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Letter to the editor:

RECENT STUDIES ON KAEMPFEROL AND ITS BIOLOGICAL AND PHARMACOLOGICAL ACTIVITIES

Jae Kwang Kim[1], Sang Un Park[2*]

[1] Division of Life Sciences and Bio-Resource and Environmental Center, College of Life Sciences and Bioengineering, Incheon National University, Incheon 22012, Korea
[2] Department of Crop Science, Chungnam National University, 99 Daehak-ro, Yuseong-gu, Daejeon, 34134, Korea

* **Corresponding author:** Sang Un Park, Department of Crop Science, Chungnam National University, 99 Daehak-ro, Yuseong-gu, Daejeon, 34134, Korea, Tel.: +82-42-821-5730, Fax: +82-42-822-2631, E-mail: supark@cnu.ac.kr

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Dear Editor,

Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one) is a natural flavonol exhibiting different metabolic functions. It is most commonly found in a variety of plants and plant derived foods including grapes, kale, bean, broccoli, tomatoes, spinach, tea, and ginkgo biloba leaves (Cid-Ortega and Monroy-Rivera, 2018; Devi et al., 2015).

The biosynthesis of kaempferol is completed in four major steps. In the first step, a phenylpropanoid metabolic pathway occurs in which phenylalanine is converted into 4-coumaroyl-CoA. Subsequently, 4-coumaroyl-CoA is combined with three molecules of malonyl-coA to form naringenin chalcone (a tetrahydroxychalcone) through the action of chalcone synthase. In the third step, naringenin chalcone is exchanged with naringenin, and its hydroxyl group is involved in the formation of dihydrokaempferol. Finally, dihydrokaempferol, which has a double bond, is converted into kaempferol (Calderón-Montaño et al., 2011; Santos-Buelga et al., 2019).

Several papers have reported the positive effects of dietary kaempferol in reducing the risk of chronic diseases, such as cancer, liver injury, obesity, and diabetes (Imran et al., 2019; Wong et al., 2019). Kaempferol exhibits anti-inflammatory properties and has been used to cure many acute and chronic inflammation-induced diseases, such as intervertebral disc degeneration and colitis, post-menopausal bone loss, and acute lung injury (Ren et al., 2019). Herein, we summarize the most recent published findings on the biological and pharmacological activities of kaempferol (Table 1).

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Table 1: Recent studies on the biological and pharmacological activities of kaempferol

