The anti-diabetic potential of polysaccharides extracted from members of the cucurbit family: A review

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Abstract

Diabetes is a growing global problem and a heavy financial burden on health care services. It is estimated that over 380 million people suffer from this condition which causes many deaths each year in addition to being associated with increased risk of other health problems. Traditional medicine is a promising area of research in diabetes therapy as it is widely accessible and it is believed that over 200 plants have anti-diabetic properties including members of the cucurbit family. Studies in animal and human models have shown that treatment with some cucurbits has hypoglycaemic effects and stimulates beta cell regeneration in addition to other anti-diabetic effects which are equal to that of commonly prescribed anti-diabetic drugs. It has also been shown that at least one of the bioactive components which stimulate these effects is a polysaccharide.

Keywords: traditional medicines; cucurbit; pumpkin; polysaccharides; anti-diabetic; pectin

1. Introduction

Traditional medicine is the only medicine available to 75 % of the planet's population (Yamada, 2008) and is therefore of significant interest and carbohydrates and glycoconjugates are important in disease related applications (Rudd and Dwek, 2006). Plants are often used in traditional medicine with over 200 species thought to be beneficial in the treatment of diabetes (Jia, Gao and Tang, 2003), many of these traditional medicines are thought to have active polysaccharide components (Fu, Shi and Li, 2006).

The *Curcurbiteae* family, also referred to as cucurbits (**Figure 1**), are a group of fruit producing plants (Weng and Sun, 2012). They form a very large group with approximately 130 genera and 800 species and can be cultivated worldwide (Dhiman, Gupta, Sharma, Gill and Goyal, 2012) and make popular food crop plants (Behera, Sureja, Islam, Munshi and Sidhu, 2012) some of these species include pumpkins, squashes, gourds and melons (Huang, Tan, Tan and Peng, 2011; Noelia, Roberto, de Jesus and Alberto, 2011; Song, Zhang, Zhou, Zhang, Hu and Li, 2012; Weng and Sun, 2012).

Figure 1 Seen on this image is a selection of cucurbits of the South Korean Genebank in Suwon (2010). Including luffas (*Luffa aegyptiaca*), wax gourds (*Benincasa hispida*), bottle gourds (*Lagenaria siceraria*), snake gourds (*Trichosanthes cucumerina*), pumpkins, gourds and squash (*Cucurbita sp*.). Reproduced with kind permission from Crops for the Future (http://www.cropsforthefuture.org/).

Cucurbits are of interest because of the extensive range of medicinal properties they have been reported to exhibit (Dhiman, *et. al*. 2012). Traditional medicine, particularly the Chinese (Fu, *et al*., 2006) and Ayurvedic systems (Chaturvedi, 2012), have made use of various parts of cucurbit plants; including the seeds and flesh of the fruits they produce (Dhiman, *et. al*. 2012). There are reports of traditional medicinal polysaccharides exhibiting a number of important physiological properties including: tumour growth inhibition, wound healing, immunomodulating and hypoglycaemic effects (Fu, *et al*., 2006; Inngjerdingen, *et. al*., 2007; Košťálova, Hromádková, Ebringerová, Polovka, Michaelsen and Paulsen, 2013).

It is believed that over 200 plants have blood glucose lowering properties, including many common plants such as those belonging to the cucurbit family (Jia, *et. al*., 2003) of which the active ingredient of several has been shown to be a polysaccharide such as that found in pumpkin (Fu, *et al*., 2006). Yet currently plant polysaccharides as medicines are under researched. Polysaccharides can be difficult to characterise due to their natural variability in terms of composition, structure, molecular weight and conformation. The polysaccharides found in the fruit of a plant may differ due to many factors including the fruit development (Li, Fan, Yang and Shen, 2006), ripeness of the fruit and the environment in which the plant was grown (Dong, Cui, Song, Zhao, Ji, Lo and Tsim, 2003). Polysaccharides are less researched than other bioactive molecules such as proteins because they are more difficult to work with, they are more difficult to obtain as they are not coded for directly, they are also relatively easy to break down in digestion so delivery mechanisms would need to be looked at more carefully (Duus, Gotfredsen and Bock, 2000).

It is known that, like proteins, polysaccharides are capable of interacting with an organism causing a change in biological activity (Yang and Zhang, 2009). The interaction and effect of the interaction varies greatly due to the conformation (Yang and Zhang, 2009) and other potential interactions of the polysaccharide (Patel, *et al*., 2007; Heinze, *et. al*., 2011). Polysaccharides are known to be able to modulate the immune system through the stimulation of macrophages (Schepetkin and Quinn, 2006) have anti-tumour effects (Wasser, 2002), reduce inflammation (Wu, Duan, Liu and Cen, 2010) and as a hypoglycaemic agent (Xiong and Cao, 2001; Zhang and Yao, 2002; Cai, Yan and Li, 2003). Polysaccharides from food plants such as the cucurbiteae family may make very good medicines as they are often eaten in the diet and are therefore unlikely to be harmful to the patient (Wang, Zhang and Dong, 2012).

