



# **Comparative Study on the Antidiabetic Efficacy of Unripe and Ripe Fruit Extracts of *Siraitia grosvenorii* and the Possible Mechanism of Action**

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## **Authors' contributions**

*This work was carried out in collaboration among all authors. Authors DL, TA and FL conceptualized and designed the study. Authors XX, ZY, XY and TA performed the experiments. Authors XX, FL and TA performed the statistical analysis, while authors XX, FL, TA and DL prepared the manuscript. All authors read and approved the final manuscript.*

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## **ABSTRACT**

**Aims:** The ripe fruit of *Siraitia grosvenorii* (Swingle) C. Jeffrey (Cucurbitaceae) is used in Traditional Chinese Medicine (TCM) for treatment of diabetes. The ripe fruit is very edible, nutritious and of high sweet taste, while the unripe fruit which is usually very bitter and not edible, has not been widely studied. Therefore, the aim of this study is to evaluate the antidiabetic activity of the unripe fruit of *S. grosvenorii* and to compare it with that of the ripe fruit as well as to determine their possible mechanism of action.

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**Methodology:** The method of streptozotocin-nicotinamide induced diabetic animal model in mice was employed and mice with blood glucose greater than 9.0 mmol/l were selected for treatment with unripe fruit extract (UFE) and ripe fruit extract (RFE) for 24 days. Alpha-glucosidase and alpha amylase enzymes inhibitory assays for determination of possible mechanism of action, were performed.

**Results:** The RFE exhibited better efficacy in antidiabetic activity than the UFE, though the later displayed better potency in activity. The RFE, UFE (300 mg/kg) and glibenclamide exhibited significant ( $P < 0.05$ ) percentage blood glucose reduction (PBGR) of 67.04, 60.69 and 62.88%, respectively, in diabetic mice. Alpha glucosidase assay showed median inhibitory concentration ( $IC_{50}$ ) value of 7.60 and 6.62 mg/ml for RFE and UFE, respectively, while the alpha amylase inhibitory assay exhibited percentage inhibition of 84.78 and 95.10% for RFE and UFE (25 mg/ml), respectively.

**Conclusion:** The ripe and unripe extracts of *S. grosvenorii* exhibited antidiabetic activities, and RFE proved a better efficacious activity than UFE, which showed more potent activity. In addition, the antidiabetic activity is likely being mediated through alpha glucosidase and alpha amylase enzymes inhibition.

**Keywords:** *Siraitia grosvenorii* fruit; antidiabetic; efficacy; alpha glucosidase.

## 1. INTRODUCTION

Diabetes Mellitus (DM) is one of the leading causes of death worldwide, particularly the adult onset type, known as Insulin-Dependent Diabetes Mellitus (IDDM or T2DM) which can be managed with oral hypoglycaemic agents. Reports showed that the global prevalence of DM in 2019 was 463 million people, with a projected rise to about 578 million and 700 million people by the year 2030 and 2045, respectively [1]. Diabetes affects the quality of life of individuals with its attendant co-morbidities and huge economic burden. It is a chronic disease characterized by hyperglycaemia and/or insulin resistance, micro and macro vascular complications, with identifiable pathological link to obesity and cardiovascular diseases [2]. The prevalence of DM in China has been estimated to be 10.9% of the population, amounting to about one-third of world's DM cases [3]. Diverse cultures of the world manage DM with traditional medicines mainly from medicinal plants and animal sources. In Traditional Chinese Medicine (TCM), the preparation from the ripe fruits of *Siraitia grosvenorii* Swingle (Cucurbitaceae), known as Monk fruits, indigenous to southern part of China, is used to manage diabetes [4]. Reports showed that the ripe fruits of *S. grosvenorii* contain mainly cucurbitane glycosides, known as mogrosides, which are responsible for its extremely sweet taste and antidiabetic effects. In comparison, unripe fruits of *S. grosvenorii* have bitter taste, which is mainly due to the presence of bitter mogroside II [5]. The antidiabetic effect of ripe fruits of

*S. grosvenorii* and their mogrosides have been variously reported [6,5], while little is known about the antidiabetic potentials of the unripe fruit. Many other pharmacological actions of *S. grosvenorii*, such as anticancer, anti-inflammatory, immunomodulatory and antimicrobial, have been reported [6,5]. Therefore, the aim of this study was to evaluate the antidiabetic activities of unripe fruits of *S. grosvenorii* and to compare the effect with that of ripe fruits using diabetic induced animal model, as well as to determine the possible mechanism of action using *in-vitro* models of alpha glucosidase and alpha amylase carbohydrate metabolizing enzymes' models.

