Medical Oncology (2021) 38:66
https://doi.org/10.1007/s12032-021-01508-8

REVIEW ARTICLE

Luteolin and cancer metastasis suppression: focus on the role of epithelial to mesenchymal transition

Yaseen Hussain[1] · Jing Hao Cui[1] · Haroon Khan[2] · Michael Aschner[3] · Gaber El-Saber Batiha[4] · Philippe Jeandet[5]

Received: 23 February 2021 / Accepted: 5 April 2021 / Published online: 5 May 2021

Abstract

Epithelial to mesenchymal transition (EMT) is a physiological process that assumes a primary role in the induction of cancer metastasis. This results in increased cell renewal, and resistance to cell death and therapies. EMT, therefore, represents an effective strategy for regulating cancerous cell activity. A need for efficacy and low cytotoxicity epithelial to mesenchymal transition modifying drugs has led to the investigational testing of the efficacy of plethora of different groups of phytonutrients. Luteolin is a natural flavonoid inhibits the growth of cancer cells by various mechanisms, such as the stimulation of cancer cell apoptosis, cell cycle arrest, inhibition of cell replication, tumor growth, improvement of drug resistance, prevention of cancer cell intrusiveness and metastasis. This review article focuses on the anti-cancer and anti-metastatic potential of luteolin targeting various transcription factors, markers and signaling pathways associated with the repression of epithelial to mesenchymal transition.

Keywords Luteolin · Cancer metastasis · Epithelial to mesenchymal transition (EMT) · Luteolin and EMT

Introduction

Cancer is the most prevalent threat to public health showing a massive disease burden. The critical and special characteristic of cancer cells is reflected in their ability to invade healthy tissue and to migrate from their main site to peripheral sites, in response to enhanced and persistent division and proliferation. This form, referred to as metastasis, leads to over 90% of the mortality of human cancer [1]. The metastasis cascade is typically composed of several steps: localized incursion; systemic circulation intravasation; transport survival, extravasations, micro metastasis settlement in distant sites; and macroscopic metastasis colonization [2]. Luteolin has a range of beneficial properties, including anti-inflammatory and anticancer [3]. The underlying mechanisms of these properties have not been completely understood, but are partially due to properties regulating luteolin redox and estrogen. The mechanism for luteolin specific cytotoxicity in cancerous but not in healthy cells have yet to be established [4].

Cancer cells undergo drastic and complex changes in the expression pattern of adhesion molecules during tumor progression. The separation of cells from the basal tissue and the presentation of a cell result in these modifications—an intrusive phenotype. The epithelial-mesenchymal

✉ Haroon Khan
hkdr2006@gmail.com; haroonkhan@awkum.edu.pk

Jing Hao Cui
jhcui@suda.edu.cn

Gaber El-Saber Batiha
gaberbatiha@gmail.com

Philippe Jeandet
philippe.jeandet@univ-reims.fr

1 College of Pharmaceutical Sciences, Soochow University, Jiangsu 221400, People's Republic of China

2 Department of Pharmacy, Abdul Wali Khan University Mardan, Mardan 23200, Pakistan

3 Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY 10463, USA

4 Department of Pharmacology and Therapeutics, Faculty of Veterinary Medicines, Damanhour University, Damanhour 22511, Egypt

5 Research Unit, Induced Resistance and Plant Bioprotection, EA 4707, SFR Condorcet FR CNRS 3417, Faculty of Sciences, University of Reims Champagne-Ardenne, PO Box 1039, 51687 Reims Cedex 2, France

transformations commonly recognize the pre-mentioned changes [5]. Epithelial-mesenchymal transformations are the mechanism by which epithelial cells are converted into mesenchymal cells and it has been shown that many human malignancies play a significant role in cancer metastasis [6, 7].

In both normal development and cancer metastasis, epithelial-mesenchymal transformations play an essential role. Cancer metastasis is not only a hallmark of disease development, but also the primary cause of failure of treatment and death [8]. A long series of concurrent, interrelated steps facilitate cancer metastasis. Many cancer patients are diagnosed with metastasis, poor prognosis, often at an advanced stage [9]. For cancer treatment, an effective therapeutic agent designed to target the metastasis process is therefore important. At any of the metastasis phases, a failure or insufficiency can interrupt the phase [10].

For the treatment of a number of solid cancers, including, breast, pancreatic, colorectal, oesophago-gastric and lung cancer, neoadjuvant therapy, comprising chemo, radiation, and hormone therapy, shows efficacy. Improved diagnosis is likely to occur in cancers down regulated by neoadjuvant therapy [11–13]. Around 20% of patients treated with neoadjuvant therapy have a beneficial response that lengthens survival [11]. Radiotherapy, however, has been reported to carry risks of short-term toxicity and long-term complications such as radiation exposure to structures that is neighboring. In addition, about 40 to 60 percent of patients do not react to neoadjuvant therapy while awaiting surgery [15–17].

Epithelial-mesenchymal transformations (EMT) represent a novel therapeutic strategy with increased percentage of patients who respond to neoadjuvant therapy. In order to increase the effectiveness of treatment and mitigate non-specific toxicity, photochemical have recently been investigated for possible auxiliary use [12]. In addition, it has been recognized that epithelial cells require multiple molecular pathways to acquire a mesenchymal phenotype. Numerous genes are abundantly expressed during the epithelial-mesenchymal transformations process, as shown by genetic screening [19–21]. The EMT mechanism, ultimate cancer growth and metastasis have been correlated with many indirect pathways and a collection of signaling molecules. Such signals might play a significant role in guiding the cancer cell EMT process, thus forecasting patient care and clinical outcomes. Collectively, the reversal or inhibition of EMT and its concerned signaling pathways by phytochemicals could be a very potential therapeutic strategy that may eliminate or restrict cancer metastasis [13].

During EMT, cancer cells become susceptible to metastasis by dropping the epithelial-specific protein expression and mesenchymal development properties by greater mesenchymal-specific protein expression. EMT is among the most important causes of neoadjuvant therapy resistance that results in poor tumor growth. Therefore, herein, we address studies relevant to EMT and highlight luteolin's efficacy in reversing EMT or regulate the epithelial to mesenchymal transformations signal, paving the way for inhibition of tumor regression through luteolin-EMT interaction.

Luteolin

Luteolin is a pure yellow crystal bioflavonoid. It exists naturally in the plant kingdom and is commonly used in the production of various traditional medicines for the treatment of ailments due to its abundance in edible plants [14, 15]. Due to its anti-inflammatory and antioxidant properties, Luteolin has been shown to be a potent nitrogen and oxygen-containing reactive species scavenger [16].

Chemistry

Luteolin is a 3′, 4′, 5, 7-tetra hydroxyl flavonoid. It exhibits three benzene rings in its structure with a chemical composition of C_6-C_3-C_6 carbon atoms. Within the structure (Fig. 1), the initial two rings are pure benzene based, while the third ring at 2–3 position is composed of oxygen-carbon double bond [17]. The biochemical and biological properties of luteolin are associated with the presence of hydroxyl group and moieties attached at 2–3 bonds [18]. Luteolin is also glycosylated, as are other flavonoid, and its glycoside is hydrolyzed to free luteolin during intestinal absorption. Apart from it, a few molecules of luteolin are also transformed into glucuronides after moving via the intestinal mucosa. Luteolin is heat stable in nature so interestingly cannot be loosed during cooking [19].

Sources

In various vegetables such as broccoli, fennel, onion leaves, parsley, carrots, cauliflowers, peppers, and chrysanthemum flowers, luteolin is one of the important food-based phytonutrients. It is abundant in fruits, with apple skin deemed as

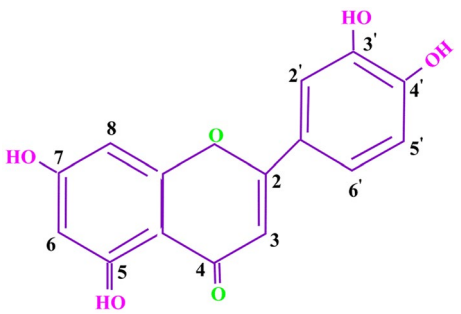

Fig. 1 Chemical structure of Luteolin

a major source of luteolin [20]. With 37.96 mg/100 g, the vegetable (broccoli, fennel, onion leaves, parsley, carrots, cauliflowers, peppers) is a popular source of luteolin, accompanied by raw Chinese celery with 35 mg/100 g of luteolin. In herbs, the prominent source of luteolin is oregano, with a maximum concentration of 1,029 mg/100 g. Mostly in case of fruits and plants, healthy origins of luteolin with 1.5 and 16.7 mg/100 g luteolin, respectively, are pure peel-free lemons and fresh sage [4]. A detail of luteolin sources are shown in Table 1.

