Received: 27 September 2020 | Revised: 4 January 2021 | Accepted: 25 January 2021

DOI: 10.1002/ptr.7044

REVIEW

WILEY

Anticancer activity of the plant flavonoid luteolin against preclinical models of various cancers and insights on different signalling mechanisms modulated

Shabir Ahmad Ganai[1] | Farooq Ahmad Sheikh[2] | Zahoor Ahmad Baba[1] | Mudasir Ahmad Mir[3] | Mohd Ayoob Mantoo[4] | Manzoor Ahmad Yatoo[1]

[1]Division of Basic Sciences and Humanities, FoA, SKUAST Kashmir, Sopore, Jammu & Kashmir, India

[2]Division of Genetics and Plant Breeding, FoA, SKUAST Kashmir, Sopore, Jammu & Kashmir, India

[3]Department of Microbiology, Government Medical College, Anantnag, Jammu & Kashmir, India

[4]Division of Entomology, FoA, SKUAST Kashmir, Sopore, Jammu & Kashmir, India

Correspondence
Shabir Ahmad Ganai, Division of Basic Sciences and Humanities, SKUAST-Kashmir, Sopore, Jammu & Kashmir, 193201, India.
Email: shabir.muntazir82@gmail.com

Funding information
Science and Engineering Research Board, India, Grant/Award Number: YSS/2015/001267

Various signaling mechanisms contribute significantly to the development of multiple cancers. Small molecules with the potential of influencing a wide variety of molecular targets may prove as broad-spectrum anticancer agents. Flavonoids from plant sources are strongly emerging as promising antineoplastic molecules because of their ability to hamper different cancer-driving signaling pathways. Further, these flavonoids offer an additional benefit due to their congenital antioxidant potential. This paper discusses the anticancer activity of luteolin against a number of cancers including leukemias, prostate cancer, pancreatic cancer, breast cancer, lung cancer, colorectal cancer, melanoma, liver, gastric, and brain cancer. Strong emphasis has been laid on key molecular mechanisms impacted by luteolin for exerting antineoplastic effect. Importantly, certain epigenetic targets like histone deacetylases (HDACs), DNA methylation regulator enzymes that are influenced by this befitting flavone for inducing cytotoxicity in certain preclinical cancer models, have also been made the part of this review. Additionally, the significantly improved therapeutic benefits of luteolin in combination with other therapeutics are comprehensively discussed. The current loopholes in luteolin research are also considered, which may open novel routes for further valuable studies on this promising flavone.

KEYWORDS
colorectal cancer, histone deacetylases, leukemia, liver cancer, lung cancer, luteolin, melanoma, pancreatic cancer, prostate cancer

1 | INTRODUCTION

Cancer is currently the second prime cause of death across the globe. In 2018, 9.6 million deaths were attributed to cancer and is thus a serious health concern throughout the world (Siegel, Miller, & Jemal, 2020). Flavonoids derived from plants are potentially emerging as candidate molecules for therapeutic purpose. Certain flavones like chrysin and apigenin have proved their anticancer potential in different cancer models (Ganai, Sheikh, & Baba, 2020; Yan, Qi, Li, Zhan, & Shao, 2017). Another plant flavone luteolin is gaining importance for its antineoplastic properties. Luteolin (3′,4′,5,7-tetrahydroxyflavone), belonging to flavone subgroup of flavonoids, has two benzene rings in addition to one oxygen-containing ring. The structure possesses seven double bonds and four hydroxal groups, and its biochemical and biological activities have been ascribed to the hydroxal moieties and 2–3 double bonds (Figure 1) (Chan, Galati, Pannala, Rice-Evans, & O'Brien, 2003; Imran et al., 2019).

1.1 | Luteolin absorption and its different sources

Luteolin in plants occurs in the form of glycoside, and during absorption its free form is liberated. While passing through the intestinal mucosa, some amount of luteolin is changed to glucuronides (Yasuda,

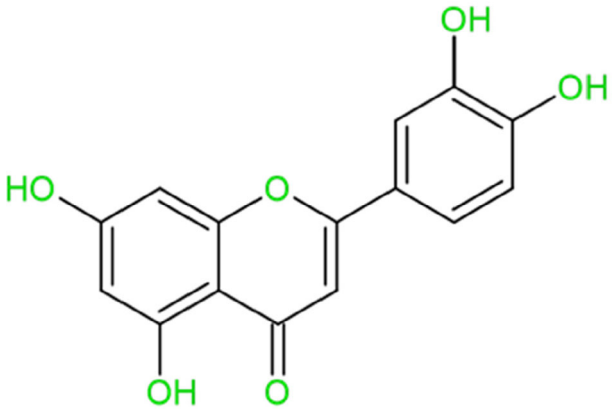

FIGURE 1 Chemical structure of the flavone luteolin. This flavone has three rings, among which one is oxygen-containing and the rest are benzene rings. Structure drawn by ACD/ChemSketch (Freeware) [Colour figure can be viewed at wileyonlinelibrary.com]

Fujita, Hosoya, Imai, & Shimoi, 2015). Luteolin is not heat-labile and its losses while cooking are comparatively low (Le Marchand, 2002; Y. Lin, Shi, Wang, & Shen, 2008). Luteolin occurs abundantly both in vegetables and fruits, including parsley, celery, leaves of onion, peppers, carrots, cabbages, skin of apples, and chrysanthemum flowers (Miean & Mohamed, 2001; Neuhouser, 2004).

Various flavonoids including luteolin have been quantitatively estimated from more than 60 tropical plants (edible ones). Among those, only some have shown the presence of luteolin. For instance, broccoli contains 74.5 mg of luteolin/kg dry weight, whereas bird chilli contains 1,035.0 mg/kg, green chilli 33.0 mg/kg, and onion leaves 391.0 mg/kg. Dried asam gelugur, limau purut leaves, local celery, white radish, carrot, french bean, belimbi leaves, and belimbi fruit were found to contain 107.5, 30.5, 80.5, 9.0, 37.5, 11.0, 464.5, and 202.0 mg/kg, respectively, of luteolin (Miean & Mohamed, 2001).

1.2 | Conventional medicinal uses of luteolin and its emerging targets

Luteolin-containing plants were used in Chinese traditional medicine for treating different ailments including inflammatory diseases, high blood pressure, and cancer (Harborne & Williams, 2000). The anticancer effect of luteolin has been attributed to its ability to induce apoptosis, its antiproliferative effect, and its ability to suppress angiogenesis and metastasis. Luteolin has the peculiar capacity to cross the blood–brain barrier and thus can be used for treating brain cancer as well (Wruck et al., 2007). Emerging findings suggest that luteolin modulates epigenetic targets such as histone deacetylases (HDACs) and DNA methyltransferases (DNMTs)/DNA demethylases. The HDAC inhibitory activity of luteolin has been demonstrated through recombinant HDAC assays. This flavone showed inhibitory activity against all members of Class I HDACs but to different extents. Among Class IIa HDACs, only HDAC5 and 9 were inhibited by luteolin. Among Class IIb members, only HDAC10 is targeted by this flavone. Maximum inhibitory effect of luteolin has been seen on HDAC2 followed by HDAC3, HDAC9, HDAC8, HDAC10, HDAC5, and HDAC10 (Godoy, Lucas, Bender, Romanick, & Ferguson, 2017). Moreover, the binding inclination of luteolin has also been evaluated against Class I HDACs through a futuristic in silico approach (Ganai, Farooq, Banday, & Altaf, 2018).

1.3 | Different mechanisms of luteolin-induced anticancer effect

Luteolin exerts anticancer effect through many mechanisms. While in certain cases the pro-oxidant activity of luteolin has been linked to cancer cell apoptosis, in others the antioxidant property of this flavone has been related to a cytotoxic effect. The antiinflammatory function of luteolin has been found to be responsible for its antineoplastic effect in some cancers. As discussed in the following paragraphs, thatluteolin inhibits certain critical cancer triggering signaling pathways such as mTOR, MAPK, and others. Emerging findings indicate that luteolin-induced anticancer effect is due to the inhibition of certain classical HDACs (epigenetic mechanism).

A pro-oxidant elicits oxidative stress by facilitating the production of reactive oxygen species (ROS) or by interfering with the antioxidant machinery of the cells. Antioxidants form the premier defense in cells against stress. As an example, luteolin by acting as a pro-oxidant sensitized lung cancer cells to tumor necrosis factor (TNF)-triggered apoptosis. Apoptosis induced by TNF is impeded by nuclear factor kappa beta (NF-κβ), which gets activated in response to the former. Luteolin treatment enhanced TNF-induced death in lung cancer cells by enhancing ROS accumulation through suppressing the activity of superoxide dismutase (SOD). This ROS elevation, in turn, suppressed the activity of NF-κβ but potentiated c-Jun N-terminal kinase (JNK) (Ju et al., 2007). Taken together, TNF-induced lung cancer cell apoptosis is enhanced synergistically by luteolin through ROS-mediated NF-κβ suppression and by the potentiation of the aforementioned kinase.

Another study attributed the luteolin-induced death of colon cancer cells to its antioxidant effect. Following luteolin treatment, the mitochondrial and intracellular ROS were alleviated through activation of two antioxidant enzymes, namely SOD and catalase. Further, the reduced-glutathione (GSH) level and GSH synthetase expression were elevated following luteolin application in these cells (Kang et al., 2017). Thus, by facilitating antioxidant activity and by triggering the famous MAPK signaling, luteolin was able to induce apoptotic death in HT-29 cells.

Evidence-based studies have proved that luteolin administration improves the condition of diethylnitrosamine-induced liver cancer in mice models. Peritoneal administration of luteolin (20 μg/kg of body weight) alternately modulated the levels of various proteins such as α-fetoprotein, SOD, AST, and ALT. Moreover, this small molecule alleviated the levels of glutathione as well as cytokines related to inflammation including interleukin-2 and interferon-γ (Zhang, Yang, & Wang, 2016). Luteolin via strong HDAC inhibition strengthened the

cisplatin-induced cytotoxicity in lung cancer cells and tumor xenografts of LNM35 cells (Attoub et al., 2011). In a colon cancer model, luteolin inhibited the activity and decreased the protein levels of DNA methyltransferases and multiple classical HDACs for invigorating the Nrf2 pathway. Apart from this, antioxidant enzyme levels were found to be raised on usingì this inhibitor (Zuo et al., 2018). It is thus clearly seen that the anticancer activity of luteolin may be partially due to the derepression of the *Nrf2* gene through an epigenetic route (Figure 2).

The gist of these evidences is that luteolin in some cases may induce cytotoxic effect by acting as pro-oxidant and in some cases as an antioxidant. In certain cases, luteolin reduces the molecular players involved in inflammation, among others. Activation of certain signaling pathways such as MAPK and Nrf2 is induced by luteolin for killing cancer cells. Luteolin influences certain epigenetic modification enzymes including classical HDACs, thus showing therapeutic effect in atypical (cancer) cells.

1.4 | Mechanism of luteolin-evoked cell cycle arrest

Inhibition in progression of the cell cycle has been noticed after treatment with luteolin in breast cancer cells. While this inhibition was associated with significant increase in p21 at protein level, the protein levels of survivin and cyclin D1 were found to be increased (L. Huang, Jin, & Lan, 2019). Programmed cell death may also be mediated

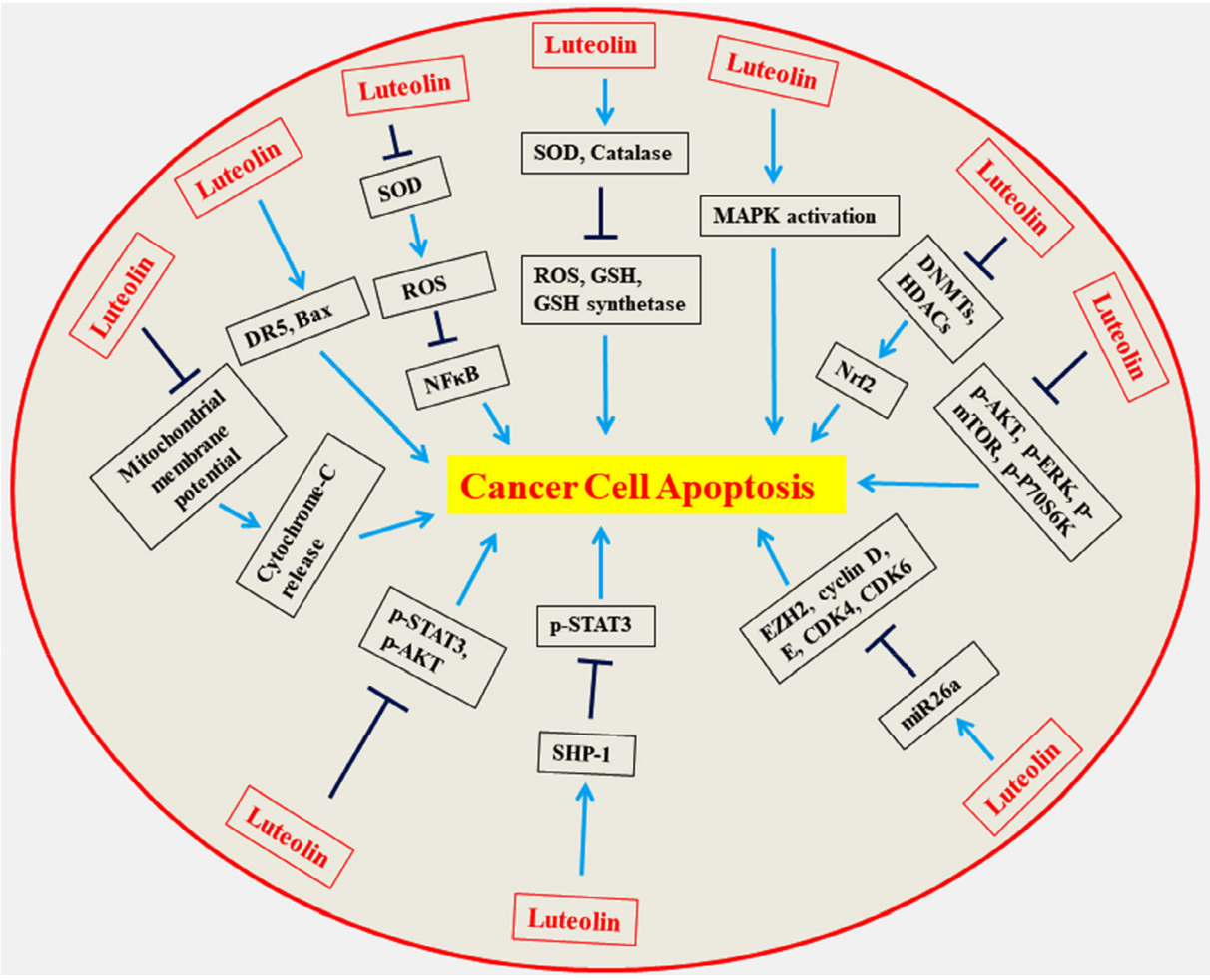

FIGURE 2 Overview of different molecular mechanisms through which luteolin exerts anticancer effect. As a pro-oxidant, luteolin enhances reactive oxygen species (ROS) production by attenuating superoxide dismutase (SOD) activity. Enhanced ROS production results in subsequent suppression of NFκB activity but energizes JNK resulting in lung cancer cell apoptosis. Luteolin as an antioxidant lowers ROS production through activation of catalase and SOD. Reduction in GSH synthetase and activation of MAPK finally induce apoptosis in colon cancer cells. Another mechanism by which luteolin induces apoptosis in colon cancer cells is via derepression of *Nrf2* by inhibiting the expression and activity of DNMTs and multiple classical HDACs (epigenetic mechanism). Luteolin in prostate cancer cells escalates the expression of miR26a by suppressing H3K7me3-specific methyltransferase (EZH2) triggering cell cycle arrest and eventual apoptosis. In gastric cancer cells, luteolin promoted dephosphorylation of STAT3 through SHP-1 (phosphatase), thereby eliciting cell death. While in certain cancers luteolin induced death by lowering p-AKT, p-mTOR, and p-ERK, decrease in mitochondrial membrane potential and enhanced cytosolic cytochrome *c* levels were responsible for provoking apoptosis [Colour figure can be viewed at wileyonlinelibrary.com]

through arrest of the cell cycle. Following treatment with luteolin, colon cancer cells manifested significantly higher percentage of cells in the G2/M phase and fewer cells in the synthetic or S phase. Proteins regulating G2/M transition, namely cyclin B and CDC2, were downregulated at the protein level in luteolin-treated LoVo cells, while CDK2 and cyclin A protein expression was upregulated dose-dependently (Z. Chen, Zhang, Gao, & Shi, 2018). Another study proved that luteolin arrested non-small-cell lung cancer cells in G2 phase by inhibiting cyclin A expression and CDC2 phosphorylation (Cai et al., 2011).

1.5 | Overview of luteolin-induced autophagy

Luteolin has shown promising activity against hepatocellular carcinoma. Viability of SMMC-7721 cells was reduced on luteolin use in a dose- and time-dependent fashion. Luteolin increased the count of apoptotic cells besides the intracellular autophagosomes. Luteolin facilitated the transformation of LC3B-I to LC3B-II and elevated Beclin 1 expression (Cao et al., 2017). Luteolin-induced apoptosis got hampered on co-treatment with chloroquine, an autophagy inhibitor.

TRAIL, a well-known cytokine, induces apoptosis in cancer cells without imparting toxicity to normal cells. The effect of luteolin in conjunction with TRAIL has been studied on TRAIL-resistant Huh7 cells. Induction of autophagic flux has been reported in human liver cancer cells on luteolin application. Chloroquine, a known specific autophagy inhibitor, attenuated this flux by supressing the expression of DR5 substantially. It has also been reported that prior incubation with SP600125 (a c-Jun N-terminal kinase inhibitor) markedly hampered the luteolin-elicited enhancement of DR5 expression. This clearly indicates that DR5 expression is facilitated by JNK activation. Moreover, it has been seen that for TRAIL sensitization, phosphorylation of Akt has a crucial role (Nazim & Park, 2019). Thus TRAIL-induced apoptosis is increased by luteolin through autophagy and JNK-dependent expression of DR5 (Figure 3).

