Mechanistic Insight into the Anticancer Activity of Luteolin

Subjects: Oncology

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Luteolin, a flavone found in numerous fruits, vegetables, and herbs, has exhibited a number of biological activities, such as anticancer and anti-inflammatory. Luteolin inhibits tumor growth by targeting cellular processes such as apoptosis, cell-cycle progression, angiogenesis and migration.

luteolin apoptosis and cell cycle anti-metastasis anti-inflammation

1. Apoptotic and Cell Cycle Arrest Mechanisms of Luteolin

Apoptosis induction (natural cell death) and cell cycle arrest are known to be promising drug targets opted for by a variety of chemotherapeutics and phytochemicals. Luteolin is found to possess both extrinsic as well as intrinsic mechanisms of apoptotic cell death in cancer (**Figure 1**). For instance, Wang et al., 2018 evaluated PARP (poly (ADP-ribose) polymerase) cleavage and upregulation of Fas and Fas ligand (FasL) along with increased levels of caspases-8 and -3 [1]. For instance, a recent study has shown that administration of 25 µM luteolin significantly reduces cell viability by inducing apoptosis in p53-deficient cell lines by significantly increasing the cell proportion at the sub-G_0/G_1-phase of cell cycle and decreasing the cell proportion at S-phase [2]. It increased p53 phosphorylation and p53-targeted downstream gene expression, initiating apoptosis and cell cycle arrest [3]. Suppression of CDK2 activity in cancerous cells HT-29 and OCM-1 cells is related to G_1 cell cycle arrest [4]. Dose- and time-dependent effects of luteolin were observed on the cytotoxicity of human colon cancerous LoVo cells with IC50 of 66.70 µmol/L (24 h) and 30.47 µmol/L (in 72 h). Similar results were observed in the human colon HCT-15 cell line [5]. This was due to the cell cycle arrest at G_2/M phase that ultimately resulted in cellular apoptosis [6]. Luteolin leads to the inactivation of essential cell-cycle proteins such as cyclin B, CDC2 (cell division control), procaspase-9 in mice models and upregulated cyclin A, APAF-1, cytochrome C, caspase-9 and-3, and cyclin-dependent kinases (CDK) 2 [6]. These proteins play a very essential role in cell division and cell cycle progression. It effectively suppresses the expression levels of p-STAT3 (signal transducer and activator of transcription), p-Akt, p-EGFR (epidermal growth factor receptor), and p-Erk1/2 (extracellular signal-regulated kinase) in cancerous cell lines [4]. Inhibiting CDC1/CDK2 and cyclin B1/CDC2 proteins successfully arrested the cell at the G_2/M transition. Cytochrome c and APAF 1 (apoptotic protease activating factor1) activates caspase recruitment domain (CARD) which in turn activates caspase-9 to form apoptotic bodies. This initiates caspase-3 and other caspase cascade reactions resulting in apoptosis of the cell [7]. Similar effects were also observed in esophageal cancer Eca109 cell

line and A172 and U-373MG, human glioblastoma cell lines [8][9]. The apoptosis of breast cancer cell line MDA-MB-231 was observed to be induced by downregulating human telomerase reverse transcriptase protein (hTERT). It inhibited the phosphorylation of NF-κB (nuclear factor kappa B) inhibitor α and its subsequent target gene c-Myc (master regulator of cell cycle) followed by the suppression of hTERT [10]. Treatment of cancerous cells with luteolin significantly decreased BCL-2 (B cell leukemia/lymphoma 2) and VEGF (vascular endothelial growth factor) expression, while increasing the expression of BAX protein (Bcl-2-associated X protein). This signaling initiated the mitochondrial-modulated function to cause cell death [11]. A recent study has shown luteolin to suppress tumor proliferation by inducing apoptosis through MAPK pathway (mitogen-activated protein kinase) activation. LIM domain kinase (LIMK) 1 protein and its associated proteins (such as Ki-67, p-LIMK, p-cofilin), which are highly expressed in the lung cancer cell line, are significantly inhibited by luteolin [12]. It also induced potential mitochondrial membrane collapse, thereby leading to cytochrome c release, and an increased expression of BAX by inhibiting the expression of Bcl-2. Furthermore, it also enhanced the expression of death receptors DR5, which activated caspase-8/-9/-3 cascades in MCF-7 cells [13]. These overall mechanisms also significantly decreased the tumor size and weight, thereby leading to cell-cycle arrest and apoptosis [6]. Furthermore, luteolin inhibited the proliferation of human colon adenocarcinoma cell line HT29 by increasing the expression of Caspase-1, Gasdermin D and IL-1β, members of pyroptosis, a form of cell death [14].

