

Herbal Medicine in Diabetes Mellitus: Effectiveness of Punica Granatum Peel Powder in Prediabetics , Diabetics and Complicated Diabetics.

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Abstract

Diabetes mellitus (DM) is a common worldwide chronic metabolic disorder. Heredity and obesity are well known risk factors for diabetes. DM is one of the earliest described health problems, nevertheless it is still incurable disease. Patients with DM have to be kept on regular insulin or oral hypoglycemic drugs (OHD), for adequate glycemic control. These medications have its own side effects including hematological disorders. These side effects besides the complications of DM itself influence patient's quality of life. The introduction of safe, tolerable and comparatively cheap natural remedies in management of DM will solve this problem. Punica Granatum peel powder (PGPP) is a natural remedy obtained with grinding dried pomegranate peel. Ingestion of a teaspoonful of PGPP before meals was found to have a strong hypoglycemic effect on both normal and diabetic animals and humans. This article reviewed meticulously the role of PGPP in management of pre-diabetics, diabetics and complicated diabetics.

Keywords: Herbal Medicine, Diabetes Mellitus, Punica granatum, pre-diabetics.

1. Introduction

Diabetes Mellitus is a chronic metabolic disorder characterized by deranged metabolism of carbohydrates, lipids and proteins. Its incidence in Saudi Arabia is rising this was related to increased incidence of predisposing and precipitating factors of diabetes (Al-Nozha *et al.* 2004). Obesity, sedentary life style, emotional stress and family history are the most important risk factors for diabetes. The main feature of DM is hyperglycemia, which is the main pathologic insult for most of the clinical and laboratory manifestations of DM. Etiologically DM is broadly classified into primary and secondary DM according to whether the main pathology is pancreatic or extra pancreatic (Gerstein *et al.* 2007). Primary DM is further classified into two types, insulin dependent DM (IDDM) in which there is absolute insulin deficiency and non insulin dependent DM (NIDDM) with relative insulin deficiency. NIDDM or type 2 diabetes is the most prevalent type of DM (Knowler *et al.* 2009), fortunately it could be prevented by avoiding the aforementioned risk factors (Crandall *et al.* & Heikes *et al.* 2008).

Although DM is the earliest described metabolic disease, yet it is still incurable disease (Prasanth *et al.* 2009). However with the discovery of islet cell transplantation (IST) long life cure obtained in some cases. Nevertheless IST is not available in many healthcare centers besides it is too expensive. Furthermore IST is applicable for patients with type 1 diabetes and carries the risk of post-transplant rejection (Close *et al.* 2005).

The recent introduction of Chinese herbology in various health problems, acted as an attracting force that diverted researchers to the use of medicinal plants in many diseases (Gupta & Sharma 2006). Due to its wide spread DM was in the center of these diseases (Dhanbal 2004 & Shokeen *et al.* 2008). Some researchers suggested Punica Granatum juice, flower or peel extract (PGPE) as a natural remedy in DM, others recommend thier use in prevention of DM in prediabetics (Huang *et al.* 2005). This article reviewed meticulously the role of PG in DM. Due to the reported higher content of antioxidants in PGP (Yunfeng *et al.* 2006) accordingly this article focused on the effect of PGPP in patients with DM, whether in prevention, treatment or in delaying complications.

2. Historical background

Pomegranates scientifically known as Punica granatum have been cultivated and known by ancient cultures and was used in traditional medicine of these cultures. The ancient Egyptians cultivated pomegranates and utilized it in a diversity of health troubles. Tell now Egyptian farmers and their families used to eat pomegranate extensively in winter considering that it has a protective effect against influenza. Also they advised any bride and her bridegroom to consume pomegranates as they believe that it enhances reproduction and improves sexual performance. Furthermore Egyptian, farmers knew that the colour of pomegranate juice on clothes is steady and could not be removed easily, accordingly they use it together with Hibiscus to colour textiles (Seeram *et al.* 2006).