Key findings	Reference
Kaempferol can provide prophylactic treatment for alcoholic liver injury (AALI) in mice by increasing the level of butyrate receptors, transporters, and tight junction proteins in intestinal mucosa.	Chen et al., 2020
Kaempferol has the ability to protect $CdCl_2$-induced memory deficits and hippocampal apoptosis through its antioxidant potential and the inhibition of Akt/mTOR.	El-Kott et al., 2020
Kaempferol protects retinal ganglion cells from high-glucose-induced injury via extracellular signal-regulated kinases (ERK) and vasohibin-1 signaling.	Zhao et al., 2020
Kaempferol is a promising therapeutic candidate for the treatment of prostate cancer, in which the androgen signaling pathway and vasculogenic mimicry are combined.	Da et al., 2019
Kaempferol shows potential bone-sparing effects by enhancing estrogen signaling followed by activation of the WNT signaling pathway.	Sharma and Nam, 2019
Kaempferol acts as an anticancer agent in MFE-280 endometrial carcinoma cells via apoptosis induction, cell cycle arrest, and inhibition of the mTOR/PI3K/Akt signaling pathway.	Lei et al., 2019
Kaempferol has a positive role in the development of porcine parthenotes by reducing oxidative stress and increasing mitochondrial function.	Yao et al., 2019
Kaempferol and 5-fluorouracil (5-FU) work synergistically to inhibit cell proliferation and inducing apoptosis in colorectal cancer cells via the suppression of thymidylate synthase or the reduction of p-Akt activation. Therefore, kaempferol and 5-FU may be used together as an effective therapeutic strategy for colorectal cancer.	Li et al., 2019
It is well known that the accumulation of D-ribose induced advanced glycation end-products (AGEs) and reactive oxygen species (ROS) production in mesangial cell causes mitochondrial apoptosis. Kaempferol may reduce these changes and its protective effect could be related to the repair of autophagy.	Zhang et al., 2019
Kaempferol exhibits a protective effect on human aortic endothelial cells (HAECs) against inflammatory injury through the inactivation of nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways as well as the up-regulation of miR-203.	Cui et al., 2019
Kaempferol has the potential to suppress the proliferation and endorsed autophagy of human gastric cancer SNU-216 cells by up-regulating miR-181a and inactivating the MAPK/ERK (extracellular regulated protein kinases) and phosphatidylinositol 3 kinase (PI3K) pathways.	Zhang and Ma, 2019
Kaempferol shows potential anti-osteoarthritis (OA) effects, exhibiting the down-regulation of miR-146a and repressing the expression of decorin.	Jiang et al., 2019
Kaempferol can be used effectively to reduce lung damage caused by lipopolysaccharide (LPS) by changing TNF receptor associated factor-6 (TRAF6) polyubiquitination. Therefore, kaempferol may act as a novel molecular target to alleviate acute lung injury.	Qian et al., 2019
Kaempferol displays anti-depressive effects, which may be interceded at least in part by its enhanced antioxidant and anti-inflammation effects via the up-regulation of protein kinase B/β-catenin cascade (AKT) activity in the prefrontal cortex of chronic social defeat stress (CSDS) in mice.	Gao et al., 2019
Kaempferol shows neuroprotective effects against striatum injury induced by LPS. The possible mechanisms for its neuroprotective effects involve anti-neuroinflammation, showing blood–brain barrier (BBB) integrity and the down-regulation of the high mobility group box 1(HMGB1)/toll-like receptor 4 (TLR4) pathway.	Yang et al., 2019
10 μM Kaempferol enhances primordial follicle activation and cell proliferation in the PI3K/AKT pathway and reduces DNA fragmentation in ovine preantral follicles cultured *in vitro*.	Santos et al., 2019

Table 1 (cont.): Recent studies on the biological and pharmacological activities of kaempferol

