Biomedicine & Pharmacotherapy 112 (2019) 108612

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Luteolin, a flavonoid, as an anticancer agent: A review

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ARTICLE INFO

Keywords:
Flavonoids
Luteolin
Breast cancer
Stomach
Prostate
Colon
Skin cancer

ABSTRACT

Many food-derived phytochemicals and their derivatives represent a cornucopia of new anti-cancer compounds. Luteolin (3,4,5,7-tetrahydroxy flavone) is a flavonoid found in different plants such as vegetables, medicinal herbs, and fruits. It acts as an anticancer agent against various types of human malignancies such as lung, breast, glioblastoma, prostate, colon, and pancreatic cancers. It also blocks cancer development *in vitro* and *in vivo* by inhibition of proliferation of tumor cells, protection from carcinogenic stimuli, and activation of cell cycle arrest, and by inducing apoptosis through different signaling pathways. Luteolin can additionally reverse epithelial-mesenchymal transition (EMT) through a mechanism that involves cytoskeleton shrinkage, induction of the epithelial biomarker E-cadherin expression, and by down-regulation of the mesenchymal biomarkers *N*-cadherin, snail, and vimentin. Furthermore, luteolin increases levels of intracellular reactive oxygen species (ROS) by activation of lethal endoplasmic reticulum stress response and mitochondrial dysfunction in glioblastoma cells, and by activation of ER stress-associated proteins expressions, including phosphorylation of eIF2*α*, PERK,

Abbreviations: AEG-1, astrocyte-elevated gene-1; AKT, activated protein kinase; AR, androgen receptor; AP-1, activator protein-1; ATM, ataxia telangiectasia mutated; Bcl-2, B-cell lymphoma 2; BEAS-2B, bronchial epithelial cells; BTG2, B-cell translocation gene 2; BW, body weight; CAMP, Cyclic adenosine monophosphate; CCP, cell cycle pathway; CDK, cyclin-dependent kinase; Cdc42, cell division cycle 42; CEA, carcinoembroyonic antigen; CHOP, C/EBP homologous protein; COX-2, cyclooxygenase-2; CDK2, cyclin dependent kinase-2; DR-5, death receptor 5; EGF, epidermal growth factor; EGFRSP, epidermal growth factor receptor signaling pathway; EMT, epithelial-mesenchymal transition; ER, endoplasmic reticulum; ESCC, esophageal squamous-cell carcinoma; ER, estrogen receptor; ERK, extracellular signal-related kinase; ESP, estrogen signaling pathway; FASN, fatty acid synthase inhibitors; GAK, G-associated kinase; GGT, γ-glutamyl transferase; GRP, glucose-regulated proteins; GSK-3β, glycogen synthase kinase; HGF, hepatocyte growth factor; Hif-1α, hypoxia-induced factor-1α; HNF4α, hepatocyte nuclear factor 4α; HNSCC, head and neck squamous cell carcinoma; HSP90, heat shock protein-90; ICAM-1, intercellular adhesion molecule-1; IFNAR2, interferon receptor 2; IGF-1, insulin-like growth factor-1; iNOS, inducible nitric oxide synthase; IL-8, interleukin-8; c-JNK, c-Jun N-terminal kinase; LFA-3, lymphocyte function-associated antigen 3; LNCaP, lymph node carcinoma of the prostate; MAPK, mitogen activated protein kinase; MCF-7, Michigan Cancer Foundation; MDR1, multi drug resistance; MMP-2, matrix metalloproteinase-2; mTOR, Mechanistic target of rapamycin; NAT, *N*-acetyltransferase; NPC, nasopharyngeal carcinoma; NDRG1, N-myc downstream regulated gene 1; NF-κB, Nuclear factor kappaB; N4ICD, Notch4 intracellular domain; Nrf2, nuclear factor erythroid 2; NSCLC, non-small cell lung cancer; OCSC, oral cancerstem cells; PARP, Poly(ADP-ribose) polymerase; PDEF, prostate-derived Ets factor; PLK1, Polo-Like Kinase-1; p-EGFR, phosphor epidermal growth factor receptor; PTK, protein tyrosine kinase; RCC, renal cell carcinoma; ROS, Reactive oxygen species; RSK-1, ribosomal S6 kinase; SphK-2, sphingosine kinase; STAT3, signal transducer and activator of transcription 3; STAT6, signal transducer and activator of transcription 6; TAMs, Tumor-associated macrophages; TGF-β1, transforming growth factor; TNBC, triple-negative breast cancers; TNF-α, Tumor nuclear factor alpha; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; VEGF, Vascular endothelial growth factor; YB-1, Y-box binding protein-1; XIAP, X-linked inhibitor of apoptosis protein

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https://doi.org/10.1016/j.biopha.2019.108612
Received 19 September 2018; Received in revised form 6 January 2019; Accepted 23 January 2019

CHOP, ATF4, and cleaved-caspase 12. Accordingly, the present review article summarizes the progress of recent research on luteolin against several human cancers.

1. Introduction

Cancer is a major health problem across the globe which refers to a group of diseases caused by abnormal cell growth with invasive potentials [1]. A high proportion of cancer incidence and deaths are due to different environmental and genetic factors such as high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, alcohol consumption, exposure to radiation, chronic infections, and heredity [2]. Introducing novel bioactive components with natural origins, particularly from plant sources, may be considered as a new and reliable therapeutic element to treat different types of human cancers on the basis of their selective molecular targets [3,4].

In addition, oxidative stress plays a crucial role in the pathophysiology of different types of cancer. Therefore, much attention has been paid to antioxidants as novel therapeutic strategy for cancer [1]. During the past two decades, plant-derived bioactive compounds have been reported as novel health-giving agents for prevention and/or mitigation of different human diseases such as cancer, inflammation, cardiovascular, and neurodegenerative diseases [5]. Among these compounds, more than 5000 flavonoids have been identified and are distributed in a wide range of plants. On the basis of their chemical structures, these flavonoids have been grouped into 10 categories, 6 of which including flavones, flavanones, anthocyanidins, flavonols, isoflavones, and catechins are commonly present in the human diet. Many of these flavonoids possess documented anticancer activity both in animal and cellular model systems [6]. Flavonoids such as luteolin are important natural antioxidants which have potent anticancer effects under both in vitro and in vivo conditions [1]. Luteolin (3,4,5,7-tetrahydroxy flavone, Fig. 1) is a natural flavonoid, extensively present in many plant species. It is particularly present in fruits and vegetables, such as celery, chrysanthemum flowers, sweet bell peppers, carrots, onion leaves, broccoli, and parsley [7 8]. In Chinese traditional medicine, plants rich in luteolin have been utilized in the treatment of diseases such as hypertension, inflammatory disorders, and cancer. Luteolin exhibits multiple biological effects such as anti-inflammation, anti-allergy, and anticancer, and can function as either an antioxidant or a pro-oxidant biochemically. In addition, the biological effects of luteolin could be functionally related to each other; for example, the anti-inflammatory activity may be linked to its anticancer property [9].