In Upper Egypt there is an important tradition that farmers used to eat pomegranate pulp and drink its juice, then the peel is left to dry and boiled in water. People who have abdominal pains, diarrhea, and dysentery drink the boiled PP on empty stomach, followed by a spoonful of honey. Sometimes they grinded the peel and those with abdominal pains have a spoonful of this powder together with honey also while fasting. They claimed that if you do not use honey in conjunction with PGPP you will feel dizzy, sweaty, and nauseated after a while, besides honey ameliorates the bitter taste of PGPP . Recently many researchers proved and discovered the scientific basis of the use of PGPP in Egyptian traditional medicine (Mathabe *et al.* 2006; Vasconcelos *et al.* 2006; Aqil and ahmed 2007; Lansky and Newman 2007; Forest *et al.* 2007; Jurenka 2008; Turk *et al.* 2008).

Pomegranate is primarily a fruit of middle east and grow extensively in many Arabic countries, particularly in Egypt and Saudi Arabia. Also it is widely cultivated in India and Southeast Asia. In America it is cultivated mainly in Arizona and California. Pomegranates have been mentioned in holly Quran more than once. Furthermore Prophet Mohamed advised his followers to eat the whole pomegranate seeds as there is a seed from paradise in each pomegranate fruit. Also, Earlier Muslims believed that pomegranate peel has a potent protective effect on the stomach. Pomegranate was mentioned in other Holly books as Torah and Bible. Some Jewish believed that the holly tree where the God talked to Musa is a pomegranate tree (Stover and Mercure 2007).

3. Composition and effects of PGPP

3.1 Proximate composition of PGPP

PGP was the focus of research for many researchers this was due its wide array of health effects. Analysis of PGPP using modern analytical techniques revealed that PGP extract (PGPE) composed of water, sugar, protein, and fiber. Reducing and non reducing sugars constituted the main bulk of PGPP followed by crude fiber, as shown in figure 1(Naseem *et al.* 2012).

PGP was found to have a strong antioxidant effects, this was attributed to its high concentration of polyphenols including catechins , quercetins , ellagitannins, ellagic acids, gallotannins, gallagic acids, ferulic acids, anthocyanins (Gil *et al.* 2000; Zhang *et al.* 2007). A study in china proved that PP has the highest antioxidant concentration among peels, seeds or pulps of 28- different types of fruits (Guo *et al.* 2003). Also it was proved that PGPE contained higher antioxidants fractions compared to pulp extract (Tomas-Barberan *et al.* 2001; Chidambara 2002) and figure 2 revealed comparison of antioxidants between pomegranate pulp and peel extracts.

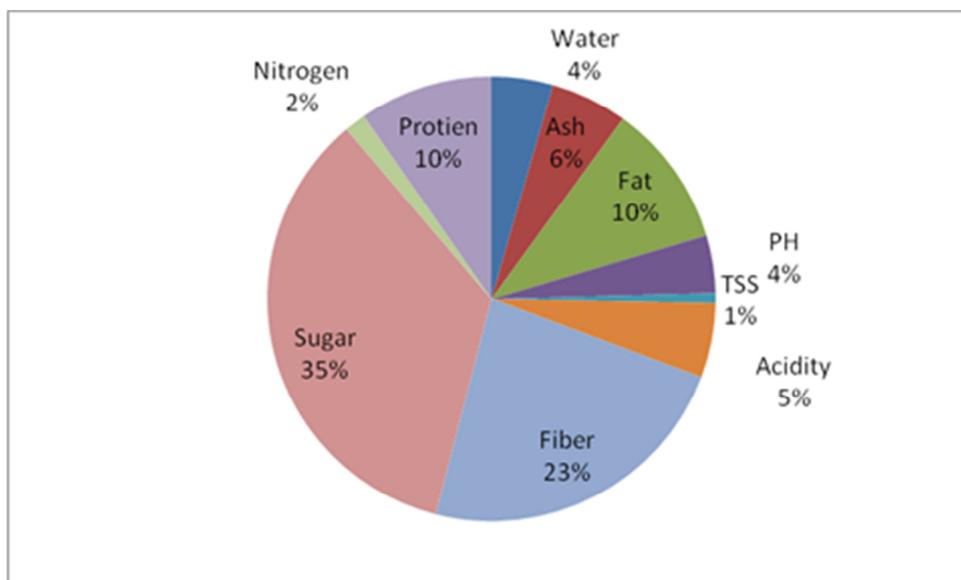


Figure 1: Proximate composition of Punica Granatum peel extract (Naseem *et al.* 2012).