Key findings	Reference
Kaempferol prevents hepatocyte apoptosis, protecting mice from liver failure by regulating the endoplasmic reticulum(ER) stress-glucose-regulated/binding immunoglobulin protein 78 (Grp78)-C/EBP-homologous protein (CHOP) signaling pathway. Therefore, kaempferol can be used to treat acute liver failure (ALF).	Wang et al., 2019
Kaempferol amends adipogenic differentiation in 3T3-L1 cells in mature adipocytes by promoting the down-regulation of Cebpa gene expression and decreasing lipid accumulation by exerting its positive effects on the levels of Pnpla2 and Lipe mRNA. From these findings, kaempferol can be considered to exhibit an anti-obesity effect.	Torres-Villarreal et al., 2019
Kaempferol acts as a topical wound healing agent during the treatment of both non-diabetic and diabetic wounds.	Özay et al., 2019
Kaempferol has the ability to inhibit cell migration by targeting extracellular signal-regulated kinases 1/2 (ERK1/2) signaling in human retinal pigment epithelial cells.	Chien et al., 2019
Kaempferol exhibits an anti-inflammatory effect by inhibiting the translocation of cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) proteins and enhancing the down-regulation of pro-inflammatory cytokines.	Yeon et al., 2019
Kaempferol shows a protective effect on oxidative stressed-human retinal pigment epithelium (RPE) cell damage due to its antioxidant activity and anti-apoptosis function. Therefore, kaempferol has a potential role in the prevention and therapeutic treatment of age-related macular degeneration (AMD) and other retinal diseases mediated by oxidative stress.	Du et al., 2018
Kaempferol can protect the proliferation, migration, and invasion of hepatic cancer HepG2 cells by down-regulating miR-21 and up-regulating phosphatase and tensin homologue (PTEN) as well as inactivating the PI3K/AKT/mammalian target of rapamycin (mTOR) signaling pathway.	Zhu et al., 2018
Kaempferol reduces oxidized low-density lipoprotein (ox-LDL)-induced apoptosis in human aortic endothelial cells (HAECs) by up-regulating miR-26a-5p via the inactivation of the TLR4/NF-κB signaling pathway, shedding light on the molecular mechanism where kaempferol alleviates ox-LDL-induced endothelial cell (EC) apoptosis.	Zhong et al., 2018
Kaempferol exhibits strong antioxidant activity on erythrocytes as well as inhibitory effects on the growth of cancerous bladder cells by inducing apoptosis and S-phase arrest.	Wu et al., 2018
Kaempferol has the ability to inhibit proliferation, but can also induce apoptosis and autophagy in A549 cells. In addition, kaempferol can up-regulate miR-340, along with PTEN and inactivates the PI3K/AKT pathway.	Han et al., 2018
Kaempferol can be used to promote glucose metabolism in skeletal muscle and inhibits gluconeogenesis in the liver, demonstrating the anti-diabetic action of kaempferol.	Alkhalidy et al., 2018a
Kaempferol can activate the inositol-requiring-1 (IRE1)-c-Jun N-terminal kinase (JNK)-CHOP signaling from cytosol to the nucleus and G9a inhibition activates autophagic cell death in gastric cancer (GC) cells.	Kim et al., 2018
Kaempferol can alleviate streptozotocin (STZ)-induced memory impairment in ovariectomized (OVX) rats by enhancing endogenous hippocampal antioxidants, such as superoxide dismutase and glutathione, and reducing neuroinflammation. Therefore, kaempferol can be used as a potential neuroprotective agent against cognitive deficit in Alzheimer's disease (AD).	Kouhestani et al., 2018
Kaempferol has been used to reduce rat pulmonary artery pressure in an endothelium-independent manner via large-conductance Ca^{2+}-activated $K^{+}(BK_{Ca})$ channel, soluble guanylate cyclase (sGC), protein kinase A (PKA) pathways and the inhibition of Ca^{2+}-influx through L-type calcium channels.	Mahobiya et al., 2018

Table 1 (cont.): Recent studies on the biological and pharmacological activities of kaempferol

