*Bull. Health Sci. Technol. **2018, 16(1): 12-20**. ISSN 0858-7531*

EFFECT OF KIWIFRUIT ON METABOLIC HEALTH

Nalinee Poolsup[1], Naeti Suksomboon[2] and Wei Lin[2*]

[1]Department of Pharmacy, Faculty of Pharmacy, Silpakorn University, Nakhon-Pathom, Thailand
[2]Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand

*Corresponding author : wei.lin@student.mahidol.ac.th

Abstract: Kiwifruit is known as "*Actinidia*" containing antioxidants, fiber, vitamins that seems beneficial for metabolic health. The purpose of this study was to systematically evaluate the effect of kiwifruit on metabolic health. Literature search was conducted on PubMed, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, ScienceDirect, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Proquest, Latin American and Caribbean Health Sciences Literature (LILACS), International Clinical Trials Registry Platform (ICTRP), Australia New Zealand Clinical Trials Registry (ANZCTR), ClinicalTrials.gov, Clinical Trial Results, China National Knowledge Infrastructure (CNKI) and Wanfang Standards Database (WFSD) up to November 2017 without language restriction. European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA) conferences were also searched. Randomized controlled trials (RCTs) which compared kiwifruit with placebo or no pharmacotherapy were included. The outcomes were fasting plasma glucose (FPG), glycosylated hemoglobin (A1C), 2-hour postprandial glucose (2h-PG), body weight (BW), homeostasis model assessment of insulin resistance (HOMA-IR), blood pressure (BP), total cholesterol (TC), triglyceride (TG), high-density lipid (HDL), and low-density lipid (LDL). Quality of studies was assessed by Cochrane risk of bias tool. Among 639 studies identified, 4 RCTs were included in this systematic review involving 85 hypercholesterolaemic men patients, 178 hypertensives and 122 diabetes patients. Three studies were in English language and one study was in Chinese language which was translated into English. Based on those evidences, kiwifruit seems to have positive effects on metabolic health with improvement of HDL.

Keywords: *Actinidia*, kiwifruit, metabolic diseases, blood glucose, lipids

บทคัดย่อ: **ผลของกีวี** (Kiwifruit) **หรืออาจรู้จักในชื่อ** Actinidia **ประกอบด้วยสารต้านอนุมูลอิสระ เส้นใยอาหาร และวิตามินต่างๆ ที่เป็นประโยชน์ต่อสุขภาพด้านระบบเมตาบอลิก งานวิจัยฉบับนี้มีวัตถุประสงค์เพื่อทบทวนวรรณกรรมอย่างเป็นระบบเกี่ยวกับประสิทธิผลของผลกีวีต่อภาวะเมตาบอลิก ทำการสืบค้นข้อมูลงานวิจัยที่ถูกตีพิมพ์จากฐานข้อมูลอิเล็กโทรนิกส์ ได้แก่** Pubmed, CENTRAL, Scopus, ScienceDirect, CINAHL, Proquest, LILACS, ICTRP, ANZCTR, clinicaltrial.gov, China National Knowledge Infrastructure (CNKI) **และ** Wanfang Standards Database (WFSD) **ที่ได้รับการตีพิมพ์จากอดีตจนถึงเดือนพฤศจิกายน ปี พ.ศ.** 2560 **โดยไม่มีข้อจำกัดด้านภาษา รวมถึงสืบค้นงานวิจัยจากงานประชุมวิชาการ** EASD **และ** ADA **งานวิจัยทางคลินิกเชิงสุ่ม** (RCT) **ในมนุษย์ที่ศึกษาเกี่ยวกับผลกีวีเปรียบเทียบกับยาหลอก หรือเปรียบเทียบกับการไม่ได้รับการรักษาใดๆ ได้ถูกคัดเข้าในการศึกษาครั้งนี้ ผลลัพธ์ที่ประเมิน ได้แก่ พลาสมากลูโคสขณะอดอาหาร**(FPG), **ฮีโมโกลบินเอวันซี** (A1C), **พลาสมากลูโคสหลังรับประทานอาหาร** 2 **ชั่วโมง** (2h-PG), **น้ำหนักตัว** (BW), homeostasis model assessment of insulin resistance (HOMA-IR), **ระดับความดันโลหิต** (BP), **คอเลสเตอรอล** (TC), **ไตรกลีเซอร์ไรด์** (TG), **ไขมันเอช ดี แอล** (HDL) **และไขมันแอล ดี แอล** (LDL) **คุณภาพงานวิจัยถูกประเมินตามเกณฑ์ของ** Cochrane risk of bias tool **ผลการวิจัยพบว่า งานวิจัยทั้งหมด** 4 **ฉบับถูกคัดเลือกเข้าในการศึกษา ประกอบด้วยผู้ป่วยเพศชายที่เป็นโรคไขมันในเลือดสูงจำนวน** 85 **ราย โรคความดันโลหิตสูง** 178 **รายและ โรคเบาหวาน** 122 **ราย งานวิจัยจำนวน** 3 **ฉบับตีพิมพ์เป็นภาษาอังกฤษ และ** 1 **ฉบับตีพิมพ์เป็นภาษาจีนซึ่งต่อมาถูกแปลเป็นภาษาอังกฤษ ข้อมูลจากการศึกษานี้สนับสนุนว่า ผลกีวีมีแนวโน้มที่เป็นประโยชน์ต่อภาวะเมตาบอลิกและไขมันชนิด** HDL