On the other hand, cancer continues to be a global concern, despite the technological and pharmaceutical improvements over the past two decades [10]. Research findings indicated that approximately 90–95% of all cancers are attributed to lifestyle, such as alcohol consumption, obesity, food additives, among other things, and the remaining 5–10% to defective genes [11]. Herbs have been used for years, either as complementary therapy or dietary agents, to influence cellular signaling [12]. In this respect, many reports have indicated that luteolin provide a wide range of preventive and therapeutic options against different types of cancer. An excellent review that dealt with the cancer prevention and therapeutic potential of luteolin was published by Lin et al. several years ago [9].

Structure activity relationship studies are a helpful tool to predict biological activities. There is only limited data available regarding luteolin in this regard. The ortho-dihydroxy structure in the B-ring and the 2,3-double bond in conjugation with the 4-oxo function of the C-ring providea good anti-oxidant capacity of luteolin [13]. Luteolin can form chelates with metal ions, however, it is not oxidized during the chelation process. Luteolin can suppress proliferation of various kinds of tumor cells in vitro with IC50 from about 3 to 50 μM, and inhibited tumor growth effectively in vivo when administered, e.g., in concentrations of 50 to 200 ppm in food [14]. In carcinogenesis, luteolin has been known to hamper the progression of carcinogenesis, (cell transformation, metastasis, invasion, and angiogenesis) through multiple mechanisms including suppression of kinases, regulation of cell cycle, induction of apoptotic cell death, and reduction of transcription factors [13]. Induction of apoptotic cell death is associated with anticancer activities of luteolin, which involve DNA damage, redox regulation, and protein kinases in suppression of proliferation of cancer cells [11]. In numerous human cancer cell lines including gastric, prostate and melanoma, luteolin exhibits cell cycle arrest during the G1 phase, whereas G1 cell cycle arrest induced by luteolin is linked to suppression of the CDK2 activity in colorectal cancer HT-29 and melanoma OCM-1 cells [12,13]. Based on the above discussion, and owing to the wide range of preventive and therapeutic options of luteolin against various types of cancer, this review focuses on the current knowledge of the chemo-preventive and therapeutic ability of this natural flavonoid against different types of cancer, along with its mechanisms of action. Below are details of documented antitumor activities of luteolin against different types of cancer. Different signaling pathways affected by luteolin are shown in Fig. 2.

2. Anticancer perspectives

2.1. Breast cancer

The ability of luteolin to suppress the expression of cancer promoting proteins, reduce the tumor size, growth viability and progestin-dependent VGF secretion, increase the expression of Bax are amongst the promising mechanistic routes. Being a promising anticancer agent, luteolin has a significant potential to inhibit proliferation and to suppress the expression of p-STAT3, p-EGFR, p-Akt, and p-Erk1/2 in MCF-7 breast cancer cells induced by EGF. It also suppresses the EGF-induced activities of EGFR signaling pathway in human breast cancer cell lines. Perhaps, the signal transducer and activator of transcription 3 (STAT3), MAPK/Erk1/2, and PI3K/Akt are the main pathways that explain the effect of luteolin on epidermal growth factor (EGFR) signaling [14]. In 7,12-dimethylbenz(a)anthracene-induced tumor, earlier investigations indicated that a moderate dose of luteolin (10 mg/kg) can inhibit the development of large tumors, and can significantly lower the levels of vascular endothelial growth factor (VEGF) in Sprague-Dawley rats [15]. It additionally inhibited cell cycle, tube formation, and the expression of Notch signaling-related proteins, and regulated miRNAs in MDA-MB-231 human breast cancer cells [16]. Furthermore, luteolin lowered tumor cell viability, progestin-dependent VEGF secretion from breast cancer cells, and growth of MPA-dependent human breast cancer cell xenograft tumors. It also decreased the blood-vessel density and blocked the MPA-induced acquisition of stem cell-like properties in T47-D and BT-474 breast cancer cells [17].

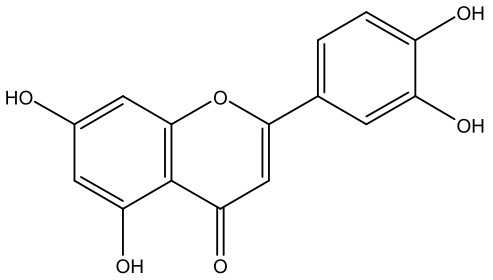

Fig. 1. Chemical structure of luteolin.

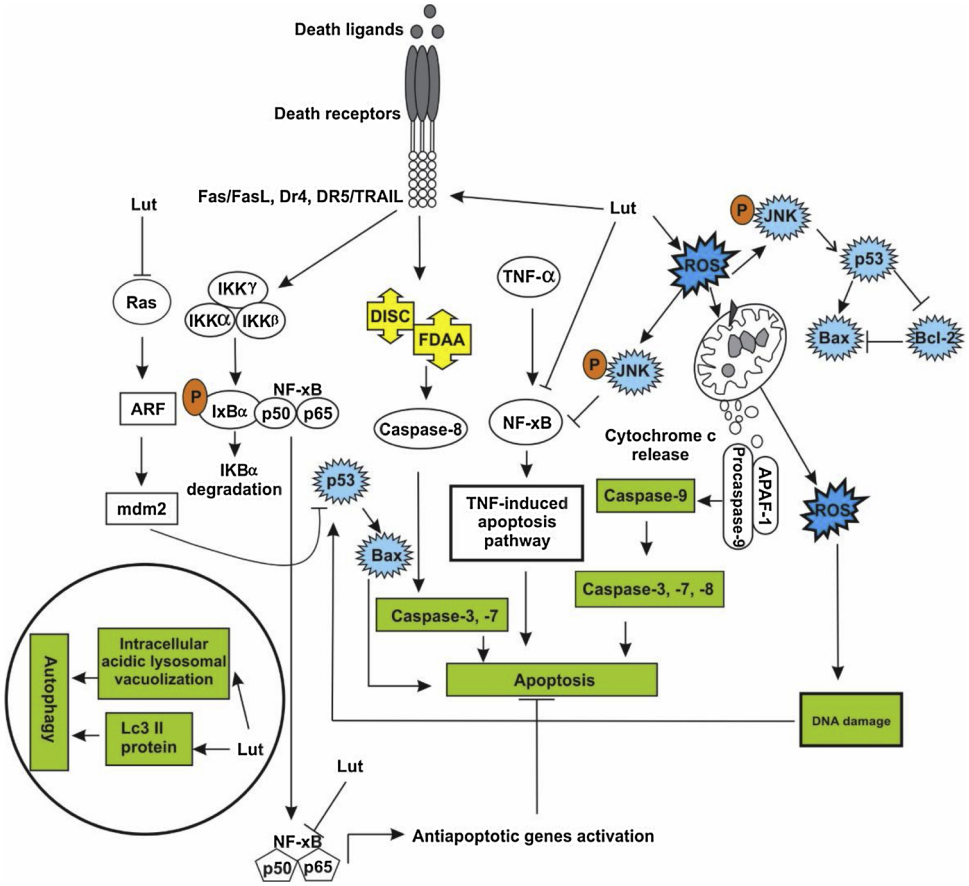

Fig. 2. A schematic drawing presenting signaling pathways affected by luteolin.

