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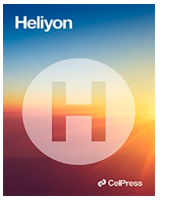

Review article

Revisiting luteolin: An updated review on its anticancer potential

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ABSTRACT

Numerous natural products found in our diet, such as polyphenols and flavonoids, can prevent the progression of cancer. Luteolin, a natural flavone, present in significant amounts in various fruits and vegetables plays a key role as a chemopreventive agent in treating various types of cancer. By inducing apoptosis, initiating cell cycle arrest, and decreasing angiogenesis, metastasis, and cell proliferation, luteolin is used to treat cancer. Its anticancer properties are attributed to its capability to engage with multiple molecular targeted sites and modify various signaling pathways in tumor cells. Luteolin has been shown to slow the spread of cancer in breast, colorectal, lung, prostate, liver, skin, pancreatic, oral, and gastric cancer models. It exhibits antioxidant properties and can be given to patients receiving Doxorubicin (DOX) chemotherapy to prevent the development of unexpected adverse reactions in the lungs and hematopoietic system subjected to DOX. Furthermore, it could be an excellent candidate for synergistic studies to overcome drug resistance in cancer cells. Accordingly, this review covers the recent literature related to the use of luteolin against different types of cancer, along with the mechanisms of action. In addition, the review highlights luteolin as a complementary medicine for preventing and treating cancer.

1. Introduction

The global morbidity and mortality rate from cancer is staggering. According to WHO report on February 3, 2022, cancer is the prime cause of mortality on a global level, In 2020, an estimated 10 million fatalities were attributed to lung cancer (1.80 million deaths out of 2.21 million cases), colon cancer (0.91 million deaths out of 1.93 million cases), and breast cancer (0.91 million deaths

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Abbreviations

ABTS	2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
ALP	Alkaline phosphatise
ALT	Alanine Transferases
AMPK	Adenosine monophosphate (AMP)–activated protein kinase (AMPK)
AST	Alanine Phosphatases
APAF1	apoptotic protease activating factor 1
ATF4	Activating Transcription Factor 4
BAX	Bcl-2 Associated X-protein
Bcl-X_L	Eight helical structures of B cell lymphoma
C4H	Enzyme *trans*-cinnamate 4-hydroxylase
CHI	Chalcone isomerase
COX-2	Cyclooxygenase 2
DOX	Doxycycline
DPPH	1,1-diphenyl-2-picrylhydrazyl
EMT	Epithelial-to-mesenchymal transition
F3′H	Enzyme flavonoid 3′-hydroxylase
FNS I	Flavone synthase I
HCT116	Human colorectal cancer cell line
HRMECs	Human retinal microvascular endothelial cells
iNOS	Inducible nitric oxide synthase
IL-6	Interleukin 6
LPS	Lipopolysaccharides
MAPK	Mitogen-activated protein kinase
MCF-7	Michigan Cancer Foundation-7 (breast cancer cells)
MDA-MB 231	M.D. Anderson - Metastatic Breast 231
MDM2	Oncoprotein is a cellular inhibitor of the p53 tumor suppressor
MTT	3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyltetrazolium bromide (for a colorimetric assay that measures cell metabolic activity)
NADPH	Nicotinamide adenine dinucleotide phosphate
NC	Naringenin chalcone
NF-kB	Nuclear factor kappa B
NO	Nitric oxide
PCV	Packed Cell Volume
4CL	p-coumarate 4-ligase
PERK	Phosphorylation of protein kinases
Phe	Phenylalanine
PI3K/Akt	Phosphatidylinositol 3′-kinase – protein kinase B/Akt
PLC/PRF/5, HepG2, SK-Hep-1 and HA22T/VGH	Human hepatocellular carcinoma cells
PLK-1	Polo-like kinase 1
RBCs	Red Blood Cells
ROS	Reactive oxygen species
STAT6	Signal transducer and activator of transcription 6
TK6	lymphoblast cell line, where TK is thymidine kinase
TNF	Tumor Necrosis Factor
TRAIL	TNF-related apoptosis-inducing ligand
VEGF	Vascular endothelial growth factor
VV-IL-24	Oncolytic vaccinia virus- Interleukin 24
XIAP	X-linked inhibitor of apoptosis protein

out of 1.93 million cases). Additionally, 0.68 million deaths occurred among 2.26 million cases [1]. Chemotherapy is a plausible treatment option for cancer patients, but the adverse effects and high death rate warrant an alternate treatment plan involving physiologically safe medications and naturally occurring substances that stand out as strong therapeutic contenders. Furthermore, this exacerbates the requirement for safer substitutes with maximum potency for detecting the tumor cells to traditional medicines resistance in cancerous cells [2].

Naturally occurring polyphenols and flavonoids not only suppress the growth and continuance of such malignancies by regulating the main monitoring pathways but also improve the cancerous cell's sensitization. These natural products offer a potential anticancer profile. Moreover, anticancer phytochemicals target a variety of interrelated oncological pathways at once, thus preventing relapse

and thwarting resistance mechanisms in cancer cells [3]. Phenolics provide a noteworthy multidimensional profile of mechanisms of action in tumor pathways among the different natures of anti-oncologic phytochemicals. Within this context, luteolin (3,4,5,7-tetrahydroxy flavone, Fig. 1) is a natural flavonoid, significantly present in numerous fruits and vegetables, including celery, chrysanthemum flowers, carrots, and onion leaves. This particular phenolic phytochemical, which belongs to the flavone class of flavonoids, has been utilized to treat cancer by lowering angiogenesis, metastasis, and cell proliferation, and by causing apoptosis and cell cycle arrest [4]. In addition, luteolin can act as either an antioxidant or a pro-oxidant, and exhibit several biological activities such as anti-allergy, anti-inflammatory, and anti-cancer properties [5].

Recent research indicates that luteolin exerts anticancer properties in malignancies by controlling the expression of several oncological pathways that induce carcinogenesis. It exerts a protective effect in opposition to oxidative stress and endothelial cell mitochondrial dysfunction. It protects against H_2O_2-induced oxidative stress by modulating ROS-mediated P38 MAPK/NF-κB and calcium-evoked mitochondrial apoptotic signaling pathways [6]. Additionally, findings showed that luteolin inhibits the epithelial-to-mesenchymal transition (EMT) involved in the growth, progression, and metastasis of cancer cells. These phenomena are caused by the cytoskeleton being depleted, biomarker E-cadherin being expressed more frequently, and vimentin and N-cadherin being expressed much less frequently after that [7]. Furthermore, due to its outstanding neuroprotective characteristics, luteolin can alleviate the spinal cord and brain damage caused by 1-methyl-4-phenylpyridinium. It downregulates and inhibits cellular pathways such as X-linked inhibitor of apoptosis protein (XIAP), phosphatidylinositol 3′-kinase (PI3K)/Akt, and nuclear factor kappa B (NF-kB) [8]. Luteolin occurs naturally as a glucoside as depicted in Fig. 1. Several studies highlighted the antioxidant, anticancer, anti-inflammatory, and neuroprotective properties of luteolin. It also inhibits liposaccharides (LPS)-stimulated TNF-, IL-6, and NO in a murine macrophage. Similarly, luteolin caused a significant decrease in alveolar macrophage and peripheral macrophage RAW 264.7 cell lines' secretions of INF-, IL-6, COX-2, and inducible nitric oxide synthase (iNOS) when LPS was present. Moreover, luteolin reduces brain tissue inflammation and controls many cells signaling pathways in neurodegenerative illnesses and neuronal cell death. Luteolin, a flavone exists in numerous medicinal plants and herbs, exhibits a range of therapeutic effects like anti-inflammatory, antioxidant, neuroprotective, and analgesic characteristics that can be most useful in the management of pain [9].

