, Caspase 3/7/9, Bad Bax, ↓Expression AKT, Bcl-2	*In vitro*	(112) Wang et al.
		↑Expression miR-203, ↓Expression Src Kinase, AKT2	*In vitro*	(125) Saini et al.
		↓Expression Sonic Hedgehog, stem cell viability	*In vitro*	(116) Wang et al.
		↓MAPK, Epithelial-mesenchymal transition	*In vivo*	(121) Liang et al.
		↑Expression of CHOP-independent DR5, ↑TRAIL induction	*In vitro*	(128) Jung et al.
		↓NF-κB expression, ↑TRAIL receptor expression	*In vivo* and *In vitro*	(127) Kamat et al.
		Augmentation of Cisplatin cytotoxicity, ↑Expression p53, ↓Expression ERK, survival proteins	*In vivo* and *In vitro*	(130) Park et al.
		Augmentation of 5-flourouracil cytotoxicity	*In vitro*	(131) Afsharmoghadam et al.
		Augmentation of paclitaxel cytotoxicity	*In vitro*	(132) Wei et al.
		↓Expression Sp1,3,4, ↓Expression EGFR mRNA	*In vivo*	(123) Chadalapaka et al.
		↑Proteasomal degradation Sp1,3,4	*In vitro*	(124) Chadalapaka et al.
		↓Proteasomal degradation KLF5, ↓Expression Hippo effectors YAP/TAZ, ↓Activity Cyclin D1	*In vivo*	(110) Gao et al.
		↓Phosphorylation Aurora A, ↑Mitotic spindle defect, G/M Phase arrest	*In vitro*	(115) Liu et al.
		↓Expression of ERK5/AP-1, ↓EMT	*In vitro*	(119) Liu et al.
Bisdemethoxy-curcumin	Curcumin analog	↑Intratumoral CD8 T cell infiltration, myeloid suppressors	*In vivo*	(133) Shao et al.
Resveratrol	Grapes, Mulberries, peanuts, Itadori tea	↓Phosphorylation JNK1/2, ERK1/2, ↓MAPK pathway activation, ↓Expression MMP2/9	*In vitro*	(140) Bai et al.
		↑Rapamycin-induce mTOR inhibition, ↓Rapamycin-induced AKT escape	*In vitro*	(141) Alayev et al.
		↑Production ROS, ↑Expression cytochrome C, caspase 3/9	*In vitro*	(142) Lin et al.
		↓Nuclear translocation STAT3, ↓Expression surviving, cyclin D1, c-myc, VEGF	*In vivo* and *in vitro*	(139) Wu et al.
		↑Expression Bad, ↓Expression Bcl-2	*In vitro*	(143) Stocco et al.
		↑Phosphorylation p38 MAPK, ↓CDK4, cyclin D1, phosphorylated Rb, FGF-2	*In vitro*	(145) Bai et al.
		↓Expression miR-21	*In vitro*	(144) Zhou et al.
		Augmentation of Adriamycin cytotoxicity, ↓Expression of MDR gene MRP1,LPR,GST,Bcl-2, ↓Expression Topo-II	*In vitro*	(116) Wang el al.
Green Tea Polyphenols, Epigallocatechin Gallate (EGCG)	*Camellia sinesis*	↓Activity PI3K/AKT pathway, ↓Expression Bcl-2	*In vitro*	(154) Qin et al.
		↓Expression HSP-27, Bcl-2, ↑Expression Bad	*In vivo* and *In vitro*	(155) Chen et al.
		↓Expression VEGF, ↓Attenuation NK cell response	*In vivo*	(156) Hsieh et al.
		↓Expression N-cadherin, ↑Expression E-cadherin	*In vivo*	(157) Reiger-christ et al.
		Prevention of tumor cell implantation	*In vivo*	(158) Jankun et al.
		↓Expression NF-kB, cell migration	*In vivo* and *in vitro*	(159) Luo et al.
		↓Translocation p65, ↓Expression NF-kB, MMP9, urokinase	*In vitro*	(160) Qin et al.
Sulforaphane	Cruciferous vegetables	↑Inhibition KEAP1, ↓Proteasomal degradation Nrf-2	*In vivo*	(169) Dinkov-Kostova et al.
		↑Expression caspase, cytochrome-C, ↓Expression survivin	*In vitro*	(170) Wang et al.

