

## Review of Traditionally Consumed Antidiabetic Fruits in the Diet

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**Abstract:** According to the WHO's report, the risk of diabetes is increasing and one in eleven people now have diabetes. By 2030 the patients with diabetes will increase in a sharp manner like doubling the number nowadays, and so 90% will carry type-2 diabetes. To put the blood glucose level under control, in a stable level with low deviations is the effective way to prevent or delay type-2 diabetes. Hence, the use of traditional herbal supplements and fruit-vegetable extracts stands out and commonly used all over the world in high volumes. The use of traditional herbs has advantage on the lowering the cost of medication, and one another advantage is the avoiding the side effects such as flatulence, diarrhoea, tiredness and upset stomach.

The objective of this review was to evaluate in vitro and in vivo studies (animal and human) of some antidiabetic fruits. Health benefits of the antidiabetic fruits is well-recognized and traditionally consumption of some fruits draw attention for the prevention of type-2 diabetes due to their active hyperglycemic constituents.

The publications cited originate from electronic databases such as Google Scholar, Pubmed, Web of Science, Scopus, Wiley-Blackwell and Springer. Scientific name of the fruits, the words antidiabetic, hypoglycemic and type 2 diabetes were used as keywords for search.

Certain fruits may be used in the management of diabetes (acarbose-like activity) due to some bioactive compounds of fruits such as polyphenols and essential oils, which inhibit digestive enzymes or act as insulin like molecules. This review highlights the benefits of antidiabetic fruits, and active chemical constituents of them. These fruits have significant role in the control of type-2 diabetes.

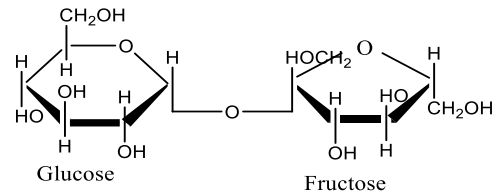
**Keywords:** Antidiabetic Fruit; Hypoglycemic; Type 2 Diabetes; Phenolics; Essential oil

### 1. Introduction

Carbohydrates cover about 56% of the usable energy in the diet (Paulev & Zubieta, 2004). Two or more mono-saccharides combine to synthesize oligo- and polysaccharides. While generating energy oligo- and polysaccharides are catabolized to the monosaccharides. Sucrose is a disaccharide and synthesized by the reaction between glucose and fructose (Figure 1).

Sucrase (EC 3.2.1.48) is an enzyme that catalyze the enzymatic hydrolysis of sucrose in humans. In the studies it was reported that sucrase locates in the intestinal surface of enterocytes and is

released by intestinal microvillus cells (Marieb, 2004). The  $\alpha$ -1,2 and  $\alpha$ -1,4 glycosidic bonds of sucrose are hydrolysed by the active site of sucrase.

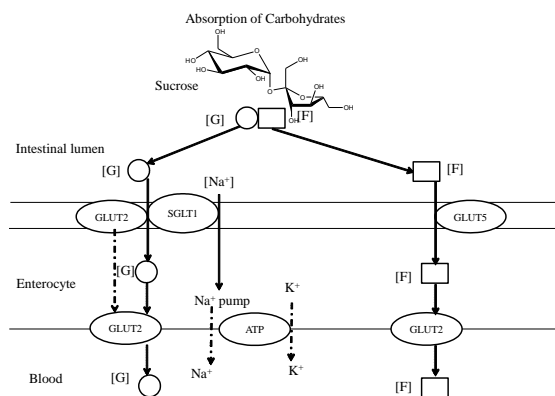


Sucrose

**Figure 1:** Structure of sucrose, maltose and isomaltose.

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There are some transporters which is responsible from transport of liberated glucose and fructose from sucrose. These transporters are the sodium-dependent glucose transporter SGLT1 (active transport) and sodium-independent transporter GLUT2 (facilitated) (Goodman, 2010). Two Na<sup>+</sup> molecules are to be connected to SGLT1, to permit glucose binding to allow glucose to enter the enterocytes (Figure 2). Glucose is also able to be transported through GLUT2 that is present at the basal surface of the intestine. Following that glucose sustains to enter the blood circulation and fructose follows the same path to enter and exit the cells via GLUT2. Following the absorption of postprandial glucose in the blood, it is transported to body cells via the bloodstream (Figure 2). Insulin is secreted from the pancreatic β-cells to maintain the glucose homeostasis in the body and insulin allows uptake of glucose to the muscle and adipose tissues (Leney and Tavare, 2009; Govers, 2014). After hydrolysis of glucose from sucrose post-prandial blood glucose level starts to increase and hydrolyzed fructose is utilized in the liver to generate components such as glucose, glycogen and pyruvate (Törrönen et al., 2010). Hence those metabolism steps may have role in the improvement type-2 diabetes.



**Figure 2** Carbohydrate absorption (Paulev & Zubieta, 2004). G: glucose

In the development of diabetes glucose has significant role. Deficient or impaired insulin signaling results in high blood glucose level hence insulin resistance/deficiency cause type-2 diabetes. The expected glucose level of human is ~4 mM (72 mg/dl). After food intake such as a proper meal, temporarily it may get higher to level <7.8 mM (140 mg/dl) (NICE, 2011). The raise of the blood glucose level has influence on the secretion of the insulin, there after the muscle cells absorb the excess glucose and store as

glycogen (Nelson and Cox, 2000). Accordingly, if the blood glucose becomes to the normal level, the insulin begins to reduce. Because of the shortage in the insulin production or enough production level but ineffective feature of the insulin stimulates the type-2 diabetes. The ineffective insulin is conceptualized as insulin resistance and high blood glucose level is conceptualized as hyperglycemia (Nelson and Cox, 2000).

The International Diabetes Federation (2016) reported that more than 371 million people suffer from the diabetes. Moreover, it is projected that more than 550 million people by 2030 which means 9,5 % of the world population will be having type-2 diabetes (Ogurtsova et al., 2016). One another issue in academic research sheds light onto the medical costs of the type-2 diabetes patients. In the European countries 1/10 of the healthcare costs are for the diabetes (196 billion USD in 2010), and the 2030 projection for these costs are to be 235 billion USD in 2030 (Zhang et al., 2010).