## 2. MATERIALS AND METHODS

### 2.1 Preparation of Plant Materials

Ripe fruits of *Siraitia grosvenorii* were collected in the month of November. The fruits were washed and cut into smaller bits and were heat-extracted with water at 120°C and filtered, as previously described with modifications [7,8]. The filtrate was cooled to room temperature loaded to an HPD-100 microporous resin column which was successively eluted by H<sub>2</sub>O and 50%EtOH. The 50%EtOH elution was collected and after removing solvent, was freeze dried to obtain the ripe fruits extract, a light brown powder, (RFE) and stored in safe dry place for further use. Similarly, the same procedure was performed with the unripe fruits to obtain the unripe fruits extract (UFE) powder, and then stored till further use.

## 2.2 Animals

Adult ICR male mice (18-22 g) purchased from Hunan SJA Laboratory Animal Co. Ltd, China, were used in the study. The animals were maintained under standard laboratory conditions and had free access to standard chow (Feed Function, Hunan SJA, Ltd.) and water. On transfer to the work area, animals were allowed two weeks of acclimatization before the commencement of the experiments.

## 2.3 Reagents

Streptozotocin (STZ) and nicotinamide were purchased from MedChem Express, USA; Na<sub>2</sub>HPO<sub>4</sub>, KH<sub>2</sub>PO<sub>4</sub>, KCl, citric acid monohydrate, sodium citrate, sodium citrate, 3,5-Dinitro salicylic acid and potassium sodium tartrate tetrahydrate were purchased from Shanghai Aladdin Biochemical Technology Co Ltd., China; dimethyl sulfoxide, NaCl, NaOH and NaCO<sub>3</sub> were purchased from Xilong Scientific Co., Ltd., China; alpha glucosidase, alpha amylase and p-nitrophenyl α-D-glucopyranoside were purchased from Shanghai Yuanye Biotechnology Co Ltd., China; while acarbose and glibenclamide were bought from National Institutes for Food and Drug Control and Beijing Solarbio Science and Technology Co., Ltd. All in China.

## 2.4 Equipment

SP-Max 3500FL Multifunctional Microplate Reader of Shanghai Shan Pu (Shanghai Flash Spectrum Biological Technology Co., Ltd., China).

## 2.5 Induction of Diabetes

Mice after two weeks of acclimatization in the laboratory were treated with streptozotocin (STZ, 200 mg/kg) and nicotinamide (230 mg/kg) using the Streptozotocin-Nicotinamide model as described by Furman [9], with little modifications. Briefly mice were divided into groups of 10 animals per group for the treatments and controls. On experimental day, mice were fasted for 6-8 hrs before STZ treatment. Water was provided as normal. Nicotinamide (230 mg/kg; i.p.) was administered 15 mins before STZ (200 mg/kg; i.v., tail vein) in 50 mM sodium citrate buffer (pH 4.5). The STZ was prepared fresh and administered within 5 mins of dissolution. Control group received only the buffer solution. The treatment was monitored for two weeks and blood glucose level measured with OneTouch UltraEasy Glucometer (LifeScan Inc., UK).

Mice blood was collected by tail snipping, and mice with blood glucose level (BGL) greater than 9.0 mmol/l were selected for antidiabetic studies.

## 2.6 Treatment of Diabetic Animals

Diabetic mice were subjected to daily treatment with the ripe and unripe fruits extract of *S. grosvenorii* solubilized in distilled water, at two dose levels of 150 and 300 mg/kg. They were divided into seven groups (n =7); groups I and II received RFE while III and IV received UFE at 150 and 300 mg/kg, respectively. Groups V and VI are the negative (distilled water, 5 ml/kg) and diabetic control (distilled water, 5 ml/kg), respectively and group VII, was the positive control (glibenclamide, 5 mg/kg). The BGL was measured every four days for sixteen days and then on day twenty-fourth. Percentage blood glucose reduction (PBGR) was calculated at the end of the treatment period relative to blood glucose level on day zero, with the following formula:

$$PBGR = (BGL_0 - BGL_T / BGL_0) \times 100.$$

Where,

PBGR = Percentage blood glucose reduction, BGL<sub>0</sub> = Blood glucose level at day zero, BGL<sub>T</sub> = Blood glucose level at a particular day.

In addition, the body weights of mice were determined weekly for the period of treatment.

