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Luteolin mediated targeting of protein network and microRNAs in different cancers: Focus on JAK-STAT, NOTCH, mTOR and TRAIL-mediated signaling pathways

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ABSTRACT

There has always been a keen interest of basic and clinical researchers to search for cancer therapeutics having minimum off-target effects and maximum anticancer activities. In accordance with this approach, there has been an explosion in the field of natural products research in the past few decades because of extra-ordinary list of natural extracts and their biologically and pharmacologically active constituents having significant medicinal properties. Apparently, luteolin-mediated anticancer effects have been investigated in different cancers but there is superfluousness of superficial data. Generalized scientific evidence encompassing apoptosis, DNA damage and anti-inflammatory effects has been reported extensively. However, how luteolin modulates deregulated oncogenic pathways in different cancers has not been comprehensively uncovered. In this review we have attempted to focus on cutting-edge research which has unveiled remarkable abilities of luteolin to modulate deregulated oncogenic pathways in different cancers. We have partitioned the review into various sections to separately discuss advancements in therapeutic targeting of oncogenic protein networks. We have provided detailed mechanistic insights related to JAK-STAT signaling and summarized how luteolin inhibited STAT proteins to inhibit STAT-driven gene network. We have also individually analyzed Wnt/β-catenin and NOTCH pathway and how luteolin effectively targeted these pathways. Mapping of the signaling landscape has revealed that NOTCH pathway can be targeted therapeutically. NOTCH pathway was noted to be targeted by luteolin. We have also conceptually analyzed how luteolin restored TRAIL-induced apoptosis in resistant cancers. Luteolin induced an increase in pro-apoptotic proteins and efficiently inhibited anti-apoptotic proteins to induce apoptosis. Luteolin mediated regulation of non-coding RNAs is an exciting and emerging facet. Excitingly, there is sequential and systematic accumulation of clues which have started to shed light on intricate regulation of microRNAs by

Abbreviations: JAKs, Janus kinases; STAT, signal transducers and activators of transcriptions; TH1, T helper type 1; CFH, complement factor H; SOCS, suppressor of cytokine signaling; MLC, monocyte lineage cell; mTAMs, metastatic TAMs; SHP-2, Src homology domain 2 containing tyrosine phosphatase-2; S100A7, S100 calcium-binding protein A7; EMT, epithelial-mesenchymal transition; NICD, NOTCH intracellular fragment; VEGF, vascular endothelial growth factor; HUVECs, human umbilical vein endothelial cells; RSK, p90 ribosomal S6 kinase; YB-1, Y-box binding protein-1; TRAIL, TNF-related apoptosis-inducing ligand; JNK, c-Jun N-terminal kinase; XIAP, X-linked inhibitor of apoptosis protein; DRPs, dynamin-related proteins; DISC, death inducing signaling complex; EGFR, epidermal growth factor receptor; MLL3, mixed-lineage leukemia 3; miRNAs, microRNAs; HK1, hexokinase 1; MDM4, mouse double minute 4 Homolog; GAK, cyclin G-associated kinase; DEDD2, death effector domain-containing protein 2; AIM2, absent in melanoma 2; dsDNA, double-stranded DNAPDTX patient-derived human tumor xenograft; UGTs, UDP-glucuronosyltransferases; OATPs, organic anion transporters; COMT, catechol-O-methyltransferase; MMP-2, metalloproteinase-2.

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luteolin in different cancers. Collectively, sophisticated information will enable us to develop a refined understanding of the multi-layered regulation of signaling pathways and non-coding RNAs by luteolin in different cancers.

1. Introduction

Advancements in functional genomics and synthetic biology have revolutionized the field of natural products research because of deeper and sharper analysis of target protein network of natural products in different diseases. We have entered an exciting era of interdisciplinary research where cross-fertilization of natural product research and molecular biology has produced wealth of scientifically verified information. High-throughput technologies have opened new horizons for harnessing of the pharmacological properties of medicinally important plants. Luteolin has started to attract attention of researchers because of its ability to therapeutically target oncogenic cell signaling pathways in different cancers.In this review our main aim is to comprehensively analyze protein regulatory networks reported to be modulated by luteolin in different cancers. We have partitioned this multi-component review into various sections. We have focused on different oncogenic deregulated pathways which played instrumental role in onset and progression of cancer. More importantly, we set spotlighton the pathways reported to be regulated by luteolin in various cancers.

2. Targeting of STAT signaling

JAKs (Janus kinases) are physically associated with intracellular tails of the receptors. Ligand binding induced conformational changes in receptors that triggered downstream signaling pathway. Active JAKs phosphorylated tyrosine residues in the cytosolically located segments of the receptor which created binding sites for the attachment of STAT (Signal transducers and activators of transcriptions). STAT proteins phosphorylated by JAK formed dimers and shuttled into the nucleus to stimulate the expression of target genes. Undeniably, the chemical diversity presented by natural products offers better opportunities of discovery of active leads targeting the JAK–STAT signaling pathway.

STAT1 signaling regulated TH1 (T helper type 1) cell-specific production of cytokine that altered both immunological functions and inflammatory responses by shifting the balance between TH1 and TH2 cells. Deficiency of STAT1 abrogated IFN responsiveness and consequentially mice succumbed to viral and bacterial infections. STAT1-driven signaling has dualistic role in cancer progression. STAT1 has been shown to suppress [1,2] and promote cancer [3].

STAT2 is also involved in tumor suppression via induction of apoptosis [4]. Additionally, sufficient scientific evidence pointed towards oncogenic role of STAT2. Knockdown of STAT2 in melanoma cells suppressed proliferation and colony forming ability of melanoma cells [5]. STAT2 played contributory role in the promotion of colorectal and skin carcinogenesis [6].

STAT4 transcriptionally upregulated CFH (complement factor H) and promoted lung cancer. SOCS (Suppressor of cytokine signaling) negatively regulated STAT4 in lung cancer cells [7].

Interleukin-35 interacted with GP130 and IL12RB2 and transduced the signals intracellularly through activation of the p-STAT1-p-STAT4 heterodimer [8]. A specific neutralizing antibody for IL12A was used for depletion of IL35 in mice. Combinatorial strategy consisting of IL35 neutralization and gemcitabine induced significant reduction of MLC (monocyte lineage cell) infiltration, formation of microvessels and shrinkage of tumor volume [8].

