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Kaempferol from Medicinal Plants: A Comprehensive Review of its Anti-Diabetic Effects

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ABSTRACT

Due to the high prevalence of diabetes and the promising effects of Kaempferol, this review assesses its molecular, cellular, and metabolic effects relevant to diabetes. A comprehensive search of PubMed, Scopus, Web of Science, Science Direct, and Google Scholar was conducted for articles published between 2010 and 2023 using relevant keywords. Kaempferol modulates glucose metabolism, enhances hepatic enzyme activity, and improves lipid profiles through multiple mechanisms. Specifically, it protects pancreatic β-cells by inhibiting apoptosis, promoting proliferation, and increasing their number, which is valuable in preventing and treating type 2 Diabetes Mellitus. Studies show that kaempferol reduces serum HbA1c levels (by an average of 20% if used for more than six months) and fasting blood glucose while increasing insulin sensitivity. Oral administration of kaempferol (5 mg/kg) reduced blood glucose levels as compared to metformin (50 mg/kg), while it does not have the harmful effects of metformin and other medications. Meanwhile, another therapeutic difference between Kaempferol is that, compared to other supplements and medications, it has positive effects on other systems of the body rather than destructive and negative effects, including on the liver and kidney systems. However, effects on weight vary across studies, possibly due to differences in dosage and study duration. Kaempferol also plays a multi-target role in diabetic nephropathy therapy, primarily via anti-oxidative stress and anti-inflammatory effects. Further clinical trials are needed to clarify conflicting results and fully establish its therapeutic potential in diabetes management.

Keywords: Kaempferol, Diabetes, Flavonoid, Insulin resistance, Diabetic nephropathy, Glucose metabolism, Inflammation, Metabolic effects

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INTRODUCTION

Diabetes causes death and disability and is one of the main health priorities all over the world [1]. As estimated, 285 million people worldwide have diabetes, and it is likely to increase to 439 million people by 2030 [2]. According to the statistics, there were about 49 million Americans with diabetes, of which about 19 million people were unaware of it [3-4]. There are 4.8 million Iranians with diabetes, and more than half of them are unaware of it [5]. There are two classifications of diabetes: types 1 and 2, with the former being the most common type in children and adolescents, which is caused by autoimmunity against beta cells, producing insulin insufficiently or almost completely [6-7]. The highest rate of type 1 diabetes is in Finland (37-45 thousand people per hundred thousand children under 15 years old), which is 400 times higher than in countries like Venezuela and parts of China [8]. Type 1 diabetes statistics In America, there are 15-17 thousand people per hundred thousand children less than 15 years old [9]. Diabetes type 2 is a type of metabolic disorder associated with high blood glucose in conditions of relative lack of insulin and insulin resistance (IR) [10-12]. In patients with diabetes, optimization of treatment includes maintaining blood sugar in the controlled range. Proper control of blood sugar is the first preventive measure in the management of diabetic patients [13]. Managing glucose levels in individuals with diabetes is crucial, as inadequate control of the condition can greatly impact their quality of life. Furthermore, uncontrolled blood sugar can increase the likelihood of developing diabetes-related complications [14]. The primary categories of these complications include microvascular diseases, macro vascular diseases, and immune system disorders. Notably, nephropathy, retinopathy, diabetic neuropathy, cardiovascular diseases, and cerebrovascular incidents are among the most prevalent complications associated with poor diabetes management

[15]. There are several strategies available to help keep blood sugar levels within a suitable range for these patients, including dietary modifications, weight management, regular exercise, and taking walks [16].

Medication is one of the strategies for managing glucose levels, with insulin being a key option. Besides insulin, various other medications can assist in regulating blood sugar levels in the body. Some of these medications stimulate the pancreas to increase insulin production, while others effectively inhibit the liver's release of glucose. Additionally, some drugs work by preventing the kidneys from reabsorbing glucose [17].

