Properties of flavonoids in the treatment of bladder cancer (Review)

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Received June 9, 2022; Accepted August 15, 2022

DOI: 10.3892/etm.2022.11612

Abstract. Given its high recurrence and rapid progress, bladder cancer (BLCA) treatment has become a major problem for clinicians. BLCA is difficult to control even with surgical resection and extensive use of chemotherapeutic drugs. The non-toxicity and ease of accessibility of natural compounds have attracted much attention in recent years. Flavonoids serve an essential role given their antioxidant, antibacterial, anticancer and cardiovascular properties. They are mainly divided into several subclasses; flavones, flavanones, flavonols, flavanols, anthocyanins isoflavones and chalcones. Over the years, the role of flavonoids in BLCA has been extensively studied. The present review provided a comprehensive overview of the classification of flavonoids and substantiate the role of epithelial-mesenchymal transition, cancer stem cells, angiogenesis, epigenetic regulation and programmed cell death in BLCA. The present review emphasized that flavonoids for BLCA treatment are worthy of further study and anti-BLCA drugs have huge prospects for clinical use.

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Abbreviations: ATM, Ataxia telangiectasia mutated; BCG, bacillus Calmette Guerin; BLCA, bladder cancer; CDKs, cyclin-dependent kinases; ceRNAs, competitive endogenous RNAs; CHK1, checkpoint kinases 1; circRNA, circular RNA; COX, cyclooxygenase; CSCs, cancer stem cells; Cys2, cysteine; DNMTs, DNA methyltransferases; EGCG, epigallocatechin gallate; EIF5A2, eukaryotic translation initiation factor 5A2; EMT, epithelial-mesenchymal transition; EPI, epirubicin; ER, endoplasmic reticulum; FKA, flavokawain A; GSH, glutathione; GSPs, grape seed proanthocyanidins; HDACs, histone deacetylases; HO, heme oxygenase; ICI, immune checkpoints inhibitor; IFN, interferon; IOS, isoliquiritigenin; lncRNA, long noncoding RNA; MIBC, muscle-invasive BLCA; miRNA, microRNA; NMIBC, non-muscle invasive BLCA; OCT4, octamer-binding transcription factor 4; PSPA, purple sweet potato anthocyanin; ROS, reactive oxygen species; RT, radiotherapy; TFs, transcription factors; UPII, uroplakin II; VEGF, vascular endothelial growth factor

Key words: bladder cancer, flavonoids, apoptosis, cell cycle

Contents

1. Introduction

Bladder cancer. The number of patients diagnosed with bladder cancer (BLCA) is the tenth highest globally and men are ~3-4 times more likely to develop BLCA than women (1,2). BLCA can be divided into muscle-invasive BLCA (MIBC) and non-muscle invasive BLCA (NMIBC). However, given the high mortality and progression of MIBC and the high recurrence rate of NMIBC, bladder cancer remains a difficult problem worldwide (3,4). The value of bacillus Calmette Guerin (BCG) against immunotherapy in NMIBC is widely recognized. Nonetheless, with the use of BCG, a number of problems have appeared, such as BCG intolerance, poor effectiveness and tumor recurrence (5). Radical cystectomy and peripheral lymph node dissection is the gold standard treatment for advanced MIBC. However, in some cases, patients cannot tolerate surgery or want to retain urinary bladder function because of other disease conditions (6). Accordingly, a new therapeutic approach for BLCA is warranted.

Over the years, next-generation sequencing has revealed a number of therapeutic targets for BLCA and the use of immune checkpoints inhibitor (ICI) has offered hope for BLCA patients (7). Nevertheless, since ICI is expensive and patient response rates are low, significant emphasis has been placed on

combining drugs, hoping they will complement each other (8). Natural plant compounds are considered a good source of combination chemotherapy due to their availability (9).

Flavonoids. Phytochemicals are bioactive compounds extracted from natural plants, which have been widely studied to treat diseases, especially cancer, *in vivo* and *in vitro*, since they are easily obtained, highly safe and non-toxic (10). Polyphenolic compounds are widely recognized because of their wide distribution and variety. More than 8,000 polyphenol compounds have been identified in nature. They represent essential plant products that can be used against cardiovascular diseases and for cancer prevention and treatment in humans (11). Flavonoids are a subgroup of polyphenols which represent secondary metabolites. Flavonoids are widely regarded as the most common polyphenols in fruits, chocolate, flowers, vegetables and tea. Their pharmacological effects have attracted much interest, including antioxidant, antibacterial anti-inflammatory, cardiac and liver protective and anticancer properties (12,13). In addition, they have been documented to prevent breast, colorectal, thyroid, prostate, lung and ovarian cancers (13). However, flavonoids are rarely used clinically, possibly because of their low solubility, poor absorption and lack of accurate epidemiological data (13).

The effects of flavonoids on BLCA have also been studied *in vivo* and *in vitro*, but no study has hitherto systematically cataloged them. Several types of flavonoids have been reported to interfere with BLCA through biological mechanisms such as reactive oxygen species (ROS), apoptosis, ferroptosis, cancer stem cells (CSCs), epithelial-mesenchymal transition (EMT) and cell cycle arrest. The present study summarized current evidence based on the mechanism and classification to provide a foothold for future research.

2. Mechanism

DNA damage and cell cycle arrest. DNA damage is usually caused by damage to single-base or double strands of DNA in tumor cells by external and internal stimuli such as chemotherapy drugs. Double strand breaks have the most lethal effects on cells (14). Cells can activate several biological signals and processes in response to DNA damage, including cell cycle arrest, apoptosis and checkpoint activation, collectively called DNA damage response (15). The cell cycle is roughly divided into four phases: G_1 (proteins preparation), S (DNA replication), G_2 (checking the integrity of replication) and M (Mitosis). The daughter cells then go into a resting state, known as the G_0 phase (16). It is well-established that cell cycle progression is largely regulated by cyclin-dependent kinases (CDKs), which phosphorylate key substrates to maintain the normal course of the cell cycle (17). Cell cycle arrest in the G_1/S phase mainly depends on Ataxia telangiectasia mutated (ATM) activation. Notably, ATM directly activates P38MAPK, checkpoint kinases 2 (CHK-2) and P53 leading to the accumulation of P21. The activation of ATM- and Rad3-related (ATR) and checkpoint kinases 1 (CHK1) lead to phosphorylated CDC25 and S or G_2/M phases arrest (18,19). DNA damage in cancer cells provides an opportunity for DNA repair by blocking the cell cycle. However, if cancer cells are not repaired properly, they will die (20) (Fig. 1). Treatment with flavonoids can damage DNA in BLCA cells, leading to cell cycle arrest. The sustained action of the drug can eventually lead to cell death, such as apoptosis and other programmed cell death.

ROS. ROS are free radicals or molecules with one or more unpaired electrons. The production of ROS in the cell depends mainly on the oxidative stress signal stimulation by the electron transport chain of mitochondria (21). In addition, inflammatory cells and several enzymatic cell complexes are involved in ROS production. The extrinsic sources of ROS mainly include radiation or drugs (22). ROS exhibit a two-way regulatory effect on cancer cells. Cancer cells exhibit a mild to moderate increase in ROS due to genetic mutations or metabolic changes, which help activate ROS-sensitive signaling pathways and promote proliferation, invasion and differentiation of cancer cells. Nevertheless, as a result of chemotherapy and other drugs, the level of ROS is significantly elevated, which can cause cancer cells to exceed existing redox limits, leading to apoptosis, autophagy, or DNA damage (23). A number of flavonoids can reportedly activate ROS levels and induce BLCA cell death.

Apoptosis, autophagy and ferroptosis

Apoptosis. The therapeutic role of apoptosis in cancer has been extensively explored and understanding the mechanism of apoptosis can help to improve knowledge of the role of flavonoids. Apoptosis can lead to cell shrinkage, even the secretion of vesicles, nuclear fragmentation and chromatin condensation. Apoptosis can be divided into mitochondrial apoptosis and death receptor apoptosis (24). The death receptor signal originates from the activation of death receptors, including TNFR1 and Fas (CD95), through the stimulation of TNF and Fas ligand in extrinsic cells (25). The death receptors can recruit associated adaptive proteins (TNF receptor type 1-associated death domain protein and Fas-associated death domain protein) to further induce caspase-8 splicing activation (26). Finally, pro-caspase-3 is activated by cleaved caspase-8 and executes the apoptotic signal (27). The intrinsic apoptotic pathway, also known as mitochondrial-dependent apoptosis, is stimulated by high concentrations of intracellular Ca^{2+}, oxidative stress and hypoxia. This phenomenon leads to changes in mitochondrial membrane permeability, BAK/BAX activation and oligomer formation and the release of cytochrome-c (28). However, the release is dynamically regulated by the intracellular pro-apoptotic proteins BAD and BID and the anti-apoptotic protein BL-2. Cytochrome c, Apaf-1 and caspase-9, an apoptosome complex, activate apoptosis by cleaving caspase-3 (29). In addition, prolonged endoplasmic reticulum (ER) stress may induce apoptosis, related to the activation of caspase-12 to induce cleaved caspase-3/9 (30).

Autophagy. Autophagy (macroautophagy) is the process of breaking down intracellular material by forming double membraned vesicles (autophagosomes) to engulf proteins or organelles for their degradation and transport to lysosomes (31). The activation of mTOR and adenosine monophosphate-activated protein kinase (AMPK) signaling pathways and the formation of angiotensinogen protein complexes, including UNC-51-like kinase-1 (ULK1)/Autophagy related protein 13 (ATG13)/focal adhesion kinase-interacting protein of 200 kDa (FIP200)/Autophagy related protein 101 (ATG101) and

