Chapter

Antidiabetic Principle in *Cucumis sativus* L.

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Abstract

Diabetes is one of the leading cause of death globally. One of the strategies towards managing diabetes is the antidiabetic drugs which has recorded a huge success but accompanied with different degrees of side effect, hence, the use of natural plants products is encouraged. Several reports of antidiabetic medicinal plants have flooded literature but few has led to identification of active ingredient in such. *Cucumis sativus* is one of such plants reported to have antidiabetic property but there is little or no data on the active agent. This chapter therefore provides report on the active principle and mechanism of action underlying the antidiabetic activity of *C. sativus.*

Keywords: diabetes, *Cucumis sativus*, flavonoids, kaempferol

1. Introduction

Diabetes is a disorder where the body cells cannot use glucose effectively due to low insulin (Type 1 diabetes) or insulin insensitivity (Type 2 diabetes), therefore the blood glucose level increases [1]. It is characterized by a fasting blood glucose level higher than 126 mg/dL. It is one of the top 10 causes of death globally. About 463 million adults are living with diabetes; by 2045 this will rise to 700 million and Diabetes caused 4.2 million deaths in 2019 [2].

In 2017, total estimated cost of diagnosed diabetes in the U.S. was $327 billion [3].

Some complications of diabetes are oxidative stress, dyslipidaemia, endoplasmic reticulum (ER) stress [4, 5], retinopathy [6], neuropathy [7], nephropathy [8], cardiovascular complications [9], and ulcerations [10].

The management of diabetes has involved many approaches in order to enhance the availability of insulin, boost insulin sensitivity and reduce alpha glucosidase activity [11].

From research, people with excess weight can greatly manage diabetes by engaging in moderate and considerate weight loss plan, also exercise can help control blood sugar levels, reduce glycated hemoglobin and reduce insulin resistance.

Antidiabetic drugs are pharmacological substances that are employed in treating hyperglycemia when life style modifications do not bring desired effects [12]. They are categorized into different classes and they work either to enhance synthesis of insulin or reduce blood glucose level using different strategies.

These antidiabetic drugs are very effective in treating hyperglycemia, but despite this success, there has been increased side effects accompanying their use. Therefore, there is increased search for antidiabetic agents from medicinal plants with little or no adverse effects. Experimental reports have validated the presence of antidiabetic substances in medicinal plants [13–15]. One of such plants reported to have antidiabetic property is *Cucumis sativus*. Saidu *et al*.'s study reported the hypoglycemic property of methanolic fruit pulp extract of *Cucumis sativus* [16].

This chapter focuses on the antidiabetic principle identified in *Cucumis sativus* L.

2. Flavonoids

Flavonoids are a class of plants secondary metabolites made up of polyphenolic structures that contribute to the color and fragrance of fruits and flowers, therefore, they constitute a significant part of the human diet [17]. As a large class, flavonoids are subdivided into groups based on the structure of their carbon rings and these include flavanols, flavones, chalcones, flavonones, flavanonols and isoflavones. They are abundantly distributed in vegetables, fruits and some beverages. Flavonoids possess a wide range of health-promoting properties like the antioxidant effect, anti-carcinogenic, anti-inflammatory and antidiabetic capabilities. They display these properties by modulating the functions of some cellular enzymes as well as inhibition of different enzymes like lipo-oxygenase, cyclo-oxygenase, phosphoinositide 3-kinase and xanthine oxidase [18, 19]. Therefore, they are indispensable components in various pharmaceutical, cosmetics and medicinal applications. One of the flavonoids that possesses antidiabetic property is kaempferol.

3. *Cucumis sativus* L.

Cucumis sativus L. also known as Cucumber is a creeping plant in the family Cucurbitaceae. It is a fruit native to India and widely cultivated around the world. It is consumed fresh in salads, fermented (pickles) and as cooked vegetable [20].