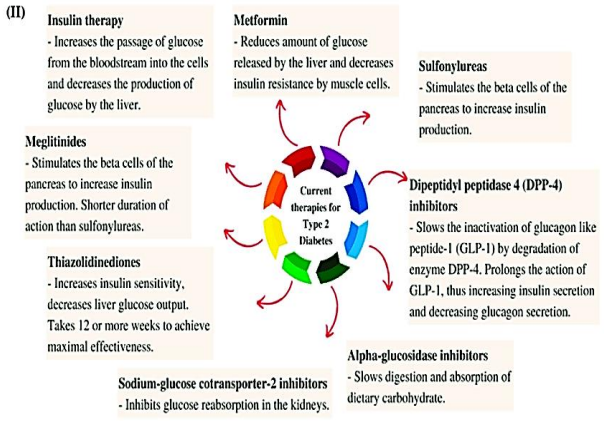

Fig. 1 Diabetes and its common treatments

Recent research shows the positive performance of some herbal medicines on blood sugar control and cellular and molecular changes in diabetic patients (Fig. 1) [9].

Kaempferol is one of these plant-based medicines. Kaempferol is a relatively small group of flavonoids. Flavonoids as secondary metabolites produced by plants in a prolonged natural selection process [18]. Kaempferol with the chemical formula C15H10O6 is a chemical compound with the PubChem ID 5280863 (Fig. 2) [7].

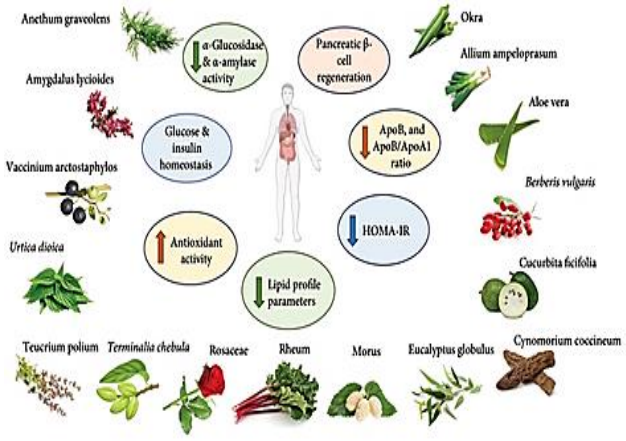

Fig. 2 Traditional herbal medicines and their hypoglycemic effects

It is widely present in the roots, stems, flowers, leaves, and fruits of higher plants. At present, pharmaceutical grade accounts for a significant share. In the dietary supplement industry, kaempferol is primarily used in immune-boosting products and anti-inflammatory formulations, with potential applications in other health areas. It can also be used as a new generation of antioxidant preservatives [19]. Given the high prevalence of diabetes and the lack of a complete effective treatment for this disease, this research has been aimed at comprehensively reviewing the molecular, cellular, and metabolic effects of Kaempferol on diabetes.

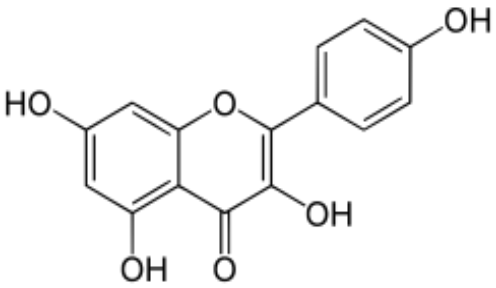

Fig. 3 Chemical structure of kaempferol

Recently been shown in some studies that Kaempferol has a positive effect on diabetic patients (Fig. 3).