The medication used for the treatment of the diabetes are most commonly drug intake. However, the drugs are used in high amounts all around the world, there are many side effects such as flatulence, diarrhea, tiredness and upset stomach. Acarbose, metformin, sulphonylureas, and glitazones are major components in the chemical drugs which are intaken by the patients. These components have different impact on the blood glucose level. For instance, acarbose puts the control on the glucose level to rise in high level after meals; metformin affects the liver to avoid releasing glucose to the blood; sulphonylureas has impact on the pancreas; and glitazones has impact on the body cells sensitivity.

Herbal treatment is opening another way for the diabetes to avoid the side effects aforementioned. Dabaghian and colleagues (2012) reported that around 3 million diabetic patients in the USA utilized herbal remedies and supporting this case WHO reported that approximately ¾ of the world population prefer traditional herbal remedies for health issues arise. In these cases, daily dietary intake of the humans may help to prevent type-2 diabetes. As the blood glucose level has impact on the diabetes, for the treatment or prevention of the type-2 diabetes, the blood glucose level must be regulated. To decrease the blood glucose level

two different processes can be followed: digestive enzymes for disaccharides can be inhibited and/or inhibition of the glucose transporters (GLUTs and SGLT1) to stop/decrease glucose absorption in the intestine.

Thus, controlling the blood glucose level will decrease the risk of diabetes and related diseases such as obesity, heart disease, damage the kidney, retina and peripheral nerves (Williamson and Carughi, 2010; Hauner et al., 2012).

Most of the people prefer to use plants as they are safer (as they have no side effects compared to synthetic drugs), cheaper and more efficient (Durmuskahya and Ozturk, 2013). Depending on the region different plants and its parts (the whole plant, flower, leaf, bark or fruit) may be used for the treatment of diabetes.

In this review, it was aimed to report antidiabetic activity of fruits that analyzed through *in vitro* and/or *in vivo* methods in the literature. It was discovered that polyphenols and essential oils of some fruits have effect on regulating the sugar level in the blood, and so they can be used to prevent type-2 diabetes. For instance *Sarcopoterium spinosum*, Japanese apricot, *Ficus deltoidea*, *Passiflora ligularis*, *Persea Americana*, *Rosa canina*, *Vaccinium myrtillus*, *Terminalia catappa* L., *Myristica fragrans*, *Pimenta dioica*, *Momordica charantia*, *Sarcopoterium spinosum*, Mango, *Pyracantha fortuneana*, *Chrysophyllum cainito* L., *Pometia pinnata*, *Malus communis* L., *Empetrum nigrum* L., *Momordica charantia*, *Zizyphus lotus*, *Xylopiya aethiopia*, *Morinda Citrifolia* L., *Malus communis* L., *Coriandrum sativum* L., *Juglans regia* L., *Sorbus umbellata*, *Fritsch var. Cretica*, *Schneider* and encapsulated *Citrus limon Osbeck* were reported for their inhibitory activity on  $\alpha$ -amylase and  $\alpha$ -glucosidase enzymes (Smirin et al., 2010; Park et al., 2012; Misbah et al., 2013; Saravanan and Parimelazhagan, 2014; Oboh et al., 2014; Asghari et al., 2015; Guder et al., 2015; Adefegha et al., 2016; Loizzo et al., 2016; Khatib et al., 2017; Elyasiyan et al., 2017; Sekar et al., 2017; Putri et al., 2017; Wei et al., 2017; Doan et al., 2018; Sukiman et al., 2018; Yegin et al., 2018; Hyun and Kim 2018; Hwang, 2018; Yegin et al., 2018; Deniz et al., 2018; Raimov and Fakir., 2018; Incegul et al., 2018; Marmouzi et al., 2019; Mohammed et al., 2019; Simomara et al., 2019). *Juniperus communis*, *Eugenia jambolana*, *Foeniculum vulgare*, *Secale cereale* L., *Carum*

*carvi* and *Capparis spinosa* L., *Rosa canina* L., *Rhus coriaria* L., *Phaleria macrocarpa*, *Persea americana* Mil., *Pithecellobium dulce* Benth, *Carum carvi*, *Vacciniummyrtillus*, *Backhousia citriodora* oil, *Vanilla planifolia* Andrews were analyzed for their antidiabetic effects using STZ or alloxan induced rats (Medina et al., 1993; Kelkar and Kaklij (1997); Ozbek, 2002; Ozbek et al., 2002; Eddouks et al., 2004; Orhan et al., 2009; Mohammadi et al., 2010; Rabyah et al., 2012; Thenmozhi et al., 2012; Pradeepa et al., 2013; El-Soudi et al., 2014; Erjaee et al., 2015; Asgary et al., 2015; Mishra et al., 2019; Kanedi et al., 2019). There are also some clinical studies reported about the antidiabetic effects of fruits such as *Sumac Rhuscoriaria* L., *Berberis* fruit, *Rosa canina* L., *Citrus junos* Tanaka, *Balanites aegyptiaca* Del., *Cambuci*, *cagaita*, *camu-camu*, *jaboticaba* juices (Shidfar et al., 2013; Moazezi and Qujeq, 2014; Dabaghian et al., 2015; Hwang et al., 2015; Rashad et al., 2017; Balisteiro et al., 2017).

## 2. Antidiabetic Activity of Dietary Fruits in In-vitro Studies

The effect of dietary components in lifestyle in the prevention and management of type 2 diabetes has been getting attention for long time. Most of the in-vitro studies indicate that intake of fruits and their polyphenol or essential oil compounds have antidiabetic effects which are listed in Table 1 and then briefly explained.