Synergistic growth inhibition of different glioblastoma cells has been quantified on the combined use of luteolin and silibinin. This combination proved to be more effective than standard chemotherapy involving bis-chloroethylnitrosourea (BCNU) or temozolomide (TMZ). The growth inhibition on combined treatment has been found to be due to apoptosis induction and full obstruction of migration plus invasion. Autophagy induced by rapamycin in glioblastoma cells was inhibited by a combination of luteolin and silibinin through increased expression of miR-7-1-3p (tumor suppressor). Overexpression of this miR enhanced the antitumor potential of silibinin and luteolin under in vivo condition (Chakrabarti & Ray, 2016).

2 | LUTEOLIN IN ANTICANCER THERAPY

Luteolin has shown antiinflammatory and anticancer effects. Certain epidemiological studies have found that luteolin intake has a negative correlation with the risk of some cancers. The anticarcinogenic and antiinflammatory effects of this inhibitor have been attributed to its antioxidant and free-radical quenching ability. Luteolin has been reported to hamper or obstruct cancer cell development by offering

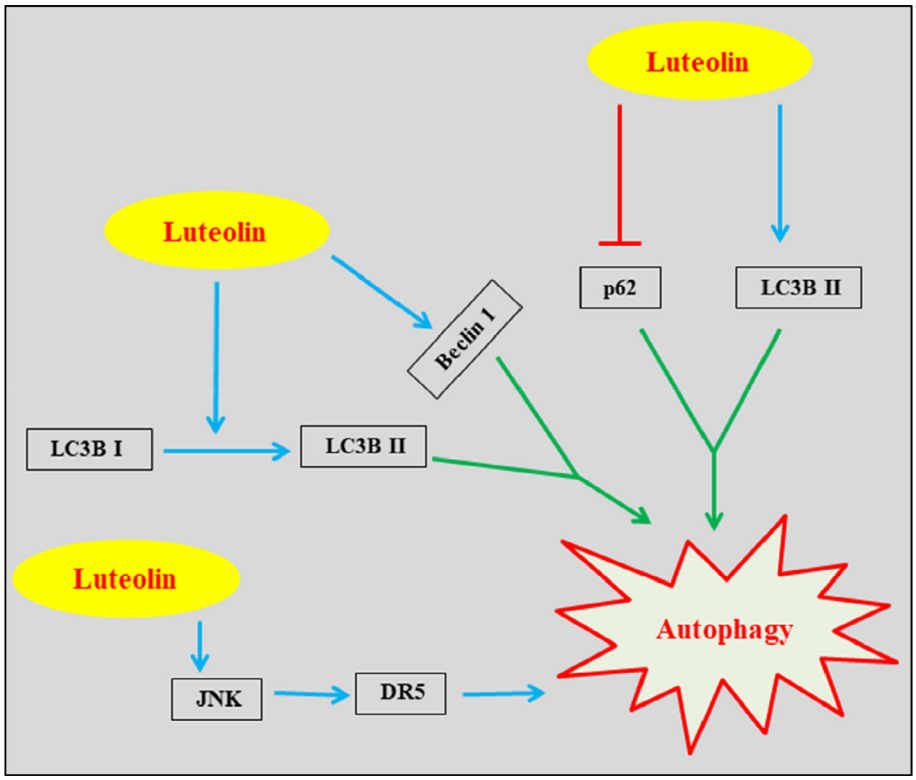

FIGURE 3 Mechanism of luteolin-induced autophagy in cancer cells. Luteolin treatment favors conversion of LC3B I to LC3B II and enhances the Beclin-1 (key player in autophagy) expression in human hepatocellular carcinoma cells. In glioma cells, luteolin elicited autophagy by decreasing the p62 protein on one hand and by increasing the LC3B II protein, on the other. Human liver cancer cells on exposure to luteolin showed induction of autophagy, which occurred as a result of the activation of JNK. This kinase then enhanced the expression of DR5, finally causing autophagy [Colour figure can be viewed at wileyonlinelibrary.com]

protection from cancer-inducing stimuli, antiproliferative effect, and induction of cell cycle arrest.

This inhibitor proved relatively effective in inhibiting cancer cell proliferation both under in vitro (IC_{50} between 3 and 50 μM) and in vivo conditions (5–10 mg/kg i.p.) (Kawaii, Tomono, Katase, Ogawa, & Yano, 1999). Luteolin has the ability to penetrate skin due to which it may serve as a remedy for skin cancer. These findings suggest the possible use of luteolin in chemoprevention. Studies involving a series of human carcinoma cells showed that luteolin has strong activity against stomach carcinoma (IC_{50}: 7.1 μg/ml) followed by cervical cancer (IC_{50}: 7.7 μg/ml), lung cancer (IC_{50}: 11.7 μg/m), and bladder cancer (IC_{50}: 19.5 μg/ml) (Cherng, Shieh, Chiang, Chang, & Chiang, 2007). The antineoplastic activity of luteolin against different cancers is discussed in the following section.

2.1 | Luteolin against leukemias

Leukamia, a cancer originating in blood-producing tissue (generally the bone marrow), results in the excessive production of abnormal white blood cells. These cells function in the body as defenders against infection. In 2019, more than 61,000 people were anticipated to suffer from leukemia, of which 22,840 were expected to die. This cancer occupied the sixth position as the common cause of cancer deaths in the United States from 2011 to 2014.

Dietary flavones are growing in acceptance as therapeutic agents against several cancers including leukemias (Chahar, Sharma, Dobhal, & Joshi, 2011; I. K. Wang, Lin-Shiau, & Lin, 1999). Luteolin showed the most potent inhibitory effects on the growth of two human leukemic cell lines (CEM-C1/CEM-C7) among the seven tested compounds including some dietary substances (Post & Varma, 1992). Experimental evidences confirm that luteolin treatment induces growth inhibitory effects in human promyelocytic leukemia cells (HL-60). These effects resulted in the induction of morphological differentiation into granulocytes (Takahashi, Kobori, Shinmoto, & Tsushida, 1998). The promising effect of luteolin against HL-60 cells has also been demonstrated. Luteolin showed 50% growth inhibitory effect after 96 h at the concentration of 15 ± 1.1 μM. This flavone isolated from *Vitex rotundifolia* (fruit) induced apoptotic cell death in these cells, as evidenced by the morphological changes and DNA fragmention. These evidences prove that luteolin has strong potential of being used for chemopreventive and chemotherapeutic purposes (Ko, Kang, Lee, Kim, & Lee, 2002).

Luteolin has been reported to induce antiproliferative effect in HL-60 cells in a concentration-dependent manner. Among the 23 flavonoids tested against these cells, luteolin occupied second rank in showing the strongest antiproliferative effect (Chang et al., 2007). Another study showed that luteolin induced apoptotic cell death in HL-60 cells in a time-dependent manner. This inhibitor alleviated the mitochondrial membrane potential and facilitated cytochrome *c* release, resulting in caspase activation and subsequent cleavage of poly-(ADP-ribose) polymerase (PARP) and another factor known as the DNA fragmentation factor (DFF-45). Besides, luteolin treatment was found to induce the cleavage of the proapoptotic proteins Bad and Bax and the antiapoptotic proteins Bcl-2 and Bcl-X_L. Thus in a nutshell, luteolin-induced apoptosis in HL-60 cells follows a mitochondrial pathway (Cheng, Huang, Lai, & Pan, 2005).

It is well established that the first step in arylamine metabolism is N-acetylation, which is carried out by the enzyme arylamine N-acetyltransferase (NAT). In intact human and mouse leukemia cells (HL-60 and L1210 respectively), luteolin showed inhibition of cytosolic NAT activity in a dose-dependent manner. Like paclitaxel, luteolin proved to be an uncompetitive inhibitor of NAT activity as determined by steady-state kinetic analysis (Y. C. Li, Hung, Yeh, Lin, & Chung, 2001). Moreover, luteolin impeded the NA–2-aminofluorene adduct formation in defined cell models like paclitaxel (Y. C. Li et al., 2001; Lu et al., 2002).

It has been reported that an oncoprotein, namely the pituitary tumor-transforming gene 1 (PTTG1) protein, regulates cell proliferation (Vlotides, Eigler, & Melmed, 2007). Elevated expression of this gene has been demonstrated in various cancer cell types including leukemia. Anticancer activity of luteolin has been studied in various human myeloid leukemia cells showing differential expressions of this gene. Luteolin in the concentration range 25–100 μM markedly reduced cell viability in THP-1, HL-60, and K562 cells without affecting the normal peripheral blood mononuclear cells, as evidenced by cell viability study. Potent luteolin-induced apoptosis was seen in cells with elevated PTTG1 protein levels (undifferentiated myeloid leukemia cells) compared to differentiated cells with lower expression of this protein, as evidenced by the flow cytometry and western blot data analysis. The effectiveness of luteolin on cell cycle regulation was impaired in leukemic cells in which *PTTG1* knockdown had been performed by shRNA. Cells with *PTTG1* knockdown on luteolin exposure showed a decline in apoptotic proteins and at the same time showed higher levels of anti-apoptotic proteins like Mcl-1, Bcl-2, and p21 hampering the apoptosis vigorously (P.-Y. Chen, Tien, et al., 2018). Thus, it is quite evident that luteolin-facilitated apoptosis of leukemic cells is modulated by the dissimilar expression profile of *PTTG1*. These findings clearly indicate that luteolin may serve as an effective therapeutic in treating leukemias associated with elevated expression of this oncoprotein.

Therapeutic effects of luteoloside (luteolin-7-glucoside) have been studied on chronic myeloid leukemia cells K562. The defined gulcoside triggered cell death through induction of apoptosis as enhanced percentage of apoptotic cell population and chromatin fragmentation has been observed in treated cells. Moreover, luteoloside escalated the expression of pro-apoptotic Bax and mitigated the expression of antiapoptotic Bcl-2 protein. The intensity of the antiproliferative effect of luteoloside in K562 cells followed a dose- and time-dependent trend (IC_{50} = 30.7 μM) with much less toxicity towards normal cells (IC_{50} = 91.8 μM). Further, treatment with luteoloside downregulated cyclin B1 and resulted in G2/M phase arrest (Shao, Liang, & Dai, 2016). The crux from this study is that luteoloside-provoked apoptosis is mediated by Bax and Bcl-2 proteins and occurs through a mitochondrial pathway (Table 1).

TABLE 1 Compendium of various molecular players modulated by luteolin or its combination in leukemias and prostate and breast cancer

Flavone/combination	Cancer type	Targets upregulated	Targets downregulated	Molecular players activated	Molecular players inhibited	Evidence
Luteolin	Leukamia			Caspases		Cheng et al., 2005
					Arylamine N-acetyltransferase	Y. C. Li et al., 2001
Luteoloside		Bax	Bcl-2, cyclin B1			Shao et al., 2016
Luteolin	Prostate cancer		Androgen receptor			Chiu & Lin, 2008
			IL-8, IL-1β, IL-6, TNF-α		AKT, ERK in addition to mTOR, P70S6K	Pratheeshkumar et al., 2012
		E-cadherin				Zhou et al., 2009
		FZD6			Wnt signaling	Han et al., 2018
			Anoctamin 1 (ANO1)		Anoctamin 1 (ANO1)	Seo et al., 2017
			miR-301			Han et al., 2016
		miR-26a	EZH2			Kanwal, Moreton, Franco, & Gupta, 2018
Luteolin	Breast cancer		hTERT			L. Huang et al., 2019
					VEGF secretion	Cook et al., 2015
		FOXO3a			PI3K/Akt signaling	C.-H. Lin et al., 2015
			ERα		PI3K-Akt signaling	L. M. Wang et al., 2012
			EGFR		MAPK	E. J. Lee, Oh, & Sung, 2012
					Notch signaling	Sun et al., 2015
			Bcl-2, AEG-1, MMP-2			Y. Jiang et al., 2013
			Vimentin, slug, β-catenin			D. Lin et al., 2017
					VEGF secretion	Cook, Liang, Besch-Williford, & Hyder, 2017
				ATR and p53 signaling		Rao, Satelli, Moridani, Jenkins, & Rao, 2012
		Death receptor 5		Caspase 8, 9, 3		Park et al., 2014
		OPCML	DNMT1		Sp1 and NFκB	Dong et al., 2018
Luteolin + 4-hydroxytamoxifen			Cyclin E2			Tu et al., 2013
Luteolin + doxorubicin					Glycolytic flux	Du et al., 2008
Luteolin + celecoxib			p-AKT			Jeon & Suh, 2013
Luteolin + paclitaxel		Caspase 8, 3, Fas				M. Y. Yang et al., 2014
Luteoloside		Bax	Bcl-2, cyclin B1			Shao et al., 2016

2.2 | Luteolin in antiprostate cancer therapy

Excluding skin cancer, prostate cancer is considered the most common cancer in the American male population. It is the second leading cause of death in American men after lung cancer (Ganai, 2017). In most prostate cancer samples, overexpression of HDAC1, 2, and 3 has been reported (Nakagawa et al., 2007). Plant-derived flavones are emerging as potent therapeutic agents against this cancer (Ganai, 2017).

It is well established that androgen receptor (AR) has potent implications in prostate cancer development and progression. Moreover, studies have shown that downregulation of this receptor attenuates prostate cancer signaling (Buchanan, Irvine, Coetzee, & Tilley, 2001). Studies have been made to explore the underlying molecular mechanism of luteolin-induced inhibition of prostate cancer cell proliferation. Luteolin exerted an antiproliferative effect and resulted in the induction of apoptosis in prostate cancer cells including LNCaP, PC-3, and DU145 cell lines. However, the growth inhibitory effect of luteolin in the last two cell lines was less pronounced, indicating their lesser susceptibility. Luteolin concurrently supressed prostate-specific antigen (PSA) levels (intracellular and secreted) besides downregulating the mRNA and protein levels of AR following a dose- and time-dependent pattern (Chiu & Lin, 2008). Luteolin disrupted the interaction between AR and its partner heat-shock protein 90, thereby promoted its proteasomal degradation. In SCID mice, this flavone reduced the LNCaP xenograft tumor growth.

Invasion, metastasis, and angiogenesis are requisites for tumor growth. Luteolin has shown antiangiogenic activity in in vitro, in vivo, and ex vivo models. In vitro studies involving rat aortic ring assay have demonstrated that this flavone could restrain the key events of the angiogenesis process. These events include microvessel sprouting and proliferation in addition to migration, invasion, and so on. Luteolin impeded the activation of matrix metalloproteinases such as MMP-2 and MMP-9. In human prostate cancer cells (PC-3), luteolin substantially alleviated the levels of proinflammatory cytokines including IL-1β, IL-6, IL-8, and TNF-α (Pratheeshkumar et al., 2012). In a prostate cancer xenograft mouse model, the volume and weight of solid tumors were markedly reduced on luteolin (10 mg/kg/day) treatment, clearly showing that luteolin restrains tumorigenesis by hampering angiogenesis. Luteolin-mediated reduction in cell viability and induction of apoptosis in prostate cancer cells was associated with the inactivation of the critical kinases AKT and ERK in addition to mTOR and P70S6K. Inactivation of these kinases was found to be due ton the downregulation of their active (phosphorylated) forms and not due to their total protein levels. Besides, the production of MMP-2 and MMP-9 was inhibited by this flavone in HUVEC cells (Pratheeshkumar et al., 2012). Speaking concisely, luteolin obstructs prostate tumor growth by restraining angiogenesis provoked by endothelial growth factor receptor 2.

E-Cadherin, which is the epithelial cell marker, functions in cell–cell adhesion. Increased cell invasion has been reported on alleviated expression of this protein (Hay & Zuk, 1995). Studies have been made for finding the crosstalk between luteolin treatment and the status of E-cadherin. They have revealed that luteolin-induced reduction in cancer cell invasion is mediated by this cell adhesion protein. Induction of E-cadherin on luteolin treatment was found to be mediated through mdm2 (E3-ubiquitin protein ligase). Overexpression of this ligase or knockdown of the adhesion protein rescued the luteolin-induced inhibition of cell migration. Luteolin-induced mdm2 inhibition was found to be mediated by AKT, as overexpression of active AKT lessened the induction of E-cadherin following luteolin treatment. Implantation of PC3 cells in nude mice resulted in spontaneous lung metastasis of these cells. This spontaneous migration was restrained by luteolin administration in these in vivo models (Zhou et al., 2009). From these findings, it is clear that luteolin may serve as potent dietary therapeutic for vanquishing invasive prostate cancers.

Luteolin has great impact on prostate cancer stemness, and efforts have been made to unravel the underlying molecular pathways. It has been demonstrated that the suppression of prostate cancer on luteolin treatment is due to the inhibition of Wnt signaling. This inhibition of Wnt signaling by luteolin treatment has been related to the upregulation of the frizzled class receptor 6 (FZD6). Thus, FZD6 acts as a tumor suppressor possessing the ability to rescind prostate cancer stemness. In vitro, luteolin has been found to hamper prostate cancer cell proliferation, self-renewal, and migration besides the expression of various markers of prostate cancer stem cells (Han et al., 2018). From these findings, it is obvious that luteolin may prove as effective therapeutic strategy in prostate cancer triggered by atypical activation of Wnt signaling.

In prostate cancer, the calcium-activated chloride channel anoctamin 1 (ANO1) is highly amplified. Decline of either ANO1 expression or its functional activity plays a substantial role in curbing cell proliferation, migration, and invasion of the defined cancer cells (Figure 4) (W. Liu, Lu, Liu, Huang, & Wang, 2012). Cell-based screening of nearly 300 bioactive natural products revealed luteolin as a novel and potent inhibitor of this calcium-activated chloride channel (Seo et al., 2017). Luteolin strongly inhibited the above-mentioned channel (IC_{50} = 9.8 μM) in a dose-dependent manner as indicated by electrophysiological studies. No alteration in intracellular calcium signaling was seen in PC-3 cells on luteolin treatment. Luteolin impeded cell proliferation and migration more effectively in prostate cancer cells expressing elevated levels of ANO1 than in ANO1-deficient prostate cancer cells. Importantly, luteolin obstructed not only the functional activity of the ANO1 channel but also potentially reduced the translational levels of ANO1 (Seo et al., 2017).

Taken together, these findings strongly suggest that the anticancer effect of luteolin in overexpressing ANO1 prostate cancer cells is due to its ability to hamper the functional activity of ANO1 besides downregulating the protein levels of the latter.