There is a great potential for luteolin, as a chemopreventive food ingredient. In this respect, it interacts with several recognized targets to prevent the growth of cancer by causing cell cycle arrest and apoptosis [7]. Another promising effect of luteolin is its potential to stop angiogenesis and tumor cell metastasis. Therefore, luteolin could be a potential therapeutic agent for synergistic research and may be able to overcome the drug resistance of cancer cells [5]. Luteolin exhibits active biological properties that include anticancer, antimicrobial, and anti-inflammatory properties. However, we are particularly intrigued by its anticancer potency reported by researchers over the years. By focusing on apoptosis, cell-cycle progression, and angiogenesis, luteolin is known to inhibit tumor growth. It kills cells by increasing BAX, caspase-3, and p21 while decreasing Akt, PLK-1, cyclin-B1, cyclin-A, CDC-2, CDK-2, and Bcl-2. It has been demonstrated to increase STAT3 protein degradation and limit their activation in several cancer cells. Current seminal studies highlighted the luteolin's anticancer effect and thus its promising role in the field of chemoprevention. In this regard, the vegetables and herbs containing luteolin include lettuce, cabbage, kale, thyme, parsley and rosemary [10].

Recently published reports revealed that luteolin decreases carcinogenesis by interfering with cell cycle progression, preventing proliferation, exerting apoptosis, and limiting malignant cell migration and invasion [11]. For instance, luteolin can slow the spread of cancer in breast cancer cell lines [12], colorectal cancer [13], lung cancer [14], and prostate cancer [15]. Luteolin's anticancer properties are controlled by its capacity to engage with several molecular target sites and modify various signaling pathways in tumor cells [16]. In this respect, the occurrence of hydroxyl groups in flavonoids is key to their biological activity. In addition, C═C between C2 and C3 is what gives luteolin its powerful anti-oxidative characteristics, and the four –OH groups at the positions of C3', C4', C5, and C7 are what give it its effective biocidal activity. Because carbonyl oxygen is present at C4 sites, it is powerful against bacteria.

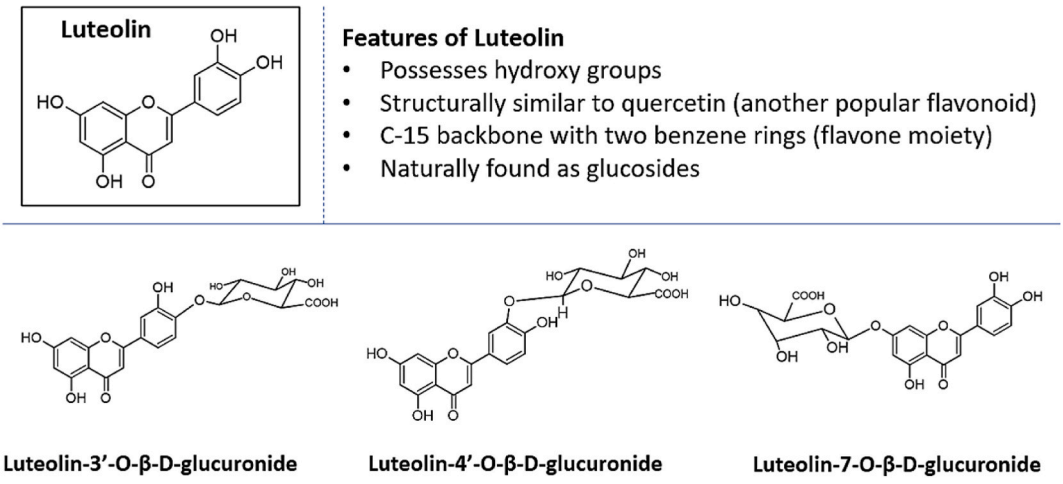

Fig. 1. Chemical structure of luteolin and its glucosides.

Biologically, powerful luteolin derivatives have also been reported. According to a recent investigation by Lo et al. (2021), mono-acylated luteolin derivatives have improved anti-proliferative properties against the cancer cell lines HCT116 and MDA-MB-231 [17]. In a related study, Ravishankar and coworkers identified a 4-thiomethoxy derivative, a luteolin derivative, as an anti-angiogenic. The luteolin derivative identified was chosen for cancer treatment due to its anti-angiogenic properties, meaning that it inhibits the formation of new blood vessels that tumors need to grow and spread. In addition, the derivative induced apoptosis (programmed cell death) in ovarian cancer cells, suggesting that it has the potency as a therapeutic agent against the diseased condition [18]. In conclusion to the previous discussion and alleviating effects of luteolin against several types of cancer, this work is a focused and comprehensive evaluation of the current state of knowledge on luteolin as an anticancer agent. Further, an update on the recent findings on luteolin that includes new studies on the mechanism of action of luteolin and its potential as a therapeutic agent is discussed. By providing a detailed and up-to-date assessment of luteolin's anticancer potential along with the mechanisms of action, we hope that future research shall contribute toward effective cancer therapies. Below are details related to the biosynthesis and anticancer properties of luteolin against different types of cancer.

2. Biosynthesis of luteolin

Phenyl propanoids, derived from phenylalanine molecules are substances that are responsible for plant growth, cellular metabolism, and biotic and abiotic stimuli [19]. After the shikimate route, the phenylpropanoid pathway begins. Both phenylpropanoid and flavonoid pathways diverge from the main secondary metabolite pathway. Next, the phenylpropanoid pathway involves generation of secondary metabolic phytochemicals that produce the luteolin. Depicted in Fig. 2 is a schematic representation of the biosynthesis of luteolin.

The initial step in the production of flavonoids is the conversion of phenylalanine (Phe, an amino acid) by the enzyme phenylalanine ammonia-lyase to *trans*-cinnamic acid, which is then converted to *trans*-coumaric acid by the C4H enzyme (i.e. t-cinnamate 4-hydroxylase), and finally to naringenin chalcone by the enzyme chalcone isomerase (CHI). This will be converted to naringenin, a crucial substance that serves as a necessary step in the biosynthesis of luteolin. The enzyme flavonoid 3′-hydroxylase (F3′H), which adds a hydroxyl (-OH) group at the 3′ position in the beta ring, also converts naringenin to eriodictyol as shown in Fig. 2 [20].