คำสำคัญ: Actinidia, metabolic diseases, **กีวี**, **น้ำตาลในเลือด**, **ไขมัน**

INTRODUCTION

Metabolic syndrome (MetS) is metabolic abnormalities involving diabetes mellitus, lipid metabolism, elevated blood pressure and central obesity (Amihaesei and Chelaru, 2014). Healthy lifestyle including diet control and fruit supplement has benefits for management and prevention of this kind of diseases (Gammon *et al.*, 2014). Kiwifruit is coined as one delicious fruit in our daily life.

Kiwifruit is also known as "mihoutao" or *Actinidia*. It is a member of Ericales order, Actinidiaceae family, genus *Actinidia* (Shastri *et al.*, 2012). The genus *Actinidia* varies, containing around 60 species (Ferguson, 1984; Ferguson, 1999). *Actinidia chinensis* (hairless skin, gold flesh) and *Actinidia deliciosa* (hairy skin, green flesh) belong to *Actinidia* species, which only existed originally in China since Tang Dynasty (7th century A.D.) and their familiar and popular brand names are "Hort16A" and "Hayward" respectively. Recently, much more famous brand of kiwifruit in the market is "Zespri". In China, *Actinidia cheninsis* locates in the east area and along the coast, such as Henan, Anhui, Fujian and Guangdong, but *Actinidia deliciosa* exists inland to the west region, for example, Sichuan, Guizhou and Yunnan (Huang and Ferguson, 2001). In addition to these two species, the third one is *Actinidia arguta* (hardy, hairless), and there are also other species of kiwifruit, such as *Actinidia kolomikta* and *Actinidia polygama* (frost-resistant, ornamental plant) (Singletary, 2012).

Kiwifruit contains a variety of antioxidants (ascorbic acid, carotenoids, flavonoids, phytosterols) and fiber. The possible active compositions playing a role in glucose lowering effect are phenolic components and flavonoids (quercetin and isoquercitrin). The possible anti-diabetic mechanism of isoquercitrin is that inhibits α-glucosidases activity and glucose 6-phosphatase and also its potency is similar to 1-deoxynojirimycin (an α-glucosidase inhibitor) (Kurakane. *et al.*, 2011). Quercetin possibly demonstrates positive effects in diabetes through attenuating oxidative stress and maintaining pancreatic β-cell integrity (Coskun *et al.*, 2005). Quercetin stimulates insulin secretion by the direct activation of L-type Ca^{2+} channels to increase [Ca^{2+}] ion (Bardy *et al.*, 2013).

