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KAEMPFEROL: A Key Emphasis on its Counter-Wired Potential

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Abstract:- Kaempferol is a naturally existing flavonol that can be found in plants and other sources. It has a number of health advantages and is a vital component of many products made from plants. The most prevalent polyphenols in the average person's diet are flavonoids, which are mostly found in fruits, vegetables, and plant-based drinks. Kaempferol is well recognized for its antioxidant qualities, which prevent the production of ROS and lipid peroxidation and have a variety of other effects. In addition to being an antioxidant, Kaempferol also possesses functional and nutraceutical qualities that lessen oxidative damage to biological cells. High dosage of flavonoids has been demonstrated in studies to potentially lower the risk of lymphatic filariasis and cancer.

Keywords:- *Flavonoids, Antioxidant, Lymphatic Filariasis, Cancer, Nutraceuticals.*

I. INTRODUCTION

The use of medicinally active plants in Chhattisgarh, India, remains paramount in traditional medicine to treat various ailments of the nation. Additionally, these plants are essential resources for the development of novel drugs. There is an abundance of enthusiasm for using antioxidants from natural sources rather than synthetic antioxidants in the manufacture of pharmaceuticals. Because antioxidants not only act as antioxidants, but they also have functional and nutraceutical properties that aid in reducing oxidative damage to cells in the human body [1].

Among all the chemical compounds, flavonoids have the highest antioxidative activity. Flavonoids are cleft into a number of groups based on their chemical harmony, namely isoflavonoid, flavones, catechins (flavanols), flavonols, anthocyanins flavanones, chalcones, and neoflavonoids [2]. It is already recognized that polyphenols (such as flavonoids) have antioxidant properties [3]. The shikimate pathway is the best way to synthesize flavonoids [4] a process occurring in plant plastids; [5,6,7]. More than 2000 compounds are known, about 500 of which exist as free aglycones and the rest as C-glycoside (aglycones attached directly to flavonoid skeleton as C-C covalent) or O-glycosides (aglycone combined to hydroxyl oxygen).

Although flavonols are lipophilic in nature at their free state as aglycones, most flavonols yielded in plants are bound with sugar moieties, glycosidic form, and are hydrophilic [8]. The existent of hydroxyl functional group in flavonols are essential and potent binding sites for sugar such as O [9]. The most commonly attached sugar to flavonols are monosaccharides such as arabinose, glucose, galactose, xylose, rhamnose and the disaccharide rutinose (formation of β- glycosidic bond to link glucose and rhamnose) [10].

A growing number of studie supports Kaempferol as a breast cancer chemotherapy agent with clear therapeutic benefits [11]. Flavonoids are the most common polyphenols in human diet, which are found in vegetables, fruits and plants-based beverages primarily, and are the key ingredients of numerous plant-based products. Epideminilogical and animal studies show that high doses of flavonoids may scale down the uncertainty of cancer and lymphatic filariasis [12,13]

Kaempferol is most encountered aglycone flavonoid in its glycoside form. This is a tetrahydroxyflavone with four hydroxy groups at 3,5,7 and 4 position. Kaempferol is found in Camelia sinensis (Tea tree) and has various beneficial health effects. Kaempferol (3,5,7-trihydroxy-2-(4-hydroxy -phenyl)-4H-chrimen-4-one) is a natural occurring hydrophobic polyphenol aromatic compound with diverse metabolic functions [14]. Apple, tomatoes, green tea, green beans, potatoes, brussels sprouts, spinach, grapes, cucumbers, lettuce, broccoli, peaches, ripe blackberries, onions, raspberries and pumpkins are common sources [15].

Kaempferol is named for German physician, naturalist and historian Engelbert Kaempfer, who worked to spread medicinal awareness and knowledge from Japan to the West in 17th century [16].

As with other nutraceutical and dietary supplements, it is always recommended to consume Kaempferol-rich food as part of an equitable diet rather than relying solely on dietary supplements [17]. Kaempferol strive a protective effect in non mutated cells while inducing apoptosis in these mutant cells these aspects are mainly related to kaempferol's pronounced antioxidant action, i.e., direct action on antioxidant enzymes, effectively inhibiting ROS production and lipid peroxidation, ultimately resulting in a wide

spectrum of action. Through a broad-spectrum activity, it can overcome the occurrence of cell damage [18].