Likewise, luteolin biosynthesis results from oxidation by creating a C═C between the C2 and C3. In this respect, flavone synthase catalyses the oxidation of flavanones to flavones. It is interesting to note that flavone is biosynthesized by two distinct enzymes, flavone synthase I (EC 1.14.11.22) and flavone synthase II. Flavone synthase II (FNS II), a membrane-bound cytochrome P450 dependent monooxygenase, is present in a variety of plants, whereas flavone synthase I (FNS I), a soluble dioxygenase, was extracted and isolated from members of the *Apiacea* family. FNS I is a member of 2-oxoglutarate-dependent dioxygenases family, which is engaged in several metabolic processes in plants, fungi, bacteria, and animals as well. The unusual substrate specificity of FNS I, one of the five 2-oxoglutarate-dependent enzymes engaged in the biosynthesis of flavonoids, is thought to contribute to its high pathway specificity. The 2,3-desaturation of the flavanone is catalysed by the flavone synthases I and II in a single step, resulting in the synthesis of apigenin from naringenin and luteolin from eriodictyol, respectively. The cytochrome P450-dependent monooxygenase flavonoid 3′-hydroxylase is needed to carry out an extra hydroxylation step that results in the synthesis of the dihydroxylated B-ring compound luteolin. This pathway shows the two potential paths to luteolin (through eriodictyol or apigenin) [21].

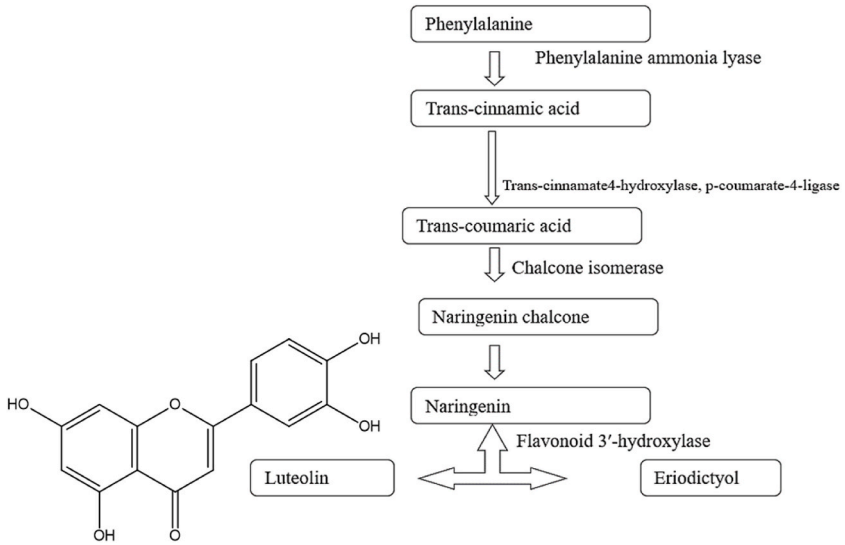

Fig. 2. Biosynthesis of dietary luteolin.

3. Anticancer properties of luteolin and its mechanism of action

As described in Section 1, luteolin mediates the expression of cancerous cells through cell cycle arrest, apoptosis induction, cell proliferation, mitigation of metastasis, and angiogenesis [4]. The antitumor potential of luteolin has been recognized in malignancies where it strongly regulated the expression of multidimensional cancer formation cascades [22]. It promoted stress stimuli in the endoplasmic reticulum of glioblastoma and caused mitochondrial impairment, which induced the formation of ROS in cells [6]. Furthermore, these episodes stimulate the expression of proteins linked to oxidative stress through modulation of phosphorylation of ATF4, PERK, cleaved caspase 12, and eIF2α. This natural flavone can alleviate EMT which is linked to metastasis and proliferation of cancer cells. These processes are induced by cytoskeleton dwindling and an increase in the level of mRNA of E-cadherin, with a subsequently marked decrease in the mRNA levels of vimentin and N-cadherin [22]. Moreover, luteolin holds efficacy to alleviate brain trauma and damage of the spinal cord exerted by 1-methyl-4-phenylpyridinium because of its potent neuroprotective actions. Additionally, cancer cells sensitization modulated by luteolin alleviates the cytotoxicity induced by chemotherapy as a result of suppression and downregulation of cellular cascades including X-linked inhibitor of apoptosis protein, phosphatidylinositol 3′-kinase/Akt, and nuclear factor kappa B [8]. Due to all these efficacies of luteolin against cancer cells, this compound has attracted much attention to serving as an efficacious candidate in the development of therapeutic agents for the treatment of cancer. The anticancer efficacy of luteolin against various kinds of cancer is highlighted in the inset of Fig. 3.

Luteolin prompts apoptosis in cancerous cells by activating caspases and causing mitochondrial dysfunction. It also inhibits cell proliferation by blocking cell cycle progression and reducing DNA synthesis and repair. Furthermore, it suppresses metastasis by inhibiting the epithelial-to-mesenchymal transition (EMT) and suppressing mesenchymal markers expressions such as vimentin and N-cadherin. Luteolin also inhibits angiogenesis by suppressing pro-angiogenic expressions particularly, that of VEGF. It modulates signaling pathways including the PI3K/Akt and NF-κB pathways, which are involved in various aspects of cancerous cell survival and metastasis. Overall, the multiple and diverse mechanisms of action of luteolin on cancer cells make it a promising compound in the development of novel anticancer drugs [23].

3.1. Breast cancer

Enhanced bioavailability of luteolin was obtained through forming mono-acylated derivatives. The luteolin derivatives displayed better antiproliferative and antioxidant activities against MDA-MB-231 breast cancer [17]. In another work, luteolin induced cell cycle arrest specifically in the S phase by decreasing telomerase levels and inhibiting phosphorylation of NF–κB inhibitor α in MDA–MB–231 cells. Consequently, this led to a reduction in mRNA expression levels of human telomerase reverse transcriptase, which encodes the catalytic subunit of telomerase. Moreover, luteolin caused the suppression of breast cancerous cell development and induced apoptosis to regulate its progression [24].

In addition, research findings showed that luteolin causes morphological alterations to the nucleus and exerts inhibition in cell cycle G1 and sub-G1 phase's progression in MCF-7 breast cancer cells. Luteolin also increased mRNA levels of caspase and death receptors like DR5. It enhanced caspase-9/-8/-3 activity and inhibited the poly-ADP ribose polymerase, a major index that aids a cancer cell to repair itself in a dose-dependent fashion. Moreover, luteolin stimulated the impairment of mitochondrial membrane

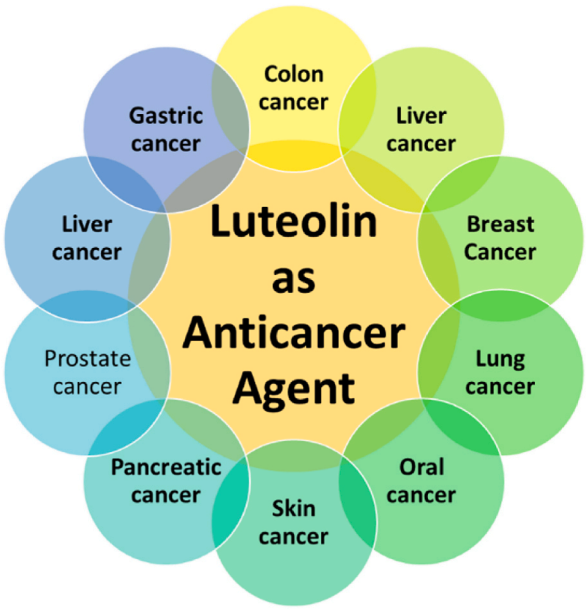

Fig. 3. Luteolin against different forms of cancer.