Flavonoids possess ACE inhibition activity and quercetin belonging to flavonoid has been identified in kiwifruit (Guerrero *et al.*, 2012). In vitro, both aqueous and 70% ethanol kiwifruit extracts at 10 and 50 mg/mL concentrations inhibited ACE, a key regulator of blood pressure through the renin-angiotensin system (Jung *et al.*, 2005).

The polyphenols prevent lipoproteins from oxidation, reduce LDL-C and TG levels (Jung *et al.*, 2005; Rush *et al.*, 2006). Formation of nitric oxide in the endothelium and inhibition of inflammatory reactions and platelet aggregation were stimulated by inhibition of lipid peroxidation of cell membranes and the oxidation of LDL. *Actinidia deliciosa* 'Hayward' improved the lipid profile in rats. And kiwifruit possesses abundant dietary fiber. Especially, the soluble fraction (SDF) of fiber binds with exogenous cholesterol to lower cholesterol and triglycerides in the blood, reduce its absorption and lower the reabsorption of fatty acids, and attenuate LDL-C formation (Leontowicz *et al.*, 2013).

Based on the available evidence of in vitro and animal studies, kiwifruit has beneficial effects on metabolic health, and may be used as alternative management of metabolic health. It is valuable to be further investigated. The objective of this systematic review was to evaluate the effect of kiwifruit on metabolic health.

MATERIALS AND METHODS

Study design

A systemic review was conducted following Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) (Moher *et al.*, 2015) and selection of related studies and study procedure was shown in Figure 1.

Data sources

Studies that assessed the effect of kiwifruit on metabolic health were selected. Literature search was conducted on PubMed, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, ScienceDirect, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Proquest, Latin American and Caribbean Health Sciences Literature (LILACS), International Clinical Trials Registry Platform (ICTRP), Australia New Zealand Clinical Trials Registry (ANZCTR), ClinicalTrials.gov, Clinical Trial Results, China National Knowledge Infrastructure (CNKI) and Wanfang Standards Database (WFSD) up to November 2017 without language restriction. European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA) conferences were also searched.

Search strategy was performed using medical subject headings (Pal *et al.*) terms: kiwifruit, *Actinidia*, metabolic diseases, diabetes, lipid, blood pressure, blood glucose and followed by keyword search using ("*Actinidia chinensis*" or "*Actinidia deliciosa*" or "*Actinidia arguta*" or "*Actinidia kolomikta*") AND ("hypertension" or "fasting plasma glucose" or "2 hour postprandial glucose" or "cholesterol" or "A1C"). The related citation was manually searched. Non-English language literatures were translated into English.

Selection criteria

This review selected studies based on study design. Randomized control trials (RCTs) that evaluated the effect of kiwifruit on metabolic health were collected. Study procedure showed as Figure 1.

Data extraction

Standardized forms was used to collect related information (author, publication year, study design, sample size, treatment duration, study arms, age, baseline and endpoint such as mean A1C or FPG or 2h-PG or BW or HOMA-IR or TG or HDL or LDL or BP of all included studies.

Quality assessment

Quality of study and methodology were assessed through the items in the Cochrane risk-of-bias tool (Higgins *et al.*, 2011) (such as random sequence generation, allocation concealment, blinding of participants and personnel and outcome assessment, and incomplete data and selective reporting). Results of bias would be judged as high risk, low risk or unclear risk. Data extraction and study quality assessment were performed independently by two investigators. Any inconsistencies were resolved by a third reviewer.