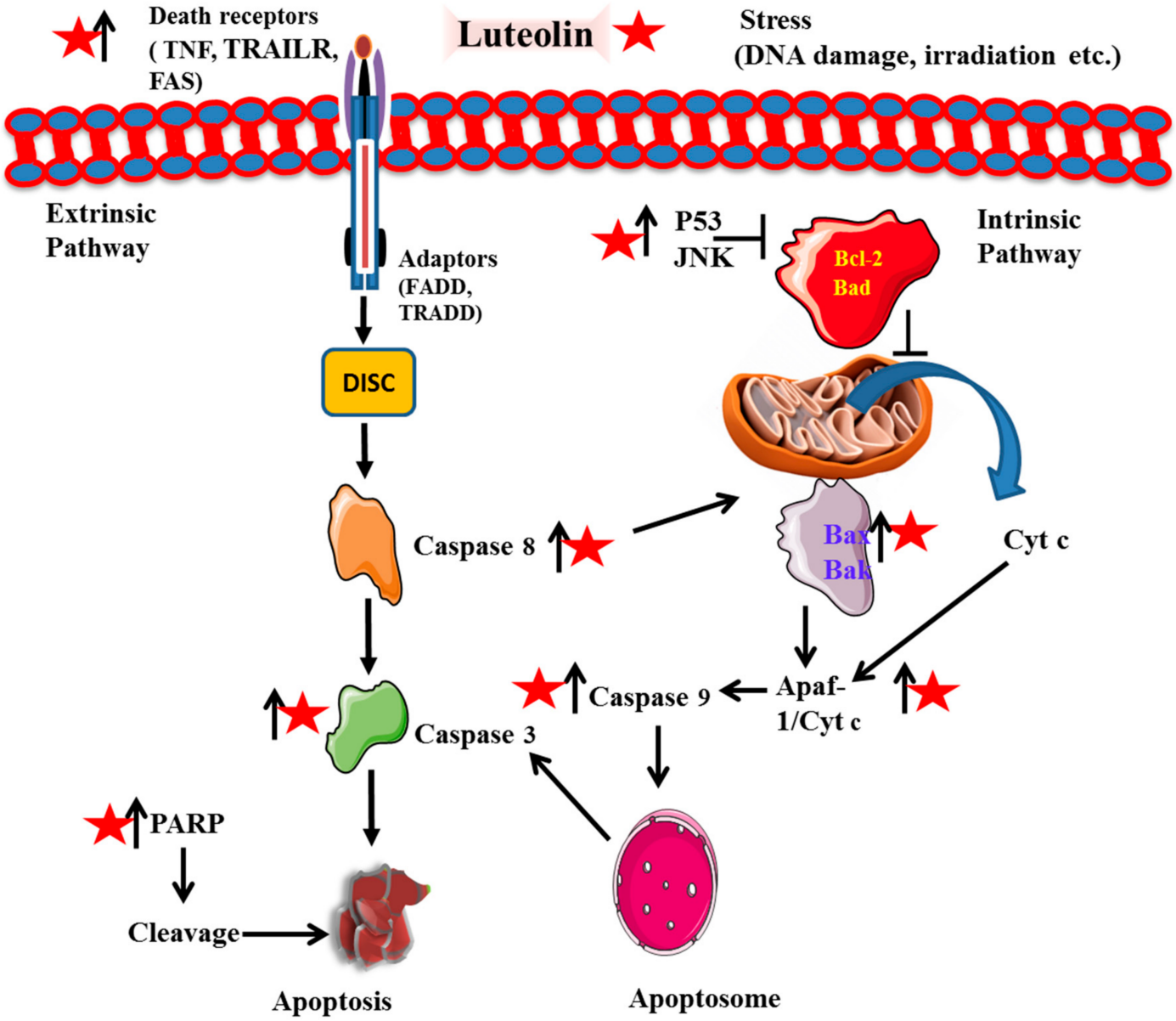

Figure 1. Intervention of luteolin into apoptotic mechanisms of cancer cells. Luteolin is represented by a red star, whereas arrows designate up (↑) and downregulation (↓) of the molecules. It modulates the expression of anti-apoptotic factor (Bcl-2), and apoptotic (Bax, Bak, Cyt c, Caspases and Apaf) for the progression of natural cell death.

2. Autophagy- Inducing Mechanism of Luteolin

Autophagy is a process that degrades cells and removes toxic substances from cells that are under stress, and functions as a self-degradation system [15]. The autophagy process is classified into different types i.e., micro, macro and chaperone-mediated autophagy that transmits to the lysosome. Macroautophagy is a metabolic process that wraps protein cells to form autophagosomes with a bilayer membrane, the membrane fuses with the lysosomal membrane and degrades the wrapped protein by hydrolyzing [16]. Luteolin affects various pathways, i.e., it is involved in autophagy that includes nucleation and elongation that prevents the progression of cancer. Luteolin

attenuates Wnt signaling (Wingless-related integration site) pathway for the upregulation of fizzled class receptor to downgrade cancer cells. Beclin1 plays an important role in autophagy, a process involved in cell survival that increases during cell stress and decreases over the cell cycle. The Beclin1 regulates autophagy during the initiation step that suppresses tumors and downregulates the Beclin1 expression in cells. Luteolin affects the ER chaperone binding and activates stress sensors and induces autophagy [17]. The Beclin1 promotes protein light chain formulation that effects elongation steps through the downregulation of light chains. Autophagy can also help in the survival of cells in cancer cells with Beclin1 downregulation [18].