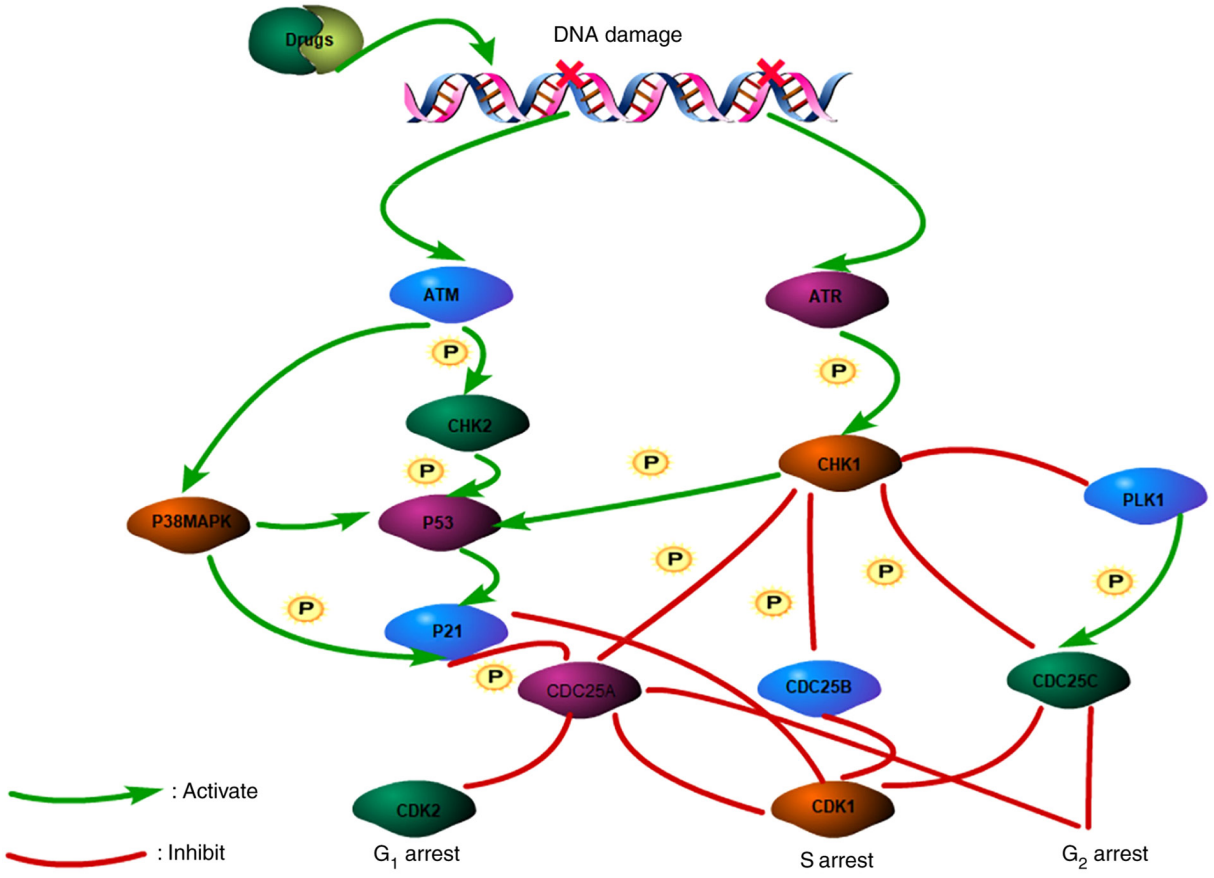

Figure 1. G_1 arrest: ATM can phosphorylate CHK2 to activate the P53 pathway and the accumulation of P21 and finally cause the ubiquitination degradation of CDC25A to suppress CDK2. S and G_2 arrest: CHK1 is primarily activated by ATR, which promotes CDC25A/B/C degradation and inhibits CDK1 and cell cycle progression (18,19,187,188). ATM, Ataxia telangiectasia mutated; CHK, checkpoint kinase; CDC25, cell division cycle 25; CDK, cyclin-dependent kinase; ATR, ataxia-telangiectasia-mutated-and-Rad3-related kinase.

Beclin1/Vacuolar protein-sorting 34 (VPS34)/Autophagy related protein 14 (ATG14)/Autophagy/Beclin1 regulator 1 (AMBRA1) complexes, are necessary conditions for the formation of autophagosomes (32). Subsequently, damaged proteins or organelles are loaded by autophagy cargo receptors such as P62 to dock with LC3 on the vesicles and enter the autophagosome. The autophagosome ultimately depends on the fusion of lysosomes for degradation (33). The role of autophagy in cancer is a two-way process that inhibits cancer growth and contributes to cancer progression (34). Therefore, more emphasis should be placed on the expression of autophagy-related proteins in different doses of flavonoid intervention.

Ferroptosis. The discovery of iron death has given new directions to the treatment mechanisms of cancer. The activation of lipid ROS mainly depends on the breakdown of the glutathione (GSH) reduction system and the regulation of *system xc*-(xCT) transporters, including cysteine (Cys2) and glutamate (35). Depletion of GSH often results from decreased intracellular Cys2. GSH is an essential adjunct to glutathione peroxidase 4 (GPX4) in reducing peroxide. Depletion of GSH leads to intracellular peroxide overload and induces ferroptosis (36). Transferrin can transport Fe^{3+} inside the cell and is catalyzed and reduced to Fe^{2+} by the six-transmembrane epithelial antigen of prostate 3. Then the divalent metal transporter 1 can transport Fe2+ to the labile iron pool and induce ferroptosis (37). As a classical tumor suppressor gene, the activation of P53 seems to activate ferroptosis by inhibiting the expression of SLC7A11 to regulate the uptake of cystine (38). However, ferroptosis in natural compounds against cancer has been largely understudied. The mechanism of flavonoid in BLCA of mutant P53 and wild-type P53 may be different and further studies are needed to study whether ferroptosis is involved (Fig. 2).

Epigenetics and modification. Epigenetics refers to the indirect regulation of genes in the DNA sequence, which causes gene silencing or overexpression and affects cell phenotype and biological function (39). Epigenetic regulation and modification can be divided into DNA methylation, histone methylation, acetylation, ubiquitination and ncRNA (noncoding RNAs) (40). DNA methylation is one of the earliest and most widely studied modifications, involving methylation of the 5-carbon of the Cytosine-phosphate-Guanine islands cytosine residue, called 5-methylcytosine (41). Aberrant DNA methylation is common in cancer genomes. Natural plant compounds are thought to influence DNA methylation patterns by altering the global hypomethylation of oncogenes and the hypermethylation of suppressor genes, affecting the progression of cancer (42). The methylation and acetylation of histone modifications are the most widely studied. Histone methylation changes the structure and

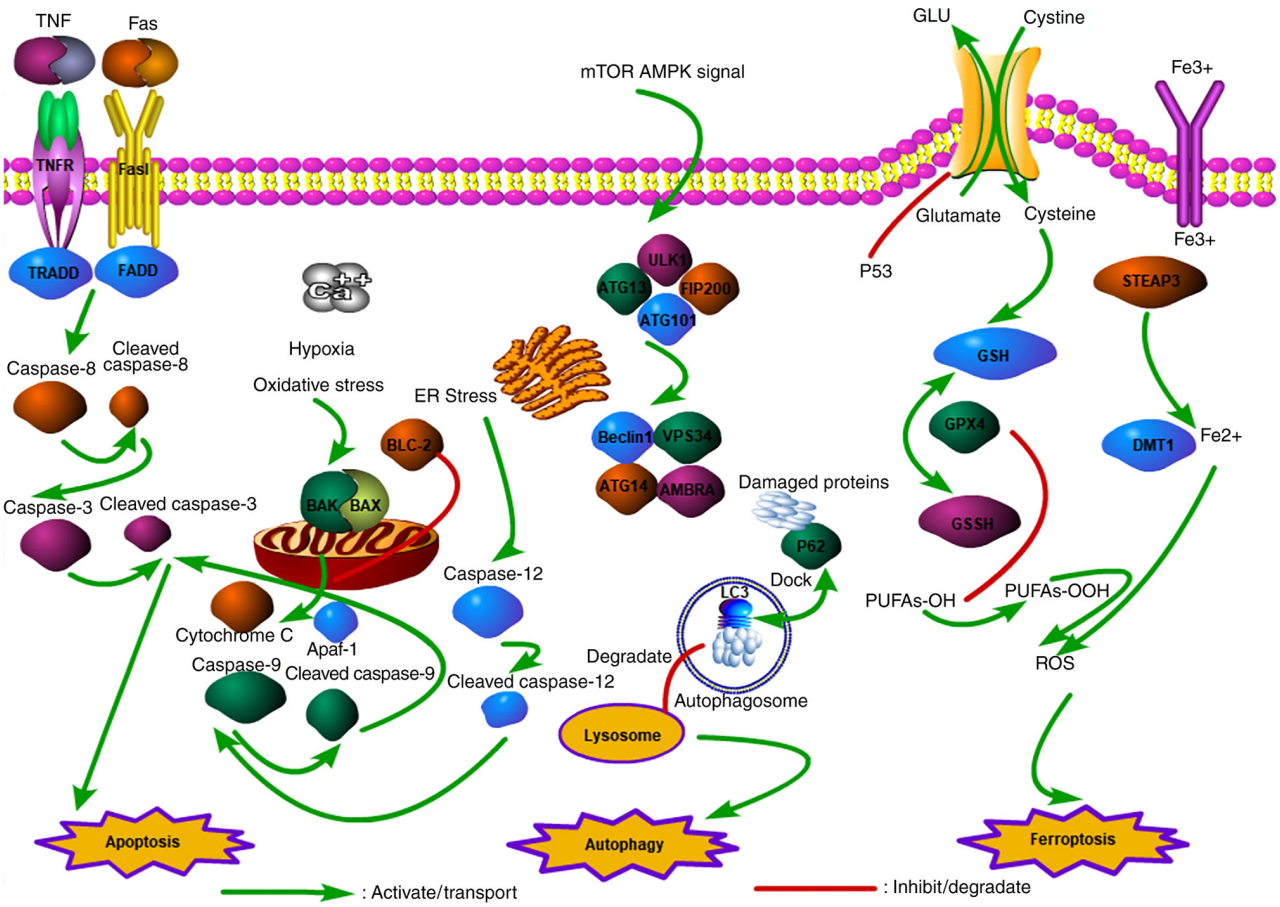

Figure 2. The apoptotic pathway mainly includes TNF and Fas-mediated exogenous apoptotic pathway and mitochondrial-dependent endogenous pathway. Activation of caspase-3 is the key mechanism of apoptosis. Autophagy relies on lysosomes digesting damaged proteins or organelles contained in autophagosomes. LC3 is considered to be an essential protein involved in it. GPX4 and GSH have a synergistic effect. Moreover, GPX4 can inhibit the conversion of PUFAs-OH to PUFAs-OOH, thus inhibiting lipid oxidation. GPX4, glutathione peroxidase 4; GSH, glutathione.

function of chromatin, mainly through histone methyltransferases and histone demethylases, associated with prognosis in a variety of cancers and regulated by the active ingredients of Chinese herbs (43). The acetylation of histones is mainly achieved by histone acetyltransferases and histone deacetylases (HDACs). The acetyl group of acetyl coenzyme A can be transferred to the terminal of histone amino acids by histone acetyltransferase to enhance DNA expression and transcription. However, HDAC removes the acetyl group, resulting in chromatin densification and gene transcription suppression (44). Proto-oncogenes may be activated by hyperacetylation, while hypoacetylation of tumor suppressor genes is usually limited to the promoter and induces gene silencing, closely related to cancer phenotypes and traits (45). These epigenetic regulatory enzymes may be used as therapeutic targets for BLCA.

microRNAs (miRNAs) are noncoding RNAs of ~17-25 nucleotides involved in almost all biological functions of cancer, including proliferation, invasion, metastasis, angiogenesis and apoptosis (46). miRNAs have been found to act on the 3' UTR site of mRNA to suppress its expression. Large numbers of miRNAs are reportedly upregulated or downregulated in cancer, suggesting that they can act as biomarkers in cancer (47). Researchers have investigated the relationship between competitive endogenous RNAs (ceRNAs) and cancer. Long noncoding RNAs (lncRNAs) and circular RNAs (circRNAs) can directly target mRNAs and sponge miRNA to regulate mRNAs expression. Notably, lncRNA/miRNA/mRNA and circRNA miRNA/mRNA interact to form ceRNAs networks that serve regulatory roles in cancer progression or suppression (48).