Glucose is the source of energy used by the brain so it is essential that there is always glucose in supply in the body, including in times of fasting (Rang, Dale, Ritter and Flower, 2007). More energy is available in the food we eat than is needed in one burst so in healthy individuals the excess is stored as glycogen or fat (Rang, *et al*., 2007). The most important hormone in the regulation of how much is stored and how much is used is insulin. The greater the level of insulin the greater the amount of glucose is stored. However when blood sugar levels drop the insulin produced is reduced and there is an increase in the production of other hormones including glucagon, adrenaline, glucocorticoids and growth hormone which increase the levels of blood sugar through conversion of stored energy back to glucose (Rang, *et. al*., 2007).

Diabetes mellitus is a fairly common condition arising from defects in production or action of insulin which causes hyperglycaemia (Nelson, Lehninger and Cox, 2008). Non-diabetic humans have a blood sugar level of between 4 and 7 mmol/L however non-controlled diabetic patients have a much higher concentration of glucose in their blood. If left untreated many complications can arise, which may even lead to death (Yadav, Morris, Harding, Ang and Adams, 2009).

The high prevalence of diabetes and other health issues associated with this disease is a financial burden on already stretched health care services. A study of health problems with U.S. patients with diabetes showed that sufferers are more likely to suffer from fair or poor health than non-sufferers (Gregg, *et. al*, 2000). These health problems include heart problems, kidney disease, impaired vision, limb loss and general poor health than non-diabetic patients in addition to needing on-going health checks and, in many cases, insulin (Yadav, *et. al*., 2009). Diabetes influences the quality of life of the patients as well as forcing them to undergo lifestyle changes such as regular monitoring of their blood glucose levels (Smyth and Heron, 2006). It is estimated that over 380 million people suffer from this condition (**Figure 2**) and is the cause of more than 2.9 million deaths each year (Yadav, *et. al*., 2009) with these figures projected to rise over the next 30 years. The majority of people suffering from diabetes are aged between 45 and 64 therefore are not elderly and so the care they will require is likely to be needed for many years (Cockram, 2000; Wild, Roglic, Green, Sicree and King, 2004).

There are two classes of diabetes mellitus known as Type 1 Diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM). T1DM is much less common with only 5 - 10 % of all diabetes cases being type 1 (Inzucchi, 2004). This type of diabetes usually presents itself early in life though can occur at any age with some cases not being seen until the patient is elderly (Adams, *et. al*, 2011). It is caused by damage to beta cells, which produce insulin, due to an auto-immune reaction. This damage causes greatly reduced or absent insulin production (Serreze, Flemming, Chapman, Richard, Leiter and Tisch, 1998), as a result patients with type 1 diabetes have to inject themselves with insulin to modulate their blood glucose levels (Atkinson and Eisenbarth, 2001). T2DM is also known as non-insulin dependent diabetes mellitus (Nelson, *et. al*., 2008). The majority of cases of diabetes are type 2 (Raslova, 2010). Typically type 2 diabetes is slow to develop with symptoms often initially going un-noticed for many years; it is frequently associated with older, obese patients. Unlike patients with type one diabetes, T2DM patients do not always have a problem with the production of insulin and sometimes they produce more insulin than should be needed however faults in their insulin-response system cause them to have reduced or total lack of insulin action, these individuals are referred to as being insulin-resistant (Nelson, *et.al*. , 2008).

