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Review Article

Kaempferol Review on pharmacological action in treatment of various diseases

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Abstract
Since millions of years ago, medicinal plants have been a major source of therapeutic medicines. The majority of medications that have been found are either natural ingredients or their derivatives. It is a true reality that nature is the source of an apparently infinite variety of molecule configurations. These structures can be enhanced to create scaffolds of innovative medications for the treatment of a variety of illnesses. They are also rich sources for the production of robust chemotypes and pharmacophores. "Natural products" refers to substances originating from plants, marine organisms, bread molds, microorganisms, and both terrestrial and invertebrate animals. These compounds are recognized for their remarkable drug-like qualities and wide range of chemical compositions, which support their multi-targeted action. These substances include flavonoids that include benzopyran and hydroxyphenyl groups, i.e. Flavonoid compound kaempferol, sometimes referred to as kaempferol 3 or kaempferide, is found naturally in tea and a variety of common fruits and vegetables, such as gooseberries, beans, broccoli, and cabbage. The major goal of this study is to provide an overview of the numerous pharmacological actions of kaempferol in treating disorders, as well as the ongoing research into the underlying mechanisms. Numerous acute and chronic inflammation-induced illnesses, such as colitis and inter-vertebral disc degeneration, as well as postmenopausal bone loss and acute lung injury, may be treated with it. Moreover, it protects the heart and brain function, inhibits vascular endothelial inflammation, fights cancer, liver damage, obesity, and diabetes, and may be used to treat fibro proliferative illnesses like hypertrophic scar.

Key words: kaempferol, flavanoids, cancer, inflammation, Natural product

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Introduction

Chemically, kaempferol is 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one. It is a naturally occurring flavonoid of the flavonoid type and can be isolated from a variety of common fruits and vegetables, such as apples, grapefruit, beans, broccoli, cabbage, gooseberries, grapes, kale, strawberries, tomatoes, and citrus fruits. Additionally, it has been found in most of medicinal plants, such as Ginkgo biloba, Sophora japonica, and Equisetum spp. Euphorbia pekinensis (Rupr.). since kaempferol lowers oxidative stress and functions as an antioxidant, it is presently being investigated as a potential cancer treatment [1]. It functions as a geroprotector, a human urine metabolite, a human blood serum metabolite, a plant metabolite, an antibacterial agent, and a human xenobiotic metabolite. It is a conjugate acid of a kaempferol oxoanion and belongs to the family of flavonols, which also includes 7-hydroxyflavonol and tetrahydroxyflavone. Natural products containing kaempferol are mostly found in Visnea mocanera, Lotus ucrainicus, and other organisms about which data are known.

Another naturally occurring flavonoid that has been identified from plants such as grapefruit, delphinium, and witch hazel is kaempferol. The melting point of kaempferol, a yellow, crystalline solid, is 276-278℃. It dissolves fairly effectively in hot ethanol and diethyl ether but just marginally in water[2]. Figure 1 showed structure for Kaempferol.

