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Review Article

A Review on Biomedical Properties of The Antioxidant Luteolin

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Abstract: 3′, 4′, 5, 7-tetrahydroxyflavone, luteolin, which is present in Onions, Broccoli and other dietary suppliments, is an important flavinoid, present in our daily nutrition in less than 1 mg/day. Various Epidemiological studies have led to the discovery of the anti-inflammatory and anti-carcinogenic effects of luteolin. These properties are partly due to its anti-oxidant and free radical scavenging capacities. Luteolin was found to delay or block the development of cancer cells *in vitro* and *in vivo* by protection from carcinogenic stimuli, by the inhibition of tumor cell proliferation, by the arrest of cell cycle and by the induction of apoptosis through the suppression of cellular pathways, which induce the tumor suppressor p53. Luteolin was found to be the most effective flavinoid in inhibiting the tumor cell proliferation. Luteolin is being used to cure skin cancer. In this review, we focus on the reasons for the anticancer role and the molecular mechanisms which favours this property.

Keywords: Luteolin, apoptosis, p53, skin cancer, Pharmacology.

Introduction

Luteolin, 3′, 4′, 5, 7-tetra-hydroxyflavone, belongs to a group of compounds, that occur naturally, called flavonoids. Flavonoids are polyphenols that play an important role in defending plant cells against microorganisms, insects, and UV irradiation [1]. It has been found that flavonoids possess anti-cancer properties [2, 3]. There is good evidence suggesting that flavonoids contribute to the cancer-protective effect of fruits and vegetable food [4]. Flavonoids acts by blocking several activities in the progression of carcinogenesis, including cell transformation, invasion, metastasis and angiogenesis, through inhibiting specific kinases, reduction of transcription factors, by cell cycle regulation, and by inducing apoptosis [5].

The structure of luteolin consists of a C6-C3-C6 structure and has two benzene rings (A, B) a third, oxygen-containing (C) ring, and a 2−3 carbon double bond. Luteolin also possesses hydroxyl groups at carbons 5, 7, 3′, and 4′ positions as in (Fig.1) [6]. The hydroxyl moieties and 2−3 double bond are important structure features in luteolin that are associated with its biochemical and biological activities such as anti-inflammatory and anti-carcinogenic activities [7].

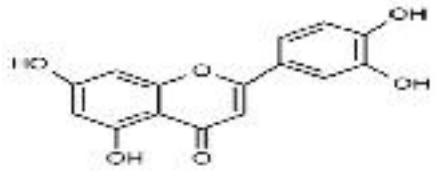

Fig.1: Structure of Luteolin.

Plants and fruits rich in luteolin such as celery, parsley, broccoli, onion leaves, carrots, peppers, cabbages, apple skins, and chrysanthemum flowers, have been used as Chinese traditional medicine for the treatment of hypertension, inflammatory diseases, and skin cancer [8, 9, 10, 11]. Luteolin is found in plant materials, often in the form of glycosides, which are usually metabolized by the intestinal bacteria, cleaved and glucuronated during uptake in the gut and metabolized in the organism [12]. When it comes to the pharmacological activities of luteolin, it is often associated with its ability to induce apoptosis, which involves redox regulation, DNA damage, protein kinases, which inhibit the proliferation of cancer cells and suppression of metastasis and angiogenesis. Notably, luteolin sensitizes a variety of cancer cells to therapeutically induced cytotoxicity through suppression of cellular pathways and inducing apoptosis pathways. Luteolin is blood-brain barrier

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permeable, rendering it applicable to the therapy of central nerve system diseases, including brain tumor [13]. However, further research is needed in order to fully identify the immunological benefits of this compound.

Biochemical Activities of Luteolin

a) *Anti-Carcinogenic Activity:* Cancer is the uncontrolled growth of cells, due to mutation. A typical carcinogenic process can be divided into three stages: initiation, promotion, and progression [14]. In the first stage, i.e., the initiation stage, the potential carcinogen (pro-mutagen) is converted to a mutagen by enzymes such as cytochrome P450. The mutagen then reacts with DNA to induce irreversible genetic alteration including mutations, transversions, transitions, and/or small deletions in DNA. In the promotion stage, alterations in genome expression occur to favor cell growth and proliferation. During the progression stage, tumor establishes and becomes irreversible; it is characterized by karyotypic instability and malignant growth in an uncontrolled manner [15]. The transformed cells then acquire a number of characteristic alterations, including the capacity to proliferate in a signal-independent manner, to invade surrounding tissues and metastasize to distant sites. In addition, cancer cells elicit an angiogenic response, evade all mechanisms that limit cell proliferation, such as apoptosis and senescence, and elude immune surveillance [16].

