**A review on Pharmacological Potential of Kaempferol**

Abstract

It is preferable to consume naturally occurring bioactive metabolites derived from diet rather than synthetic materials in order to prevent health-related diseases. Kaempferol (KMF), one of the plant-derived polyphenols, is regarded as a useful functional food ingredient with a variety of therapeutic purposes, including anti-cancer, antiepileptic, and antidiabetic effects. The current review provides an overview of the several kinds of KMF molecular targets in cancer cells and other illnesses related to health. Furthermore, the review emphasises the facts related to absorption, metabolism, and epidemiology. Even though there is encouraging evidence that it can help control diseases, further research is necessary to understand its toxicity, safety concerns, and mode of action in managing health.

**Keywords:** kaempferol; health-promoting effects; oxidative stress; inflammation; anti-diabetic effect; cancer therapy, epilepsy.

Introduction

Prof. Albert Szent Gyorgyti of the University of Szeged in Hungary discovered a novel chemical compound that was isolated from oranges in 1930. Initially designated as vitamin P, it was thought to be a new member of the vitamin family but was later identified as a flavonoid [1]. Flavonoids are polyphenolic substances that are mostly present in fruits and vegetables. They are also the main ingredient in a number of herbal remedies. According to human and animal epidemiological research, flavonoids can reduce the risk of a number of diseases[2-3]. The intake of flavonoids has been linked to health-promoting viewpoints. Human intake is estimated to range from 20 to 1,000 mg/day, depending on the population's dietary habits[4]. The main flavonoid in edible plants is kaempferol.

Plants of many kinds, including fruits, vegetables, and Chinese herbs, contain it. Kaempferol has been linked to anti-cancer, anti-inflammatory, anti-oxidant, anti-depression, anti-epilepsy, and improved cerebral blood flow, according to a number of studies [5-9]. Plant parts that naturally arise contain the flavonoid kaempferol (3,4′,5,7-tetrahydroxyflavone). Broccoli, cabbage, and spinach are among the leafy green vegetables that are the richest in kaempferol, a flavonoid. The highest concentration of kaempferol is found in spinach, which has an astounding 55 mg per 100 g, followed by broccoli at 7.2 mg and cabbage at 47 mg. In comparison to onions, which have an impressive 4.5 mg per 100 g, blueberries only have 3.17 mg[10].

It is important to note that this chemical has the ability to be both antioxidant and anti-inflammatory, two essential qualities that are crucial for managing pathogenesis. According to a recent study, diquat treatment resulted in increased production of intracellular ROS, increased depolarization of the mitochondria, and apoptosis, which was convoyed by cell cycle arrest in the G1 phase, disruption of the function of the intestinal epithelial barrier, and decreased cell migration.Kaempferol overturned the diquat-induced actions. This discovery additionally demonstrated that kaempferol's protective effects were connected to increased mRNA levels of genes involved in the anti-oxidant system and cell cycle progression, increased Nrf2, an anti-oxidant transcription factor, and up-regulated tight junction abundance[11].

**Chemical structure of kaempferol**

Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)π 4 H-1-benzopyran-4-one) (molecular weight: 286.2 g/mol) is sometimes referred to as tetrahydroxyflavone, kaempferol-3, and kaempferol flavonol. C15H10O6 is its molecular structure formula. With a melting point of 276–278 ◦C, the pure monomer result is a yellow crystalline powder that is soluble in hot ethanol, ether, and alkali and just weakly soluble in water[12-14].

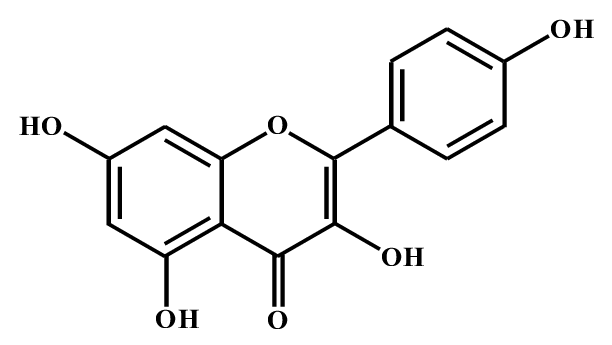
Flavonoids are typically found as glycosides in plants (Fig. 2). Astragalin (kaempferol-3-Oglucoside), populnin (kaempferol-7-O-glucoside), nicotiflorin (K-3-rh), and kaempferitrin (kaempferol-3,7-dirhamnoside) are the most significant kaempferol glycosides. In kaempferol-3-O-avruyl-diglucoside-7-O-glucoside, kaempferol-3-Ocafeyl-diglucoside-7-O-glucoside, kaempferol-3-O-coumaryl-diglucoside-7-O-glucoside, and kaempferol-3-O-p-coumaryl-diglucoside-7-Oglucoside, the O-glycoside of kaempferol can be acylated with hydroxycinnamic acid[15]