Further studies have revealed that luteolin inhibits growth and induces apoptosis both in androgen-sensitive (LNCaP) and androgen-independent (PC3) prostate cancer cell models. MicroRNA (miR) array analysis has shown that luteolin substantially lowered miR-301. High expression of this miR has implications in markedly shorter overall survival. Studies have shown that the proapoptotic gene *DEDD2* is its direct target. Luteolin-induced effect got soothed on overexpressing

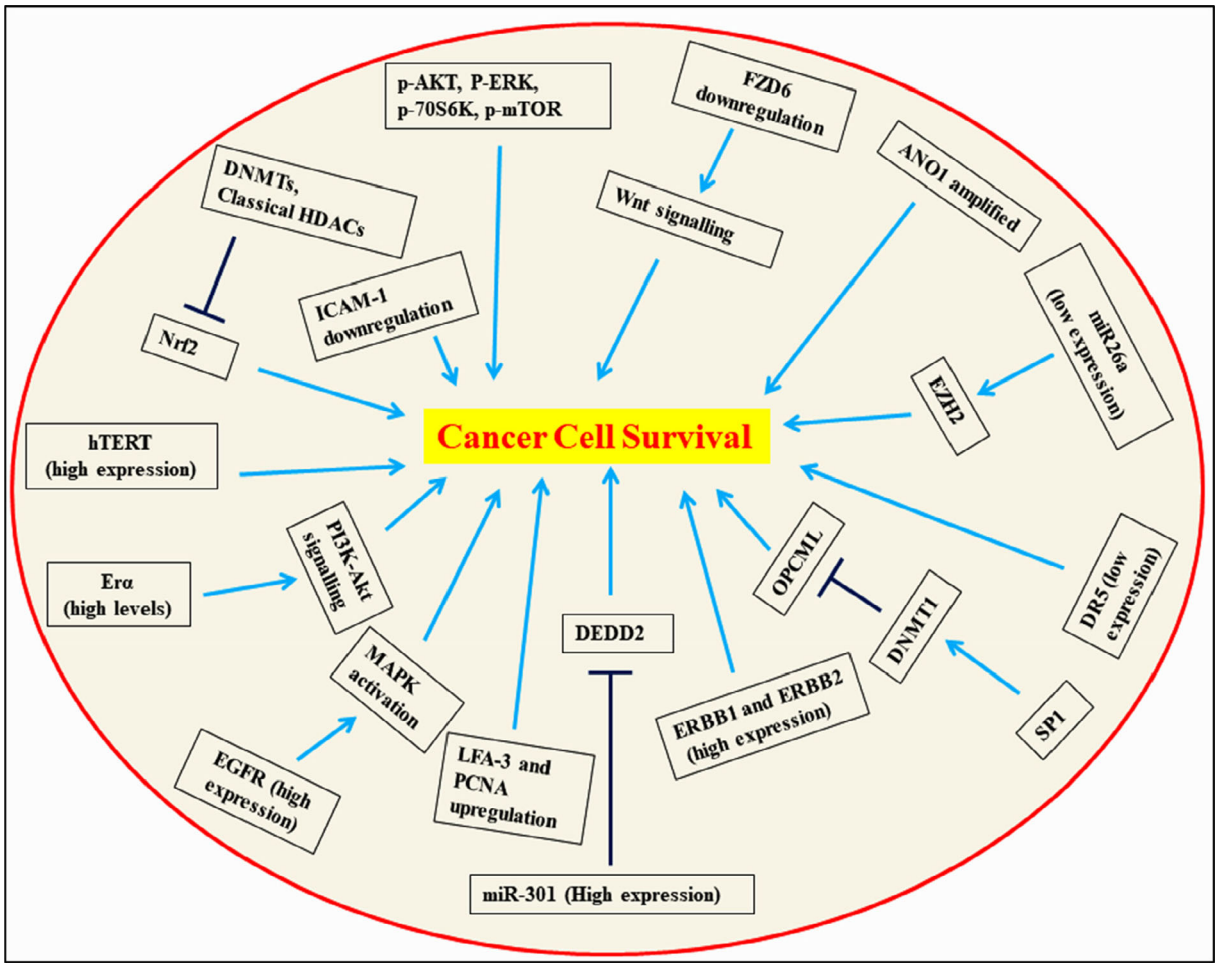

FIGURE 4 Different survival mechanisms operating in various cancer types. *FZD6*, the tumor suppressor, in downregulated condition maintains prostate cancer survival via the activation of Wnt signaling. Low expression of miR26a removes *EZH2* supression and thus facilitates survival. Sp1 activity by enhancing DNMT1 levels prevents the expression of the tumor suppressor *OPCML* in breast cancer cells, preventing their death. Higher expression of ERBB1 and ERBB2 in the defined cells also favors their survival. High expression of miR-301 in prostate cancer cells prevents the expression of *DEDD2* (proapoptotic gene) and thus prevents their apoptosis. High levels of Erα triggers PI3K-Akt signaling, preventing the death of cancer cells. Apart from this, repression of *Nrf2* by DNMTs and many zinc-dependent HDACs and high hTERT expression support the survival of atypical cells. Besides AKT, mTOR and ERK in their phosphorylated forms also make the conditions feasible for survival of abnormal/cancer cells [Colour figure can be viewed at wileyonlinelibrary.com]

miR-301, further confirming that antiproliferative effect of this inhibitor is mediated through the defined miR (Han et al., 2016). These findings suggest the possible use of luteolin as a remedy for prostate cancers overexpressing miR-301.

Du145-III cells possess strong potential for invasion because of their enhanced tendency to migrate and hyperexpress/secrete MMP 9. These cells have vasculogenic mimicry properties and show enhanced expression of various cancer stem cell markers such as Nanog, Sox2, ABCG2, and CD44. MMP-9 was found to be critical for induction of this mimicry and enhanced stemness of these cells. The effect of luteolin on the invasion capacity and stemness of Du145-III cells was studied with respect to the Janus kinase (JNK) pathway. Luteolin treatment negated the invasive potential of these cells and downregulated the expression of certain cancer stem cell markers. Moreover, the phosphorylation of JNK got reduced on treatment with luteolin (Tsai et al., 2016). Taken together, mitigation of the aggressiveness and stemness of Du145-III cells on luteolin treatment is due to modulation of the JNK pathway.

The early stages of prostate cancer can be attenuated by hormonal ablation therapy, as this therapy delays the progression rate. With time, this dependence is overcome, the aggressiveness escalates, and the cells metastasize (Bubendorf et al., 2000). Clinical trials have shown that pomegranate juice restrains prostate cancer progression (Albrecht et al., 2004). Components of this juice, namely luteolin, ellagic acid, and punicic acid, have been demonstrated to have growth inhibitory effect both on hormone-dependent and hormone-independent prostate cancer cells. Moreover, the defined combination hampered their migration and chemotaxed towards a chemokine crucial for metastasis, namely CXCL12 (L. Wang et al., 2014). The defined combination inhibited prostate cancer metastasis under in vivo conditions. This combination, when administered in a tumor-induced severe combined immunodeficiency (SCID) mouse model curbed primary

tumor growth, obstructed the CXCL12/CXCR4 axis, and thus allowed no tumor to metastasize. This combinatorial strategy proved to be antiangiogenic and prevented human endothelial cell tube formation. Angiogenic factors such as interleukin-8 and vascular endothelial growth factors were also inhibited by the triplet combination (L. Wang et al., 2014). From these results, it is seen that the combination of luteolin, ellagic acid, and punicic acid attenuates the progression and metastasis of prostate cancer cells through multiple mechanisms.

Site-specific histone methyltransferases play a crucial role in chromatin remodeling and transcriptional silencing. Enhancer of zeste homolog 2, which is the catalytic subunit of the polycomb repressive complex 2 (PRC2), performs the trimethylation of histone H3 on the lysine residue at the 27th position. H3K27me3 carried out by this catalytic subunit results in epigenetic gene silencing, providing impetus to several human cancers including prostate cancer (Y. A. Yang & Yu, 2013). MiR-26a, which is a noncoding microRNA, modulates the expression of EZH2, which is often lost during the progression of cancer (D.-N. Ma et al., 2016). Luteolin treatment upregulates this microRNA and supresses EZH2, resulting in cycle arrest and apoptosis in prostate cancer cells. Constitutive expression of EZH2 is high in prostate cancer cells (DU145 and PC-3). Luteolin (5–20 μM) markedly inhibited EZH2 and H3K27me3 in a time- and dose-dependent manner. This treatment further enhanced the expression profile of miR-26a in the above-mentioned prostate cancer cells. Overexpression of this miRNA subdued the cell-cycle regulatory molecules including cyclin D and E besides the cyclin-dependent kinases CDK4 and CDK6 (Kanwal et al., 2018).

These findings lead to the conclusion that miR-26a is lost during the continuance of prostate cancer. This mi-RNA has growth-suppressive functions. Luteolin-induced therapeutic effect in prostate cancer cell lines is mediated through the upregulation of this miRNA, which in turn represses H3K7-specific methyltransferases EZH2 in prostate cancer cells (Table 1 and Figure 2).

2.3 | Luteolin as promising flavone for tackling breast cancer

Breast cancer is considered as the second topmost cause of cancer-related deaths among women. This most commonly diagnosed cancer leads to nearly 40,500 deaths of women in United States. About 12% women, which means one in eight, develop invasive breast cancer in their lifetime. This cancer also affects males but only rarely, and the death rate in males is negligible compared to females. It has been estimated that more than 3.3 million breast cancer survivors exist currently in the United States (Waks & Winer, 2019).

Luteolin showed antiproliferative effect against the breast cancer cell line MDA-MB-231 in a dose-dependent manner. It also enhanced the rate of apoptosis in these cells. Moreover, luteolin treatment modulated several players including the nuclear factor-κB inhibitor α and its downstream target gene c-Myc, and downregulated human telomerase reverse transcriptase (*hTERT*) encoding the functional subunit of telomerase (L. Huang et al., 2019). Thus it is noticeable that luteolin-induced antiproliferative effect in breast cancer cells is mediated by hTERT, thereby suggesting it as a potential target for breast cancer therapy.

In postmenopausal women, combinatorial hormone therapy involving estrogen and progestin enhances breast cancer risk. Estrogen therapy alone is not sufficient to facilitate the risk of breast cancer. Studies on the human breast cancer cells T47-D and BT-474 have shown that progestins induce vascular endothelial growth factor (VEGF), which is a strong angiogenic. Luteolin exposure decreased the viability of breast cancer cells and attenuated progestin-induced VEGF secretion. In a nude mice model, treatment with the defined inhibitor reduced the growth of medroxyprogesterone acetate (synthetic progestin)-dependent xenograft tumors. Luteolin lowered blood vessel density and the expression of VEGF in xenograft tumor. Progestin treatment prepares the breast cancer cells to acquire stem cell-like characteristics, and this induction has been reported to get obstructed on luteolin treatment (Cook et al., 2015). Thus, in short, luteolin curbs the progestin-induced effects in human breast cancer xenografts, including the growth, angiogenesis, and stem cell properties.

The antiproliferative effect of two flavones including luteolin has been studied on three breast cancer cell lines, namely Hs578T, MDA-MB-231, and MCF-7. Luteolin showed strong antiproliferative effect in these cells in a time- and concentration-dependent manner. This effect of luteolin has been attributed to its ability to inhibit phosphoinositide 3-kinase (PI3K) and protein kinase B (PKB)/Akt, which in turn results in the induction of forkhead box O3 (FOXO3a). This is followed by the uregulation of FOXO3a target genes including the cyclin-dependent kinase inhibitors (*p21* and *p27*) (C.-H. Lin et al., 2015). These findings clearly indicate that luteolin has chemopreventive properties and may serve as a potential lead molecule and therapeutic for the effective management of breast cancer.

Insulin-like growth factor 1 (*IGF-1*) promotes the growth of many breast neoplasms, as it induces cell proliferation by activating signal transduction pathways. Luteolin strongly blocked the cell (MCF-7) proliferation induced by IGF-1. This inhibitor substantially lowered the phosphorylation level of IGF-1R and Akt without altering the phosphorylation of Erk1/2. Additional studies demonstrated that the luteolin-induced growth inhibitory effects on IGF-1-stimulated breast cancer cells are mediated through the estrogen receptor alpha (ERα), as a marked decline was seen in its expression in treated cells. ERα knockdown in breast cancer cells reduced the growth inhibitory effects of luteolin, clearly suggesting this receptor as a possible luteolin target (L. M. Wang et al., 2012). Collectively, it is noticeable that the IGF-1-mediated pathway (PI3K-Akt) is dependent on the expression of ERα. Luteolin downregulates ERα, which in turn weakens IGF-1-mediated PI3K-Akt signaling, culminating in growth inhibition.

Growth inhibitory effects of luteolin have also been studied on MDA-MB-231 estrogen receptor (ER) negative breast tumor. Cell growth inhibition has been reported upon luteolin use, as evidenced by the reduced *3H-thymidine* incorporation. Transcriptional down-regulation of EGFR and the subsequent inhibition of EGF-induced

MAPK activation were seen on treatment with luteolin. Supplementation of luteolin (0.01% or 0.05%) substantially alleviated tumor burden in MDA-MB-231-inoculated nude mice (E. J. Lee et al., 2012).

Effect of luteolin on the crosstalk between miRNAs and Notch signaling has been studied both under in vitro and in vivo conditions. This treatment markedly interfered with cancer cell (MDA-MB-231) survival besides Notch signaling-associated proteins. Inhibition of Notch signaling by luteolin occurs through miRNAs (Sun et al., 2015). Overexpression of fatty acid synthase has strong implications in various cancers. Luteolin and other flavonoids inhibited the growth of breast cancer cells by inhibiting fatty acid synthesis. This cytotoxic effect induced by flavonoids was rescued on exogenous addition of palmitate (Brusselmans, Vrolix, Verhoeven, & Swinnen, 2005). Therefore, the antineoplastic effect of luteolin and other flavonoids is due to their inhibitory activity of fatty acid synthase.

Therapeutic effect of luteolin on breast cancer angiogenesis and invasion has been studied. Treatment with a defined inhibitor showed antiproliferative effect in a dose- and time-escalated manner. Exposure of breast cancer cells MCF-7 with luteolin (60 μmol/L) for 48 h lowered the migration rate by 71.07%, AEG-1 expression by 82.34%, and MMP-2 by 85.70%. Moreover, the expression of B-cell lymphoma 2 (Bcl-2) protein was lowered in luteolin-treated cells (Y. Jiang et al., 2013). From these findings, it can be concluded that luteolin has a promising effect against breast cancer, which may be attributed to its ability to reduce Bcl-2 protein, its anti-angiogenic effect, and its ability to lower the expression of *astrocyte elevated gene-1 (AEG-1)* and MMP-2.

Experimental evidences suggest that strongly metastatic triple negative breast cancer cells on prior luteolin treatment showed attenuated migration and invasion in a dose-dependent manner. Moreover, this flavonoid substantially reversed their epithelial-to-mesenchymal transition (EMT). This was evidenced from the changed morphological characteristics, reduced epithelial markers, and elevated mesenchymal markers besides the transcription factors implicated in EMT. Luteolin significantly hampered breast cancer lung metastases in an in vivo study involving a xenograft model. Moreover, in primary tumor tissues luteolin significantly lowered the expression of vimentin and Slug, molecules promoting EMT. Importantly, luteolin treatment alleviated the expression of β-catenin both at the message and translational level both under in vitro and in vivo setups. β-Catenin overexpression rescued the luteolin-induced therapeutic effects in breast cancer cells, further confirming that signaling occurs via this protein (D. Lin et al., 2017). It is quite plausible that luteolin suppresses breast cancer metastasis by preventing EMT by decreasing β-catenin.

It is well proved that triple-negative breast cancer cells altogether lack the three receptors targeted by chemotherapeutic agents. For dealing with such types of breast cancer, one has no option but to use highly toxic and aggressive nontargeted therapies. Alternative therapeutic regimens that are safe and effective are desperately required to tackle this concern. Studies with an in vivo metastatic mouse model have proved that luteolin suppresses metastases of human breast cancer cells including MDA-MB-435 and MDA-MB-231 (4175) LM2 to lungs. Moreover, luteolin inhibited the viability and migration of these cells in vitro. In MDA-MB-231 (4175) LM2 cells, luteolin provoked apoptosis and markedly restrained the secretion of VEGF in these cells. Besides, the migration of MDA-MB-231 (4175) LM2 cells was curbed on using the antibody against VEGF receptor (KDR) and not by VEGF antibody exposure (Cook et al., 2017). Thus, luteolin shows antimetastatic effect partly by inhibiting VEGF production and VEGF receptor-mediated activity.

The effectiveness of luteolin as a chemotherapeutic has also been studied in the context of multidrug resistant (MDR) cancers. The antiproliferative effect of this flavone was investigated on two MDR cancer cell lines expressing elevated levels of P-glycoprotein and ABCG2 (drug transporters). Luteolin induced apoptosis in these resistant cells without hampering the transport activity of defined transporters. Luteolin-incited cell death was found to be mediated by the modulation of various molecular players. These include free-radical generation, DNA damage, activation of ATR and p53 signaling pathways, attenuation of NF-kB signaling, p38 pathway activation, and diminution in the levels of antiapoptotic proteins (Rao et al., 2012). Taken together, luteolin exhibits antiproliferative effect against MDR breast cancer cells without impairing the function of drug transporters.

Another study with MCF-7 breast cancer cells has revealed that luteolin induces apoptosis in these cells by modulating several molecular players. Luteolin elevated death receptor 5 (DR5) and caused caspase-mediated pathway activation. The activities of various caspases including 8, 9, and 3 increased on luteolin treatment in a dose-dependent manner. Moreover, reduction in mitochondrial membrane potential and subsequent cytochrome *c* release have been reported on flavone treatment (Park et al., 2014). Enhanced expression of Bax and inhibition in Bcl-2 expression have been demonstrated in the above-mentioned cells.

Multiple genes involved in estrogen signaling and cell cycle pathway in MCF-7 breast cancer cells have been reported to be modulated by the flavone-based HDAC inhibitor luteolin. Among the estrogen signaling pathway genes regulated by this flavone, NCOR1, TAF9, NRAS, NRIP1, GTF2H2, DDX5, POLR2A, and NCOA3 are prominent. The cell cycle genes PLK1, CCND1, CDKN1A, PCNA, and CCNA2 have been found to be regulated by luteolin. These conclusions have been drawn from the experimental evidences got from cRNA microarray and real-time PCR (qPCR) studies. From chromatin immunoprecipitation (ChIP) studies, it has become clear that luteolin modified H4 acetylation at the promoter of PLK-1 gene, suggesting that this flavone regulates gene transcription through an epigenetic mechanism involving the acetylation of histone H4 (Markaverich, Shoulars, & Rodriguez, 2011).