Metastasis was significantly reduced in mice orthotopically implanted with STAT6-knockdown 4T1 cells. Knockdown of STAT6 reduced mTAMs (metastatic TAMs)-induced metastatic colonization [9].

JAK/STAT signaling has a central role in carcinogenesis. In this section, we will be focusing on the reported evidence related to luteolin mediated inhibition of STAT proteins. STAT proteins have been shown to transcriptionally regulate myriad of genes in different cancers (shown in Fig. 1).

Type I interferons (IFN-α/β) are versatile and multifunctional cytokines which transduce the signals by binding to the cell surface IFN receptors (IFNAR1/2) [10]. cAMP-activated PKA inhibited the tyrosine phosphorylation of JAKs, STATs and IFNARs. Luteolin reduced intracellular levels of cAMP through activation of IFNAR2-bound phosphodiesterase activity. Reduction in the levels of cAMP consequentially resulted in inactivation of PKA. Inactive PKA was unable to trigger dephosphorylation of STAT1 by SHP-2 (Src homology domain 2 containing tyrosine phosphatase-2) in cancer cells [10]. Collectively, these findings suggested that cAMP-activated PKA interfered with STAT1-driven signaling by exerting inhibitory effects on STAT1 by SHP-2. However, luteolin drastically reduced the levels of cAMP and cAMP-activated PKA to potentiate STAT1-driven signaling to inhibit cancer progression.

Luteolin markedly reduced phosphorylated levels of STAT3 in PANC-1 and SW1990 cells [11]. Luteolin worked effectively with paclitaxel and potently reduced p-STAT3 levels in MDA-MB-231 cells [12]. Luteolin and paclitaxel induced regression of tumor in mice subcutaneously injected with MDA-MB-231 cells [12].

S100 calcium-binding protein A7 (S100A7) has been shown to play crucial role in activation of epithelial-mesenchymal transition (EMT) signaling and enhanced metastasizing potential of cancer cells [13]. Phosphorylated-STAT3 has been shown to transcriptionally upregulate S100A7. Luteolin reduced p-STAT3 and inhibited S100A7 expression [13].

Claudin-2 was found to be frequently overexpressed in A549 cells [14]. Phosphorylated-STAT3 was noted to transcriptionally upregulate Claudin-2 in A549 cells. However, luteolin reduced p-STAT3 levels and consequently downregulated Claudin-2 [14].

Major chaperone systems of the cell, namely heat shock proteins, use the energy of ATP binding and hydrolysis to carry out their functions. Recent advancements have allowed the interactions of clients with HSP90 and its co-chaperones to be resolved at a finer resolution. HSP90 overexpression severely impaired luteolin-mediated degradation of tyrosine (705)-phosphorylated STAT3 and luteolin also promptly reduced the quantities of some of the proteins of the HSP90 interactome [15]. Luteolin interfered with the interaction between STAT3 and HSP90 and promoted both tyrosine (705)- and serine (727)-phosphorylated STAT3 degradation by proteasome-dependent mechanism (shown in Fig. 1). Additionally, molecular modeling clearly indicated that luteolin demonstrated higher binding affinity for ATP-binding pocket of HSP90 [15].

Interestingly, luteolin-mediated disruption of HSP90 and STAT3 had also been reported in gastric cancer cells. Detailed mechanistic insights revealed that luteolin activated SHP-1, a protein tyrosine phosphatase which dephosphorylated STAT3 and reduced expression of its target genes particularly, Mcl-1, Bcl-xl and Survivin [16].

Based on these exciting findings, it can be deciphered that luteolin inhibited nuclear accumulation of STAT proteins to "switch off" the regulation of target genes. However, we still have to uncover the involvement of negative regulators of STAT activation. It needs to be seen if luteolin used (PIAS, SOCS) to inactivate STAT proteins in different cancers. In the upcoming section, we will focus on luteolin mediated targeting of NOTCH pathway.

3. Regulation of wnt/β-catenin pathway by luteolin

Deregulation of Wnt/β-catenin signaling played core role in carcinogenesis. Studies have shown that Wnt signals are transmitted through discrete routes; by a well-characterized "canonical" Wnt/β-catenin pathway, or by "non-canonical" transduction cascade.

Luteolin markedly increased the mRNA levels of FZD6 in PC-3 spheres. Additionally, luteolin enhanced the transcriptional activities of FZD6 promoter in PC-3 sphere-derived cells [17].

Luteolin dose-dependently reduced mRNA and protein levels of β-catenin in MDA-MB-231 and BT5−49 cancer cells [18]. Metastatic nodules on the surface of the lungs were observed in the mice xenografted with breast cancer cells. Luteolin markedly decreased the number of nodules in the lungs of xenografted mice. Luteolin inhibited colon carcinogenesis by reducing Azoxymethane-induced cellular proliferation through repression of GSK-3β, β-catenin and cyclin D1 [19].

4. NOTCH signaling

NOTCH signaling pathway is highly intricate and recent breakthroughs have enabled us to develop a sharper understanding of the pathway. Binding of the ligand to the NOTCH receptor resulted in the generation of a proteolytically cleaved form of NOTCH intracellular fragment (NICD) that translocated into the nucleus to transcriptionally modulate various genes (shown in Fig. 2). In this section, we will discuss available scientific evidence related to targeting of NOTCH pathway by luteolin. Luteolin exerted inhibitory effects on expression levels of NOTCH-1 and its downstream genes HES1, HEY1 and HEY2 in MDA-MB-231 and MCF-7 cells [20].

NOTCH1 overexpression induced an increase in secretion of VEGF in Hs-746 T gastric cancer cells [21]. While there was a notable reduction in VEGF secretion after treatment with luteolin. NOTCH1 overexpression partially rescued VEGF secretion in luteolin-treated cells [21]. Luteolin inhibited tubular formation of HUVECs through suppression of proliferative and migratory abilities of HUVECs. Luteolin reduced VM formation of gastric cancer cells. Besides, in a co-culture assay, interaction between gastric cancer cells and HUVECs promoted cell migration [21].

p90 ribosomal S6 kinase (RSK) played crucial role in growth and survival of Triple-negative breast cancer cells [22]. RSK phosphorylated Y-box binding protein-1 (YB-1) and transcriptionally upregulated NOTCH4 (shown in Fig. 2). siRNA-based silencing of YB-1 decreased NOTCH4 mRNA and consequently reduced the levels of N4ICD. Likewise, knockdown of RSK1/RSK2 resulted in reduction of NOTCH4 mRNA and N4ICD. Importantly, N4ICD was also found to be essential for activation of RSK/YB-1 pathway [22]. Luteolin is a promising RSK inhibitor and substantially suppresses RSK-mediated phosphorylation of YB-1 to transcriptionally downregulate NOTCH4. Therefore, these aspects revealed that positive transcriptional regulation of NOTCH4 proved to be helpful in potentiating RSK/YB-1 pathway.