**Table 1.** Summary of antidiabetic activity of dietary fruits *in-vitro* studies

Analysed/ polyphenols	major	Plant Food	Experimental model	Effect	Reference
Catechin and epicatechin	and	<i>Sarcopoterium spinosum</i>	Adipose tissue and hepatocytes cells	Increased insulin secretion	Smirin et al., 2010
Hydroxycinnamic acid, chlorogenic acids		Japanese apricot	$\alpha$ -Glucosidase enzymes, murine 3T3-L1 fibroblasts cells	20% inhibition of $\alpha$ -glucosidase activity, insulin-like activity	Park et al., 2012
Flavan-3-ol monomers, proanthocyanidins, and C-linked flavone glycosides		<i>Ficus deltoidea</i>	Rat intestinal $\alpha$ -glucosidase	IC <sub>50</sub> : 0.473 mg/ml	Misbah et al., 2013
Ellagic acid, gallic acid, and rutin.		<i>Passiflora ligularis</i>	$\alpha$ -Amylase and $\alpha$ -glucosidase enzymes	Inhibition of $\alpha$ -amylase: 82.56 % $\alpha$ -glucosidase: 75.36 %	Saravanan and Parimelazhagan, 2014
Syringic acid, eugenol, vanillic acid, isoeugenol, guaiacol, kaemferol, catechin		<i>Persea Americana</i>	$\alpha$ -Amylase and $\alpha$ -glucosidase enzymes	IC <sub>50</sub> mg/ml: $\alpha$ -amylase 0.057 and $\alpha$ -glucosidase 0.241	Oboh et al., 2014
Daucosterol and D-glucono-1,4-lactone		<i>Rosa canina</i>	Yeast $\alpha$ -glucosidase	IC <sub>50</sub> : 0.3 $\mu$ g/ml	Asghari et al., 2015
Anthocyanins, malvidin-3-O-glucoside		<i>Vaccinium myrtillus</i>	$\alpha$ -Amylase and $\alpha$ -glucosidase enzymes	IC <sub>50</sub> $\mu$ g/ml: $\alpha$ -amylase 61.3 and $\alpha$ -glucosidase 128.9	Guder et al., 2015
Chlorogenic acid, ellagic acid and kaempferol	acid, and	<i>Terminalia catappa</i> L.	$\alpha$ -Amylase and $\alpha$ -glucosidase enzymes	IC <sub>50</sub> $\mu$ g/ml: $\alpha$ -amylase 510.11 and $\alpha$ -glucosidase 583.33 $\mu$ g/ml	Adefegha et al., 2016
Rhamnetin, lutein, ferulic acid, quercetin-3-O-glucoside and rutin		<i>Myristica fragrans</i>	$\alpha$ -Amylase and $\alpha$ -glucosidase enzymes	IC <sub>50</sub> of $\alpha$ -amylase 62.1 and $\alpha$ -glucosidase 75.7 $\mu$ g/ml The IC <sub>50</sub> of acarbose for $\alpha$ -amylase 50.0 and $\alpha$ -glucosidase 35.5 $\mu$ g/ml	Loizzo et al., 2016
		<i>Pimenta dioica</i>			

					$\alpha$ -Amylase 147.9 and $\alpha$ - glucosidase 152.8 $\mu\text{g/ml}$	
Coumarin, alkaloid, steroid and phenols	<i>Momordica charantia</i>	Intestinal glucosidase	$\alpha$ -	Low inhibition of $\alpha$ -glucosidase activity		Khatib et al., 2017
Catechins phenolics	and <i>Sarcopoterium spinosum</i>	inhibition activity of $\alpha$ -amylase and $\alpha$ - glucosidase enzymes	$\alpha$ -	IC <sub>50</sub> $\mu\text{g/ml}$ : $\alpha$ -amylase 0.29 and $\alpha$ -glucosidase 0.125 mg/ml		Elyasiyan et al., 2017
		3T3-L1 adipocytes cells		Increased insulin secretion and improved the transmission of insulin signalling		
Magniferin	Mango	$\alpha$ -Amylase and $\alpha$ - glucosidase enzymes	$\alpha$ -	IC <sub>50</sub> of: mango, magniferin and acarbose is 112.8, 36.84 and 21.33 $\mu\text{g/ml}$		Sekar et al., 2017
				Acarbose: 0.064 ppm Mango: 64.71 ppm		Putri et al., 2017
Proanthocyanidin	<i>Pyracantha fortuneana</i>	Intestinal glucosidase	$\alpha$ -	IC <sub>50</sub> : 0.15 $\mu\text{g/mL}$		Wei et al., 2017
Phenols, glycosides, terpenoids, saponin	tannin, <i>Chrysophyllum cainito</i> L and	$\alpha$ -Amylase and $\alpha$ - glucosidase enzymes	$\alpha$ -	IC <sub>50</sub> ( $\mu\text{g/ml}$ ) of: fruit 1.20 and acarbose 198.17		Doan et al., 2018
Tannins and saponins	<i>Pometia pinnata</i>	Intestinal glucosidase	$\alpha$ -	IC <sub>50</sub> of methanol extract 169.81 $\mu\text{g/ml}$		Sukiman et al., 2018
Quercetin glycosides, procyanidin B2, chlorogenic acid, epicatechin, phloretin glycosides	<i>Malus communis</i> L.	Inhibition of amylase and glucosidase	$\alpha$ - $\alpha$ -	IC <sub>50</sub> ( $\mu\text{g/ml}$ ) of $\alpha$ - amylase 501.08 and $\alpha$ -glucosidase 924.93		Yegin et al., 2018
Anthocyanins, proanthocyanidins and flavonoids	<i>Empetrum nigrum</i> L.	Inhibition of amylase and glucosidase	$\alpha$ - $\alpha$ -	IC <sub>50</sub> ( $\mu\text{g/ml}$ ) $\alpha$ - glucosidase 0.5 and $\alpha$ -amylase 100		Hyun and Kim 2018
Catechin, flavonoids,	<i>Momordica</i>	Intestinal	$\alpha$ -	At 100 $\mu\text{g/ml}$ of		Hwang, 2018

caffeic acid, p-coumaric acid, ferulic acid, isoflavones, terpenes, and glucosinolates	<i>charantia</i>	glucosidase			inhibition of $\alpha$ -glucosidase (%) bitter melon 30.0 and acorbose 22.6	
Gallic acid, ferulic and vanillic acids, rutin, catechin and epicatechin	<i>Zizyphus lotus</i>	Inhibition of amylase and glucosidase	$\alpha$ - $\alpha$ -	IC <sub>50</sub> ( $\mu$ g/ml) amylase 31.9 and $\alpha$ -glucosidase 27.95		Marmouzi et al., 2019
Oleanolic acid, sesquiterpenoids, diterpenoids, triterpenoids	<i>Xylophia aethiopica</i>	Inhibition of amylase and glucosidase	$\alpha$ - $\alpha$ -	IC <sub>50</sub> values ( $\alpha$ -amylase: 89.02 $\pm$ 1.12 mM, $\alpha$ -glucosidase: 46.05 $\pm$ 0.25 mM		Mohammed et al., 2019
$\alpha$ -Ketoglutaric and malic acid	<i>Morinda Citrifolia</i> L.	Intestinal glucosidase	$\alpha$ -	IC <sub>50</sub> 28.99 $\mu$ g GAE/ml		Simomara et al., 2019

Smirin and colleagues (2010) studied the effect of *Sarcopoterium spinosum* extract (SSE) in the management of diabetes employing *in vitro* and *in vivo* methods. They discovered that due to catechin and epicatechin content of SSE, the root extract of *Sarcopoterium spinosum* indicated insulin-like effect in skeletal muscle, adipose tissue and hepatocytes cells and increased insulin secretion *in vitro*. It was also reported that SSE improved glucose tolerance but did not affect fasting glucose level of genetically diabetic male KK-Ay mice when they fed in short term period with the extract. In addition, chronic administration of SSE decreased blood glucose level, plasma insulin and free fatty acid and was reported as beneficial for hypoglycemic effect.