## 2.7 Alpha Glucosidase Enzyme Inhibition Assay

The methods of Apostolidis et al. [10] and Subramanian et al. [11] with little modification were employed. Briefly, the RFE, 50 μl (100, 50, 25, 12.5, 6.25 and 3.125, 1.5625 mg/ml, 5% DMSO solutions) prepared with phosphate buffer saline (PBS; pH 6.8) were added to separate wells in triplicates in 96-well plates and 25 μl of PBS containing α-glucosidase solution (1.0 U/ml) added to every well and incubated at 37°C for 10 mins. Afterwards 25 μl of 5 mM 4-NPGP (4-nitrophenyl-α-D-glucopyranoside) solution in PBS was also added to each well at timed intervals with 100 μl of PBS to each well and mixed gently, then incubated again for 5 mins at 37°C. About 75 μl of 200 mM of sodium carbonate solution was added to each well to terminate the reaction. The absorbance was measured at 405 nm using the micro-plate reader. The percentage inhibition was calculated using the formula;

$$\% \text{ Inhibition} = \{(AC-AT)/AC\} \times 100.$$

Where,

AC is absorbance of control (containing all reagents except extract) and AT is net absorbance extract. AT is calculated as AT1-AT2 where AT1 is the absorbance of the entire mixture, while AT2 is the absorbance of the blank which is the absorbance of the mixture without the enzyme. AC (100% Enzyme activity) = AC1-AC2, where AC1 is the test control while AC2 is the control blank.

Afterwards, same procedure was repeated for the unripe extract (UFE) and the positive control standard agent, acarbose.

### 2.8 Pancreatic (A)-Amylase Inhibition Assay

The method described by Apostolidis et al. [10] was employed. Briefly, 25 µl of RFE (at various concentrations (25, 12.5, 6.25 and 3.125 mg/ml solutions) prepared with PBS (pH 6.9 with 0.006 M sodium chloride) was added to separate wells in triplicates plus 25 µl of 20 mM PBS containing α-amylase solution (0.5 mg/ml) (4 U/ml) and incubated in 96-well plates at 37°C for 10 mins. The 25 µl of 0.5% starch solution (SS) in PBS was added to each well at timed intervals and further incubated at 37°C for 10 minutes. The reaction was terminated by addition of 50 µl of 96 mM of dinitrosalicylic acid (DNSA) colour reagent. The microplate was incubated in a boiling water bath for 5 mins and cooled to room temperature and diluted with 50 µl distilled water. The absorbance was measured at 540 nm using micro-plate reader. The % inhibition was calculated using the formula;

$$\% \text{ Inhibition} = \{(AC-AT)/AC\} \times 100.$$

Where,

AC (Test control – Control blank) is absorbance of control (contains all reagents except extract) represents 100% enzyme activity, and AT is net absorbance extract. AT is calculated as AT1-AT2 where AT1 is the absorbance of the entire mixture, while AT2 is the absorbance of the blank which is the absorbance of the mixture without the enzyme.

Afterwards, same procedure was repeated for the unripe extract (UFE) and the positive control standard agent, acarbose.

## 2.9 Statistical Analysis

Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) software version 21, using one-way ANOVA, and Dunnet test for multiple comparisons. Results were expressed as mean ± SEM. Also Graph Pad Prism version 7 was employed. Values at  $p < 0.05$  were considered significant.

## 3. RESULTS

### 3.1 Treatment of Diabetic Animals

Diabetic mice groups that received UFE and RFE exhibited significant ( $p < 0.05$ ) and dose dependent reduction in blood glucose level after 24 days of treatment when compared with the pre-treatment level at day zero. In addition, the non-diabetic group (NC) and the diabetic control (DC), that received distilled water each, maintained normal and high blood glucose levels, respectively, throughout the treatment period (Table 1). The RFE (300 mg/kg) exhibited highest significant ( $P < 0.05$ ) antidiabetic activity, with percentage blood glucose reduction (PBGR) of 67.04%, compared to 60.69% of UFE (300 mg/kg) and 62.88% of glibenclamide, after 24 days treatment. However, at lower dose of 150 mg/kg after the treatment duration, the UFE showed a more potent activity than the RFE, with PBGR of 63.30% and 63.00%, respectively (Table 2). Therefore, RFE exhibited a better blood glucose lowering effect during the period of treatment, hence a better efficacy than the effect of UFE which indicated a more potent activity. There was non-significant reduction in the body weights of diabetic mice during the treatment period (Table 3).

### 3.2 Alpha Glucosidase Enzyme Inhibition Assay

The RFE and UFE exhibited potent dose dependent percentage inhibition of alpha glucosidase enzyme at different tested concentrations. The RFE showed a better activity with highest percentage inhibition of 98.48% against that of 85.90% of UFE, at maximum tested concentration (50 mg/ml). The standard drug acarbose, showed non-dose dependent inhibition of the enzyme at the tested concentrations. The  $EC_{50}$  of alpha glucosidase assay for the RFE and UFE was calculated to be 7.60 and 6.62 mg/ml respectively, obtained from the graph of inhibition against log concentration (Fig. 1). Acarbose also showed a potent, non-dose dependent inhibitory effect on the alpha glucosidase (Fig. 2).