Ligand binding activated NOTCH and promoted nuclear accumulation of NICD to the nucleus, where it formed a complex with β-catenin and regulated gene network [23]. Luteolin played role in disassembly of β-catenin and NICD. Intraperitoneal injection of luteolin effectively induced regression of tumors in mice xenografted with MKN28 cells. Additionally, NOTCH1, Ki-67 and β-catenin expression levels were noted to be significantly reduced in tumors from luteolin-treated xenografted mice [23].What emerges from much of the recent literature is that NOTCH signaling works synchronously with different pathways to fuel cancer development and progression. However, we still have outstanding questions related to luteolin mediated inhibition of proteolytically processed NICD and how luteolin interfered with assembly of NICD with transcriptional multi-protein machinery to control the expression of target genes in different cancers.

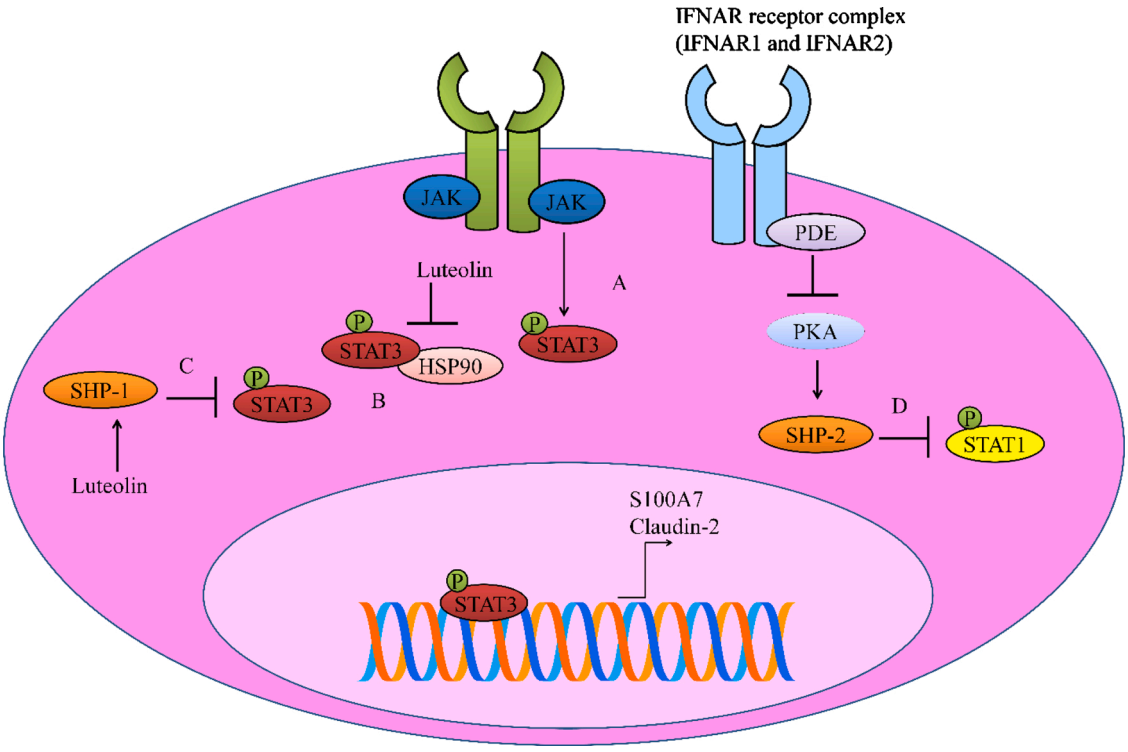

Fig. 1. Diagrammatic representation of regulation of JAK-STAT pathway by luteolin. (A) Luteolin inhibited phosphorylation of STAT3 and blocked its entry into the nucleus to trigger stimulation of genes which promoted cancer. (B) Luteolin disassembled HSP90 and STAT3 and promoted degradation of STAT3. (C) Luteolin also induced an increase in the levels of SHP-1 which dephosphorylated STAT3 and interfered with its activity. Activation of IFNAR2-bound phosphodiesterase activity sequentially reduced the levels of cAMP and inactivated PKA. Inactive PKA was unable to trigger dephosphorylation of STAT1 by SHP-2.