In a similar fashion, luteolin was found to attenuate production of ROS in MCF-7 cells, and to reduce doxorubicin-induced ROS generation. However, in presence of the estrogen receptor (ER) antagonist ICI 182,780, and the ER-negative MDA-MB-453 human breast cancer cell line, luteolin attenuated doxorubicin-induced cytotoxicity. Furthermore, luteolin effectively increased the antiapoptotic protein Bcell lymphoma 2 (Bcl-2) in MCF-7 cells expressions as compared to doxorubicin-treated cells [18]. Similarly, a group of researchers found that the combined treatment of luteolin and celecoxib has synergistic effects through Akt inactivation and extracellular signal-regulated kinase (ERK) signaling inhibition in MCF-7 and MCF7/HER18 cells, and *via* Akt inactivation and ERK signaling activation in MDA-MB-231 and SkBr3 cells [19]. Luteolin additionally disturbed cell cycle progression at the sub-G1 and G1 phases, enhanced the expression of death receptors such as DR5, and activated caspase cascades. It also enhanced the activities of caspase-8/-9/-3 in a dose-dependent fashion and activated poly(ADP-ribose) polymerase(PARP). Moreover, in apoptosis of extrinsic and intrinsic pathways, activation of caspases-8 and -9 induced caspase-3 activity. Research findings also revealed that through inhibition of Bcl-2 expression, luteolin enhances mitochondrial membrane potential collapse and release of cytochrome c, and increases Bax expression [20] (Table 1).

Sabzichi et al. showed that in MDA-MB 231 cells, luteolin loaded in phytosomes induces the bioavailability of luteolin and enhances passive targeting in breast cancer cells. On the other hand, the combined therapy of cells with nanoparticles-containing luteolin and doxorubicin resulted in highest percentage of cell death. However, luteolin-loaded nanoparticles decreased the expression of downstream genes for Nrf2 gene at the mRNA level in cells to a greater extent than luteolin alone. Additionally, these luteolin-loaded nanoparticles significantly reduced Nrf2downstream genes expression including multi drug resistance gene (MDR1) and heme oxygenase 1 (Ho1) inhibition, and caused a considerable increase in cancer cell death [21]. Similarly, treatment of human breast cancer MDA-MB-231 cells with luteolin and paclitaxel lowered both the tumor size and weight, activated the caspases-8 and -3, and enhanced the expression of Fas ligand. Furthermore, the increased Fas expression was attributed to the blocking of STAT3 in an orthotropic tumor model [22]. Likewise, administration of luteolin in MCF-7 cells, at a dose of 60 μmol/L for 48 h, suppressed the proliferation of cancer in a dose- and time-dependent fashion via decreasing the expression of Bcl-2 protein, reducing the migration rate by 71.07%, and by decreasing the expression of AEG-1 and MMP-2 by 82.34% and 85.70%, respectively [23].

in vitro studies indicated that interleukin-8 (IL-8) and matrix metalloproteinase 9 (MMP-9) play an important role in the proliferation of breast cancer. In 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-treated MCF-7 breast cancer cells, luteolin suppressed the IL-8 expression and MMP-9 activation [24]. It additionally inhibited mRNA expression by suppression of the mitogen activated protein kinase (MAPK) signaling pathway, and down-regulation of nuclear AP-1 and NF-κB. Furthermore, luteolin suppressed the TPA-induced phosphorylation of ERK ½ and inhibited the ERK 1/2 pathways following IL-8 and MMP-9 expression [24]. In a similar fashion, luteolin inhibited p90 ribosomal S6 kinase (RSK)1 and RSK2 kinase activity, and suppressed the growth of triple-negative breast cancers (TNBC), including TIC-enriched populations. Luteolin also displayed activity against drug-resistant cells such as primary x43 cell line, and suppressed mammosphere formation and monolayer growth. Luteolin also suppressed the RSK/ Y-box binding protein-1 (YB-1) signaling on TIC-enriched populations [25]. Moreover, studies of *in vitro* and *in vivo* MDA-MB-231 ER-negative breast tumor growth found that luteolin inhibits cell growth, suppresses (3) H thymidine incorporation, causes cell cycle arrest at the G2/M and S stages,

Table 1
Summary of Luteolin affections in different types of cancer.

Cancer type	Cell proliferation	Cell survival signaling	Apoptosis	Angiogenesis	Metastasis	Dose of Luteolin
Breast cancer	Inhibit MAPKs, PI3K-Akt, CDK2	Inhibit PI3K-Akt, EGFR, NF-κB, MAPKs	Activate DR5, caspases-8 and -9, Fas, Bax	Inhibit VEGF, MMP-9, PI3k/Akt	Inhibit PI3k/Akt	10 mg/kg 60 μmol/L for 48 h, suppressed the proliferation of cancer
Colon cancer	–			Inhibit MMP-9		1.2 mg /kg b.w
Pancreatic cancer	–	Inhibit EGFR, NF-κB	Activate Bax	Inhibit NF-κB,	Inhibit NF-κB	–
Prostate cancer	–		Inhibit FASN	Inhibit VEGF, MMP-9	Inhibit IL-6	–
Glioblastoma	Inhibit PI3K-Akt	Inhibit PI3K-Akt, PKC	Activate P53, Inhibit XIAP	Inhibit NF-κB, PI3k/Akt	Inhibit PI3k/Akt, NF-κB	–
Oral cancer	–	–	Activate Fas, P53		Inhibit IL-6	–
Lung cancer	Inhibit MAPKs,	Inhibit NF-Kb, MAPKs	Activate caspases-3 and -9, Bax, JNK Inhibit Bcl-XL,	Inhibit VEGF, MMP-9, NF-κB, HIF-1α	Inhibit IL-6, FAK, NF-κB	50 μM
Kidney cancer	–	–	Activate DR5, Caspases, Bax, p53, JNK	–	–	–
Cervical and placental cancer	Inhibit PI3K-Akt	Inhibit PI3K-Akt	Activate DR5 Inhibit Bcl-XL	Inhibit PI3k/Akt	Inhibit PI3k/Akt	–
Ovarian Cancer	–	–	–	–	Inhibit FAK	–
Skin cancer				Inhibit MMP-9		–
Liver cancer	Inhibit PI3K-Akt	Inhibit PI3K-Akt, NF-κB	Activate Bax, P53 Inhibit Bcl-XL	Inhibit NF-κB	Inhibit NF-κB	
Gastric cancer	–	–	Activate Bax, P53	Inhibit VEGF, MMP-9	–	40 mg/kg
Oesophageal and bladder cancer	–	–	Activate p53, JNK	–	–	–

and induces apoptosis. In addition, it lowers the expression of AKT, PLK1, DC2, cyclin B(1), cyclin A, Bcl-x, and CDK2, and improved the Bax and p21 expressions [26].