Park and colleagues (2012) investigated the antidiabetic effect of 50 commonly consumed fruit and vegetables in Korea either in whole juice (WJ) samples or ethanolic extract (EE). Firstly, inhibition of  $\alpha$ -glucosidase enzymes was investigated in the presence of commonly consumed fruits and vegetables. Japanese apricot (20.0 %) showed the highest inhibition activity within the WJ fruits. Among ethanolic extract of the fruits; pear (28.3%), Japanese apricot (17.4%), cucumber (13%) and plum (8%) had better  $\alpha$ -glucosidase inhibitory activity compared to other EE fruits. Following those analyses to obtain the insulin-like activity of those fruits, murine 3T3-L1 fibroblasts cells were used with/without insulin. From WJ fruits only Japanese apricot demonstrated insulin-like activity but EE fruit

cucumber, pear and plum indicated insulin-like activity with insulin sensitizing ability.

To regulate the blood glucose level, the use of tea bags and/or capsules of *Ficus deltoidea* is getting popular in Malaysia. Water and ethyl acetate fraction of the fruit was investigated for its antidiabetic activity with *in vitro* methods. In contrast to above researches, Misbah and colleagues (2013) did not observe any correlation between phenolic content and antidiabetic activity of the fruit. The IC<sub>50</sub> value of rat intestinal  $\alpha$ -glucosidase inhibition of the fruit's water extraction was detected as 0.473 mg/ml. It was concluded that the antidiabetic activity of the fruit may be about other polar plant components and phenolics together (Misbah et al., 2013).

Antidiabetic activity of *Passiflora ligularis* fruits were analyzed using various solvents extractions. Acetone extract of the fruit exhibited the highest phenolic compound and showed significant inhibitory activity on  $\alpha$ -amylase (82.56 %) and  $\alpha$ -glucosidase (75.36 %) enzymes (Saravanan and Parimelazhagan, 2014).

*Persea americana* (avocado) fruit and leaf were reported due to its inhibitory activity on  $\alpha$ -amylase and  $\alpha$ -glucosidase enzymes (Oboh et al., 2014). The research reported that the inhibition of  $\alpha$ -amylase with fruit is higher than the leaf. In contrast the inhibitory activity of leaf on  $\alpha$ -glucosidase was better than fruit. The inhibition activity of fruit may be related to rich constituent of phenolics such as syringic acid,

epigallocatechin, isoeugenol, kaempferol, catechin, ferulic acid, apigenin, and epigallocatechin-3-O-gallate.

Asghari and colleagues (2015) investigated the inhibitory activity of *Rosa canina* fruit on yeast  $\alpha$ -glucosidase with different extraction methods. Solvents used in those methods are n-hexane, ethyl acetate, acetone and methanol. The acetone extract showed the highest inhibition with an  $IC_{50}$  value of 0.3  $\mu$ g/ml. The fruit contains high amount of phytosterols (daucosterol and D-glucono-1,4-lactone) and their  $IC_{50}$  values of yeast  $\alpha$ -glucosidase activity were calculated as 13.3 and 6.5  $\mu$ M respectively which is lower than acarbose ( $IC_{50}$  16.1  $\mu$ M).

A research analyzed the antidiabetic activity of bilberry (*Vaccinium myrtillus* L.) fruit using different extraction solvents. Bilberry is rich in anthocyanin constituent and this can influence its inhibitory activity. The inhibition of  $\alpha$ -amylase was found highest for methanol extraction with an  $IC_{50}$  value of 61.3  $\mu$ g/ml and for  $\alpha$ -glucosidase activity  $IC_{50}$  value was detected highest for ethanolic extraction as 128.9  $\mu$ g/ml (Guder et al., 2015).

Adefegha and colleagues (2016) investigated the effect of almond (*Terminalia catappa* L.) fruit parts (hull and drupe) extracts on  $\alpha$ -amylase and  $\alpha$ -glucosidase enzymes. For both  $\alpha$ -amylase and  $\alpha$ -glucosidase the drupe extract exhibited the highest inhibition with an  $IC_{50}$  value of 510.11 and 583.33  $\mu$ g/ml, respectively. The major components of the fruit were identified as chlorogenic acid, ellagic acid and kaempferol and the result of this study indicated that the antidiabetic activity might be related with those phenolic contents.

In recent years dried powder of nutmeg mace (*Myristica fragrans*) and pimento (*Pimenta dioica*) is using as spice and functional ingredient due to its effect on carbohydrate digestive enzymes;  $\alpha$ -amylase and  $\alpha$ -glucosidase. Loozio and colleagues found that mace inhibited  $\alpha$ -amylase and  $\alpha$ -glucosidase with an  $IC_{50}$  value of 62.1 and 75.7  $\mu$ g/ml, respectively. While acarbose inhibited  $\alpha$ -amylase and  $\alpha$ -glucosidase activity 50.0 and 35.5  $\mu$ g/ml respectively, pimento inhibited them 147.9 and 152.8  $\mu$ g/ml, respectively (Loozio et al., 2016).

Ethanolic and aqueous extracts of *Momordica charantia* fruit was tested for its  $\alpha$ -glucosidase inhibitory activity and phytochemicals screening (coumarin, alkaloid, steroid and phenol) (Khatib et al., 2017). Both extracts showed low inhibition effect on  $\alpha$ -glucosidase activity however previous study of the authors tested *in vivo* activity of the fruit and found that fruit was indicated high antidiabetic activity. Therefore, it was concluded that its antidiabetic activity is not related with the inhibition of digestive enzymes, but it might be about the carbohydrate transport or uptake mechanism (Khatib et al., 2017).