potential with subsequent cytochrome *c* release. This increased the expression of Bax and suppression in Bcl-2 expression. Overall, luteolin induced apoptosis and cell cycle arrest in cancer cell lines [11]. Similarly, luteolin displayed anticancer action against MDA-MB-543 cells through apoptosis induction, cell cycle regulation, and antiproliferative action. The compound induced a significant reduction in the growth of cancer cells in a time-dependent fashion. Reduction in sub-G1 phase cell population indicated cell cycle arrest by the compound in cancerous cells [25]. Luteolin targets human telomerase reverse transcriptase, which can stop BC cell growth and the development of tamoxifen resistance in BC. Therefore, it can be a potential natural medication to prevent BC invasion and metastasis [26].

3.2. Colon cancer

Mono-acylated derivatives of luteolin were reported to show antioxidant and anticancer actions against HCT116 colon cancer cells. Acylation of the –OH groups enhances the lipophilicity of the derived molecules which increases their bioavailability. In addition, the ant-oxidant action of the luteolin derivatives against 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) radicals was similar to that of the parent compound, luteolin [17]. Luteolin was shown to inhibit the cell cycle at the G2/M phase and induce apoptosis in colon cancer cells. A flow cytometric study indicated that the compound causes apoptosis and enhances the G2/M phase cell cycle in LoVo colon cancer cell lines in a dose- and time-dependent manner. Similarly, it was found through Western blotting analysis that luteolin confers inhibitory action against the proliferation of cells in LoVo human colon cells by causing cell cycle arrest and inhibiting cell division in cycle 2 and cyclin B1. These reactions are regulated by deoxyadenosine triphosphate-regulated stimulation of apoptotic protease activating factor 1 (APAF1). Furthermore, it was shown that there is a reduction in the body weight in mice with colon tumor. In conclusion, these data show the chemotherapeutic and chemopreventive potential of luteolin against colon cancer cells in humans [27]. Similarly, Yoo and coworkers reported the anticancer action of luteolin against colon tumor via autophagy and apoptosis. HCT116 cells showed elevation in p53 phosphorylation and expression of the p53 target gene, which then results in cell cycle arrest and apoptosis following luteolin treatment. Hence, luteolin induced autophagy in p53 wild-type cells. This is an indication that autophagy by the compound is dependent on p53 [28].

Numerous investigations revealed luteolin's involvement in colorectal cancer cells. By inducing apoptosis in colorectal cancer cells, Kang et al. (2019) showed that luteolin exerts anticancer properties on those cells through the enhanced Nrf2 transcription caused by its promoter's DNA demethylation [29]. Furthermore, luteolin enhanced the expression of apoptotic proteins and antioxidant enzymes by increasing the engagement between Nrf2 and p53. These results highlight the possible application of luteolin in cancer treatment and prevention [30]. Similarly, luteolin exhibited inhibitory effects on HCT116 cell growth and colony synthesis. Moreover, luteolin stimulated Nrf2's mRNA and protein expression as well as the antioxidant enzymes HO-1 and NQO1, which detoxify it in phase II. Most significantly, luteolin can stop the activities of histone deacetylases (HDAC) and DNA methyltransferases (DNMT) to epigenetically regulate Nrf2 expression. Furthermore, luteolin induced autophagy and apoptosis in HCT116 colon cancer cells via a p53-dependent mechanism. By acting through the MAPK pathway, luteolin has been shown to stop the growth of colorectal cancerous cells, halt the cell cycle, damage DNA, and accelerate apoptosis, suggesting that luteolin may prove to be a useful adjuvant for CRC treatment in the future [31].

3.3. Gastrointestinal cancer

The anticancer effect of luteolin in various models was found to be linked to the modulation of different proteins and signal transduction cascades [23]. Overall, research findings showed that luteolin confers its pharmacological actions by abrogating cyclin E, MMP-2, cyclin D1, vimentin, Bcl2, N-cadherin and stimulating E-cadherin, Bax, and p21 expressions in gastric tumor cells. A decrease in the expression of p-PI3K, p-mTOR, p-AKT, p-STAT3, and Notch1, and an increase in the level of p-P38 signal transduction in gastric tumor cells confirms luteolin's anticancer activities [32]. Within this context, the use of luteolin (40 mg/kg) resulted in an effective abrogation of cancer growth in BGC-823 gastric tumor xenografts in experimental mice. Published reports showed that luteolin suppresses the immune system's activation and the expressions of VEGF-A and MMP-9; this prevents the growth of cancer. Additionally, the compound remarkably inhibited cancer growth in cMet-overexpressing individual-derived xenograft model, and immunohistochemistry works showed that luteolin markedly reduced cMet, ki-67, and MMP-9 expression in cancerous tissues. Moreover, luteolin inhibited invasiveness and proliferation and enhanced apoptosis of c-Met overexpressing gastric tumor cells (SGC7901 and MKN45). Furthermore, it improved the stimulation of proteins linked to apoptosis including poly (ADP-ribose) polymerase-1 and caspase-3 and downregulated MMP-9. In addition, luteolin reduced phosphorylation and expression of cMet and knockdown the phosphorylation of ERK and Akt, and the downstream phosphorylated levels of Akt were discovered not to be dependent on cMet [33]. Luteolin considerably inhibits the proliferation, invasion, and migration of gastric tumor cells in a time- and dose-dependent fashion, causing apoptosis in *in vitro* models and inducing a reduction in the development of tumour cells in *in vivo* models [34]. In this respect, luteolin treatment induced EMT reversion through cytoskeleton shrinkage and elevation in E-cadherin expression and downstream of the mesenchymal markers such as Snail, vimentin, and N-cadherin in gastric tumor cells. Moreover, it inhibited Notch1 signal transduction [34].

Additionally, luteolin prevented umbilical vein endothelial cell lines from forming tubes by inducing a reduction in cell proliferation and migration. In an investigation of gastric tumor cells, the molecule inhibited vasculogenic mimicry Hs-746T tumor cell lines and suppressed the secretion of VEGF through inhibition of Notch1 expression in gastric tumors. Therefore, it was proposed that luteolin inhibits the formation of vasculogenic mimicry and angiogenesis in gastric tumor cells by decreasing the secretion of VEGF based on the expression of Notch1 [35]. Gastric cancer (GC) is the second major cause of cancer-related death globally and the fourth

most frequent gastrointestinal malignancy [36]. Even with the endoscopy examination and increase in the rate of earlier diagnosis of GC combined with timely surgical resection, long-term survival remains unsatisfactory due to higher metastasis, recurrence drug resistance, and the lack of effectiveness to reverse advanced GC [37]. The detailed mechanism of luteolin's effect on GC is poorly understood, albeit few seminal studies that investigated the effect of luteolin on GC.