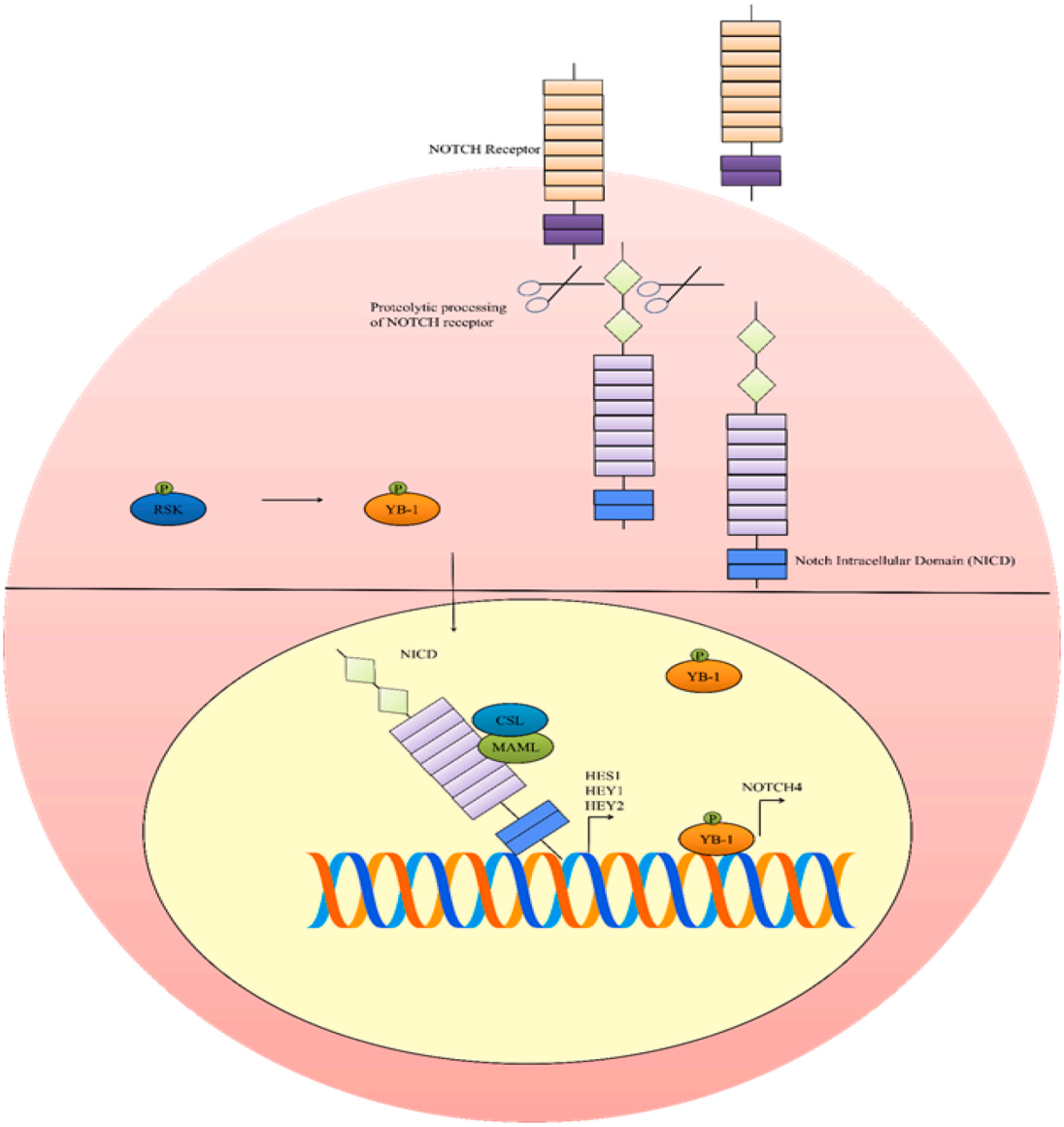

Fig. 2. Ligand binding to transmembrane NOTCH receptors resulted in generation of proteolytically cleaved form of NOTCH primarily known as NOTCH intracellular domain (NICD), which translocated to the nucleus to bind to the transcription factor CSL. Mastermind-like (MAML) coactivator proteins also interacted with the complex and promoted loading of additional proteins of transcriptional machinery for activation of target genes of NOTCH (HES1, HEY1, HEY2). p90 ribosomal S6 kinase (RSK) phosphorylated Y-box binding protein-1 (YB-1) and transcriptionally upregulated NOTCH4.

5. Targeting of TRAIL-driven pathway

TNF-related apoptosis-inducing ligand (TRAIL) has emerged as an important anticancer agent because of its excellent ability to differentially kill cancer cells while leaving normal cells intact. Initial laboratory findings were very promising, and it paved the way for in-depth analysis of TRAIL as an effective anticancer molecule. However, subsequent studies pointed towards the bottlenecks associated with harnessing of true potential of TRAIL. Molecular studies unveiled underlying mechanisms which played contributory role in development of resistance against TRAIL-based therapeutics. TRAIL transduced the signals intracellularly through death receptors. However, downregulation of death receptors significantly compromised TRAIL-driven apoptosis in cancer cells. Moreover, imbalance of stoichiometric ratios of pro- and anti-apoptotic proteins also severely disrupted apoptosis inducing ability of TRAIL.

Luteolin increased JNK and decreased AKT phosphorylation. Pretreatment with a JNK inhibitor significantly abolished JNK phosphorylation and inhibited DR5 upregulation [24]. Collectively these findings suggested that luteolin potentiated TRAIL-driven apoptosis in TRAIL-resistant Huh7 cells.

Luteolin potentiated the expression of FasL, TRAIL, and FADD in HeLa cells [25]. Luteolin also promoted release of cytochrome c and inhibited Bcl-xL and Bcl-2 expression (shown in Fig. 3). Luteolin inhibited E6/E7 oncogenes and efficiently induced apoptosis in HeLa cells [25].

Oncolytic viral vectors carrying TRAIL gene have been shown to be significantly enhance killing of cancer cells. However, this strategy was found to be ineffective against TRAIL-resistant cancers. Luteolin has been shown to improve TRAIL-mediated apoptosis in resistant colorectal cancer cells via inhibition of XIAP and activation of caspase-9 [26]. Luteolin and oncolytic viral vector carrying TRAIL gene considerably reduced tumor growth in mice xenografted with HT-29 cells [26]. Luteolin induced cleavage of the Bid and exerted repressive effects on Mcl-1 and c-FLIP (shown in Fig. 3). Luteolin also upregulated DR4 and DR5 to re-sensitize renal cell carcinoma cells to TRAIL [27].