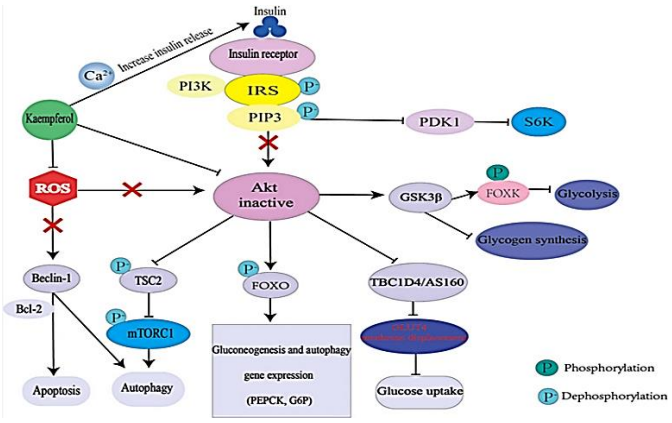

Fig. 4 Kaempferol hypoglycemic effects

MATERIALS AND METHODS

The current research is a comprehensive review that aimes to assess the effects of kaempferol on diabetes, focusing on molecular, cellular, and metabolic mechanisms. A systematic search was conducted in Scopus, Web of Science, PubMed, Google Scholar, and ScienceDirect for articles published between 2010 and 2023 using keywords: kaempferol, diabetes, flavonoid, insulin resistance, diabetic nephropathy, glucose metabolism, inflammation and metabolic effects between 2010 and 2023. The following search string was used in PubMed: (Kaempferol, diabetes, and flavonoid or "metabolic effects" or "metabolic disorders" or "insulin resistance" or "diabetic nephropathy" or "glucose metabolism" and or inflammation). Similar search strings, adapted for each database, were used in the other databases. The search was limited to articles published in English with available full texts. Articles were included if they reported original research on the effects of kaempferol on diabetes-related outcomes under in vitro, in vivo, or clinical studies. Letters to the editor, short communications, conference abstracts, and articles without full-text availability were excluded. Then, titles and abstracts of retrieved articles were screened for relevance. Duplicate articles were removed using EndNote. Full-text articles that met the inclusion criteria were then retrieved and assessed in detail. Two independent reviewers evaluated the articles, and any disagreements were resolved through discussion and consensus.

Table 1 Articles about role of Kaempferol in diabetic patients

No	First author and year	Effective amounts and form of kaempferol	Method	Results
1	Hana Alkhaliy (2018)	Oral administration of kaempferol (50 mg/kg/day)	Experimental design	Kaempferol significantly improved blood glucose control in obese mice, which was associated with reduced hepatic glucose production and improved whole body insulin.
2	Yan Yang (2022)	Different dosages and different methods of using	Narrative review	kaempferol at concentrations as low as 1 mM increases mitochondrial Ca2+ uptake by approximately 85%.
3	Maulana Yusuf (2023)	Oral administration of kaempferol (4.9 to 60 mg/kg)	Nonsystematic review	kaempferol and its derivatives will become promising drugs for treating liver disease.
4	S. Mohan (2013)	Different dosages and different methods of using flavonoids		Flavonoids are capable of improving, stabilizing and long sustaining the insulin secretion, human islets and pancreatic cell respectively.
5	William T.Moore (2017)	Dietary intake of flavonol kaempferol (0.05% in the diet)	Experimental design	Dietary kaempferol treatment preserved functional pancreatic β-cell mass and prevented hyperglycemia and glucose intolerance in STZ-induced diabetic mice.
6	Lan Bai (2019)	Dietary intake of 25–50 μM	Narrative review	Kaempferol could protect pancreatic β-cells and inhibit β-cell apoptosis, promote proliferation, and increase the number of islet β-cells via various mechanisms
7	Jie Ren (2019)	Oral administration of kaempferol (25 mg/kg)	Nonsystematic review	Kaempfero has beneficial effects against cancer, liver injury, obesity and diabetes, inhibits vascular endothelial inflammation, protects the cranial nerve and heart function
8	Qicha Hu (2021)	5–50 μM kaempferol as a solution	Systematic review	Flavonoids reverse the process of renal fibrosis by inhibiting oxidative stress and inflammation and reduce renal cell damage by promoting renal podocyte autophagy.
9	Flavien Bermont (2020)	10 μM kaempferol as a solution	Randomized clinical trial	Kaempferol activates coupling in insulin-secreting cells by modulating mitochondrial calcium uptake.
10	Raghad Khalid AL-Ishaq (2019)	Oral administration of kaempferol (5 mg/kg)	Narrative review	Flavonoids improve the pathogenesis of diabetes and its complications through the regulation of glucose metabolism, hepatic enzymes activities, and a lipid profile.