Pharmacokinetics

In order to comprehend and clarify the relationship better, between luteolin in vitro activities and luteolin in vivo actions, a successful awareness of the ADME processes (absorption, distribution, metabolism and excretion) of this compound is becoming increasingly important. The absorption of food-released dietary luteolin by chewing will rely on their physicochemical characteristics, like molecular size, shape, solubility in water and pKa. Luteolin being aglycone is absorbed from small intestine [32]. Luteolin and its metabolites are preferentially to the gastrointestinal, liver, kidney, and lungs. The elimination pathway of conjugated luteolin is regulated by biliary excretion. Pharmacokinetic tests have shown that luteolin in the rat intestine is quickly and effectively absorbed and then extensively metabolized, which was responsible for a low 17.5% availability of unchanged luteolin [33].

Methylation has also been identified as an essential metabolic pathway of luteolin, in addition to glucuronidation. One such investigation indicated that luteolin could be methylated into chrysoeriol and diosmetin by catechol-O methyltransferase in rats [34]. Luteolin is susceptible to substantial metabolism after oral administration on the basis of these previous studies and thus reaches systemic circulation predominantly as conjugated metabolites. However, the entire pharmacokinetic profile of systemic luteolin metabolites, not to include the tissue distribution and excretion route of each metabolite, is not yet clearly established.

The key conjugate metabolism of luteolin is uridine diphospho-glucuronosyl transferase and sulfotransferases in an in vivo study. Luteolin, on the other hand, displays a faster rate of elimination when orally administered to rats, and catechol-O-methyl transferase is possibly a significant mechanism that triggered lower exposure to luteolin [34, 35]. The pharmacokinetics of luteolin and luteolin-7-O-glucoside isolated from *Dendranthema morifolium* shows that the later one is hydrolyzed into luteolin in GIT followed by systemic circulation absorption [36]. An absorption and excretion study of luteolin has shown that luteolin is absorbed efficiently with a slow phase excretion from the living system which indicates a hypothesis for the accumulation of luteolin in the body [37]. It can be inferred from luteolin study that luteolin is passively absorbed in rat intestine and that its absorption in the jejunum and duodenum is more effective than in the colon and ileum. The bioavailability of luteolin in peanut hull extract was considerably higher than that of pure luteolin [38].

The pharmacokinetics of luteolin and its glucuronides/sulphate conjugates were analyzed in rats administered as an intravenous bolus or oral solution after a single 50 mg/kg dose of luteolin. The results demonstrated that, luteolin has high distribution volume and high clearance. Also after intravenous and oral administration, double peaks were observed, indicating enterohepatic recirculation after an oral administration [39]. In short, the pharmacokinetic studies of luteolin clearly indicate that it can be useful clinically.

Table 1 Various source of luteolin and its concentration

Source		Contents (mg/100 mg)	References
Vegetables	Dried parsley	19.75 ± 0.08	[20–23]
	Chinese celery	34.87 ± 0.04	
	Radicchio	37.96 ± 0.10	
	Hot chili	5.11 ± 0.01	
	Raw spinach	1.11 ± 0.01	
	Beets	0.37 ± 0.03	
	Cauliflowers	0.08 ± 0.007	
	Cabbage	0.04 ± 0.008	
	Chinese cabbage	0.06 ± 0.009	
	Pepper Serrano	4.14 ± 0.02	
	Fresh peppermint	11.33 ± 0.02	
Plants	Rosemary	4.00 ± 0.20	[24–26]
	Chives	0.15 ± 0.07	
	Sage	16.70 ± 0.7	
Herbs	Thyme	51 ± 3.40	[27–29]
	Oregano	1028 ± 5.6	
	Berries	69 ± 2.30	
Fruits	Peel-free lemons	1.50 ± 0.03	[30, 31]
	Leaves of sweet potato	0.20 ± 0.01	

Luteolin in cancer

Luteolin suppresses cancer-promoting protein expression, decreases tumor growth, viability growth, VGF secretion based on progestin, and increases Bax expression are amongst others promising mechanical pathways. As a potential agent against cancer, luteolin exhibits prevents proliferation of cells and disrupts EGF-induced p-STAT3, p-Akt, p-EGFR and p-Erk1/2 expression conducted at Breast cancer cell lines especially MCF-7. In addition, it inhibits the

EGFR up regulating activity induced by EGF in the cell lines of human breast cancer [40–43]. Earlier studies into the 7, 12-dimethylbenz anthracene-induced tumor have shown luteolin prevents the growth of large tumors and to drastically reduce vascular endothelial growth factor levels in rats [44].

Luteolin also alters the cell cycle, the forming of channels; the expression proteins linked to Notch signaling and controlled miRNAs in breast cancer cells (MDA-MB-231) of human. In addition, luteolin decreases the viability of tumor cells, vascular endothelial growth factor secretion based on progestin and the development of xenograft tumors of human breast cancer cells dependent on medroxyprogesterone acetate. It also reduces the density of blood vessels and prevents the acquisition of stem cell-like characteristics in breast cancer cells (T47-D/BT-474) induced by medroxyprogesterone acetate [45, 46]. A group of researchers found that inactivation of Akt and ERK signaling blockage in MCF-7 and HER18 breast cancer cell line and same mechanism with MDA-MB-231 and SkBr3 cells were found exhibiting synergistic effects of the combined therapy of luteolin and celecoxib [47]. In addition, luteolin disrupted the progression at the sub-G1 as well as G1 levels of the cell cycle, increased the expression of death receptors (DR5), while triggered caspase cascades. Apart from it, the activation of caspases-8 and -9 mediated caspase 3 involvement in the apoptosis of extrinsic and intrinsic pathways. Study results have also shown that luteolin increases collapse of the membrane potential associated with mitochondrion and release of cytochrome c by inhibition of Bcl-2 and increases Bax expression [48].

MDA-MB-231 is a human breast cancer cell line, treated with luteolin and paclitaxel decreased both tumor weight and size, triggered caspase-8, -3, and increased Fas ligands expression. In addition, the increased Fas expression in a xenograft tumor model was due to the blockage of STAT-3. Similarly, luteolin administration in MCF-7 cells, suppressed cancer proliferation in a time and dose-dependent manner by reducing Bcl-2 protein expression, curbing the rate of migration by 71.07 percent, reducing MMP-2 and AEG-1 expression by 82.34 and 85.70 percent, respectively [43, 49]. In vitro studies have shown that interleukin-8 and metalloproteinase matrix 9 play a significant role in proliferating metalloproteinase cancer of the breasts. Treated with 12-O-tetradecanoylphorbol-13-acetate, activation of MMP-9 and stimulation of IL-8 were inhibited by luteolin in MCF-7 breast cancer cells. Apart from it, it blocked the expression of mRNA via suppression of the signaling pathway of mitogen activated protein kinase while down-modulation of NF-kB and AP-1 [50].

Luteolin significantly impairs MCF-7 cell proliferation stimulated by IGF-1, inhibits cell cycle growth, and activates cell death. Also, without disrupting Erk1/2 phosphorylation, luteolin reduced IGF-1-dependent IGF-1R and pAkt pathway based on significantly [51]. Definitively, it is concluded from the gathered literature that luteolin is capable of tackling breast cancer through multiple pathways.

Luteolin's anti-inflammatory and antioxidant action is responsible for its efficacy in colon cancer along with its serious comorbidities, notably its decreasing effect on the expression of iNOS and COX-2. In addition, its resisting activity on MMP-2 and 9 expressions has also provided important proof of its ability to handle cancer of the colon. By suppressing the expression of P and aryl hydrocarbon receptor-dependent cytochrome P450 enzyme activity, luteolin on colon cancer cells line of human has been shown to provide an inhibitory effect. In addition, luteolin decreased the transport of elevated metabolites of B(a)P due to its Interaction with resistance protein transporter concerned with breast cancer cells. Luteolin hindered both the metabolism of Phase-I and Stage III transport, which induces an intracellular threefold accumulation of B (a)P radioactively labeled for further proceedings [52].