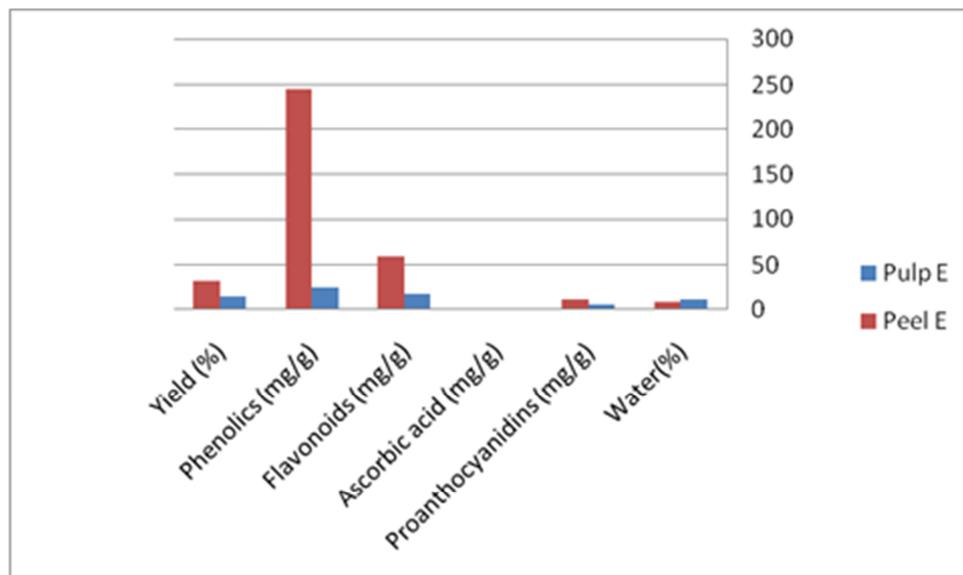


Figure 2: Main antioxidant fractions contained in pomegranate peel and pulp extracts (Li *et al.* 2006).¹³ Considering minerals contained in PGPP it was found that it is rich in Ca, P, K, and Na. Also it has a considerable amount of Fe, Zn, Mn, Cu and Se. However it does not contain Mg. Furthermore PGPP is rich in vitamins C, E, and A (Waheed *et al.* 2004; Rowayshed *et al.* 2013). These vitamins proved to have strong antioxidant effects besides their immunogenic and epithelial protecting effects (Huxley and Niel 2003). Also, PGPP contained good amount of Thiamine and Riboflavin, as depicted in figure 3.

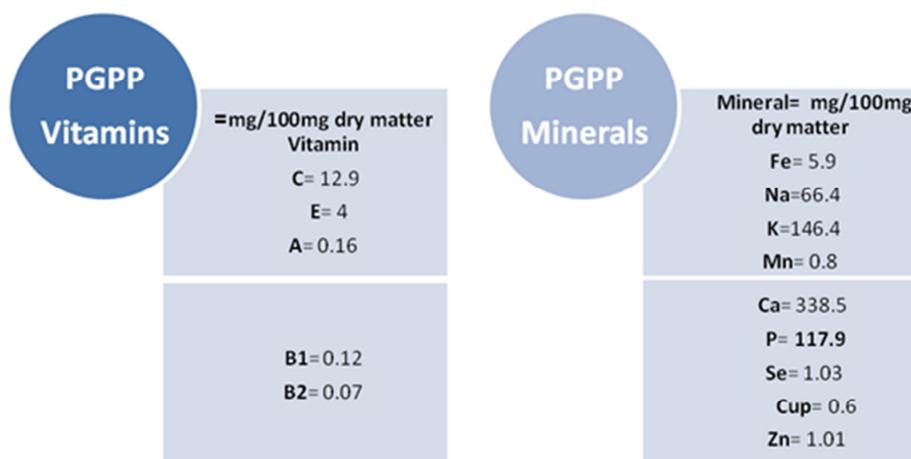


Figure 3. Vitamins and minerals content of PGPP (Punica Granatum peel powder).