Key findings	Reference
The protective mechanism of kaempferol in mouse primary hepatocyte injury induced by ethanol has been reported to be due to its involvement in the synchronous, early and persistent inhibition of mitochondrial and microsomal cytochrome P450 2E1 (CYP2E1), cytosolic heat shock protein 70 (Hsp70), and nuclear and cytosolic specificity protein 1 (SP1).	Zhou et al., 2018
Kaempferol may be considered a naturally occurring anti-diabetic compound that works by preventing glucose production and enhancing insulin sensitivity. The suppression of hepatic gluconeogenesis by kaempferol is considered to occur through its direct inhibitory action on the enzymatic activity of pyruvate carboxylase (PC)	Alkhalidy et al., 2018b
Kaempferol has been reported to delay the loss of climbing ability and memory, prevent oxidative stress, and inhibit acetylcholinesterase activity. Therefore, kaempferol may be utilized as a possible therapeutic agent to prevent the progression of AD.	Beg et al., 2018
Both checkpoint kinase 2 (Chk2) and death receptors play important roles in the anticancer activity of kaempferol observed in A2780/CP70 cells. These findings provide more evidence for the anti-ovarian cancer properties of kaempferol and demonstrate that kaempferol could be used as a potential adjuvant therapy for ovarian cancer.	Gao et al., 2018
Kaempferol can be used to act against γ-radiation-induced tissue damage and mortality via inhibiting oxidative stress and modulating apoptotic molecules both *in vivo* and *in vitro*.	Wang et al., 2018
When using kaempferol for bone regeneration purposes it has been revealed that it reduces glucocorticoid-induced bone loss and enhanced bone regeneration at the fractured site, demonstrating the positive role of flavonoids on bone health.	Adhikary et al., 2018
Kaempferol exhibits gastroprotective ability, which may occur by preserving gastric mucous glycoproteins levels, preventing neutrophil accumulation and myeloperoxidase activity, regulating the levels of pro-inflammatory cytokines, and enhancing nitric oxide (NO) production.	Li et al., 2018
Kaempferol decreases sepsis-induced acute lung injury in mice by preventing the oxidative stress, inducible NO synthase (iNOS), and intercellular adhesion molecule 1 (ICAM-1) pathways.	Rabha et al., 2018
Kaempferol reduces the lipid profile, infracted area, and oxidative stress in isoprenaline-induced myocardial injury in rats.	Vishwakarma et al., 2018
Kaempferol prevents the migration and invasion of fibroblast-like synoviocytes (FLSs) in rheumatoid arthritis (RA) by suppressing the activation of the MAPK pathway without hampering the expression of TNF-α receptors.	Pan et al., 2018
Kaempferol enhances apoptosis and impedes multidrug resistance in a concentration-dependent manner without any differential effect on leukemic cells. Therefore, kaempferol may be used as an appropriate alternative for all-trans retinoic acid (ATRA) in acute promyelocytic leukemia (APL) patients.	Moradzadeh et al., 2018
Kaempferol can inhibit angiogenesis by suppressing hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor receptor 2 (VEGFR2) activation via ERK/p38 MAPK and PI3K/Akt/mTOR signaling in endothelial cells.	Kim, 2017
Kaempferol targets estrogen-related receptor α (ERRα) and prevents angiogenesis in human retinal endothelial cells (HRECs) under high glucose conditions. Therefore, kaempferol can be considered a potential drug for controlling the progression of diabetic retinopathy.	Wu et al., 2017
Kaempferol imparts a starting point for the development of novel anti-biofilm drugs, which may decrease the risk of bacterial drug resistance, inhibiting *Staphylococcus aureus* biofilm-related infections.	Ming et al., 2017
Apigenin, hesperidin, and kaempferol exhibit an anti-adipogenic and delipidating effect in human adipocytes derived from human mesenchymal stem cells (MSCs).	Gómez-Zorita et al., 2017

Table 1 (cont.): Recent studies on the biological and pharmacological activities of kaempferol

Key findings	Reference
Kaempferol helps to induce hepatocarcinoma cell death via an ER stress and CHOP-autophagy signaling pathway. Therefore, kaempferol may be used as a potential chemopreventive agent for patients with hepatocellular carcinoma.	Guo et al., 2017
Kaempferol can prevent and reverse ventricular fibrosis and cardiac dysfunction affording an experimental basis for the clinical treatment on ventricular fibrosis.	Liu et al., 2017
Kaempferol sensitizes ovarian cancer cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis by up-regulation of death receptors 4 and 5 (DR4 and DR5, respectively) through an ERK/JNK/CHOP pathway.	Zhao et al., 2017
Kaempferol significantly reduces interleukin-1β-stimulated pro-inflammatory mediators in rat OA chondrocytes by preventing the activation of the NF-κB pathway. Therefore, kaempferol can be used as an anti-inflammatory and anti-arthritis agent.	Zhuang et al., 2017
Kaempferol as a precursor increases coenzyme Q (Q) levels via combining its ability to upregulate sirtuin-3. Therefore, kaempferol is a potential candidate for the design of drugs aimed toward increasing endogenous Q biosynthesis, particularly in the kidneys.	Fernández-Del-Río et al., 2017
Kaempferol can be applied to treat myocardial ischemia-reperfusion injury in diabetic rats by reducing AGE-RAGE/MAPK induced oxidative stress and inflammation.	Suchal et al., 2017
Kaempferol reveals protective effects toward H9N2 virus-induced inflammation via the suppression of themyeloid differentiation factor 88 (TLR4/MyD88)-mediated NF-κB and MAPKs pathways. Therefore, kaempferol can be considered as an effectual drug used for the treatment of influenza virus-induced ALI.	Zhang et al., 2017
Kaempferol exhibits a cytoprotective effect against the lipotoxic activation of autophagy via an AMPK/mTOR pathway.	Varshney et al., 2017
Kaempferol can be utilized for the clinical treatment of uterine fibroids due to its inhibitory effect on the proliferation of uterine fibroids cells.	Li et al., 2017

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Conflict of interest

The authors declare no conflict of interest.