The results of the articles presented in Table 1 are discussed and compared with those of other studies.

RESULTS AND DISCUSSION

This study aimed to offer a recent overview of the literature on the metabolic impacts of Kaempferol in diabetes and its potential molecular and cellular mechanism of action. Details of the articles are presented in Table 1.

Protective Effects of Kaempferol

Figure 4 indicates the main anti-diabetic effects and mechanisms of oral kaempferol.

Protective Effects of Kaempferol against Streptozotocin (STZ)- induced Diabetes Mellitus (DM)

Based on results of studies, kaempferol may help prevent STZ-induced diabetes by reducing mitochondrial damage. The potential mechanisms behind the kaempferol protective effects may involve the scavenging of free radicals and enhancement of antioxidant status [20]. In the study by Alkhalidy et al., kaempferol was shown to prevent weight loss and food intake reduction induced by STZ, as well as mitigate renal damage and changes in various biochemical parameters. Treatment with dietary kaempferol preserved the functional mass of pancreatic β-cells and helped prevent glucose intolerance and hyperglycemia in STZ-related diabetic mice [21]. kaempferol can maintain mitochondrial function of the liver in STZ-related diabetic rats. Additionally, the activities of mitochondrial respiratory chain enzymes showed a significant reduction in STZ-related diabetic rats compared to controls. However, administering kaempferol led to a significant restoration of these enzyme activities to levels close to normal when compared to diabetic control rats [22]. Previously, Al-Numair demonstrated that kaempferol administration exhibits beneficial antihyperglycemic and hypolipidemic effects in STZ-related diabetic rats [21]. kaempferol can reduce mitochondrial damage in STZ-induced diabetic rats [23].

Protective Impacts of Kaempferol against Alloxan-related DM

Alloxan as a classical diabetogenic chemical has selective cytotoxic effects on pancreatic β-cells, leading to β-cell destruction and type 1 diabetes. Previously, Yakubu Ojochenemi found that flavonoids like kaempferol prevented the rise in plasma glucose induced by alloxan in rats [24]. Yang and Chen reported that flavonoids such as kaempferol normalize glycaemia in alloxan-treated animals, too [25]. It can finally be concluded that kaempferol may normalize glycaemia in alloxan-treated animals. The induction of diabetes mellitus by alloxan may be prevented by kaempferol administration. Based on the conclusions and interpretations of various studies this effect may be the result of antiradical/chelatory properties of the flavonoids used. However, inhibition of renal glucose reabsorption may be also involved in the hypoglycaemic effect of kaempferol.

Effects of Kaempferol on Insulin Resistance (IR) and Secretion

Kaempferol has demonstrated promising effects on insulin resistance (IR) and insulin secretion, key factors in type 2 diabetes (T2DM). Several studies suggest that kaempferol can improve insulin sensitivity by modulating various signaling pathways. For instance, in 3T3-L1 adipocytes, kaempferol enhanced glucose uptake without affecting adipogenesis, suggesting a direct effect on insulin signaling [26, 27] This effect may be mediated by increased phosphorylation of Akt, a key signaling molecule downstream of the insulin receptor [28]. Furthermore, kaempferol has been shown to activate AMP-activated protein kinase (AMPK) in both muscle and adipose tissues [29]. AMPK activation promotes glucose uptake and fatty acid oxidation, leading to improved insulin sensitivity [30].

In addition to its effects on insulin sensitivity, kaempferol may also enhance insulin secretion. Wronka et al. demonstrated that kaempferol enhances glucose-stimulated insulin secretion by influencing mitochondrial Ca2+ uptake in pancreatic β-cells [31]. This effect may be particularly relevant in individuals with T2DM who have impaired glucose-stimulated insulin secretion [32]. kaempferol increases insulin secretion, by increasing the activity of PI3K, and increases glucose uptake by muscle and fat cells by increasing the production of glucose transporters [28].