Table 1 Some Common Sources Of Kaempferol

Sl	Sources	Examples	Ref.
1	***Tea***	Green tea Black tea	[19] [19]
2	Herbs & Spices	Fennel Chili peppers Dill Parsley Thyme Oregano	[20] [20] [20] [20] [20] [20]
3	Nuts	Almonds Pecans	[21, 25]
4	Beans and legumes	Soyabeans Pinto Beans Lentils	[21] [21] [21]
5	Berries	Strawberrie Blueberrie Raspberrie	[21] [21] [21]
6	Vegetables & Fruits	Tomato Onion Broccoli Spinach Kale Apple Grapes Lemon Orange	[19] [19] [19] [19] [19] [19] [19] [19] [19]
7	*Medicinal plants*	Toona sinensis St. John's wort Sambucus nigra Pinus sylveste Moringa oleifera Lycin Max Ilex Hypericum perforatum Ginkgo biloba Euphorbia pekinensis Endive Cuscuta chinensis Coccinia grandis Aloe vera	[21] [21] [21] [23] [20] [21] [21] [21] [21] [21] [21] [24] [22] [21] [21]
8	Dark Chocolate and Cocoa	Cocoa beans	[21]
9	Wine	Fermentation of grapes skin	[19]

II. PHYSICOCHEMICAL PROPERTIES OF KAEMPFEROL

Kaempferol is a yellow-colored solid powder with molecular formula $C_{15}H_{10}O_6$ and MW 286.24g/mol with MP 276 – 278 ºC [25]. When heated at 278-280ºC it decomposes and emits acrid smoke and fumes [26]. It is solubilized in warm alcohol, acetic acid, alkalies or ether [25]. Not soluble in benzene, slightly solubilized in chloroform, high solubility in ethanol, ethyl ether, acetone [27]. In water 440mg/L at 25ºC [28].

A. Chemical Structure

In the structure of flavonoids, it consists of a heterocyclic ring (ring C) attached to two phenyl rings (ring A and B) [29]. Kaempferol and quercetin both share the same 3- hydroxy flavone backbone, but quercetin differs from kaempferol by having an extra hydroxyl group at the R1 position.

The number of the presences of hydroxyl group changes the chemical reactivity of the compound. Thus, Kaempferol is more stable chemically as compared to

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quercetin as it has one less hydroxyl group [30]. Aglycones, the free state of flavonols, have lipophilic (fat-soluble) properties. However, the majority of flavonols synthesized from plants are attached to a sugar moiety, the glycoside form which by nature lipophobic (water-soluble) [31].

All three rings have the ability to be linked to sugar moieties, such as O- glycosides, through their hydroxyl functional group [29]. Galactose, rahamnose, arabinose, glucose and xylose monosaccharides are the sugar moieties that are most commonlt attached to flavonols [32]. Glucose and rhamnose are connected by a β- glycosidic bond to form rutinoside, which is a disaccharide [31].

B. Pharmacokinetics Of Kaemferol

Kaempferol - loaded formulations are marketed as herbal and dietary supplements [33]. Kaempferol and its glycosylated derivatives are cardioprotective, neuroprotective [34], antioxidant [35], antimicrobial [36], anti-inflammatory [37], anti-proliferative [38], anti-viral [39], anti-diabetic [40], antitumor and also have anticancer activities [41].

- *Antioxidant Activity*

Kaempferol exhibits strong antioxidant properties, which enable cells to defend themselves from oxidative damage brought on by free radicals. By assisting neutralization of these harmful molecules, it decreases the risk of chronic illnesses such as cancer, neuro-degenerative disorders and cardiovascular diseases [42].

- *Anti-Inflammatory Effects*

Kaempferol has been found to possess anti-inflammatory qualities, that can help alleviate inflammation in the body. Inflammation that persists over time is associated with several diseases, including arthritis, asthma and inflammatory bowel disease. Kaempferol's anti-inflammatory action may help in managing these conditions [37].

- *Cancer Prevention*

Kaempferol has attracted attention for its potential anti-cancer effect. Research suggests that it could inhibit the growth of cancerous cells, cause apoptosis (cell death) in cancer cells, and reduce the development of new blood vessels that tumors need to grow (anti-angiogenesis). It has encouraging and promising results against various types of malignancies, including pancreatic, lung, breast, colon and prostate cancers [41].