Song et al. (2017) demonstrated that luteolin selectively killed drug-resistant STAT3 overactivated GC cells [38]. Treating GC cells with luteolin inhibited STAT3 phosphorylation and decreased the target gene expression Mcl-1, Bcl-xl, and survival. Moreover, in vivo studies confirmed the inhibitory characteristics of luteolin on tumor growth and progression. These studies postulated the crucial importance of SHP-1 in obliterating luteolin's suppressive action on STAT2 and cell death. Zang et al. (2017) examined the effect of luteolin on cell proliferation, migration, invasion, and apoptosis using CCK-8, flow cytometry, *trans*-well assay, RT-PCR, and Western blot assays [34]. These researchers reported that luteolin reduced Notch1 signaling and reversed EMT by cytoskeleton shrinkage and induced expression of epithelial biomarkers called E-cadherin and downregulating N-cadherin, snail and vimentin (mesenchymal biomarkers). *In vivo* studies demonstrate that luteolin exerts tumor growth suppression. In this context. Pu et al., 2018 conducted in vitro and in vivo studies to investigate the effect of luteolin on the cell cycle and its viability [32]. They observed that luteolin affected certain signalling pathways such as Notch1, PI3K, AKT, mTOR, ERK, STAT3, and P38. Furthermore, the molecular activity of luteolin was found to affect expressions of certain miRNAs.

3.4. Lung cancer

Luteolin is efficacious against cancer of the lungs. Findings indicated that the compound stimulates the accumulation of ROS that mediate the expression of tumor necrosis factor-activated cascade in lung cancerous cells. It up-regulates the expression of c-Jun N-terminal kinase and down-regulates the NF-κB expression, thus stimulating the lung cancer cells apoptosis caused by tumor necrosis factor. It targets many cancer pathways in combating lung cancer, including redox stress, production of ROS, cell cycle arrest, induction of autophagy, initiation of apoptosis, and suppression of cell proliferation, which ultimately results in the death of tumour cells [22]. Furthermore, the pro-apoptotic action and cell cycle inhibition mechanism of luteolin in lung carcinoma cells (A549) were proposed by Cai and co-workers [39]. By using the Western blot analysis, these researchers showed that luteolin activates JNK, elevates cleavage of caspase-3 and procaspase-9, and augments Bax production. It additionally exerts inhibition of NF-κB TNF-α-regulated *trans*-nuclear translocation [39]. Similarly, Meng and colleagues showed that luteolin inhibits human non-small cell lung cancer (A549) cells through induction of apoptosis and inhibition of migration [40]. It exerts an anti-proliferation effect and induces apoptosis in A549 lung adenocarcinoma cells through an increase in the activation of caspase-9 and -3, reduced Bcl-2, the elevation of Bax expressions, the phosphorylation of MEK and its down-stream kinase ERK, and the activation of Akt. Furthermore, inhibition of MEK-ERK indicates that the MEK-ERK signaling pathway plays a significant role in mediating the pro-apoptotic effect and anti-migration effects of luteolin [40].

According to molecular mechanism and action, luteolin induced apoptosis in NCI–H460 human non-small cell lung cancer cells by controlling both extrinsic and intrinsic cascades, which were inhibited by z-Val-Ala-Asp-fluoromethylketone [41]. This suggests that luteolin can stimulate apoptosis that is dependent on caspase. Furthermore, it induced apoptosis through the phosphorylated homologous eukaryotic initiation factor 2 alfa/C/EBP protein, suggesting a possible connection between endoplasmic reticulum stress and luteolin-induced programmed cell death in NCI–H460 cells. Furthermore, luteolin was shown to activate autophagy, and when autophagy was inhibited, programmed cell death was reduced. As a result, it was found that luteolin-induced autophagy functions as a mechanism for cell death [41]. In a different study, luteolin enhanced Sirt1-regulated apoptotic cell death in NCI–H460 cells, demonstrating its anticancer properties [42,43]. Furthermore, by lowering the mRNA levels of LIM domain kinase signaling-related targets, including as p-cofilin and phosphorylated LIM domain kinase, it enhanced cleaved caspase-3 levels and decreased cyclin D1 expression. Additionally, the substance decreased the levels of p-cofilin, phosphorylated LIM domain kinase, and Ki-67, which all prevented the formation of tumors in the xenograft created from lung tumour patients [43].

Tumor-associated macrophages play crucial roles in the progression of cancer [44]. In this respect, Choi et al. (2016) reported that luteolin blocks the addition of phosphate group to STAT6 (a major IL-4 downstream signal) and induces a reduction in the mRNA levels of M2-associated genes. They also discovered that luteolin induces a reduction in Lewis lung carcinoma cell lines migration in a manner that was chemokine (C–C motif) ligand 2 dependent [45]. Furthermore, immunity-based therapy is a remarkable therapeutic approach to treating cancer [23]. Immune checkpoint compounds upregulation is linked to the impaired cytotoxic T-cells and exhausted phenotype to overcome the immunity of the host. By interfering with the interaction between programmed death-ligand 1 and programmed death protein 1, inhibitors of the immune checkpoint can reverse the ability of the immunity to fight against tumor cells [46]. Jiang and coworkers showed that luteolin, apigenin, and an anti-programmed death protein-1 antibody interact to influence the expression of programmed death-ligand 1, and anticancer actions were determined in Kristen rat sarcoma virus mutant with lung cancer. In addition, these researchers found that luteolin and apigenin inhibit the growth of lung cancer, enhance programmed cell death, and reduce the mRNA levels of interferon-gamma-induced programmed death-ligand 1 by lessening STAT3 phosphorylation. Also, the two compounds showed strong anticancer actions in xenograft models of Lewis lung and H358 cells, and treatment with the monoclonal programmed death protein 1 antibody elevated the T-cell infiltration to cancer tissues. These results suggest that a combination treatment between luteolin or apigenin and programmed death protein 1 could have a synergistic action in human non-small cell lung cancer cells with K-Ras-mutant. The combination therapy involves radiotherapy and anticancer agents which enhances the therapeutic effectiveness an essential strategy for several tumor types. It is based on the approach that antitumor agents employ a different mode of action to radiotherapy. This may elevate the response of tumor cells to the action of ionizing radiations. Such anticancer agents are called radiosensitizers [47]. In lung cancer cells, combination therapy of ionizing radiation and luteolin

enhanced programmed cell death through Bcl-2 downregulation with subsequent stimulation of caspase-9, -8, and -3. Also, the molecule caused the addition of phosphate to p38 MAPK and accumulation of ROS. Furthermore, combination therapy of ionizing radiation with luteolin induced suppression in the growth of cancer and elevated programmed cell death in the NCI–H460 cell xenograft mice model. It was proposed that the compound can serve as a radiosensitizer, enhancing programmed cell death by causing p38/ROS/cascade pathway [48].

