

## Exploring therapeutic potential of kaempferol in the management of diabetes

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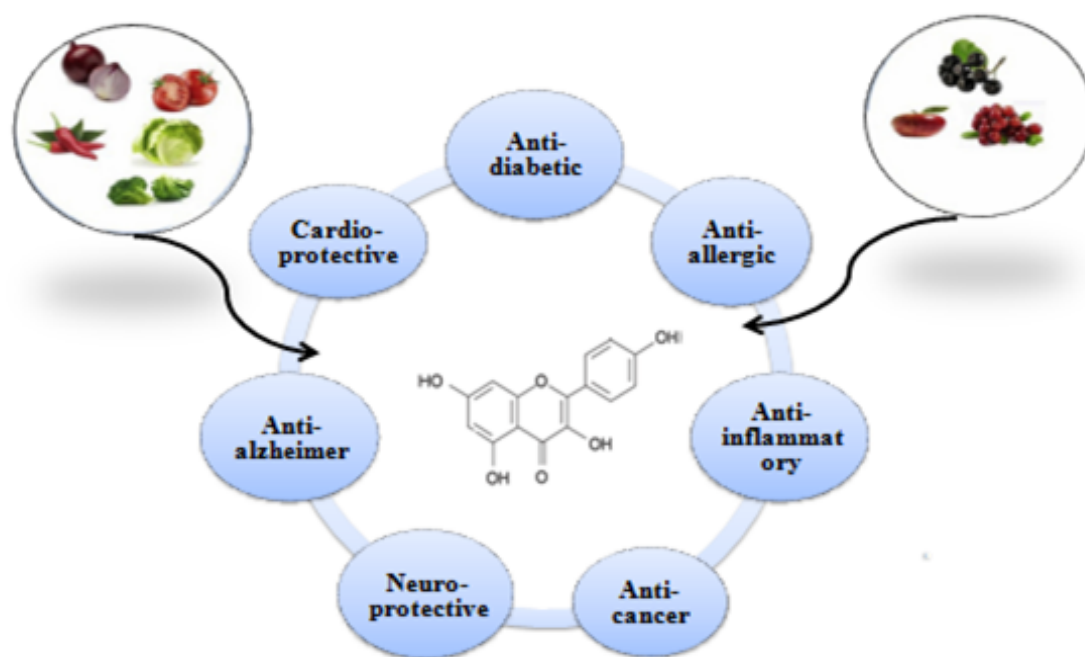
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### GRAPHICAL ABSTRACT



### ABSTRACT

Kaempferol, a dietary flavonoid abundant in fruits and vegetables, exhibits notable antioxidant, anti-inflammatory, and antidiabetic properties. This review explores its therapeutic potential in diabetes management, highlighting mechanisms including enhanced insulin sensitivity and secretion, inhibition of  $\alpha$ -amylase and  $\alpha$ -glucosidase, improved glucose uptake, and reduced oxidative stress and inflammation. Kaempferol also protects against diabetes-related complications like nephropathy, neuropathy, and cardiovascular dysfunction, while enhancing co-administered antidiabetic drug efficacy. Its safety profile indicates general tolerability, though clinical translation is limited by poor aqueous solubility, low bioavailability, and rapid metabolism. Sourcing kaempferol from fruit and vegetable waste offers a sustainable, circular-economy production route, reinforcing its promise as an antidiabetic candidate.

**KEYWORDS:** kaempferol, Diabetes mellitus, hyperglycemia, Gastro-protective, antidiabetic activity, obesity, mechanism

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## 1. INTRODUCTION

The natural compounds obtain from plants including leaves, stems, seeds and flowers have their potential against various diseases. The prevention of infection capability evidence in pure natural product has been evidence through antidiabetic potential, anti-oxidant, anti-inflammatory, anti-microbial, hepatoprotective, neuroprotective, and cardio protective activities. In addition, original compounds have been essential in the quest for new medications, especially concerning cancer and infectious illnesses [1,2]. The remedial area such as cardio-vascular diseases and many sclerosis is additional [3,4,5]. Herbs are a rich source of antioxidants and antidiabetic substance and their bioactive components certainly play a significant role of preventing illness [6,7]. KMP is a flavonoid present in many vegetables and fruits, it has been demonstrated to reduce inflammation, oxidative stress, and modulate biological processes. Previous studies found that lipopolysaccharide increased intra-cellular reactive oxygen species levels, which decreased after kaempferol therapy. This substance reduced the inflammation levels in which enhanced significantly following lipopolysaccharide contact additionally [8].