Luteolin significantly inhibits IGF-1-stimulated MCF-7 cell proliferation, blocks cell cycle development, and triggers apoptosis, in a dose- and time- dependent fashion. Furthermore, luteolin considerably reduced IGF-1-dependent IGF-1R and pAkt without disturbing Erk1/2 phosphorylation. Research findings also revealed that ERα directly participated in IGF-1-induced cell growth inhibitory effects of luteolin, which effectively reduced ERα expression. These results show that luteolin exerts its inhibitory effect via inhibition of IGF-1-mediated PI3K-Akt pathway which is dependent on ERα expression [27]. In MCF-7 breast cancer cells, luteolin regulates the number of estrogen signaling pathway (ESP) genes (NCOR1, GTF2H2, NRAS, TAF9, DDX5, NRIP1, POLR2 A, NCOA3) and cell cycle pathway genes (CDKN1A, CCNA2, PCNA, PLK1, CCND1), and alters histone H4 acetylation at the PLK-1 promoter via an epigenetic mechanism involving histone H4 acetylation [28]. Conclusively, it is inferred from the piled literature that luteolin has the ability to tackle breast cancer by different routes.

2.2. Colon cancer

The strong antioxidant and anti-inflammatory effect of luteolin is responsible for its effectiveness in colon cancer and its associated complications, particularly, its diminishing effect on iNOS and COX-2 expression. Moreover, its suppressing effect on the expression of MMP-2 and MMP-9 has also provide substantial evidence for its ability to tackle the colon cancer

Recent studies revealed that luteolin suppresses the ceramide anabolism to complex sphingolipids, and inhibits activation of Akt and sphingosine kinase (SphK)-2 [29,30]. Research findings also showed that treatment of rats with dimethylhydrazine (20 mg/kg b.w./week) triggers renal bleeding and colon polyps, and considerably increases cyclooxygenase-2 (COX-2), carcinoembryonic antigen (CEA), and oxidative stress [31]. However, oral treatment with luteolin (1.2 mg/kg BW) lowered the expressions of nitric oxide synthase (iNOS) and COX)-2 [32,33]. On the other hand, intraperitoneal administration of azoxymethane (AOM) (15 mg/kg b.w.) for 3 weeks (once a week) activated colon carcinogenesis in Balb/C mice through elevation of tumor markers such as 5′ nucleotidase (5′ND), γ-glutamyl transferase (GGT), CEA), and cathepsin-D (Cat-D). Furthermore, oral treatment with luteolin (1.2 mg /kg b.w./day) significantly lowered these tumor markers and additionally lowered expressions of MMP-2 and MMP-9 [34].

In a study conducted by Bothe et al. (2010), luteolin was shown to exhibit an inhibitory effect on human colon carcinoma cells via suppressing the B(a)P-induced expression and the arylhydrocarbon receptor-dependent cytochrome P450 enzyme activity. Moreover, luteolin reduced apical transport of B(a)P metabolites due to its association with the transporter breast cancer resistance protein. Additionally, luteolin inhibited both Phase-I metabolism as well as phase-III transport, causing a 3-fold intracellular accumulation of radioactively labeled B (a)P to occur [35]. On the other hand, luteolin plays a protective role against the azoxymethane (AOM)-induced mouse colon carcinogenesis by (a) decreasing the tumor size and incidence, (b) decreasing the number of argyrophillic nucleolar organizer region (AgNOR)/nucleus, and (c) increasing cell nuclear antigen (PCNA) index. It exerts its colon carcinogenesis inhibitory effect by lessening AOM-induced cell proliferation which involves key components of Wingless and Int (Wnt) signaling pathways such as β-catenin, glycogen synthase kinase (GSK)-3β, and cyclin D1 [36].

Intraperitoneal injection of azoxymethane (15 mg/kg b.w.) in Balb/C mice, induced colon cancer and elevated the activities of mitochondrial enzymes such as α-keto dehydrogenase (α-KDH), succinate dehydrogenase (SDH), and isocitrate dehydrogenase (ICDH). Azoxymethane also induced lipid peroxidative end products such as conjugated dienes, protein carbonyl (PC), and malondialdehyde (MDA).

Similarly, orally administered luteolin, at a dose of 1.2 mg /kg b.w., in mice reversed these changes and decreased the secondary marker of colon cancer mucin depleted foci (MDF) in AOM-induced colon cancer animals [35–37].

2.3. Pancreatic cancer

The luteolin has been proven beneficial in the management of pancreatic cancer by inducing apoptosis, cell cycle arrest, and suppressing the protein phosphorylation and signaling. Owing to its promising anticancer effect, luteolin induces apoptosis in pancreatic cancer cells *in vivo via* suppression of the K-ras/GSK-3β/NF-κB signaling pathway, which is accompanied by release of cytochrome c, activation of caspase 3, and lowering of the Bcl-2/Bax ratio [38]. Treatment of BxPC-3 human pancreatic cancer cells with luteolin (15 μM, 24 h) significantly reduced nuclear GSK-3β and NF-κB p65 expression [39]. Similarly, administration of luteolin at the rate of 20 μM in MiaPaCa-2 cancer cells markedly reduced the cellular protein phosphorylation and growth, modulated protein tyrosine kinase (PTK) activities including that of EGFR, and suppressed the activities of PTK which cause autophosphorylation of EGFR and transphosphorylation of enolase. In addition, research findings revealed that luteolin (a) lowers the phosphotyrosyl levels of 125-, 170-, 110-, 65-, 60-, 44-, 30- and 25-kDa proteins, (b) induces apoptosis, (c) shrinks cell morphology, DNA fragmentation, and poly(ADP-ribose)polymerase (PARP) degradation in a time-dependent fashion, and (d) lowers the cellular protein phosphorylation and cellular proliferation [40].

2.4. Prostate cancer

The chemo preventive and chemotherapeutic role of luteolin in prostate cancer can be attributed to its ability to inhibit invasiveness of cancer cell, stop the progress of cell growth, initiate apoptosis, reduce extracellular matrix contraction, diminish the Rho signaling, and suppress the VEGF-induced phosphorylation. Luteolin exhibits chemopreventive and chemotherapeutic role against prostate cancer. In the highly invasive Du145-III prostate cancer cells, luteolin lowered the malignancy of these cells and inhibited cancer cell invasiveness [41]. Similarly, luteolin suppressed the androgen-sensitive and androgen-independent PCa cell line growth, markedly down-regulated the miR-301, and induced apoptotic cell death in LNCaP and PC3cells [42]. In prostate fibroblast cell lines, luteolin synergistically inhibited TGF-β-induced myofibroblast phenotypes, inhibited TGF-β-induced extracellular matrix contraction, and suppressed downstream TGF-β-induced signaling which involves activation of AKT and ERK. Rho signaling appeared to be responsible for TGF-β-induced fibronectin expression and luteolin suppressed activation of RhoA [43]. In PC-3 cancer cell lines, combined treatment of luteolin with gefitinib (a) significantly affected the viability of cells, (b) effectively down-regulated GAK protein expression, and (c) increased miR-5703 and miR-630 expression. It was also found that exogenous overexpression of miR-630 results in growth arrest of tumor cells [44].