Researchers employed the mouse cecal ligation and puncture (CLP) model to investigate the potential mitigating effects of luteolin on lung injury in vivo. Zhang et al. (2021) illustrated the robust anti-inflammatory properties of luteolin through the stimulation of Treg activity. Mice subjected to CLP and treated with luteolin exhibited a noteworthy decrease in the levels of caspase-11, caspase-1, gasdermin D (GSDMD), IL-1α, and IL-1β proteins compared to the control group. Luteolin administration in mouse lung tissue resulted in reduced glutathione levels and superoxide dismutase activity, along with a significant decrease in malondialdehyde levels. Additionally, the expression of TNF-α and IL-10 mRNA in lung tissue was diminished upon luteolin treatment. The findings further indicated that luteolin mitigates sepsis-induced acute lung damage in mice by inhibiting NF-κB, oxidative stress, components of the iNOS pathway, and intercellular adhesion molecule (ICAM)-1 [49]. Luteolin inhibits NF-κB activation and activates the AKT/Nrf2 pathway, making it a promising treatment option for $HgCl_2$-induced lung injury. Luteolin reduces the damage caused by LPS-induced bronchopneumonia both in vivo and in vitro by downregulating miR-132. These results gave rise to a theoretical framework for additional research on luteolin's potential use in treating paediatric bronchopneumonia. In RAW264.7 cells activated by LPS, luteolin suppressed the activity of proinflammatory mediators (iNOS/NO, HMGB1, COX-2, and NF-κB). To sum up, luteolin has been shown to ameliorate lung injury brought on by HgCl2, LPS, and CLP [50,51].

3.5. Oral cancer

Research findings indicated that luteolin strongly inhibits the rate of proliferation and the activities of CD44 positive and acetaldehyde dehydrogenase in oral cancer stem cell lines. In addition, the combination treatment of luteolin and radiotherapy strongly inhibited metastasis and invasion of oral cancer, thus it was proposed that the compound reverses oral tumor cells' radiosensitivity [52].

3.6. Skin cancer

In skin cancer, luteolin exhibited cytotoxicity against human melanoma (A375) and human immortalized keratinocytes (HaCaT) cells. The compound confers cell cycle arrest and programmed cell death in these cells as shown by the cellular DNA fragmentation and flow cytometry analyses. In addition, luteolin incubation with cancer cell lines results in cell accumulation in the G2/M phase in HaCaT cell lines and G0/G1 phase in A375 cell lines. Induction of apoptosis, cell proliferation inhibition, and stimulation of cell cycle arrest for the apoptosis of cancer of the skin [53].

3.7. Pancreatic cancer

Luteolin exhibits ameliorative action against pancreatic cancer. Based on this, the compound alleviated pancreatic ductal adenocarcinoma cells, proliferation of cells, and improved the anti-proliferative action of TRAIL on tumor cells by decreasing miR-301-3p [54]. Luteolin (100 ppm) inhibited carcinogenesis in female Syrian golden hamsters by enhancing amylase activity and suppressing incidence and multiplicity of PDACs, Ki-67 labelling index, pSTAT3 signal transduction, neoplastic lesions progression, DPYD, and lesions [55]. Also, the molecule (150 and 75 mg/kg) inhibited the growth of the tumor in SCID mice xenograft [56]. Luteolin has been shown to exhibit chemopreventive therapeutic role against prostate cancer through induction of apoptosis, reduction in the contraction of extracellular matrix, growth inhibition, and invasion [57].

3.8. Prostrate cancer

In Du145-III isolated prostate cancer cell lines, the compound reduced vasculogenic mimicry, malignancy, and spheroid creation associated with anchorage. In addition, luteolin promoted reduction in the mRNA levels of certain tumor stem cell biomarkers and was proposed to be a possible anti-metastasis and anti-angiogenesis molecule for managing prostate cancer [58]. Research published by Zhou and coworkers in 2009 showed that luteolin inhibits the invasion of prostate cancer (PC3) cell lines through E-cadherin via the MDM2 protein, as the attack of prostate cancer cell lines by E-cadherin knockdown or overexpressing MDM2 could be restored following treatment with luteolin. In the same work, the compound inhibited MDM2, and active Akt overexpression led to a reduction of luteolin-induced E-cadherin expression. Hence, luteolin modulates E-cadherin via the Akt/MDM2 cascade in prostate cancer [57].

In another work, the antiangiogenic action of luteolin was investigated; results revealed that the compound strongly inhibits endothelial proliferation of cells activated by VEGF, invasion, chemotactic migration, angiogenesis, and tube formation by selecting the VEGFR-2-mediated Akt/ERK/mammalian target of rapamycin/P70S6K/MMPs cascade that induced reduction of prostate cancer angiogenesis and growth. The compound reduced angiogenesis (ex vivo) as investigated through a chick embryo chorioallantoic membrane analysis and in vitro, as investigated by a rat aortic ring analysis. Additionally, luteolin inhibited the growth of cancer by enhancing angiogenesis and apoptosis in human prostate xenograft mice. Hence, it decreased the production of proinflammatory proteins including TNF-α, IL-6, IL-1β, and IL-8 in prostate tumor cells [59]. Similarly, luteolin (30 μM) was effective against human prostate tumor (LNCaP) cells through enhancing apoptosis, decreasing the expression of androgen receptors, and up-regulating

prostate-derived Ets factor [60]. Prostate cancer cells rely on androgens (male sex hormones) for growth and survival. Androgen receptors are proteins within these cells that bind to androgens and trigger pro-cancerous signaling pathways. Luteolin's effect on androgen receptors suggests that luteolin can suppress the expression of these receptors and the splice variants. Splice variants are alternative forms of the androgen protein with potentially different functions. This suppression could occur through multiple mechanisms. Luteolin might directly reduce the production of androgen receptors mRNA, leading to the availability of fewer androgen receptor proteins. Certain molecules can tag androgen receptors for degradation, and luteolin might enhance this process. Even if present, luteolin might prevent androgen receptors from binding to androgens or interacting with downstream signaling pathways. By suppressing the expression or activity of androgen receptors, luteolin could potentially slow down prostate cancer cell growth and induce apoptosis [61,62].

Recently, luteolin elevated the Maspin gene expression, N-myc downstream-regulated gene 1, and B-cell translocation gene 2, and the transient gene expression analysis showed that co-transfecting the PDEF expression vector indued an elevation in the promoter actions of N-myc downstream-regulated gene 1, Maspin gene, and B-cell translocation gene 2 [23]. The compound inhibited the expression of prostate-specific antigens by down-regulating the expression of androgen receptors [60]. Moreover, luteolin decreased the mRNA levels of many genes in the cell cycle cascades and epidermal growth factor receptor signal transduction cascade in prostate tumor cells. It activated the expression of c-FOS and p21 RNA and strongly induced cell cycle arrest at the G2/M phase. Moreover, research findings showed that c-FOS or p21 silencing RNAs dramatically decreases the expression of RNA of their corresponding targets; however, it showed little effect on cells propagation, and abrogation of prostate cancer cell proliferation was not inhibited by either double silencing RNA or one silencing RNA [63]. In more recent work, the compound was found to deceased the Wnt signal transduction by increasing the mRNA level of frizzled class receptor 6 (the negative modulator of β-catenin transcriptional action) and promoting the abrogation of the stemness of prostate tumor cells [64].