3.2 Health effects of PGPP

Many researchers proved the beneficial effects of PGPP in various health problems. Most important of these effects are lowering the risky serum LDL-cholesterol, raising the good HDL-cholesterol, lowering blood glucose, enhancing insulin action and reducing blood pressure (Aviram and Donefel 2001; Rosenblat 2006). Also it has a potent anti-diarrhoeal, anti-ulcer, anti-parasitic and antimutagenic effects (Toi *et al.* 2003; Lansky and Newman 2007). These broad spectrum of preventive and therapeutic effects of PGPP in cardiovascular, metabolic and gastrointestinal disorders were proved with both animal and human studies many years ago (Huang *et al.* 2005). However the use of PGPP in clinical practice still retarded, although it is widely available in stores of traditional and herbal medicine, safe, cheap and relatively tolerable. This mainly due to unawareness of physicians and health care providers with PGPP and its wide array of medical applications.

Because of its safety and availability, PGPP attracted the attention of researchers in food processing, cosmetics and industry. PGPP was found to be highly effective and safe food preservative particularly for meat products. Furthermore it was used as a bulking agent in these products. PGPP provides these benefits through its high fiber content that reduce residual nitrite and prevent the formation of Nitrosamide and Nitrosamines, also through its bactericidal and bacteriostatic properties. The safety of pomegranate extracts was proved with

histopathological examination of rat tissues after long duration of treatment and showed no toxic effects on renal, hepatic or cardiac tissues (Cerda *et al.* 2003). Accordingly the use of PGPP in food processing and food industry will reduce the risks of the toxic and carcinogenic chemical food preservatives and could reduce the incidence of renal failure or gastrointestinal malignancies. Another important benefit of PGPE is its peculiar taste which adds flavour to food.

Dentists were also interested in pomegranate and a lot of research was conducted to prove its role in dental health whether the fruit, juice, flower or peel. Extracts of pomegranate fruit and peel were added to tooth pastes to help fight dental plaques, and was found effective in management of stomatitis and periodontal abscess (Lacopino and Wathen 1992; Menezes *et al.* 2006). These effects were attributed to the high content of punicalagin and ellagitannin in pomegranate extracts. Both exert a potent bactericidal effect against, *E. coli*, *Streptococci*, *Staphylococci*, *Proteus* and *Klebsiella* species (Braga *et al.* 2005; Voravuthikunchai and Limsuan 2006). An interesting finding was that of Sastravaha and his co-workers who found significant reduction of inflammatory markers IL-6 and IL-1B in patients with periodontal disease after implantation of biodegradable chips medicated with mixture of PGE and *Centella Asiatica* (Sastravaha *et al.* 2005; Adams *et al.* 2006).

4. Effectiveness of PGPP in pre-diabetics

4.1 What is pre-diabetes?

Pre-diabetes is a term that was long used to describe those with risk factors for development of diabetes (Alberti 2007). However, in 2005 the American diabetes Association limit this term to those with impaired glucose tolerance and impaired fasting blood glucose, and define important criteria for diagnosis of pre-diabetes (American Diabetes Association 2005). Table 1, showing laboratory diagnosis of pre-diabetes and diabetes (American Diabetes Association 2010). Pre-diabetes alone without progression to frank clinical diabetes was found to be a risk factor for development of micro-vascular disease. Persistent hyperglycemia is the main pathogenic insult of these complications (Sprague and Ellsworth 2010; Singleton *et al.* 2003).