In a study by Markaverich and Vijjeswarapu [45], it was found that treatment of PC-3 human prostate cancer cells with luteolin reduced the expression of various genes in the cell cycle pathway (CCP) and epidermal growth factor receptor signaling pathway (EGFRSP). It additionally stimulated expressions of p21 RNA and c-FOS, and caused irreversible G2/M arrest. Results also revealed that siRNA's for p21 or c-FOS significantly reduced the RNA expression of their corresponding targets with minor effects on cell propagation. In addition, luteolin inhibition of PC-3 cell proliferation could not be blocked by siRNA alone (single knockdown), or in combination (double knockdown) [45]. Furthermore, luteolin suppressed VEGF-induced phosphorylation of VEGF receptor 2. Moreover, luteolin at a dose of 10 mg/kg/d significantly lowered the pro-inflammatory cytokines IL-6, IL-1β, IL-8, and TNF-α level in PC3 cells of xenograft mouse model. It additionally, caused significant reduction in weight and volume of solid tumors, and suppressed the micro-vessel density. It also decreased cell viability, induced apoptosis, and down-regulated the ERK, AKT, P70S6K, mTOR, MMP-2, and MMP-9 expressions [46].

In a human study model, researchers found that luteolin at a concentration of 30 μM is effective against prostate carcinoma LNCaP cells by inducing cell apoptosis, up-regulating prostate-derived Ets factor (PDEF), and down-regulating androgen receptor (AR) gene expression. Luteolin also improved gene expression of PDEF, B-cell translocation gene 2 (BTG2), N-myc downstream regulated gene 1 (NDRG1), and Maspin. Transient gene expression assays indicated that co-transfection of the prostate-derived Ets factor (PDEF) expression vector enhances the promoter activities of BTG2, NDRG1, and Maspin genes. Collectively, these results suggest that luteolin blocks prostate-specific antigen expression via the down-regulation of AR expression [47].

The effect of luteolin gefitinib against PC-3 prostate cancer cells was investigated. Results revealed that treatment of these cancer cells with luteolin caused a 4-fold increase in the c-Fos gene expression, and a substantial inhibition of the cell cycle pathway (CCP) genes and G2/M arrest. These findings suggest that luteolin and gefitinib adjust CCP gene expression through a mechanism that involves EGFR-associated tyrosine kinase [48]. In prostate cancer PC3 cells, luteolin triggered expression of E-cadherin through mdm2. Additionally, treatment with luteolin could restore invasion of PC3 cells via overexpression of mdm2 or knockdown of E-cadherin. Moreover, luteolin was found to inhibit mdm2 through AKT and over expression of active AKT attenuated luteolin-induced expression of E-cadherin, suggesting that luteolin regulates E-cadherin through AKT/mdm2 pathway [49]. Luteolin also blocks the hepatocyte growth factor (HGF)-induced c-Met phosphorylation and scattering of DU145 prostate cancer cells. In DU145 cells, luteolin inhibited the HGF-induced scattering which is accompanied by reduction in c-Met protein. In addition, an inhibitor of FASN, C75, or short hairpin RNA knockdown of FASN mimicked luteolin-induced c-Met down-regulation. These results show that luteolin exerts its anticancer effect by acting as a novel HGF/c-Met inhibitor [50].

2.5. Glioblastoma

The antioncogenic perspective of luteolin against glioblastoma has been correlated with its capacity to inhibit cell growth, to induce apoptosis, to slow down and reduce invasion and migration, and to down-regulate iNOS expression. Luteolin, in combination with silibinin, exhibited an inhibitory effect against human glioblastoma T98 G (mutant p53) and U87MG (wild-type p53) cancer cell lines through multiple mechanisms including (1) inhibition of growth cells, (2) induction of apoptosis, (3) suppression of invasion and migration, (4) inhibition of rapamycin (RAPA)-induced autophagy and PKCα, (5) down-regulation of iNOS, and (6) enhancement of tumor suppressor expression of miR-7-1-3p [51]. In addition, both compounds blocked the angiogenesis and survival pathways by inducing apoptosis, and by inhibiting the XIAP, PKCα, and iNOS expressions [52,53]. In U-87 glioblastoma cells, luteolin additionally inhibited the IL-1β-mediated phosphorylation of κB inhibitor, p65 a nuclear transcription factor-κB (NF-κB), extracellular signal-regulated kinase-1/2, and c-Jun amino-terminal kinase. It also suppressed the p-AKT and triggered both expression of glucose-regulated protein 78 and caspase-3 cleavage. These activities were promoted by IL-1β, in part through increased nuclear translocation of NF-κB p65. Finally, luteolin decreased the expression of IL-1 receptor gene, where treatment with IL-1 receptor antagonist or gene silencing of IL-1 receptor prevented IL-1β/luteolin-induced COX-2 expression [53].

Cheng et al. (2013) reported that luteolin (15 and 30 μM), inhibits migration and invasion in T98 G and U-87 MG glioblastoma cells. It also effectively inhibits the filopodia assembly and exhibits reduction in Cdc42 (cell division cycle 42) protein levels and PI3K/AKT activation. Over expression of constitutive Cdc42 (Q61 L) using transient

transfection in U-87 MG cells induced a partial cell migration; however, treatment with luteolin did not affect the degradation of the protein levels of Cdc42. Furthermore, inhibition of the proteaosome pathway by MG132 caused an efficient recovery in the migration potential of U-87 MG cells and augmented the Cdc42 protein levels after luteolin treatment, suggesting that pharmacological inhibition of migration via luteolin is likely to preferentially facilitate the protein degradation of Cdc42 [54]. Effect of different concentrations of luteolin (25 and 50 μM) on SH-SY5Y neuroblastoma tumor cell line was also investigated. Luteolin showed an inhibitory effect on the growth of the cells in a dose-dependent manner. It additionally activated apoptosis, caused G0/G1 cell cycle growth arrest, and decreased the mitochondrial membrane potential [55].

In Neuro-2a mouse neuroblastoma cells, luteolin exerts an anticancer effect through multiple mechanisms such as induction of apoptotic process of cell death, induction of caspase-12, -9, and -3, knockdown of caspase-12 by siRNA transfection reduced luteolin-induced cell death, promotion of the endoplasmic reticulum (ER) stress-associated proteins expression, including C/EBP homologous protein (CHOP) and glucose-regulated proteins (GRP) 94 and 78, cleavage of ATF6α, and phosphorylation of eIF2α [56].

2.6. Oral cancer

Being a natural anticancer agent, luteolin significantly suppressed the rate of proliferation, ability of self-renewal, aldehyde dehydrogenase 1 function, and CD44 positivity of oral cancer stem cells (OCSC). Luteolin, combined with radiation, showed synergistic effect on clonogenicity and invasiveness of OCSC through inactivation of IL-6/STAT3 signaling [57]. In oral cancer SCC-25 cells, luteolin caused phosphorylation of ataxia telangiectasia mutated (ATM) and H2 AX in the pathway of DNA repair [58,59]. Similarly, luteolin decreased the SCC-4 cells viability and enhanced apoptosis by reducing the expression of cyclins, cyclin-dependent kinase (CDKs), and phosphor-retinoblastoma (p-Rb) anti-apoptotic protein. In SCC-4 cells, luteolin with paclitaxel (combined treatment), induced the cytotoxicity of paclitaxel, and consecutive doses of luteolin suppressed the growth of xenograft tumors in mice [60].

