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Kaempferol and its derivatives: Biological activities and therapeutic potential

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ABSTRACT

Kaempferol, a natural plant-origin flavonoid, exhibits therapeutic anti-inflammatory, antioxidant, anticancer, antidiabetic, and neuroprotective properties. Kaempferol acts within several distinct mechanisms like apoptotic induction in cancer cells, enzymatic inhibition, signalling pathway inhibition, and downregulation in cell viability during the G_2/M phase of cell division. This review summarizes the therapeutic effects of kaempferol against several health ailments. The recent progress on kaempferol obtained from fruits and vegetables as an antioxidant, anti-inflammatory, anticancer, antidiabetic, and neuroprotective agent and its mechanisms of action are also discussed. In addition, kaempferol has been reported to be present in wastes and byproducts from post-fruit and vegetable processing. Thus, a paradigm shift towards valorizing fruits and vegetable industrial wastes/byproducts to obtain bioactive kaempferol can support the circular economy pillar for generating wealth from waste and for finding a sustainable alternative source.

KEYWORDS: Kaempferol; Therapeutic effects; Bioactivities; Fruits and vegetable wastes; Sustainable alternative sources

1. Introduction

Flavonoids are polyphenol compounds found primarily in fruits and vegetables and are the chief constituent of several herbal concoctions. As per the epidemiological studies undertaken in humans and animals, flavonoids can limit the risk of various diseases[1,2]. One of the most prevalent flavonoids is kaempferol (3,5,7,4'-tetrahydroxy flavone) yellow in colour and has low molecular weight. Kaempferol is generally found in vegetables and fruits including traditional medicine (Table 1) and is synthesized by plants *via* an enzymatic process[3,4]. Kaempferol and its derivatives exhibit antiproliferative, antioxidant, anti-inflammatory, and antineoplastic activities. Kaempferol has also shown cytotoxicity against pancreatic and breast cancer cells[5].

Despite the outstanding pharmacological properties of kaempferol, some factors limit its use, particularly in clinical trials owing to its low bioavailability. Also, the large particle size of kaempferol restricts its water solubility. Owing to various benefits and growing demand from the market, an alternative source of kaempferol is highly needed to fulfill this demand. In this case, apart from the main sources, the use of food and vegetable waste/byproducts can act as an alternative source of kaempferol and make an immense contribution to medicinal, health, and food industries. Furthermore, the formulation and modulation of the size of kaempferol to "kaempferol nanosize formulation" can enhance its bioavailability and solubility. Based on the importance of kaempferol as revealed in the literature, its anti-inflammatory, antioxidant, antidiabetic, neuroprotective, and anticancer activities are summarized in this review. Furthermore, the use of food and vegetable waste/byproducts as an alternative source of kaempferol has also been elaborated.

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Table 1. Dietary sources of kaempferol.

Plant source	Quantity (mg/kg)	Ref
Strawberry	5-8	[6]
Gooseberry (yellow)	16	
Gooseberry (red)	19	
Onion leaves	832	[7]
Black tea	118	[8]
Chilli	39	
Papaya shoots	453	
Brinjal	80	
Pumpkin	371	
Carrot	140	
White radish	38	
Beans	14	[9]
Broccoli	72	
Cauliflower	270	[10]

2. Biological applications of kaempferol

2.1. Anti-inflammatory activity of kaempferol

Inflammation of tissues occurs due to any trauma including pathological, cellular, or vascular damages. Physiological changes like redness, pain, and function failure are indicators of inflammation[11-13], which primarily is the activation of the immune system or enzymatic response[14-16]. In addition to protecting the activity of various antioxidant enzymes, kaempferol is known to act as a scavenger of free and superoxide radicals[11]. Various modes of action, such as activation of nuclear factor kappa B (NF-κB), could be used to regulate the anti-inflammatory activity of kaempferol[17-19].

