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Hydroxycinnamic acid derivatives as antioxidant food and its implications on management and prevention of Diabetes mellitus

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Abstract
Antioxidant rich foods have been widely used as defenders of the body against excessive oxidative damage and preventing different chronic diseases among them, the Diabetes. In the food industry, the synthetic antioxidants have been widely used to control lipid oxidation and the development of unpleasant flavors. However, the toxic and carcinogenic effects derived from the consumption of some synthetic antioxidants has led many researchers to investigate the use of natural antioxidants made from edible plants. Plant polyphenols are beneficial to human health, exerting various biological effects. Hydroxycinnamic acids are the main category of phenolic acids that can bring important benefits to human health. They are widely distributed in plants and most of their pharmacological properties are a result of their antioxidant action. Moreover, recent studies suggest that derivatives of hydroxycinnamic acid, have antidiabetic properties through several mechanism and without causing side effects. They could represent a new class of antidiabetic agents for the future. This review will address the role of oxidative stress in the pathogenesis of diabetes as well as discuss current knowledge of the biological effects of hydroxycinnamic acid derivatives on the control and prevention of diabetes.

Keywords: phenolic acids, antiradical, antidiabetic, glucose metabolism, oxidative stress, functional foods

1. Introduction

According to WHO, noncommunicable diseases represent the most lethal diseases in the world. Ischemic heart disease and stroke are the leading cause of death in the world over the past 15 years, accounting for 15.2 million deaths in 2016. In addition, diabetes is also listed as a rapidly growing disease and is one of the most serious health problems of the 21st century due to disabling chronic complications and increased mortality of affected individuals [1, 2]. This increase in the number of people with noncommunicable diseases has led to an increase in the demand for nutritious foods. The consumption of biologically active ingredients in fruits and vegetables has been linked with the fight against cancer, cardiovascular disease, obesity, diabetes and disorders of the gastrointestinal tract. In addition, these foods offer an excellent opportunity to improve the public health; hence these compounds have received much attention in recent years from the scientific community, consumers, and food manufacturers [3, 4].

Plants are potential sources of natural bioactive compounds such as secondary metabolites, which have several pharmacological properties. One of the most important groups of secondary metabolites of plants are phenolic compounds or polyphenols [5]. They are widely distributed in plants and form part of the human diet. They have been much studied due to their pharmacological activities. In food, polyphenols may contribute to the bitterness, astringency, color, flavor, odor and oxidative stability [6, 7]. Plant polyphenols are natural antioxidants and most of their pharmacological properties are due to their antioxidant action [6, 8].

Phenolic compounds are constituted by a large amount of substances, among them the phenolic acids. These compounds form a diverse group that includes the widely distributed hydroxybenzoic and hydroxycinnamic acids and derivatives. Hydroxycinnamic acids are a major category of phenolic acids that may provide important benefits as antioxidants. They are widely distributed in plants and their products such as fruits, vegetables and grains [9]. Their antioxidant activity seems to be related to their molecular structure, more precisely to the presence and number of hydroxyl groups, and to double bond conjugation and resonance effects [8].

It is believed that hydroxycinnamic acids, when consumed and absorbed in ideal amounts, may aid in the reduction or neutralization of ROS formation thereby reducing the deleterious effects of these compounds on the organism (8). Experimental and clinical studies report that oxidative stress plays an important role in pathogenesis and in the development of complications of both types of diabetes mellitus. In addition, recent studies reveal that the chlorogenic acid, a phenolic acid, belongs to the hydroxycinnamic acid family appears to have hypoglycemic effects like metformin, improving resistance to insulin and other oral agents, such as glitazones, increasing glucose uptake, apparently without side effects [10,11].

Therefore, considering the antioxidant properties of the hydroxycinnamic acid family and its probable ability to improve glucose homeostasis, this review focuses on discussing the role of oxidative stress in the pathogenesis of diabetes and to demonstrate the influence of the antioxidant properties of hydroxycinnamic acid derivatives on the management and prevention of diabetes.

