

Effect of Dragon Fruit on Glycemic Control in Type 2 Diabetes: A Systematic Review

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ABSTRACT

Dragon fruit reduces blood glucose level by attenuating fibroblast growth factor-21 resistance and regenerating pancreatic cells. The purpose of this systematic review is to determine the effect of dragon fruit on glycemic control in type 2 diabetes. Literature review up to November 2016 was performed in Pubmed, CENTRAL, CINAHL, Scopus, ScienceDirect, Proquest, Web of Science, LILACS, NAPRALERT, CNKI, IPI, Indonesia OneSearch and MALRep. Three trials (N=109) met inclusion criteria and were included. The results suggested that dragon fruit may decrease fasting plasma glucose and 2-hours post-prandial glucose in type 2 diabetes. Based on the current evidence, dragon fruit may be effective in glycemic control in type 2 diabetes. Nonetheless, because of limited data and low quality of available evidence, high quality trials are warranted to further evaluate the effect dragon fruit and its clinical application.

Keywords: Dragon fruit, Type 2 diabetes, Systematic review

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Introduction

In 2016, WHO (World Health Organization) reported that the incidence of diabetes all around the world is in an increasing trend since 1980, rising from 4.7 % to a double 8.5 % in 2014 in adult population. The majority of diabetic patients are affected by type 2 diabetes (World Health Organization [WHO], 2016). Diabetes mellitus is a group of metabolic disorders of fat, carbohydrate and protein metabolism, resulting from defects in insulin secretion, insulin sensitivity or both (Dipiro et al., 2014). Diabetes can be controlled by chemical drugs and medicinal plants which have an influence on insulin secretion and blood glucose concentration (Prabhakar and Doble, 2008). Dragon fruit is one of the medicinal plants which has been reported to have a potential as diabetes mellitus treatment (Ajie, 2015). It is a member of cactus family and marketed as *Hylocereus undatus* (red peel with white flesh, white dragon fruit, white pitaya), *Hylocereus polyrhizus* (red peel with red flesh, red dragon fruit, red pitaya), *Hylocereus costaricensis* (red peel with super-red flesh, super-red dragon fruit, red pitaya) and *Selenicereus megalanthus* (yellow skin with white flesh, yellow dragon fruit, yellow pitaya) (Fanning and Diczbalis, 2013). It has hypoglycemic property through attenuating fibroblast growth factor-21 (FGF-21) resistance, improving insulin resistance, reducing oxidative stress and preserving pancreatic beta-cell function (Song et al., 2016 (b); Ismaviani, 2014). However, the results of clinical trials which assess an impact of dragon fruit on blood sugar level remain controversial.

Objective of the study

To evaluate the effect of dragon fruit on glycemic control in type 2 diabetes.

Research Methodology

Search Strategy

A literature search was conducted in MEDLINE (Pubmed), Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, ScienceDirect, Proquest, Web of Science, Latin American and Caribbean Health Sciences Literature (LILACS), Natural Product Alert (NAPRALERT), China National Knowledge Infrastructure (CNKI), Indonesian Publication Index (IPI), Indonesia OneSearch, Malaysian Academic Library Institutional Repository (MALRep), <http://clinicaltrials.gov>, <http://www.clinicaltrialresults.org/> and <http://www.controlled-trials.com>. The following medical subject headings (MeSH) terms including betacyanin, diabetes mellitus, hyperglycemia and insulin resistance were used. Key words search including [*“Hylocereus polyrhizus”* or *“Hylocereus undatus”* or *“Hylocereus costaricensis”* or *“Selenicereus megalanthus”* or “dragon fruit” or “pitaya” or “buah naga” or “betacyanin” AND “type 2 diabetes mellitus” or “insulin resistance” or “hypoglycemic effect” or “antidiabetic effect” or “blood glucose lowering effect” or “impaired plasma glucose” or “impaired glucose tolerance”] was performed. Hand search of related citation articles was also undertaken. The bibliographic databases were searched from their respective inceptions up until November 2016 without language restriction. Non-English-language articles were translated into English.

Study Selection

Resulting studies were evaluated and selected independently by two reviewers, with a final review for eligibility was made by third reviewer. Studies were selected if they were (1) randomized controlled trials (RCT) which compare effect of dragon fruit with no treatment or placebo in type 2 diabetes and (2) reporting glycemic parameters including fasting plasma glucose (FPG) or 2-hour post-prandial glucose (2HPP) or haemoglobin A1C (HbA1C).