Table 1. Laboratory diagnosis of pre-diabetes and diabetes. OGT: oral glucose tolerance, FBG: fasting blood glucose.

| Diagnosis | OGT | FBG | HBA1c |
|--------------|---------------------|----------------------|----------------|
| Normal | <140 mg/dl | < 100 mg/dl | < 5.7% |
| Pre-diabetes | 140l - 199 mg/dl | 100- 125 mg/dl | 5.7% to 6.4% |
| Diabetes | 200 mg/dl or higher | .126 mg/dl or higher | 6.5% or higher |

Symptomatology and disease progression of diabetes or pre-diabetes was found to be closely related to lipid peroxidation (LPO) and reactive oxygen species (ROS). Accordingly antioxidants were suggested agents to decrease diabetes/pre-diabetes related morbidity and mortality (Evans *et al.* 2002; Piconi *et al.* 2003). As PGPP has a high antioxidant fractions so it could be highly effective natural remedy in pre-diabetics.

4.2 Role of PGPP in prevention of diabetes in pre-diabetics

Streptozotocin (STZ) is a substance used to induce diabetes in lab animals. Its action is mediated through its cytotoxic effect on pancreatic β -cells, which was linked to the ability of STZ to induce oxidative stress. This was associated biochemically with decreased anti-oxidant enzymes, increased LPO and production of ROS (Lenzen 2008; Nizamutdinova *et al.* 2009; Szkudelski 2012). Alloxan is another substance that is used for production of diabetes in experimental animals. PGPE offered an effective protective effect against both STZ and alloxan induced biochemical derangements and DNA fragmentation in rats. Subsequently prevent and delay occurrence of DM in these animals (Enas 2004; Parmar and Kar 2007; Afreen *et al.* 2015).

Screening for pre-diabetes leads to early identification of those at risk to develop DM. Accordingly early interventions and protective measures could prevent or delay occurrence of diabetes and its complications. Physicians and health care providers should set up a preventive plan for pre-diabetics. Besides the well known dietary and life style modifications inclusion of PGPP in this plan would be highly beneficial. On the other hand treatment related side effects is nearly nil.

How PGPP prevent or delay incidence of diabetes in prediabetics?. This could be explained with the strong anti-oxidant properties of PGPP (Poyrazog 2002). Accordingly PGPP keeps the body's anti-oxidant state in its normal value. This in turn normalizes insulin release, reduces insulin resistance and allows adequate glycemic control. This was recently confirmed with the reported protective effect of PGPE against hepatic LPO through its direct or indirect action on glutathione (Kaur *et al.* 2006).

5. Possible implications of PGPP in treatment of diabetes mellitus

PGPE was found highly effective in reducing serum blood glucose, triglycerides, LDL-cholesterol and increase HDL in diabetic animals (Esmailzadeh *et al.* 2004; Armar and Kar 2007; Althunibat *et al.* 2010; Hala *et al.* 2012; wang *et al.* 2015).

A study by Tyagi revealed that 10-ml of PGPE before breakfast and after dinner, effectively lower fasting and post-prandial blood glucose in patients with type2 DM (Tyagi 2013). However in this study the sample size was small (25-patient), and the duration of follow up was short (30-days). In addition patients were uncomplicated nearly controlled diabetics.

The potency of the antidiabetic effect of PGPE was found to be increased when combined with other herbs. Afreen and his co-workers reported good glycemic control and reduced hepatic fatty changes with a combination of PGPE, *Spilanthes Paniculata* flower extract and sodium selenite in diabetic rats (Afreen *et al.* 2015).

In conclusion both human and animal research showed that PGPE effectively reduced serum blood glucose in both normal and diabetic subjects. Unfortunately human research was too little, furthermore the use of PGPP in management diabetic patients is not in mind of many physicians and medical practitioners.