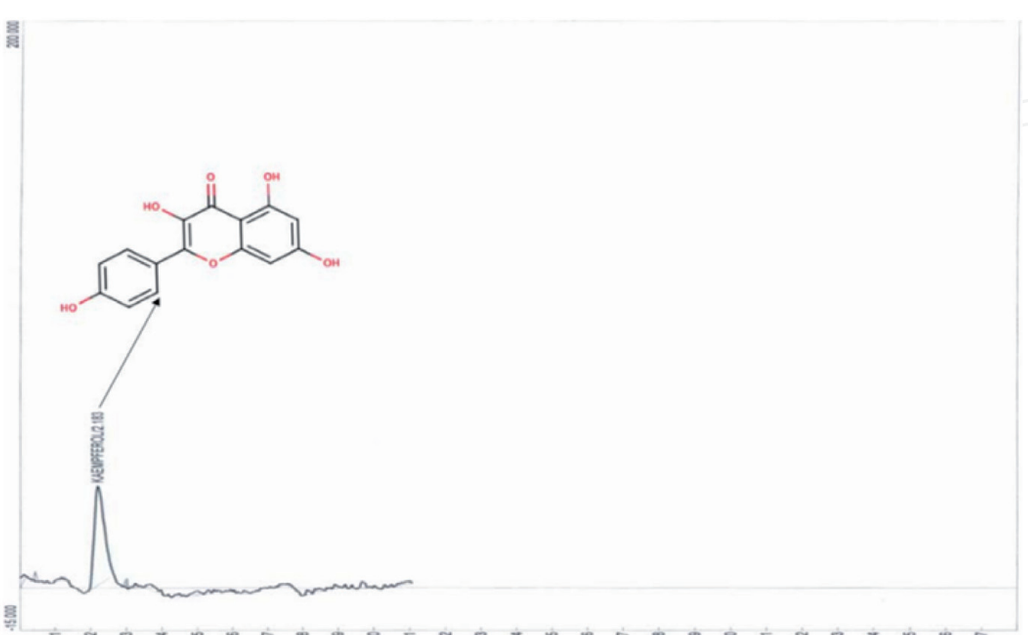

Figure 1.
High pressure liquid chromatographic profiling of the antidiabetic principle derived from Cucumis sativus fruit juice.

Cucumis sativus L. as a fruit, in addition to its nutritional value, has been reported to have some biological activities as anti-aging [21], antioxidant [22], and antidiabetic [23]. These properties have been linked to the presence of some phytochemical substances detected in *Cucumis sativus* L. like cucurbitacins [24], ascorbic acid [25], cucumerin, apigenin [26], lutein [27], quercetin 3-O-glucoside and kaempferol 3-O-glucoside [28].

Recent studies validated the presence of antidiabetic agents in *Cucumis sativus L.*

Ibitoye *et al* [29] identified the antidiabetic agent in *Cucumis sativus* L. as a flavonoid called kaempferol using HPLC (**Figure 1**).

4. Kaempferol

Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one also known as kaempferol-3, **Figure 2**) is a yellow crystalline flavonoid having a molecular weight of 286.23 with a melting point of 276–278 °C. It is soluble in hot ethanol and slightly soluble in water.

It has been isolated from different parts of different plants. Yang *et al*. separated kaempferol and its derivatives from the methanolic crude extract of *Neocheiropteris palmatopedata* by repeated column chromatography, using a Sephadex LH-20 column [30]. Orhan et al. reported the bioactivity-guided fractionation of *Calluna vulgaris* and isolated kaempferol galactoside using successive column chromatography techniques [31]. Ibitoye et al. also reported the bioactivity guided isolation of kaempferol from *Cucumis sativus* L. [26].

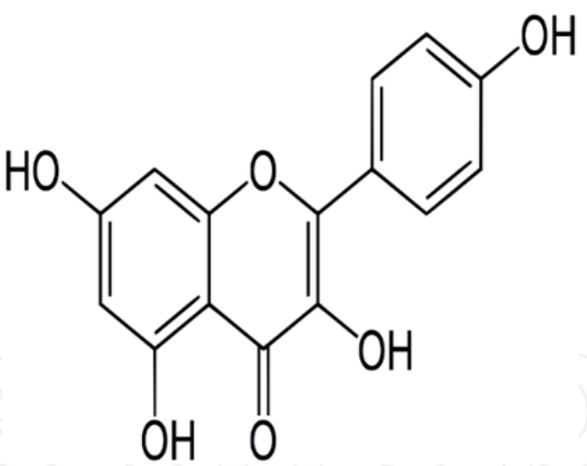

Figure 2.
Structure of Kaempferol.

5. Biosynthesis of kaempferol

Kaempferol and its derivatives are synthesized in plants by different types of enzymes. Kaempferol is synthesized by condensation of 4-coumaroyl-CoA with tripropionyl-CoA to produce naringenin chalcone, this reaction is catalyzed by chalcone synthase [32]. Naringenin chalcone is then converted into a flavanone called naringenin, which is thereafter hydroxylated by flavanone 3-dioxygenase to produce dihydrokaempferol [33]. Finally, the introduction of a double bond at the C2-C3 position of dihydrokaempferol produces kaempferol.