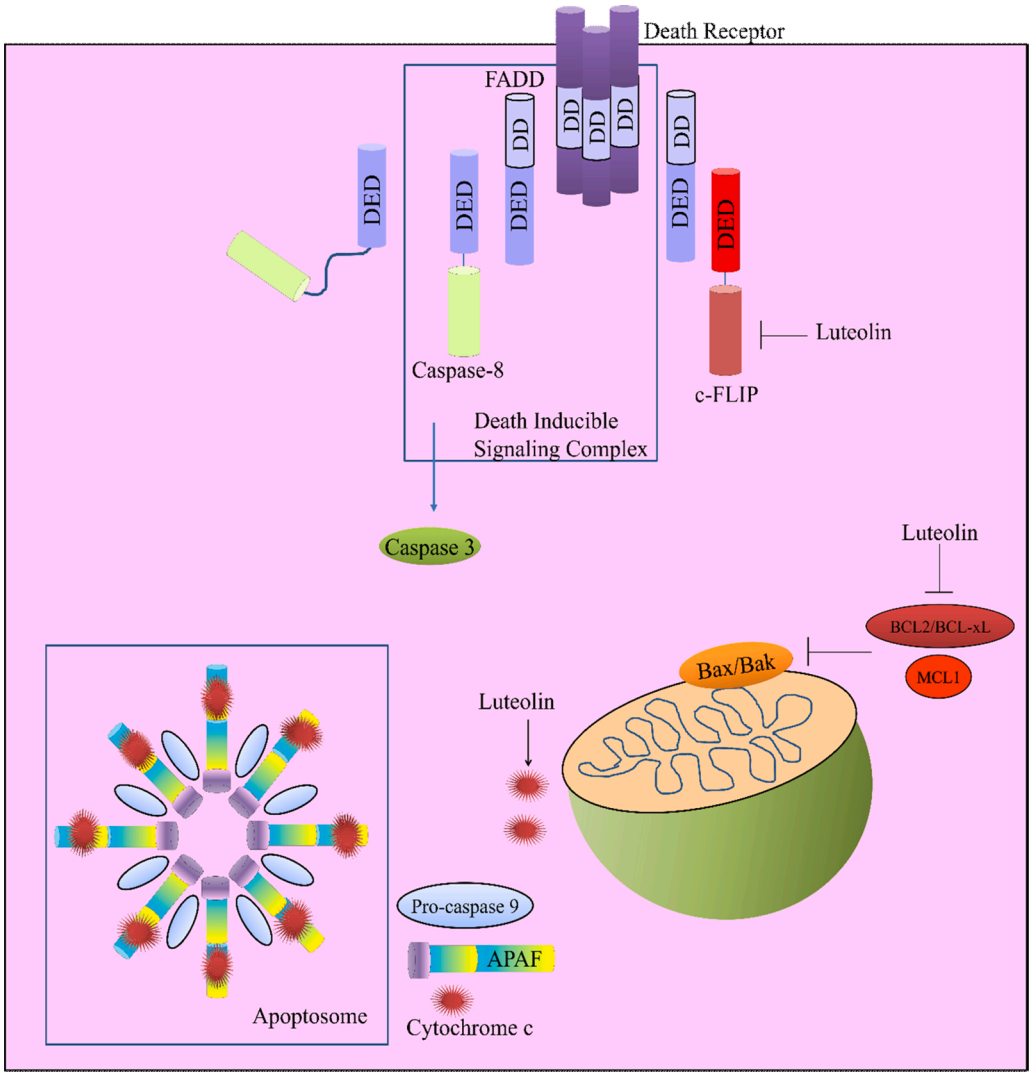

Fig. 3. TRAIL induced apoptosis by transduction of the signals intracellularly through death receptors (DR4 and DR5). Death inducing signaling complex (DISC) was formed at death receptor by assembly of FADD and pro-caspase-8 which activated caspase-8. Intrinsic apoptosis is triggered when caspase-8 mediated cleavage of Bid protein and sequentially, truncated Bid moved into the mitochondrion. Apoptosis signals triggered higher-order homo-oligomerization of BAX that formed a pore provided channel for the release of cytochrome c and SMAC/DIABLO. Bax and Bak activation and oligomerization is antagonized by anti-apoptotic members (Bcl-xL, Bcl-2 and Mcl-1). Luteolin exerted repressive effects on Mcl-1 and c-FLIP. Luteolin inhibited Bcl-xL and Bcl-2 expression.

XIAP (X-linked inhibitor of apoptosis protein) was remarkably reduced in luteolin and TRAIL-treated cells [28]. Importantly, ectopically expressed XIAP provided protection against cell death induced by luteolin and TRAIL, which revealed that luteolin sensitized TRAIL-induced apoptotic cell death through XIAP ubiquitination and proteasomal degradation [28]. TRAIL and luteolin induced regression of tumors in mice subcutaneously inoculated with A549 cells [29].

Luteolin worked effectively with TRAIL and promoted apoptosis through increasing the expression of DR5 [30]. JNK (c-Jun N-terminal kinase) played critical role in upregulating the expression of DR5. Luteolin and TRAIL considerably enhanced the levels of p-JNK. Inhibition or inactivation of JNK markedly interfered with luteolin and TRAIL-induced increase in expression levels of DR5 and translocation of DRP1 onto mitochondrial membranes [30]. Mitochondrial fission is regulated by DRPs (dynamin-related proteins) and cofactors that are required for assembly of DRP rings and spirals on the surface of mitochondria.

TRAIL-mediated signaling and TRAIL-based therapeutics have attracted remarkable spotlight. All these advancements illuminate excellent anticancer activities of TRAIL. However, resistance against TRAIL is a rapidly growing concern and we have witnessed exponential increase in the research-work about identification of natural products to restore apoptosis in resistant cancer cells. Luteolin has been shown to inhibit anti-apoptotic proteins, enhance pro-apoptotic proteins in different cancers. But it needs to be tested more comprehensively with TRAIL based therapeutics in preclinical models.

6. Interplay between apoptosis and autophagy

Mitophagy is a critical aspect of autophagy that minimizes the ability of cancer cells to undergo apoptosis. Damaged mitochondria can stimulate the apoptotic program; therefore, removal of mitochondria by autophagy can increase the threshold for the induction of apoptosis. Autophagy selectively targeted damaged mitochondria for degradation. Autophagy also interfered with apoptotic cell death by selective targeting of pro-apoptotic proteins. Moreover, autophagy selectively targeted ubiquitylated proteins. Mechanistically, ubiquitylated proteins interacted with autophagy receptors, a series of adaptors, particularly SQSTM1/p62 (sequestosome 1) that associated with both ubiquitylated substrates and LC3. Caspases activated by apoptotic pathway degraded several essential autophagy proteins to inactivate autophagic program to abolish its cytoprotective effects and to enhance cellular demise. Beclin-1 and ATG3 are critical targets and their degradation resulted in the inactivation of autophagy. Furthermore, another autophagy-related protein DCAF3/AMBRA1 (activating molecule in BECN1-regulated autophagy-1) is rapidly degraded by the combinatorial activity of calpains and caspases. To verify that caspase-mediated cleavage of AMBRA1 was necessary to induce apoptosis, AMBRA1-mutants were generated. These AMBRA1-mutants did not have cleavage site for caspase 3. Cancer cells transfected with AMBRA1-mutants were noted to be

resistant to apoptosis [31]. Intriguingly, studies have shown that different autophagy protein fragments cleaved by caspases acquire pro-apoptotic functions. 35- and 37-kDa Beclin-1 fragments generated by caspases are C-terminal Beclin-1 fragments. Caspase-induced cleavage fragments of Beclin-1 did not trigger autophagy. More importantly, treatment of isolated mitochondria with recombinant Beclin-1-C potentiated the release of cytochrome c [32]. Caspase 3-mediated cleavage of ATG4D induced pro-apoptotic activity [33].