Kaempferol enhances the radical scavenging potential and activation of T cell proliferation and regulates nitric oxide (NO) or reactive oxygen species (ROS) production in lipopolysaccharides-induced RAW 264.7 macrophage cells[17]. Zhuang *et al*. revealed that kaempferol decreases the formation of prostaglandin E_2 and NO and the expression of inducible nitric oxide synthase and cyclooxygenase (COX)-2 along with the inhibition of IκBα degradation and NF-κB[18]. In *Camellia oleifera* oil, kaempferol and other phenolic components possessed anti-inflammatory properties[19]. Glycosylated fraction showed the highest anti-inflammatory activity, as exhibited by the low level of NO, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). Hu *et al*. also demonstrated the potential of kaempferol derivative in mouse macrophage cells as an anti-inflammatory agent[20]. Kaempferol derivative exerted anti-inflammatory effects *via* the MAPK and NF-κB pathways, thus diminishing ROS levels and oxidative stress in the lungs[21].

Khajuria *et al*. demonstrated a dose-dependent anti-inflammatory activity of kaempferol in mice[22]. Kaempferol reduces inflammation in neonatal rats by inhibiting COX-1, COX-2, and TNF-α[23] and alleviates influenza virus-induced inflammation by inhibiting COX and TNF-α activities[24]. Tang *et al*. reported the anti-inflammatory activity of kaempferol and highlighted its importance in attenuation of cardiac fibroblast inflammation[25].

The underlying interactive mechanism between kaempferol and interleukin (IL)-32-induced monocyte-macrophage differentiation was explained by Nam *et al*[26]. IL-32 is a main pro-inflammatory cytokine responsible for different categories of inflammations[27-29]. The inhibition of pro-inflammatory cytokines has been attributed to the anti-inflammatory actions of kaempferol and its derivatives. Thus, many pathways have been used to study the potential of kaempferol against inflammation.

2.2. Antioxidant properties of kaempferol

Oxidative stress in cells leads to generation of free radicals and is one of the main causes of many diseases *e.g.*, autoimmune, and cardiovascular disease, senile dementia, and cancer. Oxidative stress is an imbalance between cellular oxidants and antioxidants, which ends up in poor elimination of ROS and reactive nitrogen species generated in the cells[30].

Wang *et al*.[17] studied the antioxidant potential of kaempferol and its glycosides and revealed its excellent free radical scavenging capability. In another study, the microwave-assisted extraction of kaempferol and its derivatives from *Cyclocarya paliurus* (Batal.) Iljinskaja leaves was explored by Xie *et al*[31]. The results showed that the extract possesses enhanced antioxidant activity.

By using DPPH, superoxide radical, and NO inhibition assays, Ibrahim *et al*. investigated the antioxidant properties of kaempferol and its derivatives, including a newly discovered kaempferol derivative extracted from the ethyl acetate fraction of an aqueous methanol extract of *Calothamnus quadrifidus* aerial parts[32] and reported the high antioxidant activity in inhibiting the O_2^- radical, which was comparable with ascorbic acid.

In vitro antioxidant activity of kaempferol along with its various derivatives extracted from *Chenopodium ambrosioides* (Linn.) was reported by Ghareeb *et al*[33]. The glycosidic derivative showed better *in vitro* antioxidant activity. An ABTS assay established that kaempferol was efficient in free radical scavenging, and its scavenging activity was promoted due to generation of copper-coordinated kaempferol complex as Cu(Ⅱ) ions using the Fenton reaction[34,35]. Zang *et al*. also revealed the antioxidant effect of a derivative of kaempferol obtained from soybean leaves[35]. Thus, based on the results of these studies, kaempferol and its derivatives hold great potential as antioxidant agents which can either relieve or suppress the oxidative stress in the cellular system for better health benefits.

2.3. Antidiabetic properties of kaempferol

Diabetes is a chronic illness demanding incessant medical

attention[36]. The antidiabetic effect of kaempferol in diabetic rats was demonstrated by Al-Numair *et al*[37]. The administration of kaempferol to diabetic rats significantly increased the activity of membrane-bound ATPases in various organs, leading to an increase in insulin secretion, thereby lowering the glucose concentration.

Ibitoye *et al*. showed the antidiabetic effects of kaempferol isolated from *Cucumis sativus* L in *in vitro* and *in vivo* models[38]. The extract inhibited α-amylase and α-glucosidase activity with an IC_{50} value of 652.43 and 540.42 μg/mL, respectively. The common drug known as glucagon-like peptide 1 (GLP-1) agonists is used to improve blood sugar. The effect of kaempferol on the release of GLP-1 and insulin in mice was studied by Sharma *et al*[39]. They established that kaempferol ameliorates renal injury and fibrosis by increasing the release of GLP-1 and insulin.