How PGP decreased blood sugar?. This was explained by the concomitant increase of blood insulin levels. Also, increased number of pancreatic B-cells was noted. Another possible important mechanism is its stimulatory effect on insulin receptors (Khalil 2004). In addition PGPP or E returns the anti-oxidant status to normal and offers anti-atherogenic effects (Osaw *et al.* 1987; Fenercioglu *et al.* 2010). In a trial to discover the active ingredient of PGP with anti-hyperglycemic effect, some researchers isolated a compound known as VAD (valoniec acid dilactone) from PGP extract. VAD was found to have a wide array of effects including inhibition of alpha amylase enzyme and subsequent reduction of post-prandial hyperglycemia. Effects of VAD were proven with correlation of biochemical and histopathological studies (Jain *et al.* 2012) , and further supported the idea of using PGPP in management of diabetic patients.

6. Role of *Punica Granatum* peel powder or extract in complications of diabetes mellitus

Complications of diabetes are the main cause of DM related morbidity and mortality. Recently it was found that oxidative stress plays an important role in disease progression and development of complications in diabetic patients (Sanders *et al.* 2001; Bhor *et al.* 2004; de M Bandeira *et al.* 2013) . Accordingly herbs rich in antioxidants such as PGPP could be a promising future treatment that could prevent or delay incidence of complications in diabetic patients (Kim *et al.* 2003).

PGPE showed a strong antibacterial effects on animals with skin wound, furthermore it promotes wound healing (Naseem *et al.* 2012). Figure 4 showed zone of inhibition of susceptible micro-organisms using 50ug/50ul PGPE solution, and figure 5 demonstrated the rate of wound healing in presence of 5% PGPE ointment (Osman *et al.* 2015). Wound healing properties of PGPP was attributed to its gallic acid and catechins content (Murthy *et al.* 2004). These findings suggested the efficacy of PGPP in prevention and treatment of diabetic wound infection. However further research is needed for development of PGP gels and to determine the appropriate concentration of PGPP in these topical therapies.

A recent study at AL Taif University, KSA, showed improved renal nephropathy in diabetic rats treated with PGPE. This was manifested histopathologically with healing of glomeruli and return of both glomerular capillary and tubular basement membranes to normal thickness (Ahmed *et al.* 2014). These effects were attributed to the proven antifibrotic and anti-inflammatory properties of PGPE (Toklu *et al.* 2007; Toklu *et al.* 2009). Tubulinterstitial fibrosis was found to be the main pathophysiologic mechanism of diabetic nephropathy (Qian *et al.* 2008).

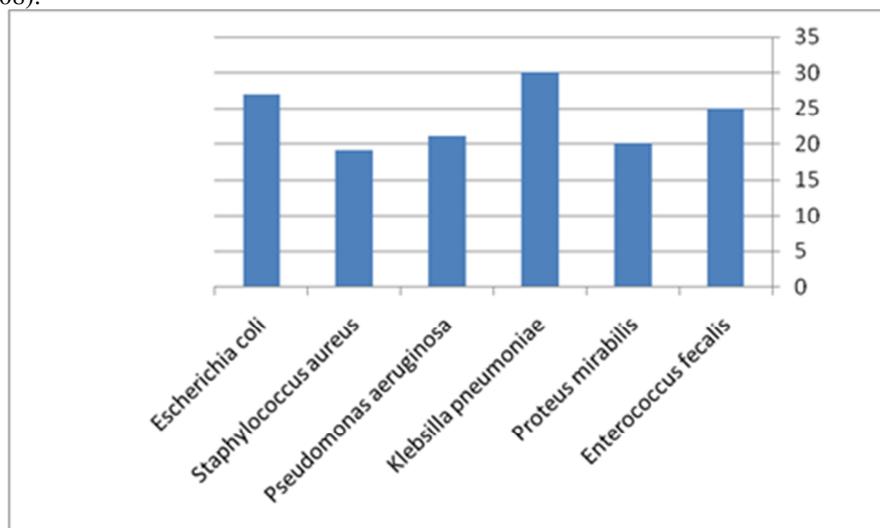


Figure 4. Zone of inhibition of susceptible bacteria using PGPE solution 50ug/50ul (Osman *et al.* 2015).