Opioid binding protein/cell adhesion molecule (OPCML), a new tumor suppressor gene, regulates cell adhesion and recognition and inhibits tumor growth via the activation of adenylate cyclase and relevant ion channels. Repression of this gene in breast cancer cells is directly related to its methylation status. Expression of *OPCML* was markedly enhanced by luteolin in breast cancer cells BT474 and MCF-7. This effect of luteolin has been related to its ability to lower intracellular methylation levels by alleviating the activities of Sp1 and

NF-κB. Sp1 promotes the expression of DNA methyltransferase 1 (DNMT1) and thus silences the expression of *OPCML*. Luteolin supresses the activity of transcription factor Sp1, thus reducing the intracellular levels of DNMT1, which in turn enhances the expression of OPCML. Proliferation and induction of apoptosis have also been reported in above-discussed cell lines on use of luteolin (Dong et al., 2018). This outcome indicates that luteolin lowers the expression of the epigenetic enzyme DNMT1 by restraining the activity of Sp1 and consequently elevates the expression of the tumor suppressor (OPCML).

Studies have been performed for identifying the oncogenic molecules modulated by luteolin in human breast cancer cells. Experimental findings suggest that the cyclin E2 level of tumor cells is 4.89-fold higher than in normal paired tissue samples. Even higher levels of this cyclin have been seen in tamoxifen-resistant (TAM-R) breast cancer (MCF-7) cells. Luteolin (5 μM) reduced the cyclin E2 protein level either alone or in combination with 4-hydroxytamoxifen (100 nM). Combinatorial therapeutic strategy involving 4-hydroxytamoxifen with luteolin showed synergistic therapeutic effect against TAM-R cells. It has been found that luteolin sensitizes these resistant cell lines to 4-hydroxytamoxifen (Tu et al., 2013). These facts reflect that luteolin significantly lowers the cyclin E2 level and can be used as a potent chemosensitizer for circumventing the taxomifen resistance in breast cancer subjects.

Luteolin has been found to sensitize doxorubicin-resistant breast cancer cells under the conditions of hypoxia. Luteolin enhanced the efficacy of doxorubicin and mitigated its toxicity in 4T1- and MCF-7-bearing mice. This flavone hampered glycolytic flux without altering the uptake of glucose. Importantly, luteolin did not lower the intratumor levels of doxorubicin. Besides, the activity of SOD and catalase was reduced in tumor while it was elevated in serum under an in vivo setup (Du et al., 2008). These findings suggest that luteolin has also the potential to act as an adjuvant and thus can enhance the efficacy of anticancer drugs and concurrently may soothe the toxicity.

It has become clear now that breast cancer is heterogenous and is hormone-provoked. The combinatorial therapy involving luteolin with celecoxib has been studied extensively in the breast cancer cells MCF-7 and MDA-MB-231. This therapeutic regime showed synergistic effect and markedly reduced cell viability compared to singlet therapy involving these agents. This effect was found to follow the concentration and temporal trend. The combined treatment alleviated the phosphorylation status of Akt (Jeon & Suh, 2013).

In certain breast cancer cells, the synergistic effect of the combined therapy has been ascribed to the inactivation of Akt and attenuation of ERK signaling (MCF-7 and MCF7/HER18). Activation of ERK signaling and inactivation of Akt has been provided as a possible mechanism of the synergistic effect in other breast cancer cells including MDA-MB-231 and SkBr3 (Jeon, Ahn, Chung, Choi, & Suh, 2015). Thus, using luteolin in doublet therapy offers a novel therapeutic avenue for the effective management of breast cancer. Moreover, the doublet therapy induces the synergistic effect by partly following differential molecular mechanisms.

Low-dose combination mitigates toxicity and offers enhanced therapeutic benefits. Luteolin, a flavone-based HDAC inhibitor, has been studied in conjunction with paclitaxel against MDA-MB-231 breast cancer cells. Co-administration of these inhibitors showed improved apoptotic effect compared to individual molecules involving either luteolin or paclitaxel. Combinatorial therapy enhanced the expression of caspase 8 and caspase 3, besides elevating Fas expression. This overexpression of Fas has been related to the obstruction of the signal transducer and activator of transcription 3 (STAT3) (M. Y. Yang et al., 2014). In an orthotopic tumor model, co-treatment with these inhibitors decreased tumor size and weight, further confirming the promising effect of the combinatorial therapeutic approach.

Emerging evidences suggest that all combinations involving luteolin as one of the agents do not show additive or synergistic therapeutic benefit. Luteolin combined with doxorubicin hampered the cytotoxic effect of the latter on breast cancer cells MCF-7. Doxorubucin triggers the production of ROS in these cells and alleviates the antiapoptotic Bcl-2 protein. Combination with luteolin mitigated the ROS production and concurrently elevated the Bcl-2 protein, culminating in a cytoprotective effect (Sato et al., 2015). This means that proper selection of drug combination is crucial for the desired therapeutic effect.

Only few years ago, a study was performed involving lapatinib (dual tyrosine kinase inhibitor) and luteolin in combination against the breast cancer cells BT474. Although these inhibitors singly showed the antiproliferative effect against the above-mentioned cells, their combination showed a more than additive effect (synergistic effect). The combinatorial therapy alleviated the expression of *ERBB1* and *ERBB2* both at the message and protein level. Moreover, this combination lowered the phosphorylation status of AKT and ERK1/2 (Zhang, Yang, Huang, Liu, & Zhang, 2017).

Luteolin at concentrations of 25–200 μM reduced the viability of various cancer cell lines including MCF7/6 and MDA-MB231-1833. The invasive potential of these cells was soothed on using sublethal doses of this flavone-based HDAC inhibitor (Attoub et al., 2010). The crux of this study was that synergistic therapeutic effect of the defined drug combination could be attributed to apoptosis induced by the shutdown of AKT and ERK signaling. Recently, the effect of luteolin was studied in breast cancer cells having tamoxifen resistance but estrogen receptor positive status. Luteolin not only restrained proliferation but also induced apoptosis in these cells. G2/M arrest and reduced mitochondrial membrane potential were observed following luteolin exposure. Further, PI3K/AKT/mTOR signaling was hampered by luteolin, and synergistic escalation in apoptosis was reported on using luteolin in combination with mTOR, AKT, or PI3K inhibitors. Luteolin by way of inducing MLL (mixed-lineage leukemia)-3 transcriptionally suppressed the Ras gene family (H. T. Wu et al., 2020). Luteolin-induced repression of Ras genes was mediated through an epigenetic mechanism. Luteolin enhanced the histone H3 lysine 4 monomethylation (H3K4me), eventually silencing this gene (Table 1 and Figure 2).

2.4 | Luteolin as promising therapeutic agent against pancreatic cancer

Pancreatic cancer falls under the most aggressive human cancers and is expected to outclass breast cancer to become the third premier cause of cancer-related deaths in America. Conventional therapeutic approaches have improved the relative 5-year survival rate by only 8%, emphasizing the serious need of futuristic therapies to back-pedal the poor prognosis of this neoplasm (Ganai, Rashid, Abdullah, & Altaf, 2017).

The plant-derived flavone and HDAC inhibitor luteolin has shown propitious effect against prostate cancer. Expression of prosurvival proteins such as BCL-2 has considerable implications in malignancy, progression, and cancer chemoresiatance. Thus, therapeutic agents that can downmodulate or restrain the activity of this protein may prove fruitful in circumventing pancreatic cancer. Amplification of this prosurvival protein in pancreatic cancer cells has been reported to have a role in survival of these cells, which in turn leads to poor patient outcome. Experimental evidences suggest that luteolin directly binds to BCL-2 and displaces the partner protein BAX from the hydrophobic cleft of the former. These processes enhance mitochondrial membrane permeability, driving the pancreatic cells to death. Luteolin noticeably reduced tumor growth in a pancreatic cancer cell xenograft model (Z. Li, Zhang, Chen, & Li, 2018).

This inhibitor has been found to modulate the epidermal growth factor receptor (EGFR) tyrosine kinase activity in MiaPaCa-2 pancreatic cancer cells. Treatment of these cells with 20 μM luteolin altered protein tyrosine kinase activities including that of EGFR. This treatment lowered the phosphorylation status of EGFR and enolase. Induction of apoptosis was seen only by prolonging the treatment beyond 24 h (E. J. Lee et al., 2012).

Thus luteolin-induced death in pancreatic cancer cells is mediated by the modulation of intrinsic EGFR kinase. Emerging evidences suggest that fatty acid synthase has great impact on the proliferation of cancer cells, and targetting this enzyme has been reported to attenuate proliferation in these cells. Luteolin alleviated cellular proliferation, besides fatty and nucleic acid biosynthesis. Moreover, this flavone controls energy production and its effect has been found to be equal to that of the known inhibitor C75 (Harris et al., 2012). This suggests fatty acid synthase pathway as a promising target for preventing cancer.

Luteolin, which potentially inhibits this pathway, may serve as a propitious therapeutic against monotonous pancreatic cancer. The combinatorial therapeutic approach involving luteolin with gemcitabine has also been evaluated against pancreatic tumors under an in vivo setup. This combination was tested in an orthotopic mouse model for a duration of 6 weeks. Pancreatic tumor growth was evaluated by measuring its mass. Induction of apoptotic cell death in pancreatic tumor cells was seen after the combined treatment. This cell death was attributed to the inhibition of various signaling pathways including K-ras, GSK-3β, and NF-κB due to which Bcl-2 levels declined, triggering the relaease of cytochrome *c* and subsequent activation of caspase 3 (Johnson, Dia, Wallig, & Gonzalez de Mejia, 2015).

A study regarding the crosstalk of luteolin treatment and inhibition of angiogenesis level was performed on different pancreatic cancer cell models (PANC-1, CoLo-357, and BxPC-3). Luteolin treatment resulted in apoptotic signaling by reducing the levels of Bcl-2, enhancing caspase 3 activation, and consequently PARP cleavage. Chorioallantoic membrane (CAM) assay showed that this flavone restrained proliferation and vessel growth under in vivo conditions. Luteolin downregulated the concentration of VEGF in the spent (conditioned) medium from human pancreatic cells. Previous treatment of HUVEC cells with this dietary flavone reduced capillary-like structure formation. Mitigation in the levels of VEGF in the conditioned medium was attributed to the downregulation of the message levels of VEGF (Cai et al., 2012).

Therapeutic effect of luteolin and the underlying molecular mechanism were studied in mice models with severe acute pancreatitis (SAP). Luteolin-treated SAP mice showed marked intensification of heme oxygenase 1 (HO-1) expression in the pancreas as well as in serum. Moreover, this plant-derived inhibitor markedly enhanced the levels of IL-10 (Xiong et al., 2017). Taken together, these findings suggest that luteolin secures mice from SAP by stimulating HO-1-mediated antioxidant and antiinflammatory activities.

Extensive studies regarding the effect of luteolin on the epithelial-to-mesenchymal transition (EMT) and trespassing of pancreatic cancer cells have been performed. The signaling mechanism involved has also been delineated in this regard. Luteolin mitigated invasiveness of pancreatic cells by restraining STAT3 activity. It has been reported that IL-6 triggers STAT3 activity, resulting in the elevation of EMT characters and MMP secretion. IL-6-induced STAT3 activity and thesubsequent triggering of EMT and MMP secretion was found to get hampered by luteolin (X. Huang et al., 2015).

Evidence-based findings suggest that glycogen synthase kinase-3β (GSK-3β) activity has implications in pancreatic cancer cell proliferation and survival. Among the various tested compounds isolated from citrus fruit, luteolin showed the highest inhibitory activity (IC_{50} = 1.5 μM) against this kinase (Figure 2) (Johnson, Rupasinghe, Stefani, Schuler, & Gonzalez de Mejia, 2011). These findings suggest that luteolin may serve as a promising therapeutic against pancreatic tumors (Table 2).

2.5 | Luteolin in anticolorectal cancer therapy

Among the cancers affecting both sexes (men and women), colorectal cancer (CRC) occupies second rank as the major cause of cancer-related deaths in America. In both men and women, this cancer is regarded as the third most prevalent cancer (Bhandari, Woodhouse, & Gupta, 2017). Transformation of normal colonic epithelium into adenocarcinomas occurs as a result of collection of genetic and epigenetic alterations. Aberrant DNA methylation has strong implications in the progression and metastasis of this cancer (Coppede, 2014).

Epigenetic modifications have now been understood to play a considerable role in the pathophysiology of CRC. Luteolin has the potential to modulate several signaling mechanisms having

TABLE 2 Summary of different molecular targets influenced by luteolin intervention in pancreatic, colorectal, and lung cancer and melanoma preclinical models

Small molecule/ combination	Cancer name	Molecular targets upregulated	Downregulated molecular targets	Proteins/signaling activated	Proteins/signaling inhibited	References
Luteolin	Pancreatic cancer		p- EGFR			E. J. Lee et al., 2012
Luteolin + gemcitabine			Bcl-2	Caspase 3	K-ras, GSK-3β and NF-κB signaling	Johnson et al., 2015
Luteolin			Bcl-2, VEGF	Caspase 3		Cai et al., 2012
		Heme oxygenase 1				Xiong et al., 2017
					STAT3 activity	X. Huang et al., 2015
Luteolin	Colorectal cancer				GSK-3β activity	Johnson et al., 2011
			DNMT3A, DNMT3B, DNMT1, HDAC1, HDAC2, HDAC3, HDAC6, HDAC7		DNMT and HDAC activity, Nrf2 pathway	Zuo et al., 2018
		Nrf2				Kang et al., 2019
					HDAC8	Mira & Shimizu, 2015
		Bax, GSH synthetase	Bcl-2	Caspase-9 and casase-3, MAPK		Kang et al., 2017
		miR-384				Y. Yao, Rao, Zheng, & Wang, 2019
			CREB1			Y. Liu et al., 2017
Luteolin	Lung cancer				PI3K/Akt/mTOR s	Hong et al., 2014
		miR-34a-5p				Z.-Q. Jiang et al., 2018
			AIM2			Yu et al., 2019
Luteolin + IR			BCl-2	Caspase 3, 8, 9		Cho et al., 2015
Myo-inositol and luteolin			p-PDK1, p-Akt			Y. Wang, Zhang, Chen, Hong, & Wu, 2018
Luteolin			TAM RTKs			Y. J. Lee et al., 2017
		p-MEK, p-ERK		AKT activation		Meng, Chai, Li, Zhu, & Huang, 2016
			Sirt1			L. Ma et al., 2015
Luteolin	Melanoma	p- AKT1, p- PI3K	MMP-2, MMP-9, TIMP-1 and TIMP-2			X. Yao, Jiang, Yu, & Yan, 2019
		E-cadherin	N-cadherin and vimentin, p-Akt, HIF-1α			C. Li, Wang, Shen, Wei, & Li, 2019
		ATF, CHOP				Kim et al., 2016
		E-cadherin			Vimentin, β3 integrin	Ruan et al., 2012

implications in this cancer. Mounting evidences suggest that luteolin attenuates CRC carcinogenesis by triggering the Nrf2/antioxidant response element (ARE) pathway. In HCT116 and HT29 cells, luteolin hampered proliferation and cellular transformation in a dose-dependent manner. Importantly, luteolin modulated epigenetic players in these cells for bringing its therapeutic effect. Luteolin (15 and 30 μM) downregulated the protein levels of DNA methyltransferases DNMT1, DNMT3A, and DNMT3B. Moreover, luteolin also downregulated the expression of certain class I HDACs (HDAC1, HDAC2, and HDAC3) and class II HDACs (HDAC6 and HDAC7) at the protein level. Luteolin also reduced the activities of DNMT and HDAC enzymes. It has been found that luteolin at low dose (15 μM) obstructs HDAC activity effectively, as compared to higher does (30 μM) (Zuo et al., 2018). Thus it is noticeable that luteolin treatment activates the Nrf2 pathway by downregulating the expression and inhibiting the activity of DNMTs and certain classical HDACs.

Another study has further confirmed these findings. Luteolin has been found to induce *Nrf2* by facilitating DNA demethylation at its promoter site in human colon cancer cells. Moreover, this treatment has been found to modulate the interaction of Nrf2 with the tumor suppressor p53. Moreover, the expression profile of apoptosis-related proteins besides antioxidant enzymes was escalated by treatment with the flavone-based HDAC inhibitor luteolin. While the expression of DNA methyltransferases was inhibited, the expression of ten-eleven translocation (TET) DNA demethylases was enhanced. Enhancement of TET1 binding to the promoter of *Nrf2* was seen on using this flavone (Kang et al., 2019).

The cytotoxic effect of *Angelica shikokiana* extract was studied on several cancer cell lines including colorectal carcinoma. Phenolic compounds including luteolin showed potent HDAC8 inhibitory activity by occupying the trichostain A binding site (Mira & Shimizu, 2015). From this finding, one can infer that the luteolin-mediated apoptotic effect is due to its ability to elevate the expression of *Nrf2* via enhancing the binding of the transcriptional activator TET1 and facilitating the complex formation between Nrf2 and p53.

Luteolin has been found to decrease the cell viability of colorectal carcinoma cells by invoking apoptotic signaling. Moreover, this inhibitor reduced the viability of oxaliplatin-treated p53-null cells and colony formation, suggesting that luteolin can induce death in colorectal tumor (HCT116) cells devoid of functional p53 protein (Jang, Moon, Oh, & Kim, 2019).

Studies have been performed to delineate the crosstalk between luteolin treatment and the activation profile of antioxidant enzymes. While luteolin showed marked reduction in colon cancer cell (HT-29) viability, no effect was seen on normal colon cells (FHC). This induction of apoptosis was found to be mitochondria-dependent, as evidenced by the alleviated mitochondrial membrane potential and elevated mitochondrial calcium level. Moreover, Bax levels were elevated and Bcl-2 levels were declined, facilitating the release of cytochrome *c*, thereby enhancing the activation of caspase-9 and casase-3. Importantly, the levels of reduced glutathione (GSH) and the expression profile of GSH synthetase were enhanced on luteolin treatment in HT-29 cells. Moreover, luteolin-induced apoptotic effect was mediated by the activation of the mitogen-activated protein kinase (MAPK) signaling pathway (Kang et al., 2017). In a nutshell, the flavone-based HDAC inhibitor luteolin induces apoptosis in colon cancer cells by facilitating antioxidant activity and by provoking MAPK pathway while imparting any toxicity to normal colon cells.