However, it is important to note that the effects of kaempferol on insulin resistance and secretion may vary depending on the experimental conditions and the specific study population. Some studies have shown that kaempferol is more effective in improving insulin sensitivity in obese or insulin-resistant animals [33], while others have found more modest effects in lean animals [34-36]. These discrepancies may be due to differences in dosage, duration of treatment, or the presence of other confounding factors.

Protective Effects of Kaempferol against DM Complications

Kaempferol enhances the pathogenesis of diabetes and its complications by regulating glucose metabolism, hepatic enzyme activity, and lipid profiles. Its role in combating the complications of diabetes mellitus is more significant than that of other treatment methods [37].

Diabetic- Induced Hepatic Damage

Kaempferol exerts various effects on the body's metabolic system through multiple molecular and cellular mechanisms. According to Raghad Khalid AL-Ishaq's study (2019), the regulation of glucose metabolism, hepatic enzyme activity, and lipid profiles contributes to the improvement of diabetes pathogenesis [32]. Several previous studies have demonstrated that this compound possesses hepatoprotective properties. For instance, pretreatment with kaempferol in rats induced by CCl4 restored hepatic enzyme activity and reduced liver damage in acetaminophen-treated rats by enhancing SIRT1 activity [26]. In Hana Alkandahri's study, it was reported that kaempferol significantly enhanced hepatic glucose production and improved overall insulin sensitivity [20]. Kaempferol could notably improve blood glucose control in mice with obesity, which was linked to decreased hepatic glucose generation and enhanced insulin sensitivity, all with no effect on food intake, body weight gain, or fat accumulation [14]. Treatment with kaempferol increased the activity of Akt and hexokinase while reducing the activity of glucose-6 phosphatase and pyruvate carboxylase (PC) in the liver, although it did not change their protein expression levels. Kaempferol did not impact body composition, food consumption, or liver triglyceride metabolism in either obese or lean mice. The anti-diabetic effects of kaempferol are not merely secondary effects resulting from changes in these metabolic parameters [17]. Kaempferol and its derivatives show promise as potential treatments for liver disease. One study indicates that kaempferol is involved in regulating apoptotic mediators [14]. Kaempferol protects pancreatic β-cells by inhibiting β-cell apoptosis, promoting cell proliferation, and increasing the count of islet β-cells through many mechanisms. These effects are highly beneficial for the treatment and prevention of T2DM [38]. The results of this section show that Kaempferol reduces liver enzymes and improves liver glucose production and generally has protective effects on the liver.

Diabetic Vascular Inflammation and Endothelial Dysfunction

Numerous flavonoids can reduce inflammation both in vitro and in vivo. Research indicates that flavonoids lower the production of eicosanoids by inhibiting the activities of phospholipase A2 (PLA2), cyclooxygenase (COX), and lipoxygenase (LOX) [39]. Furthermore, flavonoids act as inhibitors of phosphodiesterase and protein kinases, release histamine, and modulate gene transcription, contributing to their anti-inflammatory effects [40]. Kaempferol is an active and important natural anti-inflammatory compound [19]. Kaempferol can protect against cardiovascular diseases due to modulating the function of vascular endothelium, antioxidant and anti-inflammatory properties [12], induction of nitric oxide production and vascular expansion, inhibition of platelet hyperactivity, inhibition of proliferation, and angiogenesis have a protective effect. Kaempferol reduced the expression of inflammatory adhesion molecules within cholesterol [9]. The above results revealed the anti-inflammatory impacts of kaempferol through several different mechanisms, which ultimately can prevent vascular diseases like heart disease and DM.