Luteolin has been shown to activate cytoprotective autophagy in different cancers. However, use of an autophagy inhibitor potentiated the apoptosis inducing role of luteolin [34,35]. Collectively these findings suggested that combinatorial treatment with luteolin and an autophagy inhibitor can improve the cancer suppressive roles of luteolin.

7. mTOR-driven pathway

mTOR, a serine/threonine kinase is a master regulator of cell growth and metabolism. mTOR is part of two functionally and structurally distinct molecular assemblies, mTORC1 (mTOR complex 1) and mTORC2. Luteolin has been shown to inhibit mTOR-driven pathway in different cancers.

Luteolin was found to be highly effective against EGFR (Epidermal growth factor receptor) L858R/T790 M mutation and erlotinib-resistant NSCLC. Luteolin promoted degradation of the EGFR by inducing disassembly of HSP90 and EGFR. Luteolin also robustly inactivated Akt/mTOR pathway in NSCLC cells [36].

MLL3 (Mixed-lineage leukemia 3) repressed the expression of K-Ras, H-Ras, and N-Ras through monomethylation of H3K4. Data clearly suggested that Ras gene family, an activator of PI3K, was transcriptionally repressed by luteolin in breast cancer cells. Additionally, mTOR inhibitors worked effectively with luteolin and induced apoptosis in tamoxifen-resistant breast cancer cells [37].

Phosphorylated levels of p-mTOR, and p-p70S6K were noted to be considerably reduced in luteolin-treated glioblastoma cell lines [38].

In the next section, we will provide a summary of high-quality research work related to regulation of microRNAs by luteolin in various cancers.

8. Regulation of microRNAs by Luteolin

Discovery of non-coding RNAs has added new layer of intricacy to already complicated nature of signaling pathways. MicroRNAs (miRNAs) are a class of evolutionary conservedsmall non-coding RNAs. After transcription, the miRNA precursors are processed by the nuclear endoribonuclease Drosha into pre-miRNAs, which are ~70 nucleotide-long. The pre-miRNAs are then transported to the cytoplasm, where they are cleaved into 21–23 nucleotide-long mature miRNAs by the cytosolic endoribonuclease Dicer [39–41] The mature miRNAs guide Argonaute protein to cleave complementary mRNA targets or to repress their translation). Given that there are more than 1000 miRNA genes in humans, an individual miRNA can target dozens or even hundreds of different mRNAs, and an individual mRNA can be coordinately targeted by different miRNAs. miRNAs are probably involved in all physiological and pathological processes in animals [42]. miRNA biogenesis is regulated at different levels, including the transcription of pri-miRNAs, their processing by Drosha and Dicer, transportation of pre-miRNAs from nucleus to cytoplasm, and by numerous RNA modification processes [43]. microRNAs have been broadly characterized into tumor suppressor and oncogenic miRNAs. Therefore, in the following section, we will summarize how luteolin modulated different miRNAs to prevent/inhibit cancer.

9. Tumor suppressor miRNAs: cell culture and xenografted mice based studies

In this section, we will exclusively focus on the list of tumor suppressor miRNAs and their targets regulated by luteolin in different cancers. Luteolin stimulated miRNA-203 expression in MDA-MB-453 and MCF7 breast cancer cells [44]. Importantly, expression levels of Ras and Raf were enhanced in miR-203-silenced breast cancer cells. Likewise, p-MEK and p-ERK were also noted to be enhanced in miR-203-silenced breast cancer cells [44]. These findings clearly suggested that miR-203 inhibited Ras/Raf/MEK/ERK pathway and inhibited the growth of breast cancer cells.

Luteolin and silibinin have been shown to stimulate the expression of miR-7−1-3p [45]. Moreover, miR-7−1-3p overexpression and combinatorial treatment with luteolin and silibinin induced regression of tumors in mice xenografted with U87MG and T98 G glioblastoma cells. Essentially, luteolin and silibinin worked with effective synergy and efficiently induced apoptosis in wild type p53 and mutant p53 expressing glioblastoma cells [45].

Luteolin upregulated the expression of miR-124−3p in LN229 cells [46]. Overexpression of miR-124−3p significantly increased the levels of active caspase-3, while miR-124−3p inhibition drastically lowered the levels of active caspase-3 in LN229 cells [46].

Luteolin induced an increase in the expression of miR-8080 in castration-resistant prostate cancer cells 22Rv1 [47]. miR-8080 directly targeted AR-V7 in prostate cancer cells. Whereas miR-8080 inhibition increased the levels of AR-V7. Efficacy of enzalutamide was considerably enhanced when administered in combination with luteolin. Enzalutamide and luteolin induced regression of tumors in mice inoculated with 22Rv1 prostate cancer cells [47].

miR-384 is another tumor suppressor miRNA upregulated by luteolin in colorectal cancer cells [48]. miR-384 negatively regulated pleiotrophin in colorectal cancer cells. Luteolin markedly reduced tumor growth and metastatic spread in mice subcutaneously inoculated with HT-29 cells. Luteolin inhibited metastatic spread of the HT-29 cells from the spleen to the liver. Furthermore, number of metastatic nodules in the liver was significantly reduced in luteolin-treated xenografted mice [48].

miR-34a has emerged as a versatile regulator of myriad of signaling pathways. Luteolin triggered miR-34a expression in gastric cancer cells. HK1 (Hexokinase 1) is a direct target of miR-34a [49]. Luteolin inhibited growth of the tumors in mice subcutaneously inoculated with BGC-823 cells. Importantly, tumor weight and volume were smaller in mice co-treated with miR-34a agomirs and luteolin as compared to tumor weight and volume in the mice co-administrated with miR-34a antagomirs and luteolin [49]. Bcl-2, an anti-apoptotic protein was also negatively regulated by miR-34a in gastric cancer cells [50]. Luteolin induced apoptosis in gastric cancer cells through miR-34a upregulation and miR-34a-mediated targeting of Bcl-2 [50].

Luteolin also stimulated miR-34a-5p in non-small cell lung cancer cells [51]. MDM4 (Mouse double minute 4 Homolog) has been shown to be directly targeted by miRNA-34a-5p. Luteolin induced regression of the tumors in mice subcutaneously injected with H460 cancer cells [51]. miR-6809−5p overexpression significantly inhibited tumor development in mice xenografted with Huh7 cells [52]. Luteolin induced an increase in miR-6809−5p expression and promoted targeting of flotillin-1. Enforced expression of flotillin-1 potentiated cell proliferation and suppressed apoptosis in miRNA-6809−5p-expressing Huh7 cells [52].