Only recently, the effect of luteolin has been studied on the proliferation, migration, and invasion of CRC cells. Based on experimental evidences, it has been concluded that this flavone-based HDAC inhibitor (luteolin) has no impact on CRC cell proliferation but attenuates migration and invasion both in vitro and in vivo. Molecular studies have indicated that luteolin treatment upregulates the expression of miR-384, which then mitigates the expression profile of pleiotrophin (PTN), as shown by target analysis (Y. Yao, Rao, et al., 2019). The crux of these findings is that luteolin restrains *PTN* expression by upregulating miR-384 and that it may serve as a marvellous target for vanquishing CRC.

Combinatorial therapeutic strategies involving luteolin as one of the agents have also been studied in the context of colon cancer (HCT-8 colon). Using cyanidin-3-*O*-glucoside chloride in conjunction with luteolin has shown synergistic effect in inhibiting proliferation and inducing apoptosis (Yin et al., 2019). This suggests that combined therapy involving luteolin as one of the drug candidates offers more than additive benefit for tackling colon carcinomas. Evidence-supported findings suggest that the cyclic AMP (cAMP) response element binding protein 1 (CREB1) is a propitious anticancer target. This protein promotes epithelial-to-mesenchymal transition. Luteolin was found to downregulate the expression of *CREB1* at the message level, which in turn attenuated the epithelial-to-mesenchymal transition in CRC cells. Moreover, this strategy resulted in downregulation of mesenchymal markers and reduced cell mobility. Besides, the expression at protein levels of CREB1 downstream targets was abated on flavone treatment (Y. Liu et al., 2017). Thus luteolin induces its inhibitory effect on EMT through downregulation of CREB1 (Table 2).

The plant-derived-flavone-based HDAC inhibitor luteolin showed inhibitory effect on the proliferation of LoVo colon cancer cells. This flavone resulted in apoptosis induction in these cells. However, in the chemoresistant colon cancer sub-line LoVo/Dx, the effect was less than in the previously defined colon cancer cell line (Palko-Labuz, Sroda-Pomianek, Uryga, Kostrzewa-Suslow, & Michalak, 2017). It is well established that poor aqueous solubility of luteolin hampers its therapeutic efficacy. This limitation in efficacy has been overcome by proper encapsulation of this flavone in liposomes. The encapsulated luteolin showed marked superior growth inhibitory activity against the colorectal carcinoma cells CT26 compared to luteolin in its free form. Moreover, the superior effect of encapsulated luteolin has been seen in, in vivo condition as well. Liposome-encapsulated luteolin showed better solubility and bioavailability (G. Wu, Li, Yue, Zhang, & Yunusi, 2018).

Thus, one can speculate that encapsulated luteolin may serve as an efficient therapeutic in clinical settings. Nowadays, oncolytic viruses are gaining importance as potent anticancer drugs. In colorectal carcinoma cells, the combinatorial benefit of luteolin and CD55-TRAIL has been studied. This combinatorial approach showed

synergistic anticancer effect in CRC cells. This synergistic effect was seen even in CRC mouse xenograft models (Xiao et al., 2017). All this suggests that the defined combination may prove more fruitful in tackling CRC in clinical studies.

2.6 | Luteolin versus lung cancer

In America, lung cancer is the main cancer killer in both males and females. This cancer causes more deaths than other cancers, including breast, colorectal, and prostate cancers. In fact, the number of lung cancer deaths is equal to that caused by breast, colorectal, and prostate cancers together. Studies have shown that lung cancer accounts for 27% of all cancer-related deaths. While non-small-cell lung cancer (NSCLC) has nearly 85% occurrence frequency, small-cell-lung cancer has only 15% (Zappa & Mousa, 2016).

Gefitinib and erlotinib, which are EGF receptor's tyrosine kinase domain inhibitors, are globally used as therapeutic agents against NSCLC. It has been reported the patients first respond to these drugs, but with time almost all patients acquire resistance. Luteolin, a dietary flavone and HDAC inhibitor, has been studied in this context, and it has been found that this flavone shows strong anticancer effect and erlotinib-resistant NSCLC. This effect has been seen not only at the cellular level but also in animal models. Luteolin facilitated the EGF receptor degradation by preventing the association of Hsp90 with the mutant EGF receptor and consequently restrained PI3K/Akt/mTOR signaling, culminating in apoptosis of NSCLC cells (Hong et al., 2014).

Recently, the molecular mechanism involved in luteolin-induced therapeutic effect has been studied in NSCLC both in vitro and in vivo. These studies showed that luteolin has the potential to restrain the proliferation and to induce death in these NSCLC (A549 and H460) cells. Substantial suppression of tumor growth, proliferation, and induction of apoptosis was seen on luteolin administration in an H460 xenograft tumor model. Luteolin upregulated miR-34a-5p, which in turn targets MDM4. Thus luteolin facilitates the expression of this miRNA, which in turn targets MDM4, resulting in apoptosis of NSCLC cells and tumor (Z.-Q. Jiang et al., 2018).

Further studies showed that luteolin hampers EMT in colon cancer cells by downregulating the expression of *absent in melanoma 2 (AIM2)* at both message and protein levels. This effect was also reproduced in H460 and A549 xenograft mouse models (Yu et al., 2019). Thus these findings prove that luteolin impedes EMT by lowering the expression of AIM2 and suggest it as a therapeutic target for tackling NSCLC.

Emerging evidences suggest that luteolin has the ability to sensitize NSCLC cells to radiotherapy. Pretreatment of NCI H460 and H1299 cells with luteolin sensitized these cells to γ-ionizing radiation (IR). The combined tactics proved to be more effective than either of the procedures individually. In combined therapy, induced cell death was associated with downregulation of BCl-2 and enhanced activation of caspases (3, 8, and 9). Moreover, the combined strategy delayed tumor growth by more than 21 days in a xenograft model (Cho et al., 2015). Taken together, luteolin enhances apoptotic cell death by modulating various players including p38/ROS/caspases.

The combined therapeutic effect of myo-inositol and luteolin was evaluated in human lung cancer cells (A549). The combined therapy reduced cell viability by 70%, whereas singlet therapy with myo-inositol or luteolin reduced this viability by 92% and 83%, respectively. Moreover, the combined therapy proved to be more effective in abating the expression of p-PDK1 and p-Akt in the above-mentioned cells. This effect of combinatorial therapy was found to be selective, as no substantial inhibitory effect was noted in human bronchial epithelial Beas-2B cells (Y. Wang et al., 2018). Thus luteolin-induced inhibitory effect on proliferation and migration has been attributed to its ability to supress PDK1 and Akt activation.

Studies have shown that claudin-2 is overexpressed in human lung adenocarcinomas and thus may serve as a possible target for lung cancer therapy. This protein was found to have a positive role in cell proliferation, as its knockdown hampered proliferation. Luteolin and other flavones have been found to reduce the expression of this protein in human lung adenocarcinoma cells. Luteolin use prevents the binding of STAT3 transcription factor at the promoter of *claudin-2*. It is noteworthy that phosphorylation status of this transcription factor was not altered because of luteolin (Sonoki et al., 2017). This indicates that the luteolin-induced antiproliferative effect is mediated by the inhibition of STAT3 binding to claudin-2 promoter and not by alteration of the phosphorylation status of this protein.

TAM (Tyro3, Axl, and Mer) receptor tyrosine kinases have a role in cell survival, antiapotosis, growth, and proliferation. The effect of luteolin was studied on the expression and activation of these TAM receptor tyrosine kinases in human lung cancer cells. Luteolin showed cytotoxic effect in parental lung cancer cells as well as in cisplatin-resistant A549 and H460 cell lines. While this flavone alleviated the protein levels of all the TAM receptor tyrosine kinases in A549 parental and cisplatin-resistant cells, only Axl and Tyro3 protein levels were lowered in HL60 and cisplatin-resistant HL-60 cell models (Y. J. Lee et al., 2017). In short, these findings establish that luteolin targets TAM receptor tyrosine kinases but surely not IL-8 for abrogating cell proliferation and quashing chemoresistance in human NSCLC cells.

Experimental proofs suggest that luteolin exerts antiproliferative effect in human lung cancer cells in a dose- and time-dependent manner. This flavone resulted in apoptotic induction, which was found to be caspase-dependent. Moreover, luteolin enhanced the phosphorylation of MEK and its downstream kinase target ERK besides activating Akt. Dramatic reduction in cell motility and migration was seen after incubation with luteolin. The inhibitor of the MEK–ERK pathway rescued the luteolin-induced effects, clearly indicating that the pro-apoptotic and antimigration effects of luteolin are mediated through the MEK–ERK signaling pathway (Meng et al., 2016).

Therapeutic effects of luteolin were studied in benzo(a)pyrene-induced lung carcinogenesis in mice models. This carcinogen elevated lipid peroxides and carcinoembryonic antigen (CEA) in addition to neuron-specific enolase (NSE). Moreover, the defined pyrene alleviated the levels of enzymatic antioxidants including catalase, SOD, glutathione peroxidase (GPx), and glutathione reductase (GR), in addition

to glutathione-*s*-transferase (GST). A similar effect of benzo(a)pyrene was seen on nonenzymatic antioxidants such as reduced glutathione (GSH) and vitamins C and E. Luteolin foiled all these alterations and reinstated normalcy (Kasala, Bodduluru, Barua, & Gogoi, 2016). Sirtuins, as aforementioned, are NAD+-dependent HDACs. Luteolin exerted anticancer effect in human NSCLC cells (NCI-H460) by reducing the protein levels of Sirt1 (Table 2) (L. Ma et al., 2015).

2.7 | Luteolin in melanoma therapy

The malignant tumor melanoma originates from the uncontrolled division of pigment-producing cells known as melanocytes (Tsatmali, Ancans, & Thody, 2002). The most common form of this cancer is cutaneous, but can also arise from uveal tract, mucosal surface, and leptomeninges. Malignant melanoma is considered the most truculent form of skin cancer (Linos, Swetter, Cockburn, Colditz, & Clarke, 2009). Though this cancer was rare, in the last five decades its incidence has drastically increased (Guy Jr. et al., 2015). Being highly bellicose, this cancer metastasizes far from the primary site. Keeping in view the alarming incidence rate of this cancer, developing drugs that can tackle it has become the need of the hour.

Luteolin, a plant HDAC inhibitor, is emerging as a potent therapeutic against this aggressive cancer. Studies have been carried out for understanding the effect of luteolin on the proliferation of melanoma cells and probing the underlying molecular mechanism. Proliferation and migration, besides invasion of human melanoma cells (A375), were markedly attenuated by luteolin. This inhibitor lowered the expression of various MMPs (MMP-2 and MMP-9) and tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-2). Further, luteolin decreased tumor growth of defined cells in a xenograft mouse model. This treatment also showed reduction in phosphorylation levels of AKT1 and PI3K, as evidenced by immunofluorescence and western blotting analyses (X. Yao, Jiang, et al., 2019). In conclusion, luteolin may be promising in mitigating aggressive melanoma. Tumor metastasis is the primary reason for melanoma mortality.

Therapeutic effect of luteolin on different aspects of human melanoma was studied, and it was found that this inhibitor obstructs cell proliferation in melanoma cells (A375 and B16-F10). It attenuated EMT by alleviating N-cadherin and vimentin expression besides escalating E-cadherin at both levels. Moreover, luteolin reduced the protein expression of p-Akt and HIF-1α in addition to VEGF-A, p-VEGFR-2, MMP-9, and MMP-2 (C. Li et al., 2019). These findings reveal that the antimetastasis effect of luteolin is due to the hampering of HIF-1α/VEGF signaling, the main cause for provoking EMT and angiogenesis. Efforts have been made to investigate the crosstalk between luteolin and endoplasmic reticulum stress in human melanoma cells (A2058).

Inhibition of cell proliferation and enhanced apoptotic body formation have been reported on luteolin use. This inhibitor enhanced the expression of proteins related to endoplasmic reticulum stress, such as protein kinase RNA-like ER kinase, ATF (activating transcription factor), CCAAT/enhancer-binding protein-homologous protein (CHOP), and cleaved caspase 12. The intracellular ROS levels resulting in ROS-induced apoptosis, and endoplasmic reticulum stress was enhanced on luteolin administration. This effect got soothed on treating the cells with *N*-acetyl cysteine, a well-known ROS scavenger (Kim et al., 2016). Thus, luteolin-induced apoptosis is mediated by ROS-induced ER stress in human melanoma cells.

Extensive study has been performed for understanding the effect of luteolin on EMT of murine malignant melanoma (B16F10) cells. The underlying molecular mechanism has also been delineated in this study. Hypoxia-induced changes in these cells were negated by luteolin in a dose-dependent manner. The hallmarks of EMT transformation, namely the downregulation of E-cadherin and upmodulation of N-cadherin, got back-pedaled on 5 μmol/L of luteolin. This flavone upregulated E-cadherin by obstructing the β3 integrin/FAK signaling pathway to a considerable extent. Study on metastasis model mice showed that luteolin abated metastatic lung colonization by 50%. Further, in tumor tissues this molecule culminated in elevated expression of E-cadherin and concurrent declination in the levels of vimentin and β3 integrin (Ruan et al., 2012). This study revealed that luteolin restrains hypoxia-provoked EMT in malignant melanoma cells by alleviating β3 integrin (Table 2). These findings strongly favor the use of luteolin as chemotherapeutic for tackling the therapeutically monotonous malignant melanoma.

2.8 | Luteolin in liver cancer therapy

Liver cancer is more common in males and occupies fifth rank in terms of cancer-related deaths in males. This cancer is more predominant in sub-Saharan Africa and Southeast Asia compared to United States. The 5-year survival rate for liver cancer is only 18%. Most liver cancers (70%–85%) come under the umbrella of hepatocellular carcinoma (HCC) and only 10%–20% are intrahepatic cholangiocarcinoma (ICC) (Massarweh & El-Serag, 2017; Sia, Villanueva, Friedman, & Llovet, 2017). Most liver cancer cases (nearly 80%) have been ascribed to long-term chronic infection of hepatitis B virus (HBV) and hepatitis C virus (HCV) (de Martel, Maucort-Boulch, Plummer, & Franceschi, 2015).

Luteolin also induced caspase-dependent death in the human hepatocellular carcinoma cell line (SK-Hep-1). This cytotoxic effect was somewhat lower in normal cells, namely AML12. Luteolin activated multiple caspases (caspase 8, 9, and 3) and resulted in PARP cleavage. This effect of luteolin was completely rescued by the pan caspase inhibitor carbobenzoxy-valyl-alanyl-aspartyl-[*O*-methyl]-fluoromethylketone (Z-VAD-FMK). Moreover, the expression of X-linked inhibitor of apoptosis (XIAP), Bid, and Mcl-1 was substantially alleviated by luteolin. This flavone abated the expression of osteopontin (OPN) productively both at the message and protein levels. Luteolin prevented the phosphorylation of AKT and thereby triggered apoptotic signaling. An activator of AKT, namely SC79, obstructed all the effects elicited by luteolin (Im, Yeo, & Lee, 2018). On the whole, luteolin induces caspase-dependent apoptosis in

human hepatocellular carcinoma cells by impeding the AKT/OPN pathway and imparts only little toxicity to normal cells. Combinatorial studies involving luteolin in conjunction with 5-fluorouracil have also been performed. These studies revealed that luteolin has the ability to synergize the antineoplastic effect of 5-fluorouracil in HepG2 and Bel7402 cells. This synergistic antitumor effect has been attributed to elevated bax levels, p53 expression, and PARP cleavage. Moreover, the combined therapy resulted in substantial downregulation of dihydropyrimidine dehydrogenase (Xu et al., 2016).

Extensive study has been performed regarding the effect of luteolin on the expression profile of various genes such as *ICAM-1*, *PCNA*, *and LFA-3* in H22 hepatoma tissue. While luteolin administration upregulated the ICAM-1 expression, downregulation of LFA-3 was noticed in the defined hepatoma tissue (Niu, Guo, Gan, Bao, & Ren, 2015). This means that the antitumor activity of luteolin in tumor-bearing mice can be attributed to the downmodulation of LFA-3 and PCNA and escalation of ICAM-1.

Studies have been performed on *Ixeris sonchifolia*-derived luteolin on hepatocellular carcinoma cell lines (HepG2 and Hep3B). Luteolin exposure elevated the expression profile of transforming growth factor β1, p27KIP1, Fas, p21WAF1/CIP1, and Smad4 in these cells. While apoptotic cell death was observed in Hep3B, G1 arrest occurred in HepG2 cells on treatment with luteolin (Yee et al., 2015). Thus luteolin-provoked apoptosis through G1 arrest involves three signaling pathways: TGF-β1, p53, and Fas/Fas-ligand.

Therapeutic impact of luteolin has been studied in a carcinogen-started alcohol-facilitated pre-neoplastic liver lesion mouse model. This HDAC inhibitor significantly alleviated the ferocity and degree of hepatic inflammatory foci and steatosis in carcinogen (diethylnitrosamine)-injected mice kept on ethanol diet. Moreover, this flavone markedly reduced the presence of preneoplastic lesions. Alcohol feeding resulted in the reduction of SIRT1 (Class III HDAC) activity, which was reversed by luteolin administration as evidenced by enhanced acetylation status of the forkhead box protein O1 (FoXO1) and proliferator-activated receptor gamma, coactivator 1 alpha (PGC1α) (Rafacho et al., 2015). These findings suggest that luteolin restores ethanol-depleted SIRT1 activity, which in turn results in the reduction of pre-neoplastic lesions.

The antiproliferative effect of luteolin was studied against a couple of liver cancer cell lines (SMMC-7721, BEL-7402) and normal liver cells (HL-7702). Luteolin hampered proliferation in cancer cells in a dose- and time-dependent manner. Importantly, luteolin in normal liver cells showed almost no effect, which further supports its clinical relevance. Luteolin provoked multiple mechanisms in cancer cells, including cell cycle arrest, elevation of Bax levels, mitigation of Bcl-2, activation of caspase-3, and alleviation of mitochondrial membrane potential culminating in apoptosis (Table 3 and Figure 2) (Ding et al., 2014).