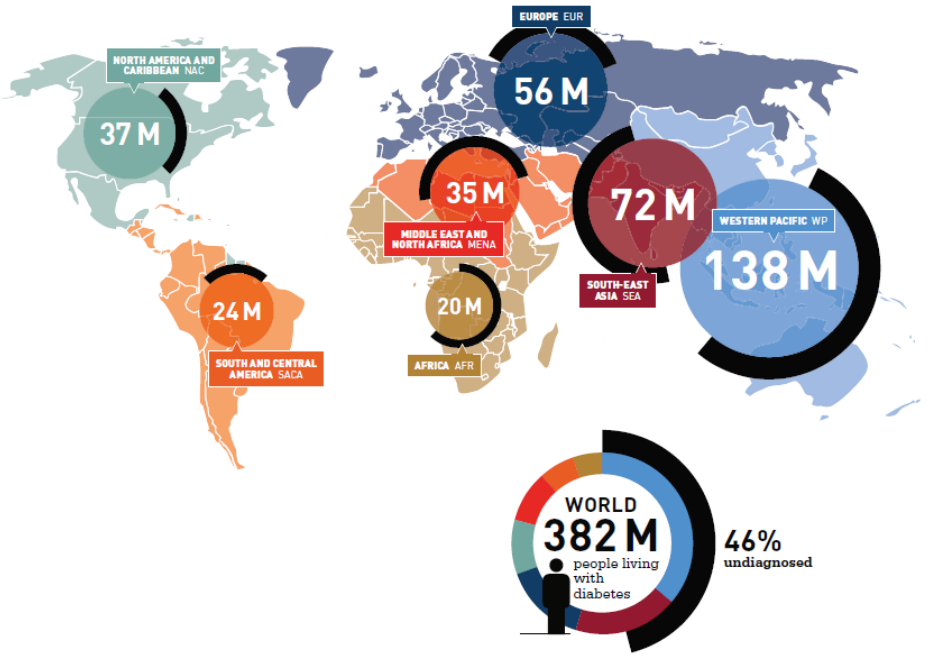

Figure 2 World map showing the prevalence estimation of diabetes by region in 2013. Data reproduced with kind permission from the Diabetes Atlas, sixth edition ©International Diabetes Federation, 2013.

Over many years research has been carried out to develop alternative novel drug delivery systems that would mimic the physiological environment by delivering insulin, in response to the blood glucose level. Formulations such as hydrogels, microcapsules, liposomes, and other soft technology systems as well as inserts and nanoparticles have been proposed (Taylor, Tanna, Taylor and Adams, 1995; Le Bourlais, Acar, Zia, Sado, Needham and Leverge, 1998; Gupta, Madan, Majumdar, and Maitra, 2000; Willoughby, Batterbury, and Kaye, 2002; Yadav, *et. al*., 2009; Adams, *et. al.*, 2011) but no universal remedy for the problems of protein/hormonal delivery have been developed and clinically proven. Consequently, patients continue to be treated by regular injections of insulin via the traditional subcutaneous route. Under these conditions, the glucose level of the patient is monitored externally and when hyperglycaemia occurs insulin is administered subcutaneously. This type of treatment is difficult and tedious and has led to lack of adherence to insulin regimens. As a result, there is increased interest in alternative/ traditional therapies based on, for example, polysaccharides.

The focus of this article is to highlight some of the recent examples of the characterisation and utilisation of cucurbit polysaccharides in diabetes management.

2. The potential role of cucurbit polysaccharides in diabetes management

Cucurbita moshata, also known as butternut squash has been used as a traditional medicine and health food in China for many years, as it is believed to be beneficial to the spleen and lungs (Li, Fu, Rui, Hu and Cai, 2005; Jiang and Du, 2011) in addition to having more specific therapeutic properties including anti-inflammatory, anti-tumour, cholesterol lowering, hypertensive, anti-parasitic and anti-diabetic effects (Fu, *et al*., 2006; Dabaghian, Kamalinejad, Shojaei and Fard, 2012)

Momordica charantia is known by several different names including: karela, bitter gourd, bitter melon, balsam pear, bitter apple, African cucumber and wild cucumber (Krawinkel and Keding, 2006). It is grown in India, China, Eastern Africa and South America and is used in many of these countries to treat a variety of ailments. It is important to note the stage of development of the fruit and therefore the physic-chemical properties of the polysaccharide are important in the bioactive potential for example the *unripe* fruit of the bitter gourd is eaten as a treatment for diabetes and scientific testing has demonstrated that it does exhibit blood glucose concentration lowering properties in both human and animal models (Kumar,

Vijayalakshmi and Salimath, 2006; Nkambo, Anyama and Onegi, 2013; Palamthodi and Lele, 2014). It has been shown that water extracts from bitter gourd increase the uptake of glucose and secretion of adiponectin from fat cells (Dhiman, *et. al*., 2012). Adiponectin is a protein which can be secreted from adipose cells, low plasma levels of adiponectin are associated with insulin resistance and levels of this hormone are seen to be significantly lower in patients with type 2 diabetes (Chandran, Philips, Ciaraldi and Henry, 2003). Some of the molecules from bitter gourd which have anti-diabetic properties include charatin, vicine, polypeptide-p and non-specific anti-oxidants (Krawinkel and Keding, 2006).