		↑G1 Phase arrest, ↑Expression p27, phosphorylation Cdk1	*In vitro*	(172) Shan et al.
		↑ROS production, mitotic arrest	*In vitro*	(173) Park et al.
		↑Expression IGFBP-3	*In vitro*	(174) Dang et al.
		↓Activity PI3K/AKT/mTOR pathway, ↓Expression N-cadherin	*In vivo* and *In vitro*	(176) Islam et al.
		↓Expression MMP2/9, COX-2, ↓EMT	*In vitro*	(178) Shan et al.
		↑Expression p38 MAPK, ↓Translocation/transcription COX-2 mRNA	*In vitro*	(179) Shan et al.
Erucin	Cruciferous vegetables	↑G2/M Phase arrest, ↓Expression Cdc25	*In vivo*	(164) Abbaoui et al.
		↑Inhibition pro-growth histone deacetylases, ↓Phosphorylation Histone H1	*In vitro*	(171) Abbaoui et al.
Genistein	Soy	↑Inhibition topoisomerase I, ↓Activation ATM/NBS1/NEMO/IKK DNA repair pathway	*In vivo*	(183) Wang et al.
		↓Phosphorylation EGFR, MAPK	Clinical Trial	(184) Messing et al.
Geninpin	Cape Jasmine	↑Expression cytochrome-C, Bax, ↓Phosphorylation PI3K/AKT	*In vivo*	(186) Li et al.
		Augmentation of cisplatin cytotoxicity Reduction of cisplatin nephrotoxicity markers	*In vivo*	(187) Mahgoub et al.
Baicalein	Haung Qin, Thyme	↓Phosphorylation Nf-kB, ↓Expression MMP2/9	*In vivo*	(189) Wu et al.
		↑G0/G1 Phase arrest, ↑Expression p16, p21, ↓Expression cyclin D1	*In vitro*	(190) Jiang et al.
		↓Expression Bcl-xL, XIAP, survivin	*In vitro*	(191) Yang et al.
		↑ROS production	*In vitro*	(192) Choi et al.
		↑Expression Bax/Blc-2 ratio ↓Phosphorylation PI3K/AKT	*In vitro*	(193) Li et al.
		↓Migration, ↓Expression microRNA-106	*In vitro*	(194) Jiang et al.
		↑Expression p38 MAPK, ↑Inhibition CDC2 Kinase	*In vitro*	(195) Chao el al.
Quercetin	American Cranberry, onion, ginkgo biloba	↑Expression p-AMPK, ↑Inhibition ecto-5′NT/CD73	*In vitro*	(198) Su et al.
		↑Extracellular AMP ↓Extracellular ADP	*In vitro*	(199) Rockenbach et al.
Isoquercetin	Broccoli, red onion, pepper, apple	↓Phosphorylation PI3K/AKT	*In vitro*	(202) Chen et al.
		↑ROS production, ↓Expression AMPK	*In vitro*	(203) Wu et al.
α-Tocopherol, γ-Tocopherol δ-Tocotrienol	Sunflower oil, safflower oil, corn oil	Augmentation of paclitaxel cytotoxicity ↓Nuclear translocation NF-kB	*In vivo*	(206) Kanai
		Augmentation of gemcitabine cytotoxicity	*In vitro*	(207) Ye et al.
Parthenolide	Feverfew	↑Inhibition NF-kB signaling, ↑Expression JNK	*In vivo*	(209) Shanmugam et al.
		↑Expression PARP, G1 Phase arrest, ↓Expression Bcl-2	*In vitro*	(210) Cheng et al.
Dioscin	*Dioscorea nipponica*	↓Methylation DAPK-1, RASSF-1a genes	*In vitro*	(212) Zhou et al.
Triptolide	Thunder of God Vine	↓Phosphorylation AKT, Cyclin D1/EI, ↑S Phase arrest	*In vitro*	(213) Ho et al.
		Augmentation of cisplatin and gemcitabine cytotoxicity	*In vitro*	(214) Yang et al.
Kaempferol	Apple, citrus fruits, ginkgo biloba, ginger	↓Phosphorylation MAPK, ↑S1 Phase arrest	*In vivo*	(216) Dang et al.
		↑Ubiquitin-mediated degradation DNMT3B, ↓Expression RecQ helicase, RFC3	*In vivo*	(217) Qui et al.
		↓AKT signaling, ↓Expression Cdk-1	*In vitro*	(218) Wu et al.
		↑Expression PTEN	*In vitro*	(219) Xie et al.
Isoliquiritigenin	Licorice root	↑Expression Bax, Bim caspase 3/9, ↓Expression Bcl-2	*In vitro*	(222) Si et al.
		Augmentation of cisplatin cytotoxicity, prevention of cisplatin nephrotoxicity	*In vitro*	(223) Moreno-Londono et al.
Escin	Horse chestnut	↓Expression NF-kB, STAT3	*In vitro*	(225) Cheng et al.