Luteolin, in contrast, provides a base for protective mechanism in carcinogenesis of the mouse colon induced by azoxymethane following shrinkage of the size and prevalence of the tumor, reducing the argyrophilic nucleolar organizer region, and increasing the index of cell nuclear antigen. By decreasing its colon carcinogenesis inhibitory effect, it exerts inhibitory cell proliferation effect induced by AOM, including Wnt, β-catenin pathways [53]. Comparably, orally administered luteolin, in mice have reversed the induced modifications and lowered the secondary marker level for a region depleted with Mucin in colon cancer animals (AOM-induced) [54]. Luteolin has been shown effective in management of the apoptosis induction, arrest of cell cycle, the down regulation of signaling and protein phosphorylation in pancreatic cancer. Luteolin induces cell death in vivo in pancreatic cancer cells due to its promising anticancer activity by suppressing the pathway of K-ras / GSK-3β / NF-μB signaling, which is followed by cytochrome c release, caspase 3 activation, and Bcl-2 / Bax ratio reduction [55]. Similarly, luteolin administration in cancer cells decreased the phosphorylation of cellular proteins development, protein tyrosine kinase modulated actions like the EGFR activity and PTK activity that triggers EGFR autophosphorylation and enolase transphosphorylation have been suppressed. Literature study also reveals that, following the mechanism of cellular proliferation and protein phosphorylation inhibition along with apoptosis as well as DNA degradation luteolin results in coping with pancreatic cancer [56].

Luteolin anti—carcinogenic and chemotherapeutic function targeting prostate cancer is related to its efficacy in suppressing the invasion in cancer cells, stop proliferation of cells, trigger apoptosis, decrease extracellular matrix expansion, decrease Rho activation, and suppress phosphorylation

induced by VEGF [57]. Likewise, the development of androgen-sensitive as well as independent prostate cancer cell line was suppressed by luteolin, significantly back-regulated by the miR-301, and mediated LNCaP and PC3 cell apoptotic cell death [58]. Combination therapy of luteolin with gefitinib greatly influenced cell viability in cell lines of prostate cancer, significantly suppressed the expression of GAK protein and increased expression of miR-5703 and miR-630 [59].

Luteolin treatment with prostate cancer cells (human PC-3) has been shown to decrease the genes up-regulation involved in multiple cell cycle and epidermal growth factor receptor signaling pathway [60]. In a study conducted in humans, researchers found that by cell apoptosis induction, up-regulation of prostate-derived Ets factor, androgen receptor down regulation and gene overexpression, luteolin at a 30 µM concentration was found effective against prostate carcinoma LNCaP cells [61]. Mechanisms include, B- cell gene-2 translocation and gene-1down stream regulation using N-myc [62, 63]. Due to its capacity to activate many critical targets, luteolin exhibits an effective potential in lung cancer therapy. Pathways involved include cell death, cell cycle progression arrest; knock down of HNF4 alpha expression, M2 and IL-4 associated genes secreted by TAM. In summary, literature has shown that, due to its natural origin, protection and affordable prices compared to conventional anti-cancer drugs, luteolin can be used an effective alternative medication for the treatment and prevention focusing a variety of cancers.

EMT: from basics to cancer involvement

EMT is a mechanism wherein epithelial cells shed their polarity and junctions during embryogenesis, creating migratory mesenchymal types of cells such as mesoderm and neural crest [64]. Initially, developmental biologists described epithelial-mesenchymal transition, a phenotypic transformation which helps to facilitate embryonic development [65]. During the gastrulation stage, the epiblast cells of the primal ectoderm experience EMT to transform into primary mesenchymal cells. At the time of palatal merger in the oral cavity, EMT transforms certain cells of each palatal layer into mesenchymal form, resulting in the development of the secondary palate to create the proper differentiation of oral and nasal cavities in mammalian cavities [66, 67].

Epithelial to mesenchymal transformation is mediated via EMT-activating transcription factors, namely, ZEB, SNAIL and TWIST families in particular. In all stages of cancer progression from initiation, primary cell proliferation, incursion, spread and metastasis to colonial expansion, as well as in therapy resistance, EMT-TFs play a significant role [64]. Conflicting perspectives emerged regarding the importance of EMT in cancer biology because the EMT is not a unified pathway-defined standardized programmed and, secondly, since EMT-TFs have several other functions in addition to triggering the 'classical' epithelial to mesenchymal transformation. The transformation from epithelial cells to cells with a mesenchymal phenotype, characterized by quintessential markers such as E-cadherin and vimentin, occurs due to classical epithelial to mesenchymal transition [68, 69].

EMT is followed by the dissolution of adhesive junction proteins and close junction destruction, resulting in epithelial cell dissociation. EMT, induces mesenchymal marker proteins expression and promotes the attachment to the extracellular matrix as well as the development of mesenchymal characteristics like spindle-shaped cell morphology and the restructuring of actin stress fibres, thus allowing individual migration and invasion via walls of lymphatic system and basement membranes. After intravasation, EMT cells survive as circulating tumor cells in the bloodstream and ultimately extravasate into surrounding tissues [70]. Cancer cells are considered to endure the MET while producing metastases to recover their epithelial features and form subsequent tumors. In addition to enhancing their motile capacities, cancerous cells experiencing EMT have more violent phenotypes, such as sensitivity to anti-cancer drugs and different pressures, senescence, anoikis inhibition, immunosuppression and cancer stem cell acquisition-like characteristics [70, 71].

Cancer cells with partial epithelial to mesenchymal transition exhibit greater risk as compared to complete mesenchymal transition [72]. Cancer cells are induced by successful metastasis despite complete loss of epithelial morphology and maximum retention of mesenchymal morphology. Thus, cancer cells with epithelial-mesenchymal phenotypes may trigger mutual cell migration via their residual epithelial feature upon acquisition of partial epithelial to mesenchymal transition and strengthen adherence to the extracellular matrix by acquiring migration of mesenchymal features. That's why the risk of partial transition is high [73]. Pathologically, regulation of E-cadherin, is found in cancer cells at the margins of tumor colonies and at the invasion front of multicellular spheres, while E-cadherin is mostly normally produced in cancer cells at the core of solid tumor nests, causing epigenetic diversity [74].

Interestingly, several researchers have also shown that any single epithelial to mesenchymal transition—inducing transcription factors activation or suppression is sufficient to induce a partial single epithelial to mesenchymal transformation programmed without any compensation from other EMT-inducing transcription factors [75, 76]. In correlation with the recognition of the presence of a partial epithelial to mesenchymal transition mechanism, the use of an in vitro models system has shown that cells with that kind of a mechanism have strengthened migration capacity

[77]. In addition, cancerous cells experiencing epithelial to mesenchymal transition display increased sonic hedgehog secretion, avoiding desert and Indian hedgehog secretion. Also, it involve to trigger accelerated metastasis by activating the Gli-1 transcription factor by epithelial-like cancer cells with poorly metastatic tendencies [78]. The single and collective cell migration is shown in Fig. 2.

Cancerous cells that are resistant to the chemotherapeutic drugs trametinib - MEK blocker, are able to restore their potential to proliferate through FGF-2 signal reactivation [79]. In contrast, the molecular mechanism for Ras in epithelial to mesenchymal transition is not fully illustrated yet. By phosphorylation of the Smads' linker domain, Ras inhibit TGF-β signals and promote suppression of their signal transduction while facilitating their deterioration [80]. Such an induction of epithelial to mesenchymal transition by Ras is shown in Fig. 3. The resulting mutants are triggered whenever the presumed phosphorylation domains are mutated throughout the linker region of Smads, relative to wild-type Smads. Similarly, the resulting mutants cause Snail induction that leads to epithelial to mesenchymal transition stimulation that are directly analogous to wild-type Smads, indicating that, in cooperation with TGF-β [81, 82]. The comprehensive exact mechanism remains uncertain, but in collaboration with Ras signals, STAT3 is partially engaged in the induction of epithelial to mesenchymal transformation by TGF-β.

Partial epithelial to mesenchymal transition is more critical than complete transition in cancer progression but not in cancer growth [83]. While research into unique markers to identify cancer cells experiencing EMT is in focus on the basis of improvements in alternative splicing during EMT. Immunocytochemical analysis reveals that in normal epithelium, certain epithelial splicing proteins differential expression are poor, and in contrast significantly up-regulated in precancerous lesions and in invasive cancer, retained in progressed cancer cells, while eventually dysregulated in aggressive frontier cells [84].