Another study on HepG2 (hepatocarcinoma cells) revealed that luteolin could restrain the growth of these cells by activating AMP-activated protein kinase (AMPK), which in turn modulates NF-κB activity. This finding suggests that the agonists of AMPK may have great anticancer effect. Luteolin induced apoptosis in HLF hepatoma cells by destabilizing STAT3 and subsequently upregulating Fas/CD95. Marked inhibition in tumor growth was seen in nude mice with xenografted tumors on luteolin administration dose-dependently (Selvendiran et al., 2006).

2.9 | Impact of luteolin on gastric cancer

This cancer is the second chief cause of cancer-related deaths across the globe. Proliferation of gastric cancer cells (MKN28 GC and Hs-746T) gets inhibited on luteolin use. Apoptosis in these cells was facilitated by luteolin by decreasing the levels of phosphorylated AKT. Additionally, suppression of gastric cancer cell motility was seen in luteolin-treated cells. This phenomenon was associated with shrinking of the cytoskeleton and decreased cell size. Suppression in the progression of gastric cancer cells was due to alleviated Notch1 expression following exposure of luteolin (Zang et al., 2017).

Specific killing of STAT3-overactivated (drug resistant) gastric cancer cells (SGC7901/DDP, HGC2, and BGC823) has been investigated. Inhibition of STAT3 phosphorylation occurs in these cells after certain period of luteolin use. This luteolin-mediated effect has been attributed to a protein tyrosine phosphatase, namely SHP-1. The defined phosphatase dephosphorylates STAT3 but this process is shielded by HSP90. This heat-shock protein forms a complex with STAT3, and on luteolin treatment HSP-90/STAT3 interaction gets disrupted, which in turn facilitates the interaction of STAT3 with SHP-1 (Figure 3). Luteolin-induced SHP-1-mediated dephosphorylation of STAT3 finally induces apoptosis in resistant gastric cancer cells. Tumors of different gastric cancer cells were developed in mouse models by injecting these cells subcutaneously. Three types of tumors were developed in these models. Mice bearing tumor formed of SGC7901/DDP (cisplatin-resistant) cells, HGC27 cells, or SGC7901 (non-drug-resistant) cells, on reaching a volume of 100 mm^3, were treated for 4 weeks with 20 mg/kg/day of luteolin, while the control group received only the vehicle. SGC7901/DDP mice showed an average tumor weight of 61.6%, while HGC27 mice showed 49.5% of the corresponding controls following luteolin treatment. However, no substantial difference in tumor volume was noted in control and luteolin-treated mice spacing non-drug-resistant tumor (Song et al., 2017).

Luteolin hampered cell growth, migration, and invasion of gastric cancer cells. This inhibitor reduced not only Notch1 in these cells but also the phosphorylated forms of mTOR, STAT3, ERK, and PI3K. Pathological and physiological processes of gastric cancer cells are regulated by the aberrant expression of various miRNAs. While the expression profile of oncogenic miRNAs (miR-155, miR-340, miR-21, miR-224) was substantially downregulated, the tumor suppressor miRNAs (miR-34a, miR-107, miR-139, miR-422a) were upregulated after subjecting the cells to luteolin (Pu et al., 2018).

Luteolin has been tested on the gastric adenocarcinoma (SGC-7901) cell line in association with oxaliplatin. This combination prevented proliferation and induced apoptosis in these cells. One of the mechanisms of this synergy was the activation of cytochrome *c*/

TABLE 3 Various molecular mechanisms modulated by the flavone luteolin in exerting anticancer effect in liver, gastric, and brain cancer models

Flavonoid name or combination used	Name of the cancer	Key players upregulated	Critical players downregulated	Pathway/ proteins activated	Proteins/ pathways restrained	Literature proof
Luteolin	Liver cancer		XIAP, bid, Mcl-1, osteopontin, p-AKT	Caspase 8, 9, 3	AKT/OPN	Im et al., 2018
Luteolin +5-fluorouracil		Bax, p53	Dihydropyrimidine dehydrogenase			Xu et al., 2016
Luteolin		ICAM-1	LFA-3, PCNA			Niu et al., 2015
		TGF-β1, p27KIP1, Smad4				Yee et al., 2015
				SIRT1		Rafacho et al., 2015
		Bax	Bcl-2	Caspase-3		Ding et al., 2014
		Fas/CD95		AMPK		Selvendiran et al., 2006)
Luteolin	Gastric cancer		Notch1			Zang et al., 2017
			p-STAT3			Song et al., 2017
		miR-139, miR-422a, miR-34a, miR-107	Notch1, p-mTOR, p-STAT3, p-ERK, p-PI3K, miR-224, miR-155, miR-21, miR-340			Pu et al., 2018
Luteolin + oxaliplatin			p-STAT3, p-AKT	Cytochrome c/ caspase signaling		Ren, Li, & Zhang, 2020
Luteolin	Brain cancer	TIMP1-2, E-cadherin	MMP2/9, N-cadherin, β-catenin, vimentin			Q. Wang et al., 2017
		Bax	Bcl-2			Zheng et al., 2017
		miR-124-3p, LC3B II	P62	MAPK activation		You, Wang, Shao, Zhi, & Yang, 2019

caspase signaling mechanism in these cells (Ren et al., 2020). Thus, for obstructing proliferation and eliciting apoptosis in gastric cancer cells, luteolin modulates several mechanisms. On one hand, luteolin lowers the phosphorylated AKT and p-STAT3, and, on the other hand, influences the expression of various miRNAs (Table 3 and Figure 2).

2.10 | Luteolin in brain cancer therapy

According to standard reports, more than 120 brain tumor types are known. While some brain tumors are fast-growing and malignant, the others may be slow-growing and nonmalignant. Glioblastoma multiforme is an example for former, while meningioma represents the benign type. Primary brain tumors develop from brain cells and are classified on the basis of the cell type or the location of brain where they get formed. Gliomas, the mostly occuring primary brain tumors, originate from glial cells, while astrocytomas develop from astrocytes. It has been estimated that 81% of brain cancers are represented by gliomas (You et al., 2019). Grade IV, the most aggressive form of glioma, is termed as glioblastoma. The latter represents almost 57% of total gliomas (Tan et al., 2020).

Another study of luteolin on glioblastoma cells has proved that this small molecule inhibits proliferation and obstructs the migration of these cells. While MMPs promote the migration of cancer cells, TIMPs reverse this process by inhibiting MMPs endogenously. Inhibition of migration of these atypical cells has been attributed to the ability of luteolin to partly upregulate the TIMP1-2 expression and decline MMP2/9. Luteolin restrained EMT in glioblastoma models by decreasing the N-cadherin, vimentin, and β-catenin and by enhancing the E-cadherin protein level (Q. Wang et al., 2017).

The concern of hydrophobicity and low bioavailability of luteolin has been overcome by forming luteolin-loaded methoxypoly (ethylene glycol) poly(caprolactone) (mPEG-PCL) micelles. These spherical micelles of luteolin/MPEG-PCL were fully dispersible in saline and could release luteolin in a sustained manner in vitro. Luteolin in micellar form showed more potent effect than free luteolin in provoking apoptosis in C6 and U87 glioma cell lines. MPEG-PCL enclosed luteolin in tumor tissues and inhibited the formation of new blood vessels. Luteolin-triggered apoptosis was found to occur through

mitochondrial pathway, as evidenced by Bax upregulation and Bcl-2 downregulation (Zheng et al., 2017). These findings indicate that micelles of luteolin/MPEG-PCL may prove promising in chemotherapy against glioma.

Positive results have been recorded for luteolin against various brain tumors including glioma and glioblastomas. Dose- and time-dependent proliferation inhibition of glioma cells has been found on incubating them with luteolin. This flavone induced apoptosis in glioma cell lines through MAPK activation and extrinsic apoptotic pathway involving fas-associated protein with death domain (FADD). Studies have shown that autophagy confers protection not only against metabolic stress but also has significance as tumor suppressor. Luteolin induced autophagy and augmented the miR-124-3p expression in glioma models. It is well known that LC3 has a crucial role in lysosomal delivery of P62 for subsequent degradation. Luteolin enhanced the protein expression of LC3B II and downregulated the p62 protein in cell models of glioma (Table 3 and Figure 3). Luteolin-induced autophagy was rescued by the autophagic inhibitor 3-methyladenine, further confirming that luteolin triggers autophagic death is glioma cells as well (You et al., 2019).

3 | CONCLUSION

Luteolin is becoming apparent as an optimistic anticancer agent. This dietary flavone has shown propitious antineoplastic effect against multiple cancers. Thus the present review took into account the promising anticancer effect of luteolin against several cancers including leukemias, melanoma, as well as pancreatic, prostate, liver, breast, colorectal, lung, brain, and gastric cancer. Luteolin induced cytotoxic effect in these cancers by modulating distinct molecular players and signaling mechanisms.

Luteolin obstructed the activity of epigenetic targets such as DNMTs, some classical HDACs, and SIRT1 for eliciting cytotoxic effect. Luteolin escalated the levels of the proapoptotic protein Bax while alleviated the antiapoptotic (Bcl2), caused caspase activation, and subsequent apoptosis of cancer cells. Luteolin-induced cytotoxic effect has been attributed in certain cases to the upregulation of Nrf2 expression and downregulation of CREB1. Moreover, modulation of several signaling pathways such as JNK, AKT, p53, GSK-3β, NF-κB, K-ras, EGFR, MAPK, Notch, HIF-1α/VEGF, and mTOR has been seen on luteolin administration. Autophagy was also induced by luteolin in some cases by triggering Beclin-1 and LC3B II and suppressing p62.

Luteolin in almost all cases showed a synergistic effect when used in association with other antineoplastic therapeutics. This anticancer activity of luteolin was found both under in vitro and in vivo conditions with no discernible toxicity towards normal cells, further authenticating its clinical applicability. However, in one study luteolin shielded breast cancer cells from doxorubicin-induced toxicity by decreasing ROS production. The possibility of antagonistic effects of combinatorial therapy can be overcome by strictly following the cytotoxic mechanism induced by the constituent therapeutics.

However, the nano-combinatorial approach, which has shown comparatively elevated therapeutic effect over ordinary combined therapy in case of certain flavones, has not been attempted for luteolin. This approach enhances the bioavailability and hence therapeutic efficacy of encapsulated drugs to a greater degree. Although luteolin has shown promising results in cancer and animal models of cancer, higher level clinical studies have not been done to date. Additionally, luteolin has been studied mainly in the context of non-epigenetic therapeutic routes, and the few recent studies discussed in this work indicate that it targets novel epigenetic routes as well. As epigenetic therapy of cancer is an emerging discipline, extensive research is required to study the modulatory effects of luteolin on various epigenetic therapeutic targets.

ACKNOWLEDGMENTS

Shabir Ahmad Ganai acknowledges financial help from the Science and Engineering Research Board in the form of a big grant (No: YSS/2015/001267).

CONFLICT OF INTEREST

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable in the present case as it is a review article and not a research paper where datasets are generated and then analysed.

ORCID

Shabir Ahmad Ganai https://orcid.org/0000-0002-4668-8248

REFERENCES

Albrecht, M., Jiang, W., Kumi-Diaka, J., Lansky, E. P., Gommersall, L. M., Patel, A., … Campbell, M. J. (2004). Pomegranate extracts potently suppress proliferation, xenograft growth, and invasion of human prostate cancer cells. *Journal of Medicinal Food*, *7*(3), 274–283. https://doi.org/10.1089/jmf.2004.7.274

Attoub, S., Hassan, A. H., Vanhoecke, B., Iratni, R., Takahashi, T., Gaben, A. M., … Petroianu, G. (2011). Inhibition of cell survival, invasion, tumor growth and histone deacetylase activity by the dietary flavonoid luteolin in human epithelioid cancer cells. *European Journal of Pharmacology*, *651*(1–3), 18–25. https://doi.org/10.1016/j.ejphar.2010.10.063

Attoub, S., Hassan, A. H., Vanhoecke, B., Iratni, R., Takahashi, T., Gaben, A.-M., … Petroianu, G. (2010). Inhibition of cell survival, invasion, tumor growth and histone deacetylase activity by the dietary flavonoid luteolin in human epithelioid cancer cells. *Eur J Pharmacol*. 2011 Jan 25;*651*(1–3), 18–25. https://doi.org/10.1016/j.ejphar.2010.10.06

Bhandari, A., Woodhouse, M., & Gupta, S. (2017). Colorectal cancer is a leading cause of cancer incidence and mortality among adults younger than 50 years in the USA: A SEER-based analysis with comparison to other young-onset cancers. *Journal of Investigative Medicine: The Official Publication of the American Federation for Clinical Research*, *65*(2), 311–315. https://doi.org/10.1136/jim-2016-000229

Brusselmans, K., Vrolix, R., Verhoeven, G., & Swinnen, J. V. (2005). Induction of cancer cell apoptosis by flavonoids is associated with their ability to inhibit fatty acid synthase activity. *The Journal of Biological*

Chemistry, *280*(7), 5636–5645. https://doi.org/10.1074/jbc.M408177200

Bubendorf, L., Schopfer, A., Wagner, U., Sauter, G., Moch, H., Willi, N., … Mihatsch, M. J. (2000). Metastatic patterns of prostate cancer: An autopsy study of 1,589 patients. *Human Pathology*, *31*(5), 578–583.

Buchanan, G., Irvine, R. A., Coetzee, G. A., & Tilley, W. D. (2001). Contribution of the androgen receptor to prostate cancer predisposition and progression. *Cancer Metastasis Reviews*, *20*(3–4), 207–223.

Cai, X., Lu, W., Ye, T., Lu, M., Wang, J., Huo, J., … Cao, P. (2012). The molecular mechanism of luteolin-induced apoptosis is potentially related to inhibition of angiogenesis in human pancreatic carcinoma cells. *Oncology Reports*, *28*(4), 1353–1361. https://doi.org/10.3892/or.2012.1914

Cai, X., Ye, T., Liu, C., Lu, W., Lu, M., Zhang, J., … Cao, P. (2011). Luteolin induced G2 phase cell cycle arrest and apoptosis on non-small cell lung cancer cells. *Toxicology in Vitro*, *25*(7), 1385–1391. https://doi.org/10.1016/j.tiv.2011.05.009

Cao, Z., Zhang, H., Cai, X., Fang, W., Chai, D., Wen, Y., … Zhang, Y. (2017). Luteolin promotes cell apoptosis by inducing autophagy in hepatocellular carcinoma. *Cellular Physiology and Biochemistry*, *43*(5), 1803–1812. https://doi.org/10.1159/000484066

Chahar, M. K., Sharma, N., Dobhal, M. P., & Joshi, Y. C. (2011). Flavonoids: A versatile source of anticancer drugs. *Pharmacognosy Reviews*, *5*(9), 1–12. https://doi.org/10.4103/0973-7847.79093

Chan, T. S., Galati, G., Pannala, A. S., Rice-Evans, C., & O'Brien, P. J. (2003). Simultaneous detection of the antioxidant and pro-oxidant activity of dietary polyphenolics in a peroxidase system. *Free Radical Research*, *37*(7), 787–794.

Chakrabarti, M., & Ray, S. K. (2016). Anti-tumor activities of luteolin and silibinin in glioblastoma cells: overexpression of miR-7-1-3p augmented luteolin and silibinin to inhibit autophagy and induce apoptosis in glioblastoma in vivo. *Apoptosis*, *21*(3), 312–328. https://doi.org/10.1007/s10495-015-1198-x

Chang, H., Mi, M. T., Gu, Y. Y., Yuan, J. L., Ling, W. H., & Lin, H. (2007). Effects of flavonoids with different structures on proliferation of leukemia cell line HL-60. *Ai Zheng*, *26*(12), 1309–1314.

Chen, P.-Y., Tien, H.-J., Chen, S.-F., Horng, C.-T., Tang, H.-L., Jung, H.-L., … Yen, J.-H. (2018). Response of myeloid leukemia cells to Luteolin is modulated by differentially expressed pituitary tumor-transforming gene 1 (PTTG1) Oncoprotein. *International Journal of Molecular Sciences*, *19*(4), 1173. https://doi.org/10.3390/ijms19041173

Chen, Z., Zhang, B., Gao, F., & Shi, R. (2018). Modulation of G2/M cell cycle arrest and apoptosis by luteolin in human colon cancer cells and xenografts. *Oncology Letters*, *15*(2), 1559–1565. https://doi.org/10.3892/ol.2017.7475

Cheng, A.-C., Huang, T.-C., Lai, C.-S., & Pan, M.-H. (2005). Induction of apoptosis by luteolin through cleavage of Bcl-2 family in human leukemia HL-60 cells. *European Journal of Pharmacology*, *509*(1), 1–10. https://doi.org/10.1016/j.ejphar.2004.12.026

Cherng, J. M., Shieh, D. E., Chiang, W., Chang, M. Y., & Chiang, L. C. (2007). Chemopreventive effects of minor dietary constituents in common foods on human cancer cells. *Bioscience, Biotechnology, and Biochemistry*, *71*(6), 1500–1504. https://doi.org/10.1271/bbb.70008

Chiu, F. L., & Lin, J. K. (2008). Downregulation of androgen receptor expression by luteolin causes inhibition of cell proliferation and induction of apoptosis in human prostate cancer cells and xenografts. *Prostate*, *68*(1), 61–71. https://doi.org/10.1002/pros.20690

Cho, H. J., Ahn, K. C., Choi, J. Y., Hwang, S. G., Kim, W. J., Um, H. D., & Park, J. K. (2015). Luteolin acts as a radiosensitizer in nonsmall cell lung cancer cells by enhancing apoptotic cell death through activation of a p38/ROS/caspase cascade. *International Journal of Oncology*, *46*(3), 1149–1158. https://doi.org/10.3892/ijo.2015.2831

Cook, M. T., Liang, Y., Besch-Williford, C., Goyette, S., Mafuvadze, B., & Hyder, S. M. (2015). Luteolin inhibits progestin-dependent angiogenesis, stem cell-like characteristics, and growth of human breast cancer xenografts. *Springerplus*, *4*, 444. https://doi.org/10.1186/s40064-015-1242-x

Cook, M. T., Liang, Y., Besch-Williford, C., & Hyder, S. M. (2017). Luteolin inhibits lung metastasis, cell migration, and viability of triple-negative breast cancer cells. *Breast Cancer*, *9*, 9–19. https://doi.org/10.2147/bctt.s124860

Coppede, F. (2014). Epigenetic biomarkers of colorectal cancer: Focus on DNA methylation. *Cancer Letters*, *342*(2), 238–247. https://doi.org/10.1016/j.canlet.2011.12.030

de Martel, C., Maucort-Boulch, D., Plummer, M., & Franceschi, S. (2015). World-wide relative contribution of hepatitis B and C viruses in hepatocellular carcinoma. *Hepatology*, *62*(4), 1190–1200. https://doi.org/10.1002/hep.27969