These properties of cancer cells are reflected by alterations in the cellular signaling pathways that control cell proliferation, motility, and survival in normal cells [17]. Luteolin is able to interfere with almost all of the characteristics of cancer cells, mainly through the following mechanisms [18].

a.1) Preventing the activation of Carcinogenic metabolism: From studies done earlier, by various cancer researchers, it was found that luteolin was able to inhibit the metabolism of carcinogens that generates active mutagens in liver microsomes [19, 20]. It was determined recently that luteolin potently inhibits human cytochrome P450 (CYP) 1 family enzymes such as CYP1A1, CYP1A2, and CYP1B1, thereby suppressing the mutagenic activation of carcinogens [21]. By suppressing these enzymes reduces the generation of active mutagens [22].

a.2) Inhibition of Cancer cells growth: Luteolin is able to inhibit the proliferation of cancer cells derived from nearly all types of cancers, as like many other flavinoids, mainly through regulating the cell cycle [23, 24]. In Eukaryotes, cell cycle consists of four distinct phases, G1, S, G2, and M phases, and they are timely regulated by cyclin-dependent kinases (CDKs) and their cyclin subunits at the two checkpoints, G1/S and G2/M [25]. The G1/S checkpoint is regulated by CDK4-cyclin D, CDK6-cyclin D, and CDK2-cyclin E. When associated with cyclin A, CDK2 controls the S-phase, while the G2/M transition is regulated by CDK1 in combination with cyclins A and B, CDK activity is negatively controlled by two groups of CDK inhibitors (CKI), INK4 and CIP/KIP families. The INK4 family members inhibit CDK4 and CDK6; while the CIP/KIP family, consisting of p21cip1/waf1, p27kip1, and p57kip2, inhibits a broad range of CDKs [26].

Various flavonoids have been found to inhibit the proliferation of many cancer cells by arresting cell cycle progression either at the G1/S or G2/M checkpoint [27]. Luteolin is able to arrest the cell cycle during the G1 phase in human gastric and prostate cancer, and in melanoma cells [28, 29, 30]. The G1 cell cycle arrest induced by luteolin is achieved by up-regulation of the CDK inhibitors p27/kip1 and p21/waf1, or direct inhibition on the CDK2 activity [31, 32]. Luteolin arrests mouse cancer cell tsFT210 at the G2/M checkpoint [33]. DNA damage-activated tumor suppressor protein p53 is involved in both the G1/S and G2/M transition regulation [34] Luteolin can bind and suppress DNA topoisomerases I and II, enzymes essential for repairing damaged DNA, and intercalates directly with the substrate DNA to cause DNA double-strand breaks [35, 36]. This action of luteolin induces cell cycle arrest though p53-mediated expression of p21/waf1 [37].

EGF receptor (EGFR) is a typical receptor protein tyrosine kinase (PTK) that mediates cell growth and proliferation. When activated by its ligands, EGFR is phosphorylated to mediate activation of downstream signaling pathways, including MAPK and PI3K/Akt [38]. Luteolin was found to inhibit the proliferation of pancreatic and prostate cancer and human epidermoid carcinoma cells, which is closely associated with the inhibition of the PTK activity and

autophosphorylation of EGFR, transphosphorylation of EGFR downstream effector protein enolase, and activation of MAPK/ERK [39]. Luteolin is able to inhibit IGF-1-induced activation of IGF-1R and Akt with the suppressed expression of cyclin D1, and it also increased the expression of p21/waf1 and proliferation in prostate cancer cells in vitro [40]. In a similar way, luteolin inhibits PDGF-induced proliferation by inhibiting PDGF receptor phosphorylation in vascular smooth muscle cells [41]. As a consequence, luteolin significantly inhibits PDGF-induced ERK, PI3K/Akt and phospholipase C (PLC)-γ1 activation, and *c-fos* gene expression suggests that the inhibitory effect of luteolin on the PDGF-induced proliferation may be mediated by blocking phosphorylation of the PDGF receptor [42]. As PDGF stimulates cancer cell proliferation, it remains to be determined whether luteolin can block PDGF-induced signaling to suppress cancer cell proliferation [43]. As discussed above, ER induces proliferation in several types of cancer cells [44]. Luteolin suppresses proliferation of prostate and breast cancer cells in both an androgen-dependent and -independent manner, suggesting that luteolin's anti-estrogen activity may at least partly contribute to its anti-proliferation effect [45, 46]. Similar observations were also made in thyroid carcinoma cell lines bearing the ER [47, 48].