In head and neck squamous cell carcinoma (HNSCC), luteolin effectively suppressed the tumor growth and histone acetylation, induced cell cycle arrest, reduced cell migration, and caused alteration in gene expression and miRNA profile including up-regulation of p53 induced miR-195/215 and let7C. In a study, a network of dysregulated genes and miRNAs was mapped along with the gene ontology categories, and the effects of luteolin were observed to be potentially at multiple levels, including gene expression, miRNA expression, and miRNA processing [61]. In human laryngeal squamous Hep-2 cells, treatment with luteolin at a dose of 50 μM significantly induced apoptosis via activation of-caspase-3 and -8, up-regulation of Fas, and down-regulation of cellular FLICE-like (c-FLIPL) inhibitory protein. Luteolin not only inhibits cell proliferation, but also induces apoptosis by activating the Fas signaling pathway at the receptor level in laryngeal squamous cell line Hep-2 cells [62]. Furthermore, in human nasopharyngeal carcinoma (NPC) cells, luteolin suppressed cell cycle development at G1 phase, prohibited entry into S phase in a dose- and time-dependent fashion, and down-regulated cyclin D1. These processes are exerted through different mechanisms which involve improvement of protein phosphorylation and proteasomal degradation that lead to lessening of CDK4/6 activity, suppression of retinoblastoma protein (Rb) phosphorylation, and inhibition of the transcription factor E2F-1 [63]. These data show that luteolin effectiveness in oral cancer is due to induction of apoptosis mainly by affecting the cyclin-dependent kinase (CDKs) proteins, cell cycle arrest, and by reduction in cell migration and alteration in miRNA sequencing.

2.7. Lung cancer

The luteolin has the potential to treat lung cancer owing to its ability to stimulate multiple responsible targets. Among these, apoptosis, cell cycle arrest, down-regulation of the expression of HNF4α, TAM-secreted CCL2, IL-4, and M2-associated genes. In human, non-small cell lung cancer (NSCLC) cell line A549, luteolin has been found very effective against cancer cell proliferation by inducing cell death and suppressing cell migration. Induction of apoptosis is associated with activation of caspases-3 and -9, altering the phosphorylation of MEK, expression of Bcl-2 family proteins (Bax, Bcl-2) and its downstream kinase ERK, and phosphorylation of Akt [64]. Tumor-associated macrophages (TAMs) play a very important role in cancer progression. In order to investigate a novel candidate that inhibits the tumor-supporting M2-like phenotype of TAMs, a murine macrophage cell line RAW 264.7 cells were treated with interleukin (IL)-4. Luteolin blocked phosphorylation of signal transducer and activator of transcription 6 (STAT6), a main downstream signal of IL-4, and decreased M2-associated genes expression. Luteolin additionally reduced migration of Lewis lung carcinoma cells in a CCL2-dependent way. Given the important role of the TAM phenotype in the tumor microenvironment, the inhibitory effect of luteolin on the monocyte recruitment and cancer migration by suppression of the TAM-secreted CCL2 may suggest a novel therapeutic approach to treat malignant tumors [65]. Similarly, luteolin significantly inhibited the hepatocyte nuclear factor 4α (HNF4α) expression and its binding to the HBV promoters in HepG2.2.15 cells. While the extracellular signal-regulated kinase (ERK) was activated by luteolin, inhibition of ERK abolished luteolin-induced HNF4α suppression. In a HBV replication mouse model, luteolin decreased the levels of HBeAg, HBsAg, HBV DNA replication intermediates, and expression of HBsAg and HBcAg [66]. Luteolin acts as an anticancer agent on NCIH460 cells via Sirt1-mediated apoptosis [67].

In NCI-H460 and -H1299 non-small cell lung cancer (NSCLC) cells of xenograft model in mice, co-treatment of luteolin and IR induced apoptotic cell death in association with down-regulation of B-cell lymphoma 2 (Bcl-2) and activation of caspase-3, -8, and -9. Inhibition of p38 MAPK decreases ROS production, whereas suppression of either p38 MAPK or ROS production attenuates apoptotic cell death and activation of caspase8 and 9. In a xenograft model, treatment with luteolin/IR delayed tumor growth and increased apoptotic cell death as compared to controls. These findings suggest that luteolin may act as a radio-sensitizer by promoting apoptotic cell death through induction of a p38/ROS/caspase cascade [68].

Pratheeshkumar et al. [69] showed that exposure of human bronchial epithelial cells (BEAS-2B) to hexavalent chromium [Cr (VI)] (5 μM) for a short period of time significantly increases ROS generation, NADPH oxidase (NOX) activation, glutathione depletion, and lipid peroxidation; these factors were effectively inhibited by treatment with luteolin in a dose-dependent fashion. In addition, treatment of BEAS-2B cells with luteolin caused a decrease in HIF-1α, COX-2, AP-1, and iNOS promoter activity triggered by Cr (VI). Moreover, luteolin protected BEAS-2B cells from malignant transformation induced by chronic Cr (VI) exposure. Furthermore, luteolin inhibited production of pro-inflammatory cytokines (IL-1β, IL-6, IL-8, TNF-α) and VEGF in chronic Cr (VI) exposed BEAS-2B cells, and suppressed multiple gene products linked to survival (Fak, Akt, Bcl-2, Bcl-xL), inflammation (NF-κB, MAPK, STAT-3, COX-2, TNF-α, iNOS), and angiogenesis (VEGF, MMP-9, HIF-1α). These findings suggest that luteolin protects BEAS-2B cells from Cr (VI)-induced cellesis by scavenging ROS and modulating multiple cell signaling mechanisms that are associated with ROS [69]. In NSCLC, luteolin displayed a substantial anti-tumorigenic effect on the EGF receptor L858R/T790 M mutation and erlotinib-resistant NSCLC both at the animal and cellular levels [70].

Pretreatment of A549 cells with luteolin prevented morphological change and down-regulation of E-cadherin activated by TGF-β1. Furthermore, the activation of PI3K-Akt-IκBa-NF-κB-Snail pathway

which leads to a decline of E-cadherin induced by TGF-β1 was also attenuated under pretreatment with luteolin [71]. Introduction of a degradation-resistant MKP-1 mutant effectively attenuated luteolin-induced JNK activation and cytotoxicity, suggesting that inhibition of the JNK suppressor MKP-1 plays a vital role in luteolin-induced lung cancer cell death [72].