REFERENCES

Adhikary S, Choudhary D, Ahmad N, Karvande A, Kumar A, Banala VT, et al. Dietary flavonoid kaempferol inhibits glucocorticoid-induced bone loss by promoting osteoblast survival. Nutrition. 2018; 53:64-76.

Alkhalidy H, Moore W, Wang A, Luo J, McMillan RP, Wang Y, et al. Kaempferol ameliorates hyperglycemia through suppressing hepatic gluconeogenesis and enhancing hepatic insulin sensitivity in diet-induced obese mice. J Nutr Biochem. 2018a;58:90-101.

Alkhalidy H, Moore W, Wang Y, Luo J, McMillan RP, Zhen W, et al. The flavonoid kaempferol ameliorates streptozotocin-induced diabetes by suppressing hepatic glucose production. Molecules. 2018b;23:E2338.

Beg T, Jyoti S, Naz F, Rahul, Ali F, Ali SK, et al. Protective effect of kaempferol on the transgenic drosophila model of alzheimer's disease. CNS Neurol Disord Drug Targets. 2018;17:421-9.

Calderón-Montaño JM, Burgos-Morón E, Pérez-Guerrero C, López-Lázaro M. A review on the dietary flavonoid kaempferol. Mini Rev Med Chem. 2011;11: 298-44.

Chen J, Xuan YH, Luo MX, Ni XG, Ling LQ, Hu SJ, et al. Kaempferol alleviates acute alcoholic liver injury in mice by regulating intestinal tight junction proteins and butyrate receptors and transporters. Toxicology. 2020;429:152338.

Chien HW, Wang K, Chang YY, Hsieh YH, Yu NY, Yang SF, et al. Kaempferol suppresses cell migration through the activation of the ERK signaling pathways in ARPE-19 cells. Environ Toxicol. 2019;34:312-8.

Cid-Ortega S, Monroy-Rivera JA. Extraction of kaempferol and its glycosides using supercritical fluids from plant sources: A review. Food Technol Biotechnol. 2018;56:480-93.

Cui S, Tang J, Wang S, Li L. Kaempferol protects lipopolysaccharide-induced inflammatory injury in human aortic endothelial cells (HAECs) by regulation of miR-203. Biomed Pharmacother. 2019;115:108888.

Da J, Xu M, Wang Y, Li W, Lu M, Wang Z. Kaempferol promotes apoptosis while inhibiting cell proliferation via androgen-dependent pathway and suppressing vasculogenic mimicry and invasion in prostate cancer. Anal Cell Pathol (Amst). 2019;2019: 1907698.

Devi KP, Malar DS, Nabavi SF, Sureda A, Xiao J, Nabavi SM, et al. Kaempferol and inflammation: From chemistry to medicine. Pharmacol Res. 2015;99:1-10.

Du W, An Y, He X, Zhang D, He W. Protection of kaempferol on oxidative stress-induced retinal pigment epithelial cell damage. Oxid Med Cell Longev. 2018; 2018:1610751.

El-Kott AF, Bin-Meferij MM, Eleawa SM, Alshehri MM. Kaempferol protects against cadmium chloride-induced memory loss and hippocampal apoptosis by increased intracellular glutathione stores and activation of PTEN/AMPK induced inhibition of Akt/mTOR signaling. Neurochem Res. 2020;45:295-309.

Fernández-Del-Río L, Nag A, Gutiérrez Casado E, Ariza J, Awad AM, Joseph AI, et al. Kaempferol increases levels of coenzyme Q in kidney cells and serves as a biosynthetic ring precursor. Free Radic Biol Med. 2017;110:176-87.

Gao W, Wang W, Peng Y, Deng Z. Antidepressive effects of kaempferol mediated by reduction of oxidative stress, proinflammatory cytokines and up-regulation of AKT/β-catenin cascade. Metab Brain Dis. 2019;34: 485-94.