Kaempferol, extracted from *Ginkgo biloba*, could regulate hepatic gluconeogenesis and blood glucose homeostasis in obese mice[40]. The results confirmed that kaempferol, when administered orally, considerably enhanced blood glucose control, linked with lowered hepatic glucose generation and amended whole-body insulin sensitivity without changing body weight, food intake, or adiposity.

Alkhalidy *et al*. found that kaempferol considerably controlled blood glucose levels in mice by decreasing the production of hepatic glucose and enhancing insulin sensitivity[41]. The antidiabetic effects of kaempferol glycosides purified from unripe soybean leaves in mice were extensively studied by Zang *et al*[42]. Kaempferol glycoside treatment decreased fasting blood glucose and serum HbA1c levels and alleviated insulin resistance.

2.4. Neuroprotective properties of kaempferol

Kaempferol displays a multipotential neuroprotective effect by modulating many pro-inflammatory signaling pathways[42]. The relationship between the defensive effect of kaempferol and repeated exposure to chlorpyrifos and memory dysfunction in rats was established by Hussein *et al*[43]. Kaempferol administration protected against chlorpyrifos-induced neuronal damage significantly. Kaempferol exerted its neuroprotective effects by inhibiting *GSK3β* gene expression and inducing Nrf2 expression in the brain tissues. The results suggested that repeated exposure to chlorpyrifos is related to oxidative stress along with memory deficits in rats. Nevertheless, kaempferol administration successfully attenuated the chlorpyrifos-induced brain toxicity, probably *via* the modulation of the GSK3β-Nrf2 signaling pathway.

Han *et al*. studied the protective effects of kaempferol against neuronal loss and behavioral discrepancies in mice with Parkinson's disease (PD)[44]. Kaempferol prevented neuronal degeneration in PD by inhibiting lipid peroxidation.

Das *et al*. investigated the role of kaempferol in improving hypoxic neurodegeneration in the hippocampus and revealed the signaling mechanisms of kaempferol administration under hypoxic conditions[45]. The effects of kaempferol against the transgenic *Drosophila* articulating human amyloid beta-42 was studied by Beg *et al*[46]. The results revealed that kaempferol deferred the loss of climbing ability and memory, as well as diminished oxidative stress.

In another study, kaempferol protected neurodegeneration by preventing NLRP3 inflammasome activation in mice[47]. It was demonstrated that kaempferol improved the expression of the cleaved CASP1 along with the disruption in NLRP3-PYCARD-CASP1 complex assembly and a simultaneous reduction in IL-1β secretion. Kaempferol also promoted macroautophagy/autophagy in microglia, which resulted in a decrease in the expression of NLRP3 protein, thereby deactivating the NLRP3 inflammasome.

Li *et al*. found that kaempferol ameliorated inflammation in brain tissue injury in rats[48]. Kaempferol treatment reduces cerebral infarct volume, inflammation, and disruption in the blood-brain barrier after cerebral injury. Besides, kaempferol decreased the phosphorylation of transcription factor NF-κB p65, thus preventing the expression of several pro-inflammatory proteins.

Kaempferol exhibited anti-depressive effects by increasing antioxidant capabilities and anti-inflammatory activity through AKT/β-catenin cascade activity in the prefrontal cortex of mice with chronic social defeat stress[49]. Kaempferol-3-*O*-glucoside prevented depression-like behavior during the perinatal period[50] by modulating the susceptibility of depressive behavior.

Kaempferol is effective against neuroinflammation and blood-brain barrier dysfunction[51]. Kaempferol decreases the generation of inflammatory proteins in brain tissues and protects blood-brain barrier integrity. Additionally, kaempferol considerably decreases the levels of high mobility group box-1 and curbed inflammatory pathways in both transcriptional and translational stages[51]. It also can inhibit mitochondrial damage in neurons with oxygen-glucose deficiency[52].