Diabetic- Induced Neuropathy

Both human and animal studies have demonstrated that kaempferol can decrease OS, lower hyperglycemia, and help prevent diabetic complications, like diabetic retinopathy, nephropathy, and peripheral neuropathy. In diabetic rats, kaempferol corrected hyperglycemia and partially alleviated pain reactions by modulating nitrative and oxidative stress, as well as decreasing the formation of advanced glycation end products (AGEs) [41]. Kaempferol may be advantageous in chronic diabetes, slowing the progression of diabetic neuropathy and potentially aiding in the management of diabetic neuropathic pain [42]. Similarly, research indicated that treating diabetes with kaempferol (at 25, 50, and 100 mg/kg/day orally) decreased the onset of diabetic nephropathy (DN) and diminished pain sensations [16]. Kaempferol also lowered circulating concentrations of oxidants and cytokines in mice while mitigating the development of diabetic neuropathy and related pain sensations [9]. Ultimately, it can be concluded that kaempferol slows the progression of diabetic neuropathy through various mechanisms, with the most significant factor being the reduction of blood glucose levels over the medium to long term.

Diabetic- Induced Nephropathy

Based on research, non-enzymatic glycosylation of proteins is the main cause of diabetic problems as well as cardiovascular disorders, retinopathy, nephropathy and neuropathy [14]. Antioxidants seem to have effective inhibitory effects on glycosylation of proteins. Flanoids like kaempferol are one of these antioxidants. Flavonoids have inhibitory effects on the consequences of diabetes and their consumption can prevent the occurrence of many problems in diabetic people [16]. According to a study by Dilip Sharma (2019), there is substantial experimental evidence indicating that dietary kaempferol inhibits RhoA/Rho Kinase and may serve as a potential therapeutic agent to alleviate kidney damage caused by diabetes or high glucose levels [40]. Noroozi *et al*. noted that the beneficial effects of flavonoids are due to their ability to enhance intracellular vitamin C levels, decrease capillary permeability and rupture, and enhance the immune system, all of which contribute to lowering the risk of diabetes-related complications [43]. Kaempferol has been shown to reverse renal fibrosis by inhibiting OS and inflammation while promoting autophagy in renal podocytes, thereby reducing renal cell damage [28]. Kaempferol acts through multiple targets and pathways in the treatment of DN, particularly through its anti-OS and anti-inflammatory properties, which are linked to apoptosis, glomerular protection, and kidney fibrosis [22]. Furthermore, the protective effects of kaempferol against DN highlight the potential of flavonoids in treating this condition [19]. In conclusion, kaempferol plays a versatile and multi-faceted role in the management of diabetic nephropathy, a major complication of diabetes.

Other Effects of KM

The effect of kaempferol is observed in the changes in mRNA expression levels of connective tissue growth factor (CTGF) and fibronectin in NRK-52E and RPTEC cells exposed to high glucose conditions [40]. The consumption of kaempferol, which has high antioxidant activity, cleans free radicals. The data shows the studies of different flavonoids on the damage caused by ischemia-reperfusion it reduces and this is done by interfering with the activity of nitric oxide synthase, and it causes vasodilation [19], xanthine oxidase plays a role in the path of oxidative damage, especially after ischemia-reperfusion [38]. Xanthine oxidase is a source of free radicals in the reperfusion phase. Oxygen molecules react and lead to the release of superoxide free radicals [32]. Flavonoids have the ability to inhibit xanthine oxidase and protect the body against oxidative damage resulting from ischemia-reperfusion [44]. Due to its unique features in antioxidant processes, the ability to trap free radicals using various methods such as nitric oxide and xanthine oxidase, and various therapeutic effects such as anti-arteriosclerosis effects [45], Kaempferol as a flavonoid has received much attention from researchers. Paraoxonase-1 is a calcium-dependent enzyme that associates with HDL and prevents atherosclerosis by inhibiting LDL oxidation. Various antioxidants, including flavonoids, have been shown to enhance the activity of the paraoxonase enzyme [46]. Kaempferol exhibits beneficial effects against liver damage, obesity, cancer, and diabetes; it also protects cranial nerve function, suppresses vascular endothelial inflammation, and supports heart health, making it a potential treatment for fibroproliferative disorders such as hypertrophic scars [47]. Furthermore, an analysis of kaempferol's effects on apoptosis and DNA damage demonstrated its ability to effectively inhibit the proliferation of the triple-negative breast cancer cell MDA-MB-231, with a stronger effect observed in these cells compared to the estrogen receptor-positive BT474 cell line. Thus, kaempferol could be a promising candidate for the effective treatment of breast cancer [48]. The above findings indicate that due to its unique properties in antioxidant processes, kaempferol has the ability to trap free radicals using different methods and can prevent other diseases that may occur with diabetes, including heart diseases and different types of cancer.