Elyasiyan and colleagues (2017) analyzed the antidiabetic effect of *Sarcopoterium spinosum* (S. spinosum) rich in catechins and phenolics. Firstly, they measured the inhibition activity of  $\alpha$ -amylase and  $\alpha$ -glucosidase enzymes and reported the  $IC_{50}$  values as 0.29 and 0.125 mg/ml respectively. Then glucose uptake into 3T3-L1 adipocytes showed that it also increased insulin secretion and improved the transmission of insulin signaling that leads to the induction of glucose uptake.

Ripe and unripe mango fruit contains magniferin which is a xanthone glycoside and may decrease blood glucose level due to its inhibitory activity on carbohydrate digestive enzymes. The  $IC_{50}$  value of  $\alpha$ -glucosidase enzymes with mango, magniferin and acarbose was found as 112.8, 36.84 and 21.33  $\mu$ g/ml respectively (Sekar et al., 2017). In another study Putri and colleagues (2017) also observed the antidiabetic activity of peel, flesh, endosperm, and endocarp of the 4 type of mango fruits. While the  $IC_{50}$  value of acarbose was found as 0.064 ppm, the ethanolic extract of the *manalagi* endosperm had the highest inhibitory activity with  $IC_{50}$  value of 64.71 ppm. Therefore, as well as the fruit the peel of the fruit may be also used as an alternative to control blood glucose level even it did not indicate as good inhibitory activity as positive control (acarbose).

*Pyracantha fortuneana* fruit (PFF) is a fruit which is rich in proanthocyanin. The results of the research indicated that PFF inhibited  $\alpha$ -glucosidase in a non-competitive type with the  $IC_{50}$  value of 0.15  $\mu$ g/ml (Wei et al., 2017). The study also demonstrated the inhibitory mechanism of proanthocyanins on  $\alpha$ -glucosidase.

Doan and colleagues (2018) analyzed the hypoglycemic activity of *Chrysophyllum cainito*

L with both *in vitro* and *in vivo* methods. The inhibition of  $\alpha$ -glucosidase activity of the extract and acarbose were found as  $IC_{50}$  1.20 and 198.17  $\mu$ g/ml respectively. The extract was administered to normal and alloxan-induced diabetic mice at 500 mg/kg and found that fasting blood glucose level significantly reduced in diabetic mice. Thus, antidiabetic activity of the fruit comes from its effect on glucose uptake stimulation and  $\alpha$ -glucosidase inhibition due to its phenols, tannin, glycosides, terpenoids, and saponin content.

In a recent research, antidiabetic activity of *Pometia pinnata* was studied using various solvents (methanol, ethyl acetate, n-hexane) for the fruits extraction (Sukiman et al., 2018). It was reported that the  $IC_{50}$  values of  $\alpha$ -glucosidase for the methanol, ethyl acetate, n-hexane extract of the *P. pinnata* was obtained as 169.81  $\mu$ g/mL, 505.55  $\mu$ g/mL and 263.18  $\mu$ g/mL respectively. The phenolic content of the methanolic extraction was higher than other solvent extractions therefore this may be related with better inhibitory activity on  $\alpha$ -glucosidase enzyme.

Yegin and colleagues (2018) investigated the inhibition of  $\alpha$ -amylase and  $\alpha$ -glucosidase activity by *Malus communis* L. (Piraziz apple). The authors analyzed the antidiabetic activity by spectrophotometry. Piraziz apple inhibited  $\alpha$ -amylase and  $\alpha$ -glucosidase with  $IC_{50}$  values of 501.08 and 924.93  $\mu$ g/ml respectively. When they used acarbose as a positive control, they found that the inhibition of  $\alpha$ -amylase and  $\alpha$ -glucosidase with  $IC_{50}$  values of 94.35 and 75.20  $\mu$ g /ml respectively. They concluded that the inhibition activity of acarbose was higher than Piraziz apple for both  $\alpha$ -amylase and  $\alpha$ -glucosidase enzymes.

Crowberry (*Empetrum nigrum* L.) has been traditionally used due to its rich anthocyanins content, together with proanthocyanins and flavonoids (Hyun and Kim 2018). Ethyl-acetate fraction of the fruit extract exhibited significant inhibition of  $\alpha$ -glucosidase and  $\alpha$ -amylase activities with an  $IC_{50}$  of 0.5 and 100  $\mu$ g/ml respectively. The correlation analysis indicated that the significant inhibition of  $\alpha$ -glucosidase and  $\alpha$ -amylase activities by the ethyl acetate fraction was due to the presence of polyphenolic compounds.

Bitter melon (*Momordica charantia*) is a phenolic rich fruit and there are some researches about its

antidiabetic activities. The taste of bitterness comes from catechin, flavonoids, caffeic acid, p-coumaric acid, ferulic acid, isoflavones, terpenes, and glucosinolates content of the fruit. The inhibitory activity of bitter melon and acarbose was discovered for  $\alpha$ -glucosidase enzyme. At 100  $\mu$ g/ml of bitter melon extract and acarbose concentration the percentage inhibition was found as 30.0 and 22.6, respectively (Hwang, 2018).

Marmouzi and colleagues (2019) investigated the antidiabetic activity of *Zizyphus lotus* (Rhamnaceae) fruit. The major components of the fruit were gallic acid, ferulic and vanillic acids, rutin, catechin and epicatechin. The fruit demonstrated inhibition activity against  $\alpha$ -amylase and  $\alpha$ -glucosidase enzymes with an  $IC_{50}$  value of 31.9 and 27.95  $\mu$ g/ml respectively.

Ethiopian pepper (*Xylopi aethiopica* (Dunal) A. Rich) is a type of fruit which is used as spice in West and Central Africa. The major constituents of the fruit were oleanolic acid, sesquiterpenoids, diterpenoids, triterpenoids and polyphenol. Oleanolic acid (OA) indicated a significant inhibition effect with lower  $IC_{50}$  values ( $\alpha$ -amylase:  $89.02 \pm 1.12$  mM,  $\alpha$ -glucosidase:  $46.05 \pm 0.25$  mM) than other fractions and the acarbose (Mohammed et al., 2019).

*Morinda citrifolia* L. is a fruit which is used as nutraceutical beverage due to its antidiabetic and antioxidant activities. In one of the recent papers, the antidiabetic activity of fermented *Morinda* fruit juice was tested and its  $IC_{50}$  value calculated as 28.99  $\mu$ g GAE/ml. It was concluded that the antidiabetic activity may be due to the organic acid ( $\alpha$ -ketoglutaric acid and malic acid) composition of the fermented fruit (Simomara et al., 2019).