During epithelial to mesenchymal transition, the alternate splicing of fibroblast growth factor receptor-encoding

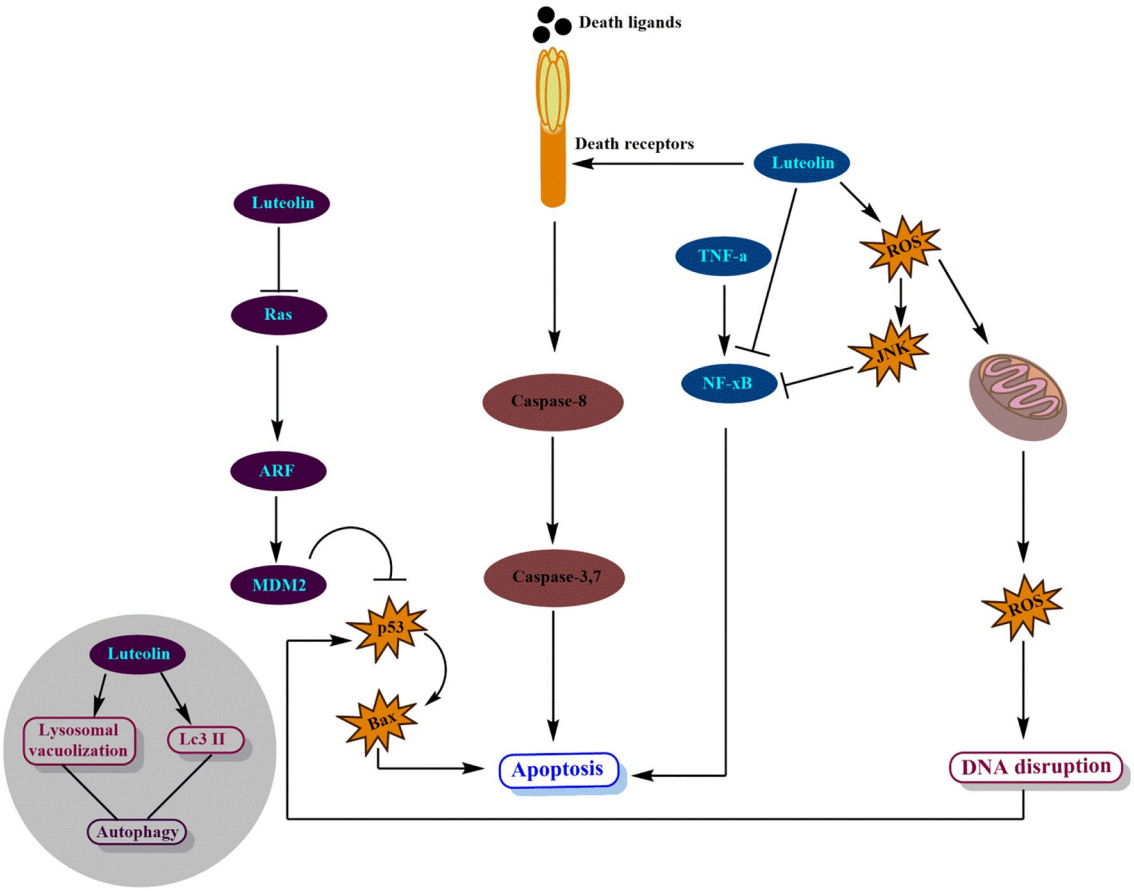

Fig. 2 Single and combine cancer cell migration and invasion. First portion shows the single cancerous cells migration. It is also termed as mesenchymal migration. The morphology of such migration is similar to fibroblast. The second portion shows the collective migration of cancer cells. Such a migration is featured by clusters of multi cells just like a grapes bunch and is led by fibroblast migration and invasion of cancer cells. N stands for N-cadherin while E for E-cadherin

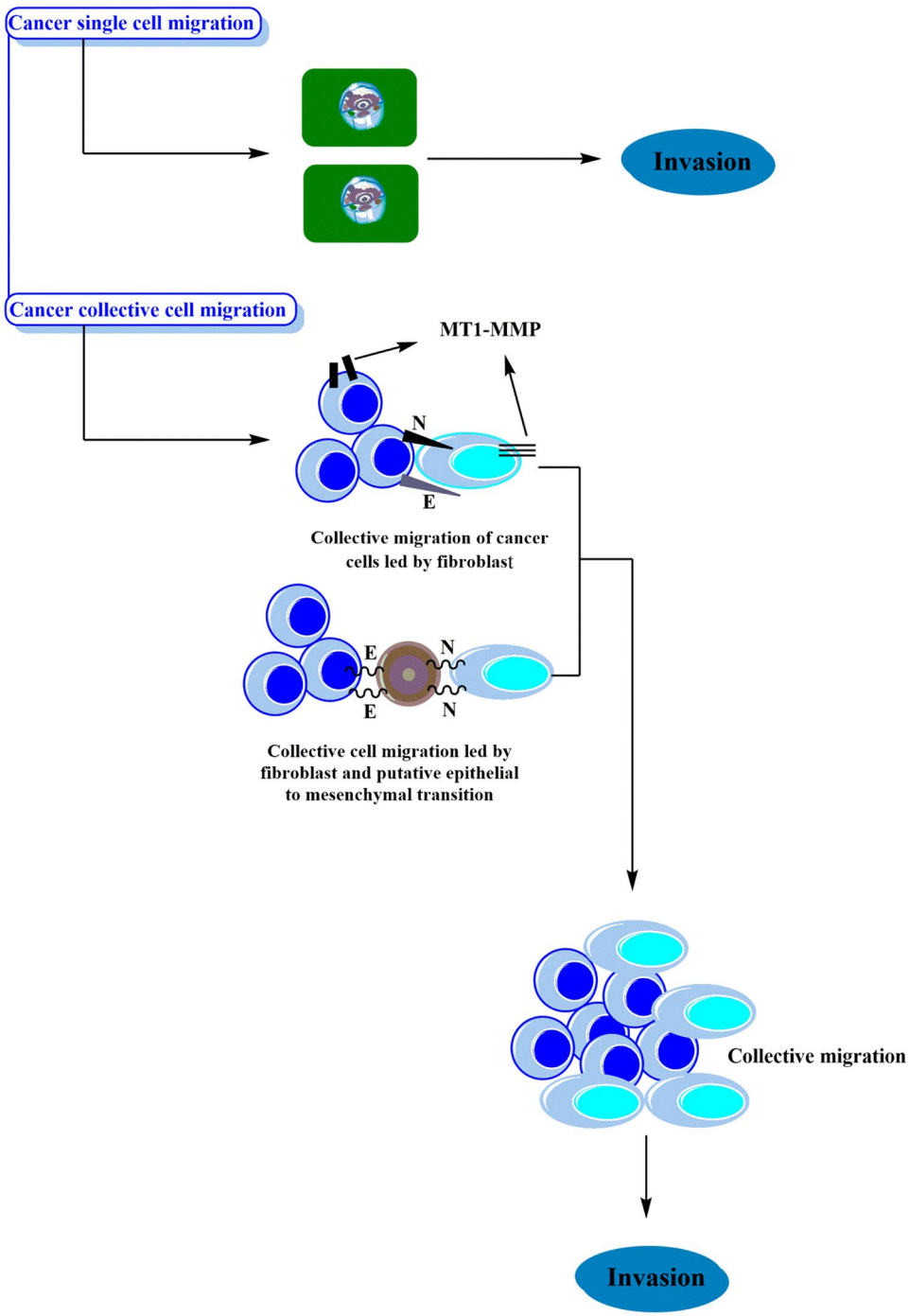

Fig. 3 Single and combine cancer cell migration and invasion. The Ras signaling stimulates TGF that in turn induces transcription factors and ultimately leads to activation of epithelial to mesenchymal transition. The suppression of TGF by Ras signaling inhibit the cell growth while STAT-3 also leads to induction of epithelial to mesenchymal transition via mediation of TGF. TGF; transforming growth factor, Ras; rat sarcoma, STAT; signal transducer and activator of transcription

translations is induced by epithelial splicing regulatory proteins (ESRP1 and ESRP2). These regulatory proteins get bind specifically to alternatively spliced transcript regions encoding growth factor receptor, cluster of differentiation - 44, catenin p122, and Mena (mammalian ena—a protein family) [85]. Although the roles of specific ESRPs differ substantially from one another, in epithelial cells these regulating proteins are predominantly expressed while epithelial to mesenchymal transition enduring cells these proteins are highly down regulated. Epithelial to mesenchymal transition following transcriptional mechanisms are shown schematically illustrated in Fig. 4.