Another study and investigate of kaempferol promote regular epithelial cells from COPD airway by shifting gene expression. The base of finding concluded that kaempferol may improve expression of gene concerned in epithelial growth in COPD [9]. P. aeruginosa-caused in lungs through diminishing of cytokines neutrophil in filtration production, which was associated with less mortality substance enhanced.

Furthermore it has been stated that kaempferol helps protect against harm from UVB rays by reducing damage to the mitochondria oxygen species caused by reactive. It does this by neutralize immediate oxygen species and also by preventing depolarization of the mitochondrial membrane along with the movement of the cell membrane [10,11]. This evaluation thoroughly examines

how kaempferol contributes to disease control by stimulating and diminishing different biological functions.

## 2. METHODOLOGY

The digital resources including Scopus, PubMed, Medline, Google Scholar and Web of Science were searched for information regarding kaempferol and its uses of different diseases. The inquiry employed terms such as origins of kaempferol, free radical scavenging, oxidative stress reduction, inflammation response, anti-inflammatory capabilities, blood sugar regulating effects, liver protective benefits, brain protective benefits, heart protective benefits, anti-microbial fighting properties, cancer research studies, trials, combined effects, and nanotechnology formulation.

The literature of compared experimental trials, randomized, and epidemiological studies related to KMP, while editorials analysis.

### 3. Sources and daily intake of kaempferol

Kaempferol is a naturally occurring dietary flavonoid [12]. It is found abundantly in plant-based foods, with leafy green vegetables and certain beverages being the primary contributors to human dietary intake. You can incorporate kaempferol into your diet by eating a different category of fruits, vegetables, and herbs. The most concentrated dietary sources include: [13,14]

- Vegetables: Spinach (~ 55 mg per 100g), kale (~ 47 mg per 100g), and broccoli (~ 7.2 mg per 100g).
- Spices & Herbs: Capers and saffron are exceptionally dense in kaempferol.
- Beverages: Black tea is the major dietary beverage source, often yielding up to 11.8 mg per 100 mL, alongside green tea.
- Other Foods: Onions, apples, berries, and beans also contain measurable quantities. [15, 16]

Table 1:- Source of Quercetin

| S.No. | Plant name               | Family         | Geographical source                                           | Ethno-botanical uses                                                                   | Reference |
|-------|--------------------------|----------------|---------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------|
| 1     | Capers                   | Capparaceae    | West/Central Asia, and parts of Australia.                    | anti-inflammatory, antioxidant, and digestive properties                               | 17        |
| 2     | Saffron                  | Iridaceae      | Khorasan and Farse provinces, India and Afghanistan           | anti-inflammatory, antioxidant, cardiovascular diseases, anti-anxiety, and Alzheimer's | 18        |
| 3     | Green Onions (Scallions) | Amaryllidaceae | Asia                                                          | respiratory issues, digestive ailments, and inflammation                               | 19        |
| 4     | Arugula                  | Brassicaceae   | Europe (Spain, Italy) North and South America, and South Asia | Anti-diabetic, anti-diuretics and skin diseases                                        | 20        |
| 5     | Spinach                  | Amaranthaceae  | Iran and Central Asia.                                        | antioxidant, anti-inflammatory                                                         | 21        |
| 6     | Kale                     | Brassicaceae   | North America                                                 | treat digestive distress, as blood purifiers                                           | 22        |
| 7     | Dill                     | Apiaceae       | North Africa, and Southern                                    | stomach cramps in infants                                                              | 23        |