Data extraction and quality assessment

Data from eligible studies were extracted and recorded independently by two reviewers. Disagreements were resolved by a third reviewer. The following data were extracted from each study: main author, year of publication, country of study origin, study design, study population, number of patients, duration of study, dragon fruit product and dose, baseline and endpoint values of outcome measure and details of treatment and control. The quality of trials was assessed by five-point quality scale developed by Jadad et al. (1996) which contains three items (randomization, double blinding and withdrawal or drop out). The maximum score possible was five points. The quality of studies was considered as low (Jadad score < 3) or high (Jadad score \geq 3).

Results

Study selection

The study selection method was presented in **Figure 1**. A total of 536 records were identified through databases and other sources including hand search of related citation articles. 119 records were excluded because of duplication. After screening the titles and abstracts, 411 records of phytochemical, animal, agricultural, industrial and in-vitro studies and review articles were removed. Two studies in prediabetic subjects (Akhiruddin, 2013; Widyastuti and Noer, 2015) were removed. One trial (Firdayati, 2015) was excluded because the study design is not clear and only abstract is available. Finally, three randomized controlled trials met the inclusion criteria were included in the systematic review.

Studies characteristics

A total of three studies were involved in this systematic review. In all trials, the effect of dragon fruit was assessed in comparison with no treatment. The preparation of dragon fruit was red dragon fruit juice or fresh red dragon fruit. One trial was in English and two trials in Indonesian language. The duration of studies was 10 days to 7 weeks and sample size range from 28 to 51 participants. Two to three treatment arms for different dosage of dragon fruit were compared with no treatment group. The characteristics of the included studies are presented in **Table 1**.

Methodological quality

All studies (Hadi et al., 2012; Hapsari et al., 2015; Wiardani et al., 2014) were described as randomized controlled design but did not report methods for random sequence generation and not describe usage of double-dummy method. So, they were graded as low quality. The quality assessment of the included studies by Jadad's scoring system is shown in **Table 2**.