Angiogenesis. Angiogenesis primarily involves the growth of new capillary blood vessels from the existing vascular system complex process (49), usually due to the proliferation and migration of endothelial cells following stimulation to form primary sprouts. The new vascular structures are formed by forming the basement membrane (50). Cancer cells require nutrients and oxygen to maintain their growth through pathological angiogenesis, which depends mainly on the overactivation of angiogenic factors. The most important of these is the VEGF family, which serves a role in tumor progression (51). Nevertheless, a single angiogenesis inhibitor can only block tumor progression to some extent. Angiogenesis inhibitors interfere with other normal physiological functions in humans, including blood pressure maintenance, kidney function and wound healing. It should be borne in mind that inhibiting VEGF signaling to block tumor angiogenesis is associated with a risk of hypertension (52).

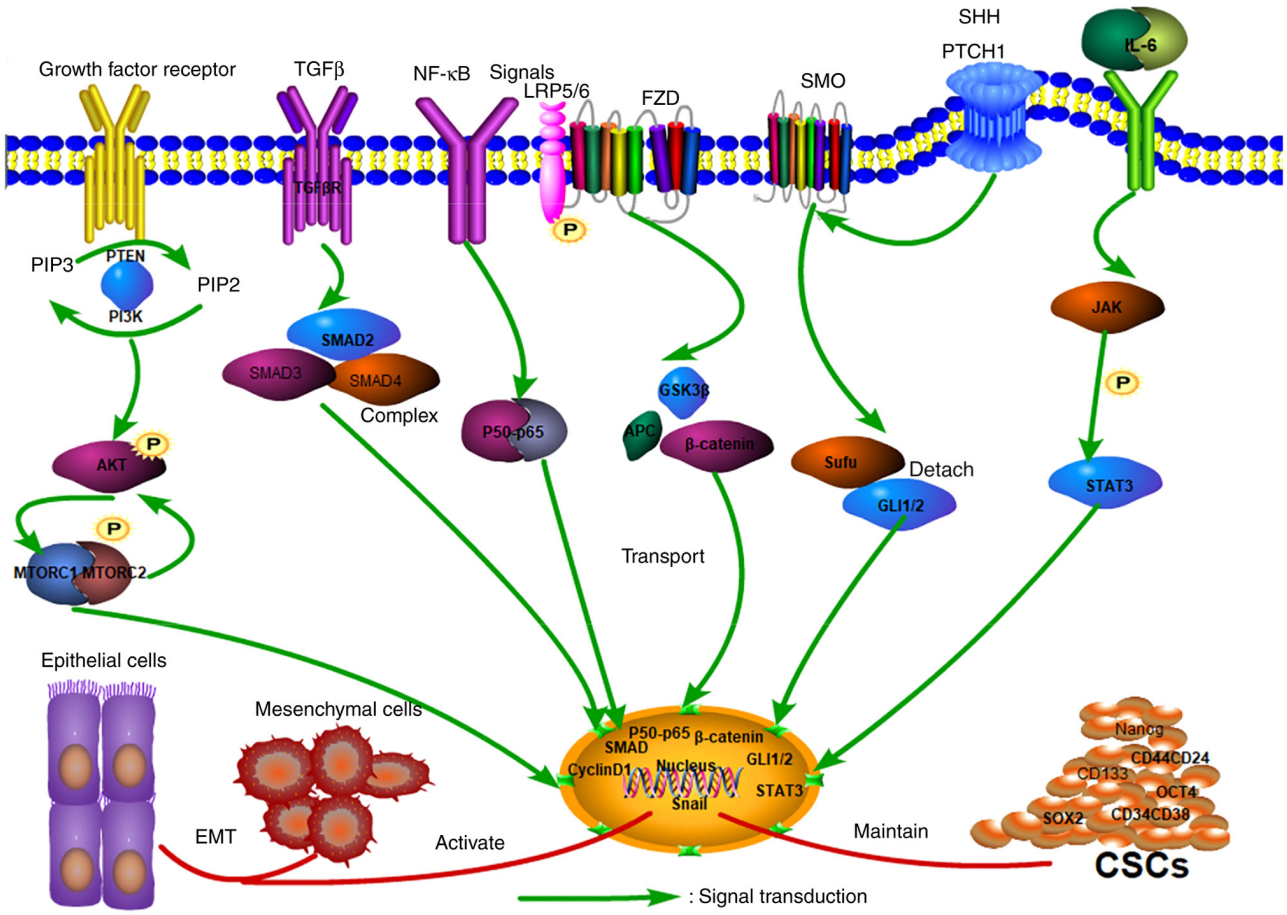

Figure 3. CSCs and EMT signaling pathways: After the activation of the WNT pathway, β-catenin is transported to the nucleus. During SHH signal transduction, the PTCH1 transmembrane protein receptor activates SMO and GLI 1/2 transcription factor detachment from SUFU to increase snail expression. IL-6 can activate STAT3 to modulate EMT and CSCs. P50-p65 is an important factor for NF-κB signal to exert biological function. Activation of the SMAD complex leads to enhancement of tumor progression. PI3K and PTEN antagonize each other and further regulate mTORC1/2 by phosphorylating AKT (58,189). CSCs, cancer stem cells; EMT, epithelial-mesenchymal transition; SHH, Sonic Hedgehog; PTCH1, Patched 1; PTEN, phosphatase and tensin homolog.

CSCs and EMT

CSCs. Similar to adult stem cells, cancer stem cells (CSCs) are special cells capable of unlimited renewal and differentiation, thus contributing to the progression, metastasis and chemotherapy resistance of malignant tumors (53). The quest for molecular markers of CSCs has become a research hotspot in recent years leading to the discovery of $CD34^{+}CD38^{-}$ leukemic cells and $CD44^{+}CD24^{-}$ breast cancer cells. These CSCs play a role in drug resistance in each type of cancer and are associated with poor pathological characteristics (54). CD133 is reportedly responsible for tumorigenesis in CSCs (55). Transcription factors (TFs) are inducers of CSCs and promoters of their function. Key TFs such as octamer-binding transcription factor 4 (OCT4), Krüppel-like factor 4 (KLF4), Sry-related HMG box 2, Nanog and c-MYC play a key role in this process. Moreover, WNT, NF-KB. STAT3 and Hedgehog signal pathways can help maintain and transform CSCs (56). The anticancer effects of drugs could be mediated by targeting and inhibiting specific biomarkers and the cancer-promoting pathways involved in maintaining CSCs.

EMT. EMT is a process in which epithelial cells lose apical adhesion and transform into more invasive mesenchymal cells. The loss of E-cadherin and the increase of N-cadherin and Vimentin expression are important mechanisms of EMT (57). In addition to the morphological changes, EMTcells possess stem cell properties. This phenomenon enables EMT and GSCs regulation by similar pathways, including the WNT, STAT3 and NF-κB and Hedgehog pathways (58,59). The PI3K/AKT/mTOR signal pathway is a classical pathway regulating cell growth and differentiation. It also regulates and induces EMT and CSCs to control cancer cells, proliferation, invasion and metastasis (60). It is widely acknowledged that these EMT-related signaling pathways contribute to tumor cell progression, invasion and drug resistance (53) (Fig. 3).

3. Flavonoids on BLCA

Classification. Flavonoids have a basic skeleton consisting of a 15-carbon (C6-C3-C6) phenylpropanoid chain, with two aromatic rings (A and B) and a C heterocyclic pyran ring in the middle connected to A and B (61). Compounds that are connected to the 3C position of the C ring to the B ring are termed isoflavones. However, in other types of flavonoids, B rings are linked to the 2C, including flavones, flavanones, flavonols, flavanols and anthocyanins. Flavones have only one keto group at the 4C position and have a double bond between 2C and 3C, while flavanones (dihydroflavones) have no double bond structure. Flavanols have no keto group but have one

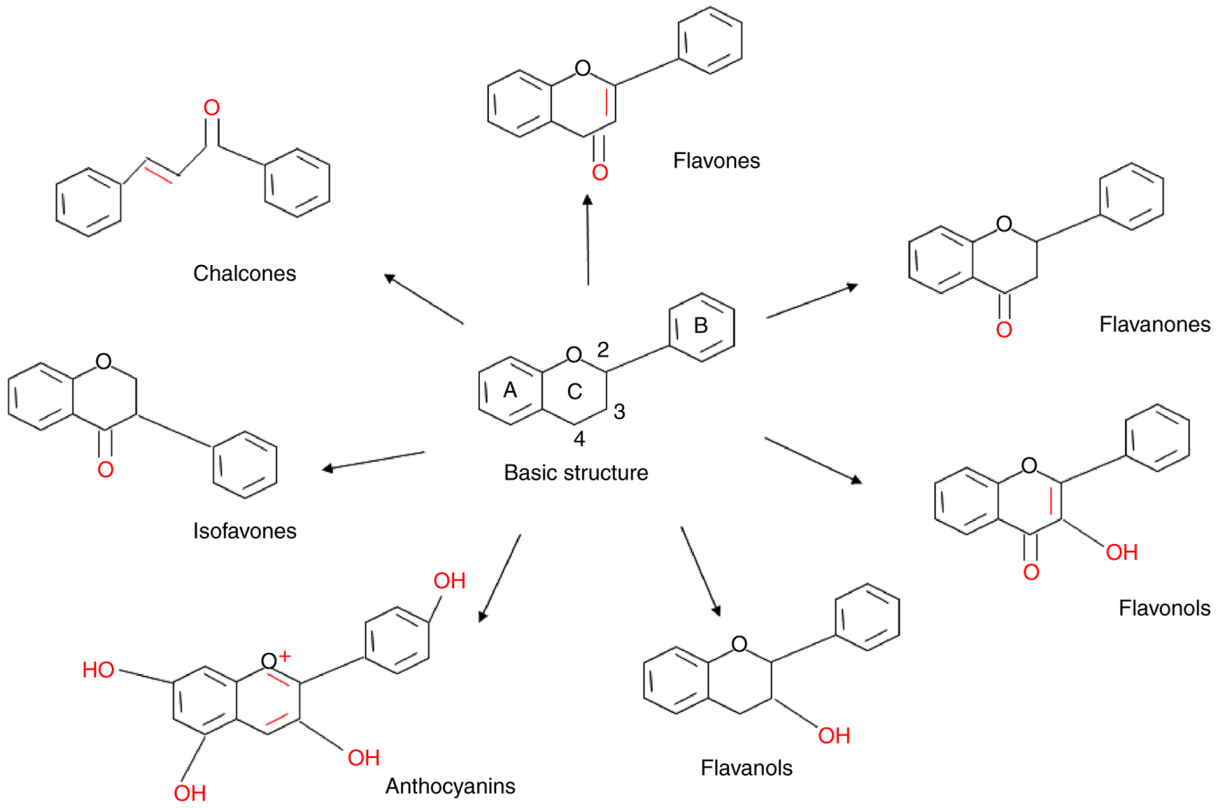

Figure 4. The classification of flavonoids. The main features are highlighted in red.

hydroxyl group at the 3C position and no double bonds between positions 2 and 3. The anthocyanins are replaced by multiple hydroxyl groups, including the 3C position and the C ring has double bonds. Flavonols have a hydroxyl group at 3C and a keto group at 4C. Finally, chalcones lack the ring C of the basic flavonoid structure (62,63). (Fig. 4). The flavonoids inhibit the development of BLCA through different mechanisms, which will be discussed in detail later (Table I).