3.9. Liver cancer

Liver cancer is the world's third largest cause of cancer mortality [65]. The burden and aetiology of liver diseases have changed during the last decade [66,67]. In this respect, Cao et al. (2018) showed that luteolin reduces the SMMC-7721 cell viability in a time- and dose-dependent fashion. Furthermore, luteolin induced G0-/G1-phase arrest and enhanced caspase 8, and reduced bcl-2 at mRNA and protein levels as evidenced by RT-PCR and Western blot analyses [68]. Furthermore, luteolin enhanced the number of intracellular autophagosomes, accelerated LC3B–I to LC3B-II conversion, and elevated Beclin 1 expression. Finally, co-treatment with chloroquine (an autophagy inhibitor) reduced the effects of luteolin on cell apoptosis. Nazim and Park in 2019 demonstrated the synergistic effect of luteolin and TRAIL therapy and their mechanisms on TRAIL-resistant Huh7 cells [69]. Luteolin caused an autophagic flow in human liver cancer cells and THE autophagy inhibitor, chloroquine, dramatically lowered DR5 expression. Wang et al. (2021) confirmed the synergistic mechanism of VV-IL-24 (oncolytic vaccinia virus) and luteolin to cause tumor growth inhibition via single therapy [66]. Their studies involved MTT assay on various cancer lines to confirm the luteolin's effect on tumor cells. Similarly, flow cytometry and Western blot assays confirmed both luteolin and VV-IL-24 synergistic effects on liver cancer cell apoptosis further substantiated by in vivo models.

3.10. Kidney cancer

Luteolin suppresses the growth and proliferation of kidney cancerous cells both in vitro and in vivo. Typically, luteolin exerts apoptosis and angiogenesis, and suppresses the activation of the PI3K/Akt and NF-κB signaling pathways, involved in the growth and survival of cancer cells. It also enhances the cytotoxicity of chemotherapy drugs in kidney cancer cells, suggesting that it could be administered in addition with standard drugs to improve their activities. Furthermore, luteolin has been shown to alleviate the side effects associated with chemotherapy, making it an attractive drug candidate for the management of kidney cancer therapeutics [7,66,70].

4. Clinical applications of luteolin

Luteolin exerts anticancer effects by targeting various signaling pathways. It has been demonstrated to induce cell cycle arrest and apoptosis in cancer cell lines by suppressing the PI3K/Akt/mTOR pathways. Luteolin inhibits the NF-κB signaling pathway that is responsible for inducing cytokines and growth factors that promote tumorigenesis. Luteolin can also sensitize cancer cells to chemotherapy and radiotherapy by inhibiting the drug efflux pump and reducing DNA damage repair. These findings reveal that luteolin can act as a chemosensitizer and radio-sensitizer in modern cancer therapeutics [66,71,72].

4.1. Cardiovascular diseases

Luteolin exhibits cardioprotective effects as the molecule lowers oxidative stress and inflammation. It inhibits NADPH oxidase activity, a key enzyme responsible for the formation of ROS in the cardiovascular system. In addition, luteolin suppresses the expression of pro-inflammatory cytokines such as IL-6 and TNF-α and reduces the adhesion of leukocytes to endothelial cells. These effects lead to alleviating atherosclerosis, hypertension, and myocardial infarction [73].

The cardioprotective effect of luteolin could be attributed to its antioxidant properties and to decreases in the two main pro-inflammatory cytokines, TNF-α and IL-18, which are connected to heart failure [74]. In this regard, Ding et al. (2019) found that

by lowering inflammation, luteolin dramatically decreased AS in ApoE−/− mice given a high-fat diet. Additionally, these researchers found that luteolin inhibits oxidized, low-density lipoprotein-induced inflammation (including the mRNA synthesis of ICAM-1, VCAM-1, TNF-α, and IL-6) in vitro via decreasing signal transducer and activator of transcription 3 (STAT3). They also showed that luteolin might be a suitable candidate for the treatment atherosclerosis and that STAT3 might be a potential therapeutic target that delays the progression of the disease [75]. As mentioned before, the beginning and development of atherosclerosis are associated with inflammatory infiltration of the arterial wall and failure of lipid metabolism. Taking luteolin supplementation caused a reduction in the aortic root expression of the inflammatory cytokines IL-6 and TNF-α, the macrophage marker CD68, and the macrophage chemokine CCL2. Furthermore, it has been shown that luteolin decreases the generation of inflammatory cytokines and macrophage chemokines in ThP-1-derived macrophages in a dose-dependent manner [76].

4.2. Diabetes

Luteolin improves insulin sensitivity and reduces inflammation. It also enhances glucose uptake and glycogen synthesis by activating the AMPK signaling pathway, a key regulator of glucose metabolism. As already discussed in earlier sections, luteolin inhibits the NF-κB signaling pathways and expressions of IL-1β and IL-6 which result in insulin resistance and improved glucose homeostasis [77].

4.3. Inflammation

Besides inhibiting the formation of pro-inflammatory cytokines like IL-6, IL-1β, and TNF-α, and reducing the activities of NF-κB, luteolin can inhibit the activation of NLRP3 inflammasome, which is necessary for the maturation and secretion of IL-1β and IL-18. All these pathways and modes of luteolin's action can act as an effective anti-inflammatory agent [78,79].

5. Toxicological profiles of luteolin

Plant secondary metabolites are used to either control or treat a particular disease or its symptoms. These metabolites must be administered at a precise dose to prevent interference with other cellular processes. In this context, human retinal microvascular endothelial cells (HRMECs) were treated against the anti-angiogenic action to study the toxicity of the luteolin. Treatment with 10 M of luteolin caused no harmful effects, whereas 100 M of luteolin influenced the cells [10,80]. In a different experiment, treatment of human lymphoblastoid TK6 cells with luteolin at a dose of 2.5 M led to cytotoxic effects at 24 h. In this respect, the alkaline comet test and H2A.X protein levels were also used to detect DNA damage at concentrations of 5 and 10 M of luteolin [81]. In a study using female Sprague Dawley rats, high dosages of the traditional medicine *Verbena officinalis*, which contains luteolin 3-methyl ether 7-glucuronosyl-(1–2)-glucuronide caused prenatal toxicity [82]. Similarly, Vero cells and lymphocytes exposed to high doses of luteolin experienced DNA damage [83]. The safety of using luteolin in treatments is emphasized by toxicity studies, as a larger dosage may result in negative effects. Consequently, extensive research into the toxicity of luteolin may shed additional light on the optimal dose concentration for treating diseases. Similarly, in TK6 cells, luteolin caused concentration-dependent cytotoxicity and genotoxicity. Additionally, luteolin induced toxicity in TK6 cells that express CYP1A1 and 1A2. To create the lesser harmful metabolite called diosmetin, luteolin is methylated in TK6 cells. Furthermore, the increased toxicity is caused by CYP1A enzymes that partially undo luteolin's methylation [81].