In a study by Pan *et al*., kaempferol is used as a therapeutic agent to prevent and cure neurodegenerative illnesses like PD[53]. The results indicate that kaempferol inhibited apomorphine-induced rotational behavior, lipid peroxidation, IL-6, and TNF-α while increasing the antioxidant markers in a PD rat model and SH-S5Y5 cells.

The potential of kaempferol on reducing cerebral injury was reported by Wang *et al*[54]. The results revealed that upon treatment with kaempferol, a decrease in the cerebral infarct volume and the neurological score after cerebral ischemia-reperfusion was observed, suggesting kaempferol could protect against cerebral ischemia-reperfusion-induced brain damage. The use of kaempferol as an alternative agent for treating neurological disorders has been established, however, extensive research is needed to establish it as a sustainable resource against neurological diseases.

2.5. Anticancer properties of kaempferol

Cancer development involves its initiation, promotion, and progression[55]. The antineoplastic efficacy of kaempferol against malignancies of the esophagus, pharynx, breast, liver, ovary, stomach, lung, pancreas, and bladder is well documented and is one of its most significant features. However, the specific mechanism of kaempferol's effectiveness against certain malignancies remains unknown. Foods containing high content of kaempferol have specifically been linked to a lower risk for skin, liver, and colon cancers. The possible mechanisms of its action include apoptotic induction, cell cycle arrest at the G_2/M phase, downregulation of epithelial-mesenchymal transition-related markers, and the phosphoinositide-3-kinase/protein kinase B (Akt) signaling pathways[56–58].

The cytotoxic effects of kaempferol-3-*O*-rutinoside against human colorectal carcinoma (HCT-116), human breast adenocarcinoma (MCF-7), human hepatocellular carcinoma (HepG2), human osteosarcoma, and human pulmonary adenocarcinoma (A549) cell lines are reported by Melek *et al*[59].

Wang *et al*. showed kaempferol exerted an inhibitory effect on pancreatic cancer *via* regulation of ROS[60] and revealed the tissue transglutaminase (TGM2) gene is a crucial target for kaempferol that induced ROS-related apoptosis in pancreatic cancer. Kaempferol could promote *in vitro* apoptosis by increasing ROS generation involved in the Akt/mTOR signaling.

Yao *et al*. reported the anticancer effects of kaempferol against esophagus squamous cell carcinoma[61]. The flow cytometric analysis showed that treatment with kaempferol induced the G_0/G_1 phase arrest in tumor cells, consequently, changing the protein expression involved in cell cycle regulation. Apart from suppressive potential against cell proliferation, kaempferol significantly inhibited tumor glycolysis. The mechanistic studies showed that kaempferol directly inhibited epidermal growth factor receptor activity, along with suppression of the downstream signaling pathways.

In vitro cytotoxic effects of kaempferol and its portions against various cancer cell lines, *viz.*, A2780 (ovarian), H460 (lung), A431(skin), MIAPaCa2 (pancreas), Du145 (prostate), HT29 (colon), MCF-7 (breast), BE2-C (neuroblastoma), SJ-G2, U87 and SMA (glioblastoma) were studied by Pham *et al*[62]. The obtained 50% growth inhibition values confirmed that kaempferol exhibited strong cytotoxicity.

Kim *et al*. investigated the anticancer activity of kaempferol against gastric cancer[63]. Kaempferol induced autophagy and cell death in gastric cancer, boosting LC3-Ⅰ to LC3-Ⅱ conversion and downregulating p62. Additionally, the results suggested an autophagic cell death *via* the activation of the IRE1-JNK-CHOP signaling, indicating endoplasmic reticulum stress response by kaempferol.

In a study of Yang *et al*.[64], kaempferol inhibited ovarian cancer cell growth with IC_{50} values of 25-50 μM. Nevertheless, the cytotoxicity of kaempferol was insignificant against the normal SV40 cells (IC_{50}>120 μM). This compound could induce the OVACAR-3 cell cycle arrest in the G_2/M phase and inhibit the MEK/ERK and STAT3 signaling pathways.