The involvement of EMT-TFs in cancer is exacerbated by the fact that their additional objectives are sometimes tumor-specific and anti-redundant. For example, in breast cancer SNAIL has been shown to cause metastasis. Yet, it has no influence on metastases in a model of pancreatic cancer. Even so, ZEB1 supports metastasis in pancreatic cancer, as

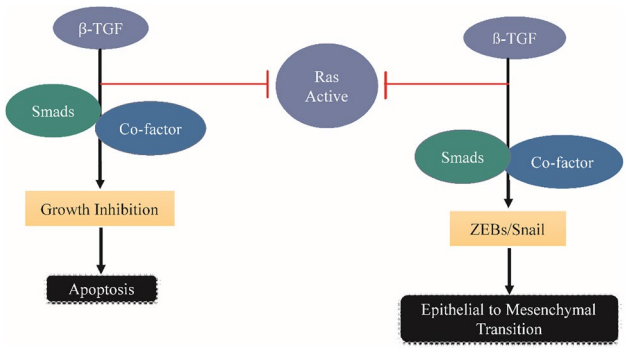

Fig. 4 Ras and TGF synergistic effect for triggering epithelial to mesenchymal transition. The alternative splicing series is induced by epithelial to mesenchymal transitional factors after reducing the expression of epithelial slicing regulatory proteins. Thus, the splicing programme induction favors the concerned transition

compared to SNAIL [86, 87]. As seen in melanoma, members of the same EMT transcription factors family may also have antagonistic roles, where ZEB1 encourages tumor and ZEB2 decreases tumor assertiveness. Therefore, it seems that triggering EMT is now the only unifying factor of EMT associated transcription factors that have several unique functions. The fact that EMT-TFs are commonly expressed and have significant effects on numerous non-epithelial tumors is another reason why the word EMT in cancer biology sometimes creates confusion. That involves glioblastomas, melanomas, multiple forms of sarcoma, and even leukemia [88–90].

In most tumor forms, EMT are likely to encourage tumors, but they are in some tumors can even be suppressive and sometimes alter their frameworks on the progress phase i.e. dissemination versus colonization. The pleiotropic roles of EMT, however and the detection of their unique effects on various types of human tumors at various stages of progression will also influence the development of therapy strategies to combat tumor growth from initiation to metastasis.

Luteolin and EMT

Luteolin triggers epithelial to mesenchymal transition results in targeting various pathways that ultimately leads to cancer therapy. In women the colorectal cancer is the second while in men third most common cancer. Luteolin-induced mesenchymal-to-epithelial transformation leads to colorectal cancer therapy via reduction of mesenchymal marker expressions and inhibition of in vitro cell proliferation [91]. In addition, as discussed before, during the development of multiple epithelial cell carcinomas, epithelial-mesenchymal transformation typically occurs and is intimately associated with the invasion and metastasis of different tumors, such as colorectal cancer [92]. During tumor development, proliferation, and metastasis, the modulation of signaling pathways like the TGF-β, Smads, JAK2 or STAT3 pathways plays an important role [93].

Natural products have been shown as effective anti-cancer agents against colorectal cancer metastasis and invasion. For example, luteolin's efficacy in colorectal cancer indicates that this natural product apart from inhibition of cAMP responsive element binding protein-1 (CREB-1) expression also inhibits epithelial to mesenchymal transition. As a result cope with the colorectal cancer [94].

Cadherin N and E are adhesion molecules. The expression of E-cadherin is predominant in epithelial cells while the N-cadherin is expressed in mesenchymal domain [95]. In addition to transcription factors, the multifunctional cytokines like TGF-β induces epithelial to mesenchymal transition via posing many various biological processes like differentiation, migration and proliferation [96]. In this regard it has been shown that TGF-β triggered epithelial to mesenchymal transition in pulmonary cancer is inhibited by luteolin. PI3K/Akt-NF-κB-Snail-E-cadherin signaling pathway is the main mechanism behind dealing with lung cancer by luteolin [97]. In addition to it, in a research study conducted on non-small cell lung cancer reveals that luteolin significantly targets focal adhesion kinase and β-1 integrin. Its inhibition leads to reversal of hypoxia induced epithelial to mesenchymal transition in non-small cell lung cancer [98].

Similarly, another research on such scenario showed that, by shrinking the cytoskeleton, stimulating the biomarker associated with epithelial transition like E-cadherin expression while down regulating the biomarkers concerned with mesenchymal transition i.e., N-cadherin, vimentin as well as Snail, luteolin significantly reversed epithelial to mesenchymal transition. In addition to it, luteolin also inhibited notch-1 signaling while it's down regulation ultimately leads to inhibition of metastasis in gastric cancer. The complex formed by β-catenin and notch-1signaling in gastric cancer was significantly regulated by luteolin that further blocked invasion and migration. That suggests that in the treatment of gastric cancer, luteolin may act as an efficient anti-tumor drug [99].

Cancer cell metastases are evocative of epithelial-mesenchymal transition that typically occurs in embryonic growth, cell regeneration, and distant metastasis. It should be noted that the use of medicinal herbs or their bioactive constituents has become a more and more interesting prospect to cancer treatment via targeting such a metastatic process [100]. In this regard a research study was conducted on breast cancer (triple negative) to check the luteolin effect focusing epithelial to mesenchymal transition. The results indicate that, β-catenin was down regulated by luteolin that in turn reversed the epithelial to mesenchymal transition and suppressed breast cancer metastasis [101]. Skin cancer has

attracted an attention worldwide [102]. Recently an in vitro and in vivo study on hypoxia induced epithelial to mesenchymal transition showed that luteolin significantly revered the epithelial to mesenchymal transition in skin cancer cells. It suggests that Luteolin's reversal of EMT can be effectively used as a way of cancer therapy [103].

In malignant cancers, elevated ubiquitin E2S ligase leads to cell motility via activation of epithelial to mesenchymal transition. The high level of ubiquitin E2S ligase also mimics the invasive and metastatic behaviors of cancer cells. Such an epithelial to mesenchymal transition signaling was reversed by luteolin taking its part in treating cervical cancer [104]. Ovarian cancer is the worst among all gynecologic cancers due to delayed detection, prevalence, as well as chemical resistance growth. Hypothetically it is believed that in ovarian cancer cells resistant to paclitaxel, epithelial to mesenchymal transition is up-regulated while luteolin knockdown the epithelial to mesenchymal transition and can contribute to chemo sensitization. It was found in a research study that, transcription factors and markers associated with epithelial to mesenchymal transition are up regulated in ovarian cancer accompanied by paclitaxel resistance. Luteolin significantly suppress the expression of proteins associated with these markers and transcription factors overcoming the epithelial to mesenchymal transition in ovarian cancer metastasis [105].

Pancreatic carcinogenesis is closely associated with acinar-ductal metastasis and proliferation. Luteolin is suspected to have possible anti-pancreatic cancer activity. The results of a recent study on pancreatic cancer showed that, luteolin via inhibition of epithelial to mesenchymal transition exhibit its anti-pancreatic cancer potential. The mechanism involved were reduction of SOX-9 protein and p-STAT-3 [106]. As chemo preventive/anti proliferative agent, luteolin demonstrate amazing capability and can do that by minimizing tumor progression via reversing epithelial to mesenchymal transition in epidermal cancer. Luteolin triggers reversal of cadherin switching as well as down regulate the associated markers of epithelial to mesenchymal transition in A431-III cells of epidermal metastatic cancer [107].

Conclusion and remarks

Epithelial to mesenchymal transition induction facilitates tumor metastasis by inducing aggressive and anti-apoptotic processes in cancer cells. Therapeutic resistance and disease progression are facilitated by diverse cancer cells with stimulated EMT signaling feature. As an alternative treatment for cancer metastasis, phytonutrients have attracted attention given their anticancer effects, low toxicity and easy adoption as nutritional supplements. The signaling molecules and factors associated with epithelial to mesenchymal transition are targeted by many phytochemicals including luteolin. A variety of signaling pathways, including TGF-β, Smads, FGF, and β-catenin signaling, are used to induce epithelial to mesenchymal transition. All these signaling pathways are subject to regulation by luteolin.

It nonetheless remains essential to evaluate the use of the potential of luteolin to impose a synergistic effect on epithelial to mesenchymal transition signaling pathways by increasing their systemic availability in various associated models. The influence of luteolin on the expression pattern and the behaviors of miRNAs that regulate epithelial cell-mesenchymal properties have not been discussed elaborately that need further focus and attention.

In nutshell, the integration into clinics of the promising findings from luteolin is the need for the moment to set the stage for bioactive phytochemicals to evolve as a safer option therapy for cancer metastasis abridgment by potentially disrupting the process of epithelial to mesenchymal transition.

Declaration

Conflict of interest No conflict of interest is declared by authors.