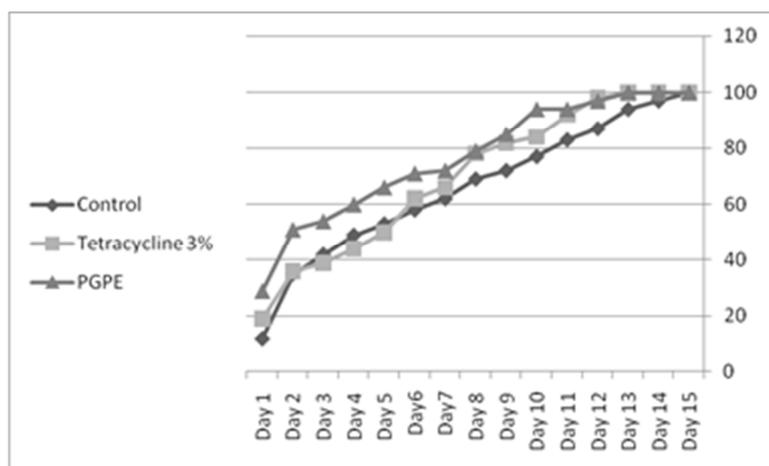


Figure 5. Rate of wound healing in presence of 5%PGPE compared to 3% tetracycline ointment and the control. (Osman *et al.* 2015).

PGPE was found to have a pre-biotic effect on the gut microbiota. This was accompanied with down regulation of the inflammatory markers such as IL-6, IL-1B, and COX-2 in colon cells and gut fatty tissue. This in turn lowers LDL-cholesterol (Neyrinck *et al.* 2013). These findings provide strong evidence that PGPP would be highly effective in prevention of cardiovascular complications in diabetes, and in improvement of lipid profile of the patient.

7. Conclusion

In conclusion this review demonstrated the various effects of PGPP or PGPE in management of pre-diabetics, diabetics and complicated diabetics. However most of the research concerning effects of PGPP were in experimental animals. Considering that PGPP is a natural remedy with little or no side effects we recommend that it is the time to rely on PGPP in management of different types of DM at different stages of the disease. PGPP extract is also well tolerated by patients apart from the unpleasant bitter taste that could be combated with concomitant honey ingestion. Furthermore we assumed that with the introduction of PGPP in DM will decrease the incidence of dangerous hypoglycemic attacks that caused by long acting OHD. Accordingly, we recommended the prescription of PGPP for patients with primary or secondary DM whether IDDM or NIDDM. However, further large scale clinical trials are still needed to ensure whether PGPP could totally substitute insulin or OHD. Also to recommend the appropriate dosing and monitoring. In these trials long term follow up is recommended in an attempt to reinsure the preventive effect of PGPP in diabetes related complications. Also these trials have to focus on human research and to assess patient preference and adherence to PGPP.

On the other hand, most of the research conducted so far concerned with PG in DM focused on type 2 diabetes. This may be because the main mechanism of action of PGPP is through stimulation of beta-cell function and enhancement of cellular regeneration. Accordingly sufficient percentage of functioning beta cells is needed for the action of PGPP. In type 1 DM there is nearly absolute insulin deficiency and auto-immune destruction of beta cells, and when DM is clinically evident nearly 90% or more of beta cells is destroyed. Even though we recommend further clinical trials of PGPP in type 1 diabetics. We assumed that if PGPP has little or no role in glycemic control it will play an important role to prevent or delay incidence of complications. Also PGPP will be safe in other types of secondary DM particularly in gestational diabetes.

We assumed that the introduction of PGPP in treatment of pre-diabetics, diabetics or complicated diabetics to start as an adjunctive therapy with the present OHD. Next, gradual reduction of the dose of OHD and increase in PGPP concentration, till complete withdrawal of OHD. This method will prevent the incidence of unexpected diabetic comas.

Conflict of interest: The author declared that there were no conflict of interest associated with this research.

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