Ding, S., Hu, A., Hu, Y., Ma, J., Weng, P., & Dai, J. (2014). Anti-hepatoma cells function of luteolin through inducing apoptosis and cell cycle arrest. *Tumour Biology*, *35*(4), 3053–3060. https://doi.org/10.1007/s13277-013-1396-5

Dong, X., Zhang, J., Yang, F., Wu, J., Cai, R., Wang, T., & Zhang, J. (2018). Effect of luteolin on the methylation status of the OPCML gene and cell growth in breast cancer cells. *Experimental and Therapeutic Medicine*, *16*(4), 3186–3194. https://doi.org/10.3892/etm.2018.6526

Du, G. J., Song, Z. H., Lin, H. H., Han, X. F., Zhang, S., & Yang, Y. M. (2008). Luteolin as a glycolysis inhibitor offers superior efficacy and lesser toxicity of doxorubicin in breast cancer cells. *Biochemical and Biophysical Research Communications*, *372*(3), 497–502. https://doi.org/10.1016/j.bbrc.2008.05.080

Ganai, S. A. (2017). Plant-derived flavone Apigenin: The small-molecule with promising activity against therapeutically resistant prostate cancer. *Biomedicine & Pharmacotherapy*, *85*, 47–56. https://doi.org/10.1016/j.biopha.2016.11.130

Ganai, S. A., Farooq, Z., Banday, S., & Altaf, M. (2018). In silico approaches for investigating the binding propensity of apigenin and luteolin against class I HDAC isoforms. *Future Medicinal Chemistry*, *10*(16), 1925–1945. https://doi.org/10.4155/fmc-2018-0020

Ganai, S. A., Rashid, R., Abdullah, E., & Altaf, M. (2017). Plant derived inhibitor Sulforaphane in combinatorial therapy against therapeutically challenging pancreatic cancer. *Anti-Cancer Agents in Medicinal Chemistry*, *17*(3), 365–373. https://doi.org/10.2174/1871520616666160607004729

Ganai, S. A., Sheikh, F. A., & Baba, Z. A. (2020). Plant flavone Chrysin as an emerging histone deacetylase inhibitor for prosperous epigenetic-based anticancer therapy. *Phytotherapy Research*. https://doi.org/10.1002/ptr.6869

Godoy, L. D., Lucas, J. E., Bender, A. J., Romanick, S. S., & Ferguson, B. S. (2017). Targeting the epigenome: Screening bioactive compounds that regulate histone deacetylase activity. *Molecular Nutrition & Food Research*, *61*(4), 1600744. https://doi.org/10.1002/mnfr.201600744

Guy, G. P., Jr., Thomas, C. C., Thompson, T., Watson, M., Massetti, G. M., & Richardson, L. C. (2015). Vital signs: Melanoma incidence and mortality trends and projections - United States, 1982-2030. *MMWR. Morbidity and Mortality Weekly Report*, *64*(21), 591–596.

Han, K., Lang, T., Zhang, Z., Zhang, Y., Sun, Y., Shen, Z., … Min, D. (2018). Luteolin attenuates Wnt signaling via upregulation of FZD6 to suppress prostate cancer stemness revealed by comparative proteomics. *Scientific Reports*, *8*(1), 8537. https://doi.org/10.1038/s41598-018-26761-2

Han, K., Meng, W., Zhang, J. J., Zhou, Y., Wang, Y. L., Su, Y., … Min, D. L. (2016). Luteolin inhibited proliferation and induced apoptosis of prostate cancer cells through miR-301. *Oncotargets and Therapy*, *9*, 3085–3094. https://doi.org/10.2147/ott.S102862

Harborne, J. B., & Williams, C. A. (2000). Advances in flavonoid research since 1992. *Phytochemistry*, *55*(6), 481–504.

Harris, D. M., Li, L., Chen, M., Lagunero, F. T., Go, V. L. W., & Boros, L. G. (2012). Diverse mechanisms of growth inhibition by luteolin, resveratrol, and quercetin in MIA PaCa-2 cells: A comparative glucose tracer

study with the fatty acid synthase inhibitor C75. *Metabolomics: Official Journal of the Metabolomic Society*, *8*(2), 201–210. https://doi.org/10.1007/s11306-011-0300-9

Hay, E. D., & Zuk, A. (1995). Transformations between epithelium and mesenchyme: Normal, pathological, and experimentally induced. *American Journal of Kidney Diseases*, *26*(4), 678–690.

Hong, Z., Cao, X., Li, N., Zhang, Y., Lan, L., Zhou, Y., … Luo, L. (2014). Luteolin is effective in the non-small cell lung cancer model with L858R/T790M EGF receptor mutation and erlotinib resistance. *British Journal of Pharmacology*, *171*(11), 2842–2853. https://doi.org/10.1111/bph.12610

Huang, L., Jin, K., & Lan, H. (2019). Luteolin inhibits cell cycle progression and induces apoptosis of breast cancer cells through downregulation of human telomerase reverse transcriptase. *Oncology Letters*, *17*(4), 3842–3850. https://doi.org/10.3892/ol.2019.10052

Huang, X., Dai, S., Dai, J., Xiao, Y., Bai, Y., Chen, B., & Zhou, M. (2015). Luteolin decreases invasiveness, deactivates STAT3 signaling, and reverses interleukin-6 induced epithelial-mesenchymal transition and matrix metalloproteinase secretion of pancreatic cancer cells. *Oncotargets and Therapy*, *8*, 2989–3001. https://doi.org/10.2147/ott.s91511

Im, E., Yeo, C., & Lee, E. O. (2018). Luteolin induces caspase-dependent apoptosis via inhibiting the AKT/osteopontin pathway in human hepatocellular carcinoma SK-Hep-1 cells. *Life Sciences*, *209*, 259–266. https://doi.org/10.1016/j.lfs.2018.08.025

Imran, M., Rauf, A., Abu-Izneid, T., Shariati, M. A., Khan, B., Imran, A., … Gusain, P. (2019). Luteolin, a flavonoid, as an anticancer agent: A review. *Biomedicine & Pharmacotherapy*, *112*, 108612.

Jang, C. H., Moon, N., Oh, J., & Kim, J.-S. (2019). Luteolin shifts Oxaliplatin-induced cell cycle arrest at G_0/G_1 to apoptosis in HCT116 human colorectal carcinoma cells. *Nutrients*, *11*(4), 770. https://doi.org/10.3390/nu11040770

Jeon, Y. W., Ahn, Y. E., Chung, W. S., Choi, H. J., & Suh, Y. J. (2015). Synergistic effect between celecoxib and luteolin is dependent on estrogen receptor in human breast cancer cells. *Tumour Biology*, *36*(8), 6349–6359. https://doi.org/10.1007/s13277-015-3322-5

Jeon, Y. W., & Suh, Y. J. (2013). Synergistic apoptotic effect of celecoxib and luteolin on breast cancer cells. *Oncology Reports*, *29*(2), 819–825. https://doi.org/10.3892/or.2012.2158

Jiang, Y., Xie, K. P., Huo, H. N., Wang, L. M., Zou, W., & Xie, M. J. (2013). Inhibitory effect of luteolin on the angiogenesis of chick chorioallantoic membrane and invasion of breast cancer cells via downregulation of AEG-1 and MMP-2. *Sheng Li Xue Bao*, *65*(5), 513–518.

Jiang, Z.-Q., Li, M.-H., Qin, Y.-M., Jiang, H.-Y., Zhang, X., & Wu, M.-H. (2018). Luteolin inhibits tumorigenesis and induces apoptosis of non-small cell lung cancer cells via regulation of MicroRNA-34a-5p. *International Journal of Molecular Sciences*, *19*(2), 447. https://doi.org/10.3390/ijms19020447

Johnson, J. L., Dia, V. P., Wallig, M., & Gonzalez de Mejia, E. (2015). Luteolin and gemcitabine protect against pancreatic cancer in an Orthotopic mouse model. *Pancreas*, *44*(1), 144–151. https://doi.org/10.1097/mpa.0000000000000215

Johnson, J. L., Rupasinghe, S. G., Stefani, F., Schuler, M. A., & Gonzalez de Mejia, E. (2011). Citrus flavonoids luteolin, apigenin, and quercetin inhibit glycogen synthase kinase-3beta enzymatic activity by lowering the interaction energy within the binding cavity. *Journal of Medicinal Food*, *14*(4), 325–333. https://doi.org/10.1089/jmf.2010.0310

Ju, W., Wang, X., Shi, H., Chen, W., Belinsky, S. A., & Lin, Y. (2007). A critical role of luteolin-induced reactive oxygen species in blockage of tumor necrosis factor-activated nuclear factor-kappaB pathway and sensitization of apoptosis in lung cancer cells. *Molecular Pharmacology*, *71*(5), 1381–1388. https://doi.org/10.1124/mol.106.032185

Kang, K. A., Piao, M. J., Hyun, Y. J., Zhen, A. X., Cho, S. J., Ahn, M. J., … Hyun, J. W. (2019). Luteolin promotes apoptotic cell death via upregulation of Nrf2 expression by DNA demethylase and the interaction of Nrf2 with p53 in human colon cancer cells. *Experimental & Molecular Medicine*, *51*(4), 40–40, 14. https://doi.org/10.1038/s12276-019-0238-y

Kang, K. A., Piao, M. J., Ryu, Y. S., Hyun, Y. J., Park, J. E., Shilnikova, K., … Hyun, J. W. (2017). Luteolin induces apoptotic cell death via antioxidant activity in human colon cancer cells. *International Journal of Oncology*, *51*(4), 1169–1178. https://doi.org/10.3892/ijo.2017.4091

Kanwal, R., Moreton, S., Franco, D., & Gupta, S. (2018). Abstract 251: Luteolin-mediated increase in miR-26a inhibits prostate cancer cell growth and induces cell cycle arrest targeting EZH2. *Cancer Research*, *78*(13 Supplement), 251. https://doi.org/10.1158/1538-7445.Am2018-251

Kasala, E. R., Bodduluru, L. N., Barua, C. C., & Gogoi, R. (2016). Antioxidant and antitumor efficacy of Luteolin, a dietary flavone on benzo(a) pyrene-induced experimental lung carcinogenesis. *Biomedicine & Pharmacotherapy*, *82*, 568–577. https://doi.org/10.1016/j.biopha.2016.05.042

Kawaii, S., Tomono, Y., Katase, E., Ogawa, K., & Yano, M. (1999). Antiproliferative activity of flavonoids on several cancer cell lines. *Bioscience, Biotechnology, and Biochemistry*, *63*(5), 896–899. https://doi.org/10.1271/bbb.63.896

Kim, J. K., Kang, K. A., Ryu, Y. S., Piao, M. J., Han, X., Oh, M. C., … Hyun, J. W. (2016). Induction of endoplasmic reticulum stress via reactive oxygen species mediated by Luteolin in melanoma cells. *Anticancer Research*, *36*(5), 2281–2289.

Ko, W. G., Kang, T. H., Lee, S. J., Kim, Y. C., & Lee, B. H. (2002). Effects of luteolin on the inhibition of proliferation and induction of apoptosis in human myeloid leukaemia cells. *Phytotherapy Research*, *16*(3), 295–298. https://doi.org/10.1002/ptr.871

Le Marchand, L. (2002). Cancer preventive effects of flavonoids—A review. *Biomedicine & Pharmacotherapy*, *56*(6), 296–301. https://doi.org/10.1016/S0753-3322(02)00186-5

Lee, E. J., Oh, S. Y., & Sung, M. K. (2012). Luteolin exerts anti-tumor activity through the suppression of epidermal growth factor receptor-mediated pathway in MDA-MB-231 ER-negative breast cancer cells. *Food and Chemical Toxicology*, *50*(11), 4136–4143. https://doi.org/10.1016/j.fct.2012.08.025

Lee, Y. J., Lim, T., Han, M. S., Lee, S. H., Baek, S. H., Nan, H. Y., & Lee, C. (2017). Anticancer effect of luteolin is mediated by downregulation of TAM receptor tyrosine kinases, but not interleukin-8, in non-small cell lung cancer cells. *Oncology Reports*, *37*(2), 1219–1226. https://doi.org/10.3892/or.2016.5336

Li, C., Wang, Q., Shen, S., Wei, X., & Li, G. (2019). HIF-1alpha/VEGF signaling-mediated epithelial-mesenchymal transition and angiogenesis is critically involved in anti-metastasis effect of luteolin in melanoma cells. *Phytotherapy Research*, *33*(3), 798–807. https://doi.org/10.1002/ptr.6273

Li, Y. C., Hung, C. F., Yeh, F. T., Lin, J. P., & Chung, J. G. (2001). Luteolin-inhibited arylamine N-acetyltransferase activity and DNA–2-aminofluorene adduct in human and mouse leukemia cells. *Food and Chemical Toxicology*, *39*(7), 641–647. https://doi.org/10.1016/S0278-6915(01)00009-6

Li, Z., Zhang, Y., Chen, L., & Li, H. (2018). The dietary compound luteolin inhibits pancreatic cancer growth by targeting BCL-2. *Food & Function*, *9*(5), 3018–3027. https://doi.org/10.1039/c8fo00033f

Lin, C.-H., Chang, C.-Y., Lee, K.-R., Lin, H.-J., Chen, T.-H., & Wan, L. (2015). Flavones inhibit breast cancer proliferation through the Akt/FOXO3a signaling pathway. *BMC Cancer*, *15*(1), 958. https://doi.org/10.1186/s12885-015-1965-7

Lin, D., Kuang, G., Wan, J., Zhang, X., Li, H., Gong, X., & Li, H. (2017). Luteolin suppresses the metastasis of triple-negative breast cancer by reversing epithelial-to-mesenchymal transition via downregulation of beta-catenin expression. *Oncology Reports*, *37*(2), 895–902. https://doi.org/10.3892/or.2016.5311

Lin, Y., Shi, R., Wang, X., & Shen, H. M. (2008). Luteolin, a flavonoid with potential for cancer prevention and therapy. *Current Cancer Drug Targets*, *8*(7), 634–646.

Linos, E., Swetter, S. M., Cockburn, M. G., Colditz, G. A., & Clarke, C. A. (2009). Increasing burden of melanoma in the United States. *The Journal of Investigative Dermatology*, *129*(7), 1666–1674. https://doi.org/10.1038/jid.2008.423

Liu, W., Lu, M., Liu, B., Huang, Y., & Wang, K. (2012). Inhibition of ca(2+)-activated cl(–) channel ANO1/TMEM16A expression suppresses tumor growth and invasiveness in human prostate carcinoma. *Cancer Letters*, *326*(1), 41–51. https://doi.org/10.1016/j.canlet.2012.07.015

Liu, Y., Lang, T., Jin, B., Chen, F., Zhang, Y., Beuerman, R. W., … Zhang, Z. (2017). Luteolin inhibits colorectal cancer cell epithelial-to-mesenchymal transition by suppressing CREB1 expression revealed by comparative proteomics study. *Journal of Proteomics*, *161*, 1–10. https://doi.org/10.1016/j.jprot.2017.04.005

Lu, K. H., Lin, K. L., Yang, C. C., Hsia, T. C., Hsiao, Y. M., Chou, M. C., … Chung, J. G. (2002). The effect of paclitaxel on gene expression and activity of arylamine N-acetyltransferase and DNA-2-aminofluorene adduct formation in human leukemia HL-60 cells. *Food and Chemical Toxicology*, *40*(5), 705–713. https://doi.org/10.1016/S0278-6915(01)00129-6

Ma, D.-N., Chai, Z.-T., Zhu, X.-D., Zhang, N., Zhan, D.-H., Ye, B.-G., … Tang, Z.-Y. (2016). MicroRNA-26a suppresses epithelial-mesenchymal transition in human hepatocellular carcinoma by repressing enhancer of zeste homolog 2. *Journal of Hematology & Oncology*, *9*(1), 1. https://doi.org/10.1186/s13045-015-0229-y

Ma, L., Peng, H., Li, K., Zhao, R., Li, L., Yu, Y., … Han, Z. (2015). Luteolin exerts an anticancer effect on NCI-H460 human non-small cell lung cancer cells through the induction of Sirt1-mediated apoptosis. *Molecular Medicine Reports*, *12*(3), 4196–4202. https://doi.org/10.3892/mmr.2015.3956

Markaverich, B. M., Shoulars, K., & Rodriguez, M. A. (2011). Luteolin regulation of estrogen signaling and cell cycle pathway genes in MCF-7 human breast cancer cells. *International Journal of Biomedical Sciences*, *7*(2), 101–111.

Massarweh, N. N., & El-Serag, H. B. (2017). Epidemiology of hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *Cancer Control*, *24*(3), 1073274817729245. https://doi.org/10.1177/1073274817729245

Meng, G., Chai, K., Li, X., Zhu, Y., & Huang, W. (2016). Luteolin exerts pro-apoptotic effect and anti-migration effects on A549 lung adenocarcinoma cells through the activation of MEK/ERK signaling pathway. *Chemico-Biological Interactions*, *257*, 26–34. https://doi.org/10.1016/j.cbi.2016.07.028

Miean, K. H., & Mohamed, S. (2001). Flavonoid (myricetin, quercetin, kaempferol, luteolin, and apigenin) content of edible tropical plants. *Journal of Agricultural and Food Chemistry*, *49*(6), 3106–3112. https://doi.org/10.1021/jf000892m

Mira, A., & Shimizu, K. (2015). In vitro cytotoxic activities and molecular mechanisms of Angelica shikokiana extract and its isolated compounds. *Pharmacognosy Magazine*, *11*(Suppl 4), S564–S569. https://doi.org/10.4103/0973-1296.172962

Nakagawa, M., Oda, Y., Eguchi, T., Aishima, S., Yao, T., Hosoi, F., … Tsuneyoshi, M. (2007). Expression profile of class I histone deacetylases in human cancer tissues. *Oncology Reports*, *18*(4), 769–774.