The high amount of luteolin may cause lethal autophagy in lung cancer, proving induction of caspase-dependent programmed cell death. The major role of luteolin was reported to increase LC3 (microtubule-associated protein 1A/1B-light chain 3) puncta and autophagy flux by activating caspases and beclin1 [9][19]. Luteolin also inhibited cancer cell development via the Wnt β-catenin pathway, and may clearly halt the cell cycle by decreasing Akt-phosphorylation, which further leads to dephosphorylation and triggers GSK-3 (glycogen synthase kinase). Upon activation of GSK-3, the level of cyclin D1 phosphorylation rises at Thr-286, with proteasomal destruction [20]. During sensitization of cancer cells luteolin makes a significant impression on cleaving caspase and inhibits cancer cells by stimulating autophagy. Luteolin, upon activation of MAPK activation, decreases the proliferation that leads to the downregulation of P62, leading to autophagy and induces FADD (Fas-associated death domain)-mediated apoptosis [21]. Therefore, luteolin in cancer therapy could be beneficial to reduce tumor cell survival and proliferation via autophagy regulation (**Figure 2**).

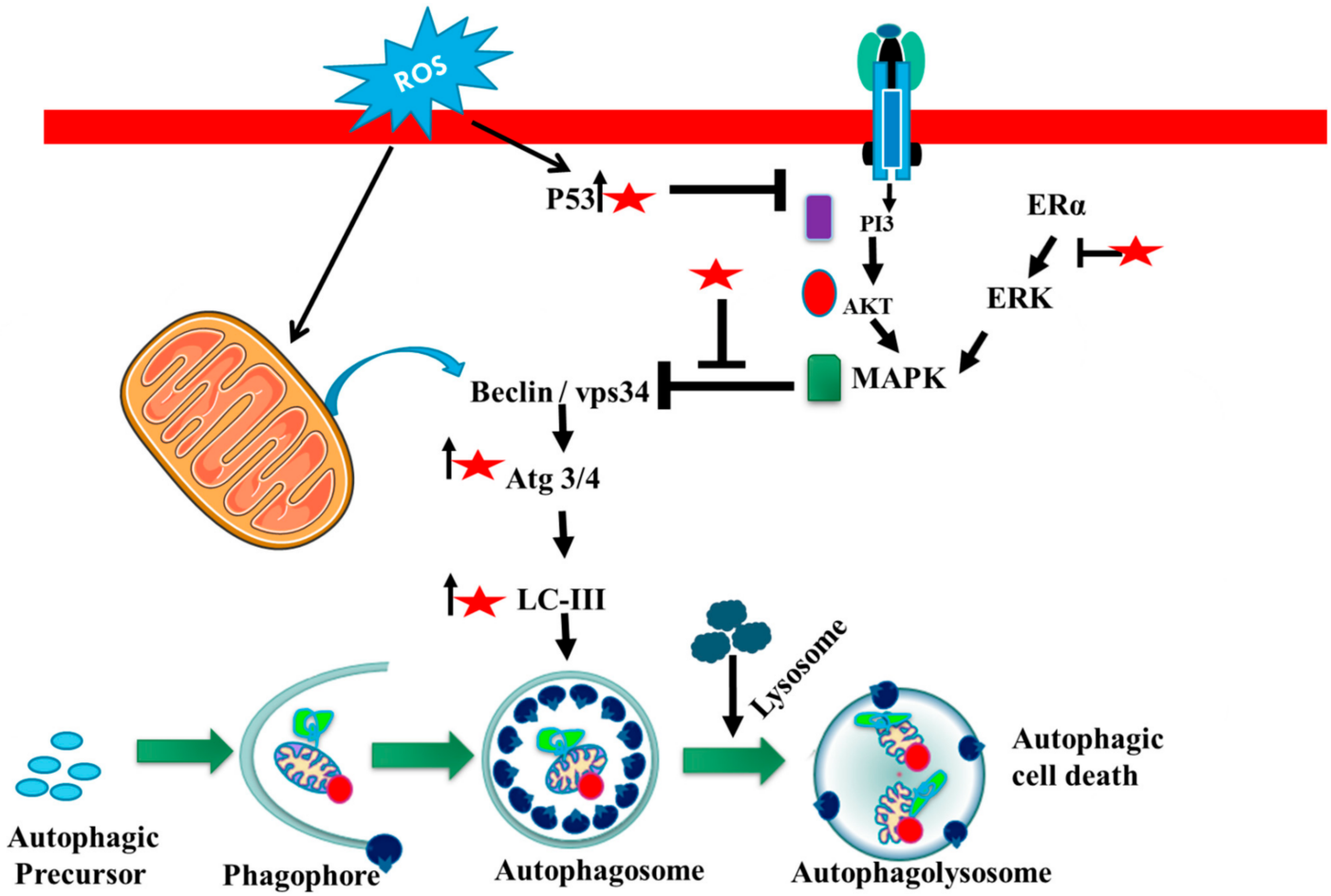

Figure 2. The role of luteolin in regulation of autophagy. Luteolin is found to modulate the expression of autophagic molecules including MAPK, Beclin1, and LC3 to initiate autophagy in cancer. Luteolin is represented by a red star, whereas arrows designate up (↑) and blockage (⊥) of the molecules.