|    |               |                |                                |                                                                    |       |
|----|---------------|----------------|--------------------------------|--------------------------------------------------------------------|-------|
|    |               |                | Russia,India and pakisthan     |                                                                    |       |
| 8  | Brown Mustard | Brassicaceae   | Central Asia & India           | joint pain, arthritis, rheumatism, and muscle aches                | 24    |
| 9  | Pumpkin       | Cucurbitaceae  | South America (Argentina)      | antioxidant, anti-inflammatory, antimicrobial, and antidiabetic    | 25    |
| 10 | Ginger        | Zingiberaceae  | India, China, and Nigeria      | colic, indigestion, and diarrhea                                   | 26,27 |
| 11 | Cauliflower   | Brassicaceae   | China, India, Spain, and Italy | Neuropathy, anti diabetic, reduce risk of stroke.and anti-oxidants | 28    |
| 12 | Chinese       | Fabaceae       | Yunnan and Guizhou             | Reduce BP , Cholesterol And Dyspepsia                              | 29    |
| 13 | Blueberries   | Ericaceae      | North America and europe       | Anti-diabetic and inflammation and cognitive function              | 30,31 |
| 14 | Onions        | Amaryllidaceae | Central asia                   | Anti-oxidant, cardio-protective,                                   | 32    |
| 15 | Black Tea     | Theaceae       | China and india                | Anti diabetic , anti-oxidants                                      | 33    |

Table 2. Illness brought on by oxidants and free radiation

| Human system          | Disease                                     |
|-----------------------|---------------------------------------------|
| CNS                   | Stroke, Depression Alzheimer's              |
| Cardiovascular system | Atherosclerosis,Hypertension,Cardiomyopathy |
| Respiratory system    | Asthma                                      |
| Excretory system      | Rena failure                                |
| Skeletal system       | Arthritis, rheumatism                       |
| Metabolic system      | Diabetics                                   |
| Multiorgans           | Cancer , inflammation aging                 |

#### 4. THERAPEUTIC ROLE OF KAEMPFEROL

Kaempferol is a naturally occurring dietary flavonoid that manages diseases primarily by down regulating inflammation, combating oxidative stress, and inducing cancer cell apoptosis. By modulating interconnected cellular pathways, it shows potent therapeutic promise in treating cancer, metabolic disorders, and neurological conditions[17].

The different types of mechanism involved in disease management are describe below:

##### 4.1. Anti-oxidant Potential

Antioxidant potential refers to a compound's or food's capacity to neutralize harmful free radicals, effectively delaying or preventing cell and tissue damage caused by oxidative stress.

This capability is crucial for mitigating aging, inflammation, and chronic diseases like cancer and cardiovascular disorders [34].

Plant-based foods naturally pack the highest antioxidant potential due to secondary metabolites like polyphenols and flavonoids [35].

- Spices & Herbs: Cloves, oregano, and cinnamon are widely documented as some of the most concentrated antioxidant sources.
- Berries: Blackberries, blueberries, and strawberries are excellent dietary powerhouses.
- Nuts: Walnuts possess the highest antioxidant content among nuts, followed by pecans and pistachios.
- Other: Dark chocolate, fava beans, and green lentils are also incredibly high

##### 4.2. AntiInflammatory Potential

The antiinflammatory potential of a substance or diet refers to its ability to prevent or reduce tissue swelling, pain, and chronic inflammation. By inhibiting pro-inflammatory markers (like cytokines, COX, and LOX enzymes), these agents help mitigate underlying risks for diseases like arthritis, cardiovascular

conditions, and diabetes. Extensive clinical and biochemical studies exist for those looking to review the mechanisms of action. You can look at research on medicinal plants or read published reviews evaluating anti-inflammatory potential of some medicinal plants .

#### 4.3. Antidiabetic Activity

The growth of new medications focuses on preventing the harmful progression of these diseases in light of the international pandemic of diabetes and obesity. A recent study found that KMP, a original, has good antidiabetic properties. Thus, the border research and pharmacological mechanism of KMP in treatment of diabetes were thoroughly summarized in this study [36]. It exhibits significant antidiabetic activity by lowering blood glucose, ameliorating insulin resistance, and protecting pancreatic  $\beta$ -cells from oxidative damage

#### 4.4. Hepatoprotective Activity

It regulate so because many physiological functions, the liver is a very important organ. These actions are associated with several vital functions, such as secretion, metabolism, and storage.