Pumpkins (*Cucurbita moshata duch*) are known to contain several bioactive molecules including proteins, peptides, polysaccharides, sterols and para-aminobenzoic acid. These components can be found in seeds, flesh of the fruit and the leaves (Yadav, Jain, Tomar, Prasad and Yadav, 2010; Adams, *et. al*., 2011; Patel, 2013; Adams, Imran, Wang, Mohammad, Kök, Gray, Channell and Harding, 2014). Pumpkin has been shown several times to have anti-diabetic properties and the majority of these bioactive chemicals are concentrated in the fruit (Behera, *et al*., 2012). The polysaccharide extracted from *Cucurbita moshata* (PP1-1) caused a significant, non-competitive inhibition of α-glucosidase at concentrations of 0.7-0.9 mg/ml tested in an enzymatic reaction (Song, *et. al*., 2012). It has also been shown that powdered pumpkin from the species *Cucurbita moshata duch* has hypoglycaemic properties in human type 2 diabetes sufferers (Chen, Wang, Jie, Huang and Zhang, 1994) which was shown to be due to polysaccharide components (Xiong and Cao, 2001; Norfezah, Hardacre and Brennan, 2011). Protein-bound polysaccharides have been demonstrated to be capable of lowering blood glucose concentrations, increasing serum insulin levels and improving glucose tolerance in rats which have been treated with alloxan which destroys their β cells and therefore induces diabetes, it is thought that this effect may have been due to the antioxidant nature of the polysaccharide protecting the pancreatic β cells (Li, Fu, Yukui, Guanghui and Tongyi, 2005)

A clinical study of 30 T2DM patients were treated with polysaccharide granules from pumpkin and compared to a control group, urination and blood tests were monitored and the results showed an improvement in the treated patients, this shows that polysaccharides from pumpkin are capable of controlling glycaemia (Shi, Xiong, Cao and Kang, 2003).
Water-extracted pumpkin polysaccharides were shown to possess superior hypoglycaemic properties compared to glibenclamide in alloxan-induced diabetic rats (Zhang, 2004). This is

perhaps partially explained by the fact that pumpkin is rich in pectin, (Fissore, Ponce, Stortz, Rojas and Gerschenson, 2007), which when consumed is reported to control glycaemic levels and reduce the need for insulin when fibre-rich foods are consumed by patients with diabetes (Guillon and Champ, 2000).

Melons have been shown to have anti-diabetic effects (Perkins-Veazie, 2010), as little as 1 % supplement with ethanol extract from *Citrullus vulgaris* (commonly known as watermelon) rind has been shown to have a significant lowering effect on blood glucose and raises serum insulin concentrations in rats, using immunohistochemistry it was determined that this is due to watermelon having a protective effect on the pancreatic β cells (Ahn, Choi, Kim and Ha, 2011). A high dose of watermelon juice has also been shown to have hypoglycaemic and hypolipidemic effects in diabetic rats (El-Razek and Sadeek, 2011).

Other cucurbits which are believed to have anti-diabetic properties include a variety of gourds: *Cucurbita ficifolia* (fig leaf gourd), *Trichosanthes cucumerina* (snake gourd) and *Benincasa hispida* (wax gourd) (Dhiman, *et. al*., 2012; Palamthodi and Lele 2014). A variety of *Cucurbiteae pepo* better known as a courgette or zucchini may have anti-diabetic effects which are thought to stem, at least partially, from its antioxidant properties (Hamissou, Smith, Carter and Triplett, 2013).

The fibrous inside of the mature fruit of sponge gourd (*Luffa cylindrica*) often known as a luffah or a bath sponge is often used as a cleaning sponge, a component of shock absorbers, for making filters or as part of the sole of shoes however the immature fruit can be eaten. They are believed to be good for diabetes (Bal, Hari, Radha, Madhusudan, Bhuwon and Madhusudan, 2004) and ethanol extracts from *Luffa aegyptiaca* (another species of sponge gourd) leaves have been shown to decrease blood sugar level in alloxan induced diabetic rats as much as the popularly used pharmaceutical treatment metformin without having a significant effect on healthy control rats (El-Fiky, Abou-Karam and Afify, 1996).

Sharmin *et. al.* (2012) looked at the hypoglycaemic and hypolipidemic properties of three species from the cucurbiteae family: *Cucumbis sativus* (cucumber), *Lagenaria siceraria* (white pumpkin) and *Luffa acutangula* (ridge gourd). Tests were carried out using crude ethanol extracts from the fruits of these cucurbits which were given to alloxan induced diabetic rats. Results of blood glucose levels, cholesterol levels, triglyceride levels, low

density lipoprotein levels and improvement in glycolysis from injected doses of 200 mg/kg extract were looked at alongside healthy control rats, diabetic rats and diabetic rats injected with 150 mg/kg of metformin. Results (**Figure 3**) show a significant decrease in blood glucose in alloxan induced diabetic rats when treated with cucurbit extracts. Hyperglycaemic potency is highest in the cucumber followed by the white pumpkin and then the ridge gourd though all three had significant anti-hyperglycaemic effects. Cholesterol and is reported to be high in alloxan induced diabetic rats, this study also demonstrated the cholesterol lowering action of cucumber extract, white pumpkin extract and ridge gourd extract as can be seen in **Figure 4** (Sharmin, Khan, Akhtar, Alim, Islam, Anisuzzaman and Ahmed, 2012).