2.8. Kidney cancer

The effectiveness of luteolin in kidney cancer can be ascribed to induction of apoptosis, down-regulation of Mcl-1 and FLIP, and to its oxidative stress diminishing perspective. In renal cell carcinoma (RCC), the combined effect of luteolin and TRAIL caused significant extrinsic and intrinsic apoptosis. Sensitization was associated with Bid cleavage, down-regulation of Mcl-1 and FLIP, inactivation of DR4/DR5 protein expression, cell surface presentation, Akt and signal transducer and activator of transcription-3 (STAT3) [73]. Furthermore, researchers showed that administration of cisplatin (20 mg/kg) in C57BL/6 mice caused renal damage, enhanced blood urea nitrogen and creatinine levels, oxidative stress, tubular damage, and apoptosis. On the other hand, treatment with luteolin (50 mg/kg for 3 days) markedly improved the renal dysfunction, decreased tubular cell damage, oxidative stress, and apoptosis. Moreover, it significantly decreased the levels of p53 and its phosphorylation, Bax, PUMA-α, and caspase-3 activity [74].

Qu and coworkers [79] found that treatment of 786-O renal cell carcinoma (RCC) cells, as well as A498 and ACHN, with luteolin induces cell apoptosis and death. It also down-regulates Akt and up-regulates apoptosis, c-Jun N-terminal kinase (JNK), signal-regulating kinase-1 (Ask1), and p38 activities, through activation of protein phosphatase 2 A (PP2 A). In addition to being a concurrent substrate of caspases and event of cell death, heat shock protein-90 (HSP90) cleavage might also play a role in driving further cellular alterations and cell death through an Akt-related mechanism [75].

2.9. Ovarian cancer

In ovarian cancer (OVCA) cell lines, luteolin displayed anticancer potential through reduction of phosphorylation of FAK and ERK, which leads to reduced nuclear translocation of p65 [76]. Luteolin also reduced the aromatase mRNA and protein expression in a dose- and time-dependent fashion, promoted aromatase protein degradation, and inhibited estrogen biosynthesis in KGN cells derived from human ovarian granulosa cells [77]. Luteolin's effect on ovarian cancer related complications can be attributed to its ability to halt cancer promoting biomarkers.

2.10. Cervical and placental cancer

Luteolin has shown potential to inhibit invasiveness activation by ubiquitin E2S ligase (UBE2S) through epithelial-mesenchymal transition (EMT) signaling. It also reversed cell motility induced in malignant cancer by UBE2S through EMT signaling. Luteolin additionally inhibited the hypoxia-induced factor (Hif)-1α signaling in cervical cancer cell lines, and lowered UBE2S expression [78]. In human papillomavirus (HPV)-positive cervical cancer cells, luteolin suppressed the expression of human papilloma virus E6 and E7 oncogenes, and showed cytotoxic activity. It also increased the expression levels of death receptors and death receptor downstream factors such as DR5/TRAIL, Fas/FasL, and FADD, as well as increased the activity of caspase-3 and -8 in a dose-dependent fashion. In addition, treatment with luteolin induced reduction of the mitochondrial membrane potential, release of cytochrome c, and suppression of Bcl-xL and Bcl-2 expressions [79]. Tai and coworkers [80] reported that the preventive role of luteolin against HeLa cervical cancer cells involves stimulating IFN-β-induced Janus kinase/signal transducer and promotion of transcription (JAK/STAT) activator pathway. This is achieved via phosphorylation of Jak1, STAT1/2, and Tyk2, which leads to accumulation of STAT1 in the nucleus and to IFN-α-regulated gene expression. Furthermore, the cAMP-degrading activity of PDE bound with Type-I interferon receptor 2 (IFNAR2) was enhanced by luteolin which also reduced the intracellular cAMP level. This suggests that the effect of luteolin on the JAK/STAT pathway proceeds via PDE [80].

A number of researchers found that luteolin up-regulates the death receptor 5 (DR5) which acts as a receptor for TRAIL. Additionally, luteolin, along with exogenous soluble recombinant human TRAIL, acts synergistically to induce apoptosis in HeLa cells. A combination of TRAIL and luteolin influenced Bid cleavage and the induction of caspase-8. Furthermore, human recombinant DR5/Fc chimera protein, DR5 siRNA, and caspase inhibitors significantly reduced apoptosis induced by co-treatment with TRAIL and luteolin [81,82]. In JEG-3 and JAR cells, presented as important placental models, luteolin reduced the viability of these cells, triggered apoptosis and loss of mitochondrial membrane potential, and inhibited PI3K/AKT pathway. In addition, it was shown that luteolin can influence the proliferation of JEG-3 and JAR cells in the presence of pharmacological inhibitors such as PI3K/AKT, mTOR, and ERK1/2 MAPK [83]. These results reflect the beneficial role of luteolin in cervical cancers, which can be related to its ability to inhibit the invasiveness, cell motility reversion, halting the hypoxia-induced factor (Hif)-1α signaling, and to promotion and stimulation of IFN-β-induced Janus kinase/signal and 5 (DR5) expression.

2.11. Skin cancer

Luteolin in combination with quercetin exerted a preventive role through multiple mechanisms in the highly invasive tumor cell lines A431-III and A431-P via reversing cadherin switching, down-regulating epithelial-mesenchymal transition (EMT) markers, and abolishing the ability of invasion. It additionally reversed the overexpression of MMP-9 which resulted in induction of epithelial-mesenchymal transition (EMT) in A431-P cells. Luteolin also caused reduction in levels of epidermal growth factor (EGF)-induced markers of EMT, and caused the restoration of cell-cell junctions, and enhanced E-cadherin [84,85]. Furthermore, administration of luteolin reduced UVB-induced cell death by blocking intrinsic apoptotic signaling. On the other hand, research findings revealed that treatment with luteolin inhibits inflammatory mediators such as Prostaglandin-E (2) and IL-1alpha. These results suggest that luteolin inhibits different aspects of sunburn response, which results ultimately in an increased survival of normal keratinocytes, whereas the sensitivity of malignant cells to UVB remains unchanged [86]. In SKH-1 hairless mice, luteolin inhibited tumor incidence, multiplicity, and overall size, and suppressed the expression of UVB-induced cyclooxygenase-2 and activator protein-1 and nuclear factor-kappaB activity in JB6 P + cells [87].

Alpha-melanocyte-stimulating hormone (alpha-MSH) enhances tyrosinase activity and melanin production, whereas luteolin suppresses tyrosinase activity, melanin production, cAMP levels, and adenyl cyclase in B-16 melanoma cells in a dose-dependent fashion [88]. Similarly, luteolin suppresses the colony formation, induces apoptotic cell death, and causes cell cycle arrest (G0/G1 and G2/M) in A375 (human melanoma) and HaCaT (human immortalized keratinocytes) cells [89]. These results clearly indicate that luteolin is beneficial in skin cancer, and it exerts its action on cadherin reversal, switching, down-regulating epithelial-mesenc hymal transition (EMT) markers. Moreover, reducing the inflammatory mediators such as Prostaglandin-E (2) and IL-1alpha also strengthened its antioncogenic ability.