The both metabolic waste and toxic substances in addition to synthesis organ can detoxify [37].

The biochemical processes (growth, diet, energy production, and reproduction) in addition to its function are involved in digestive system. It helps in bile secretion, vitamin storage, and the metabolism of fat and carbohydrates. [38]. Because of these functions, liver disease remains major public health issues [39]. When the liver's cells, tissues, structures, and functions suffer harm, it is referred to as liver disease. This harm may result from germs (such as, viruses, bacteria and parasites) and autoimmune disorders (like immune hepatitis and primary liver cirrhosis).

#### 4.5. Kaempferol as an anti-hypolipidemic agent

Research indicates that kaempferol improves lipid profiles and reduces the risks of cardiovascular disease and atherosclerosis. In in-vitro studies on human liver cells, kaempferol reduces oleic acid-induced fat accumulation and aids in the uptake of low-density lipoprotein cholesterol . In animal models, kaempferol supplementation has been shown to reduce visceral fat, lower plasma triglyceride and total cholesterol levels, and increase high-density lipoprotein cholesterol .[40]

#### 4.6. Gastro-protective Effects

It is attractive as a pure substance such as KMP has been creating to have gastro-protective properties. The protective benefits and potential processes by which KMP guards against gastric mucosal damage due to acute ethanol exposure were assessed. The findings indicate that KMP not ably lowered the ulcer index, enhanced preventive index, maintained glycoprotein levels in gastric mucosa, and safeguarded mucosa from injury. The study evaluated how kaempferol offers protective advantages and the possible mechanisms by which it shields against damage to the gastric mucosa caused by sudden exposure to ethanol. Results showed that kaempferol significantly reduced ulcer index, improved the preventive index, preserved glycoprotein levels within gastric mucosa, and protected the mucosa from harm [41].

#### 4.7. Neuro-protective Effects

Neurological disorders represent a major factor contributing to illness and death. Existing treatment methods often lead to negative side effects. In this context, natural substance have demonstrated their neuroprotective abilities by influencing several biological processes, including inflammation and oxidative stress. Oxidative stress and inflammation significant contributors to the onset of numerous diseases and health issues.

Research has extensively examined chronic inflammation within the central nervous system, recognizing it as a potential the emergence and advancement of several neurodegenerative disorders [42]. Activated microglia immune cells reside in the central nervous system, are acknowledgement as a significant contributors to the onset of neuro-inflammation [43]. Oxidative stress plays a crucial role in the aging process and serves as a common factors leading to cellular death [44,45]. Natural substances like kaempferol have demonstrated potential benefits in managing diabetes. Research indicates that kaempferol may improve the function and increase the concentrations of antioxidant enzymes, including superoxide dismutase (SOD) and glutathione (GSH)[46]. The study results show that exposure to kaempferol in flies with Alzheimer's disease led to a postponement in the decline of their memory and climbing skills. Furthermore, kaempferol was found to lower the levels of acetyl cholinesterase activity as well as oxidative stress [47].

#### 4.8. Antimicrobial Effects

Gram negative strains are quite disturbing especially in hospital where vulnerable patients are at a higher risk of antibiotics resistance particularly [48]. The Multidrug-resistant (MDR) strains, our food supply also poses a risk due to their extensive use of antibiotics. Infection treatment, growth promotion, and prevention in livestock [49]. Extracts from many sections of plants, including stems, fruits, roots, and flowers, are frequently used to limit the growth of microorganisms [50]. In addition to their antibacterial property, they have potential to be utilized as preservatives [51].

#### 4.9. Wound Healing potential

Inflammation is critical condition several physiological processes, including homeostasis, elimination of dangerous microbes, damaged tissues, and wound healing [52]. Inflammation phase are longer than necessary, it can happen a problem and delay of wound healing process [53,54]. The wound healing potential of kaempferol was performed to examine was critical study.