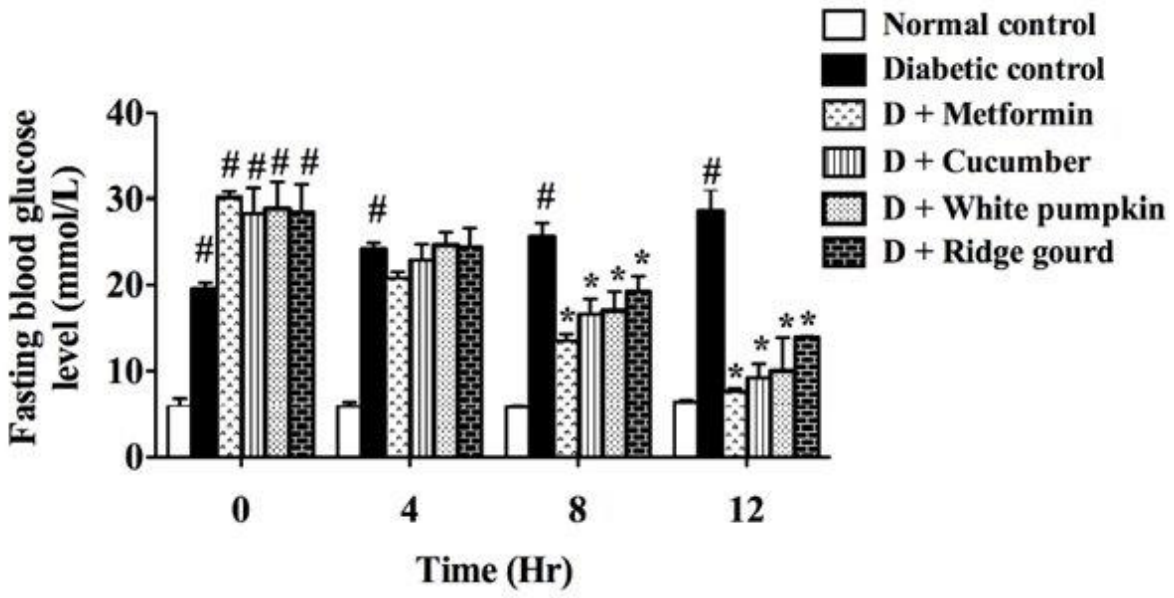

Figure 3 Effects of various cucurbits on the fasting blood glucose levels of alloxan induced diabetic rats over time. # indicates a significant increase in blood glucose levels when compared to the healthy control and * indicates a significant decrease compared to the heal (Sharmin, *et. al*., 2012). Reproduced with kind permission from Prof. A.K.M. Azharul Islam Editor-in-Chief, Journal of Scientific Research.