RESULTS AND DISCUSSION

Characteristics of studies

After databases searching, a total of 639 studies were identified, 282 duplicated studies were excluded. 340 studies of photochemistry, plant grow, agriculture, review, food process, animal and in vitro were excluded after title and abstract screening. Finally, 17 full texts of potential RCTs were evaluated for eligibility. One study (Mishra *et al.*, 2016) was excluded as

it was conducted in healthy people. Four studies (Beck *et al.*, 2010; Dizdarevic *et al.*, 2014; Karlsen *et al.*, 2013; Kim *et al.*, 2011) were excluded because they included patients with other diseases (such as constipation). Five studies (Chang and Liu, 2009; He, 2008; Mishra *et al.*, 2017; Recio-Rodriguez *et al.*, 2015; Zhu *et al.*, 2002) were excluded for non-randomized design. After detailed assessment of full texts of three studies (Gammon, Kruger, Brown, *et al.*, 2014; Gammon, Kruger, Conlon, *et al.*, 2014), we found that they were the same study design with different study objectives but they with same data. Therefore, of these, three studies were excluded. Finally, four studies (Gammon *et al.*, 2013; Hong *et al.*, 2008; Sun *et al.*, 2017; Svendsen *et al.*, 2015) were eligible in this systematic review. The flow diagram of study selection was shown as Figure 1. The characteristics of the included studies are summarized in Table 1.

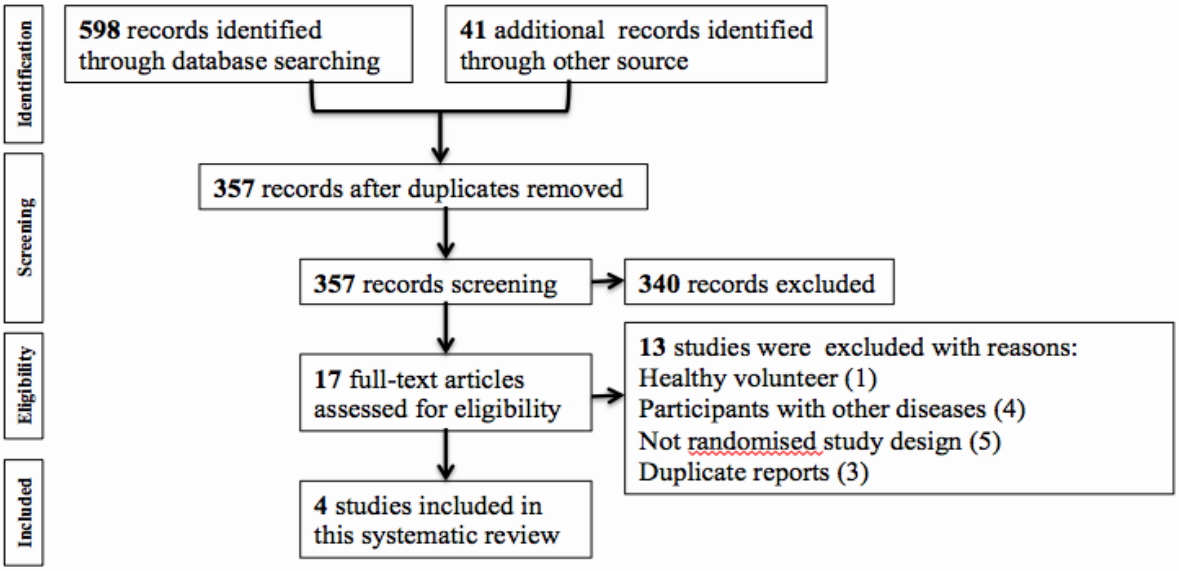

Figure 1. Flow diagram of studies selection.

Evaluation of risk of bias in included studies

Cochrane risk of bias tool was used to assess the risk of bias for the included studies Risk of bias graph (Figure 2) and risk of bias summary (Figure 3) were presented.