Flavones. Flavones are characterized by being unmodified at 3C and can be oxidized at 4C. They can coexist with anthocyanins and flavonols in flowers and act as plant protectors. They are usually found in tea, parsley and citrus fruits (64).

Apigenin. Apigenin (4',5,7,-trihydroxyflavone), usually extracted from parsley, has been found to induce the loss of mitochondrial membrane potential leading to T24 cell apoptosis and cell cycle arrest via the PI3K/AKT pathway (65,66). Apigenin can reduce GSH levels in cells and activate ROS. This suggests that Apigenin might induce ferroptosis in BLCA cells and warrants further study (65,66). The urokinase-type plasminogen activator receptor (uPAR) is a cell surface glycoprotein and serves a role in inhibiting tumor invasion. Apigenin has been found to control the expression of uPAR and T24 cell invasion by inhibiting AP-1 and NF-kB signals (67).

Luteolin. Luteolin (3,4,5,7-tetrahydroxyflavone) is found in various plants and has attracted much interest for its anticancer role (68). Luteolin can exert more significant damage to BLCA cells than Apigenin by inducing apoptosis and cell cycle arrest (69). It was found that Luteolin could upregulate P21 expression and inhibit mTOR signal transduction to control the progression of BLCA in T24 cells and mouse xenograft models (70). The Bacillus Calmette-Guerin (BCG) vaccine is well known for its role in preventing recurrence and controlling the progression of BLCA. Interestingly, the combination of Luteolin and BCG has been reported to induce apoptosis of BLCA cells and increase the sensitivity of BCG. This finding suggests that Luteolin has great clinical potential in the treatment of BLCA (71).

Tangeretin. As one of the abundant ingredients in citrus peel, tangeretin (4',5,6,7,8-Pentamethoxyflavone) has anticancer and antioxidant properties. Proteomics technology analysis of tangeretin-related targets and signals suggests it could lead to mitochondrial dysfunction and apoptosis in BLCA cells via the release of cytochrome c (72).

Chrysin. Chrysin (5, 7-dihydroxyflavone) is mainly found in honey, propolis and some plants (73). Chrysin can activate ROS and ER stress to induce BLCA cell apoptosis and growth arrest via reducing STAT3 activation (74). Chrysin inhibits cell proliferation and migration through DNA damage. The anticancer mechanism depends on the state of TP53. In mutated TP53 cells, chrysin causes G_2/M arrest in BLCA cells and the downregulation of SRC, PLK1 and HOXB3 genes. DNA hypermethylation is also found to be involved (75).

Baicalein. Baicalein (5,6,7-Trihydroxyflavone) is a flavone isolated from *Oroxylum indicum* that can induce BLCA cell apoptosis (T24; 5637; 253J). Current evidence suggests that caspase enzymes (caspase-3/9) and ROS can be activated in T24 and 5637 cells by baicalein (76-78). Ferritin heavy chain 1 is a key determinant of BLCA cell ferroptosis following baicalein treatment. Moreover, the inhibition of BLCA cells is associated with the accumulation of ROS and intracellular

Table I. The classification and mechanism of flavonoids on BLCA.

Author, year	Flavonoids	Source	Compounds	Technique	Mechanisms	(Refs.)
(Zhu, Mao *et al*, 2013; Shi Shiao *et al*, 2015; Xia, Yuan *et al*, 2018)			Apigenin	*in vitro*	ROS; GSH; apoptosis; cell cycle; PI3K/ AKT; uPAR	(65-67)
(Kilani-Jaziri, Frachet *et al*, 2012; Yang, Wang *et al*, 2014; Iida, Naiki *et al*, 2020)			Luteolin	*in vitro*; *in vivo*	Apoptosis; cell cycle; mTOR	(69-71)
(Lin, Huang *et al*, 2019)			Tangeretin	*in vitro*	Apoptosis; mitochondrial dysfunction	(72)
(Xu, Tong *et al*, 2018; Lima, Almeida *et al*, 2020)			Chrysin	*in vitro*	ER stress; apoptosis; ROS; STAT3; TP53	(74,75)
(Li, Zhang *et al*, 2013; Wu, Tsai *et al,* 2013; Choi, Park *et al*, 2016; Yang, Liu *et al*, 2018; Kong, Chen *et al*, 2021)	Flavones	Flowers, tea, parsley, citrus fruits, leaves	Baicalein	*in vitro*; *in vivo*	Apoptosis; ROS; ferroptosis; cell cycle	(76-80)
(Lv, Liu *et al*, 2019)			Scutellarin	*in vitro*	EMT; PI3K/AKT; MAPK	(82)
(Goan, Wu *et al*, 2019)			Nobiletin	*in vitro*	PI3K/AKT; ER stress; mitochondrial dysfunction	(84)
(Tian, Tong *et al,* 2019)			Orientin	*in vitro*	Hedgehog; NF-κB; apoptosis	(85)
(Wei, Liu *et al*, 2012; Rockenbach, Bavaresco *et al*, 2013; Oršolić, Karač *et al*, 2016; Su, Peng *et al*, 2016; Tan and Liu, 2017; Oršolić, Odeh *et al,* 2020; Adami, Diz *et al,* 2021; Cho, Yu *et al,* 2021; Dong, Hao *et al,* 2021)	Flavonols	Fruits vegetables (apples onions, kale, tomatoes, grapes berries)	Quercetin	*in vitro*; *in vivo*	Apoptosis; DNA damage; ROS; cell cycle; autophagy; nucleotides catabolism; chemotherapy sensitization; network pharmacology	(88-93,95-97)
(Tao, He *et al,* 2017; Lee and Tuyet, 2019; Alban, Monteiro *et al,* 2020)			New complexes of quercetin	*in vitro*	Radiosensitization; AKT; AMPK/mTOR	(98-100)
(Chen, Chen *et al,* 2016; Ran, Wang *et al,* 2016; Wu, Liu *et al*, 2017)			Isoquercitrin	*in vitro*; *in vivo*	PI3K/AKT; PKC; AMPK; STAT3; cell cycle	(102-104)
(Xie, Su *et al,* 2013; Dang, Song *et al,* 2015; Qiu, Lin *et al,* 2017; Wu, Meng *et al,* 2018)			Kaempferol	*in vitro*; *in vivo*	DNA methylation; apoptosis; cell cycle; c-met/p38; PTEN TP53; apoptosis; cell cycle	(106-109)
(Wu, Ning *et al,* 2013; Gándara, Sandes *et al,* 2014; DT, Savio *et al,* 2017; Imai-Sumida, Chiyomaru *et al*, 2017; Sun, Guan *et al,* 2017; Li, Sun *et al,* 2018; Prack Mc Cormick, Langle *et al,* 2018; Barros, Lima *et al,* 2020)			Silibinin	*in vitro*; *in vivo*	DNA acetylation; Angiogenesis lncRNA; PI3K/AKT; KRAS; EMT; NF-κB; CSCs	(110-117)

Table I. Continued.

Author, year	Flavonoids	Source	Compounds	Technique	Mechanisms	(Refs.)
(Chung and Kim, 2016; Huang, Cheng *et al,* 2019; Xu, Shi *et al*, 2022)			Casticin	*in vitro*	Radiosensitivity; PDT; TM7SF4; DNA damage; ROS	(119-121)
(Shin, Won *et al*, 2017) (Pan, Li *et al,* 2016)			Morin	*in vitro*	MMP9; cell cycle	(123)
(Pan, Li *et al,* 2016)			Icaritin	*in vitro*	Autophagy	(124)
(Kim, Lee *et al,* 2008)	Flavanones	Citrus fruits (oranges), grapes	Naringin	*in vitro*	Cell cycle; Ras/Raf/ERK	(126)
(Liao, Kuo *et al,* 2014)			Naringenin	*in vitro*	MMP2; AKT	(127)
(Juhem, Boumendjel *et al,* 2013)			Flavanone derivative	*in vitro*	Cell cycle; apoptosis; mitotic spindle formation	(128)
(Chen, Yu *et al,* 2016)	Flavanols	Fruits (bananas, apples, peaches and pears)	Catechin	*in vitro*; *in vivo*	Nanoparticles; PI3K/AKT; CSCs; apoptosis; Hedgehog; NF-κB; MMP-9; autophagy; chemotherapy sensitization	(135)
(Qin, Wang *et al,* 2012; Jankun, Keck *et al,* 2014; Feng, Ho *et al,* 2017; Luo, Wei *et al,* 2017; Luo, Lung *et al,* 2018; Lee, Chen *et al,* 2019; Sun, Song *et al,* 2019; Luo, Zhu *et al,* 2020; Yin, Li *et al,* 2021)			EGCG	*in vitro*; *in vivo*		(136-144)
(Li, Ji *et al,* 2018; Li, Yu *et al*, 2018)	Anthocyanins	Flowers, Fruits (cranberries, red grapes, raspberries strawberries, blackberries blueberries)	PSPA	*in vitro*	Apoptosis; cell cycle; PI3K/AKT	(148,149)
(Fishman, Johnson *et al,* 2012; Liu, Zhang *et al,* 2016; Yang, Gao *et al*, 2021)			GSPs	*in vitro*	TGF-β; EMT; cell cycle; apoptosis	(150-152)
(He, Wu *et al,* 2016)	Isoflavones	Leguminous plants	Daidzein	*in vitro*; *in vivo*	FGFR3; cell cycle; apoptosis	(154)
(Wang, Wang *et al*, 2013; Park, Cha *et al,* 2019)			Genistein	*in vitro*; *in vivo*	Apoptosis; cell cycle; PI3K/AKT; NF-κB	(156,157)
(Köksal Karayildirim, Nalbantsoy *et al,* 2021)			Prunetin	*in vitro*	TNF-α; apoptosis; cell cycle	(158)
(Jiang, Chen *et al,* 2018; Liu, Li *et al,* 2018; Ye, Kan *et al,* 2019; Du, Zhang *et al,* 2020)			Puerarin	*in vitro*; *in vivo*	Apoptosis; cell cycle; mTOR/p70S6K; SIRT1/P53; ncRNAs	(160,161,163,164)
(Wu, Zhang *et al,* 2017)			Formononetin	*in vitro*	miR-21; PTEN	(165)
(Yuan, Li *et al,* 2013;						

Table I. Continued.