3. Antiangiogenic and Antimetastatic Action of Luteolin

It is well established that angiogenesis plays a prominent role in the occurrence, invasion and metastasis of tumors. Significant findings on the antiangiogenic and antimetastatic properties of luteolin have yielded positive results [22][23][24]. Studies have demonstrated that luteolin inhibits breast cancer invasion via inhibiting VEGF production and the receptor activity, and also it decreases the expression of markers for epithelial–mesenchymal transition and inclination towards metastasis. Some studies have also demonstrated that luteolin suppresses angiogenesis by stabilizing hyaluronic acid, an anti-angiogenic barrier. It has been observed that if hyaluronic acid is catalyzed by hyaluronidase, a cascade of events results in neo-vascularization. Luteolin, on the other hand, is found to be a potent inhibitor of hyaluronidase in maintaining the barriers of neovasculature [24][25][26][27][28].

The ability to invade surrounding tissue and migrate from the primary site is an important characteristic of cancer. Varied studies have also shown that luteolin blocks the expression of MMPs, pro-inflammatory cytokines such as TNF-α (tumor necrosis factor), IL-6 (interleukin), IL-1, NF-κB, and endothelial migration, the factors involved in

tumor progression and metastasis [29][30][31]. It has been observed that luteolin acts on tumor-associated macrophage (TAM) and other associated immune cells which releases chemokines, e.g., C-X-C chemokine receptor type 4 (CXCR4, a growth factor involved in the metastasis of cancer [29][30][32].

Luteolin not only downregulates the expression of anoctamin 1, a calcium-activated chloride channel, but also inhibit its functional activity that leads to inhibition of cell proliferation, migration and invasion in prostate cancer cells [33]. Furthermore, epithelial to mesenchymal transition (EMT) plays an important role in cancer metastasis. Luteolin causes repression of EMT via targeting several associated transcription factors, markers and signaling pathways [25]. Additionally, luteolin treatment resulted in the loss of cell–cell adhesion and an increased cell invasion via increased expression of E-cadherin by inhibiting mdm2 through the AKT pathway in prostate cancer PC3 cells [34].

Studies have shown that crucial signal transduction pathways involved in cancer cell metastasis and progression are blocked by luteolin, for example, EGFR activation. Luteolin has shown to block the EGFR-signaling pathway, thereby reducing cell invasion and metastasis. Studies have demonstrated the inhibitory potential of luteolin on focal adhesion kinase (FAK) activity in cancer thereby halting cell invasion [35][36]. Luteolin has been found to be effective and exert an inhibitory effect on the proliferation, migration, and invasion of different cancers via acting on and altering the PI3K/AKT, mTOR (the mammalian target of rapamycin), ERK, and p38 signaling pathways and their associated molecules [37] (**Figure 3**). Despite the availability of many in vitro and in vivo studies, not many clinical studies have been conducted to explore the beneficial properties of luteolin [38][39]. The need of the hour is to explore dedicated model studies on the antimetastatic and antiangiogenic properties of luteolin, along with the delineation of cancer inhibitory pathways.