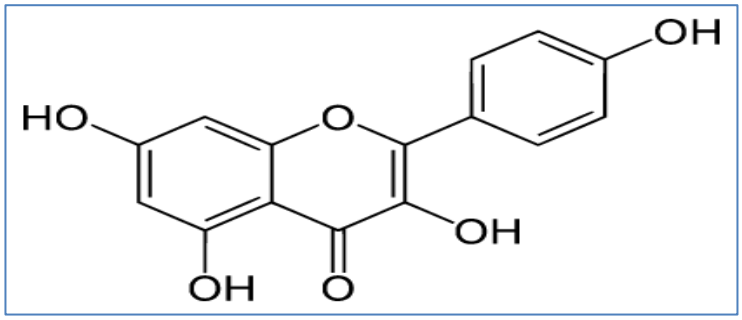

Figure 1 Sturcture for Kaempferol

The anti-inflammatory actions of KP are its most well-known character and It has been shown that KP is useful for both acute and chronic inflammatory illnesses, such as acute lung damage and postmenopausal bone loss and colitis, as well as intervertebral disc degeneration. The prevention of cancer is KP's second most significant aspect. In addition to benign conditions like uterine fibroids, its anti-cancer properties have been shown in esophageal, breast, cervical, hepatocellular, ovarian, gastric, non-small cell lung, leukemia, cholangiocarcinoma, pancreatic, bladder, and osteosarcoma cancers. The precise processes by which KP works to combat various cancer types, as well as how it helps with liver damage, obesity, diabetes, and metabolic syndrome symptoms, are still unknownKP may also cure fibroproliferative illnesses, such as hypertrophic scar, protect the cranial nerve, prevent vascular endothelial inflammation, and maintain heart function[3]. Flavonoids are typically found in the kingdom of plants as glycosides. Astragalin (KPF-3-O-glucoside) and kaempferitrin (KPF-3,7-dirhamnoside) are the two most significant KPF glycosides. KPF-3-O-caffeoyl diglucoside-7-O-glucoside, KPF-3-O-sinapoyl diglucoside-7-O-glucoside, KPF-3-O-feruloyl diglucoside-7-O-glucoside, and KPF-3-O-p-coumaroyl diglucoside-7-O-glucoside are examples of O-glycosides that can be acylated with hydroxycinnamic acids like ferulic, sinapic, p-coumaric, and caffeic acids [4]. Given its low cost and non-toxic nature, KP holds significant commercial significance as a nutritional element. One of the flavonoids that can be extracted from plants is this one. Using two KP glycosides found in tea seeds, enzymatic hydrolysis provides a practical and affordable technique for preparing KP. Furthermore, a quick way to extract naturally occurring physiologically active chemicals from plant materials is using supercritical fluid extraction [5]. While low bioavailability represents a significant challenge, nanotechnology has surfaced as a potentially effective solution [6]. The function of KP in disease and the current debate over treatment are summed up in this review. The purpose of this work is to present data in support of the potential use of KP in treating human ailments.

Various biological sources of Kaempferol

Several plants that are known to contain kaempferol molecules are used in traditional medicinal practices worldwide. It's noteworthy to observe that their present impacts under investigation often correlate with their traditional applications. In the perspective of traditional herbal medicine, kaempferol-containing plants are still recognized as essential components of traditional Chinese medicine [7], and their application is still important worldwide. Researching these traditional methods can result in new treatments and the identification of drugs, as has already been demonstrated [8]. Clove flower, also known as dingxiang, is used to warm the kidneys and fend off cold invasions; related symptoms include diarrhea, hiccups, vomiting, impotence, and weakness in the legs [9]. Bupleurum chinense, sometimes referred to as radix bupleuri, is a component of several herbal formulae that balance weaker yang-stage illnesses; certain of these formulas also have antimalarial properties. To remove heat and wind from the outside, other recipes that incorporate B. chinense are utilized [10]. More specifically, B. chinense roots are the source of radix bupleuri [11]. It has a broad spectrum of pharmacological effects, according to current phytochemical studies [12–17]. Additionally, geranium is utilized in traditional medicine for anti-inflammatory and anti-microorganism purposes [18, 19]. Recent studies have confirmed geranium's anti-inflammatory properties. The plant Astragalus creticus [20] is used to warm the meridians and drive away cold, either on its own or in herbal mixtures. It is perfect for correcting the scarcity of the stomach, spleen, and lung meridians by warming the meridians. It is used as a diuretic, in cases of weakness in the body, to treat digestive system issues, or just as a food supplement in Western medicine terms [21]. Numerous ethnobotanical uses exist for this, one of the most common genuses of plants [22–28]. Comparing the parallels between these plants' uses in various medicinal systems would be intriguing. Last but not least, propolis a bee product that contains plant elements rather than actual plants is a crucial component of numerous medical systems. It has anti-inflammatory and maybe anti-diabetic effects, which is why traditional Chinese medicine uses it [29, 30].