one In Vitro study found curcumin to reduced proliferation of BC stem cells through suppression of Sonic Hedgehog (116).

Curcumin has been observed to suppress and reverse EMT. Laing and Shi both observed this to be a result of Wnt/β-catenin modulation, while Liu and Sun demonstrated this to result from suppression of the ERK5/AP-1 pathway (117–120). Lastly, Laing et al. found curcumin could protect against the development of EMT in teratogen-exposed urothelial cells through regulation of MAPK activity (121).

Curcumin may make epigenetic alterations to pro-growth cell signaling pathways in BC cell lines by decreasing expression of SP transcription-factor repressor miRNA and possibly decreasing expression of EGFR mRNA (122–124). Similarly, curcumin was seen to induce apoptosis through inducing hypomethylation miR-203 and reducing downstream expression of the pro-growth factors Src kinase and AKT2 (125).

Curcumin has been investigated as additive agent to Bacillus Calmette-Guerin (BCG), the current gold standard for NMIBC treatment. In Vivo investigation found that BCG combined with complexed curcumin/cyclodextrin reduced tumor size in orthotopic rat models more than BCG treatment alone (126). BCG therapy is thought to exert its anti-tumor effect through induction of TRAIL in host immune cells, which mediates cancer cell apoptosis (127). Kamat found curcumin to have an additive effect on TRAIL treatment of BC both In Vivo and In Vitro through downregulation of NF-κB and upregulation of TRAIL receptors (127). Similar In Vitro data by Jung found curcumin to act synergistically with TRAIL via CHOP-independent DR5 upregulation (128).

Curcumin has been investigated for augmentation of cytotoxic agents (129). Park showed curcumin to augment cisplatin-induced apoptosis both In Vivo and In Vitro through induction of ROS, targeting of ERK, and concurrent upregulation of p53 and downregulation of survival proteins (130). In Vitro studies found curcumin to augment the anti-proliferative effects of 5-flurouracil and paclitaxel (131,132).

Aside from augmentation of chemotherapeutics, curcumin has been observed to target bladder cancer's multi-drug resistance (MDR) pathways. Shao demonstrated In Vivo that the curcumin derivative bisdemethoxycurcumin may prevent MDR in metastatic bladder cancer by increasing intratumoral CD8+ T-cell infiltration, elevating IFN-γ blood level, and decreasing intratumoral myeloid-derived suppressor cells (133). Similarly, Zhang found combined cisplatin/curcumin to synergistically downregulates Keapl-Nrf2, a common MDR mechanism (134).