### 3. Antidiabetic Activity of Dietary Fruits in In-vivo Studies

#### Animal Studies:

Antidiabetic activities of commonly consumed fruits, rich in phenolics and volatiles, in animal studies were presented in Table 2.

**Table 2.** Summary of antidiabetic activity of dietary fruits in animal studies



Analysed/ major polyphenols	Plant Food	Experimental model	Type of interaction	Effect	Reference
$\alpha$ -Pinene, sabinene, quercetin-hexoside, isoscutellarein-8-O-hexoside	<i>Juniperus communis</i>	STZ-induced female Wistar rats	250 mg/kg bw (body weight) of fruit administration for 24 days	Decreased blood glucose level and body weight	Medina et al., 1993
Flavones, saponins, proteins and tannins	<i>Eugenia jambolana</i>	STZ-induced Wistar rats	1.25 mg/kg bw	Blood glucose level decreased 50 %	Kelkar and Kaklij (1997)
Trans-anethol, fenchon, limonen, methyl chavicol, $\alpha$ -felandren	<i>Foeniculum vulgare</i>	Alloxan induced diabetic rats	Saline: 0.2 ml glibenclamide: 3 mg/kg Foeniculum vulgare Mill. essential oil: 5 ml/kg	Blood glucose level significantly reduced at 4h Glibenclamide reduced the blood glucose level significantly at 1, 2, and 24h.	Ozbek, 2002
Ferulic acid dehydromer (diFA), caffeic acid, sinapic acid	<i>Secale cereale L.</i>	Alloxan induced diabetic and normal rats	Saline: 0.2 ml Glibenclamide: 3 mg/kg Extract: 5 ml/kg	Extract indicated lower antidiabetic activity compared to glibenclamide Decreased blood glucose level only between 0-4 h.	Ozbek et al., 2002
Rutin, carvone, limonene, carveol, dihydrocarveol, thymol	<i>Carum carvi</i> and <i>Capparis spinosa L.</i>	Healthy and STZ induced diabetic rats	20 mg/kg of extract administered to rats for 14 days	Blood glucose level reduced Plasma insulin concentrations did not change	Eddouks et al., 2004
Anthocyanin, several glycosides of quercetin	<i>Rosa canina L.</i>	Healthy and STZ induced diabetic rats	Different solvent extracts of the fruit were administered 250 mg/kg for 7 days	The extract (water fraction) that has the lowest phenolic content exhibited the highest reduction of blood glucose level Reduction may be due to oligosaccharide rich of water fraction	Orhan et al., 2009
Gallic acid, protocatechuic acid, <i>p</i> -OH-benzoic acid and vanillic acid	<i>Rhus coriaria L.</i>	Alloxan induced diabetic wistar rats	Ethanollic extract of fruit were given to rats at a dose of 200 mg/kg for 21 day	Blood glucose level of the diabetic rats decreased 26% compared to control group.	Mohammadi et al., 2010
Kaempferol, myricetin, naringin, and rutin	<i>Phaleria macrocarpa</i>	STZ induced diabetic male Sprague Dawley rats	Different fractions of extract given	Methyl and n-butanol fractions lowered plasma	Rabyah et al., 2012

			to rats at a dose of 1 g/kg for 12 days	insulin level significantly Dose-dependently inhibited glucose transport across isolated rat jejunum	
Hydroxybenzoic and hydroxycinnamic acids and procyanidins	<i>Persea americana</i> Mil.	STZ induced diabetic and normal male Wistar Albino rats	Rats were treated for 8 weeks at a dose of 300 mg/kg bw hydro-methanolic extract and its sub fractions	n-Hexane fractions of the extract exhibited the highest antidiabetic activity	Thenmozhi et al., 2012
Quercitrin, rutin, kaempferol, naringin and daidzein	<i>Pithecellobium dulce</i> Benth	STZ induced diabetic and normal male Wistar Albino rats	Rats were fed orally with 300 mg/kg bw of extract for 30 days.	Significant reduction in blood glucose level, glycosylated hemoglobin, urea and creatinine.	Pradeepa et al., 2013
Carvone, $\gamma$ -Terpinene and Limonene	<i>Carum carvi</i>	STZ-induced diabetic and normal rats	Rats were administered with 10 mg/kg bw caraway essential oil	<i>Carum carvi</i> essential oil exhibited renoprotection against diabetic nephropathy due to its essential oil.	El-Soudi et al., 2014
				<i>Carum carvi</i> seed oil supplementation decreased blood glucose level in diabetic rats.	Erjaee et al., 2015
Anthocyanins	<i>Vaccinium myrtillus</i>	Diabetic alloxan rats	Rats were administered with bilberry (2 g/d) and glibenclamide (0.6 mg/kg bw) for 4 weeks.	Extract decreased plasma glucose level better than glibenclamide.	Asgary et al., 2015
Citral	<i>Backhousia citriodora</i> oil	High-fat diet (HFD) and streptozotocin (STZ) induced diabetic rats	Rats were treated with 45 mg/kg bw of citral for 28 days	Citral and glibenclamide decreased blood glucose level at 55.3% and 58.7%, respectively.	Mishra et al., 2019
<i>o</i> -Guaiacol, <i>p</i> -creosol, <i>p</i> -vinylguaiacol, <i>p</i> -hydroxybenzaldehyde, vanillic acid and vanillin	<i>Vanilla planifolia</i> Andrews	Diabetic alloxan male mice	150 mg/ml of extract were administered to mice for 20 days	Decreased blood glucose level	Kanedi et al., 2019

*Juniperus communis* is a type of berry reported as antidiabetic fruit. The researchers administered the healthy and STZ-induced female Wistar rats with the fruit and observed that 250 mg/kg body weight (bw) of fruit administration for 24 days decreased blood glucose level and body weight significantly (Medina et al., 1993).

In another study antidiabetic compound was extracted from the fruit of *Eugenia jambolana* and then analyzed for its antidiabetic activity. Kelkar and Kaklij (1997) analyzed the effect of *Eugenia jambolana* on the blood glucose levels of STZ-induced Wistar rats. The identified antidiabetic compounds were peptidyl glycan and an oligosaccharide (Mw 6.0 and 1.2 kD). It was observed that loading peptidyl glycan preparation to rats at a dose of 1.25 mg/kg body weight (bw) decreased the blood glucose level by 50 % and oligosaccharide (8.0 mg/kg bw) reduced 30%.