Biological action of Kaempferol

Studies have been conducted on the possible antibacterial qualities of pure kaempferol molecules and extracts containing the compound [31, 32]. Due of the extreme complexity within the family of kaempferol derivatives and the variation in form and functions among the many species of bacteria, it has been

challenging to investigate the mechanisms behind the antibacterial activity of kaempferol. On the other hand, several hypotheses about the possible mechanisms of action in specific bacteria have been put out and confirmed. For example, studies [33] have demonstrated that quercetin and kaempferol 3-O-b-(200-acetyl) galactopyranoside exhibit antibacterial properties by rupturing the cell membrane, which leads to the DNA breaking and apoptosis of M. luteus cells. [34] Kaempferol was also the flavonoid that ruptured Escherichia coli cell membranes the best. The findings were supported by evidence of bacterial protein leakage
into the extracellular environment. Further, kaempferol and quercetin inhibit the fatty acid synthesis of Mycobacterium, Pseudomonas aeruginosa, and Vibrio cholerae by their interactions with 3-oxyacyl-[acyl carrier protein] reductase (FabG) and enoyl-acyl carrier protein reductase [35–37]. This prevents the formation of bacterial biofilms and impairs the functionality of the cell membrane. Kaempferol, the most potent flavonoid which is directly inhibiting the bacterial DNA gyrase in *E. Coli*, exhibited another significant antibacterial action [38]. Similarly, in methicillin-resistant Staphylococcus aureus, kaempferol inhibited DNA gyrase [39]. Furthermore, research suggests that kaempferol may inhibit DNA helicases precisely SAPriA in Staphylococcus aureus.[40]. Additionally, anti-porphyromonas gingivalis, anti-prevotella intermedia, and anti-cutibacterium acnes properties have been noted for kaempferol compounds [41]. As may be seen below, the study has previously demonstrated the antibacterial efficacy of the S. hymettia extract against Enterobacter cloacae and other bacteria. There were hints of antibacterial action in the Helichrysum compactum extract, which included both pure kaempferol and kaempferol-3-O-glucoside.[42] This characteristic might also be found in the Nephelium lappaceum extract, which exhibits antibacterial properties due to the presence of kaempferol constituents [43]. With reference to Micrococcus luteus, Bacillus subtillis, Bacillus cereus, Escherichia coli, Enterobacter aerogenes, Staphylococcus aureus, and Pseudomonas aeruginosa, It was found that (kacip Fatimah) a native herb of Malaysia also known as Labisa pumila Benth, has some antibacterial action.[44] It has been demonstrated that uapaca heudelotti extract is beneficial not only against various illnesses but also against S. pneumoniae. It's also important to keep in mind that, although some kaempferol-containing extracts may not have much of an antibacterial impact on their own, they may enhance the effectiveness of some antibiotics [45, 46]. Figure 2. Flow charts shows the roles of kaempferol in the treatment of various diseases.