Gao Y, Yin J, Rankin GO, Chen YC. Kaempferol induces G2/M cell cycle arrest via checkpoint kinase 2 and promotes apoptosis via death receptors in human ovarian carcinoma A2780/CP70 cells. Molecules. 2018;23:E1095.

Gómez-Zorita S, Lasa A, Abendaño N, Fernández-Quintela A, Mosqueda-Solís A, Garcia-Sobreviela MP, et al. Phenolic compounds apigenin, hesperidin and kaempferol reduce in vitro lipid accumulation in human adipocytes. J Transl Med. 2017;15:237.

Guo H, Lin W, Zhang X, Zhang X, Hu Z, Li L, et al. Kaempferol induces hepatocellular carcinoma cell death via endoplasmic reticulum stress-CHOP-autophagy signaling pathway. Oncotarget. 2017;8:82207-16.

Han X, Liu CF, Gao N, Zhao J, Xu J. Kaempferol suppresses proliferation but increases apoptosis and autophagy by up-regulating microRNA-340 in human lung cancer cells. Biomed Pharmacother. 2018;108: 809-16.

Imran M, Rauf A, Shah ZA, Saeed F, Imran A, Arshad MU, et al. Chemo-preventive and therapeutic effect of the dietary flavonoid kaempferol: A comprehensive review. Phytother Res. 2019;33:263-75.

Jiang R, Hao P, Yu G, Liu C, Yu C, Huang Y, et al. Kaempferol protects chondrogenic ATDC5 cells against inflammatory injury triggered by lipopolysaccharide through down-regulating miR-146a. Int Immunopharmacol. 2019;69:373-81.

Kim GD. Kaempferol inhibits angiogenesis by suppressing HIF-1α and VEGFR2 activation via ERK/p38 MAPK and PI3K/Akt/mTOR signaling pathways in endothelial cells. Prev Nutr Food Sci. 2017;22:320-6.

Kim TW, Lee SY, Kim M, Cheon C, Ko SG. Kaempferol induces autophagic cell death via IRE1-JNK-CHOP pathway and inhibition of G9a in gastric cancer cells. Cell Death Dis. 2018;9:875.

Kouhestani S, Jafari A, Babaei P. Kaempferol attenuates cognitive deficit via regulating oxidative stress and neuroinflammation in an ovariectomized rat model of sporadic dementia. Neural Regen Res. 2018;13:1827-32.

Lei X, Guo J, Wang Y, Cui J, Feng B, Su Y, et al. Inhibition of endometrial carcinoma by Kaempferol is interceded through apoptosis induction, G2/M phase cell cycle arrest, suppression of cell invasion and upregulation of m-TOR/PI3K signalling pathway. J BUON. 2019;24:1555-61.

Li Q, Hu X, Xuan Y, Ying J, Fei Y, Rong J, et al. Kaempferol protects ethanol-induced gastric ulcers in mice via pro-inflammatory cytokines and NO. Acta Biochim Biophys Sin (Shanghai). 2018;50:246-53.

Li Q, Wei L, Lin S, Chen Y, Lin J, Peng J. Synergistic effect of kaempferol and 5-fluorouracil on the growth of colorectal cancer cells by regulating the PI3K/Akt signaling pathway. Mol Med Rep. 2019;20:728-34.

Li Y, Ding Z, Wu C. Mechanistic study of the inhibitory effect of kaempferol on uterine fibroids *in vitro*. Med Sci Monit. 2017;22:4803-8.

Liu Y, Gao L, Guo S, Liu Y, Zhao X, Li R, et al. Kaempferol alleviates angiotensin II-induced cardiac dysfunction and interstitial fibrosis in mice. Cell Physiol Biochem. 2017;43:2253-63.

Mahobiya A, Singh TU, Rungsung S, Kumar T, Chandrasekaran G, Parida S, et al. Kaempferol-induces vasorelaxation via endothelium-independent pathways in rat isolated pulmonary artery. Pharmacol Rep. 2018; 70:863-74.