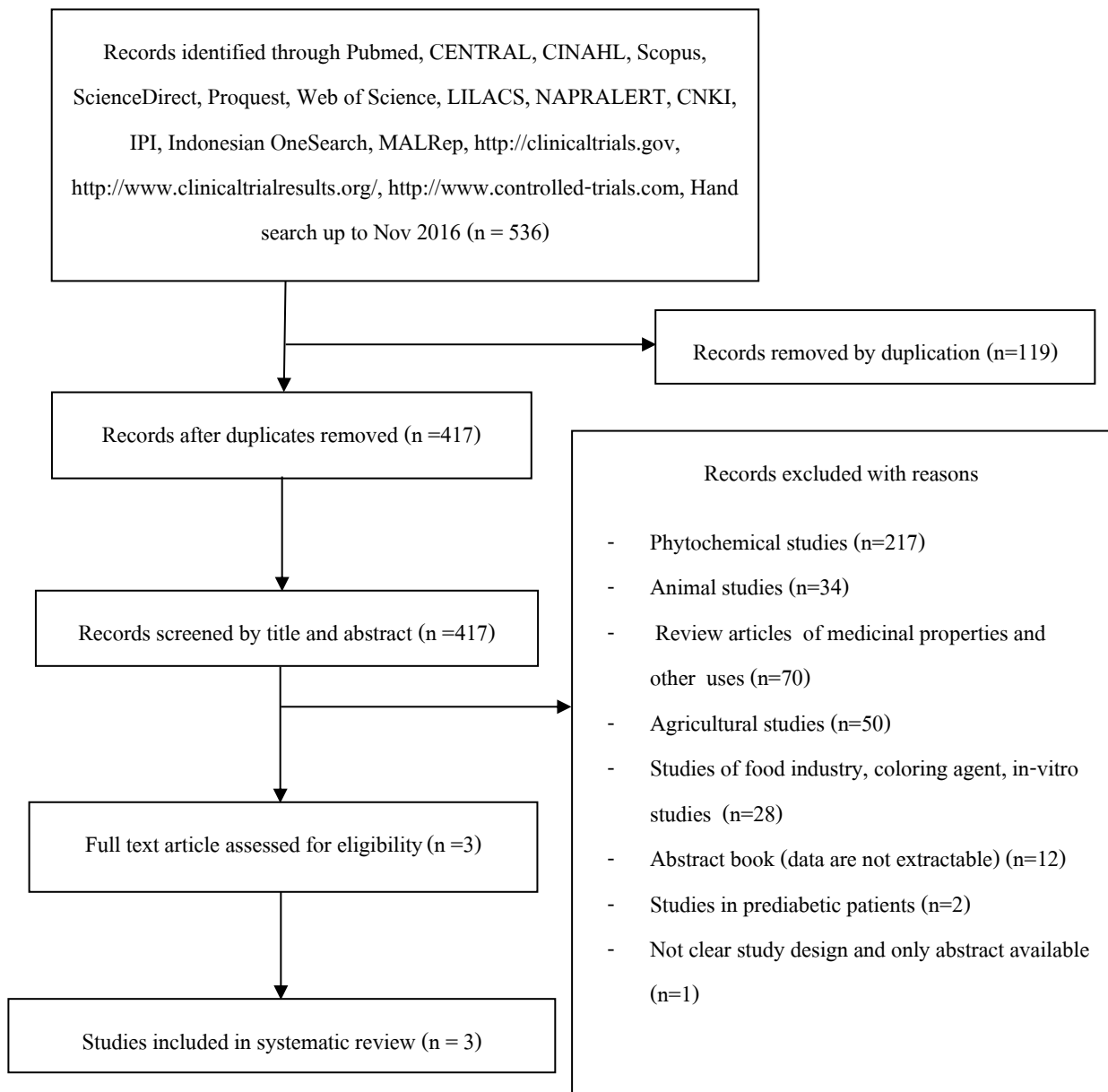


Figure 1: Study selection process

Effect on glycemic control

The study conducted by Hadi et al. (2012) revealed that supplementation of 400 g and 600 g red dragon fruit (*Hylocereus polyrhizus*)/day for 4 weeks lowered the mean FPG by 24.02 % and 34.87 % respectively whereas control group showed an increase in blood glucose level. Similarly, the result of the study by Wiardani et al. (2014) showed that treatment with 100 g and 200 g of red dragon fruit (*Hylocereus polyrhizus*) in 250 ml juice/day for 10 days lowered the blood glucose level. The mean 2HPP level was decreased by 27.7 mg/dL for 100 g dragon fruit juice, 79.1 mg/dL for 200 g dragon fruit juice versus 22.5 mg/dL for control group. In contrast, the study conducted by Hapsari et al. (2015) showed that giving 180 g red dragon fruit (*Hylocereus costaricensis*)/day for 15 days did not decrease FPG level. The mean FPG level increased by 6.26 ± 40.24 mg/dL (mean \pm SD) in control group and 13.33 ± 48.08 mg/dL in treatment group. However, the result in this study was insignificant with $p=0.659$. The data are presented in **Table 1**.

Discussion

This systematic review revealed that supplementation of dragon fruit may possibly improve glycemic control and be beneficial as an add-on therapy in type 2 diabetes. The blood glucose lowering effect of dragon fruit can be explained by the following mechanisms. Firstly, white pitaya juice improved insulin resistance by attenuating serum fibroblast growth factor-21 (FGF-21) resistance [Song et al., 2016 (a)]. FGF-21 is a metabolic regulator produced by liver and adipose tissue and there is a positive relationship between serum FGF-21 and hepatic and adipocyte insulin resistance index (Chavez et al., 2009). Betacyanin in dragon fruit reduced FGF-21 by increasing expression level of its receptors (Beta-Klotho and fibroblast growth factor receptor-2) as well as its target genes including Egr 1 and cFos (Song et al., 2016 (a); Song et al., 2016 (b); Song et al., 2015). Moreover, dragon fruit is a rich source of polyphenolic content and flavonoid (Tenore et al., 2012). Flavonoid structure has the high reactive hydroxyl group. It stabilizes the reactive oxygen species (ROS) by reacting with the reactive compound of the radical (Nijveldt et al., 2001). This can contribute to inhibition of ROS in pancreatic cells and regeneration of cells. In animal model, ethanol extract of dragon fruit showed preventive effect in histopathological picture of pancreatic cells (Anand et al., 2010; Asyari, 2009).