2. The role of oxidative stress on the pathogenesis of Diabetes Mellitus

Free radicals or reactive species (RS) are reactive chemical entities that containing one or more unpaired electrons. There are several groups of RS such as:

- RS of oxygen or ROS

- Superoxide anion radical ($O_2^{-•}$),
- Hydroxyl radical ($OH^•$)
- Hydrogen peroxide
- Alcoxilla ($RO^•$)
- Peroxyl ($ROO^•$)
- Perhydroxyl ($HOO^•$)
- Oxygen singlet ($^1O_2$)

- Transition Metals Complexes

- Fe^{+3} / Fe^{+2}
- Cu^{+2} / Cu^{+}

- Radicals of Carbon

- Trichloromethyl ($CCl_3^•$)

- Sulfur Radicals

- Thiol ($RS^•$)

- Radicals of Nitrogen (RNS)

- Phenyldiazine (C_6H_5 N = $N^•$)
- Nitric oxide ($NO^•$), [7].

RS can be produced by endogenous or exogenous sources. In the body, they can be generated as a consequence of the normal metabolism of the cell, being important for various physiological functions. Free radicals are constantly produced and eliminated from the body. This is thanks to a finely regulated system to maintain very low levels of ROS, that is, its production and disposal are well balanced. However, under certain circumstances, this balance can be disrupted for a number of reasons, such as: increasing of the level of endogenous and exogenous compounds that go into self-oxidation together with ROS production; depletion of low molecular weight antioxidant reserves; decreased or inactivation of antioxidant enzymes; and finally certain combinations of two or more of the factors listed above, which could cause disruption of cellular metabolism and regulation, as well as damage to cellular constituents, leading to oxidative stress [12].

The high consumption of hypercaloric diets leads to an increase in ROS production that induces oxidative stress. In addition to this, this type of di*et al*so cause the rise in blood glucose, which also leads to an overproduction of ROS by mitochondria [7, 13].

Another consequence of diabetic hyperglycemia is the formation of glycation end products (AGEs), which may play a deleterious role to the body [14, 15]. AGEs constitute a wide variety of molecules formed from non-enzymatic amino carbonyl interactions between sugar or lipid reducers and oxidized proteins, aminophospholipids or nucleic acids. The formation of AGEs under physiological conditions occurs slowly and plays an important role in the aging process. However, the formation of AGEs is accelerated under conditions of hyperglycemia or oxidative stress. Some cells, such as monocytes and macrophages, have receptors of AGEs (RAGEs) on their membrane [16]. The interaction between AGEs and RAGEs activates a secondary pathway of signal transduction, such as protein kinase C (PKC). The main target of AGEs signaling is the nuclear transcription factor, NF-kB, which is translocated to the nucleus, resulting in increased transcription of numerous proteins. The NF-kB is found in all cell types and is involved in cellular responses to stimuli such as stress, free radicals, ultraviolet radiation, viral or bacterial antigens. The activation of NF-kB can trigger pro or antiapoptotic cascades, but in β-cells its action is predominantly pro-apoptotic. Furthermore, the NF-kB and its target genes, such as TNF, IL-1 and IL-6, are known to be essential in the development of insulin resistance [17, 18].

Diabetes also induces changes in the activity of glutathione peroxidase and glutathione reductase enzymes, which are found in cells that metabolize peroxide in water and convert glutathione disulfide to glutathione [19]. Any change in their levels will make the cells prone to oxidative stress and, consequently, to cell damage [20].

Studies also suggest that hyperglycemia induces deficiency in the production of catalase (CAT), an enzyme that regulates the metabolism of hydrogen peroxide. Thus, in catalase deficiency, the beta cell of the pancreas, which contains many mitochondria, undergoes oxidative stress, producing even more ROS, leading to pancreatic b-cell dysfunction, ultimately, to diabetes [19, 20].

In order to combat deleterious effects of oxidative stress on the body, endogenous antioxidants are used to neutralize the high number of free radicals and keep cells protected against their toxic effects and contributing to disease prevention [21]. Antioxidant enzymes include superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT), which play a vital role in eliminating these oxidants and prevent cell lesions [22]. However, plants are also excellent sources of natural antioxidants [23-27]. Subsequently, it will be discussed the compounds derivatives of hydroxycinnamic acid, with special emphasis on its chemical composition, antioxidant effects, its influence on glucose metabolism and possible implications on management and prevention of diabetes and its complications.