Ming D, Wang D, Cao F, Xiang H, Mu D, Cao J, et al. Kaempferol inhibits the primary attachment phase of biofilm formation in *Staphylococcus aureus*. Front Microbiol. 2017;8:2263.

Moradzadeh M, Tabarraei A, Sadeghnia HR, Ghorbani A, Mohamadkhani A, Erfanian S, et al. Kaempferol increases apoptosis in human acute promyelocytic leukemia cells and inhibits multidrug resistance genes. J Cell Biochem. 2018;119:2288-97.

Özay Y, Güzel S, Yumrutaş Ö, Pehlivanoğlu B, Erdoğdu İH, Yildirim Z, et al. Wound healing effect of kaempferol in diabetic and nondiabetic rats. J Surg Res. 2019;233:284-96.

Pan D, Li N, Liu Y, Xu Q, Liu Q, You Y, et al. Kaempferol inhibits the migration and invasion of rheumatoid arthritis fibroblast-like synoviocytes by blocking activation of the MAPK pathway. Int Immunopharmacol. 2018;55:174-82.

Qian J, Chen X, Chen X, Sun C, Jiang Y, Qian Y, et al. Kaempferol reduces K63-linked polyubiquitination to inhibit nuclear factor-κB and inflammatory responses in acute lung injury in mice. Toxicol Lett. 2019;306: 53-60.

Rabha DJ, Singh TU, Rungsung S, Kumar T, Parida S, Lingaraju MC, et al. Kaempferol attenuates acute lung injury in caecal ligation and puncture model of sepsis in mice. Exp Lung Res. 2018;44:63-78.

Ren J, Lu Y, Qian Y, Chen B, Wu T, Ji G. Recent progress regarding kaempferol for the treatment of various diseases. Exp Ther Med. 2019;18:2759-76.

Santos JMS, Lins TLBG, Barberino RS, Menezes VG, Gouveia BB, Matos MHT. Kaempferol promotes primordial follicle activation through the phosphatidylinositol 3-kinase/protein kinase B signaling pathway and reduces DNA fragmentation of sheep preantral follicles cultured in vitro. Mol Reprod Dev. 2019;86:319-29.

Santos-Buelga C, González-Paramás AM, Oludemi T, Ayuda-Durán B, González-Manzano S. Plant phenolics as functional food ingredients. Adv Food Nutr Res. 2019;90:183-257.

Sharma AR, Nam JS. Kaempferol stimulates WNT/β-catenin signaling pathway to induce differentiation of osteoblasts. J Nutr Biochem. 2019;74:108228.

Suchal K, Malik S, Khan SI, Malhotra RK, Goyal SN, Bhatia J, et al. Molecular pathways involved in the amelioration of myocardial injury in diabetic rats by kaempferol. Int J Mol Sci. 2017;18:E1001.

Torres-Villarreal D, Camacho A, Castro H, Ortiz-Lopez R, de la Garza AL. Anti-obesity effects of kaempferol by inhibiting adipogenesis and increasing lipolysis in 3T3-L1 cells. J Physiol Biochem. 2019;75: 83-8.

Varshney R, Gupta S, Roy P. Cytoprotective effect of kaempferol against palmitic acid-induced pancreatic β-cell death through modulation of autophagy via AMPK/mTOR signaling pathway. Mol Cell Endocrinol. 2017;448:1-20.

Vishwakarma A, Singh TU, Rungsung S, Kumar T, Kandasamy A, Parida S, et al. Effect of kaempferol pretreatment on myocardial injury in rats. Cardiovasc Toxicol. 2018;18:312-28.

Wang H, Chen L, Zhang X, Xu L, Xie B, Shi H, et al. Kaempferol protects mice from d-GalN/LPS-induced acute liver failure by regulating the ER stress-Grp78-CHOP signaling pathway. Biomed Pharmacother. 2019;111:468-75.