How to Use, Toxicity and Cautionary Notes

Kaempferol's limited bioavailability and poor water solubility hinder its widespread use in clinical settings [13]. The amount of this flavonoid naturally absorbed by the human body is only 1–2 grams per day, resulting in plasma concentrations within the micromolar range. Nevertheless, kaempferol can significantly enhance mitochondrial Ca2+ uptake by approximately 85% at concentrations as low as 1 mm [19]. There are two potential strategies to improve kaempferol's bioavailability. The first involves binding kaempferol to another substance that has a higher affinity for the transporter protein, which facilitates the transport of compounds with greater affinity out of the cell while allowing those with lower affinity to remain and exert their effects [14]. The second strategy utilizes nanocarriers to enhance permeability and achieve systemic circulation by coating kaempferol with nanoparticles [15]. According to research, administering kaempferol for 28 days did not reveal any clinical signs of toxicity, nor were there any treatment-associated alterations in body or organ weights compared to the control group [19]. Additionally, hematological parameters like white blood cell count, red blood cell count, platelet count, hemoglobin (Hb) levels, hematocrit, mean corpuscular hemoglobin concentration, red cell distribution width, and platelet distribution width showed no significant changes between the treated groups and the control [49]. Increased consumption of kaempferol may decrease iron bioavailability and/or lower folic acid levels in cells, potentially leading to adverse effects in patients with deficient iron and/or folic acid levels [50]. Kaempferol can be carcinogenic and toxic; however, these effects have not been observed in in vivo studies [51]. One study involved the oral administration of kaempferol over a period of 540 days, concluding that there was no increase in tumor incidence. It was suggested that the low oral bioavailability of kaempferol mitigated any genotoxic effects [52]. Additionally, kaempferol has been reported to be contraindicated for patients with folic acid and iron deficiencies, as it decreases their bioavailability and cellular uptake. Furthermore, kaempferol is also contraindicated for cancer patients undergoing etoposide therapy, as it can interfere with the drug's bioavailability [53]. The results of this section show that there is still no proper way to use kaempferol, and there is a need for more research in this field. On the other hand, this substance may have side effects that are unknown, and more clinical research is needed in this field.

CONCLUSION

In summary, this comprehensive review highlights the diverse molecular, cellular, and metabolic effects of kaempferol relevant to diabetes management. Kaempferol has demonstrated the ability to improve glucose metabolism, enhance insulin sensitivity, protect pancreatic β-cells, and mitigate diabetic complications through various mechanisms, including AMPK activation, antioxidant activity, and anti-inflammatory effects. However, there are several limitations that warrant consideration. The existing evidence is primarily based on preclinical studies, and more well-designed, large-scale clinical trials are needed to confirm the efficacy and safety of kaempferol in humans with diabetes. Further research is also needed to elucidate the optimal dosage and formulation of kaempferol, as well as to identify potential drug interactions. Additional studies are also needed to explore the potential of kaempferol as a preventive agent for individuals at high risk of developing diabetes. Despite these limitations, the findings of this review suggest that kaempferol holds promise as a potential therapeutic agent for diabetes. With further research, kaempferol may one day be incorporated into clinical practice as a valuable tool for preventing and managing this chronic disease.

Conflict of Interest

The author declares no known competing interest.

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Not applicable.

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