A unique multi-tier platform was employed to examine the toxicological profile of luteolin, apigenin, quercetin, and genistein, derived from flavone, flavanol, and isoflavone, to determine the effects of flavonoid structure on toxicity. MCF-7 cell proliferation assay showed weaker estrogenic activity for genistein, apigenin, quercetin, and luteolin at 10^{-12} to 10^{-7} M, which was agreed with the prediction of molecular docking studies. Genistein and luteolin demonstrated considerable production of toxicity in the chicken embryonic assay (45–477 μg/kg) with a death rate of up to 40%, which was consistent with the simulation results of the Toxicity Estimation Software Tool. At 5×10^{-3} pmol/plate, luteolin, quercetin, and apigenin displayed mutagenicity. Results also revealed that compounds have non-monotonic dosage responses similar to those observed with endocrine-disrupting chemicals [84].

Doxorubicin (DOX), a medication used to treat lung cancer, has adverse oxidative, inflammatory, and apoptotic reactions. In a study, a male Wistars rat (age: 10 weeks; weight: 160 5 g) with DOX-induced blood and lung dysfunction was used as a test subject. The following treatments were administered to randomly assigned groups of rats (n = 10): control, luteolin solely (100 mg/kg; per os), DOX (2 mg/kg), and rats co-administered with luteolin (50 or 100 mg/kg) and DOX for 14 days. The ultimate body weights, relative organ weights, and platelet, red, and white blood cell counts were all negatively affected by DOX alone. In contrast to increased oxidative stress biomarkers, caspase-3 activity, and pro-inflammatory cytokines, DOX significantly ($p > 0.05$) decreased lung antioxidant capability and anti-inflammatory cytokines. These biochemical changes in the lung of experimental rats were also accompanied by morphological damage. Co-treatment with luteolin, dose-dependently, reduced oxidative stress in the lungs of rats and corrected DOX-mediated alterations in survival. Also, when DOX and luteolin were administered together, pro-inflammatory cytokines and apoptotic indicators were decreased. Additionally, red, white, and platelet counts were elevated, and pathological damage in the rat lungs was lessened. In essence, luteolin dose-dependently reduced the toxicities caused by DOX in the lungs and hemopoietic systems. In conclusion, luteolin is a phytochemical that exhibits antioxidant properties and can be given to patients receiving DOX-chemotherapy to prevent the development of unexpected adverse reactions in the lungs and hemopoietic system exposed to DOX [85].

Although luteolin exerts positive pharmacological characteristics, its safety profile is not yet completely explored. A study was conducted to examine how luteolin affects blood and liver functions and to formulate any appropriate recommendations for its

therapeutic use. In this study, 33 adult albino rats were employed. The modified Lorke's method was used to determine the oral LD50 of luteolin in 13 rats. The biochemical, hematological, and histological tests were conducted for 28 days on the remaining 20 rats by dividing them into four groups of 5 rats each (n = 5 per group). Group I (the control group) received 10 mL/kg of distilled water orally. Luteolin doses (oral, in mg/kg) of 50, 100, and 200 were given to the remaining three experimental rat groups. Blood samples were taken from each rat in the various groups before treatment, on the 14th and 28th day, following repeated daily dosing. Rat livers were analyzed for possible histopathological changes. Results revealed that while WBCs were not enhanced, all doses of luteolin significantly (p 0.05) elevated several blood indices such as RBCs, PCV, and Hb. Results showed that alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP), among other liver enzymes, increased significantly (p 0.05). Moreover, results revealed that luteolin is hepatoprotective at low dosages (50 mg/kg) and increases hepatic enzyme activity at high doses (200 mg/kg) and chronic dosages. Based on histological findings, no major liver damage was reported [86]. Such studies demonstrate the need to optimize luteolin dosage for wider clinical and chemotherapeutic applications.

5. Uses of nanotechnology in luteolin delivery as anti-cancer agent

An innovative method of chemoprevention that delivers luteolin is using nanotechnology. Hydrophobic luteolin was synthesized to create water soluble polymer-encapsulated nano-luteolin, to investigate its anticancer properties against head, neck, and lung cancer. Similar to luteolin, nano-luteolin was shown to suppress the growth of squamous cell carcinoma of the head and neck (SCCHN) cells (Tu212 cell line) and lung cancer cells (H292 cell line) in vitro. The IC_{50} values of luteolin and nano-luteolin in Tu212 cells were 4.13 and 6.96 μM, respectively. The luteolin and nano-luteolin IC_{50}s in H292 cells were 15.56 and 14.96 μM, respectively. Comparing nano-luteolin to luteolin, in vivo studies using a tumor xenograft mouse model showed that the latter significantly inhibits the growth of SCCHN cancer. This implies the potential use of luteolin in clinical settings for chemoprevention [87]. Moreover, luteolin has been found to be a good candidate for synergistic studies and has the potential to reverse medication resistance in cancer cells. The mechanism by which luteolin causes cell death involves the upregulation of BAX, caspase-3, and p21 and the downregulation of Akt, PLK-1, cyclin-B1, cyclin-A, CDC-2, CDK-2, Bcl-2, and Bcl-xL. Additionally, it suppresses STAT3 activation and increases STAT3 protein degradation in a variety of cancer cells; it inhibits STAT3 signalling [88].

6. Conclusions

Obtaining anti-cancer products through dietary source serves as a cost-effective and healthy alternative to chemically synthesized drugs. Luteolin is an active bio-ingredient that exhibits characteristic anti-cancer potency in the treatment of a wide range of cancers through several mechanisms such as apoptosis and cell cycle arrest, metastasis, and angiogenesis inhibition. The key to its promising anti-cancer efficacy lies in its distinctive oxidative nature. Its unique molecular interactions with several target sites and signalling pathways in tumor cells further enhances its anti-cancer activity. Besides its antioxidant capacity, its significant hepato-protective and cardioprotective capabilities makes it a promising candidate for use in conjunction with DOX-chemotherapy, which would play a key role in its preventive role of adverse reactions in the lungs and hematopoietic systems.

7. Limitations

To determine the amount of luteolin glucosides and/or intact luteolin that would contribute to its improved physiological activity, further investigations are required. However, researchers have shown that microemulsion-administered luteolin may enhance the bioavailability of luteolin with a positive impact on its metabolic profile. This could serve as a strong foundation for the development of microemulsion systems for the best possible delivery of luteolin in future research plans. Yet, safety concerns of luteolin administration requires special attention in response to future advanced experimental plans based on the optimization of its effective doses, bioavailability, and toxicological profiles.

Data availability statement

No data was used for the research described in the article.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Abdur Rauf: Writing – review & editing, Supervision, Conceptualization. **Polrat Wilairatana:** Writing – review & editing, Visualization, Investigation, Data curation. **Payal B. Joshi:** Writing – original draft, Visualization, Methodology, Data curation. **Zubair Ahmad:** Writing – original draft, Methodology, Data curation. **Ahmed Olatunde:** Writing – original draft, Validation, Methodology. **Nabia Hafeez:** Writing – original draft, Validation, Methodology. **Hassan A. Hemeg:** Writing – original draft, Validation, Methodology, Investigation. **Mohammad S. Mubarak:** Writing – review & editing, Visualization, Validation, Supervision, Methodology.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:No competing interests If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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