The cytotoxicity of kaempferol and its mode of action of apoptotic induction on bladder cancer cells were investigated by Wu *et al*[65]. Kaempferol displayed an effective inhibition of bladder cancer cells. The molecular mechanism revealed that kaempferol inhibited bladder cancer cell proliferation by apoptosis and suppressing the function of unwanted enzymes. Chen *et al*. investigated the anti-metastatic efficacy of kaempferol and its molecular mechanism in human osteosarcoma cells and found that kaempferol therapy lowered enzymatic activity and protein levels[66].

The cytotoxic effects including pro-apoptotic properties of kaempferol on HL-60 and NB4 leukemia cells were reported by Moradzadeh *et al*[67]. Kaempferol could reduce cell viability and enhance the sub-G_1 populace in the tested leukemic cells. Also, it promoted apoptotic cell death by inhibiting multidrug resistance in a concentration-dependent manner.

Sezer *et al*. reported the anticancer effect of kaempferol on HCT-116 cells by estimating total oxidant and antioxidant status, and 8-hydroxydeoxyguanosine levels. Kaempferol also reduced oxidative stress index levels in cancer cells in comparison with untreated cells[68].

Mahgoub *et al*. found that kaempferol derivatives extracted from 80% methanol extract of *Callistemon viminalis* exhibited cytotoxic activity against MCF-7 cells and demonstrated greater activities against HepG2 cells[69].

The anticancer activity of the soursop leaf extracts (*Annona muricata* L.) against HeLa cervical cancer cells and non-carcinogenic fibroblast cells was studied by Yathzamiry *et al*[70]. The results of the MTT assay revealed that the leaf extract exhibited toxicity to both the cell lines, however, the ethanolic extract inhibited cell viability of HeLa cervical cancer cells and showed lower cytotoxicity towards fibroblast cells.

Cai *et al*.[71] reported kaempferol derivatives displayed moderate to high cytotoxicity against cancer cells in comparison to cisplatin. Kaempferol inhibited the growth of renal cell carcinoma without inducing cytotoxicity[72]. The inhibition of metalloproteinase-2 protein by kaempferol could be attributed to the downregulation of Akt and focal adhesion kinase (FAK) phosphorylation, while kaempferol showed an anti-metastatic effect on the RCC 786-O cells. Li *et al*. studied the anticancer activity of kaempferol in combination with 5-fluorouracil against colorectal cancer cells[73]. The combination treatment strongly inhibited the PI3K/Akt pathway activity. Yin *et al*.[74] showed the anticancer effects of kaempferol derivatives extracted from Mongolian oak cups on HepG2 cells[74].

Table 2. A summary of biological activities and the cellular and molecular mechanisms of kaempferol and its derivatives.