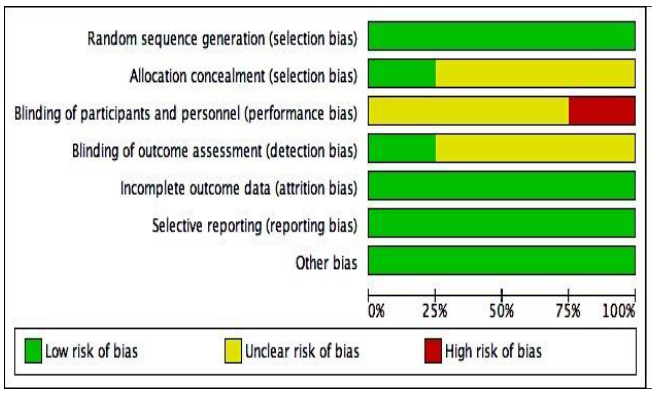

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

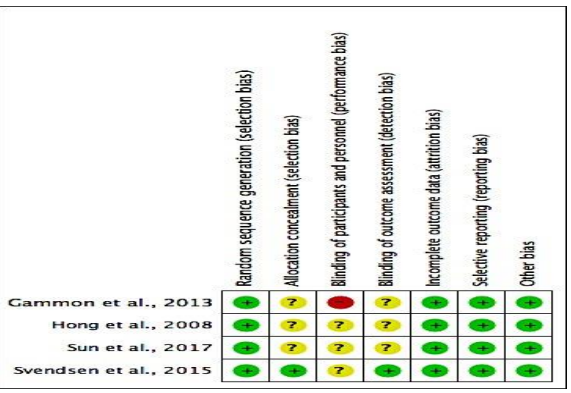

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Table 1. Characteristics of included studies.

Author (year)	Study design	Treatment (species)	Sample size	Study arms	Treatment duration	Inclusion criteria	Outcome measurement
Gammon et al., (2013)	Randomized controlled cross-over	Kiwifruit (*A. deliciosa*)	87 (43:44)	Group 1: healthy diet followed by healthy diet + 2 green kiwifruit/d Group 2: healthy diet + 2 green kiwifruit/d followed by healthy diet	12 weeks	-Hypercholesterolemic men -LDL concentration > 3.0 mmol/L -TG concentration < 3.0 mmol/L	SBP, DBP, HDL, TC, LDL, TG, BW
Svendsen et al., (2015)	Randomize controlled parallel trial	Kiwifruit (*A. chinensis*)	118 (58:60)	Group 1: 3 kiwifruit/d (approx. 360g) Group 2: 1 apple (*Malus domestica*)/d (approx. 160g)	8 weeks	-SDP 130-159 mmHg -DBP 85-99 mmHg -BMI <35 kg/m^2	BP, Endothelial function
Hong et al., (2008)	Randomize controlled parallel trial	Kiwifruit capsules (New Zealand)	60 (30:30)	Group 1: 2 New Zealand kiwifruit capsules, tid Group 2: 2 placebo capsules, tid	42 days	-Age ranged from 30-69 years old -Hypertensive patients except secondary hypertension	BP, (general items: TC, TG, LP-a, GLU, BUN, SOD, Cr, IL-2)
Sun et al., (2017)	Randomize controlled parallel trial	Kiwifruit juice (*A. chinensis*)	122 (61:61)	Group 1: 10 mL kiwifruit juice daily Group 2: 10 mL liquid placebo daily	9 months	-T2DM -Seldom consumed fruits daily -25 ≤ BMI≤ 39 kg/m^2 -BW were stable within three months	A1C, FPG, 2h-PG, BW, LDL, HDL, TC

Abbreviation: *A. deliciosa: Actinidia deliciosa, A. chinensis: Actinidia chinensis,* A1C: Glycosylated hemoglobin, approx.: approximate, BMI: Body mass index, BP: Blood pressure, BUN: Blood urea nitrogen, BW: Body weight, d: day. Cr: Creatinine. DBP: Dilated blood pressure, FPG: Fasting plasma glucose, GLU: Glucose, HDL: High density lipid, IL-2: Interleukin-2, LDL: Low density lipid, LP-a: Lipoprotein-a. SBP: Systolic blood pressure, SOD: Superoxide dismutase, TC: Total cholesterol, TG: Triglyceride, tid: three times a day, 2h-PG: 2 hour postprandial glucose.

Table 2. Effect of kiwifruit on cardiovascular metabolism in the included RCTs.