**Bioavailability of Kaempferol**

Few researches have been done to assess the bioavailability of kaempferol conjugates obtained from food. De Varies et al. conducted a crossover research to investigate how well participants (n = 15) absorbed and digested 27 mg of kaempferol from black tea over the course of three days. Kaempferol's urine excretion was 2.5% of the amount consumed, indicating a higher absorption rate compared to quercetin's 0.5% urinary excretion. This suggested that while black tea has a higher quercetin content than kaempferol, the tea's glycoside type had a higher bioavailability.  
After consuming 12.5 mg of kaempferol from broccoli for 12 days, the amount of kaempferol that was absorbed and digested was measured. 0.9% of kaempferol was excreted in the urine [16-17].

**Natural sources of kaempferol**

Phytochemical screening of a variety of medicinal plants, including species of Magnoliophyta, Pteridophyta, and Pinophyta, revealed the presence of kaempferol flavonoids and their derivatives. Within the division Magnoliophyta (Angiosperms), kaempferol has been detected in species belonging to Pteridophyta, Pinophyta, and Magnoliophyta as well as Liliopsida (Monocotyledons). In the division Magnoliophyta (Angiosperms), kaempferol has been found in both Liliopsida (Monocotyledons) and Magnoliopsida (Dicotyledons); in Pteridophyta, kaempferol and its derivatives have been identified in Aspidiaceae, Aspleniaceae, Blechnaceae, Cyatheaceae, Dennstaedtiaceae, and Equisetaceae; in Pinophyta (Gymnosperms), kaempferol and its derivatives have been found in Ginkgoaceae and Taxaceaend Magnoliopsida (Dicotyledons); in Pteridophyta, kaempferol and its derivatives have been identified in Aspidiaceae, Aspleniaceae, Blechnaceae, Cyatheaceae, Dennstaedtiaceae, and Equisetaceae; in Pinophyta (Gymnosperms), kaempferol and its derivatives have been found in Ginkgoaceae and Taxaceae [18-21].



Pharmacokinetics

Numerous studies have demonstrated the vast spectrum of biological activities of kaempferol; however, some of these actions are limited in vivo due to its high metabolism and low bioavailability. Understanding how kaempferol is metabolised after oral administration is crucial because it is a frequent food element and is best administered orally. Like other flavonoids, kaempferol is typically consumed as a glycoside and is mostly absorbed in the small intestine. Although data suggests that it can also be absorbed through increased diffusion or active transport, its lipophilic nature makes passive diffusion easier. Gut of the tiny. Although research suggests that it can also be absorbed through increased diffusion or active transport, its lipophilic nature makes passive diffusion the most convenient method of absorption [21-22].

**Health benefits of kaempferol**

**Anticancer properties**

Among its most important characteristics is its well-established antineoplastic activity against cancers of the oesophagus, pharynx, breast, liver, ovary, stomach, lung, pancreas, and bladder. Nevertheless, it is still unclear how exactly kaempferol works to prevent some cancers. Particularly, kaempferol-rich foods have been associated with a decreased incidence of colon, liver, and skin malignancies. Apoptotic induction, cell cycle arrest at the G2/M phase, downregulation of markers linked to the epithelial-mesenchymal transition, and the phosphoinositide-3-kinase/protein kinase B (Akt) signalling pathways are among the potential mechanisms of action [24-26].

A crucial factor in the initiation and development of bladder cancer is genomic DNA methylation. In this regard, it has been discovered that kaempferol, as a chemopreventive drug, modulates DNA methylation, suppresses the protein levels of DNA methyltransferases (DNMT3B), and induces 103 differential DNA methylation positions (dDMPs), which are linked to 50 hypermethylated and 53 hypomethylated genes.   
Furthermore, it causes an early breakdown of DNMT3B by using cycloheximide to inhibit protein synthesis[24].