Resveratrol

Resveratrol is a polyphenolic compound found naturally in grapes, mulberries, and peanuts (135). It has been identified as the active agent in Itadori tea, a staple of Japanese folk medicine, and is thought to be the ingredient of red wine which accounts for wine's cardioprotective effect (135,136). Resveratrol is a polyphenol and contains two aromatic rings connected by a methanediyl group (137). It has a poor aqueous solubility of 0.03 mg/mL, and rat models have found approximately 2.6% oral bioavailability with distribution of 0.2 L/h and predominate phase II hepatic metabolism (138). Interestingly, encapsulation of resveratrol in casein nanoparticles was shown to increase its bioavailability to 26.5% (138).

In Vivo studies showed resveratrol to inhibit proliferation and induce apoptosis of BC by decreasing transcription of STAT3 and expression of VEGF and FGF-2 (139,140). Interestingly, resveratrol was also found to induce S-phase arrest through activation of the Sirt1-p53 pathway (139). Several additional In Vitro studies pointed to reduction of proliferation and induction of apoptosis via inhibition of mTOR/AKT signaling, ROS-mediated induction of cytochrome C and caspase 3/9, and induction of Bcl-2 (141–144). It is notable that Stocco found resveratrol to demonstrate dose-dependent induction of ROS at concentrations over 20 µM, while protecting cells from oxidative stress at levels below 20 µM, suggesting its potential for chemoprevention (143).

Bai found resveratrol decreased adhesion, invasion, and migration of bladder cancer cells in a dose-depended manner (145). This was thought to occur through decreased phosphorylation of MAPK pathway components JNK1/2 and ERK1/2, and resultant decreased expression of MMP-2 and MMP-9 (145).

Wang investigated resveratrol as a potential additive to Adriamycin for treatment of bladder cancer In Vitro (116). It was found that resveratrol lowered the IC_{50} of Adriamycin in MDR bladder cancer cells through decreasing expression of MDR genes (116). A potential barrier to use of resveratrol in treatment of BC is its low bioavailability and rapid metabolism. Indeed, Yang showed that the major metabolite of resveratrol, resveratrol monosulfate, did not have any effect on BC cell proliferation or apoptosis when used alone (146).

Green Tea Polyphenols

Green tea is a common drink worldwide and has shown anti-inflammatory, anti-bacterial, and anti-oxidant properties (147). Most health benefits of green tea are attributed to the polyphenolic compound epigallocatechin-3-gallate (EGCG) (148). EGCG contains a trihydroxyphenyl B-ring which is thought to be the source of its antioxidant properties (149). Animal models show 26.5% oral bioavailability of EGCG, while results in human models remain mixed (150,151). EGCG undergoes extensive phase II hepatic metabolism (151).

EGCG has been shown to inhibit BC proliferation and induce apoptosis In Vivo through decreasing phosphorylation of PI3K and AKT, as well as increasing activity of pro-apoptotic proteins caspase-3 and PARP (152). Mechanisms shown In Vitro include CpG demethylation of promoters indicated BC growth and decreased anti-apoptotic and heat-shock protein expression (153–155).

Heish showed enhanced ability of EGCG to inhibit BC tumors In Vivo through complexation with gold nanoparticles (pNG), a strategy which has been investigated with several chemotherapeutics (156). Not only did this study find the EGCG-pNG complex to induce apoptosis, but the complex reduced expression of tumor VEGF and attenuation of NK immune cells (156).

EGCG has shown potential in reducing cancer cell migration. In Vivo and In Vitro data showed intravesical EGCG to inhibit N-cadherin, matrix metalloproteinases, and translocation of NF-κB (157–160).