Author (year)	Groups	SBP (mm Hg)			DBP (mm Hg)		
		Before	End-study	P value*	Before	End-study	P value*
Gammon et al., (2013) [a]	Group 1	122.0	124.0	0.90	70.9	72.3	0.80
	Group 2	122.0	124.0		70.9	72.6	
Svendsen et al., (2015) [b]	Group 1	127.0 ± 14.0	126.0 ± 14.0	0.76	84.0 ± 9.0	81.0 ± 9.0	0.18
	Group 2	129.0 ± 14.0	127.0 ± 16.0		85.0 ± 7.0	83.0 ± 8.0	
Hong et al., (2008) [b]	Group 1	138.35 ± 14.93	132.25 ± 10.97	>0.05	85.88 ± 12.69	80.90 ± 7.13	>0.05
	Group 2	136.83 ± 20.05	135.43 ± 15.07		85.57 ± 13.14	81.27 ± 8.79	

DBP: Dilated blood pressure. SBP: Systolic blood pressure.
[a]Geometric mean. [b]Mean ± SD.
*comparing between kiwifruit vs. control

Table 3. Effect of kiwifruit on lipids metabolism in included RCTs.

Author (year)	Groups	TC, mmol/L			TG, mmol/L			LDL, mmol/L			HDL, mmol/L		
		Before	End-study	P value*	Before	End-study	P value*	Before	End-study	P value*	Before	End-study	P value*
Gammon et al., (2013) [a]	Group 1	6.23	6.10	0.96	1.62	1.55	0.71	4.07	3.92	0.50	1.34	1.39	0.004
	Group 2	6.23	6.11		1.62	1.58		4.07	3.95		1.34	1.35	
Hong et al., (2008) [b]	Group 1	4.96 ± 1.08	4.75 ± 0.93	-	1.86 ± 1.31	1.97 ± 1.48	-	-	-	-	-	-	-
	Group 2	4.40 ± 1.07	4.34 ± 0.80		2.32 ± 2.67	1.86 ± 1.06		-	-	-	-	-	-
Sun et al., (2017) [b]	Group 1	5.7 ± 1.2	4.6 ± 1.4	0.02	2.8 ± 1.2	1.8 ± 1.1	0.01	3.8 ± 1.0	3.0 ± 1.1	0.01	1.3 ± 0.3	1.6 ± 0.3	0.01
	Group 2	5.6 ± 1.2	5.5 ± 1.1		2.7 ± 1.1	2.6 ± 1.3		4.0 ± 1.2	3.9 ± 1.2		1.2 ± 0.2	1.2 ± 0.2	

HDL: High density lipids. LDL: Low density lipids. TC: Total cholesterol. TG: Triglyceride.
[a]Geometric mean. [b]Mean ± SD.
*comparing between kiwifruit vs. control
"-": No data available.

Table 4. Effect of kiwifruit on glucose metabolism in included RCTs.

Author (year)	Groups	HOMA-IR			A1C, %			FPG, mmol/L			2h-PG, mmol/L			BW, kg		
		Before	End-study	P value*	Before	End-study	P value*	Before	End-study	P value*	Before	End-study	P value*	Before	End-study	P value*
Gammon et al., (2013) [a]	Group 1	0.85	0.93	0.75	-	-	-	5.50	5.60	0.93	-	-	-	86.4	86.7	0.86
	Group 2	1.16	1.15		-	-	-	5.60	5.70		-	-	-	86.4	86.6	
Hong et al., (2008) [b]	Group 1	-	-	-	-	-	-	6.26 ± 2.64	6.04 ± 1.78	-	-	-	-	-	-	-
	Group 2	-	-	-	-	-	-	5.19 ± 0.47	5.45 ± 0.92		-	-	-	-	-	-
Svendsen et al., (2015) [b]	Group 1	-	-	-	-	-	-	-	-	-	-	-	-	74.8 ± 17.5	75.1 ± 12.0	0.14
	Group 2	-	-	-	-	-	-	-	-		-	-	-	78.8 ± 12.7	78.8 ± 13.5	
Sun et al., (2017) [b]	Group 1	6.4 ± 3.4	6.2 ± 3.9	0.44	8.9 ± 1.6	8.4 ± 1.9	0.38	8.4 ± 1.2	8.0 ± 1.3	0.39	14.9 ± 2.6	14.0 ± 3.2	0.32	81.6 ± 17.5	80.1 ± 15.4	0.54
	Group 2	6.6 ± 3.5	6.4 ± 2.9		8.7 ± 1.8	8.5 ± 1.6		8.7 ± 1.5	8.3 ± 1.2		14.1 ± 3.7	13.9 ± 3.4		82.8 ± 17.1	80.6 ± 15.3	