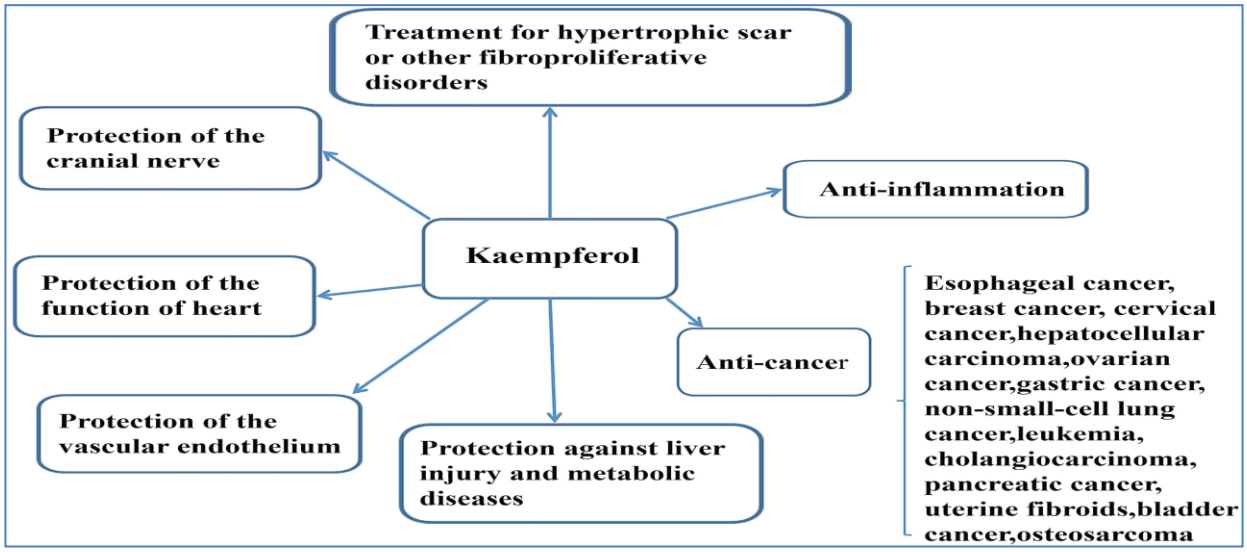

Figure 2. Flow charts shows the roles of kaempferol in the treatment of various diseases.

Biosynthetic Pathways of Kaempferol

The plastids of plants undergo a mechanism known as the shikimic acid pathway [47] for the synthesis of flavonoids. There are known to be around 2000 compounds, of which approximately 500 exist in a free-aglycone state and the remainder as O- or C-glycosides.[48] While flavonols exhibit lipophilic characteristics when they are free as aglycones, the majority of flavonols that are generated in plants are bonded to a sugar molecule, known as the glycoside form, and are therefore soluble in water [49]. Each flavonol has hydroxyl functional groups, which may serve as sites of coupling to saccharides in the form of O-glycosides [50]. Monosaccharides including glucose, rhamnose, galactose, arabinose, and xylose and the disaccharide rutinose are the saccharides that are most frequently associated to flavonols [51].

Antifungal Properties of Kaempferol

Compared to its antibacterial activity, kaempferol's antifungal activity is less well-established. Flavonoids suppress the growth of most fungi, including Saccharomyces cerevisiae, Aspergillus fumigatus, Aspergillus niger, and Candida albicans [52]. Occasionally, they cause other medications to become more sensitive, which indirectly affects the growth of fungi. Studies have shown that kaempferol is a more effective antifungal agent than quercetin. According to recent research, kaempferol has a minimum inhibitory concentration (MIC) of 256 µg/mL against the three types of Cryptococcus: C. tropicalis, C. albicans, and C. neoformans [53]. Not much research has been done on the mechanisms behind the antifungal activity of these flavonoids. Recently published study indicates that the primary mechanism by which

kaempferol inhibits fungal growth is by rupturing the plasma membrane, a process that also affects the synthesis of proteins, nucleic acids, and mitochondria.. Researchers have also looked into how both flavonoids prevent the growth of fungal biofilms. They discovered that when exposed to flavonoids, the biomass and metabolic activity of C. orthopsilosis and C. metapsilosis both decreased. These results are consistent with current studies that have demonstrated that kaempferol reduces the growth of microbial biofilms, possibly by reducing cellular adhesion to abiotic surfaces, as has been shown for S. aureus and C. albicans [54]. The studies have demonstrated that the mature Candida species biofilm is resistant to flavonoids. Kaempferol increased the metabolic activity of both Candida orthopsilosis and Candida albicans sensu stricto. It's possible that changes in the number of viable cells don't always correlate with these variations in metabolic response. Given that biofilms' metabolic activity varies during the different stages of biofilm formation, it's possible that this is a reaction to the stress brought on by exposure to flavonoids [55].