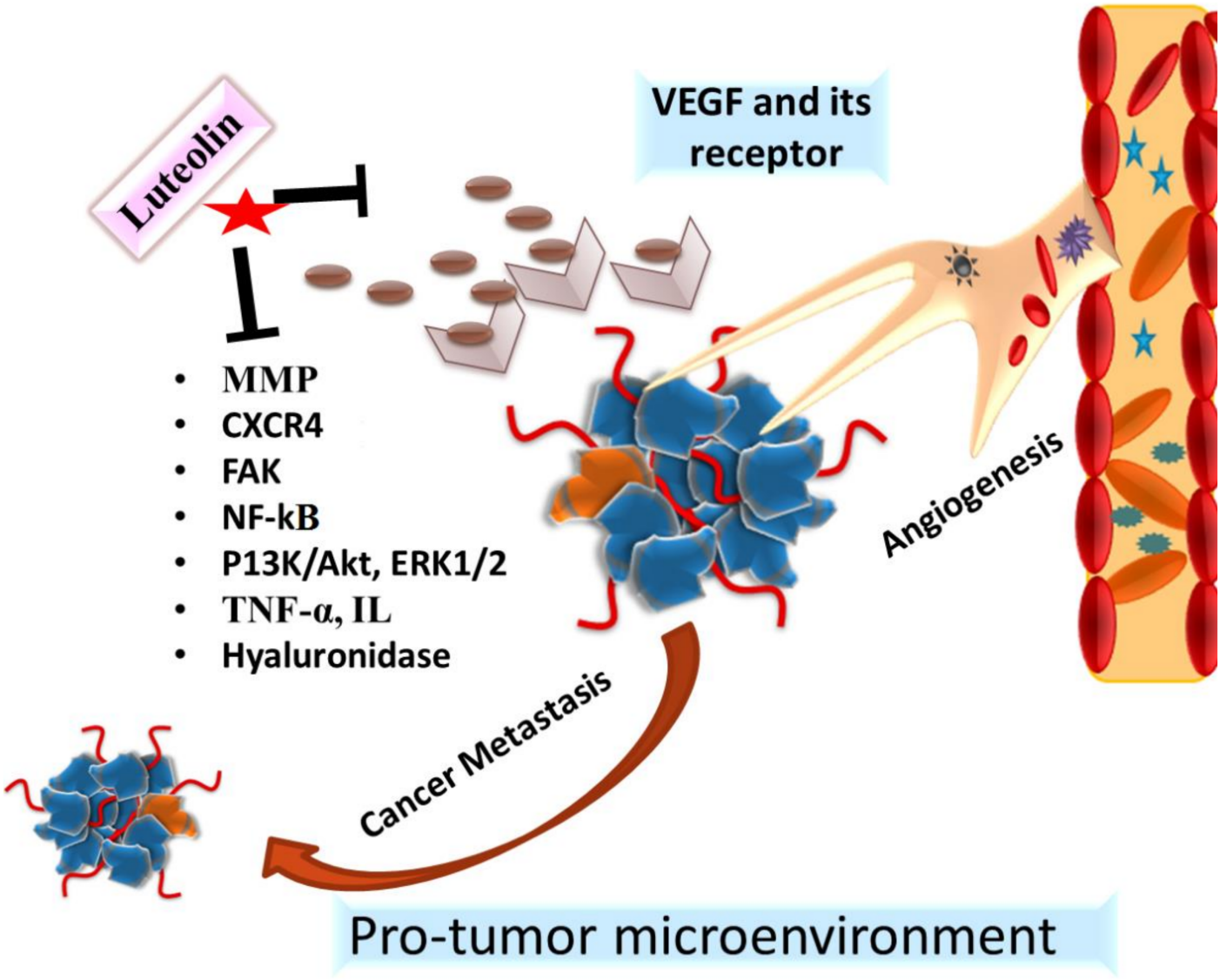

Figure 3. Molecular mechanisms of antiangiogenic and antimetastatic activities of luteolin. It regulates the expression of angiogenic (VEGF/VEGFR), and metastatic proteins (MMPs, CXCR4, FAK, PI3K/AKT, mTOR, ERK) to inhibit neo-asculature and cancer migration respectively.

4. Immunomodulatory Mechanisms of Luteolin

Inflammatory reaction occurs in response to harmful a stimulus such as injury, stress and microbial invasion. It is carried out by immune and non-immune cells in a well-defined coordinated manner in order to maintain homeostasis, through activation of signaling pathways. Numerous flavonoids have been reported for their anti-inflammatory activity and are under clinical trials to be used for drug development. Luteolin is one of the flavonoids having anti-inflammatory mechanism at micromolar concentrations and acting as a promising compound for further development [40]. Luteolin is nontoxic in nature, but not granted generally recognized as safe status by USFDA. The anti-inflammatory mechanisms of the action of luteolin relates to its ability to inhibit NO production, nitric oxide synthase (iNOS) expression, and ROS production. Furthermore, luteolin activates antioxidant enzymes, scavenge

reactive oxygen species (ROS), promotes leukotriene production, adhesion- molecule membrane-binding-inhibition, hyaluronidase and elastase activity, vascular-permeability reduction and cell membrane-fluid modulation, mast cells-stabilization inhibition, proinflammatory cytokine-expression suppression, NF-κB pathway, Akt and the mitogen-activated protein kinase (MAPK)-pathway inhibition (**Figure 4**).