There is no much data on the pharmacokinetics of Kaempferol, however, flavonoids are extensively metabolized by the colonic microflora [34, 35].

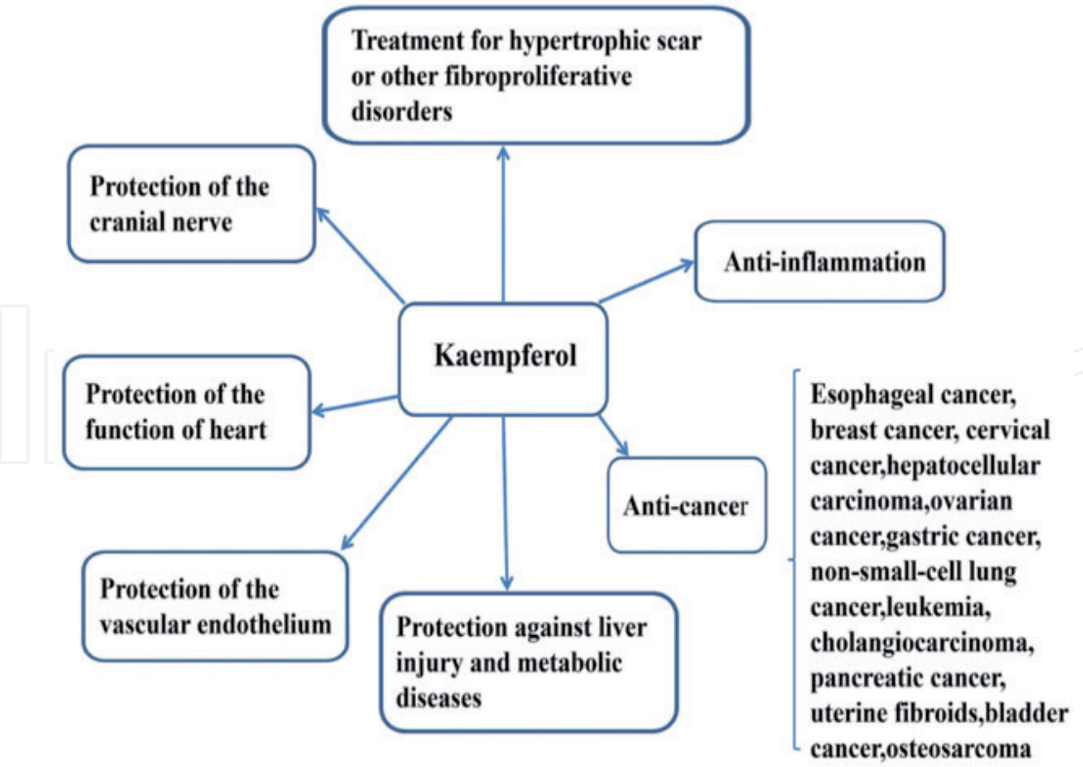

Figure 3.
Biological roles of Kaempferol.

Intestinal permeability study of kaempferol shows it undergoes significant biotransformation, with only a small fraction of the unchanged kaempferol able to cross the intestinal barrier [36].

It has been isolated from tea as well as common vegetables and fruits like beans, broccoli, cabbage, grapes, strawberries, tomatoes, apples and grapefruit [37].

Kaempferol has anti-inflammatory and anti-cancer properties, protects the liver and prevent metabolic diseases (**Figure 3**). The most well-known of its properties are its anti-inflammatory effects by decreasing lipopolysaccharide (LPS)-induced tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) expression and also by increasing the number of activated macrophages [38]. Kaempferol is a dietary flavonoids that occur in fruits, vegetables, beverages, chocolates, herbs and plants [39] and reported to possess anti-diabetic property.

6. Mechanism of antidiabetic action of kaempferol

Kaempferol has been reported to lower blood glucose [40], inhibit α -amylase and α -glucosidase [41]. This section addresses the mechanism of action of Kaempferol under the following headings.