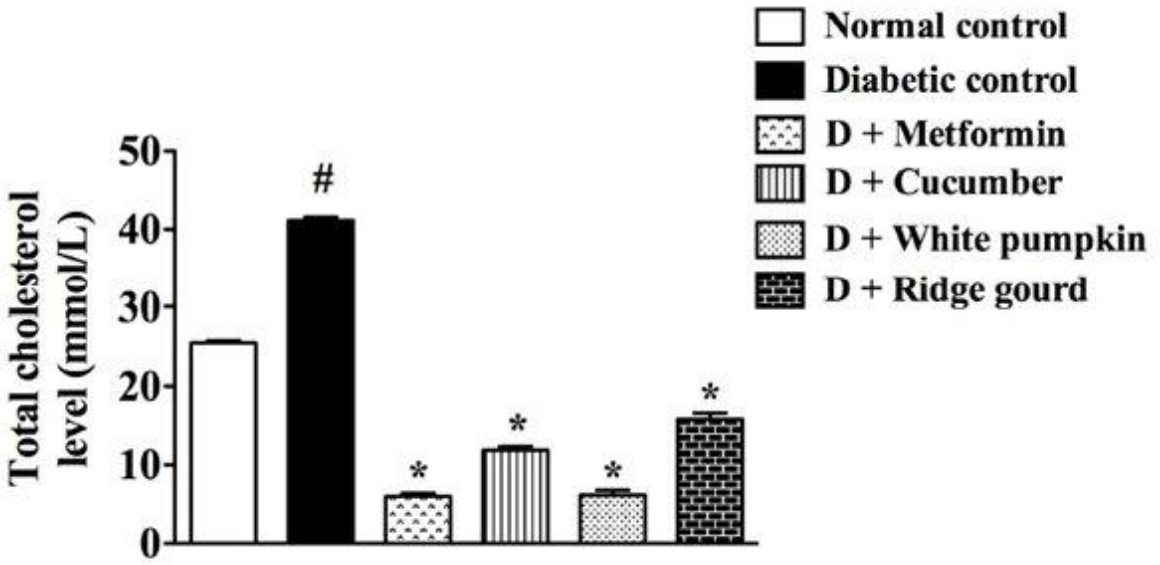

Figure 4 Total cholesterol levels from the serum of alloxan induced diabetic rats compared to a healthy control group where # represents significant increase in cholesterol levels compared to healthy and * represents a significant decrease in total cholesterol (Sharmin, *et. al*., 2012). Reproduced with kind permission from Prof. A.K.M. Azharul Islam Editor-in-Chief, Journal of Scientific Research.

A further study (Zhang, Chen, Zhang, Jin, Li and Yao, 2003) demonstrated similar beneficial effects on blood glucose concentration, total cholesterol and triglyceride levels with the oral administration of water soluble pectin-like polysaccharide consisting of glucose, galactose, arabinose and rhamnose and hexuronic acid extracted from *Cucurbita moschata.* This polysaccharide was tested on alloxan induced diabetic rats and also contained a control drug comparison however Xiaoke pills (a Chinese patented drug) were used rather than metformin. The study also showed glycosylated haemoglobin and beta cell proliferation in the pancreas of alloxan induced diabetic rabbits treated with the polysaccharide from the cucurbit (Zhang, *et. al*., 2013).

Figure 5 shows an electron microscope image of stained cells in the islets of langerhans from three groups of rabbits. The control group (A) is healthy rabbit pancreas cells with a clear mass of stained beta cells, Group B was from an alloxan induced diabetic rabbit pancreas and group C is from alloxan induced diabetic rabbits treated the polysaccharide extracted from *Cucurbita moshata.* The beta cells were stained deep purple-red using orange G-brilliant green stain. As can be seen from the images beta cell regeneration is induced by the oral

administration of the polysaccharide. As yet there is still no mechanism for the anti-diabetic effects of the cucurbit polysaccharide (Zhang, *et. al*., 2013). Similarly beta cell regeneration has been reported in streptozotocin induced diabetic rats treated with juice from bitter gourd (Ahmed, Adeghate, Sharma, Pallot and Singh, 1998).

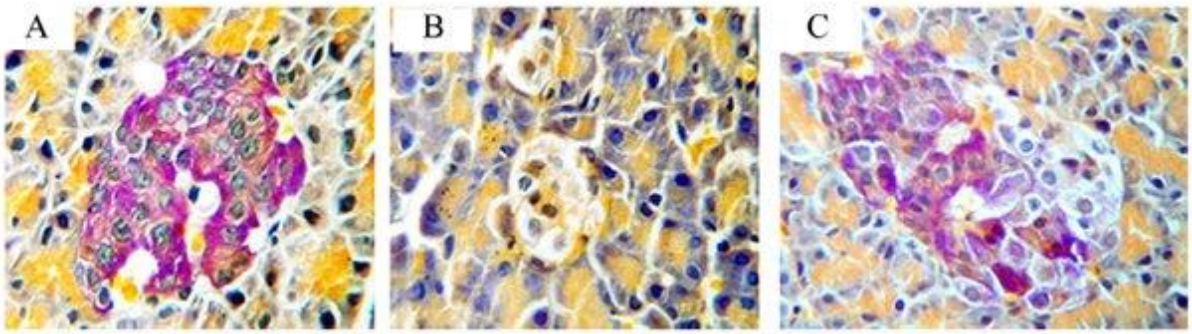

Figure 5 Effect of polysaccharide from *Cucurbita moschata* on beta cells. Images from an electron microscope. A is from a healthy control group, B is from a diabetic control group not treated for diabetes and C is from the pancreas of a rabbit treat with injected polysaccharide from *Cucurbita moschata* (Zhang, *et. al*., 2013). Reproduced with kind permission from Elsevier.

The effect of pumpkin on insulin levels and glucose tolerance in diabetic rats was investigated. Diabetes was induced with alloxin and various doses of protein bound polysaccharide extracted from pumpkin were given orally to rat groups. The results showed that the protein bund polysaccharide lowered the blood glucose concentration, increased the serum production and improve glucose tolerance (Li, *et. al*., 2005); this is similar to other experiments done with other cucurbits and suggests beta-cell regeneration like that seen with bitter gourd.

Table 1 The effect of protein bound polysaccharide from pumpkin on blood glucose tolerance and serum insulin levels. Group 1 rats were healthy controls (not shown in the table). With kind permission from Springer Science+Business Media: *Plant Foods for Human Nutrition*, Effects of protein-bound polysaccharide isolated from pumpkin on insulin in diabetic rats, **60**, 2005, 13-16, Quanhong, Caili, Yukui, Guanghui and Tongyi, **Table 3**).