3. Hydroxycinnamic acid derivatives

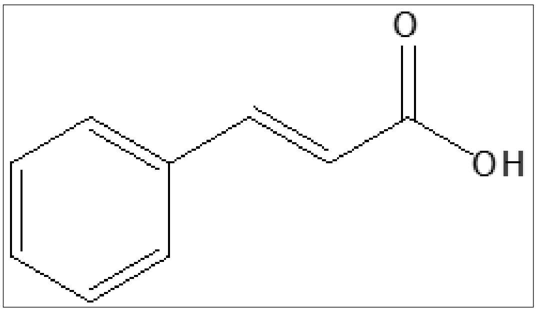
3.1. Source and chemical structure of hydroxycinnamic acid derivatives

The hydroxycinnamic acids derivatives are aromatic compounds with to three-carbon side chain (C6-C3) [28]. Among the most common and well-known hydroxycinnamic acids derivatives are cinnamic acid, *o*-coumaric acid, *m*-coumaric acid, *p*-coumaric acid, caffeic acid, ferulic acid and synapic acid (Fig. 1). These compounds may occur as free carboxylic acids or esters formed by condensation with hydroxylic acids such as quinic and tartaric acid, flavonoids or carbohydrates. They also occur as amides, formed by the condensation of parent acid with an amino acid or an amine [9]. Chlorogenic acid (Fig. 1) which is formed by the condensation of caffeic acid with quinic acid (5-*O*-caffeoylquinic acid) is probably the most abundant soluble hydroxycinnamic acid derivatives [7, 9].

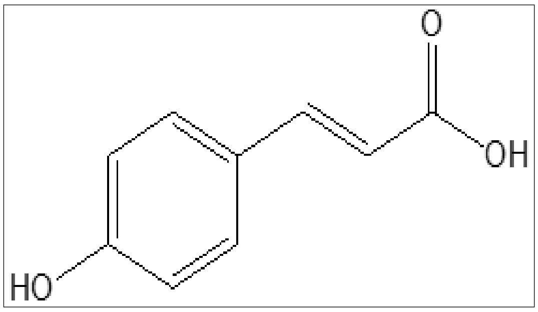
The hydroxycinnamic acids derivatives are the most widely distributed phenolic acids in plants. They have been found in most plant families, including many species that are consumed as food or made into beverages and found in medicinal plants. They represent one of the most abundant secondary metabolites present in the great majority of fruits, being found in higher concentrations in the immature fruits, since the concentration of these compounds tends to reduce with the maturation of the fruits [9, 24].

The hydroxycinnamic acid derivatives are the most abundant antioxidants in our diet and this has generated great interest from both scientists and the food and consumer industry [6, 9, 24, 27]. The main consumption of the hydroxycinnamic acid derivatives comes mainly from the consumption of coffee, fruits (fresh or juice), cereals and teas [9].

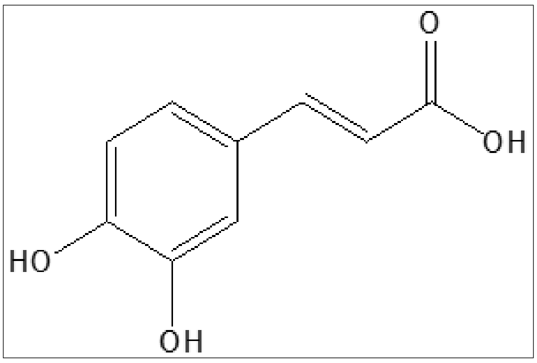
Caffeic acid, as well as other caffeoyl quinic acid derivatives, is potentially present in coffee. In addition, it is also found in important concentrates in apples, pears, berries, artichokes, eggplant and in wines. Ferulic acid is particularly abundant in cereal grains. Chlorogenic acid is also present in high amounts in coffee and in various medicinal plants. The association between caffeic-, *p*-coumaric- and chlorogenic acid is beneficially found in a variety of teas. The high intake of hydroxycinnamic acid derivatives in the diet have proven several health benefits [6, 9].