Kaempferol Antiprotozoal Action

For thousands of years, the amoeboid intracellular parasite Plasmodium has caused the well-known disease malaria. Humans can contract malaria from five of the 172 species of Plasmodium: P. malariae, P. falciparum, P. vivax, P. ovale, and P. knowlesi; the remaining species are occasional [56]. However, their biology and anatomy are fairly similar [57]. The main carriers of malaria are female Anopheles mosquitoes, which act as the parasite's vectors. The parasite then infects hepatocytes and erythrocytes. At the moment, artemisinin and artemisinin-based combination therapy (ACT) is the most widely used treatment for malaria. Furthermore, efforts to eradicate the disease in the future are threatened by the emergence of drug resistance to antimalarials [58]. Despite the serious health risks associated with endemic malaria, non-endemic nations may nevertheless be vulnerable to it. Strangely, 8-(1;1)-DMA-kaempferide was shown to have antiprotozoal effects against Plasmidium falciparum, a flavonoid that bears a striking resemblance to kaempferol. Research has shown that the extract of Eupatorium perfoliatum L. had an antiprotozoal effect against P. falciparum in vitro. Despite the presence of kaempferol in the extract, the antiprotozoal activity was mostly demonstrated by the dimeric guaianolide. Certain kaempferol metabolites were discovered to be effective against the malaria parasite when isolated in vitro [59,60]. According to, kaempferol's antiplasmodial activity in vitro cannot be associated with any mechanism involving heme-binding activity because it cannot negatively impact the formation of hemozoin. Two kaempferol glycosides have no effect on P. falciparum, according to the previously mentioned investigation. Last but not least, an extract containing pure kaempferol along with additional kaempferol components from Lotus corniculatus L. shows antiprotozoal effectiveness against Plasmodium spp [61].

Kaempferol anti-cancer activity

Kaempferol shares structural similarities with the hormone estrogen and is classified as a flavonoid. Vegetables and fruits such as broccoli, pine, ginkgo leaf, apple, grape, tomato, and green tea contain kaempferol. Kaempferol possesses cardiovascular, neuroprotective, antibacterial, anti-inflammatory, and antioxidant properties. Kaempferol can be utilized as a treatment for hormone-regulated malignancies, including leukemia, ovarian, breast, cervical, and hepatocellular carcinomas, because of its similarity to the hormone estrogen [62]. In vitro, kaempferol exhibits a mild cytostatic effect on the human cancer cell lines PC3, HeLa, and K562. Additionally, kaempferol increases program cell death in ovarian cancer cells via activating the intrinsic pathway of the p53 protein [63].

Kaempferol anti-oxidant activity

One of the several flavanols that can be establish in tea, beans, broccoli, apples, and strawberries is kaempferol. Additionally, it has been discovered in therapeutic herbs like Rosmarinus officinalis, Euphorbia pekinensis Rupr, Ginkgo biloba L, and Aloe vera (L.). Anti-inflammatory and antioxidant properties are exhibited by kaempferol [64]. It is a strong apoptosis promoter and controls several intracellular signaling cascades. Comparatively speaking, kaempferol is less harmful to healthy cells than conventional cancer chemotherapy. Furthermore, by interfering with the cell cycle at critical stages, kaempferol prevents the growth of malignant cells. As a novel chemopreventive medication, kaempferol shows great promise and may be utilized to treat UVB-related carcinogenesis.

Anti-inflammatory activity of Kaempferol

Natural flavonols, or flavonoids of the kaempferol class, can be found in a wide variety of fruits, vegetables, and herbs, such as grapes, tomatoes, broccoli, tea, and the leaves of ginkgo biloba. Numerous pharmacological properties, such as those related to antioxidant, anti-inflammatory, antibacterial, antidiabetic, and anti-cancer properties, are displayed by this physiologically active substance. Kaempferol has been shown to have anticancer properties in cancer cells from a variety of tissues, including the breast, ovarian, stomach, lung, pancreatic, and blood malignancies [85,86]. Many of the signaling pathways necessary for cancer cells to survive are disrupted by kaempferol. Kaempferol causes apoptosis in breast cancer cells by means of an extracellular signal-regulated kinase (ERK) dependent mechanism. Through the activation of p53 and the repression of cell cycle genes, kaempferol can also cause ovarian and breast cancer cells to undergo apoptosis [65]. Kaempferol not only lowers ERK and Akt activity but also causes human glioma cells to produce more ROS, which triggers apoptosi. Kaempferol cotreatment also increased the sensitivity of glioablastoma cells to doxorubicin. Similar to this, kaempferol decreases survivin protein and Akt activity, making glioma cells more susceptible to TRAIL-induced apoptosis. When coupled with 5-FU, kaempferol has an additive effect on cell death and has been demonstrated to be just as effective as 5-FU in inducing apoptosis in pancreatic cancer cells. Studies have been conducted on keampferol as a phytoestrogen as a possible target for hormone-dependent malignancies such the prostate and breast. But kaempferol worked for prostate and breast tumors that were hormone-dependent or hormone-independent. Studies have shown that kaempferol has antiangiogenic and antimetastatic properties in addition to its ability to induce cell death [66]. It has also been reported that kaempferol

antiangiogenic activity in ovarian cancer cells is caused by VEGF downregulation [67,68]. Reduced activity of matrix metalloproteinases such as MMP-2, MMP-3, and MMP-9, as well as suppression of ERK and Akt signaling have been associated with kaempferol antimetastatic effects.