			Blood glucose and tolerance at time after treatment (mmol/l)			
Group	**Dose (mg/ml)**	**Insulin (uIU/ml)**	**0 hours**	**0.5 hours**	**1 hour**	**2 hours**
Group 2	0	62.5 ± 21.18	23.65 ± 11.17	27.33 ± 9.82	22.11 ± 10.33	20.14 ± 9.85
Group 3	1000	100.4 ±33.89	12.64 ± 10.81	19.43 ± 10.90	14.81 ± 9.69	12.03 ± 9.46
Group 4	500	105.3 ± 6.73	13.23 ± 6.73	21.10 ± 9.76	15.28 ± 9.40	12.79 ± 9.18
Group 5	20	103.4 ± 38.73	13.84 ± 6.42	23.11 ± 9.27	18.13 ± 9.01	14.00 ± 8.56

Sechium edule, also known as choko, sayote, chow-chow or vegetable pear, is a member of the cucurbit family which has been investigated for its anti-diabetic properties on diabetic rats. Extract from the fruit was taken through ethanol extraction and distillation. The rats were divided into five groups: group 1- healthy controls, group 2- alloxan induced diabetic rats, group 3- alloxan induced diabetic rats treated with 5mg/kg of Glibenclamide (an anti-diabetic drug), group 4- alloxan induced diabetic rats treated with 200 mg/kg of extract from *Sechium edule* and group 5- alloxan induce diabetic rats treated with 100 mg/kg of extract from *Sechium edule*. After 21 days of treatment blood was drawn and tested for serum glucose, total cholesterol, serum triglycerides, Low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol and very low density lipoprotein (VLDL)-cholesterol. Total cholesterol levels decreased significantly as did triglycerol levels, LDL-cholesterol and VLDL-cholesterol when treated with *Sechium edule*. HDL cholesterol levels also increased in diabetic rats treated with the extract from the cucurbit when compared to the non-treated diabetic rats. Other observations in this study showed a significant decrease in blood glucose levels when treated with the *Sechium edule* extract compared with non-treated diabetic rats and the prevention of weight loss normally seen with diabetes (Maity, Firdous and Debnath, 2003).

Table 2 Biological parameters of rats treated with *Sechium edule* and controls after 21 days. With kind permission from *World Journal of Pharmacy and Pharmaceutical Sciences*, Evaluation of antidiabetic activity of ethanolic extract of *sechium edule* fruits in alloxan-induced diabetic rats, **2**, 2013, 3612-3621, Maity, Firdous and Debnath, **Table 2**).

Biochemical parameter (mg/dl)	**Healthy control**	**Diabetic control**	**Diabetic treated with 5 mg/kg Glinbenclamide**	**Diabetic treated with 200 mg/kg *Sechium edule***	**Diabetic treated with 100 mg/kg *Sechium edule***
Serum cholesterol	63.72 ± 1.29*	148.9 ± 2.77	71.48 ± 0.61*[a]	79.04 ± 0.58*[b]	86.25 ± 0.68*[b]
HDL Cholesterol	52.68 ± 0.73*	38.73 ± 2.43	55.34 ± 0.76*[a]	71.82 ± 0.77*[b]	62.01 ± 0.47*[b]
Serum LDL cholesterol	51.75 ± 1.89*	148.7 ± 2.23	60.27 ± 0.36*[a]	74.03 ± 3.36*[b]	121.7 ± 3.86*[b]
Serum VLDL cholesterol	29.4 ± 1.58*	36.97 ± 0.27	32.53 ± 0.72*[a]	31.43 ± 0.47*[b]	35.6 3± 0.43*[b]
Serum Triglycerides	147.2 ± 0.54*	242.1 ± 0.76	155.9 ± 2.02*[a]	165.1 ± 0.54*[b]	170.5 ± 0.56*[b]

*$p < 0.01$ when compared to diabetic control

[a]$p < 0.01$ diabetic rats treated with Glinbenclamide when compared with diabetic control.

[b]$p < 0.01$ diabetic rats treated with *Sechium edule* when compared with diabetic control.