7. Inhibition of α-amylase and α-glucosidase enzymes.

α-Amylase and α-glucosidase are carbohydrate hydrolyzing enzymes located in the digestive tract. α- amylase in the duodenum initiates digestion and catalyzes the hydrolysis of α-1, 4 glycosidic linkages in starch resulting into sugars such as maltose, maltotriose and branched oligosaccharides. Then, α-glucosidase present in the brush border of the intestinal epithelium (enterocytes) is responsible for the final step of carbohydrates digestion, prior to their absorption. This enzyme cleaves

terminal non-reducing 1, 4 linkages and converts the disaccharides and oligosaccharides into glucose, which is then transported by sodium/glucose co-transporter 1 (SGLT1) from the intestinal lumen to the cytosol of enterocytes. In turn, glucose transporter 2 (GLUT2), found in the basolateral membrane of enterocytes, transports glucose from cytosol to blood via facilitated diffusion.

One of the approaches to managing diabetes is to delay the absorption of glucose by the inhibition of carbohydrate hydrolyzing enzymes in the digestive tract of humans [42, 43].

Controlling the activity of these enzymes slows glucose production in the postprandial stage and this could be a therapeutic approach for people with diabetes. Hence, the search for inhibitors from medicinal plants is a great development [44].

Ibitoye et al. identified that kaempferol from *Cucumis sativus L*. lowers blood glucose and inhibited the activity of α -amylase and α glucosidase at IC_{50} of 51.24 and 29.37 μg/mL respectively [29]. This inhibition means reduction in blood glucose in the postprandial stage of alloxan-induced diabetic rats when given 165 mg/kg body weight of kaempferol from *Cucumis sativus* fruits. This evidently supports that kaempferol lowers blood glucose and inhibit α-amylase and α -glucosidase.

It may be possible that the glucose lowering activity of *C. sativus* fruits is through inhibition of α -amylase and α -glucosidase through kaempferol.

8. Maintaining glucose homeostasis

Diabetes features dysregulated glucose metabolism characterized by increased hepatic glucose production and decreased glucose oxidation. This eventually leads to deterioration in glucose control. Alkhalidy *et al* reported that kaempferol ameliorate hyperglycemia and enhance glucose tolerance in insulin deficient mice [45]. Diabetic mice displayed significantly higher pyruvate carboxylase activity. Kaempferol treatment suppressed the elevated pyruvate carboxylase activity and glucose-6 phosphatase activity in the liver suggesting that kaempferol may improve glycemic control in diabetes in part through suppressing gluconeogenesis in the liver via the regulation of pyruvate carboxylase, the first and critical step in gluconeogenesis [45]. It could therefore be a strategy for maintaining glucose homeostasis by targeting the glucose production and metabolic pathways.

9. Modulation of antioxidant profile

Generation of reactive oxygen species and free radicals contributes to the pathogenesis of diabetes [46]. This increased ROS production overruns the cellular antioxidant defense system leading to oxidative stress and damage [47]. Some diabetes research confirm this phenomenon in different diabetes model [48, 49]. Catalase, superoxide dismutase and glutathione are reduced significantly in diabetes [50]. Kaempferol reversed the alterations on oxidative stress markers in alloxan-induced diabetic rats [29].

10. Reversal of lipid profile alterations

One of the complications in diabetes is dyslipidemia, where the lipid profile is disturbed. It is usually presented with elevated levels of total cholesterol TC, triacylglycerol TAG, and low-density lipoprotein cholesterol LDLc and a reduction of high density lipoprotein cholesterol HDLc [51]. These alterations could predispose to developing

atherosclerosis and cardiovascular diseases. Reversal of these alterations in alloxan-diabetic rats suggests its anti-dyslipidemic capability [29]. Alkhalidy et al. observed that untreated diabetic mice had lower total cholesterol, HDL-cholesterol, and LDL-cholesterol levels when compared to non-diabetic mice [45]. Kaempferol treatment reversed these changes to the levels similar to those seen in non-diabetic mice.

11. Maintenance of glycoprotein content

Glycoproteins are carbohydrate-containing proteins found on the cell membrane. They play important roles in membrane transport, cell differentiation and recognition, adhesion of macromolecules to cell surface and also in the secretion and absorption of macromolecules [52]. Impaired metabolism of glycoproteins contributes to the pathogenesis of diabetes [53]. Studies have reported that alterations in concentrations of various glycoproteins contribute to human diabetes [54]. Elevated levels of glycoproteins in diabetic condition could be a consequence of impaired carbohydrate metabolism [55]. Chandramohan *et al*. reported that kaempferol reversed elevated level of hexoses, hexosamines, fucose and sialic acid (glycoprotein componets) in streptozotocin-induced diabetic rats which may be due to the activation of glucose transport mechanism and also alters insulin binding receptor specificity [56].

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