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A REVIEW ON PHARMACOLOGICAL POTENTIAL OF KAEMPFEROL

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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.

1. 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]

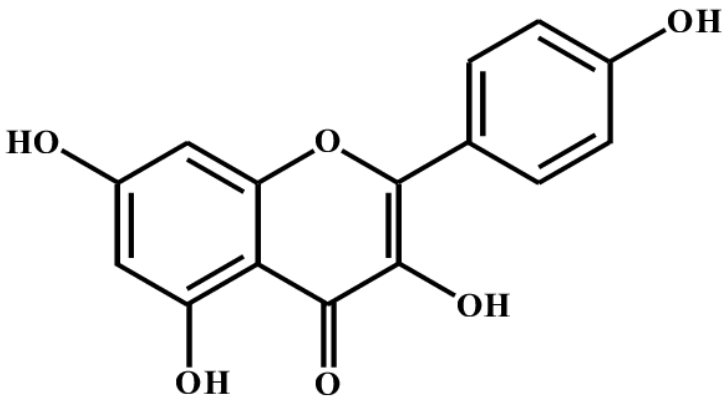
Bioavailability of Kaempferol

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].

2. 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.

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