GAK (Cyclin G-associated kinase), a versatile protein involved in clathrin-mediated membrane trafficking is frequently overexpressed in different cancers. Gefitinib and luteolin synergistically inhibited GAK-driven oncogenic signaling. Gefitinib and luteolin induced miR-630 in PC-3 cells. miR-630 is a tumor suppressor and effectively induces apoptosis in prostate cancer cells [53].

10. Oncogenic miRNA

DEDD2 (Death effector domain-containing protein 2), a pro-apoptotic molecule was directly targeted by miR-301 in prostate

cancer cells [54]. Luteolin exerted inhibitory effects on miR-301. Luteolin mediated apoptosis was impaired in miR-301-overexpressing prostate cancer cells [54].

Regulation of miRNAs by natural products has attracted tremendous appreciation. Therefore, combination of luteolin with either tumor suppressor miRNA mimics or antagomirs will further improve our understanding (Fig. 4).

11. Xenografted mice based studies

Realistic analysis of pharmacological properties can be evaluated in xenografted mice. Therefore, in this section, we have specifically focused on the knowledge obtained through preclinical testing of luteolin.

AIM2 (absent in melanoma 2), a cytosolically located innate immune receptor recognized dsDNA (double-stranded DNA). AIM2 formed a complex with ASC adaptor (apoptosis-associated speck-like protein containing a CARD) and procaspase 1 to activate AIM2 inflammasomes [55]. Studies had shown that this multi-component machinery sensed host- and pathogen-associated cytoplasmic DNA and activated caspase-1. Consequently, caspase-1 proteolytically cleaved pro-interleukin-1β (IL-1β) and pro-IL-18 to active versions. Luteolin concentration dependently lowered AIM2, procaspase-1, caspase-1, pro-IL-1β, and IL-1β in H226, A549 and H460 cells. Luteolin and taxol synergistically induced tumor regression in mice xenografted with A549 and H460 lung cancer cells. Luteolin induced significant down-regulation of AIM2, IL-1β and caspase-1 expression levels in tumor tissues of the xenografted mice [55].

PDTX (Patient-derived human tumor xenograft) models effectively mimicked the histopathological, phenotypic and genetic characteristics of the original clinical cancer [56]. PDTX models advantageously offered a robust tool for the detailed analysis of underlying mechanisms and the evaluation of clinical drugs. Luteolin induced a considerable suppression of total c-Met and phosphorylated c-Met levels in SGC7901 and MKN45 cells. Xenografts from the third generation were used for critical evaluation of luteolin tumor growth inhibitory effects in mice inoculated with c-Met-overexpressing gastric cancer cells. Excitingly, luteolin inhibited tumor growth in xenografted mice and no apparent toxicity or weight loss was observed in mice administered with luteolin [56].

Luteolin reduced levels of phosphorylated-VEGFR2. Luteolin also significantly inhibited the activation AKT, ERK, mTOR and p70S6K [57]. PC-3 prostate cancer cells were injected into the 6-weeks-old mice. After the tumors had developed, mice were injected with luteolin. Intraperitoneal administration of luteolin substantially inhibited growth of tumor volume and tumor weight [57].

MDM2 transcriptionally downregulated E-cadherin in prostate cancer cells [58]. Luteolin interfered with MDM2-mediated inhibition of E-cadherin. Importantly, MDM2 overexpression promoted invasive potential of PC3 cells. Injection of PC3 cells into the nude mice induced primary tumor formation and lung metastasis. Luteolin induced regression of tumors in xenografted mice [58].

12. Metabolism and bioavailability of luteolin

Luteolin has low oral bioavailability mainly because of complicated metabolism [59]. Regio-selective glucuronidation by UGTs (UDP-glucuronosyltransferases) and liver uptake of luteolin by OATPs (Organic anion transporters) have been comprehensively explored. These constituents also undergo glucuronidation. Luteolin-7-O-glucuronide (L-7-G) and luteolin-3′-O-glucuronide (L-3′-G) are main metabolites present in liver microsomes. OATP1B1- and OATP1B3-expressing cells demonstrated selective uptake of L-3′-G by cells. Concentration levels of L-3′-G were found to be markedly higher as compared to L-7-G in the liver of mice intravenously administered with luteolin [59].

In another study, two methylated metabolites, diosmetin and chrysoeriol, were identified in the urine of the rats intravenously administered with luteolin [60]. Data clearly indicated that methylation was mediated by COMT (catechol-O-methyltransferase). When luteolin was co-administered with a specific COMT inhibitor, formation of diosmetin and chrysoeriol was significantly reduced, whereas there was a notable rise in plasma concentration of luteolin [60].

Luteolin-7-O-glucoside suppressed p38-mediated increase in the expression of matrix metalloproteinase-2 (MMP-2) in oral cancer cells [61].

13. Nano-carriers loaded with luteolin for delivery to the target sites

Researchers are always trying to focus on naturally occurring agents having good pharmacological effect to decrease the possible side effects encountered with too much chemicals consumption. In this regard and