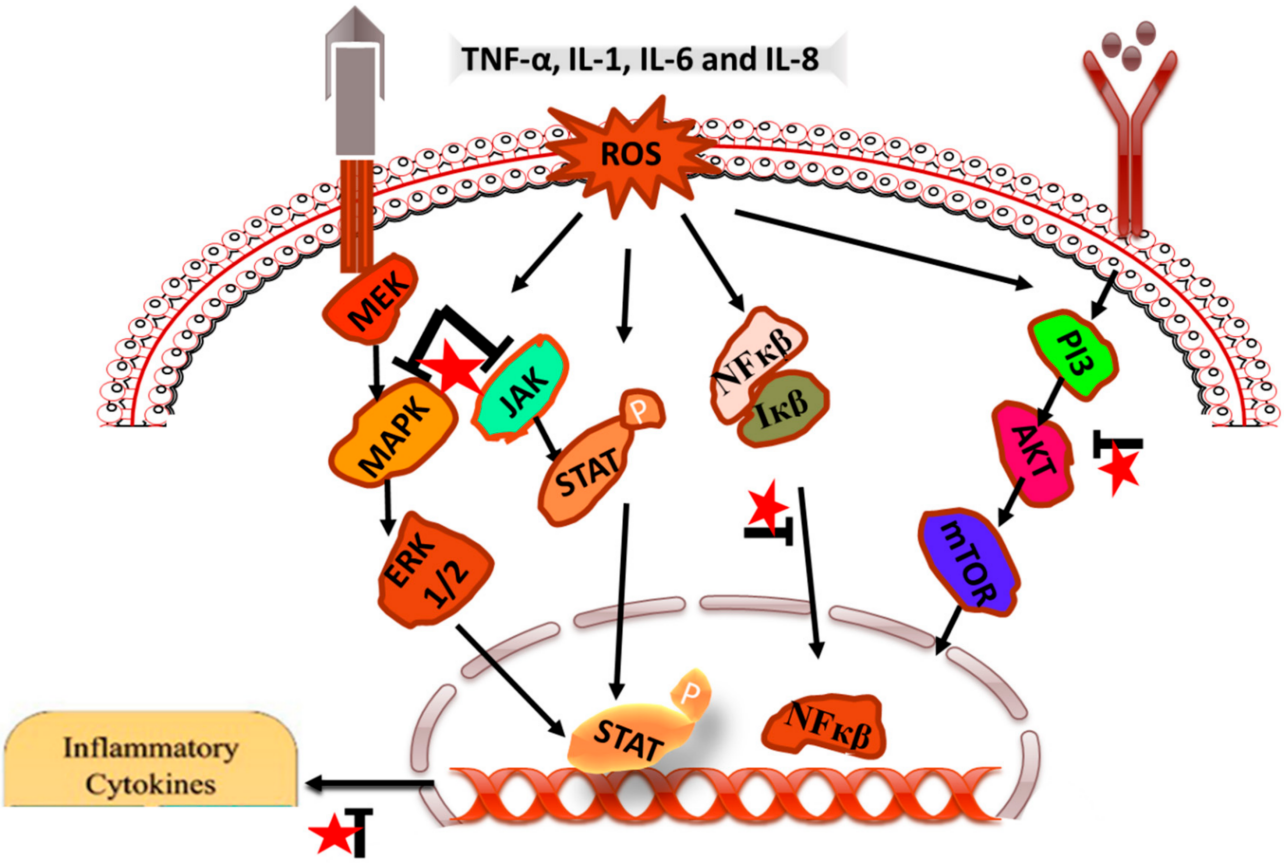

Figure 4. Different pathways inhibited and modulated by luteolin for anti-inflammatory activity. For instance, downregulation of NF-κB, Akt, MAPK, ERK, STAT, (IL)−1β, IL-6, IL-8, and TNF-α, is found to be initiated by luteolin to inhibit inflammatory microenvironment. Luteolin is represented by a red star, whereas arrow designate blockage (⊥) of the molecules.

Coordinated activation of a signaling pathway for inflammatory response is crucial to maintain the balance between pro-inflammatory and anti-inflammatory mediators [41]. By regulating the inflammatory mediators and cytokine production, luteolin has been shown to exert its anti-inflammatory effects. Acute and chronic inflammation is modulated by cytokine by acting as key modulator [42]. The level of IL-10 (anti-inflammatory) increases by the luteolin, through the interleukin (IL)−1β, IL-2, IL-6, IL-8, IL-12, IL-17, TNF-α, interferon (IFN)-β, and granulocyte-macrophage colony-stimulating factor inhibition. In addition to this, luteolin also inhibits the chemokines, along with prostaglandin and leukotriene which play a crucial role in immune cell migration [43]. Luteolin exerts its anti-inflammatory activity through the inhibition of iNOS (inducible nitric oxide synthase) function, iNOS expression, and NO production, as NO is a labile radical entity and ROS is regulated by luteolin [44]. It has been reported that luteolin acts as an activator of antioxidants and ROS scavenger [40]. Lactate dehydrogenase (LDH) production was

decreased and superoxide dismutase (SOD) activity with intracellular level of glutathione (GSH) was found to be elevated in endothelial cells after the luteolin attenuation of TNF-α-induced intracellular ROS generation [45]. Luteolin has been found to suppress the phosphatidylinositide 3-kinases (PI3K)-AKT-NF-κB-extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) pathway, which leads to a decline in ROS levels in the case of zinc-induced apoptosis of human neuroblastoma SH-SY5Y cells [46].

NF-κB transcription factor plays an important role in pro-inflammatory genes expression and its inhibition mediates the anti-inflammatory activity of luteolin. NF-κB selective stimulation leads to IκB kinase (IKK) complex-mediated IκB protein degradation via phosphorylation, which further results in nuclear translocation of NF-κB and induces the transcription of target genes. Natural compounds such as luteolin inhibit the NF-κB signaling pathway, which plays an important role in the generation of inflammation [47][48]. Mitogen-activated protein kinases (MAPK) and AP-1 signaling were also modulated by the luteolin. It was reported that in SW982 cells, luteolin affects the MAPK pathway through IL-1β-induced c-Jun N-terminal kinase (JNK) suppression and p38 kinase activation. Additionally, IL-1β-induced nuclear translocation of AP-1 inhibition was also observed [49]. ROS-scavenging activity of luteolin has also been reported through the inhibition of the MAPK pathway, which is activated by ROS [40]. It has been reported that ROS-induced activation of the MAPK pathway is attenuated by luteolin [50]. In addition to this, ERK1/2 phosphorylation is significantly enhanced by luteolin. In a ROS-activated MAPK pathway in Sprague-Dawley rats and H9c2 cells, p-p38 MAPK and p-JNK (c-Jun N-terminal kinases) levels were reported to be decreased [50]. Luteolin was also found to decrease the STAT-binding activity and STAT1 phosphorylation, which further decreases the IRF-1 (interferon regulatory factor 1) basal levels, which is a transcriptional factor regulating proinflammatory cytokine expression [51]. Therefore, it can be concluded that the luteolin exerts its anti-inflammatory activity through different mechanisms, and activity varies with the signaling pathway.