References

1. Brinckerhoff CE, Matrisian LM, et al. Matrix metalloproteinases: a tail of a frog that became a prince. Nat Rev Mol Cell Biol. 2002;3(3):207–14.
2. Yang J, Mani SA, Weinberg RA, et al. Exploring a new twist on tumor metastasis. Can Res. 2006;66(9):4549–52.
3. Imran M, Rauf A, Abu-Izneid T, Nadeem M, Shariati MA, Khan IA, et al. Luteolin, a flavonoid, as an anticancer agent: a review. Biomed Pharmacother. 2019;112:108612.
4. Lin Y, Shi R, Wang X, Shen H-M, et al. Luteolin, a flavonoid with potential for cancer prevention and therapy. Curr Cancer Drug Targets. 2008;8(7):634–46.
5. Clere N, Renault S, Corre I, et al. Endothelial-to-mesenchymal transition in cancer. Front Cell Dev Biol. 2020. https://doi.org/10.3389/fcell.2020.00747.
6. Zhang Z-y, Ge H-y, et al. Micrometastasis in gastric cancer. Cancer Lett. 2013;336(1):34–45.
7. Youn GJ, Chung WC, et al. Micrometastasis in gastric cancer. Korean J Gastroenterol. 2017;69(5):270–7.
8. Tan Z, Jiang H, Wu Y, Xie L, Dai W, Tang H, et al. miR-185 is an independent prognosis factor and suppresses tumor metastasis in gastric cancer. Mol Cell Biochem. 2014;386(1–2):223–31.
9. Conteduca V, Sansonno D, Lauletta G, Russi S, Ingravallo G, Dammacco F, et al. H. pylori infection and gastric cancer: state of the art. Int J Oncol. 2013;42(1):5–18.
10. Shao Y, Lu B, et al. The crosstalk between circular RNAs and the tumor microenvironment in cancer metastasis. Cancer Cell Int. 2020;20(1):1–13.
11. Letaief F, Nasri M, Ayadi M, Meddeb K, Mokrani A, Yahyaoui Y, et al. Potential predictive factors for pathologic complete response after the neoadjuvant treatment of rectal adenocarcinoma: a single center experience. Cancer Biol Med. 2017;14(3):327.

12. Kuruba V, Gollapalli P, et al. Natural radioprotectors and their impact on cancer drug discovery. Radiat Oncol J. 2018;36(4):265.
13. Li Z, Zhang L, Ma Z, Yang M, Tang J, Fu Y, et al. ETV1 induces epithelial to mesenchymal transition in human gastric cancer cells through the upregulation of Snail expression. Oncol Rep. 2013;30(6):2859–63.
14. Boeing T, da Silva LM, Mariott M, Andrade SF, de Souza P, et al. Diuretic and natriuretic effect of luteolin in normotensive and hypertensive rats: role of muscarinic acetylcholine receptors. Pharmacol Rep. 2017;69(6):1121–4.
15. Chen K-C, Hsu W-H, Ho J-Y, Lin C-W, Chu C-Y, Kandaswami CC, et al. Flavonoids Luteolin and Quercetin Inhibit RPS19 and contributes to metastasis of cancer cells through c-Myc reduction. J Food Drug Anal. 2018;26(3):1180–91.
16. Selvi RB, Swaminathan A, Chatterjee S, Shanmugam MK, Li F, Ramakrishnan GB, et al. Inhibition of p300 lysine acetyltransferase activity by luteolin reduces tumor growth in head and neck squamous cell carcinoma (HNSCC) xenograft mouse model. Oncotarget. 2015;6(41):43806.
17. Swaminathan A, Basu M, Bekri A, Drapeau P, Kundu TK, et al. The dietary flavonoid, luteolin, negatively affects neuronal differentiation. Front Mol Neurosci. 2019;12:41.
18. El-Toumy SA, Omara EA, Nada SA, Bermejo J, et al. Flavone C-glycosides from Montanoa bipinnatifida stems and evaluation of hepatoprotective activity of extract. J Med Plants Res. 2011;5(8):1291–6.
19. Le Marchand L, et al. Cancer preventive effects of flavonoids—a review. Biomed Pharmacother. 2002;56(6):296–301.
20. Manzoor MF, Ahmad N, Ahmed Z, Siddique R, Zeng XA, Rahaman A, et al. Novel extraction techniques and pharmaceutical activities of luteolin and its derivatives. J Food Biochem. 2019;43(9):e12974.
21. Fu Y-J, Liu W, Zu Y-G, Tong M-H, Li S-M, Yan M-M, et al. Enzyme assisted extraction of luteolin and apigenin from pigeonpea [Cajanuscajan (L.) Millsp.] leaves. Food Chem. 2008;111(2):508–12.
22. Samejima K, Kanazawa K, Ashida H, Danno GI, et al. Luteolin: a strong antimutagen against dietary carcinogen, Trp-P-2, in peppermint, sage, and thyme. J Agric Food Chem. 1995;43(2):410–4.
23. Kim DO, Padilla-Zakour OI, Griffiths PD, et al. Flavonoids and antioxidant capacity of various cabbage genotypes at juvenile stage. J Food Sci. 2004;69(9):C685–9.
24. Achour M, Saguem S, Sarriá B, Bravo L, Mateos R, et al. Bioavailability and metabolism of rosemary infusion polyphenols using Caco-2 and HepG2 cell model systems. J Sci Food Agric. 2018;98(10):3741–51.
25. Wang Q, Cheng W, Zhang Y, Kang Q, Gowd V, Ren Y, et al. A novel potent inhibitor of 2-amino-1-methyl-6-phenylimidazo [4, 5-b] pyridine (PhIP) formation from Chinese chive: identification, inhibitory effect and action mechanism. Food Chem. 2021;345:128753.
26. Lopresti AL, et al. Salvia (sage): a review of its potential cognitive-enhancing and protective effects. Drugs R&D. 2017;17(1):53–64.
27. Tzima K, Brunton NP, Rai DK, et al. Evaluation of the impact of chlorophyll removal techniques on polyphenols in rosemary and thyme by-products. J Food Biochem. 2020;44(3):e13148.
28. Manzoor MF, Ahmad N, Manzoor A, Kalsoom A, et al. Food based phytochemical luteolin their derivatives, sources and medicinal benefits. Int J Agric Life Sci IJAL. 2017;3(11):1.
29. Criste A, Urcan AC, Bunea A, Pripon Furtuna FR, Olah NK, Madden RH, Corcionivoschi N, et al. Phytochemical composition and biological activity of berries and leaves from four Romanian sea buckthorn (Hippophae rhamnoides L.) varieties. Molecules. 2020;25(5):1170.
30. Jamzadfard M, Ebrahimi H, et al. Improvement of the anxiety and depression during using Camaneur herbal distilate: comperhensive survey of the antioxidant effects. In: 3rd international conference on agricultural sciences, medicinal plants and traditional medicine (Accepted);2020.
31. Nguyen HC, Chen CC, Lin KH, Chao PY, Lin HH, Huang MY, et al. Bioactive compounds, antioxidants, and health benefits of sweet potato leaves. Molecules. 2021;26(7):1820.
32. Hollman PC, Bijsman MN, Van Gameren Y, Cnossen EP, De Vries JH, Katan MB, et al. The sugar moiety is a major determinant of the absorption of dietary flavonoid glycosides in man. Free Radic Res. 1999;31(6):569–73.
33. Deng C, Gao C, Tian X, Chao B, Wang F, Zhang Y, et al. Pharmacokinetics, tissue distribution and excretion of luteolin and its major metabolites in rats: metabolites predominate in blood, tissues and are mainly excreted via bile. J Funct Foods. 2017;35:332–40.
34. Chen Z, Chen M, Pan H, Sun S, Li L, Zeng S, et al. Role of catechol-O-methyltransferase in the disposition of luteolin in rats. Drug Metab Dispos. 2011;39(4):667–74.
35. Chen Z, Tu M, Sun S, Kong S, Wang Y, Ye J, et al. The exposure of luteolin is much lower than apigenin when oral administration of Flos Chrysanthemi extract to rats. Drug Metab Pharmacokinet, 2011; 1109130231–1109130231.
36. Lin LC, Pai YF, Tsai TH, et al. Isolation of luteolin and luteolin-7-O-glucoside from Dendranthema morifolium Ramat Tzvel and their pharmacokinetics in rats. J Agric Food Chem. 2015;63(35):7700–6.
37. Chen T, Li LP, Lu XY, Jiang HD, Zeng S, et al. Absorption and excretion of luteolin and apigenin in rats after oral administration of Chrysanthemum morifolium extract. J Agric Food Chem. 2007;55(2):273–7.
38. Zhou P, Li LP, Luo SQ, Jiang HD, Zeng S, et al. Intestinal absorption of luteolin from peanut hull extract is more efficient than that from individual pure luteolin. J Agric Food Chem. 2008;56(1):296–300.
39. Sarawek S, Derendorf H, Butterweck V, et al. Pharmacokinetics of luteolin and metabolites in rats. Nat Prod Commun. 2008;3(12):1934578X0800301218.
40. Wruck CJ, Claussen M, Fuhrmann G, Römer L, Schulz A, Pufe T, et al. Luteolin protects rat PC 12 and C6 cells against MPP+ induced toxicity via an ERK dependent Keapl-Nrf2-ARE pathway. In: Neuropsychiatric disorders an integrative approach. Springer; 2007. p. 57–67.
41. Lin CH, Chang CY, Lee KR, Lin HJ, Chen TH, Wan L, et al. Flavones inhibit breast cancer proliferation through the Akt/FOXO3a signaling pathway. BMC Cancer. 2015;15:958.
42. Lin CW, Lai GM, Chen KC, Lin TH, Fan JJ, Hsu RL, et al. RPS12 increases the invasiveness in cervical cancer activated by c-Myc and inhibited by the dietary flavonoids luteolin and quercetin. J Funct Foods. 2015;19:236–47.
43. Sato Y, Sasaki N, Saito M, Endo N, Kugawa F, Ueno A, et al. Luteolin attenuates doxorubicin-induced cytotoxicity to MCF-7 human breast cancer cells. Biol Pharm Bull. 2015;38(5):703–9.
44. Kobayashi T, Nakata T, Kuzumaki T, et al. Effect of flavonoids on cell cycle progression in prostate cancer cells. Cancer Lett. 2002;176(1):17–23.
45. González-Paramás AM, Ayuda-Durán B, Martínez S, González-Manzano S, Santos-Buelga C, et al. The mechanisms behind the biological activity of flavonoids. Curr Med Chem. 2019;26(39):6976–90.
46. Selvendiran K, Koga H, Ueno T, Yoshida T, Maeyama M, Torimura T, et al. Luteolin promotes degradation in signal transducer and activator of transcription 3 in human hepatoma cells: an implication for the antitumor potential of flavonoids. Can Res. 2006;66(9):4826–34.