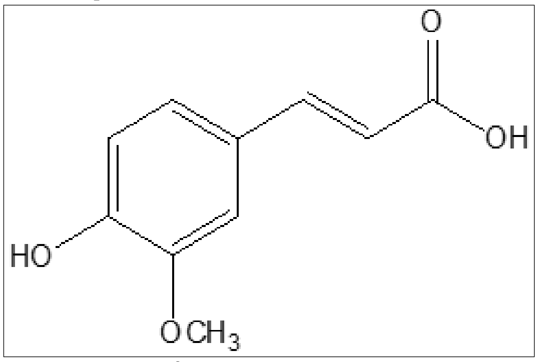
Cinnamic acid



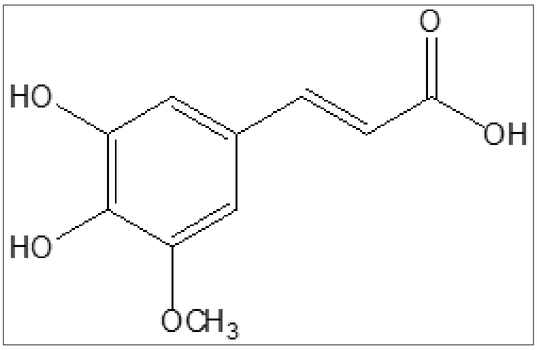
p-coumaric acid



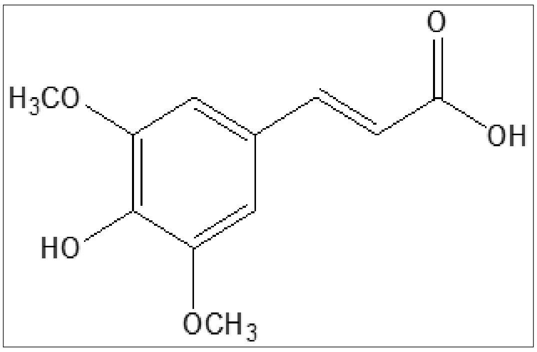
Caffeic acid



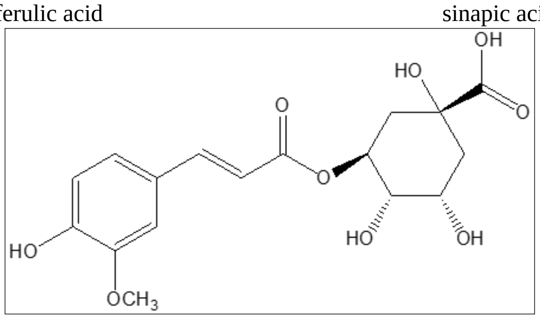
ferulic acid



5-hydroxyferulic acid



sinapic acid



Chlorogenic acid

Fig 1: Cinnamic acids commonly found in plants and ester of quinic acid with shikimic acid (chlorogenic acid)

3.2. Hydroxycinnamic acid derivatives as antioxidant

Antioxidants are able to counteract the effects of oxidative stress through two mechanisms: the first involves the inhibition of the formation of free radicals that enable a step of initiation; the second comprises the neutralization of free radicals in the propagation stage, through the donation of hydrogen atoms to these molecules, interrupting the chain reaction [7]. The hydroxycinnamic acid derivatives act as radical scavengers and sometimes as metal chelators. The antioxidant capacity of these compounds seems to be related to their molecular structure, more precisely to the position and the number of hydroxyl groups, as well as the nature of the substitutions in the aromatic rings [8, 28]. The highest antioxidant potential among the compounds of this group

was found in caffeic acid by the presence of two hydroxyls in the 3 and 4 positions [7]. This confirm the relationship between structure-activity of this phenolics compounds [28].
In addition, several authors have reported that the derivatives of hydroxycinnamic acid are potent inhibitors of low-density lipoprotein (LDL) oxidation. This type of oxidation is considered to be a key mechanism to development of atherosclerosis [6]. Regarding foods, lipid peroxidation leads to rapid development of rancid and stale flavors and it is considered a primary mechanism of quality deterioration in lipidic foods and oils [29, 30].
Because of this proven natural antioxidant potential, many researchers are interested in studying the derivatives of hydroxycinnamic acid in order to find an ideal substitute for synthetic antioxidants, since these are toxic and carcinogenic [7, 29]. A diet rich in derivatives of hydroxycinnamic acid can significantly increase the body's antioxidant potential by protecting it against diseases triggered by oxidative stress. In addition, these natural antioxidants can also be used to improve food preservation [28-30]. In this context, caffeic acid, for example, has been used as a natural antioxidant to inhibit the oxidation of fishes lipids present in different food matrices and also as bioactive food packaging [29, 31].
As described above, the antioxidant activity of hydroxycinnamic acid derivatives is widely documented in the literature, and its use as food and as food preservatives is a very promising strategy for the prevention of various diseases, such as diabetes.