Biological activity	Flavonoids	Mechanism of action	Ref
Anti-inflammatory	Kaempferol-7-*O*-glucoside, kaempferol-3-*O*-rhamnoside, kaempferol-3-*O*-rutinoside	Inhibits T-cell proliferation and NO release	[17]
	Kaempferol	Suppresses NF-κB	[18]
		Lowers the production of NO, TNF-α, IL-1β and IL-6	[19]
	Kaempferol-3-*O*-rutinoside	Inhibits IL-6, TNF-α, iNOS, and COX-2	[20]
	Kaempferol-3-*O*-glucorhamnoside	Suppresses NF-κB and MAP kinase phosphorylation	[21]
	Kaempferol-3-*O*-β-*D*-glucuronide	Inhibits IL-1β, NO, PGE_2, and LTB4	[22]
	Kaempferol	Inhibits COX-1, COX-2, and TNF-α	[23]
		Inhibits the NF-κB binding activity of DNA and myeloid differentiation factor 88	[24]
		Suppresses the release of IL-6, IL-1, IL-18 and TNF-α	[25]
		Inhibits the TLR4	[26]
Antioxidant	Kaempferol-7-*O*-glucoside, kaempferol-3-*O*-rhamnoside, kaempferol-3-*O*-rutinoside	Inhibits Con A-induced activation of T cell proliferation and NO or ROS production	[17]
	Kaempferol-3-*O*-β-*D*-glucuronide, kaempferol-7-*O*-α-*L*-rhamnoside, kaempferol	ROS scavenging	[31]
	Kaempferol-3-*O*-(600-E-p-coumaroyl)-b-*D*-glucopyranoside (6-methoxy tiliroside); in new compound, kaempferol 3-*O*-(600-E-p-coumaroyl)-b-*D*-glucopyranoside (tiliroside), kaempferol	Inhibits DPPH, superoxide, and NO radicals	[32]
	Kaempferol 3-*O*-α-*L*-$^{1}C_4$-rhamnosyl-(1'''→2")-β-*D*-$^{4}C_1$-xylopyranoside (new compound), kaempferol 3-*O*-α-*L*-$^{1}C_4$-rhamnopyranoside (afzelin), kaempferol 7-*O*-α-*L*-$^{1}C_4$-rhamnopyranoside, kaempferol	ROS scavenging	[33]
	Kaempferol [in presence of Cu(Ⅱ) ions]	Inhibits ROS	[34]
	Kaempferol 3-*O*-β-*D*-(2,6-di-*O*-a-*L*-rhamnopyranosyl) galactopyranoside	Inhibits ROS	[35]
Antidiabetic	Kaempferol	Increases insulin secretion, lowers glucose concentration, and enhances diabetic rats' antioxidant defense system	[37]
		Inhibits α-amylase and α-glucosidase, and lowers glucose	[38]
		Increases the release of GLP-1 and insulin in the DN mouse model	[39]
		Improves blood glucose control in obese mice, associated with reduced hepatic glucose production and improved whole-body insulin sensitivity	[40]
		Ameliorates hyperglycemia by suppressing hepatic gluconeogenesis and enhancing hepatic insulin sensitivity	[41]
	Kaempferol 3-*O*-β-*D*-glucopyranosyl(1→2)-*O*-[α-*L*-rhamnopyranosyl(1→6)]-β-*D*-galactopyranoside, kaempferol 3-*O*-β-*D*-glucopyranosyl(1→2)-*O*-[α-*L*-rhamnopyranosyl(1→6)]-β-*D*-glucopyranoside, kaempferol-3-*O*-β-*D*-(2-*O*-β-*D*-glucopyranosyl) galactopyranoside, kaempferol 3-*O*-β-*D*-(2,6-di-*O*-α-*L*-rhamnopyranosyl)galactopyronoside	Decreases fasting blood glucose	[42]
Neuroprotective	Kaempferol	Inhibits *GSK3β* gene expression and induction of Nrf2 expression in the brain tissues	[43]
		Inhibits lipid peroxidation-mediated mitochondrial damage by promoting lipophagy	[44]
		Downregulation of Trkβ under hypoxic conditions	[45]
		Decreases acetylcholinesterase activity	[46]
		Protects against LPS and SNCA-induced neurodegeneration	[47]
		Inhibits microglia activation, pro-inflammatory interleukins TNF-α, IL-6, IL-1β, IL-5, MCP 1, ICAM 1, and the phosphorylation of NF-κB p65 translocation as well as protects the integrity of the blood-brain barrier	[48]
		Increases the AKT/β-catenin cascade in the prefrontal cortex and reduces the concentration of inflammatory mediators IL-1β and TNF-α	[49]
	Kaempferol-3-*O*-glucoside	Important antidepressant modulator	[50]
	Kaempferol	Reduces the production of IL-1β, IL-6, TNF-α, MCP-1, COX-2 and iNOS in brain tissues; Protects blood-brain barrier integrity and increases blood-brain barrier-related proteins including occludin-1, claudin-1 and CX43 in brain of LPS-induced mice; Decreases HMGB1 level and suppresses the TLR4/MyD88 inflammatory pathway	[51]
		Inhibits Drp1 translocation and preserves mitochondrial function through alleviating HK-II detachment *via* Akt activation *in vitro* and *in vivo*	[52]
		Inhibits lipid peroxidation and IL-6 and TNF-α, and prevents the loss of tyrosine hydroxylase expression	[53]
		Reduces cerebral ischemia-reperfusion	[54]

Table 2. A summary of biological activities and the cellular and molecular mechanisms of kaempferol and its derivatives (continued).