In addition to affecting the receptors, luteolin may directly target the downstream pathways that are involved in cell proliferation. For example, protein kinase C, a family of serine-threonine protein kinases that regulates growth factor response and cell proliferation, differentiation and apoptosis [49, 50] can be inhibited in a concentration-dependent manner by luteolin in both cell-free systems and in intact cells [51]. Hence from the reports given above, it was found that the carcinogens activate cell survival pathways such as MAPK during the course of carcinogenesis; these pathways could be additional targets for flavonoids, including luteolin, in anti-carcinogenesis [52, 53].

a.3) Apoptosis of Cancer cells: Researchers have showed that uncontrolled growth of mutated cells was due to lack of apoptosis is closely associated with tumor formation [54]. The process of apoptosis consists of two pathways, the death receptor pathway (extrinsic) and the mitochondrial (intrinsic) pathway. The intrinsic pathway involves functional incapacitation of mitochondria by pro-apoptotic Bcl2 family members, including Bax, Bak, and Bik, that cause mitochondria potential loss and release cytochrome c to activate caspase 9, which in turn activates executor caspases (−3, −7) and destroys cellular proteins [55]. The extrinsic pathway is initiated by the binding of TNF family cytokines (TNFα, Fas and TNF-related apoptosis-inducing ligand, TRAIL) to their cognate death receptors, to activate caspase 8, which in turn activates downstream executor caspases [56]. The extrinsic pathway is initiated by the binding of TNF family cytokines (TNFα, Fas and TNF-related apoptosis-inducing ligand, TRAIL) to their cognate death receptors, to activate caspase 8, which in turn activates downstream executor caspases [57, 58]. Despite the complexity underlying luteolin-induced apoptosis, they can still be generalized as breaking the cell survival and death balance by either enhancing apoptosis or decreasing the survival signaling in cancer cells, which is summarized in Fig.2 [59].

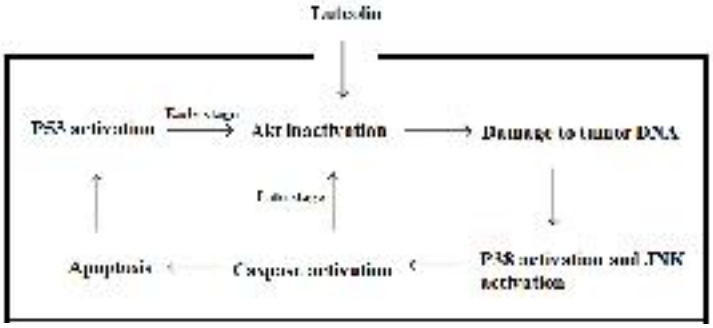

Fig.2: Apoptosis pathways and the points targeted by luteolin.

b) *Luteolin as an Anticancer or Chemotherapeutic Agent:* As mentioned in previous discussions, luteolin induces apoptosis in various cancer cells [60]. It also has inhibitory effects towards cancer cell growth [61], and suppresses tumor angiogenesis [62]. Supporting the *in vitro* results, *in vivo* experiments in nude mice with xenografted tumors showed that luteolin suppressed growth of tumors formed from human skin carcinoma, hepatoma, and human ovarian cancer cells [63] or mouse Lewis lung carcinoma [64] in a dosage-dependent manner. Luteolin was found to induce marginal cytotoxicity in normal cells [65].

Studies have shown that, the effect of luteolin is enhanced when it is given along with other therapeutic agents, i.e., combined therapy. The drugs tested which were tested along with luteolin include cisplatin [66], TRAIL [66, 66], TNFα [67, 68], and the mTOR inhibitor rapamycin [69]. Luteolin-induced up regulation of the TRAIL receptor DR5 contributes to sensitizing not only TRAIL-induced, but also other chemotherapeutic-induced cytotoxicity [70]. Cancer therapeutics are also found to activate cellular pathways, dampening their cancer cell-killing activities [71, 72]. Yet more research is needed to determine if luteolin or other flavonoids contributes to the anticancer activity of these fruits [73].