Wang J, Li T, Feng J, Li L, Wang R, Cheng H, et al. Kaempferol protects against gamma radiation-induced mortality and damage via inhibiting oxidative stress and modulating apoptotic molecules in vivo and vitro. Environ Toxicol Pharmacol. 2018;60:128-37.

Wong SK, Chin KY, Ima-Nirwana S. The osteoprotective effects of kaempferol: the evidence from in vivo and in vitro studies. Drug Des Devel Ther. 2019;13: 3497-14.

Wu P, Meng X, Zheng H, Zeng Q, Chen T, Wang W, et al. Kaempferol attenuates ROS-induced hemolysis and the molecular mechanism of its induction of apoptosis on bladder cancer. Molecules. 2018;23:E2592.

Wu Y, Zhang Q, Zhang R. Kaempferol targets estrogen-related receptor α and suppresses the angiogenesis of human retinal endothelial cells under high glucose conditions. Exp Ther Med. 2017;14:5576-82.

Yang YL, Cheng X, Li WH, Liu M, Wang YH, Du GH. Kaempferol attenuates LPS-induced striatum injury in mice involving anti-neuroinflammation, maintaining BBB integrity, and down-regulating the HMGB1/TLR4 pathway. Int J Mol Sci. 2019;20:E491.

Yao X, Jiang H, NanXu Y, Piao X, Gao Q, Kim NH. Kaempferol attenuates mitochondrial dysfunction and oxidative stress induced by H(2)O(2) during porcine embryonic development. Theriogenology. 2019;135:174-80.

Yeon MJ, Lee MH, Kim DH, Yang JY, Woo HJ, Kwon HJ, et al. Anti-inflammatory effects of kaempferol on helicobacter pylori-induced inflammation. Biosci Biotechnol Biochem. 2019;83:166-73.

Zhang F, Ma C. Kaempferol suppresses human gastric cancer SNU-216 cell proliferation, promotes cell autophagy, but has no influence on cell apoptosis. Braz J Med Biol Res. 2019;52:e7843.

Zhang N, Zhao S, Hong J, Li W, Wang X. Protective effects of kaempferol on D-ribose-induced mesangial cell injury. Oxid Med Cell Longev. 2019;2019:7564207.

Zhang R, Ai X, Duan Y, Xue M, He W, Wang C, et al. Kaempferol ameliorates H9N2 swine influenza virus-induced acute lung injury by inactivation of TLR4/MyD88-mediated NF-κB and MAPK signaling pathways. Biomed Pharmacother. 2017;89:660-72.

Zhao L, Sun J, Shi S, Qin X, Zhang K, Xu J. Kaempferol protects retinal ganglion ceils from high-glucose-induced injury by regulating vasohibin-1. Neurosci Lett. 2020;716:134633.

Zhao Y, Tian B, Wang Y, Ding H. Kaempferol sensitizes human ovarian cancer cells-OVCAR-3 and SKOV-3 to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis via JNK/ERK-CHOP pathway and up-regulation of death receptors 4 and 5. Med Sci Monit. 2017;23:5096-105.

Zhong X, Zhang L, Li Y, Li P, Li J, Cheng G. Kaempferol alleviates ox-LDL-induced apoptosis by up-regulation of miR-26a-5p via inhibiting TLR4/NF-κB pathway in human endothelial cells. Biomed Pharmacother. 2018;108:1783-9.

Zhou B, Jiang Z, Li X, Zhang X. Kaempferol's protective effect on ethanol-induced mouse primary hepatocytes injury involved in the synchronous inhibition of SP1, Hsp70 and CYP2E1. Am J Chin Med. 2018;46:1093-10.

Zhu G, Liu X, Li H, Yan Y, Hong X, Lin Z. Kaempferol inhibits proliferation, migration, and invasion of liver cancer HepG2 cells by down-regulation of microRNA-21. Int J Immunopathol Pharmacol. 2018;32:2058738418814341.

Zhuang Z, Ye G, Huang B. Kaempferol alleviates the interleukin-1β-induced inflammation in rat osteoarthritis chondrocytes via suppression of NF-κB. Med Sci Monit. 2017;23:3925-31.