Biological activity	Flavonoids	Mechanism of action	Ref
Anticancer	Kaempferol, kaempferol-7-*O*-glucoside, kaempferol-3-*O*-rhamnoside, kaempferol-3-*O*-rutinoside	-	[17]
	Kaempferol-3-*O*-rutinoside	-	[59]
	Kaempferol	Induces ROS-dependent apoptosis in pancreatic cancer cells *via* the TGM2-mediated Akt/mTOR signaling	[60]
		Inhibits cell proliferation and glycolysis in esophagus squamous cell carcinoma *via* targeting the EGFR signaling pathway	[61]
		Inhibits cell proliferation	[62]
		Autophagic cell death *via* the IRE1-JNK-CHOP pathway and inhibition of G9a in gastric cancer cells	[63]
		Induces apoptosis and G_0/G_1 cell cycle arrest and modulates the MEK/ERK and STAT3 pathways in human ovarian cancer cell	[64]
		ROS-induced hemolysis and apoptotic induction in bladder cancer	[65]
		Suppresses cell metastasis *via* inhibition of the ERK-p38-JNK and AP-1 signaling pathways in U-2 OS human osteosarcoma cells	[66]
		Increases apoptosis in human acute promyelocytic leukemia cells and inhibits multidrug resistance genes	[67]
		Increases apoptosis	[68]
	Kaempferol 3-*O*-(4"-galloyl)-β-*D*-glucopyranosyl-(1"'6")-*O*-β-*D*-glucopyranoside, kaempferol 3-*O*-β-*D*-mannuronopyranoside, kaempferol 3-*O*-β-*D*-mannopyranoside	Inhibition of ROS production reverses cancer cell phenotype	[69]
	Aminoethyl derivatives of kaempferol	Apoptotic activity	[71]
	Kaempferol	Inhibits the invasion and migration of renal cancer cells through the downregulation of Akt and FAK pathways	[72]
		Regulates the PI3K/Akt signaling pathway	[73]
	Kaempferol-derivatives from Mongolian: oak cups [kaempferol-3-*O*-(6"-di-E-p-coumaroyl)-glucoside; kaempferol-3-*O*-(2",6"-di-E-p-coumaroyl)-glucoside; kaempferol-3-*O*-(2"-*Z*,6"-E-p-coumaroyl)-glucoside; kaempferol-3-*O*-(2"-*Z*,6"-di-E-p-coumaroyl)-glucoside]	-	[74]
	Kaempferol and its glycoside derivatives {Kaempferol 3-*O*-[(6-*O*-E-caffeoyl)-β-*D*-glucopyranosyl-(1→2)]-β-*D*-galactopyranoside-7-*O*-β-*D*-glucuropyranoside, kaempferol 3-*O*-[(6-*O*-E-p-coumaroyl)-β-*D*-glucopyranosyl-(1→2)]-β-*D*-galactopyranoside-7-*O*-β-*D*-glucuropyranoside and kaempferol 3-*O*-[(6-*O*-E-feruloyl)-β-*D*-glucopyranosyl-(1→2)]-β-*D*-galactopyranoside-7-*O*-β-*D*-glucuropyranoside, isolated from aerial parts of *Lens culinaris* Medik	Increases the sensitivity of HL-60 cells to etoposide but does not increase apoptosis and ROS level induced by etoposide	[75]
	Kaempferol-3-*O*-[(6-*O*-E-feruloyl)-β-*D*-glucopyranosyl-(1→2)]-β-*D*-galactopyranoside-7-*O*-β-*D*-glucuropyranoside, kaempferol-3-*O*-{[(6-*O*-E-p-coumaroyl)-β-*D*–glucopyranosyl-(1→2)]-α-*L* rhamnopyranosyl(1→6)}-β-*D*-galactopyranoside-7-*O*-α-*L*-rhamnopyranoside, and kaempferol-3-*O*-[(6-*O*-E-caffeoyl)-β-*D*-glucopyranosyl-(1→2)]-β-*D*-galactopyranoside-7-*O*-(2-*O*-E-caffeoyl')-β-*D*-glucuropyranoside	Increases DNA damage provoked by etoposide	[76]
	Kaempferol (ethanolic extract of *Equisetum myriochaetum*)	Apoptosis or autophagy	[77]