A1C: Glycosylated hemoglobin. BW: Body weight. FPG: Fasting plasma glucose. HOMA-IR: Homeostasis model assessment of insulin resistance. 2h-PG: 2 hour postprandial glucose. [b]Mean ± SD. *comparing between kiwifruit vs. control "-": No data available

Effect of kiwifruit on cardiovascular metabolism

Among the included studies, three studies in provided outcomes of blood pressure, the results of each study revealed no significant difference between kiwifruit and control group (Table 2).

Effect of kiwifruit on lipids metabolism

Three of the included studies assessed lipids metabolism, involving TC, TG, LDL, HDL. Two studies (Gammon et al., 2013, Hong et al., 2008) showed no significant difference in TC, TG, and LDL between kiwifruit and the control group. However, Sun et al., 2017 found that kiwifruit significantly improved all of the outcomes of lipids profile and Gammon et al., 2013 also revealed a significant increase ($p=0.004$) in HDL level by kiwifruit (Table 3).

Effect of kiwifruit on glucose metabolism

Table 4 summarized two studies that reported the effect of kiwifruit on glucose metabolism (Hong et al., 2008, Sun et al., 2017). There seemed to be no effect of kiwifruit on A1C, FPG, 2h-PG, BW, or HOMA-IR.

DISCUSSION

Some studies have been investigated the effects of kiwifruit on metabolic health. For example, one study (Chang and Liu, 2009) successfully verified that 2 kiwifruits per day for 8 weeks could improve HDL and decrease LDL/HDL ratio and TC/HDL ratio in hyperlipidemic patients. In the systematic review, the results found no significant differences (either increased or decreased) on SBP, DBP, FPG, BW, and HOMA-IR among the studies with available data. The reasons may be due to the different types of participants in each study including hypercholesterolemia, hypertensive, and T2DM.

Apart from above, because some in vitro or animal studies have been successfully assessed the effects of variant parts of kiwifruit on metabolic health (Iwasawa *et al.*, 2011; Leontowicz *et al.*, 2016; Soren *et al.*, 2016). In this review, therefore, four studies have applied different types of kiwifruit including whole fresh kiwifruit, kiwifruit juice, and kiwifruit extract capsules. Besides, the dosage of each study was different, for example, two studies (Gammon *et al.*, 2013; Svendsen *et al.*, 2015) used 2 or 3 whole kiwifruits per day as intervention, one study (Sun *et al.*, 2017) employed 10 mL kiwifruit juice daily and the other one (Hong *et al.*, 2008) applied 2 kiwifruit extract capsules thrice per day. Currently there have been no specific studies exploring the dosage of kiwifruit and the effect of its. However, basing on the available studies which assessed the effects of kiwifruit, it was found that participants consumed at least one whole kiwifruit showing effects against endogenous oxidative damage (Brevik *et al.*, 2011). Intake of 2 whole kiwifruits was applied in one study (Chang and Liu, 2009) to show the effects on HDL.

CONCLUSION

The available evidence of above-mentioned studies demonstrated kiwifruit consumption consisting of fresh kiwifruit, fresh juice or kiwifruit extract capsules seem to have positive effects on metabolic health which were associated with improved HDL. However, no significant effect was shown on other metabolic parameters. Therefore, in future, more studies are needed to prove the effect of kiwifruit on metabolic health.

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