*Foeniculum vulgare* (fennel) essential oil (FEO) was analyzed for its hypoglycemic activity using alloxan induced diabetic rats. Glibenclamide was used as positive control and saline was used as a control. The blood glucose level of rats was analyzed at 0, 1, 2, 4 and 24 hours after administration of FEO, glibenclamide and saline. It was discovered that FEO only significantly decreased the blood glucose level at 4h but glibenclamide reduced the blood glucose level significantly at 1, 2, and 24h. The lethal dose (LD<sub>50</sub>) of FEO was found as 6.149 ml/kg (Ozbek, 2002).

Ozbek and colleagues (2002) analyzed the effect of *Secale cereale* L. fruit decoction extracts in alloxan diabetic and healthy rats. The blood glucose level of rats was analyzed at 0, 1, 2, 4 and 24 hours after administration of extract, glibenclamide, and saline as a control. It was observed that *Secale cereale* L. extract decreased blood glucose level between 0-4 h but observed lower antidiabetic activity compared to glibenclamide.

The essential oil content of *Cuminum cyminum* L. fruit indicated similar hypoglycemic effect with reference drug glibenclamide in the alloxan induced diabetic and healthy rats (Ceylan et al., 2003). The lethal dose (LD<sub>50</sub>) of fruit was 0.780 ml/kg.

In another study, the hypoglycaemic effects of aqueous extracts of *Carum carvi* (CC) and *Capparis spinosa* L. (CS) fruit were investigated in healthy and STZ induced rats. It was observed that administration of CC and CS aqueous extracts (20 mg/kg) to rats for 14 days decreased the blood glucose level in STZ rats but did not change normal rats. Also, the basal plasma insulin concentrations of both groups remained same in both acute and chronic treatments (Eddouks et al., 2004).

Fruit of *Rosa canina* L. is used traditionally in the management of diabetes in Anatolia. The ethanol extract of fruit was administered (250 mg/kg) to normal and STZ induced rats for 7 days. Also, different fractions of ethanolic extracts were administered to rats as well as EtOAc, n-BuOH, R-H<sub>2</sub>O. It was observed that antidiabetic activity of fruit was not related with phenolic content as R-H<sub>2</sub>O fraction demonstrates the highest inhibitory activity on blood glucose level (Orhan et al., 2009).

Mohammadi and colleagues (2010) studied fruits of *Rhus coriaria* L. (Anacardiaceae) which is traditionally used to treat diabetes in Iran. The ethanolic extract of fruit was analyzed with *in vitro* and *in vivo* studies. Alloxan induced wistar rats were fed with 200 mg extract/kg body weight. In the first day, postprandial blood glucose level was decreased by 24% and after 21-day, blood glucose level was decreased by 26% compared to control group. The maltase and sucrase activities were inhibited by 44 and 27% respectively by using extract. However, there were not any changes observed on the transcription level of INS (mRNA levels of insulin) and GLUT-4 genes. The authors concluded that the fruits of *Rhus coriaria* L. may improve the life of type 2 diabetic patients.

Anti-hyperglycemic activity of *Phaleria macrocarpa* (PM) fruit was studied with methanolic extract which was further fractionated with chloroform (CF), ethyl acetate (EAF), n-butanol (NBF) and aqueous (AF) fractions (Rabiah et al., 2012). STZ induced male Sprague Dawley (SD) rats were administered with 1 g/kg of above fractions and postprandial glucose levels were observed with intraperitoneal glucose tolerance test. While NBF fraction decreased the blood glucose level, other fractions did not affect. In addition, the rats were treated with the fractions

(1 g/kg) for 12 days and ME and NBF fractions lowered plasma insulin level significantly and dose-dependently inhibited glucose transport across isolated rat jejunum which implies an extra-pancreatic mechanism.

In one of the researches the hydro-methanolic (2:3) extract of the *Persea americana* Mil. (avacado) was administered to both STZ induced and normal male Wistar Albino rats for 8 weeks at a dose of 300 mg/kg bw. It was reported that n-hexane fraction of the extract exhibited the highest antidiabetic activity in STZ-induced rats and concluded that avocado may be beneficial to control blood glucose level (Thenmozhi et al., 2012).

Pradeepa and colleagues (2013) assessed the antidiabetic activity of polyphenol rich *Pithecellobium dulce* Benth. (Leguminosae) fruits and treated STZ induced and normal male Wistar Albino rats with 300 mg/kg bw of extract orally for 30 days. It was found that the extract rich in phenolic compounds such as quercitrin, rutin, kaempferol, naringin and daidzein may influence amorphate of blood glucose level. It was reported that the fruit is none toxic and significantly reduced the levels of blood glucose.

*Carum carvi* (caraway) is an aromatic plant and traditionally used for the treatment of metabolic disorders. El-Soudi and colleagues (2014) analyzed the renoprotective effect of caraway essential oil in male albino rats. The major essential oil of the caraway was Carvone (70.1%), and it was followed by  $\gamma$ -Terpinene (12.6%) and Limonene (5.5%). The STZ-induced and normal rats were treated with 10 mg/kg bw caraway essential oil orally for 3 weeks. The morphological examination of the kidneys is a key factor to observe diabetic nephropathy. It was showed that diabetic rats which fed with *Carum carvi* oil has an improvement with minor pathological changes in their kidneys compare to diabetic rats which were not administered with *Carum carvi* oil. Therefore, it was reported that *Carum carvi* essential oil exhibited renoprotection against diabetic nephropathy due to its essential oil. There was another study about the effect of *Carum carvi* oil on STZ-induced Wistar male

rats. The results of this study was also in agreement with Neveen and colleagues (2014) as it was reported caraway seed oil supplementation decreased blood glucose level in diabetic rats (Erjaee et al., 2015).

It is believed that *Vacciniummyrtillus* (bilberry) has antidiabetic activity and therefore it is used traditionally within the prediabetics and diabetic patients. The researchers treated the diabetic alloxan rats with bilberry (2 g/d) and glibenclamide (0.6 mg/kg bw) for 4 weeks. It was found that bilberry supplementation decreased plasma glucose level better than glibenclamide and this effect might be related with anthocyanin content of the fruit (Asgary et al., 2015).

Anti-diabetic activity of citral was studied recently using high-fat diet (HFD) and streptozotocin (STZ) induced diabetic rats. The study revealed the effect of citral on carbohydrate metabolic regulatory enzymes in the liver. Rats were treated with 45 mg/kg bw of citral for 28 days and it was discovered that citral and glibenclamide decreased blood glucose level in a percentage of 55.3 and 58.7 respectively (Mishra et al., 2019).