Kaempferol (KF) Function as a Nutraceutical

Kaempferol is a dietary flavonoid that occurs naturally in food and is an effective cancer-preventive chemopreventive drug [69]. Moreover, KF stopped EGF from activating AP1 and NF-κB. KF totally inhibited the phosphorylation of Akt that was produced by EGF, although p38, JNK, and p90 ribosomal S6 kinase were unaffected. A direct correlation between KF and PI3K was discovered by the kinase profiling experiment. The scientists used a KF pull down test to look into the direct binding interaction. The results showed that PI3K exhibited a specific type of linkage with the KF-Sepharose 4B beads. Pull down assay results for ERK, p38, and JNK kinase were negative, which is in line with KF's specific inhibition of PI3K. These findings suggest that KF binds to PI3K and prevents downstream signaling and PI3K activation.[70] The same researchers discovered that kaempferol inhibited the synthesis of COX-2 protein in mouse skin epidermal JB6 P+cells exposed to UVB light, but it is not act on the phosphorylation of the upstream MAPK regulator Src. It also decreased the transcriptional activity of COX-2 and AP-1 through a number of kinases. Nevertheless, additional research verified that kaempferol inhibited Src kinase activity. Pulldown assays show that kaempferol is Src's direct molecular target since it competes with ATP for direct binding to Src. Additionally, subsequent docking research showed that kaempferol easily docks into the ATP-binding region of Src.

Role of Kaempferol in Prevention of Ulcerative Colitis

A wide range of pharmacological activities have been demonstrated in numerous preclinical studies involving kaempferol and some of its glycosides. Park *et al.*'s recent study on kaempferol's preventative effects in UC found that giving mice kaempferol (0.1% or 0.3%) before or after feeding was helpful in reducing the colitis brought on by DSS in mice. Researchers found that plasma Leukotriene B4 [LTB (4)] significantly decreased in all animals fed kaempferol, and that NO and PGE (2) levels significantly decreased in both the pre- and postfed groups of mice given 0.3% kaempferol. Moreover, neither the pre-fed nor the postfed groups that received 0.3% kaempferol had increased MPO activity in the colonic mucosa. Furthermore, kaempferol-prefed rats showed increased levels of TFF3 mRNA, a marker for goblet cell function, suggesting its potential benefits.

Conclusions

The area of phytochemistry has been expanding quickly in recent years with the intention of creating novel medications based on substances produced from plants. In parallel, the study of historic medicinal plant uses across many locations and their potential integration into contemporary pharmaceutical and medical practices is known as ethano pharmacology. These methods are incorporated into the creative processes that serve as the impetus for the creation of novel therapeutic methods. Kaempferol-containing plants and the chemicals linked to it have been investigated for a range of biological activities and effects, including anti-inflammatory, antibacterial, antifungal, and anti-carcinogenic properties. Indeed, one of the main goals of medical research in the past few decades has been to identify natural chemicals that may have anti-carcinogenic properties. Applications for these goods have been put forth, and a summary of the corresponding new insights in the drug development of numerous such natural agents has been provided. With respect to the subject matter of this study, it can be thought with some notch of confidence that kaempferol molecules provide a novel prospect for therapeutic design given their encouraging results in the field of clinical pharmacology. The fact that many infections are becoming resistant to conventional medications makes this even more crucial. We can also hypothesize that, given the variety of kaempferol effects, medications that might treat multiple conditions could be created; for instance, by employing kaempferol as the active ingredient, infections in cancer patients could be managed. Fighting against both the infection and the cancer cells simultaneously and further research should be done on this topic.

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