**Anti-inflammatory activity of kaempferol**

Any type of trauma, including pathological, cellular, or vascular damages, results in tissue inflammation. Redness, discomfort, and loss of function are physiological changes that are indicative of inflammation [28–30], which is mainly caused by an enzymatic response or the immune system being activated. Apart from safeguarding the functions of diverse antioxidant enzymes, kaempferol is recognised for its ability to scavenge free and superoxide radicals [28]. Kaempferol's anti-inflammatory properties could be controlled by the activation of nuclear factor kappa B (NF-κB), among other mechanisms of action. Kaempferol increases the ability of RAW 264.7 macrophage cells to scavenge radicals, activates T cell proliferation, and controls the production of nitric oxide (NO) or reactive oxygen species (ROS) in response to lipopolysaccharides [31-33].

**Antiepliptic effect**

González-Trujano et al. (2017) conducted an in vitro study in which they used male Swiss Webster mice and Wistar rats that had been given pentylenetetrazol (PTZ) to induce seizures. The results showed that the Justicia spicigera Schltdl extract, which contains Kaempferitrin as its active ingredient, was able to significantly postpone the onset of both myoclonic and generalised seizures at doses of 100 and 1,000 mg per kg, as well as tonic seizures at doses ranging from 30 to 1,000 mg per kg. Furthermore, the investigation demonstrated that the combination of intraperitoneal administration of Justicia spicigera Schltdl and intracerebroventricular administration of Kämpferitrin (1 mg/ml) in the fourth ventricle enhanced the anticonvulsant action already present in the extract of Justicia spicigera Schltdl [34].

**Cardiovascular impact**   
According to a study by Suchal and colleagues, kaempferol protects diabetic male albino Wistar rats from cardiac ischemiareperfusion (IR) injury. It significantly reduces hyperglycemia, inhibits the activation of the receptor for advanced glycation end products (RAGE) axis, suppresses the production of AGEs, preserves morphological changes, and returns oxidative stress to normal. In addition, it increases ERK1/2, inhibits p38 and c-JNK proteins, and decreases IL-6, TNFα, and NFκB levels. Similarly, kaempferol inhibited apoptosis by raising the amount of the antiapoptotic protein Bcl-2 and decreasing the production of pro-apoptotic proteins like caspase-3 and Bax. It also increased the amount of Bcl-2, an antiapoptotic protein[35].

**Toxicity and safety**

Toxicology and safety Studies on kaempferol have not produced a unanimous result, but current opinion is that kaempferol's many biological actions can be advantageous or detrimental, depending on the particular environment. It has been discovered that kaempferol possesses both genotoxic and antimutagenic qualities. According to several accounts, the CYP1A1 enzyme may convert kaempferol into the more genotoxic quercetin, which is the source of its mutagenicity. According to several accounts, the CYP1A1 enzyme may convert kaempferol into the more genotoxic quercetin, which is the source of its mutagenicity [36-38].

Conclusion

This review emphasised the significance of kaempferol in mitigating a range of illnesses. The difficult part of applying kaempferol in a range of health issues is to comprehend a precise approach of cellular metabolism and mechanism along with specific delivery at targeted organelles, which requires a comprehensive interdisciplinary approach. The most significant future prospect for kaempferol is the nanoformulation of the compound, which can enhance bioavailability. Most importantly, the sources of kaempferol from fresh produce must be shifted to unused food wastes or byproducts without compromising the standard regulation of purity.