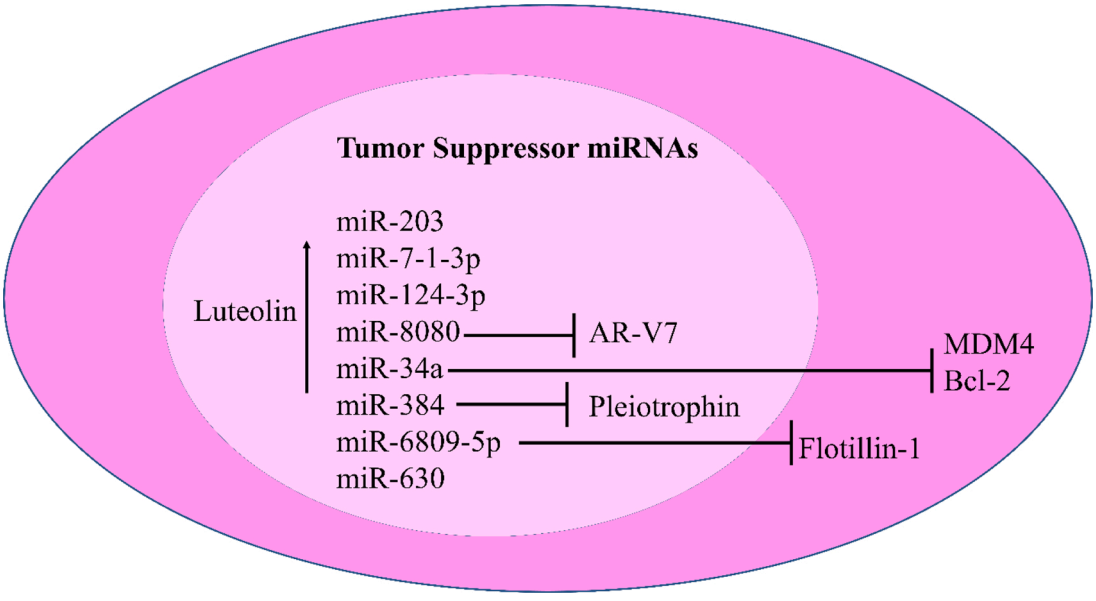

Fig. 4. Luteolin mediated upregulation of tumor suppressor microRNAs.

especially in the field of cancer management, finding a natural drug that can fight cancerous cells or prevent its proliferation is beneficial. The reason is the high safety margin of these naturally occurring substances in addition to their availability and affordable price compared to chemotherapeutic agents. Unfortunately, usually these agents had problems of solubility, bioavailability, and stability. These are considered challenges that push scientists to use recent technologies and advanced formulations to get maximum benefits of the natural agents. Nanotechnology has proved success in this concern, where the inclusion of the active agents into nanocarriers was reported in many researches to either enhance the bioavailability, increase solubility, sustain the effect or augment stability. They are enable reaching longer blood circulation of anti-cancer agents and improve their retention and permeability. One of the important characteristics as well of using nanoparticles in managing cancer is their targeting ability concentrating more of the anti-cancer agents in the target organs therefore better efficacy and lesser side effects compared to plain agents [62–64]. One of the outstanding naturally occurring plant is luteolin that proved its efficacy in managing different cancer affecting many organs and tissues; head and neck, colon, liver, skin, lung, and breast cancer [65]. The mechanism of anti-cancer effect involves triggering death of cells by initiating the apoptosis pathways, moreover, induction of cell-cycle arrest is also confirmed in carcinoma cells in lung tissues. Other organs responded to luteolin includes colon cancer cells, liver cells, esophageal, prostate, and oral squamous cancer cells [66–69]. Based on these worthwhile inhibitory and preventive results of luteolin towards many types of cancers, different formulations had been explored to improve its pharmacokinetics properties and getting out the best of it. Majumdar et al. (2014) had prepared luteolin nanoparticles as chemopreventive therapy. They described the chemoprevention by being able by using naturally occurring agents or synthetic ones to manage cancer cases either by complete prevention or slowing down its progression. Luteolin is poorly water-soluble compound, which raise a problem in formulating it as intraperitoneal or intravenous injections. Converting it to water soluble nano-luteolin was achieved via encapsulating the agent into diblock copolymer, methoxy poly (ethylene glycol) polylactic acid (PLA-PEG-OMe) to obtain nanoparticles by the emulsion-solvent evaporation method. They used cell line Tu212 for head and neck cancer and H292 cells for lung cancer to test the efficacy of the prepared formulation in vitro and xenograft mouse model of head and neck cancer for in vivo testing. Nano-luteolin had superior inhibitory effect compared to luteolin in both cell lines. Same promising results were catched from the in vivo test confirming the inhibitory effect of nano-luteolin. Luteolin-loaded phytosomes were prepared and characterized by Sabzichi et al. [70]. Thin film hydration method was adopted for the preparation of phytosomes. The obtained phytosomes loaded with luteolin had particle size 83 ± 7.9 nm and zeta potential value -29.6 ± 0.5 mV. The prepared nanocarriers had proven efficacy towards sensitizing MDA-MB 231 cells to doxorubicin in case of breast cancer. This in turn is expected to enhance the effect of chemotherapeutic agents though promoting permeability of cancerous tissues to the used agents.

Dang et al. (2014) had developed luteolin-loaded solid lipid nanoparticles (SLNs) by hot-microemulsion ultrasonic technique. They used soybean lecithin, glycerol monostearate and Tween 80 to formulate the SLNs. The average size of the obtained nanoparticles was 47.41 ± 0.51 nm. In vivo pharmacokinetic study was performed to ensure the superiority of the luteolin loaded SLNs compared to luteolin suspension and the results indicated that C_{max} was increased from 0.167 ± 0.042 to 2.591 ± 0.756 μg/mL in case of luteolin suspension and luteolin SLNs, respectively. The area under the concentration-time curve was 0.492 ± 0.149 (μg/mL h) in case of luteolin and it increased up to 1.755 ± 0.480 (μg/mL h) in luteolin loaded SLNs. The bioavailability of drug included within SLNs is 4.89 higher than pure drug. All these increments were statistically significant indicating that including luteolin in the SLNs can be used as successful mean of improving the bioavailability of the hydrophobic drug to achieve better management of cancer [71].

On the level of targeted magnetic nanoparticles for mouse fibroblast, glioblastoma (brain cancer), breast cancer, cervix cancer, and human lung cancer cell lines, Alpsoy et al. (2017) had prepared an innovative formulation. This formulation was carboxylated luteolin-functionalized superparamagnetic iron oxide nanoparticle (CL-SPION) and it was prepared by using the nanoprecipitation method. Folic acid was selected as a drug-targeting agent. Researchers used multi-steps methodology to achieve their goals consisted of synthesis of the SPION, followed by its surface modification then characterization and finally cytotoxicity evaluation of the prepared nanoparticles. Cubic nanoparticles were obtained which were proven with no toxicity on cells in concentration up to 200 μg/mL enabling their use in drug delivery [72].

14. Concluding remarks

Luteolin is gradually gaining attention and resultantly, great strides have been made in unfolding the pharmacological properties and identification of the ability of Luteolin to modulate oncogenic protein network in different cancers. However, there is a need to comprehensively analyze additional facets of regulatory role of luteolin in different cancers. TGF/SMAD pathway has not yet been explored and future studies must also uncover how luteolin modulated TGF/SMAD signaling to prevent cancer. Likewise, Sonic hedgehog (SHH)/Gli signaling has also not been explored sufficiently. These existing knowledge gaps need detailed analysis.

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