5. microRNA (miRNA) Modulations by Luteolin in Cancer

MicroRNAs (miRNAs) are endogenous, 18–22 nucleotide long noncoding RNAs that regulate gene expression post-transcriptionally by either translational repression or degradation of target mRNA [52][53]. Recent research has shown that modification of the expression of miRNAs that play significant roles in the biology of the tumor, including cell proliferation, and metastasis can reverse the cancer phenotye [54].

Research to date suggests that phytochemicals can drastically alter a number of miRNAs linked to cancer, hence preventing the onset and progression of cancer [55]. Luteolin-mediated control of miRNAs is an intriguing and growing field. It is exciting to note that a systematic and sequential accumulation of information has begun to illuminate the complex control of microRNAs by luteolin in various malignancies. Together, advanced data will allow us to create a more in-depth comprehension of how luteolin regulates signaling pathways and miRNAs on multiple levels in various malignancies. According to research involving several cancer cell lines, miR-34, a crucial tumor suppressor gene, was increased after treatment of luteolin [56][57][58][59]. Along with miR-34, studies have shown that luteolin treatment of cancer cells upregulated a number of other tumor suppressors, including miR-9, miR-7-1-3p, miR-181a, miR-5703, miR-195/215, miR-630, let-7c, miR-139, miR-221, miR- 98, miR-107, miR-422a, miR-6809-

5p, miR-224, miR-139-5p, miR- 181a, miR-124-3p miR-384, while downregulating a number of oncogenes, such as miR-340, miR-301, miR-155, miR-21 and miR-224 [60].

Furthermore, in prostate cancer cells, luteolin administration reduced cell growth and caused apoptosis by downregulating miR 301 and inducing the production of death effector domain-containing protein 2 (DEDD2), a pro-apoptotic molecule [61]. According to Zhou et al., luteolin increased the expression of miR 34 in gastric cancer cells, and miR 34 overexpression made cells more susceptible to luteolin [59]. When luteolin was given at a high dose (200 mg/kg) to a non-small cell lung cancer (NSCLC) animal model by microarray analysis, miR-34a was found to be highly expressed [57]. By increasing miR-34a-5p and targeting MDM4, luteolin also reduced carcinogenesis and triggered death in non-small cell lung cancer cells [57]. Luteolin modulates PTN via the expression of miR-384 to cause anticancer effects on colorectal cancer cells (Yao et al., 2019b). Luteolin exposes cells of pancreatic ductal adenocarcinoma, attenuates cell proliferation and enhances the anti-proliferative effect of TRAIL on cancer cells by downregulation of miR-301-3p [62]. Luteolin could significantly inhibit NOTCH signaling by regulating various miRNAs such as the upregulation of miR-121a, miR-34a, miR-224, miR-246, miR-139-5p and downregulation of miR-155 involved in tumor development and progression in breast cancer [63]. Furthermore, in the breast cancer cell line MCF-7, luteolin considerably increased miR-16 and miR-34a expression while significantly decreasing miR-21 expression and resulted in decreased cell viability, caused a large buildup of apoptotic cells in the sub-G1 and G0/G1 cell cycle phases, and triggered apoptosis by upregulating BAX, a pro-apoptotic, and downregulating Bcl-2, an anti-apoptotic protein [64]. Additionally, luteolin stimulated miRNA-203 expression and targeted Ras and Raf expression in breast cancer cells (MDA-MB-453 and MCF7). Additionally, it was discovered that breast cancer cells lacking miR-203 had increased levels of p-MEK and p-ERK, which is also found to be increased in renal cell carcinoma [65]. This indicates the role of luteolin in inhibiting cancer progression via miRNA [66]. In gastric cancer cells, luteolin administration dramatically elevated the tumor-suppressor miR-34a, miR-139, miR-107 and miR-422a levels, while considerably decreasing the oncogene miR-155, miR-340, miR-21 and miR-224 levels [58].