Author, year	Flavonoids	Source	Compounds	Technique	Mechanisms	(Refs.)
Jiang,Yuan *et al,* 2014; Yang, Jiang *et al,* 2016; Hong, Cha *et al,* 2019)	Chalcones	Fruits (tomatoes, strawberries, bearberries, pears)	Licochalcone A	*in vitro*	ER stress; apoptosis; ROS; Cell cycle; Ca^{2+}; GSH/GSSH; mitochondrial dysfunction	(167-170)
(Yuan, Li *et al,* 2014; Zhao, Yuan *et al,* 2014)			Licochalcone B	*in vitro*; *in vivo*	Cell cycle; apoptosis; MMP9; NF-κB	(171,172)
(Wang, Yuan *et al,* 2015)			Licochalcone C	*in vitro*	Apoptosis	(173)
(Patricia Moreno-Londoño, Bello-Alvarez *et al,* 2017)			Isoliquiritigenin	*in vitro*	Cisplatin-induced toxicity	(175)
(Liu, Xu *et al,* 2013; Li, Xu *et al,* 2014; Liu, Song *et al,* 2022)			Flavokawain A	*in vitro*; *in vivo*	P53; UPII; Apoptosis; Ha-ras pathway	(176-178)
(Wu, Lin *et al,* 2014)			Chalcone derivatives	*in vitro*	COX-1; Cell cycle; ROS	(179)
(Martel-Frachet, Keramidas *et al,* 2015)			IPP51	*in vitro*; *in vivo*	Cell cycle; Apoptosis; Mitotic arrest	(180)

BLCA, bladder cancer; ROS, reactive oxygen species; EMT, epithelial-mesenchymal transition; PTEN, phosphatase and tensin homolog; CSCs, cancer stem cells; ncRNAs, non-coding RNAs; miRNA, microRNA; GSH, glutathione; GSSH, glutathione persulfide; UPII, uroplakin II.

iron (79). In addition, baicalein has been found to inhibit Cyclin B1 and Cyclin D1 expression leading to cell cycle arrest and MMP2/9 mediated cell invasion and migration. In *in vivo* mouse models, only a weak role has been observed (80).

Scutellarin. Scutellarin (4', 5, 6-hydroxyl-flavone-7-glucuronide) is a natural compound obtained from *Erigeron breviscapus* with anti-oxidation and antitumor properties (81). EMT has been established to modulate tumor progression. Scutellarin is widely thought to inhibit metastasis and invasion of BLCA by suppressing EMT, PI3K/AKT and MAPK signaling pathways (82).

Nobiletin. Nobiletin (3', 4', 5, 6, 7, 8-Hexamethoxyflavone) is a ubiquitous compound extracted from citrus fruits (83). Like other flavonoids, nobiletin inhibits PI3K/AKT/mTOR and induces PERK/elF2α/ATF4/CHOP pathways, leading to mitochondrial dysfunction, ER stress and apoptosis of human BLCA cells (84).

Orientin. Orientin (8-C-β-glucopyranosyl-3', 4', 5, 7-tetrahydroxyflav-2-en-3-one) is a flavone isolated from traditional Chinese medicine. *In vitro*, orientin has been found to inhibit T24 cell proliferation and promote apoptosis by inhibiting the Hedgehog and NF-KB signaling pathways (85) (Fig. 5).

Flavonols. Flavonols are also abundantly found in fruits and vegetables. Compared with flavones, Flavonols have a hydroxyl group which can be glycosylated on the C ring. Flavonols such as quercetin and kaempferol have been extensively studied. Their intake is strongly associated with health, reducing the risk of vascular disease (63).

Quercetin. Quercetin (3,5,7,3',4'-pentahydroxyflavone) is a flavonol found in a number of fruits and vegetables (86) and a *Solanum nigrum* L. herbal active ingredient. It has long been recognized as a natural anticancer agent with high potential and has been extensively studied in animal models and cell lines for numerous cancers (87). Quercetin can reportedly inhibit the proliferation of T24 cells and damage cell morphology, leading to a decreased number of cell bodies, retraction and condensation of cytoplasm and membrane and the aggregation and roughness of membrane proteins, indicating that apoptosis and senescence are necessary for this process (88). The damage to DNA is reportedly regulated by quercetin, reducing cell colony formation in proliferating BLCA cells (89). In terms of apoptosis, the AMPK pathway is involved in inhibiting signaling pathways in BLCA by quercetin and regulates BLCA cell apoptosis (90). In BIU-87 cells, quercetin can promote BLCA cell apoptosis and autophagy. After blocking autophagy, apoptosis becomes more evident (91). In addition to stimulating apoptosis, quercetin can inhibit cell cycle progression through the TAK1/JNK signaling pathway, leading to an increased number of cells in the G_2/M phase (92). Quercetin regulates nucleotide metabolism to inhibit BLCA cells via increasing ADP hydrolysis and inhibiting the activity of ecto-5'-nucleotidase/CD73 (93). Network pharmacology can predict the relationship between drugs, targets and pathways and is widely used to study diseases and drugs (94). Network pharmacology analysis reveals that quercetin is closely related to the target genes of BLCA and apoptosis and that the PI3K/AKT pathway is involved in it (95). Quercetin may serve a role in improving BLCA cell drug resistance. Quercetin and gemcitabine exert an additive effect on gemcitabine resistance cells (T24-GCB), reducing the expression of ABC transporter (ABCC2) proteins and metabolic proteins (DCK and TKs) (96). In addition, the combination of cisplatin and

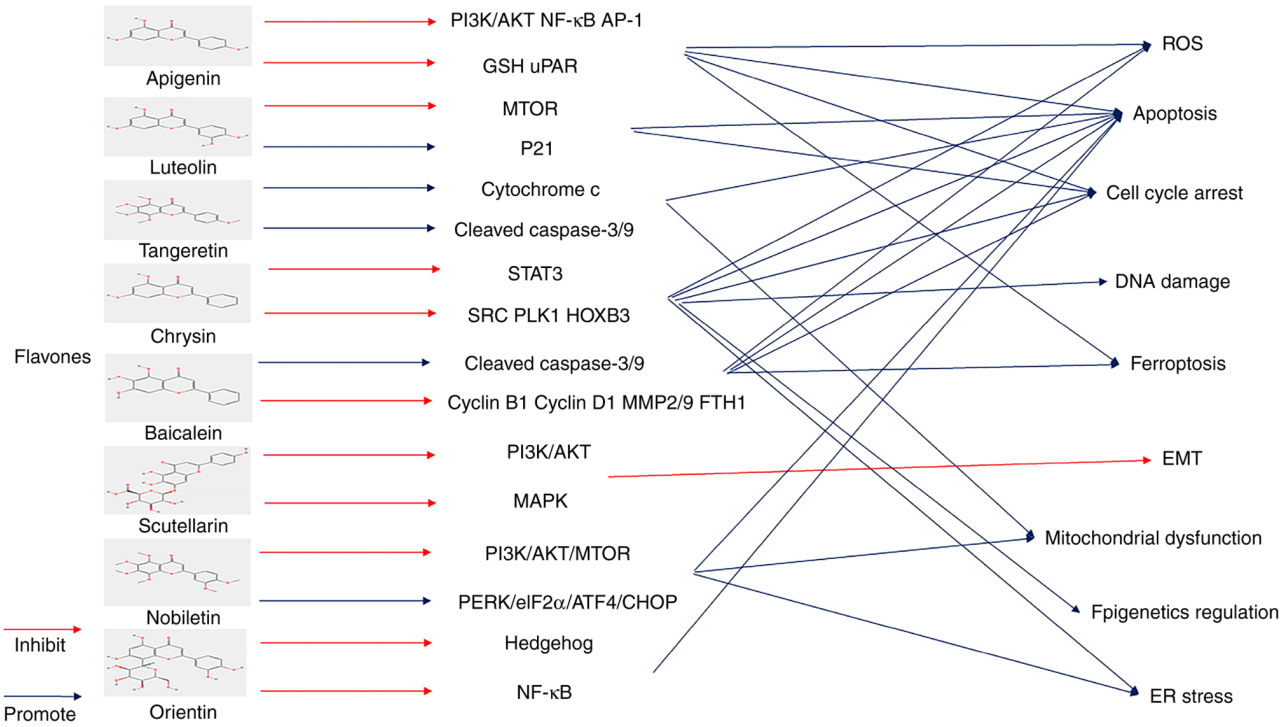

Figure 5. Flavones including Apigenin, Luteolin, Baicalein, Chrysin, Scutellarin, Tangeretin, Nobiletin and Orientin act on BLCA through various mechanisms such as apoptosis, cell cycle arrest and ROS activation. Apigenin is found to inhibit GSH production and promote ferroptosis. Additionally, Apigenin can inhibit UPAR, AP-1, or PI3K/AKT and NF-κB pathways to promote apoptosis, cell cycle arrest and ROS activation. Luteolin can inhibit mTOR and promote P21 expression to promote apoptosis and cell cycle arrest of BLCA cells. Tangeretin causes mitochondrial dysfunction and promotes the expression of apoptosis genes such as cytochrome C and cleaved caspase-3/9. Chrysin inhibits oncogenes such as SRC PLK1 HOXB3 and STAT3 expression. Baicalein can promote cell cycle arrest by regulating genes such as Cyclin B 1and D1. It also promotes the expression of cleaved caspase-3/9 and the occurrence of ferroptosis. Scutellarin can inhibit tumor EMT progression by inhibiting PI3K/AKT and MAPK pathways. Nobiletin has also been found to inhibit the activation of ER stress and apoptosis by inhibiting PI3K/AKT pathway. Orientin can promote apoptosis of BLCA cells by inhibiting Hedgehog and NF-KB pathways. The 2D structures of the compounds were obtained from the Pubchem database. Apigenin: PubChemIdentifier: CID 5280443 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5280443#section=2D-Structure). Luteolin: PubChemIdentifier: CID 5280445 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5280445#section=2D-Structure). Baicalein: PubChemIdentifier: CID 5281605 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5281605 #section=2D-Structure). Chrysin: PubChemIdentifier: CID 5281607 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5281607 #section=2D-Structure). Scutellarin: PubChemIdentifier: CID 185617 URL (https://pubchem.ncbi.nlm.nih.gov/compound/185617 #section=2D-Structure). Tangeretin: PubChemIdentifier: CID 68077 URL (https://pubchem.ncbi.nlm.nih.gov/compound/68077 #section=2D-Structure). Nobiletin: PubChemIdentifier: CID 72344 URL (https://pubchem.ncbi.nlm.nih.gov/compound/72344 #section=2D-Structure). Orientin: PubChemIdentifier: CID 5281675 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5281675 #section=2D-Structure). BLCA, bladder cancer; ROS, reactive oxygen species; GSH, glutathione; EMT, epithelial-mesenchymal transition.

quercetin promotes tumor cell death and enhances immune response and mice survival (97).

The development of new compounds based on quercetin has led to improved and more significant effects. Q-ZnCPX, a novel compound consisting of quercetin and zinc, has a stronger inhibition and anti-metastasis effect, which may ameliorate the disadvantages of quercetin, including low absorption and rapid metabolism (98). Recently, researchers have synthesized 8-trifluoromethyl-3, 5, 7, 3', 4'-O-pentamethyl-quercetin (TFQ) based on the chemical modification of quercetin by fluorination. TFQ is believed to affect BLCA growth through the AMPK/mTOR pathway (99). The usefulness and biocompatibility of nanostructures have attracted much attention. Research has shown that they could interfere with the proliferation and enhance the radiosensitization of BLCA cells by loading quercetin into titanate nanotubes (TNT) (100).