Kanedi and colleagues discovered whether the ethanolic extract of vanillin (*Vanilla planifolia* Andrews) has hyperglycemic effect in alloxan induced rats. The ethanolic extract of vanillin contains bioactive compounds of flavonoids, antioxidants, and phenols. 150 mg/ml of extract was administered to mice for 20 days. On the 20th day it was found that vanilla fruit extract decreased blood glucose level better than that glibenclamide did.

### Clinical Trials:

Antidiabetic activity of dietary fruits such as Sumac *Rhuscoriaria*, berberis fruit, *Rosa canina*, *Citrus junos*, *Balanites aegyptiac*, cambuci, cagaita, maracujá-alho, cupuaçu, camu-camu and jaboticaba in clinical trials were presented in Table 3.

**Table 3.** Summary of antidiabetic activity of dietary fruits in clinical trials

Analysed/ major polyphenols	Plant Food	Experimental model	Type of interaction	Effect	Reference
Gallic acid, methyl gallate, kaempferol, and quercetin	Sumac <i>Rhus coriaria</i> L.	Type-2 diabetic patients	Double blind randomized clinical study	Plasma glucose and HbA1c (Glycosylated hemoglobin) level significantly decreased compared to control	Shidfar et al., 2013
Anthocyanins, (delphinidin, cyanidin)	Berberis fruit	Type-2 diabetic patients	Randomized, double-blind, and placebo-controlled study	Serum glucose HbA1c level reduced compared to control	Moazezi and Qujeq, 2014
Proanthocyanidin aglycones	<i>Rosa canina</i> L.	Type-2 diabetic patients	Randomized controlled cross-over	Fasting blood glucose level significantly decreased HbA1c level did not changed	Dabaghian et al., 2015
Rutin, quercetin, tangeretin, naringin, and hesperidin	<i>Citrus junos</i> Tanaka	Prediabetic patients	Double-blind, crossover, placebo controlled	Fasting blood glucose level significantly decreased Postprandial glucose level slightly reduced	Hwang et al., 2015
Furostanol saponins, rutin, quercetin, syringic acid	<i>Balanites aegyptiaca</i> Del.	Type-2 diabetic patients	Randomised controlled cross-over	Reduced postprandial blood glucose level 26.9%	Rashad et al., 2017
Syringic acid Quercetin derivates Catechin Epicatechin Kaempferol derivates Free ellagic acid Total ellagic acid Myricetin derivates	Cambuci, camu-camu jaboticaba juices	Healthy humans	Randomised controlled cross-over	Reduced blood glucose	Balisteiro et al., 2017

Forty-two patients of type-2 diabetics were fed with Sumac *Rhus coriaria* L. for 3 months to analyze the effect of Sumac on serum glycemic status (Shidfar et al., 2013). This clinical trial was controlled as double-blind randomized study and volunteers were fed with 3 g/day sumac powder (n=22) or placebo (n=19) every day. Blood samples were collected before and after the intervention and it was found that serum glucose and HbA1c (Glycosylated hemoglobin) levels were decreased significantly in volunteers fed with sumac powder.

Moazezi and Qujeq, (2014) studied with 30 type-2 diabetic patients and fed them with berberis fruit extract for 8 weeks with a dose of 2 mg/day. The serum glucose HbA1c level of the volunteers

who consumed barberry fruit had a significant decrease compare to group consumed placebo.

*Rosa canina* L. (rose hip) fruit extract have been traditionally used as antidiabetic fruit in Iran. Type-2 diabetic patients took rose hip fruit extract and toast powder capsule (placebo) for 3 months. Blood samples were collected before and after the intervention. It was reported that while the fasting blood glucose level significantly decreased in fruit extract consumed group, HbA1c group was not significantly more than placebo group. Therefore, the researchers suggested repeating the clinical study with larger dose of the fruit (Dabaghian et al., 2015).

Hwang and colleagues (2015) studied 40 prediabetic patients fed with the ethanol extracts of *Citrus junos Tanaka* peel (YE-4250 mg/day) for 16 weeks. The intervention study was conducted in double-blind, crossover, placebo controlled. Fasting plasma glucose, postprandial glucose, and fasting plasma insulin concentrations were assessed after end of each 8 weeks. It was found that while fasting plasma glucose level significantly reduced in YE group postprandial glucose slightly decreased and results supported that YE might be a useful supplement for prediabetic patients.

The effect of ethanol extract of *Balanites aegyptiaca* Del. (BE) (Zygophyllaceae) fruits on glucose control in elderly 30 type-2 diabetic people was evaluated in a recent study. Two groups were assigned for the intervention: placebo control and BE group. During 8 weeks of the study volunteers were fed with 400 mg/day BE fruit extract capsule or placebo test. The results of the 8 weeks treatment indicated that BE fruit extract reduced postprandial blood glucose level by 26.9% (Rashad et al., 2017).

Balisteiro and colleagues (2017) studied with 23 healthy subjects and fed them with different traditionally consumed fruit juices (or cambuci, cagaita, maracujá-alho, cupuaçu, camu-camu and jaboticaba) in Brazilian. On the first visit the participants fed with 50 g white bread plus 300 mL of water (control meal) and after 1-week interval they consumed 50 g white bread plus 300 mL fruit juices (test meal). The results indicated that cambuci, cagaita, camu-camu and jaboticaba juices reduced blood glucose level compared to control.

#### 4. Conclusion

In this review, the antidiabetic potential of the selected fruits was summarized. The present data demonstrated the short and/or long-term potential and traditional usage of the antidiabetic fruits using *in vitro* and *in vivo* studies. The present studies indicated that due to phenolic and volatile contents of the fruits, they may inhibit digestive enzymes, improve insulin sensitivity, stimulate insulin secretion, decrease carbohydrate absorption and/or increase peripheral glucose uptake. *In vitro* studies explained the mechanism of action on the inhibition of  $\alpha$ -glucosidase and  $\alpha$ -amylase enzymes, cell culture experiments provide more details about fruits action to the

transport or uptake of glucose and stimulation of insulin secretion. However, there are only limited *in vivo* studies about their antidiabetic effect. Therefore, to promote rational use of these fruits it is needed to have more biological knowledge on the specific mechanism for treatment of diabetes. Further *in vivo* studies are necessary to elucidate the effect of fruits and its active constituent on carbohydrate mechanism.

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