One of the studies showed that luteolin treatment resulted in the overexpression of miR-7-1-3p that leads to inhibition of autophagy and also apoptosis induction [67]. Additionally, Yao et al. examined the relationship between miRNAs and luteolin in glioma cells. The findings showed that luteolin treatment of glioma cells dramatically enhanced miR-124-3p expression, increasing cellular cytotoxicity. By triggering apoptosis and autophagy through the activation of MAPK in glioma, luteolin may be able to inhibit the growth of tumors. In U251 cells and LN229 cells, miR-124-3p overexpression may greatly increase the amount of cleaved caspase-3. Following luteolin administration, cleaved poly (ADP-ribose) polymerase, caspase-3 and caspase-8 levels significantly increased, and these are involved in apoptosis via an extrinsic pathway. Furthermore, p38, JNK, and ERK could all be activated and phosphorylated by luteolin [68].

The anticancer properties of luteolin may be influenced by miRNA-related processes. The downregulation of oncogenes and/or activation of tumor suppressors, which can influence proliferation, migration, invasion and apoptosis in cancer cells, may be some of these methods. These results add credence to the idea that luteolin, a substance derived from natural products, may be a treatment for cancer (**Figure 5**). To establish the practical

applicability of these findings and to investigate which miRNAs are crucial for the molecular activities of luteolin in cancer, more research, particularly clinical trials, is required.

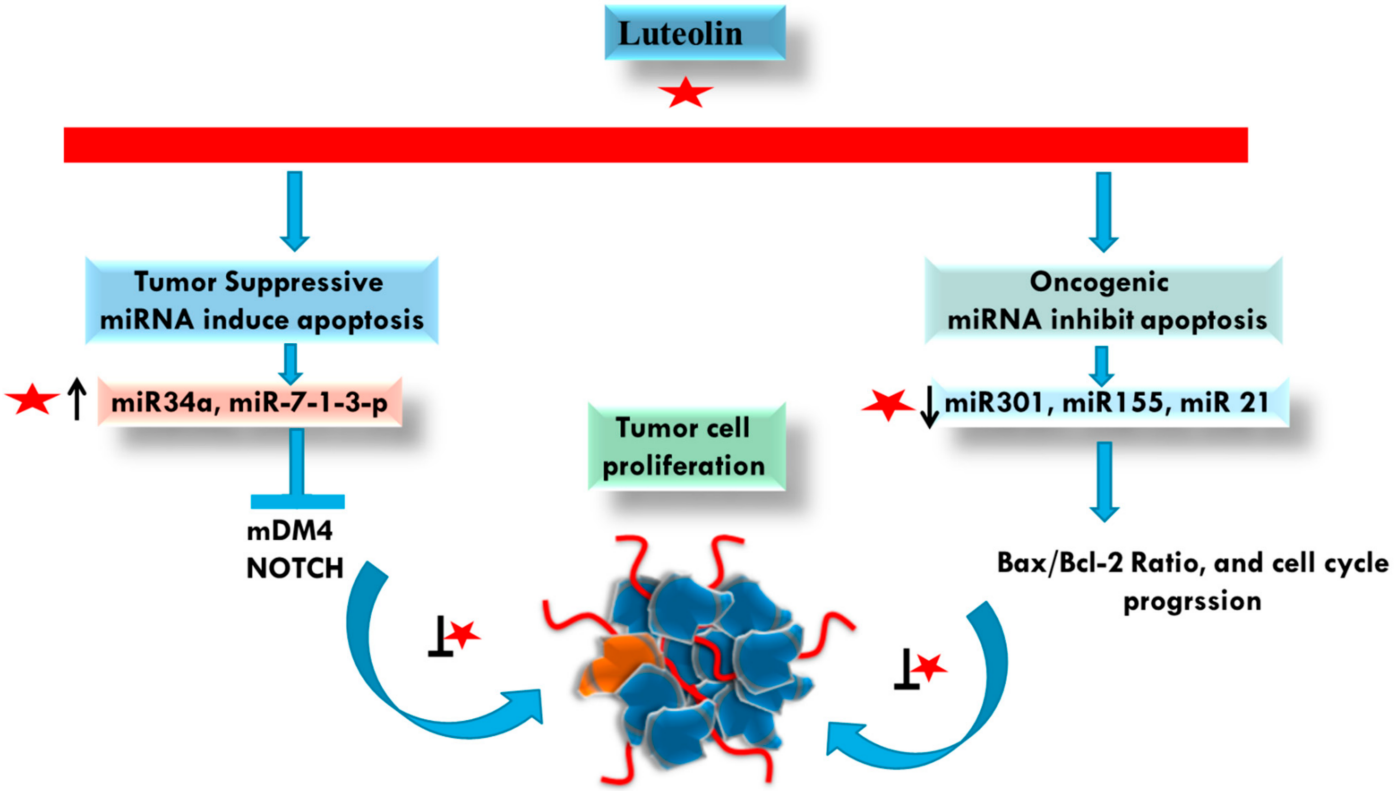

Figure 5. Regulation of cancer progression by luteolin through affecting different miRNAs. Luteolin can increase and decrease the expression of tumor suppressive (MiR34α, miR-1-3-p) and oncogenic (miR301, MiR155, miR21) miRNA, respectively. Luteolin is represented by a red star, whereas arrows designate up (↑), downregulation (↓) and blockage (⊥) of the molecules.

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