Isoquercitrin. Isoquercitrin (quercetin-3-O-glucoside) is a natural flavonoid found extensively in Chinese bayberry and other plants (101). Isoquercetin has been found to reduce protein kinase c (PKC) expression and phosphorylation of PI3K and AKT in BLCA cells. Isoquercetin can also inhibit the progression of BLCA *in vitro* and *in vivo* (102). In addition, Isoquercetin is similar to quercetin and could inhibit BLCA by activating the AMPK pathway (103). Moreover, Isoquercetin can inhibit the proliferation of EJ cells and increase G1 phase cells by regulating the expression of STAT3 and STAT3-inhibiting factors (PIAS3) (104).

Kaempferol. Kaempferol (3, 4, 5, 7-tetrahydroxyflavone) is a flavonoid found in a number of natural plant products, such as beans and vegetables. Kaempferol has anti-inflammatory, antimicrobial heart and nerve protective and antitumor pharmacological properties (105). Kaempferol is found to regulate DNA methylation in BLCA depending on the level of DNA methyltransferases (DNMTs). Kaempferol can reportedly suppress the protein levels of DNMT3B by increasing its ubiquitination (106). Kaempferol has been reported to be safe for normal bladder cells but yields a strong inhibitory effect on BLCA cells, promoting cell apoptosis and S phase arrest (107). The c-Met/p38 signal pathway has also been revealed to be involved in inhibiting BLCA by kaempferol (108). In addition,

the expression of PTEN is significantly increased by kaempferol and Akt phosphorylation is inhibited, leading to cell apoptosis (109).

Silibinin. Silibinin is a natural flavonol derived from milk thistle seeds. Its antitumor properties in bladder cancer is dependent on TP53 expression levels. A study demonstrates that in wild-type TP53 cell lines, the FRAP/mTOR, AKT2, DNMT1 and FGFR3 genes were downregulated by silibinin, while only miR203 gene expression was altered in the mutant cell line. Both could inhibit cells proliferation and promote RT4 and T24 cell apoptosis (110). In addition, G_2/M cell cycle arrest in TP53 mutant cells has been demonstrated and HTA, HDAC and HOXB3 genes are regulated via modulating mutant BLCA cell DNA acetylation, deacetylation and angiogenesis (111). It has been shown that silibinin can inhibit the expression of cyclooxygenase (COX)-2 and EMT induced by TGF-β1, which significantly inhibits transitional cell carcinoma migration and invasion (112). EMT serves an essential role in the interference effect and silibinin inhibits the ability of CSCs to control migration via regulating the β-catenin/ZEB1 signaling pathway (113). As well as inhibiting tumor cell invasion, migration and apoptosis, silibinin can regulate the actin cytoskeleton and PI3K/AKT pathways. In addition, KRAS regulated by histone H3 lysine 4 and acetylated H3 are reportedly significantly inhibited (114). lncRNAs (HOTAIR and ZFAS1) are also reported as oncogenic factors inhibited by silibinin (114). Silibinin can also relieve drug resistance to chemotherapy and radiotherapy. Improvement of chemodrug-induced chemoresistance by silibinin treatment is reportedly mediated by the NF-κB pathway (115). In mice, radiotherapy (RT)-inhibited NF-κB and PI3K pathways are enhanced by silybin (silibinin diastereomer), resulting in increased radiosensitivity of invasive cells (116). Photodynamic therapy is an anticancer therapy based on a photosensitizer that can inhibit malignant cells. 5-aminolevulinic acid is a precursor of Protoporphyrin IX with synergistic or additive effects with silybin, thus enhancing the inhibitory effect on BLCA metastases (117).

Casticin. The flavonoid casticin (3', 5-dihydroxy-3, 4', 6, 7-tetramethoxyflavone) is extracted and isolated from the *Vitex* species (118). Casticin can inhibit the migration and invasion of BLCA cells by inhibiting the expression of TM7SF4. MMP-2, MMP-9 and CyclinD1 (119). In addition, casticin has been shown to inhibit the proliferation of BLCA by inducing DNA damage via decreasing the expression of p-p53 and P-AKT (120). The role of ROS in cell damage and activation of apoptosis is well-established. Casticin has also been reported to cause changes in mitochondrial membrane potential and ROS activation in T24 cells by upregulating XAF1 and TAp73 expression (121).

Morin. Morin (2', 3, 4', 5, 7-pentahydroxyflavone) is a natural flavonoid obtained from Moraceae plants with antioxidant and antibacterial activities (122). Its inhibitory effect against invasion and migration of BLCA is regulated by MMP9 by suppressing AP-1, NF-κB and Sp-1 levels. In addition, G_1 cell cycle arrest and the decrease of CyclinD1, Cyclin E and CDK2/4 expression are reportedly induced by morin (123).

Icaritin. Icaritin (3,5,7-trihydroxy-2-(4-methoxyphenyl)-8-(3-methylbut-2-enyl)chromen-4-one) is a flavonol glycoside extracted from the genus *Epimedium* with synergistic effects with epirubicin (EPI) that can inhibit autophagy and BT5637 and T24 cell proliferation (124) (Fig. 6).

Flavanones. It is well-established that flavanones, also known as dihydroflavones, have a saturated c-ring. Flavanones are found mainly in citrus fruits such as oranges and lemons (63). Among them, hesperidin and naringin are the most abundant ingredients with anti-oxidation and anti-inflammatory properties and even maintain intestinal health (125).

Naringin. Current evidence suggests that naringin (4', 5, 7-trihydroxyflavanone 7-rhamnoglucoside) could upregulate p21WAF1 expression and induce G_1 cycle phase arrest through the RAS/RAF/ERK signal pathway in 5637 cells (126).

Naringenin. Naringenin (4', 5, 7-Trihydroxyflavanone) is a bioactive flavanone that can inhibit BLCA cell migration by suppressing MMP-2 expression and AKT activation (127).

Flavanone derivative. AG11 obtained from CB11 chalcone precursor has been reported to induce G_2/M phase cell cycle arrest and apoptosis of RT4 cells. AG11 can prevent purified tubulin from polymerizing and disrupt mitotic processes of BLCA cells *in vitro* (128).

Flavanols

Tea polyphenols (catechins). Green tea has attracted much interest worldwide for its effects on cancer prevention (129). Current evidence suggests that polyphenols, the main active compounds in tea, serve an important anticancer role (130). Catechins belong to the flavanol class of the flavonoid family and are the main component of tea polyphenols (130,131). Of these, epigallocatechin gallate (EGCG) is the most abundant and biologically active member of the catechin family, accounting for >50% of the family (132). High consumption of green tea could reduce the recurrence and progression of urothelial carcinoma (133). Notably, it has been shown that green tea polyphenols can inhibit cytoplasmic human antigen R expression in a BLCA model. In addition, it can suppress BLCA cell proliferation and angiogenesis and the expression of related proteins, including VEGF-A, heme oxygenase (HO)-1 and COX-2 (134). Mg (II)-catechin nanoparticles (Mg (II)-Cat NPs) display a significant inhibitory effect on BLCA, given their improved biocompatibility and stronger cellular uptake. In addition, eukaryotic translation initiation factor 5A2 (EIF5A2) small interfering RNA (siRNA) can be loaded into the tumor site to further enhance the anti-BLCA effect via the PI3K/AKT pathway (135).

EGCG. In animal models, EGCG prevents bladder tumor implantation and development by reducing proteolytic activity, with a slightly higher therapeutic effect compared with mitomycin C (136). Next-generation sequencing reveals the related mRNAs, miRNAs and mechanisms of EGCG on BFTC-905 cells (137). EGCG can inhibit the proliferation and migration of BLCA cells (SW780, 5637 and T24) and promote cell apoptosis by suppressing NF-KB and MMP9 and PI3k/AKT pathways (138-140). As well as apoptosis, tissue factor pathway inhibitor 2 is reported to be upregulated by EGCG to inhibit the growth of BLCA cells via decreasing promoter hypermethylation (141). Notably, low-dose EGCG promotes LC3I to LC3II, suggesting the occurrence of autophagy. The autophagy effect is blocked by a PI3K/AKT inhibitor (LY294002) (142).