### 5. SAFETY AND TOXICITY LEVEL OF KAEMPFEROL

The contradictory view of protection and toxicology of KMP. Some of the studies reported is secure consumption, while others have raised apprehensive about its possible toxicity. The KMP are following sub acute exposure in mice and study was performed to examine. The 28 days of KMP was taken orally in three separate doses. The 28 days of kaempferol administration, no treatment-related differences in body wt. or organ wt. were observed compared with control group.

Furthermore, no clinical signs of systemic toxicity were evident throughout the study period, indicating that kaempferol was well tolerated under the experimental conditions. There are No significant differences were observed between the KMP-treated and control groups with respect to hematological parameters, including platelet count, red blood cell (RBC) count, white blood cell (WBC) count, hemoglobin (Hb) concentration, mean corpuscular hemoglobin concentration (MCHC), platelet distribution width (PDW), and red cell distribution width (RDW) Furthermore, [55].

### 6. CONCLUSIONS AND FUTURE PROSPECTIVE

This review highlights kaempferol as a promising natural agent in the management of diabetes mellitus and its associated complications. Its multifaceted mechanisms—including enhancement of insulin sensitivity and secretion, inhibition of key carbohydrate-digesting enzymes, improve cellular glucose

uptake, and suppression of oxidative stress and inflammatory signaling—position it as a valuable candidate for both prevention and adjunct therapy in diabetes care. Beyond glycemic regulation, kaempferol protective effects against diabetic nephropathy, neuropathy, and cardiovascular dysfunction underscore its broader relevance in mitigating the systemic burden of chronic hyperglycemia. Its capacity to synergistically enhance the efficacy of conventional antidiabetic drugs further strengthens its potential role in combination therapeutic regimens. Nevertheless, the translation of kaempferol from experimental and preclinical settings into clinical practice remains hindered by significant pharmacokinetic limitations, particularly its poor aqueous solubility, low oral bioavailability, extensive hepatic metabolism, and rapid systemic clearance. These factors collectively restrict adequate plasma concentrations and limit sustained therapeutic action at target tissues, representing a critical bottleneck in its clinical development. Future research should focus on overcoming these delivery-related challenges through innovative formulation strategies, including nanoparticle-based carriers, liposomal and phospholipid complexes, self-emulsifying drug delivery systems, and polymeric micelles, to improve solubility, stability, and bioavailability. Structural derivatization and prodrug design may also offer viable routes to enhance metabolic stability and

target specificity. Furthermore, well-controlled pharmacokinetic and pharmacodynamics studies, along with rigorously designed randomized clinical trials, are essential to establish safe and effective dosing regimens in diabetic populations and to confirm long-term tolerability. Investigating potential synergistic effects with existing antidiabetic medications may also open avenues for combination therapies with improved efficacy and reduced side effects. From a sustainability perspective, sourcing kaempferol from fruit and vegetable processing waste offers an economically and environmentally sound strategy, supporting circular economy principles while addressing supply chain limitations. Overall, continued interdisciplinary efforts integrating pharmaceutical technology, pharmacology, and clinical research will be essential to fully harness kaempferol therapeutic potential and establish its role as a viable natural intervention in diabetes management.

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#### Abbreviations

|               |                                       |
|---------------|---------------------------------------|
| KMP           | Kaempferol                            |
| MDA           | Malondialdehyde                       |
| SOD           | Superoxide dismutase                  |
| HDL-c         | High density lipo protein cholesterol |
| LDL-c         | Low density lipo protein cholesterol  |
| TG            | triglyceride                          |
| TNF- $\alpha$ | Tumor necrosis factor- $\alpha$       |
| WBC           | White blood cells                     |
| RBC           | Red blood cells                       |
| LPS           | Lipopoly saccharide                   |
| IBD           | Inflammatory bowel disease            |
| CAD           | Coronary artery disease               |
| COPD          | Chronic obstructive pulmonary disease |
| BMI           | Body mass index                       |
| DOX           | Doxorubicin                           |
| BW            | Body weight                           |
| AuNPs         | Gold nanoparticles                    |
| MIC           | Minimum inhibitory concentration      |

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