Sulforaphane and Erucin

The isothiocyanates sulforaphane and erucin are derived from the cruciferous vegetable family, which includes broccoli, brussels sprouts, cabbage, cauliflower, collard greens, kale, and arugula (161). Two epidemiological studies have shown significant dose-dependent reduction in BC incidence with consumption of raw cruciferous vegetables, a finding attributed to high content of sulforaphane and erucin (162–164). These findings were further enforced by the fact that the anticancer benefit of cruciferous vegetable consumption was not seen when vegetables were cooked, likely due to heat-mediated reduction of isothiocyanate levels (165,166). Sulforaphane has shown 37% oral bioavailability in human models with an excretion half-life of 2.6 h, (167). There has been minimal investigation into the pharmacokinetic properties of erucin.

Sulforaphane's chemoprotective properties in normal urothelium has been attributed to potentiation of nuclear factor erythroid 2–related factor 2 (Nrf2), which induces expression of antioxidant response elements (168,169). This is mediated through inhibition of KEAP1, a protein which mediates proteasomal degradation of Nrf2 (169).

Several studies have shown sulforaphane to inhibit bladder cancer cell proliferation and induce apoptosis. In Vivo, Wang and Abbaoui pointed to inhibition of the PI3K/AKT/mTOR pathway and G2/M phase cell cycle arrest, respectively (170,171). Abbaoui attributed G2/M phase arrest to disruption of the mitotic spindle (171). In Vitro evidence has pointed to ROS production and resultant cytochrome induction, G1 phase arrest, and downregulation of NF-κB (172–174). Notably, sulforaphane induced apoptosis through ROS generation in treatment-resistant BC when combined with TRAIL (175).

Sulforaphane has shown promise for preventing EMT both In Vivo and In Vitro, through suppression of cadherins and matrix metalloproteinases (176,177). Two separate studies by Shan et al. showed sulforaphane to inhibit NF-κB and reduce COX-2, an event associated with decreased EMT in BC (178,179).

Erucin has been shown to inhibit bladder cancer proliferation and induce apoptosis through G2/M phase arrest In Vivo, and inhibition of pro-growth histone deacetylases In Vitro (168,171).

Genistein

Genistein is an isoflavone derived from soybeans that has shown promise for treatment of prostate, breast, colon, liver, and bladder cancers (180). Genistein has a chemical structure similar to estradiol and has been classified as a phytoestrogen (181). Animal models show genistein to have 38% oral bioavailability and to undergo predominately phase II hepatic metabolism (181,182). In Vivo data found genistein to cause dose-dependent inhibition of bladder cancer proliferation, induction of apoptosis, and G2/M phase arrest (183). It was theorized that Genistein directly inhibited DNA topoisomerase I, as well as delayed DNA damage repair (183).

A phase two clinical trial in pre-surgical BC patients showed consumption genistein resulted reduced EGFR phosphorylation in cancer cells, and borderline significant reduction of downstream phosphorylated MAPK (184). However, this trial was unable to note significant changes in tumor proliferation, apoptosis, or apoptotic-inhibiting markers.

Genipin

Genipin is an aglycone derived from the *Gardenia jasminoides*, or cape jasmine plant, and was in used both traditional Chinese and Ayurvedic medicine for conditions ranging from fever to intestinal worms (185). In Vivo data found that that genipin inhibits BC proliferation and induces apoptosis through inhibition of the PI3K/Akt pathway and induction of Bax and cytochrome C (186). A mouse-model study showed genipin potentiates cytotoxicity of cisplatin while simultaneously reducing markers of cisplatin-induced nephrotoxicity, suggesting the potential use of genipin as an additive to chemotherapy (187).

Baicalein

Baicalein is a flavone derived from the herb Huang Qin, which is used in traditional Chinese medicine as an anti-inflammatory (188). Baicalein has been examined both In Vitro and In Vivo for treatment of bladder, prostate, and hepatocellular cancer (188). Wu demonstrated In Vivo that baicalein inhibits bladder cancer proliferation and migration in a dose-dependent manner via reduction of phosphorylated NF-κB and MMP-2/9 expression (189). In Vitro studies pointed reduction in securin and AKT/γ-H2AX survival pathways, increased ROS production, and reduced expression of the anti-apoptotic factors Bcl-xL, XIAP, and survivin (190–192). Baicalein has been shown to induce G0/G1 phase arrest through PI3K/AKT phosphorylation and increased Bax/Bcl-2 ratio, and G2/M phase arrest through induction of p38 MAPK and inhibition of CDC2 Kinase (193–195).