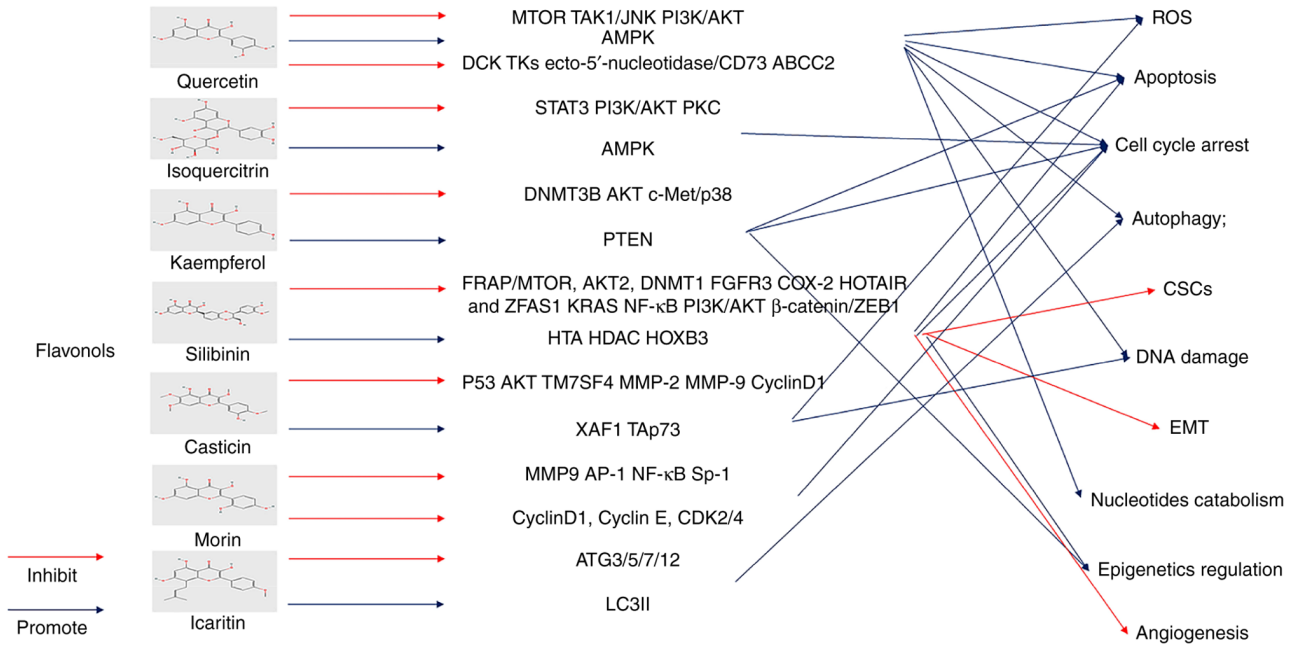

Figure 6. Flavonols can inhibit CSCs, angiogenesis and EMT of BLCA. In addition, they can promote BLCA apoptosis, autophagy, DNA damage, cell cycle arrest and so on. Quercetin inhibits BLCA progression by multiple mechanisms including promoting ROS, apoptosis, autophagy, cell cycle arrest nucleotides catabolism and DNA damage. Isoquercitrin can promote AMPK and inhibit STAT3, PI3K/AKT and PKC to regulate cell cycle. In addition to promoting apoptosis, Kaempferol also regulates epigenetics. Notably, silibinin can inhibit CSCs, EMT and angiogenesis. Casticin promotes DNA damage and ROS activation in BLCA cells by regulating XAF1 and TAp73. Morin can promote cell cycle arrest by inhibiting Cyclin D1, Cyclin E and CDK2/4. Icaritin is shown to promote the production of LC3II and inhibit the expression of ATG3/5/7/12 to promote autophagy. The 2D structures of the compounds were obtained from the Pubchem database. Quercetin: PubChemIdentifier: CID 5280343 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5280343 #section=2D-Structure). Isoquercitrin: PubChemIdentifier: CID 5280804 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5280804 #section=2D-Structure). Kaempferol: PubChemIdentifier: CID 5280863 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5280863 #section=2D-Structure). Silibinin: PubChemIdentifier: CID 31553 URL (https://pubchem.ncbi.nlm.nih.gov/compound/31553 #section=2D-Structure). Casticin: PubChemIdentifier: CID 5315263 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5315263 #section=2D-Structure). Morin: PubChemIdentifier: CID 5281670 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5281670 #section=2D-Structure). Icaritin: PubChemIdentifier: CID 5318980 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5318980 #section=2D-Structure). CSCs, cancer stem cells; EMT, epithelial-mesenchymal transition; BLCA, bladder cancer; ROS, reactive oxygen species.

The effect of EGCG on bladder CSCs has also been studied. In this respect, EGCG has been shown to inhibit the expression of CD133, CD44, ALDH1A1, OCT4 and Nanog and sonic hedgehog signaling pathways to inhibit bladder CSCs (143). It has been suggested that EGCG can be combined with docetaxel to enhance the induction of apoptosis in BLCA cells by modulating the NF-κB/MDM2/p53 pathway (144).

Anthocyanins. Anthocyanins and anthocyanidins are plant pigments that account for various colors in plants and fruits. Anthocyanins are anthocyanidins structurally modified by sugar and acyl acids found mainly in dark fruits with excellent potential to inhibit tumor progression (145,146). The combination of anthocyanins, a bladder cancer preventive agent and mitomycin C has been reported to increase BLCA cell death (147).

Purple sweet potato anthocyanin (PSPA). Purple sweet potato (PSP) is well-acknowledged as a healthy food, given its anthocyanins content. When anthocyanins cause a decline in BIU87 cell proliferation, individual volume reduction and weakened cell adhesion are observed (148). In addition, the anti-BLCA effect of PSPA is achieved by interference with apoptosis and the cell cycle via the PI3K/AKT pathway (149).

Grape seed proanthocyanidins (GSPs). GSPs have been found to further inhibit EMT by suppressing the TGF-β signal pathway and improving the invasion and migration of BLCA cells (150). Interferon (IFN) has been used for immunotherapy of BLCA for some time (151). Notably, GSPs combined with IFN enhances BLCA cell inhibition and G_1 cycle arrest (151). In addition to cell cycle interference, GSPs can induce BIU87 cell apoptosis by increasing caspase-3 activation (152).

Isoflavones. Isoflavones are mainly derived from soybean and soybean products foods. A high content of daidzein and genistein is present in isoflavones. Isoflavones are also thought to be protective agents against hormonal disorders and suppress a wide range of cancers, including prostate and breast cancer (153).

Daidzein. Daidzein (4',7-Dihydroxyisoflavone) is a natural isoflavone compound that is mainly extracted from soybeans. It suggests that daidzein can induce BLCA cell apoptosis and G_1/S cycle arrest through the FGFR3 pathway. *In vivo*, it is also demonstrated that Daidzein could inhibit the growth of xenograft tumors of RT112 cells (154).

Genistein. The anticancer effects of genistein (4', 5, 7-Trihydroxyisoflavone), a soybean isoflavone, have been documented *in vitro* and *in vivo* (155). In bladder cancer, like daidzein, genistein induces T24 cell cycle arrest and apoptosis via ROS activation and the PI3k/AKT pathway (156). Hydroxycamptothecin (HCPT) is a DNA topoisomerase I inhibitor used to treat BLCA for nearly 40 years. The NF-kB

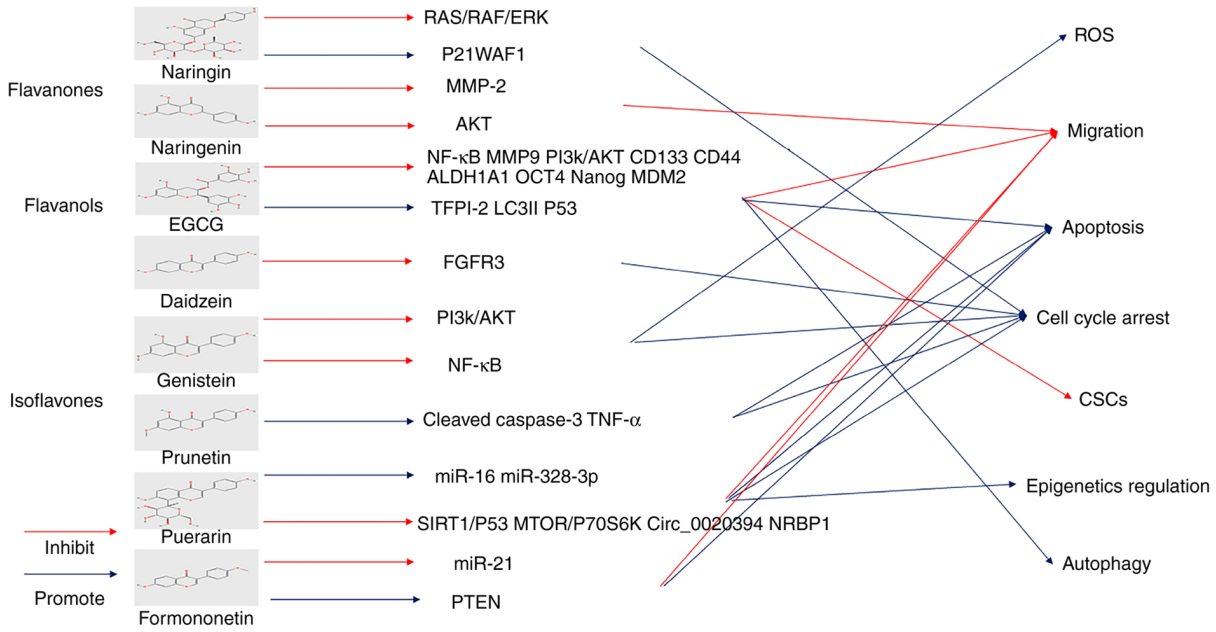

Figure 7. Flavanones include naringin and naringenin. They inhibit BLCA migration and promote cell cycle arrest by inhibiting MMP-2, AKT or RAS/RAF/ERK pathway. EGCG can inhibit CSCs and promote BLCA cells apoptosis and autophagy. Isoflavones including daidzein, genistein, prunetin, puerarin and formononetin are revealed to inhibit BLCA migration and be regulated by epigenetics. Daidzein inhibits FGFR3 expression and thus promotes cell cycle arrest. Genistein is found to inhibit the PI3K/AKT and NF-KB pathways. Prunetin promotes the expression of apoptosis genes (cleaved caspase-3 and TNF-α). Puerarin inhibits BLCA growth by regulating epigenetic regulation. Formononetin inhibits miR-21 and upregulates PTEN expression to inhibit BLCA cell proliferation and promote apoptosis. The 2D structures of the compounds were obtained from the Pubchem database. Naringin: PubChemIdentifier: CID 442428 URL (https://pubchem.ncbi.nlm.nih.gov/compound/442428 #section=2D-Structure). Naringenin: PubChemIdentifier: CID 932 URL (https://pubchem.ncbi.nlm.nih.gov/compound/932 #section=2D-Structure). EGCG: PubChemIdentifier: CID 65064 URL (https://pubchem.ncbi.nlm.nih.gov/compound/65064 #section=2D-Structure). Daidzein: PubChemIdentifier: CID 5281708 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5281708 #section=2D-Structure). Genistein: PubChemIdentifier: CID 5280961 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5280961 #section=2D-Structure). Prunetin: PubChemIdentifier: CID 5281804 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5281804 #section=2D-Structure). Puerarin: PubChemIdentifier: CID 5281807 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5281807 #section=2D-Structure). Formononetin: PubChemIdentifier: CID 5280378 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5280378 #section=2D-Structure). BLCA, bladder cancer; EGCG, epigallocatechin gallate; CSCs, cancer stem cells; miR, microRNA; PTEN, phosphatase and tensin homolog.

pathway is thought to mediate the effect of genistein on HCPT sensitivity (157).

Prunetin. The majority of isoflavones have an estrogenic effect and there are few pieces of research on Prunetin (5, 4'-dihydroxy-7-methoxyisoflavone). Prunetin, a phytoestrogen, had been found to upregulate the expression of CASP3 and TNF-α to activate RT-4 cell apoptosis and G0/G1 phase cell cycle arrest (158).

Puerarin. Puerarin (7,4'-dihydroxyisoflavone-8β-gluco pyranoside) is extracted from plants in the genus *Pueraria*, widely used in heart cerebrovascular disease, cancer and bone diseases (159). BLCA cell apoptosis can be regulated by inhibiting SIRT1/P53 and mTOR/P70S6K signaling pathways through puerarin treatment. Cell cycle arrest at the G_0/G_1 phase can be induced by puerarin (160,161). miRNA-16 has long been hypothesized to be a tumor suppressor gene that inhibits the proliferation of BLCA (162). Puerarin has been found to upregulate the expression of miR-16 (163). The circ_0020394/miR-328-3p/NRBP1 axis is also thought to be regulated by puerarin to interfere with BLCA cell migration and invasion and promote apoptosis (164).

Formononetin. Formononetin (7-hydroxy-4'-methoxyisoflavone) is mainly obtained from *Astragalus membranaceus* and can reportedly reduce the expression of miR-21 and increase PTEN expression, thus promoting T24 cells apoptosis and inhibiting invasion (165) (Fig. 7).

Chalcones. Chalcones are widely found in fruits and vegetables and are important components and biological precursors of flavonoids. They have a basic 1, 3-diaryl-2-propen-1-one chemical scaffold and two aromatic rings connected by an unsaturated α, β-carbonyl system (166). The effect of chalcones on BLCA has been extensively studied in recent years.