This review attempted to evaluate the effect of both red and white dragon fruit on glycemic control in diabetes. However, only clinical studies in two species (*Hylocereus polyrhizus* and *Hylocereus costaricensis*) of red flesh dragon fruit were identified and included. This occurrence would be explained by the fact that red flesh dragon fruit has greater content of antioxidant compared with white flesh dragon fruit. The results of antioxidant activity tests, total phenolic content and total betacyanin content are higher in red flesh than in white flesh pitaya (Kim et al., 2011; Suh et al., 2014). Since glucose lowering effect of dragon fruit is possibly derived from betacyanin content and antioxidant activity of dragon fruit, the effectiveness of red and white flesh dragon fruit may be different. However, the clinical studies are required to confirm this.

There are some limitations of the individual studies included in this systematic review. Firstly, there were relatively few subjects in each study, thus may lack statistical power. Secondly, the methodological quality of these studies was low. Several factors affecting glycemic control, such as food intake, physical exercise and education were poorly controlled. Although three studies monitored compliance to dragon fruit consumption, but the results were not reported. Patients in the type 2 diabetes studies still continued their oral anti-diabetic drugs during the study period. Moreover, none of those studies reported HbA1C as an outcome. This systematic review included not only the studies published in medical journals but also unpublished academic research. Both English and non-English language studies were considered as well. Only three studies were identified and included. Different glycemic outcomes were reported, making it not possible to pool the results of those studies. As the available evidence is limited, further high quality, well-designed larger randomized controlled trials are required and HbA1C should be commonly measured.

Conclusion

Based on the available evidence, it can be concluded that red dragon fruit may possibly be effective in glycemic control of both type 2 diabetes and be beneficial as an add-on therapy. However, due to the limited available data and poor quality of clinical studies, adequate-power, well-controlled clinical trials are required to further evaluate the clinical application of dragon fruit in these patients.

Table 1 Characteristics of the included studies

Study	Country	Duration of treatment	Patients' Characteristics	Glycemic Parameter	Study arms	Baseline Value (mmol/L) Mean \pm SD	Endpoint Value (mmol/L) Mean \pm SD
Hadi NA et al. (2012) sample size: 28	Malaysia	4 weeks	Age 20-55 years, Non-pregnant, Non-drinkers, Taking OADs instead of insulin injection	FPG	Group 1: 400 g red pitaya fruit/day (N = 7) Group 2: 600 g red pitaya fruit/day (N = 7) Group 3: No red pitaya fruit (N = 7) Group 4: Healthy subjects, no pitaya (N = 7)	6.41 \pm 0.94 11.04 \pm 3.02 9.08 \pm 2.77 4.58 \pm 0.20	4.87 \pm 0.91 7.19 \pm 3.51 9.47 \pm 2.75 4.56 \pm 0.09
Hapsari AI et al. (2015) sample size: 30	Indonesia	15 days	Age 47-78 years, Average BMI 24.71 \pm 3.69 kg/m ²	FPG	Group 1: 180 g red pitaya fruit/day (N = 15) Group 2: No red pitaya fruit (N = 15)	7.96 \pm 2.00 8.11 \pm 4.19	8.69 \pm 3.16 8.46 \pm 4.43
Wiardani NK et al. (2014) sample size: 51	Indonesia	10 days	Age 43-62 years, BMI 27.2 \pm 2.9 kg/m ² , Not use insulin injection, Not use herbal supplement	2HPP	Group 1: 100 g red dragon fruit juice/day (N=17) Group 2: 200 g red dragon fruit juice/day (N=17) Group 3: No red dragon fruit juice (N=17)	13.94 \pm 2.00 15.14 \pm 2.10 13.66 \pm 2.83	12.40 \pm 1.72 10.74 \pm 1.89 12.40 \pm 2.38

Abbreviation: FPG = Fasting plasma glucose, 2HPP = 2 hours post-prandial glucose, BMI = Body mass index, OADs = Oral anti-diabetic drugs, N = Number, SD = Standard deviation

Table 2 Quality assessment of the included studies by Jadad's Score

	Score	Hadi NA et al. (2012)	Hapsari AI et al. (2015)	Wiardani NK et al. (2014)
1. Randomization				
- Describe as randomized	1	Y	Y	Y
- Allocation sequences appropriately generated	1	N	N	N
2. Blinding				
- Describe as double blind	1	N	N	N
- Control treatment (eg. Placebo) described as indistinguishable)	1	N	N	N
3. Patient attrition				
- Attrition described for each group (including the number of patients lost or excluded, along with the reasons)	1	N	N	N
Total score	5	1	1	1
Overall quality assessment		Low	Low	Low

Y = yes, N = not described, Total score ☐ 3 was high quality, Total score < 3 was low quality

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