2.12. Liver cancer

In HepG2 and Bel7402 cells, the combined treatment with luteolin and 5-fluorouracil increased the bax/bcl-2 ratios and p53 expressions, enhanced PARP cleavage, and decreased the dihydropyrimidine dehydrogenase [90]. Niu et al. (2015) investigated the cytotoxic role of

luteolin against H22 hepatoma tissue and found that it exerts its action via up-regulating the expression of ICAM-1, down-regulating the LFA-3 expression, and decreasing the PCNA expression [91]. In a similar fashion, Yee and coworkers [92] found that luteolin has an anticancer role against HepG2 cells by inducing apoptosis, causing G1 cell cycle arrest, up-regulating the expression levels of p21WAF1/CIP1, and transforming growth factor Smad4, β1 (TGF-β1), p27KIP1, and Fas [92]. On the other hand, several scientists reported that when luteolin acts on HepG2 cells it (a) suppresses proliferation, (b) induces higher apoptotic cell death and typical apoptotic morphological changes, (c) causes cell cycle arrest at G1/S stage, (d) decreases mitochondrial membrane potential (e) increases the Bax and caspase-3 expression, and (f) reduces anti-apoptotic protein Bcl-2 level which results in the activation of caspase-3 enzyme [93,94].

Similarly, in HepG2 hepatocarcinoma cells, luteolin caused induction of cell death and reduction of tumor in a xenograft model. It also suppressed the NF-κB DNA-binding activity and caused the release of ROS; these intracellular ROS in turn mediate AMPK-NF-κB signaling [95]. In addition, luteolin activated caspase-8 and induced expression in functional Fas/CD95 in HLF hepatoma cells. Furthermore, luteolin caused a large decrease in the Tyr (705) phosphorylation of STAT3, a known negative regulator of Fas/CD95 transcription, which occurred within 20 min in the luteolin-treated cells with an increased expression of Fas/CD95. This resulted in down-regulation of the target gene products of STAT3 such as surviving Bcl-xL, cyclin D1, and vascular endothelial growth factor. Treatment with luteolin gradually decreased the expression level of Ser727-phosphorylated STAT3 followed by a rapid and clear down-regulation in the active forms of CDK5, which can phosphorylate STAT3 at Ser727 [96].

Hepatocyte growth factor (HGF), also known as scatter factor (SF), along with its receptor, the c-Met tyrosine kinase, are responsible for proliferation of a wide range of cancer cells. In this regard, several researchers investigated the effect of luteolin and other flavonoids on HGF-mediated migration and invasion of HepG2 cells. These researchers found that luteolin exhibits potent anti-migration and anti-invasion. They then concluded that luteolin inhibits HGF-induced HepG2 cell invasion through both PI3K-Akt and MAPK/ERKs pathways [97]. From the presented material it is evident that luteolin, alone or in combination, has the ability to tackle liver cancer by promoting the expression of bax/bcl-2 ratios and p53 expressions, by enhancing PARP cleavage and diminishing the dihydropyrimidine dehydrogenase, and by p-regulating the expression of ICAM-1, LFA-3, and PCNA expressions.

2.13. Gastric cancer

Research findings showed that luteolin suppresses tumor growth in cMet-overexpressing PDTX models, induces apoptosis, and considerably down-regulates the expression of MMP9, Ki-67, and cMet. It additionally inhibits propagation, decreases the invasiveness of MKN45 and SGC7901 cells, activates PARP-1 and caspase-3, down-regulates MMP9, and reduces the expression and phosphorylation of cMet, and downstream phosphorylation of ERK and Akt.

These findings indicate that luteolin exhibits significant antitumor effects in cMet-overexpressing PDTX models of gastric cancer via cMet/Akt/ERK signaling [98]. Wu et al. (2015) demonstrated that luteolin lowers the Bcl-2 expression by up-regulating miR-34a in human gastric cancer cells [99]. Similarly, luteolin at a dose of 40 mg/kg, can effectively inhibit BGC-823 gastric carcinoma xenografts in mice through stimulation of immune response and the down-regulation of VEGF-A and MMP-9 expressions [100]. In gastric cancer cell line SGC-7901, luteolin could promote the activities of caspase-3 and -9, and irradiation-induced colonogenic inhibition. It significantly down-regulated Bcl-2 and the release of cytochrome C. It additionally decreased production of PGE_2 significantly, and lowered HIF-1 alpha and VEGF expression levels [101]. Treatment with luteolin reduced the protein levels of cyclin B1, Cdc25C, and Cdc2, and up-regulated p21/cip1. Luteolin also enhanced apoptosis in gastric cancer AGS cells, increased the pro-apoptotic proteins levels including caspase-3, -6, -9, p53, and Bax, and reduced anti-apoptotic protein Bcl-2 level, thus shifting the Bax/Bcl ratio in favor of apoptosis [102]. In conclusion, multiple mechanisms have been involved in the antioncogenic perspective of luteolin in gastric cancer; these include suppression of tumor growth and down-regulation of the expression of MMP9, Ki-67 and cMet.

2.14. Oesophageal and bladder cancer

In esophageal carcinoma cells (EC1 and KYSE450), luteolin induced apoptotic cell death, activated caspase-3, and caused cell cycle arrest at G2/M phase in a dose- and time-dependent fashion.

It also down-regulated the mitochondria membrane potential, increased the expression of regulatory protein of cell cycle p21 and p53, and increased the levels of apoptosis-related proteins (CYT-c, Bim, and cPARP). Additionally, luteolin showed significant potential to inhibit the growth of esophageal squamous-cell carcinoma (ESCC) tumors in xenograft mouse models [103]. Furthermore, luteolin caused cell cycle arrest at G2 phase, sensitized BCG-induced cytotoxicity and cell apoptosis, and up-regulated expression of caspase-3 and activation of JNK [104]. These results indicate that luteolin exhibits an inhibitory effect against arylamine *N*-acetyltransferase (NAT) and gene expression in human bladder cancer T24 cells [105]. In short, luteolin can be effective in preventing oesophageal and bladder cancer by inducing cell death and cell cycle arrest at G2/M phase and through activation of caspase-3, protein expression.

3. Conclusions

Diet and consumption of bioactive compounds from natural sources (fruits and vegetables) have been recognized for their preventive role against a variety of human diseases including cancer. The inhibitory effects of phytochemicals found in plants against major diseases are well documented in the literature. Additionally, these phytochemicals can be used as complementary medicine to protect and suppress the growth of different human cancers. These food-based products, being chemo-preventive agents, are considered to be safer and more effectual against proliferation of cancer. In this context, luteolin, a flavonoid found in different fruits and vegetables has been known as an anticancer agent through inducing apoptosis and cell cycle arrest, and thorough inhibiting metastasis and angiogenesis in multiple cancer cell lines such as breast, colon, pancreatic, lung, among others. In summary, this review has shown that luteolin can be an important complementary medicine for the prevention and treatment of different types of cancers, owing to its natural origin, safety, and low-cost relative to synthetic cancer drugs. However, since most of the findings cited in the present work are based on *in vitro* and *in vivo* studies, which don't necessarily represent the effect on humans, more work on different pharmacokinetic parameters, and may involve human subjects, is needed in the future before this substance becomes a prescribed drug. Furthermore, development of standardized dosage could also be pursued in clinical trials.

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