3.3. Influence of the chemical structure and antioxidant properties of hydroxycinnamic acid derivatives in the control and prevention of diabetes

The process of maintaining blood glucose at a steady state is called glucose homeostasis. One of the results of glucose homeostasis deficiency is hyperglycemia (high blood sugar levels), that over a long period of time leads to the onset of manifestations of diabetes and its complications [32]. Failures in glucose metabolism may also lead to hypoglycemia (low blood sugar levels), which also interfere in the functioning of organ systems. In fact, hypoglycemia is a common consequence of diabetes treatment: low blood glucose levels occur most often in people who use insulin or oral hypoglycemic agents to lower their blood sugar [33-35].
Nowadays, there are several classes of oral antidiabetic agents to improve the glucose homeostasis. However, they are not able to provide stable, durable and safe glycemic control [36]. For this reason, the American Diabetes Association (ADA) recommends, when necessary, the use of two or more oral hypoglycemic agents in combination with the management of glucose levels [37]. Current oral antidiabetic drugs use different mechanisms of action to control glycemia, such as: increasing insulin secretion, inhibiting hepatic gluconeogenesis, increasing insulin receptor sensitivity, reducing carbohydrate digestion and inhibiting glucose reabsorption in proximal convoluted tubules [38].
Due to the absence of an ideal drug for the management of diabetes and its complications, many researchers have investigated the benefits of hydroxycinnamic acid derivatives in search for an effective and safe hypoglycemic agent. Surveys have shown that besides of the antioxidant potential present in the derivatives of hydroxycinnamic acid, they also have several positive effects on glucose homeostasis through several mechanisms [6, 24, 39-41].
Thus, researchers have demonstrated in experimental studies the secretagogue ability of certain derivatives of hydroxycinnamic acid, such as ferulic acid, caffeic acid, cinnamic acid and also *p*-methoxycinnamic acid. It is believed that these compounds in addition to stimulating insulin production were also able to improve tissue tolerance to glucose without leading to hypoglycemia, as in the specific case of *p*-methoxycinnamic acid [42-44]. Apparently, the presence of meta-hydroxy and para-methoxy groups on ferulic acid was a significantly important substituent as an effective insulin releasing agent [42]. This confirm the relationship between structure-activity of this phenolics compounds [28].
Ferulic acid also has the potential to regenerate the pancreatic cells of streptozotocin-induced diabetic rats and to reduce the apoptosis and the inflammation of these cells due to its antioxidant capacity by reducing pro-oxidant agents such as IL-1 and TGF-1 [45].
The cinnamic acid and its derivatives can also inhibit protein glycation by their antioxidant properties. Thus, in presence of two substituents in cinnamic acid structure, ferulic acid showed ability to protect against glucose-, fructose- and ribose-induced formation of fluorescent AGEs in Bovine Serum Albumin (BSA) [46].
Besides, cinnamic acid can inhibit the activity of α - glucosidase while the chlorogenic and caffeic acids have inhibitory effects on porcine α-amylase. This effect is the result of some structural features of the cinnamic acid, such as the introduction of the hydroxylation at the para-position and meta-position of the cinnamic acid structure. These activities of the hydroxycinnamic acid derivatives have been proved to be one of the most effective strategies to decrease the postprandial rise in blood glucose and in turn help preventing the onset of diabetes and its complications [47, 48].
Thus, all such studies prove that the hydroxycinnamic acid derivatives may be a potent antioxidant and an effective antidiabetic agent.

4. Conclusion

Despite the great variety of oral antidiabetics available, currently no drug is able to provide stable, durable and safe glycemic control to maintain the normal glucose metabolism and prevent the diabetes complications. Several studies have showed the influence of the oxidative stress on the pathogenesis of diabetes and its complications. Therefore, considering that the hydroxycinnamic acid derivatives from natural food have showed excellent antioxidant and antidiabetic activity due to its chemical structure, we suggest that these compounds should be a promising option to the management of diabetes.

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