In a 20-methycholanyrene-induced fibrosarcoma model using Swiss albino mice, luteolin administered in diet significantly suppressed tumor incidences, which are associated with reduction in lipid peroxides and cytochrome P450, increased activity of GST, and suppressed DNA synthesis [74]. Luteolin exerts chemopreventive and anticarcinogenic effects, in association with its antiperoxidative and antioxidant effects, against colon cancer [75]. Epidemiological studies suggest that dietary intake of flavonoids is inversely associated with risk of lung, prostate, stomach, and breast cancer in humans [76]. A recent population study on the association between intake of dietary flavonoids and incidence of epithelial ovarian cancer among 66,940 women showed a significant (34%) decrease in cancer incidence for the highest versus lowest luteolin intake [77]. The data suggest that dietary intake of luteolin may reduce ovarian cancer risk, although additional prospective studies are needed [78]. Dietary intake of flavonols and flavones was found to be inversely associated with the risk of lung cancer [79]. However, because of many confounding factors, luteolin's preventive potential for lung cancer still remains unclear [80]. Hence, caution should be exercised when interpreting epidemiological study as well as other results [81].

c) Other Activities Of Luteolin:

c.1) *Anti-Inflammatory Activity:* Inflammation has been one of our body's chief defense mechanisms, to protect us against infections, from pathogens. Yet chronic inflammation may result in harmful diseases such as arthritis, chronic obstructive pulmonary disease, and cancer [82]. During an infection, there is activation of macrophages due to various components of the system, that vigorously produce inflammatory molecules such as tumor necrosis factor α (TNFα), interleukins (ILs), and free radicals (ROS and reactive nitrogen species, RNS), leading to recruitment of inflammatory cells, such as neutrophils and lymphocytes, to the infection site and clearance of the pathogens [83]. High level production of inflammatory cells, could lead to cancer, hence luteolin is found to exert its anti-inflammatory effect by suppressing the production of these cytokines and their signal transduction pathways [84, 85]. Experiments with animals have showed that luteolin suppresses LPS or bacteria-induced inflammation *in vivo* [86]. LPS-induced-high mortality was effectively alleviated by luteolin, which is associated with reduction of LPS-stimulated TNFα release in serum and intercellular adhesion molecule-1 (ICAM-1) expression in the liver [87]. Luteolin was found to suppress inflammation in lung tissue that was caused by *Chlamydia pneumonia* [88].

Based on the observations that some flavonoids with strong antioxidant activities are completely ineffective in suppressing LPS-stimulated TNFα production, it is assumed that the inhibitory action of flavonoids on proinflammatory cytokine production is not directly associated with their antioxidant properties [89]. However, because luteolin is able to scavenge ROS directly and to suppress the LPS-activated nitric oxide production in activated macrophages, the antioxidant activity of luteolin atleast in part contributes to luteolin's anti-inflammatory effect [90, 91]. Because inflammation and its involved signaling pathways are strongly associated with carcinogenesis, the anti-inflammatory role played by luteolin, may contribute to cancer prevention [92, 93].

c.2) Anti-Metastasis Activity: The ability of cancer cells to migrate and invade other, surrounding healthy cells, from their primary location to secondary locations, is called Metastasis. Metastasis, has by far, contributed to over 90% of human cancer mortality [94]. The metastasis cascade is thought to consist of multiple steps: local invasion; intravasation into the systemic circulation; survival during transport, extravasation, and establishment of

micrometastases in distant organs; and colonization of macroscopic metastases [95].

Although direct evidence showing luteolin suppresses cancer metastasis is not seen in literature, available results strongly suggest that luteolin has this function [96]. Luteolin suppresses production and secretion of cytokines such as TNFα and IL-6 that can stimulate cancer cell migration and metastasis [97, 98]. Luteolin blocks the EGFR-signaling pathway and reduces cell invasion and metastasis of tumor cells [99, 100]. Luteolin also directly inhibits the MMP or hyaluronidase enzyme activity to maintain the neovascularization barrier, which may also contribute to suppressing cancer cell metastasis [111, 112]. *In vitro* studies have shown that luteolin potently inhibits migration and invasion of cancer cells through blocking the MAPK/ERKs and PI3K-Akt pathways [113, 114]. Experiments with cancer metastasis animal models are needed to verify luteolin's anti-metastasis activity.