A study looking at the hypoglycaemic effects of another member of the cucurbiteae family, *Cucurbita ficifolia* Bouché also known as chilacayote, which is used in Mexico as a treatment for diabetes showed not only that the juice has an anti-diabetic effect but that it may also be toxic (Alarcon-Aguilar, Hernandez-Galicia, Campos-Sepulveda, Xolalpa-Molina, Rivas-Vilchis, Vazquez-Carillo and Roman-Ramos, 2002). Experiments on healthy mice showed that oral and intraperitoneal administrations of freeze dried juice from the fruit of this cucurbit showed a dose dependant anti-diabetic effect. In the minutes following intraperitoneal administration of 750 to 1250 mg/kg of freeze dried chilacayote juice many deaths were observed which suggests that in high doses the juice can be toxic. 14 day oral

administrations were also investigated and it was found that they significantly reduce blood glucose levels in alloxan induced diabetic rats however once again toxicity was also observed. Current use in diabetic patients in Mexico are of a much lower dose (100 mg/kg) and no toxic effects have been seen suggesting that only high doses are toxic (Alarcon-Aguilar et. al., 2002). Toxicity effects would need to be further investigated prior to further testing and eventual approval.

Table 3 A summary of the potential anti-diabetic effect of cucurbit polysaccharides

Species	Common Name	Putative Therapeutic Effect	Reference
Citrullus vulgaris	watermelon	lowers blood glucose; increases serum insulin concentrations; protective effect on the pancreatic β cells	Ahn, *et. al*., 2011
Cucurbita ficifolia Bouché	chilacayote	lowers blood glucose	Alarcon-Aguilar, *et al*., 2002
Cucurbita moshata duch	pumpkin	lowers blood glucose concentrations; increases serum insulin levels; beta cell regeneration	Quanhong *et. al*., 2005; Zhang, *et al*., 2013
Cucumbis sativus	cucumber	lowers blood glucose	Sharmin, *et. al*., 2012
Lagenaria siceraria	white gourd	lowers blood glucose	Sharmin, *et. al*., 2012
Luffa acutangula	ridge gourd	lowers blood glucose	Sharmin, *et. al*., 2012
Luffa aegyptiaca	sponge gourd	lowers blood glucose	El-Fiky, *et. al*., 1996
Luffa cylindrica	sponge gourd	believed to be beneficial in diabetes	El-Fiky, *et. al*., 1996
Momordica charantia	karela, bitter gourd, bitter melon, balsam pear, bitter apple, African cucumber or wild cucumber	increases the uptake of glucose and secretion of adiponectin from fat cells	Dhiman, *et. al*., 2012
Sechium edule	choko, sayote, chow-chow or vegetable pear	lowers blood glucose	Maity, *et. al*., 2013

3. Conclusions

Studies have evidently shown that cucurbits are a promising area of research into plant based anti-diabetic agents (**Table 3**). There is significant evidence that fruits of the cucurbit family are effective as anti-diabetic treatments however the mode (or modes) of action is as yet unknown. The majority of tests have been carried out with crude extracts with only a few papers characterising the molecules that are being used. Where polysaccharides have been suitably characterised it appears as though pectins (or pectin-like polysaccharides) are a suitable candidate as the potentially bioactive polysaccharide (Zhang, *et al*., 2003; Fissore, *et al*., 2007; Inngjerdingen, *et al*., 2008; Grønhaug, *et al*., 2010; Košťálova, Hromádková and Ebringerová, 2013; 2014). Further knowledge the fine structure (*e.g.* sugar composition, linkage, molar mass and conformation) of these bioactive polysaccharides (and any natural variation in fine structure) could lead to potential routes to modification (Inngjerdingen, *et. al*., 2007; Košťálova, *et al*., 2013; 2014), synthesis (Flitsch, 2000; Ladmiral, Melia and Haddleton, 2004; Vázquez-Dorbatt, Lee, Lin and Maynard, 2012) or fractionation (Morris and Ralet, 2012a,b) which may produce more effective carbohydrates for use in the control of diabetes or in the supplementation of functional foods (Norfezah, *et al*., 2011; Morris and Morris, 2012). Currently there is no research to suggest whether the biologically active component of these plants is the same in each cucurbit through the effects seem to be consistent throughout the cucurbit family. It has been shown that the bioactive component in *Cucurbita moshata* is a polysaccharide (Zhang, *et. al*., 2013) though further research would be required to identify if this is true for all members of this family.

Current lack of knowledge of the structure and toxicity of the bio-active components of cucurbits does not sit well with pharmaceutical agencies and would have to be further researched in order for it to become a viable option in western medicine (Paterson, 2008) once characterised enzymatic (Fissore, *et al*., 2007; Inngjerdingen, *et. al*., 2007) or chemical modifications (Morris, Ebringerová, Harding, and Hromádková, 1999; Morris, Hromádková, Ebringerová, Malikova, Alfoldi, and Harding, 2002; Koschella, Inngjerdingen, Paulsen, Morris, Harding and Heinze, 2008) could be used to improve functionality in a similar way to previous work with other polysaccharides (Fissore, *et. al*., 2007) such as the pectic polymer from *Glinus oppositifolius* (Inngjerdingen, *et. al*., 2007).

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