Nazim, U. M., & Park, S. Y. (2019). Luteolin sensitizes human liver cancer cells to TRAILinduced apoptosis via autophagy and JNKmediated death receptor 5 upregulation. *International Journal of Oncology*, *54*(2), 665–672. https://doi.org/10.3892/ijo.2018.4633

Neuhouser, M. L. (2004). Dietary flavonoids and cancer risk: Evidence from human population studies. *Nutrition and Cancer*, *50*(1), 1–7. https://doi.org/10.1207/s15327914nc5001_1

Niu, J. X., Guo, H. P., Gan, H. M., Bao, L. D., & Ren, J. J. (2015). Effect of luteolin on gene expression in mouse H22 hepatoma cells. *Genetics and Molecular Research*, *14*(4), 14448–14456. https://doi.org/10.4238/2015.November.18.7

Palko-Labuz, A., Sroda-Pomianek, K., Uryga, A., Kostrzewa-Suslow, E., & Michalak, K. (2017). Anticancer activity of baicalein and luteolin studied in colorectal adenocarcinoma LoVo cells and in drug-resistant LoVo/dx cells. *Biomedicine & Pharmacotherapy*, *88*, 232–241. https://doi.org/10.1016/j.biopha.2017.01.053

Park, S. H., Ham, S., Kwon, T. H., Kim, M. S., Lee, D. H., Kang, J. W., … Yoon, D. Y. (2014). Luteolin induces cell cycle arrest and apoptosis through extrinsic and intrinsic signaling pathways in MCF-7 breast cancer cells. *Journal of Environmental Pathology, Toxicology and Oncology*, *33*(3), 219–231.

Post, J. F. M., & Varma, R. S. (1992). Growth inhibitory effects of bioflavonoids and related compounds on human leukemic CEM-C1 and CEM-C7 cells. *Cancer Letters*, *67*(2), 207–213. https://doi.org/10.1016/0304-3835(92)90145-L

Pratheeshkumar, P., Son, Y.-O., Budhraja, A., Wang, X., Ding, S., Wang, L., … Shi, X. (2012). Luteolin inhibits human prostate tumor growth by suppressing vascular endothelial growth factor receptor 2-mediated angiogenesis. *PLoS One*, *7*(12), e52279. https://doi.org/10.1371/journal.pone.0052279

Pu, Y., Zhang, T., Wang, J., Mao, Z., Duan, B., Long, Y., … Gao, Z. (2018). Luteolin exerts an anticancer effect on gastric cancer cells through multiple signaling pathways and regulating miRNAs. *Journal of Cancer*, *9*(20), 3669–3675. https://doi.org/10.7150/jca.27183

Rafacho, B. P. M., Stice, C. P., Liu, C., Greenberg, A. S., Ausman, L. M., & Wang, X.-D. (2015). Inhibition of diethylnitrosamine-initiated alcohol-promoted hepatic inflammation and precancerous lesions by flavonoid luteolin is associated with increased sirtuin 1 activity in mice. *Hepatobiliary Surgery and Nutrition*, *4*(2), 124–134. https://doi.org/10.3978/j.issn.2304-3881.2014.08.06

Rao, P. S., Satelli, A., Moridani, M., Jenkins, M., & Rao, U. S. (2012). Luteolin induces apoptosis in multidrug resistant cancer cells without affecting the drug transporter function: Involvement of cell line-specific apoptotic mechanisms. *International Journal of Cancer*, *130*(11), 2703–2714. https://doi.org/10.1002/ijc.26308

Ren, L.-Q., Li, Q., & Zhang, Y. (2020). Luteolin suppresses the proliferation of gastric cancer cells and acts in synergy with Oxaliplatin. *BioMed Research International*, *2020*, 9396512. https://doi.org/10.1155/2020/9396512

Ruan, J. S., Liu, Y. P., Zhang, L., Yan, L. G., Fan, F. T., Shen, C. S., … Lu, Y. (2012). Luteolin reduces the invasive potential of malignant melanoma cells by targeting beta3 integrin and the epithelial-mesenchymal transition. *Acta Pharmacologica Sinica*, *33*(10), 1325–1331. https://doi.org/10.1038/aps.2012.93

Sato, Y., Sasaki, N., Saito, M., Endo, N., Kugawa, F., & Ueno, A. (2015). Luteolin attenuates doxorubicin-induced cytotoxicity to MCF-7 human breast cancer cells. *Biological & Pharmaceutical Bulletin*, *38*(5), 703–709. https://doi.org/10.1248/bpb.b14-00780

Selvendiran, K., Koga, H., Ueno, T., Yoshida, T., Maeyama, M., Torimura, T., … Sata, M. (2006). Luteolin promotes degradation in signal transducer and activator of transcription 3 in human hepatoma cells: An implication for the antitumor potential of flavonoids. *Cancer Research*, *66*(9), 4826–4834. https://doi.org/10.1158/0008-5472.can-05-4062

Seo, Y., Ryu, K., Park, J., Jeon, D.-k., Jo, S., Lee, H. K., & Namkung, W. (2017). Inhibition of ANO1 by luteolin and its cytotoxicity in human prostate cancer PC-3 cells. *PLoS One*, *12*(3), e0174935. https://doi.org/10.1371/journal.pone.0174935

Shao, J.-L., & Liang, H.-R., Dai, J.-X. (2016). Luteoloside inhibits proliferation of human chronic myeloid leukemia k562 cells by inducing g^2/m. *phase cell cycle arrest and apoptosis*, *15*, 39–45. https://doi.org/10.1371/journal.pone.0174935

Sia, D., Villanueva, A., Friedman, S. L., & Llovet, J. M. (2017). Liver cancer cell of origin, molecular class, and effects on patient prognosis.

Gastroenterology, *152*(4), 745–761. https://doi.org/10.1053/j.gastro.2016.11.048

Siegel, R. L., Miller, K. D., & Jemal, A. (2020). Cancer statistics, 2020. *CA: A Cancer Journal for Clinicians*, *70*(1), 7–30. https://doi.org/10.3322/caac.21590

Song, S., Su, Z., Xu, H., Niu, M., Chen, X., Min, H., … Gao, Q. (2017). Luteolin selectively kills STAT3 highly activated gastric cancer cells through enhancing the binding of STAT3 to SHP-1. *Cell Death & Disease*, *8*(2), e2612. https://doi.org/10.1038/cddis.2017.38

Sonoki, H., Tanimae, A., Endo, S., Matsunaga, T., Furuta, T., Ichihara, K., & Ikari, A. (2017). Kaempherol and Luteolin decrease Claudin-2 expression mediated by inhibition of STAT3 in lung adenocarcinoma A549 cells. *Nutrients*, *9*(6), 597. https://doi.org/10.3390/nu9060597

Sun, D. W., Zhang, H. D., Mao, L., Mao, C. F., Chen, W., Cui, M., … Tang, J. H. (2015). Luteolin inhibits breast cancer development and progression in vitro and in vivo by suppressing notch signaling and regulating MiRNAs. *Cellular Physiology and Biochemistry*, *37*(5), 1693–1711. https://doi.org/10.1159/000438535

Takahashi, T., Kobori, M., Shinmoto, H., & Tsushida, T. (1998). Structure-activity relationships of flavonoids and the induction of granulocytic- or monocytic-differentiation in HL60 human myeloid leukemia cells. *Bioscience, Biotechnology, and Biochemistry*, *62*(11), 2199–2204.

Tan, A. C., Ashley, D. M., López, G. Y., Malinzak, M., Friedman, H. S., & Khasraw, M. (2020). Management of glioblastoma: State of the art and future directions. *CA: A Cancer Journal for Clinicians*, *70*(4), 299–312. https://doi.org/10.3322/caac.21613

Tsai, P. H., Cheng, C. H., Lin, C. Y., Huang, Y. T., Lee, L. T., Kandaswami, C. C., … Lee, M. T. (2016). Dietary flavonoids Luteolin and quercetin suppressed cancer stem cell properties and metastatic potential of isolated prostate cancer cells. *Anticancer Research*, *36*(12), 6367–6380. https://doi.org/10.21873/anticanres.11234

Tsatmali, M., Ancans, J., & Thody, A. J. (2002). Melanocyte function and its control by melanocortin peptides. *The Journal of Histochemistry and Cytochemistry*, *50*(2), 125–133. https://doi.org/10.1177/002215540205000201

Tu, S. H., Ho, C. T., Liu, M. F., Huang, C. S., Chang, H. W., Chang, C. H., … Ho, Y. S. (2013). Luteolin sensitises drug-resistant human breast cancer cells to tamoxifen via the inhibition of cyclin E2 expression. *Food Chemistry*, *141*(2), 1553–1561. https://doi.org/10.1016/j.foodchem.2013.04.077

Vlotides, G., Eigler, T., & Melmed, S. (2007). Pituitary tumor-transforming gene: Physiology and implications for tumorigenesis. *Endocrine Reviews*, *28*(2), 165–186. https://doi.org/10.1210/er.2006-0042

Waks, A. G., & Winer, E. P. (2019). Breast cancer treatment: A review. *JAMA*, *321*(3), 288–300. https://doi.org/10.1001/jama.2018.19323

Wang, I. K., Lin-Shiau, S. Y., & Lin, J. K. (1999). Induction of apoptosis by apigenin and related flavonoids through cytochrome c release and activation of caspase-9 and caspase-3 in leukaemia HL-60 cells. *European Journal of Cancer*, *35*(10), 1517–1525.

Wang, L., Li, W., Lin, M., Garcia, M., Mulholland, D., Lilly, M., & Martins-Green, M. (2014). Luteolin, ellagic acid and punicic acid are natural products that inhibit prostate cancer metastasis. *Carcinogenesis*, *35*(10), 2321–2330. https://doi.org/10.1093/carcin/bgu145

Wang, L. M., Xie, K. P., Huo, H. N., Shang, F., Zou, W., & Xie, M. J. (2012). Luteolin inhibits proliferation induced by IGF-1 pathway dependent ERalpha in human breast cancer MCF-7 cells. *Asian Pacific Journal of Cancer Prevention*, *13*(4), 1431–1437. https://doi.org/10.7314/apjcp.2012.13.4.1431

Wang, Q., Wang, H., Jia, Y., Ding, H., Zhang, L., & Pan, H. (2017). Luteolin reduces migration of human glioblastoma cell lines via inhibition of the p-IGF-1R/PI3K/AKT/mTOR signaling pathway. *Oncology Letters*, *14*(3), 3545–3551. https://doi.org/10.3892/ol.2017.6643

Wang, Y., Zhang, Y., Chen, X., Hong, Y., & Wu, Z. (2018). Combined treatment with myo-inositol and luteolin selectively suppresses growth of human lung cancer A549 cells possibly by suppressing activation of PDK1 and Akt. *Nan Fang Yi Ke Da Xue Xue Bao*, *38*(11), 1378–1383. https://doi.org/10.12122/j.issn.1673-4254.2018.11.17

Wruck, C. J., Claussen, M., Fuhrmann, G., Römer, L., Schulz, A., Pufe, T., … Götz, M. E. (2007). Luteolin protects rat PC12 and C6 cells against MPP+ induced toxicity via an ERK dependent Keap1-Nrf2-ARE pathway. *Journal of Neural Transmission*, (72), 57–67. https://doi.org/10.1007/978-3-211-73574-9_9.

Wu, G., Li, J., Yue, J., Zhang, S., & Yunusi, K. (2018). Liposome encapsulated luteolin showed enhanced antitumor efficacy to colorectal carcinoma. *Molecular Medicine Reports*, *17*(2), 2456–2464. https://doi.org/10.3892/mmr.2017.8185

Wu, H. T., Liu, Y. E., Hsu, K. W., Wang, Y. F., Chan, Y. C., Chen, Y., & Chen, D. R. (2020). MLL3 induced by Luteolin causes apoptosis in tamoxifen-resistant breast cancer cells through H3K4 Monomethylation and suppression of the PI3K/AKT/mTOR pathway. *The American Journal of Chinese Medicine*, *48*(5), 1221–1241. https://doi.org/10.1142/s0192415x20500603

Xiao, B., Qin, Y., Ying, C., Ma, B., Wang, B., Long, F., … Wang, Y. (2017). Combination of oncolytic adenovirus and luteolin exerts synergistic antitumor effects in colorectal cancer cells and a mouse model. *Molecular Medicine Reports*, *16*(6), 9375–9382. https://doi.org/10.3892/mmr.2017.7784

Xiong, J., Wang, K., Yuan, C., Xing, R., Ni, J., Hu, G., … Wang, X. (2017). Luteolin protects mice from severe acute pancreatitis by exerting HO-1-mediated anti-inflammatory and antioxidant effects. *International Journal of Molecular Medicine*, *39*(1), 113–125. https://doi.org/10.3892/ijmm.2016.2809

Xu, H., Yang, T., Liu, X., Tian, Y., Chen, X., Yuan, R., … Du, G. (2016). Luteolin synergizes the antitumor effects of 5-fluorouracil against human hepatocellular carcinoma cells through apoptosis induction and metabolism. *Life Sciences*, *144*, 138–147. https://doi.org/10.1016/j.lfs.2015.12.002

Yan, X., Qi, M., Li, P., Zhan, Y., & Shao, H. (2017). Apigenin in cancer therapy: Anti-cancer effects and mechanisms of action. *Cell & Bioscience*, *7*, 50–50. https://doi.org/10.1186/s13578-017-0179-x

Yang, M. Y., Wang, C. J., Chen, N. F., Ho, W. H., Lu, F. J., & Tseng, T. H. (2014). Luteolin enhances paclitaxel-induced apoptosis in human breast cancer MDA-MB-231 cells by blocking STAT3. *Chemico-Biological Interactions*, *213*, 60–68. https://doi.org/10.1016/j.cbi.2014.02.002

Yang, Y. A., & Yu, J. (2013). EZH2, an epigenetic driver of prostate cancer. *Protein & Cell*, *4*(5), 331–341. https://doi.org/10.1007/s13238-013-2093-2

Yao, X., Jiang, W., Yu, D., & Yan, Z. (2019). Luteolin inhibits proliferation and induces apoptosis of human melanoma cells in vivo and in vitro by suppressing MMP-2 and MMP-9 through the PI3K/AKT pathway. *Food & Function*, *10*(2), 703–712. https://doi.org/10.1039/c8fo02013b

Yao, Y., Rao, C., Zheng, G., & Wang, S. (2019). Luteolin suppresses colorectal cancer cell metastasis via regulation of the miR384/pleiotrophin axis. *Oncology Reports*, *42*(1), 131–141. https://doi.org/10.3892/or.2019.7136

Yasuda, M. T., Fujita, K., Hosoya, T., Imai, S., & Shimoi, K. (2015). Absorption and metabolism of Luteolin and its glycosides from the extract of *Chrysanthemum morifolium* flowers in rats and Caco-2 cells. *Journal of Agricultural and Food Chemistry*, *63*(35), 7693–7699. https://doi.org/10.1021/acs.jafc.5b00232

Yee, S. B., Choi, H. J., Chung, S. W., Park, D. H., Sung, B., Chung, H. Y., & Kim, N. D. (2015). Growth inhibition of luteolin on HepG2 cells is induced via p53 and Fas/Fas-ligand besides the TGF-beta pathway. *International Journal of Oncology*, *47*(2), 747–754. https://doi.org/10.3892/ijo.2015.3053

Yin, H., Wang, L., Wu, M., Liu, Y., Li, N., & Chen, T. (2019). Cyanidin-3-O-glucoside chloride acts synergistically with luteolin to inhibit the growth of colon and breast carcinoma cells. *Pharmazie*, *74*(1), 54–61. https://doi.org/10.1691/ph.2019.8746

You, Y., Wang, R., Shao, N., Zhi, F., & Yang, Y. (2019). Luteolin suppresses tumor proliferation through inducing apoptosis and autophagy via MAPK activation in glioma. *Oncotargets and Therapy*, *12*, 2383–2396. https://doi.org/10.2147/OTT.S191158

Yu, Q., Zhang, M., Ying, Q., Xie, X., Yue, S., Tong, B., … Ma, L. (2019). Decrease of AIM2 mediated by luteolin contributes to non-small cell lung cancer treatment. *Cell Death & Disease*, *10*(3), 218. https://doi.org/10.1038/s41419-019-1447-y

Zang, M.-D., Hu, L., Fan, Z.-Y., Wang, H.-X., Zhu, Z.-L., Cao, S., … Liu, B.-Y. (2017). Luteolin suppresses gastric cancer progression by reversing epithelial-mesenchymal transition via suppression of the notch signaling pathway. *Journal of Translational Medicine*, *15*(1), 52. https://doi.org/10.1186/s12967-017-1151-6

Zappa, C., & Mousa, S. A. (2016). Non-small cell lung cancer: Current treatment and future advances. *Translational Lung Cancer Research*, *5*(3), 288–300. https://doi.org/10.21037/tlcr.2016.06.07

Zhang, L., Yang, F., Huang, L., Liu, A., & Zhang, J. (2017). Luteolin enhances the antitumor activity of lapatinib in human breast cancer cells. *Biomedical Research*, *28*(11), 4902–4907.

Zhang, Q., Yang, J., & Wang, J. (2016). Modulatory effect of luteolin on redox homeostasis and inflammatory cytokines in a mouse model of liver cancer. *Oncology Letters*, *12*(6), 4767–4772. https://doi.org/10.3892/ol.2016.5291

Zheng, S., Cheng, Y., Teng, Y., Liu, X., Yu, T., Wang, Y., … Wei, Y. (2017). Application of luteolin nanomicelles anti-glioma effect with improvement in vitro and in vivo. *Oncotarget*, *8*(37), 61146–61162. https://doi.org/10.18632/oncotarget.18019

Zhou, Q., Yan, B., Hu, X., Li, X.-B., Zhang, J., & Fang, J. (2009). Luteolin inhibits invasion of prostate cancer PC3 cells through E-cadherin. *Molecular Cancer Therapeutics*, *8*(6), 1684–1691. https://doi.org/10.1158/1535-7163.Mct-09-0191

Zuo, Q., Wu, R., Xiao, X., Yang, C., Yang, Y., Wang, C., … Kong, A. N. (2018). The dietary flavone luteolin epigenetically activates the Nrf2 pathway and blocks cell transformation in human colorectal cancer HCT116 cells. *Journal of Cellular Biochemistry*, *119*(11), 9573–9582. https://doi.org/10.1002/jcb.27275

How to cite this article: Ganai SA, Sheikh FA, Baba ZA, Mir MA, Mantoo MA, Yatoo MA. Anticancer activity of the plant flavonoid luteolin against preclinical models of various cancers and insights on different signalling mechanisms modulated. *Phytotherapy Research*. 2021;1–24. https://doi.org/10.1002/ptr.7044