47. Sui JQ, Xie KP, Xie MJ, et al. Inhibitory effect of luteolin on the proliferation of human breast cancer cell lines induced by epidermal growth factor. Sheng li xue bao. 2016;68(1):27–34.
48. Cook MT, Mafuvadze B, Besch-Williford C, Ellersieck MR, Goyette S, Hyder SM, et al. Luteolin suppresses development of medroxyprogesterone acetate-accelerated 7, 12-dimethylbenz (a) anthracene-induced mammary tumors in Sprague-Dawley rats. Oncol Rep. 2016;35(2):825–32.
49. Cook MT, Liang Y, Besch-Williford C, Goyette S, Mafuvadze B, Hyder SM, et al. Luteolin inhibits progestin-dependent angiogenesis, stem cell-like characteristics, and growth of human breast cancer xenografts. Springerplus. 2015;4(1):444.
50. Jeon YW, Ahn YE, Chung WS, Choi HJ, Suh YJ, et al. Synergistic effect between celecoxib and luteolin is dependent on estrogen receptor in human breast cancer cells. Tumor Biol. 2015;36(8):6349–59.
51. Yang M-Y, Wang C-J, Chen N-F, Ho W-H, Lu F-J, Tseng T-H, et al. Luteolin enhances paclitaxel-induced apoptosis in human breast cancer MDA-MB-231 cells by blocking STAT3. Chem Biol Interact. 2014;213:60–8.
52. Osman NH, Said UZ, El-Waseef AM, Ahmed ES, et al. Luteolin supplementation adjacent to aspirin treatment reduced dimethylhydrazine-induced experimental colon carcinogenesis in rats. Tumor Biol. 2015;36(2):1179–90.
53. Pandurangan AK, Esa NM, et al. Luteolin, a bioflavonoid inhibits colorectal cancer through modulation of multiple signaling pathways: a review. Asian Pac J Cancer Prev. 2014;15(14):5501–8.
54. Pandurangan A, Dharmalingam P, Sadagopan S, Ganapasam S, et al. Luteolin inhibits matrix metalloproteinase 9 and 2 in azoxymethane-induced colon carcinogenesis. Hum Exp Toxicol. 2014;33(11):1176–85.
55. Pandurangan AK, Kumar SAS, Dharmalingam P, Ganapasam S, et al. Luteolin, a bioflavonoid inhibits azoxymethane-induced colon carcinogenesis: involvement of iNOS and COX-2. Pharmacogn Mag. 2014;10(Suppl 2):S306.
56. Ashokkumar P, Sudhandiran G, et al. Luteolin inhibits cell proliferation during Azoxymethane-induced experimental colon carcinogenesis via Wnt/β-catenin pathway. Invest New Drugs. 2011;29(2):273–84.
57. Pandurangan AK, Dharmalingam P, Sadagopan SKA, Ganapasam S, et al. Effect of luteolin on the levels of glycoproteins during azoxymethane-induced colon carcinogenesis in mice. Asian Pac J Cancer Prev. 2012;13(4):1569–73.
58. Johnson JL, Dia VP, Wallig M, De Mejia EG, et al. Luteolin and gemcitabine protect against pancreatic cancer in an orthotopic mouse model. Pancreas. 2015;44(1):144–51.
59. Lee LT, Huang YT, Hwang JJ, Lee PP, Ke FC, Nair MP, Kanadaswam C, Lee MT, et al. Blockade of the epidermal growth factor receptor tyrosine kinase activity by quercetin and luteolin leads to growth inhibition and apoptosis of pancreatic tumor cells. Anticancer Res. 2002;22(3):1615–27.
60. Tsai PH, Cheng CH, Lin CY, Huang YT, Lee LT, Kandaswami CC, et al. Dietary flavonoids luteolin and quercetin suppressed cancer stem cell properties and metastatic potential of isolated prostate cancer cells. Anticancer Res. 2016;36(12):6367–80.
61. Gray AL, Stephens CA, Bigelow RL, Coleman DT, Cardelli JA, et al. The polyphenols (−)-epigallocatechin-3-gallate and luteolin synergistically inhibit TGF-β-induced myofibroblast phenotypes through RhoA and ERK inhibition. PLoS ONE. 2014;9(10):e109208.
62. Tsui KH, Lin YH, Chung LC, Chuang ST, Feng TH, Chiang KC, et al. Prostate-derived ets factor represses tumorigenesisvg and modulates epithelial-to-mesenchymal transition in bladder carcinoma cells. Cancer Lett. 2016;375(1):142–51.
63. Tan X, Liu B, Lu J, Li S, Baiyun R, Lv Y, et al. Dietary luteolin protects against HgCl2-induced renal injury via activation of Nrf2-mediated signaling in rat. J Inorg Biochem. 2018;179:24–31.
64. Nieto MA, Huang RY-J, Jackson RA, Thiery JP, et al. Cell. 2016;166(1):21–45.
65. Greenburg G, Hay ED, et al. Epithelia suspended in collagen gels can lose polarity and express characteristics of migrating mesenchymal cells. J Cell Biol. 1982;95(1):333–9.
66. Nawshad A, LaGamba D, Hay E, et al. Transforming growth factor β (TGFβ) signalling in palatal growth, apoptosis and epithelial mesenchymal transformation (EMT). Arch Oral Biol. 2004;49(9):675–89.
67. Takigawa T, Shiota K, et al. Terminal differentiation of palatal medial edge epithelial cells in vitro is not necessarily dependent on palatal shelf contact and midline epithelial seam formation. Int J Dev Biol. 2004;48(4):307–17.
68. Chaw S, Majeed AA, Dalley A, Chan A, Stein S, Farah C, et al. Epithelial to mesenchymal transition (EMT) biomarkers–E-cadherin, beta-catenin, APC and Vimentin–in oral squamous cell carcinogenesis and transformation. Oral Oncol. 2012;48(10):997–1006.
69. Nijkamp MM, Span PN, Hoogsteen IJ, van der Kogel AJ, Kaanders JH, Bussink J, et al. Expression of E-cadherin and vimentin correlates with metastasis formation in head and neck squamous cell carcinoma patients. Radiother Oncol. 2011;99(3):344–8.
70. Jie X-X, Zhang X-Y, Xu C-J, et al. Epithelial-to-mesenchymal transition, circulating tumor cells and cancer metastasis: Mechanisms and clinical applications. Oncotarget. 2017;8(46):81558.
71. Furuya S, Endo K, Takahashi A, Miyazawa K, Saitoh M, et al. Snail suppresses cellular senescence and promotes fibroblast-led cancer cell invasion. FEBS Open Bio. 2017;7(10):1586–97.
72. Toll A, Masferrer E, Hernández-Ruiz M, Ferrandiz-Pulido C, Yébenes M, Jaka A, et al. Epithelial to mesenchymal transition markers are associated with an increased metastatic risk in primary cutaneous squamous cell carcinomas but are attenuated in lymph node metastases. J Dermatol Sci. 2013;72(2):93–102.
73. Yu M, Bardia A, Wittner BS, Stott SL, Smas ME, Ting DT, et al. Circulating breast tumor cells exhibit dynamic changes in epithelial and mesenchymal composition. Science. 2013;339(6119):580–4.
74. Shibata M, Shen MM, et al. The roots of cancer: stem cells and the basis for tumor heterogeneity. BioEssays. 2013;35(3):253–60.
75. Korpal M, Lee ES, Hu G, Kang Y, et al. The miR-200 family inhibits epithelial-mesenchymal transition and cancer cell migration by direct targeting of E-cadherin transcriptional repressors ZEB1 and ZEB2. J Biol Chem. 2008;283(22):14910–4.
76. Chakrabarti R, Hwang J, Blanco MA, Wei Y, Lukačišin M, Romano R-A, et al. Elf5 inhibits the epithelial–mesenchymal transition in mammary gland development and breast cancer metastasis by transcriptionally repressing Snail2. Nat Cell Biol. 2012;14(11):1212–22.
77. Son H, Moon A, et al. Epithelial-mesenchymal transition and cell invasion. Toxicol Res. 2010;26(4):245–52.
78. Neelakantan D, Zhou H, Oliphant MU, Zhang X, Simon LM, Henke DM, et al. EMT cells increase breast cancer metastasis via paracrine GLI activation in neighbouring tumour cells. Nat Commun. 2017;8:15773.
79. Manchado E, Weissmueller S, Morris JP, Chen CC, Wullenkord R, Lujambio A, et al. A combinatorial strategy for treating KRAS-mutant lung cancer. Nature. 2016;534(7609):647–51.
80. Horiguchi K, Shirakihara T, Nakano A, Imamura T, Miyazono K, Saitoh M, et al. Role of Ras signaling in the induction of snail by transforming growth factor-β. J Biol Chem. 2009;284(1):245–53.
81. Ooshima A, Park J, Kim SJ, et al. Phosphorylation status at Smad3 linker region modulates transforming growth