Quercetin and Isoquercitin

The American Cranberry (*Vaccinium macrocarpon*) has been shown to contain several bioactive phytochemicals with implications for use in cancer and other pathologies such as urinary tract infection (196). The flavonoid quercetin has been identified as one of the main bioactive phytochemicals found in cranberries and may have therapeutic efficacy (197). In Vitro studies have shown quercetin to target multiple aspects of BC pathogenesis. Su et al. found quercetin to inhibit proliferation and colony formation, induce apoptosis, and reduce migration of cell lines through increased phosphorylation of AMPK (198). Additionally, Rockenbach found that quercetin could inhibit of bladder cancer cell proliferation through increased extracellular AMP levels and decreased extracellular ADP levels (199). Finally, Ma showed quercetin induced G0/G1 cycle arrest and reduced survivin and mutant p53 (200).

Isoquercitin differs from quercetin due by the presence of a 6″-OH (ω-OH) group, and the two compounds have been found to coexist in many natural sources (201). In Vitro data from Chen et al. showed isoquercitin to inhibit bladder cancer cell proliferation as well as induce apoptosis and G1 phase arrest (202). This was paired with decreased CDK4, CDK6 and cyclin D1 levels, and decreased activating phosphorylation of PI3K and AKT (202). Additional In Vitro data from Wu et al. showed isoquercitin suppresses BC proliferation through ROS production and increased metabolic pathway variation, leading to destabilized lipid synthesis and altered anaerobic glycolysis (203).

Vitamin E

Vitamin E describes several related compounds including tocopherols and tocotrienols (204). Vitamin E compounds are most commonly found in dietary oils, such as sunflower, safflower, and corn oil (204). A metanalysis of dietary studies showed BC risk is inversely associated with consumption of α-Tocopherol, but positively associated with γ-Tocopherol, the form most commonly found in dietary sources of Vitamin E (205).

An In Vivo study found that α-Tocopherol and γ-Tocopherol inhibited tumor growth in xenograft mice through decreased NF-κB nuclear translocation (206). Notably, NF-κB activity is associated with paclitaxel resistance in BC, and this study found that coadministration of α-Tocopherol and paclitaxel produced greater inhibition than either compound alone (206). While paclitaxel is known to induce G2/M phase arrest, α-Tocopherol induced sub-G1 phase arrest, meaning that combination therapy with these agents could cause double checkpoint arrest in the cell cycle (206).

In Vitro data found δ-Tocotrienol inhibits bladder cancer proliferation and induces apoptosis through suppression of STAT3 phosphorylation (207). This study also showed addition of δ-Tocotrienol to gemcitabine increased induction of apoptosis and inhibition of proliferation (207).

Parthenolide

Parthenolide occurs naturally in the feverfew herb (*Tanacetum parthenium*), which has been used in European folk medicine to treat ailments ranging from migraine headaches to dysmenorrhea (208).

Parthenolide is an esquiterpene lactone and has been investigated in pre-clinical trials for treatment of both solid and hematogenous tumors (186). Shanmugam showed In Vivo that the water-soluble parthenolide analogue dimethylaminoparthenolide (DMAPT) inhibits BC cell proliferation through induction of oxidative stress, inhibition of NF-κB signaling, and induction of JNK (209). Cheng et al. showed In Vitro that parthenolide inhibits proliferation, induces apoptosis, and causes G1-phase arrest in BC cell lines (210). Western-blot analysis revealed that parthenolide achieved these effects through PARP activation and downregulation of Bcl-2 (210).