**References**

1. Kwon, Y. S., Kim, S. S., Sohn, S. J., Kong, P. J., Cheong, I. Y., Kim, C. M., et al. (2004). Modulation of suppressive activity of lipopolysaccharide-induced nitric oxide production by glycosidation of flavonoids. Arch. Pharmacal. Res. 27 (7), 751–756
2. 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(1): 728-734
3. Rahaman ST, Mondal S. Flavonoids: A vital resource in healthcare and medicine. Pharm Pharmacol Int J 2020; 8(2): 91-104.
4. Scalbert, A., & Williamson, G. (2000). Dietary intake and bioavailability of polyphenols. *The Journal of Nutrition*, *130*, 2073S–2085S.
5. B.B. da Luz, D. Maria-Ferreira, J.L. Dallazen, A.F. de Oliveira, J.E. Queiroz Telles, O.C. Beltrame, T.R. Cipriani, M.F. de Paula Werner, Effectiveness of the polyphenols-rich Sedum dendroideum infusion on gastric ulcer healing in rats: Roles of protective endogenous factors and antioxidant and anti-inflammatory mechanisms, J. Ethnopharmacol. 278 (2021), 114260.
6. D. Kashyap, A. Sharma, H.S. Tuli, K. Sak, S. Punia, T.K. Mukherjee, Kaempferol - A dietary anticancer molecule with multiple mechanisms of action: Recent trends and advancements, J. Funct. Foods 30 (2017) 203–219. [36] S.R. D’Mello, When Good Kinases Go Rogue: GSK3, p38 MAPK and CDKs as Therapeutic Targets for Alzheimer’s and Huntington’s Disease, Int J. Mol. Sci. 22 (11) (2021).
7. J.T. Hong, J.H. Yen, L. Wang, Y.H. Lo, Z.T. Chen, M.J. Wu, Regulation of heme oxygenase-1 expression and MAPK pathways in response to kaempferol and rhamnocitrin in PC12 cells, Toxicol. Appl. Pharm. 237 (1) (2009) 59–68.
8. L. Yu, C. Chen, L.F. Wang, X. Kuang, K. Liu, H. Zhang, J.R. Du, Neuroprotective effect of kaempferol glycosides against brain injury and neuroinflammation by inhibiting the activation of NF-κB and STAT3 in transient focal stroke, PLoS One 8 (2) (2013), e55839.
9. W. Gao, W. Wang, Y. Peng, Z. Deng, Antidepressive effects of kaempferol mediated by reduction of oxidative stress, proinflammatory cytokines and up-regulation of AKT/β-catenin cascade, Metab. Brain Dis. 34 (2) (2019) 485–494.
10. Cannataro, R.; Fazio, A.; La Torre, C.; Caroleo, M.C.; Cione, E. Polyphenols in the mediterranean diet: From dietary sources to microRNA modulation. Antioxidants **2021**, 10, 328
11. Jin, Y.; Zhai, Z.; Jia, H.; Lai, J.; Si, X.; Wu, Z. Kaempferol attenuates diquat-induced oxidative damage and apoptosis in intestinal porcine epithelial cells. Food Funct. **2021**, 12, 6889–6899
12. P. Rajendran, T. Rengarajan, N. Nandakumar, R. Palaniswami, Y. Nishigaki, I. Nishigaki, Kaempferol, a potential cytostatic and cure for inflammatory disorders, Eur. J. Med Chem. 86 (2014) 103–112.
13. Y.H.Siddique Rahul, Neurodegenerative Diseases and Flavonoids: Special Reference to Kaempferol, CNS Neurol. Disord. Drug Targets 20 (4) (2021) 327–342.
14. S. Cid-Ortega, J.A. Monroy-Rivera, Extraction of Kaempferol and Its Glycosides Using Supercritical Fluids from Plant Sources: A Review, Food Technol. Biotechnol. 56 (4) (2018) 480–493.
15. Z. Li, H.W. Lee, X. Liang, D. Liang, Q. Wang, D. Huang, C.N. Ong, Profiling of phenolic compounds and antioxidant activity of 12 cruciferous vegetables, Molecules 23 (5) (2018).
16. De Vries, J.H.; Hollman, P.C.; Meyboom, S.; Buysman, M.N.; Zock, P.L.; van Staveren, W.A.; Katan, M.B. Plasma concentrations and urinary excretion of the antioxidant flavonols quercetin and kaempferol as biomarkers for dietary intake. *Am. J. Clin. Nutr.* **1998**, *68*, 60–65.
17. Barve, A.; Chen, C.; Hebbar, V.; Desiderio, J.; Saw, C.L.-L.; Kong, A.-N. Metabolism, oral bioavailability and pharmacokinetics of chemopreventive kaempferol in rats. *Biopharm. Drug Dispos.* **2009**, *30*, 356–365
18. K.D. Yoon, D.G. Jeong, Y.H. Hwang, J.M. Ryu, J. Kim, Inhibitors of osteoclast differentiation from Cephalotaxus koreana, J. Nat. Prod. 70 (12) (2007) 2029–2032.
19. S.H. Kwon, J.I. Nam, S.H. Kim, J.H. Kim, J.H. Yoon, K.S. Kim, Kaempferol and quercetin, essential ingredients in Ginkgo biloba extract, inhibit interleukin- 1beta-induced MUC5AC gene expression in human airway epithelial cells, Phytother. Res 23 (12) (2009) 1708–1712.