- *Cardiovascular Health*

Kaempferol may have positive effects on cardiovascular health. It has been found to reduce LDL cholesterol levels, inhibit platelet aggregation and possess vasodilatory properties, which can help boost blood flow and lower the risk of heart disease, stroke and hypertension [43].

- *Neuroprotective Properties*

Studies suggest that Kaempferol may have neuroprotective effect, meaning it may help protect the brain and nerve cells from damage and degeneration. It has been investigated for potential in preventing or in the treatment of neurodegenerative illnesses such as Parkinson's and Alzheimer's diseases. [44]

- *Antimicrobial Activity*

Kaempferol exhibits antimicrobial properties and has been studied for its potential as a natural antimicrobial agent. It has shown inhibitory effect against various bacteria and fungi, suggesting its possible use in combating microbial infections [36].

- *Skin Health*

As a result of Kaempferols antioxidative and anti inflammatory properties, Kaempferol may benefit skin health. It has been explored for its potential in preventing the skin from UV radiation-induced damage and reduce inflammation and promoting wound healing [45].

- *Weight Management*

some studies have suggested that Kaempferol may help in weight management. It has been found to inhibit adipogenesis and increase fat oxidation, potentially aiding in weight loss and obesity management [46].

- *Anti-Diabetic Effects*

Kaempferol has been found to have anti-diabetic effect, which may help to regulate blood glucose levels and prevent complications associated with diabetes [40].

- *Anti Filarial Activity*

Kaempferol has been investigated for its potential as an effective agent in the treatment of lymphatic filariasis. A study proclaimed in the journal Parasitology Research in 2007 evaluated the effect of Kaempferol on Brugia malayi, one of the filariasis worm that causes LF. The researchers found that Kaempferol exhibited antifilarial activity against both adult and microfilarial stage of B. malayi *in vitro*. It was able to cut the viability of the parasites and induce morphological changes in them, leading to their death [47].

In addition to its antifilarial activity, Kaempferol has also been found to possess anti inflammatory properties. Inflammation plays a crucial aspect in the development of LF pathology and in reducing inflammation caused by the infection. Kaempferol has been delineated to inhibit the generation of pro-inflammatory chemokines and cytokines, which are responsible for the inflammatory response [48].

While the in vitro studies of Kaempferol on B. malayi are promising, further investigation is required to evaluate its efficacy *in vivo* and to figure out its optimal dosage and potential side effects. Additionally, the use of Kaempferol alone or in combination with other drugs needs to be investigated to determine its potential as a new treatment [49].

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C. Bioavailability Of Kaempferol

A study is being conducted to assess the bioavailability of Kaempferol after ingestion of legumes (Phaseolus vulgaris L.) in healthy subject by monitoring excretion and intake. Seven healthy subjects ingesting Kaempferol from beans, which reached peak excretion of hydrolyzed flavonols after 2-8 hours [50].

The difference between man and woman subjects, urine output was determine to be 6.10 +/- 5.50 % and 5.40 +/- 5.4% of the kaempferol dosage respectively. All individuals had similar excretion profiles, Despite the fact that the researcher and team discovered a 6.72-fold individual variation between the highest and lowest excretion concentration [50].

Furthermore, a correlation was observed intervening the percentage of excreted kaempferol and BMI in volunteers, with a correlation index of 0.80. all but 2 subjects showed an initial peak in excretion of kaempferol 2 hours after dosing. This investigation provides information on excretion capacity among individuals after taking kaempferol and that can be used as a biomarker for flavonol intake [50].