factor-β-induced epithelial-mesenchymal transition and cancer progression. Cancer Sci. 2019;110(2):481–8.
82. Nakano A, Koinuma D, Miyazawa K, Uchida T, Saitoh M, Kawabata M, et al. Pin1 down-regulates transforming growth factor-β (TGF-β) signaling by inducing degradation of Smad proteins. J Biol Chem. 2009;284(10):6109–15.
83. Kalluri R, Weinberg RA, et al. The basics of epithelial-mesenchymal transition. J Clin Investig. 2009;119(6):1420–8.
84. Ishii H, Saitoh M, Sakamoto K, Kondo T, Katoh R, Tanaka S, et al. Epithelial splicing regulatory proteins 1 (ESRP1) and 2 (ESRP2) suppress cancer cell motility via different mechanisms. J Biol Chem. 2014;289(40):27386–99.
85. Warzecha CC, Sato TK, Nabet B, Hogenesch JB, Carstens RP, et al. ESRP1 and ESRP2 are epithelial cell-type-specific regulators of FGFR2 splicing. Mol Cell. 2009;33(5):591–601.
86. Tran HD, Luitel K, Kim M, Zhang K, Longmore GD, Tran DD, et al. Transient SNAIL1 expression is necessary for metastatic competence in breast cancer. Can Res. 2014;74(21):6330–40.
87. Zheng X, Carstens JL, Kim J, Scheible M, Kaye J, Sugimoto H, et al. Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer. Nature. 2015;527(7579):525–30.
88. Denecker G, Vandamme N, Akay Ö, Koludrovic D, Taminau J, Lemeire K, et al. Identification of a ZEB2-MITF-ZEB1 transcriptional network that controls melanogenesis and melanoma progression. Cell Death Differ. 2014;21(8):1250–61.
89. Caramel J, Papadogeorgakis E, Hill L, Browne GJ, Richard G, Wierinckx A, et al. A switch in the expression of embryonic EMT-inducers drives the development of malignant melanoma. Cancer Cell. 2013;24(4):466–80.
90. Kahlert UD, Joseph JV, Kruyt FA, et al. EMT-and MET-related processes in nonepithelial tumors: importance for disease progression, prognosis, and therapeutic opportunities. Mol Oncol. 2017;11(7):860–77.
91. Ciombor KK, Wu C, Goldberg RM, et al. Recent therapeutic advances in the treatment of colorectal cancer. Annu Rev Med. 2015;66:83–95.
92. Lin X, Wang S, Sun M, Zhang C, Wei C, Yang C, et al. miR-195-5p/NOTCH2-mediated EMT modulates IL-4 secretion in colorectal cancer to affect M2-like TAM polarization. J Hematol Oncol. 2019;12(1):1–14.
93. Liu RY, Zeng Y, Lei Z, Wang L, Yang H, Liu Z, et al. JAK/STAT3 signaling is required for TGF-β-induced epithelial-mesenchymal transition in lung cancer cells. Int J Oncol. 2014;44(5):1643–51.
94. Liu Y, Lang T, Jin B, Chen F, Zhang Y, Beuerman RW, et al. Luteolin inhibits colorectal cancer cell epithelial-to-mesenchymal transition by suppressing CREB1 expression revealed by comparative proteomics study. J Proteomics. 2017;161:1–10.
95. Acloque H, Thiery JP, Nieto MA, et al. The physiology and pathology of the EMT: meeting on the epithelial-mesenchymal transition. EMBO Rep. 2008;9(4):322–6.
96. Eades G, Yao Y, Yang M, Zhang Y, Chumsri S, Zhou Q, et al. miR-200a regulates SIRT1 expression and epithelial to mesenchymal transition (EMT)-like transformation in mammary epithelial cells. J Biol Chem. 2011;286(29):25992–6002.
97. Chen KC, Chen CY, Lin CJ, Yang TY, Chen TH, Wu LC, et al. Luteolin attenuates TGF-β1-induced epithelial–mesenchymal transition of lung cancer cells by interfering in the PI3K/Akt–NF-κB–Snail pathway. Life Sci. 2013;93(24):924–33.
98. Ruan J, Zhang L, Yan L, Liu Y, Yue Z, Chen L, et al. Inhibition of hypoxia-induced epithelial mesenchymal transition by luteolin in non-small cell lung cancer cells. Mol Med Rep. 2012;6(1):232–8.
99. Hu L, Fan ZY, Wang HX, Zhu ZL, Cao S, Wu XY, et al. Luteolin suppresses gastric cancer progression by reversing epithelial-mesenchymal transition via suppression of the Notch signaling pathway. J Transl Med. 2017;15(1):1–11.
100. Lamouille S, Xu J, Derynck R, et al. Molecular mechanisms of epithelial–mesenchymal transition. Nat Rev Mol Cell Biol. 2014;15(3):178–96.
101. Lin D, Kuang G, Wan J, Zhang X, Li H, Gong X, et al. Luteolin suppresses the metastasis of triple-negative breast cancer by reversing epithelial-to-mesenchymal transition via downregulation of β-catenin expression. Oncol Rep. 2017;37(2):895–902.
102. Kalal BS, Upadhya D, Pai VR, et al. Chemotherapy resistance mechanisms in advanced skin cancer. Oncol Rev. 2017. https://doi.org/10.4081/oncol.2017.326.
103. Ruan JS, Liu YP, Zhang L, Yan LG, Fan FT, Shen CS, et al. Luteolin reduces the invasive potential of malignant melanoma cells by targeting β3 integrin and the epithelial-mesenchymal transition. Acta Pharmacol Sin. 2012;33(10):1325–31.
104. Lin TH, Hsu WH, Tsai PH, Huang YT, Lin CW, Chen KC, et al. Dietary flavonoids, luteolin and quercetin, inhibit invasion of cervical cancer by reduction of UBE2S through epithelial–mesenchymal transition signaling. Food Funct. 2017;8(4):1558–68.
105. Dia VP, Pangloli P, et al. Epithelial-to-mesenchymal transition in paclitaxel-resistant ovarian cancer cells is downregulated by luteolin. J Cell Physiol. 2017;232(2):391–401.
106. Huang X, Bhugul PA, Fan G, Ye T, Huang S, Dai S, et al. Luteolin inhibits pancreatitis-induced acinar-ductal metaplasia, proliferation and epithelial-mesenchymal transition of acinar cells. Mol Med Rep. 2018;17(3):3681–9.
107. Lin YS, Tsai PH, Kandaswami CC, Cheng CH, Ke FC, Lee PP, et al. Effects of dietary flavonoids, luteolin, and quercetin on the reversal of epithelial–mesenchymal transition in A431 epidermal cancer cells. Cancer Sci. 2011;102(10):1829–39.