c.3) Anti-Oxidant Activity: Luteolin also possesses excellent anti-oxidant properties. Reactive oxygen species (ROS) refers to a diverse group of reactive, short-lived, oxygen-containing species, such as superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\bullet}OH$), singlet oxygen ($^1O_2$), and lipid peroxyl radical ($LOO^{\bullet}$). ROS serve as second messengers for cellular signaling [115]. But, the overproduction of ROS was found to cause damage to DNA, lipids, proteins, neuronal disorders, as well as inducing cancer cell production. Luteolin was found to inhibit ROS-induced damage of lipids, DNA, and protein [116, 117]. Multiple mechanisms may contribute to luteolin's antioxidant effect. Firstly, luteolin functions as a ROS scavenger through its own oxidation and it also possesses the structures essential for the flavonoid's antioxidant activity: 3', 4' hydroxylation [118]. Luteolin, due to its aromatic nature, supports unpaired electrons around the M-electron system [119, 120]. Direct evidence showing luteolin as a ROS scavenger was obtained in cell-free systems [121]. Secondly, luteolin suppresses $O_2^{\bullet -}$ formation by inhibiting xanthine oxidase activity, which is a ROS-generating oxidases [122]. But, it is unclear in mammalian cells whether luteolin affects ROS generation in the mitochondria, the main ROS generation site, although it interferes with the mitochondrial electron transportation chain in parasite (leishmanial) cells [123]. Thirdly, luteolin may exert its antioxidant effect by protecting or enhancing endogenous antioxidants such as glutathione-S-transferase (GST), glutathione reductase (GR), superoxide dismutase (SOD) and catalase (CAT) [124, 125]. Luteolin suppresses lipoxygenase, cyclooxygenase, which are enzymes that catalyze oxidation of the cellular components, and ascorbic acid-stimulated malonaldehyde formation in liver lipids [126]. Finally, luteolin may chelate transition metal ions responsible for the generation of ROS and therefore inhibit lipooxygenase reaction, or suppress nontransition metal-dependent oxidation [127]. It is also noted that, the inhibition of LPS-induced $^{\bullet}OH$ production in macrophages by luteolin may be through scavenging $O_2^{\bullet -}$, inhibiting xanthine oxidase activity, or a combination of both [128].

Discussion

Documented results suggest that luteolin has a variety of beneficial properties, including those as an anti-inflammatory and anticancer agent [129]. The mechanisms underlying these properties have not been fully understood but are partially attributed to luteolin's redox- and regulating properties. It is important and interesting to determine the mechanism for luteolin's selective cytotoxicity in cancerous cells but not normal cells. It is apparent that distinct mechanisms for modulating cellular signaling pathways exist in normal cells and in malignant cancer cells. By understanding the mechanisms, we will undoubtedly facilitate the use of luteolin in cancer prevention and therapy. Although it is relatively safe, luteolin was found to worsen chemically induced colitis in mice [130]. Further studies are needed to address the safety issues of luteolin with doses effective for cancer prevention and therapy in humans [131].

Conclusion

Chronic inflammation is a critical component of tumor development [132]. Multiple lines of evidence suggest that COX-2, a rate-limiting enzyme in the synthesis of prostaglandins, is a key link between inflammation and cancer [133]. Luteolin was found to possess anti-oxidant properties. ROS overproduction was inhibited by luteolin thus, inhibiting the damage of cellular DNA, lipids and proteins and also in the killing of cancer cells. The ROS scavenging activity of luteolin, at least in part, contributes to its nature of

being an anti-inflammatory agent. Through experimental studies, luteolin was found to possess anti-metastasis activity and anti-cancer properties. The Apoptosis pathway and the activation of apoptosis in the cancer cells by luteolin clearly show the anti-carcinogenic effects of luteolin as a therapeutic agent. Luteolin was found to delay the development of tumors, inhibited the multiplication of tumors, decreased tumor volume, and suppressed the expression of inflammatory and proliferative biomarkers.

Luteolin was found to be effective against a number of cancer cells, including skin cancer. The majority of cancers are derived from many mutations [134]. Hence multitargeted kinase inhibitors, like luteolin, are anticipated to have therapeutic advantages and are emerging as new alternatives for cancer treatment [135]. Hence, luteolin was found to possess anti-cancer properties with significant with more animal model studies, to determine the toxicity of luteolin and by effective dosage studies, the compound can be used as a potential cure for cancer.

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