A pharmacokinetic find out about endive-derived Kaempferol used to be investigated in eight wholesome male and woman pairs. Kaempferol was absorbed from endive into plasma with a relatively low dose (9mg) at a mean maximum plasma concentration 0.1 µM over a period of 5.8 hours, hinting absorption from the distal component of the small intestine and /or colon. Despite a 7.5-time inter-subject variability between the greatest and lowest height plasma concentrations observed, most subjects exhibited extraordinarily steady pharmacokinetic profiles. This contrasts with the profile of different flavonoids that are primarily absorbed from the colon. A mean of 1.9% of the kaempferol was excreted within one day. Most of the volunteers also showed an early absorbance peak, possibly comparable to kaempferol-3-glucoside, and during endive. 14%. Kaempferol-3-glucuronide was the main compound present in plasma and urine. That indicates a lack of phase I hydroxylation of kaempferol. Kaempferol is absorbed more efficiently than quercetin in humans, even at low oral doses. The predominant form in plasma is the 3-glucuronide conjugate, and the small individual differences in absorption and excretion suggest that urinary kaempferol may be used as a biomarker of exposure (24)

D. Metabolism

In vitro and *in vivo* pharmacokinetic profile of kaempferol, commonly taken as a vastly polar glycoside, revealed that moderately polar aglycone are absorbed more rapidly then polyphenols [51]. The lipophilicity of Kaempferol allowed absorption into small intestine by intestinal binding enzyme, facilitated diffusion and passive or active transport [52]. Absorbed Kaempferol undergoes metabolic transformation to form glucuronide and sulfoconjugated in the liver [53]. The activity of this enzyme is higher with kaempferol-3-glucuronide than with quercetin [54].

Bacterial flora in the colon metabolizes kaempferol and its glycosides, releasing aglycones and cleaving the aglycone C3 ring to form compounds such as 4-Methylphenol, phloroglucinol, 4-hydroxyphenylacetic acid. These may be absorbed and enter into the systemic circulation., It is possible that some of the aglycones were metabolized in the kidney before excretion because the concentration of free Kaempferol was lower in urine than in blood. The aglycone and glucuronide metabolites of kaempferol were present in plasma, in the other hand sulfate metabolites were found in urine [24,55,56].

E. Kaempferol Safety

There were no human studies found that reported potential toxicity or harmful events when kaempferol was taken orally. Although *in vitro* profiles have confirmed the antioxidant effect of Kaempferol, a high level its supplementation can induce autoxidation (peroxidation) [57,58]. Only a few researchers have determined that kaempferol is antimutagenic, whereas others have found it is genotoxic [59-62]. According to several studies, the enzyme CYP 1A1 converts kaempferol to the carcinogenic compound quercetin, which is the cause of kaempferol's mutagenic effects [63,64].

In vitro, data have shown that kaempferol has toxic and carcinogenic effects, but these effects have not been reported in *in vivo* screens. Takanashi and his collaborators were administered orally for 77 weeks without an increase in tumour incidence. The low oral bioavailability of Kaempferol was thought to prevent its genotoxic effects [65]. However, animal studies found that kaempferol is highly reactive with these nutrients, thus reducing iron absorption and cellular uptake of folic acid [66]. Several *in vitro* reports have found that Kaempferol is highly reactive with these nutrients, thus reducing the absorption of iron and cellular uptake of folic acid [67,68].

F. Available Marketed Preparations:

- *Kaempferol capsules or tablets*

These formulations contain purified or synthesized kaempferol and are used for various purposes, such as antioxidant support, anti-inflammatory effects, or potential cancer prevention.

- *Topical creams or ointments*

Kaempferol can be incorporated into topical formulations for its anti-inflammatory and wound-healing properties. These preparations may be used for skin conditions or as part of cosmetic products.

- *Injectable solutions*

Kaempferol or its derivatives can be formulated as injectable solutions for targeted delivery and systemic effects. These formulations may be investigated for their potential anticancer or anti-inflammatory effects.

➢ *Combination therapies*

Kaempferol may be combined with other active compounds or drugs to enhance therapeutic efficacy. For example, it might be used with chemotherapeutic agents to increase their effectiveness or reduce side effects.

III. CONCLUSION

Kaempferol is present naturally in numerous plants, such as fruits and vegetables, along with plant products. It has been reported many times that Kaempferol possesses a wide range of health advantages. Daily intake of Kaempferol is highly recommended to stay healthy and reduce the risk of most life-threatening diseases. The conjugates of Kaempferol with other important drugs may improve the therapeutic potency of those compounds. Most studies have been conducted at doses that far exceed the oral bioavailability of kaempferol. Therefore, it seems very difficult to state the most effective dose of this flavonoid. Further research will focus on effective doses of kaempferol in clinical trials, related to low bioavailability, permeability and safe dosing requirements to offer this flavonoid as a potential new candidate for future drug development.

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