Other Phytochemicals

Dioscin has been found in several plants used in tradition Chinese medicine, including *Dioscorea nipponica* and *Dioscorea zingiberensis* (211). Zhou showed In Vitro that Dioscin inhibits proliferation and induces apoptosis of BC cells through decreasing gene methylation of DAPK-1 and RASSF-1α, mediators involved in programmed cell death pathways (212).

Triptolide is an active compound derived from thunder of god vine (*Tripterygium wilfordii*), which has been used in traditional Chinese medicine for treating inflammation and arthritis (213). Ho and Yang showed In Vitro that triptolide increased cisplatin and gemcitabine inhibition of bladder cancer cell proliferation, colony formation, and apoptosis (213,214). These studies showed triptolide to induce S phase arrest via reduction in cyclin D1 and E1, and reduction GSK3β/AKT signaling (213,214).

Kaempferol is a flavonoid found in ginger that has gained attention for its anti-diabetic, anti-inflammatory, and anticancer properties (215). In Vivo studies found kaempferol to inhibit proliferation through decreasing phosphorylation of MAPK and methylation of tumor DNA repair loci (216,217). In Vitro, Wu showed kaempferol inhibits proliferation and induces apoptosis through reduction of phosphorylated AKT levels and downregulation Cyclin D1 due to up-regulation of p21, p27 and p38 (218). Finally, Xie suggested that the In Vitro pro-apoptotic and anti-proliferative effects of kaempferol arise from induction of the PTEN tumor suppressor (219).

Pterostilbene is a phytoalexin found in blueberries, grapes, and cranberries (220). Chen et al. showed In Vitro that pterostilbene inhibits proliferation of T24 bladder cancer cells, as well as induces autophagy through inhibition of the AKT/mTOR/p70S6K pathway and activation of the MEK/ERK1/2 pathway (221).

Isoliquiritigenin is a flavonoid found in the root the *Glycyrrhiza uralensis* plant, which is used to make licorice (222). Si et al. showed isoliquiritigenin to inhibit proliferation and induce apoptosis of T24 cells In Vitro (222). These findings attributed to increased expression of proapoptotic genes Bax, Bim, Apaf-1, caspase-9 and caspase-3 and decreased anti-apoptotic Bcl-2. Additional In Vitro data from Moreno-Londono et al. showed isoliquiritigenin to prevent cisplatin-induced cytoxicity in normal kidney tubular cells while potentiating with cisplatin inhibition of BC cells (223).

Escin is a mixture of triterpenoid saponins that occurs in *Aesculus hippocastanum*, or the horse chestnut tree (224). Cheng et al. showed escin to inhibit tumor growth in xenograft mouse models, and to induce bladder cancer cells apoptosis through ROS generation and cytochrome C release (225). This study also found escin inhibits STAT3 protein expression and reduce nuclear levels of NF-κB (225).

Conclusions and Future Directions

Bladder cancer remains one of the most common malignancies worldwide, as well as the mostly financially costly cancer in the United States (2,5). Despite its high morbidity, few novel therapeutics have been discovered for treatment of bladder cancer since the development of BCG immunotherapy over 30 years ago (226). While NMBIC carries a relatively favorable prognosis, MIBC and metastatic BC have an abysmal disease-specific survival of 42% and 5% at 5 years (7). Novel approaches to treatment of BC are clearly needed. By identifying naturally occurring compounds that target key pathways of BC pathogenesis such as PI3K/Akt/mTOR, Ras/MEK/ERK MAP kinase, and NF-κB, it is possible to tap into the hidden remedies of nature and eliminate this highly morbid disease. Our lab is currently investigating the potential of several natural occurring chemicals for treatment of BC, both as solitary agents and as combination with conventional chemotherapeutics.

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Author Contributions

C.C., D.S. and P.D. performed literature review, compiled the first draft of the manuscript and prepared the figures. S.A. supervised and wrote the final draft of the manuscript. S.P, J.T., S.W. and edited and proof-read the manuscript.

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