20. M. Krauze-Baranowska, Flavonoids from the genus Taxus, Z. Nat. C. J. Biosci. 59( (1–2) (2004) 43–47. Y. Tang, F. Lou, J. Wang, Y. Li, S. Zhuang, Coumaroyl flavonol glycosides from the leaves of Ginkgo biloba, Phytochemistry 58 (8) (2001) 1251–1256.
21. I. Orhan, E. Küpeli, S. Terzio˘glu, E. Yesilada, Bioassay-guided isolation of kaempferol-3-O-beta-D-galactoside with anti-inflammatory and antinociceptive activity from the aerial part of Calluna vulgaris L, J. Ethnopharmacol. 114 (1) (2007) 32–37.
22. J.M. Gee, I.T. Johnson, Polyphenolic compounds: interactions with the gut and implications for human health, Curr. Med Chem. 8 (11) (2001) 1245–1255.
23. H.M. Lehtonen, O. Lehtinen, J.P. Suomela, M. Viitanen, H. Kallio, Flavonol glycosides of sea buckthorn (Hippopha¨e rhamnoides ssp. sinensis) and lingonberry (Vaccinium vitis-idaea) are bioavailable in humans and monoglucuronidated for excretion, J. Agric. Food Chem. 58 (1) (2010) 620–627. V. Crespy, C. Morand, C. Besson, N. Cotelle, H. V´ezin, C. Demign´e, C. R´em´esy, The splanchnic metabolism of flavonoids highly differed according to the nature of the compound, Am. J. Physiol. Gastrointest. Liver Physiol. 284 (6) (2003) G980–G988.
24. Qiu, W., Lin, J., Zhu, Y., Zeng, L., Su, M., & Tian, Y. (2017). Kaempferol modulates DNA methylation and downregulates DNMT3B in bladder cancer. *Cellular Physiology and Biochemistry*, *41*(4), 1325–1335.
25. 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. Phyther Res 2019; 33(2): 263-275.
26. Imran M, Salehi B, Sharifi-Rad J, Gondal TA, Saeed F, Imran A, et al. Kaempferol: A key emphasis to its anticancer potential. Molecules 2019; 24(12): 2277.
27. Marfe G, Tafani M, Indelicato M, Sinibaldi-Salimei P, Reali V, Pucci B, et al. Kaempferol induces apoptosis in two different cell lines via Akt inactivation, bax and SIRT3 activation, and mitochondrial dysfunction. J Cell Biochem 2009; 106(4): 643-650.
28. Folkerts G, Kloek J, Muijsers RBR, Nijkamp FP. Reactive nitrogen and oxygen species in airway inflammation. Eur J Pharmacol 2001; 429(1-3): 251-262.
29. Medzhitov R. Origin and physiological roles of inflammation. Nature 2008; 454(7203): 428-435.
30. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves’ ophthalmopathy. Clin Endocrinol (Oxf) 1997; 47(1): 9-14.
31. Wang J, Fang X, Ge L, Cao F, Zhao L, Wang Z, et al. Antitumor, antioxidant and anti-inflammatory activities of kaempferol and its corresponding glycosides and the enzymatic preparation of kaempferol. PLoS One 2018; 13(5): e0197563.
32. 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: 3925-3931.
33. Zhang T, Qiu F, Chen L, Liu R, Chang M, Wang X. Identification and in vitro anti-inflammatory activity of different forms of phenolic compounds in Camellia oleifera oil. Food Chem 2021; 344: 128660
34. González-Trujano, M. E., Domínguez, F., Pérez-Ortega, G., Aguillón, M., Martínez-Vargas, D., Almazán-Alvarado, S., et al. (2017). Justicia spicigera Schltdl. and kaempferitrin as potential anticonvulsant natural products. Biomed. Pharmacother. 92, 240–248.
35. Suchal, K., Malik, S., Khan, S. I., Malhotra, R. K., Goyal, S. N., Bhatia, J., … Arya, D.‐S. (2017). Molecular pathways involved in the amelioration of myocardial injury in diabetic rats by kaempferol. *International Journal of Molecular Sciences*, *18*(5)
36. J.A. Ross, C.M. Kasum, Dietary flavonoids: bioavailability, metabolic effects, and safety, Annu Rev. Nutr. 22 (2002) 19–34.
37. I.D. Silva, A.S. Rodrigues, J. Gaspar, R. Maia, A. Laires, J. Rueff, Involvement of rat cytochrome 1A1 in the biotransformation of kaempferol to quercetin: relevance to the genotoxicity of kaempferol, Mutagenesis 12 (5) (1997) 383–390.
38. H.P. Ciolino, P.J. Daschner, G.C. Yeh, Dietary flavonols quercetin and kaempferol are ligands of the aryl hydrocarbon receptor that affect CYP1A1 transcription differentially, Biochem. J. 340 (Pt 3) (1999) 715–722.