NO: Nitric oxide; TNF-α: Tumor necrosis factor-α; IL-1β: Interleukin-1β; IL-6: Interleukin-6; MAPKs: Mitogen-activated protein kinases; PGE_2: Prostaglandin E_2; LTB4: Leukotriene B; COX: Cyclooxygenase; TLR4: Toll-like receptor 4; Con A: Concanaval; ROS: Reactive oxygen species; GLP-1: Glucagon-like peptide 1 agonists; DN: Diabetic nephropathy; GSK-3β: Glycogen synthase kinase-3 beta; Nrf2: Nuclear factor erythroid 2 related factor 2; TRKβ: Tyrosine Kinase beta; LPS: Lipopolysaccharide; SNCA: Synuclein alpha; MCP-1: Monocyte chemoattractant protein-1; ICAM: Intercellular adhesion molecule; iNOS: Inducible nitric oxide synthase; Cx43: Connexin 43; HMGB1: High-mobility group box-1; Drp1: Dynamin-related protein 1; HK II: Hexokinase II; TGM2: Transglutaminase 2; EGFR: Epidermal growth factor receptor; IRE1: Inositol-requiring-1; JNK1: c-Jun *N*-terminal protein kinase-1; MEK: Mitogen-activated extracellular signal-regulated kinase; ERK: Extracellular signal-regulated kinase; STAT3: Signal transducer and activator of transcription 3; AP-1: Activator protein 1; FAK: Focal adhesion kinase.

Kaempferol and its glycoside derivatives isolated from aerial parts of *Lens culinaris* Medik. were found to affect the cytotoxicity of etoposide against human promyelocytic leukemia (HL-60) cells[75]. In addition, kaempferol glycoside derivatives might exhibit an inverse effect on the activity of etoposide in HL-60 cells in comparison to kaempferol. In another study, kaempferol extracted from the aerial parts of *Lens culinaris* Medik decreased DNA damage promoted by etoposide in peripheral blood mononuclear cells but did not impact DNA damage in HL-60 cells[76]. The antiproliferative activity of the ethanolic extract of *Equisetum myriochaetum* which contains kaempferol was investigated against cervical cancer cells[77]. The kaempferol fraction exhibited a lower antiproliferative activity as compared to paclitaxel. The findings indicated that the antiproliferative activity of the fraction was possibly attributed to the presence of the secondary metabolite apigenin. According to the findings of previous studies, kaempferol can be used as an anticancer agent to treat various cancers. The overall summary of the biological activities including the mechanisms of kaempferol and its derivatives is given in Table 2.

3. Kaempferol from fruit and vegetable wastes

Kaempferol and its derivatives obtained from fruit and vegetable wastes have gained great attention in recent years. The shift is largely based on the concept of sustainability of kaempferol sources to keep the demand in check and provide an alternative source. The eutectic solvent extraction for deriving kaempferol from onion peel and the antioxidant potential was reported by Pal and Jadeja[78]. They provided a key step for the biorefinery process using a green technology method. The biological activity of kaempferol obtained from fennels, carrots, lemons, and tomato wastes was reported by Di Donato *et al*[79]. In tomato byproducts, glycosidic derivatives of kaempferol have been reported[80]. Winery byproducts have been studied for the presence of kaempferol and its industrial uses, and the biological activities exhibited their potential for human health benefits[81]. However, research on kaempferol-rich fruit and vegetable waste is scarce. Therefore, extensive research can be carried out for determination, isolation, and establishment of human health benefits of kaempferol obtained from such waste.

4. Conclusion

This review highlighted the importance of kaempferol in alleviating various diseases. The challenging aspect of using kaempferol in various health ailments is to understand a precise approach of cellular metabolism and mechanism along with specific delivery at targeted organelles which needs an extensive interdisciplinary approach. The nanoformulation of kaempferol can enhance bioavailability and can be considered as the most important future prospective. Most importantly, the kaempferol sources from fresh produce need to be diverted to non-utilized food wastes or byproducts without compromising the standard regulation of purity.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

Authors' contributions

SP collected the literature and prepared the manuscript. IUHB designed the original idea, collected the literature and prepared the manuscript. RB reviewed and edited the manuscript. All the authors approved the final version of the manuscript.

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