Licochalcones. Licochalcone A (LCA) is a licorice chalcone hypothesized to have anticancer activity (167). LCA activates ROS production, mitochondrial dysfunction and ER stress leading to T24 cell apoptosis (167). A study demonstrates that T24 cells treated with LCA exhibit increased intracellular Ca^{2+} levels, Apaf-1 and caspase-3/9 expression, activation of calpain 2 and caspase-4 and ultimately leads to apoptosis ROS, the key step to promoting BLCA cell apoptosis (168). LCA is found to inhibit cell proliferation by increasing ROS levels and reducing the ratio of GSH to GSSG, which suggests the role of iron death (169). In addition, LCA is found to inhibit cell proliferation by promoting ROS-dependent G_2/M phase cell cycle arrest by decreasing cyclin A and cyclin B1 expression (170).

In addition, Licochalcone B (LCB) can reduce the expression of MMP-9 mRNA and protein, but MMP-2 does not. LCB can promote nuclear translocation of NFκB and suppress NF-κBP65 protein expression. This indicates that LCB exerts a potential therapeutic effect on the invasion and metastasis of BLCA (171). In addition, LCB can regulate the cell cycle by

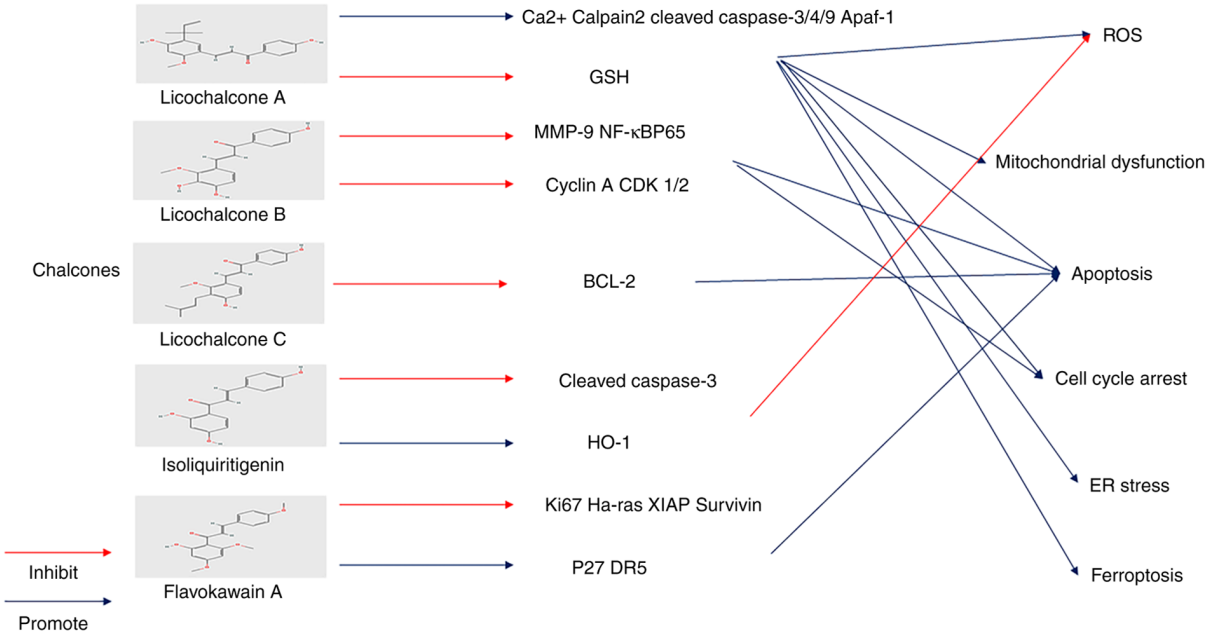

Figure 8. Chalcones can activate ER stress and ROS to induce BLCA cells apoptosis, ferroptosis and cell cycle arrest. Licochalcone A can promote intracellular Ca^{2+} level and activation of Calpain2, cleaved caspase-3/4/9 and Apaf-1 expression to induce cells apoptosis, ER stress and ROS. In addition, it can promote the occurrence of ferroptosis by regulating GSH. Licochalcone B is found to promote apoptosis and cell cycle arrest by inhibiting Cyclin A and CDK 1/2. Licochalcone C can inhibit the expression of the classical anti-apoptosis gene Bcl-2. Isoliquiritigenin protects the kidney by inhibiting cisplatin-induced ROS production. Flavokawain A mainly induces apoptosis of BLCA cells by promoting P27 and DR5 or inhibiting Ki67, Ha-ras, Xiap and Survivin expression. The 2D structures of the compounds were obtained from the Pubchem database. Licochalcone A: PubChemIdentifier: CID 5318998 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5318998 #section=2D-Structure). Licochalcone B: PubChemIdentifier: CID 5318999 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5318999 #section=2D-Structure). Licochalcone C: PubChemIdentifier: CID 9840805 URL (https://pubchem.ncbi.nlm.nih.gov/compound/9840805#section=2D-Structure). Isoliquiritigenin: PubChemIdentifier: CID 638278 URL (https://pubchem.ncbi.nlm.nih.gov/compound/638278 #section=2D-Structure). Flavokawain A: PubChemIdentifier: CID 5355469 URL (https://pubchem.ncbi.nlm.nih.gov/compound/5355469#section=2D-Structure). ER, endoplasmic reticulum; ROS, reactive oxygen species; BLCA, bladder cancer; GSH, glutathione.

inhibiting cyclin A and CDK 1/2 mRNA. LCB inhibits colony formation and promoted apoptosis of BLCA cells (172).

Licochalcone C (LCC) has also been shown to induce T24 cell apoptosis by regulating the biological function of the Bcl-2 family (173).

Isoliquiritigenin (IOS). IOS is a bioactive chalcone compound derived from licorice (174). IOS can protect proximal tubular cells (LLC-PK1) from cisplatin via the HO-1 pathway to a certain extent. Furthermore, it shows antitumor activity against BLCA cells (175).

Flavokawain A (FKA). FKA (2'-Hydroxy-4,4',6'-trimethoxychalcone) is the main chalcone extracted from the Kava plant, with non-toxic and cancer-protective characteristics in mice (176). P53 defect is widely hypothesized to contribute to the inhibitory effect of FKA on BLCA growth. SV40 large T antigen (SV40T) driven by the urothelium-specific uroplakin II (UPII) promoter can inactivate the p53 gene in BLCA. FKA in UPII-SV40T transgenic mice yields a significant inhibitory effect on solid tumors, reducing tumor burden and prolonging mice survival (177). In Ha-ras transgenic mice with UPII mutation, FKA has been shown to inhibit the proliferation of solid tumors and promote apoptosis by the Ki67 cell proliferation assay and TUNEL assay. This finding suggested that FAK could inhibit the activation of the Ha-ras gene to prevent and treat NMIBC *in vivo* (178) (Fig. 8).

Chalcone derivatives. Chalcone derivatives have been found to regulate BLCA cell growth and cycle by inhibiting COX-1 activity and platelet aggregation (179).

IPP51 (1-(2,4-dimethoxyphenyl)-3-(1-methylindolyl) propenone) is a novel derivative for chalcone that can promote apoptosis and G_2+M accumulation in BLCA cells and inhibit mitosis and destroy microtubules by promoting the production of soluble tubulin and inhibiting tubulin polymerization. In addition, IPP51 exerts an anti-angiogenesis effect (180,181).

Chemotherapy Sensitization. Flavonoids have been found to serve a powerful role in sensitizing patients to chemotherapy. Cisplatin is one of the most common chemotherapy drugs in clinical practice. It has been used for a number of years and is still the cornerstone of chemotherapy for advanced BLCA and metastasis. Reducing its side effects and making it more sensitive to patients has become a research hotspot (182,183). Current evidence suggests that isoliquiritigenin can improve the nephrotoxicity of cisplatin and increase the damage to BLCA cells (175). In addition, silibinin has been shown to alleviate chemodrug-induced chemoresistance through the NF-κB pathway (115). Chemotherapy remains an important means to treat cancer; chemotherapy drugs combined with other drugs, including immune checkpoint inhibitors, have been used to treat BLCA. However, due to the high selectivity of patients to checkpoint inhibitors, the effect is not ideal. Flavonoids represent a promising candidate for a new class of drugs that can be combined with chemotherapy to suppress the recurrence and progression of BLCA. Given that they are harmless and widely available, they bring less financial burden and psychological stress to patients.

Nanoparticles. The modification of nanoparticles offsets some of the drawbacks of flavonoids. Flavonoids are widely acknowledged for their poor targeting ability and faster metabolism, which are major concerns affecting their efficacy (184). Nanoparticles can be encapsulated and target tumors to increase their half-life and reduce immunogenicity. In addition, nanoparticles can be loaded with various drugs to improve drug resistance and with diagnostic agents for integrated treatment (185). Notably, the Mg (II)-Cat/siEIF5A2 nanoparticle combined with flavonoid and siRNA yields a stronger BLCA inhibitory effect (135). The combination of flavonoids and nanoparticles remains rare in the treatment of BLCA and deserves further study.

4. Discussion and outlook

The mechanisms underlying the therapeutic effect of flavonoids are quite extensive and the generation of ROS seems to act as a switch in a variety of mechanisms (22). Further work on ROS is warranted. The majority of studies have primarily investigated the mechanism of cell cycle arrest and apoptosis, with more emphasis needed on autophagy and ferroptosis. Indeed, autophagy has both positive and negative effects on cancer (31). Different concentrations of drugs may have different effects on autophagy. In addition, inhibition of autophagy appears to promote cell apoptosis. The autophagy changes can be accurately assessed by detecting the transformation from LC3I to LC3II (31). Accordingly, there is still much room for research on ferroptosis in flavonoids. Notably, the change in the GSH/GSSG ratio and the expression of GPX4 can reflect the occurrence of ferroptosis (36). ROS activation is also key to the occurrence of ferroptosis. P53 is not only a tumor suppressor gene but also a regulator of ferroptosis. Its upregulation can promote ferroptosis in cells by inhibiting the system Xc-transporter. CSCs play an important role in the progression of BLCA and multiple marker genes are overafctivated in CSCs. Targeting these genes, including OCT4, KLF4, c-MYC and Nanog, can inhibit the transformation of BLCA stem cells. In addition, CSCs and EMT have been documented in the abnormal activation of multiple common pathways, including the WNT, STAT3 and NF-KB pathways, which can be investigated in future studies.

5. Conclusion

In conclusion, the present study summarized the effects of flavonoid on BLCA *in vitro* and *in vivo* for the first time. It emphasized that flavonoids have good prospects for clinical application to treat BLCA.

Acknowledgements

Figs. 1, 2, 3 and 4 were drawn using Pathway Builder Tool 2.0 (Protein Lounge; https://proteinlounge.com/pathway_builder.php) (186).

Funding

No funding was received.

Availability of data and materials

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

Authors' contributions

YL, ZhL and HJ wrote the first draft and drew the figures and tables. ZaL and LD designed this article and modified it. YX revised the draft and the figures. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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