**Table 1. Blood glucose concentration of diabetic animals**

Treatment		Blood glucose concentration (mmol/L)					
Agent	Dose (mg/kg)	Day0	Day4	Day8	Day12	Day16	Day24
DC	-	24.44 ±2.89	16.32±2.53	27.82±2.28	26.08±3.24	21.45±2.99	13.23±2.39
Gli	5	22.52±3.00	23.04±3.55	16.84±3.21	12.38±1.13*	8.88±0.60*	8.36±0.34*
UFE	150	21.80±2.33	24.64±1.05	19.80±1.88	18.46±2.47	18.24±0.69	8.00±0.63*
UFE	300	20.96±2.13	22.04±1.35	20.64±0.93	15.54±0.64*	12.78±0.32*	8.24±0.51*
RFE	150	21.40±2.39	22.04±0.70	18.10±1.47	14.92±0.80*	11.54±0.58*	7.92±0.49*
RFE	300	21.48±2.22	24.04±2.05	19.54±1.75	16.62±2.97	11.82±1.30*	7.08±0.33*
NC	-	6.5±0.43	6.22±0.29	6.28±0.17	6.00±0.48	6.92±0.56	7.18±0.74

*n = 7; \*P=0.05 (ANOVA; Dunnet post hoc) compared to treatment values on day zero*

**Table 2. Percentage blood glucose reduction (PBGR)**

Treatment		Blood glucose reduction (%)					
Agent	Dose (mg/kg)	Day0	Day4	Day8	Day12	Day16	Day24
DC	-	-	33.22	-13.83	-6.71	12.23	45.87
Gli	5	-	-2.31	25.22	45.03*	60.57*	62.88*
UFE	150	-	-13.03	9.17	15.32	16.33	63.30*
UFE	300	-	-5.15	1.53	25.86*	39.03*	60.69*
RFE	150	-	-3.00	15.42	30.28*	46.07*	63.00*
RFE	300	-	-11.92	9.03	22.63	44.97*	67.04*
NC	-	-	-	-	-	-	-

*n* = 7; \**P* = 0.05 (ANOVA; Dunnet post hoc) compared to treatment values on day zero

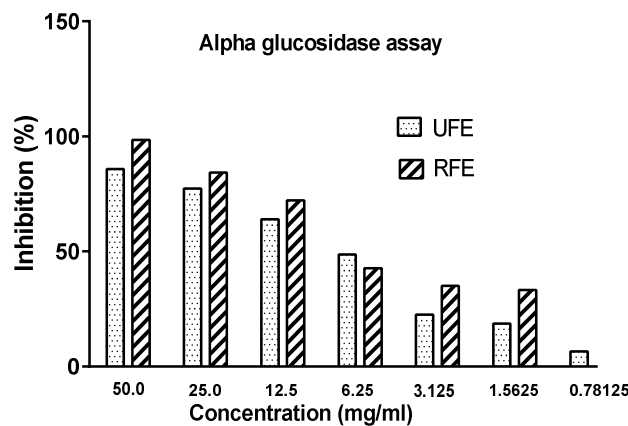
**Table 3. Change in body weight of mice**

Treatment		Body weight (g)			
Agent	Dose (mg/kg)	Day0	Day8	Day17	Day24
DC	-	35.39±1.17	32.83±1.09	30.88±1.03	30.63±1.00
	5	33.06±0.80	31.71±0.94	31.67±0.88	31.17±0.74
UFE	150	35.54±0.90	33.07±0.70	31.86±0.63	30.29±0.61
UFE	300	33.93±1.16	31.66±1.43	30.71±1.06	29.86±0.99
RFE	150	35.47±0.87	33.14±0.86	31.86±0.67	30.86±0.70
RFE	300	34.76±1.56	32.14±1.40	30.43±1.25	30.42±1.15

*n* = 7; \**P* < 0.05 (ANOVA; Dunnet post hoc) compared to treatment values on day zero

**Table 4. Alpha amylase assay**

Concentration(mg/ml)	Inhibition (%)			Concentration (Acarbose, mg/ml)
	UFE	RFE	Acarbose	
25.00	95.10	84.78	99.18	1.00
12.5	93.47	83.42	74.72	0.50
6.25	85.05	82.05	72.28	0.25
3.125	75.00	88.59	77.17	0.125



**Fig. 1. Alpha glucosidase inhibition assay of UFE and RFE**

**3.3 Pancreatic (A)-Amylase Inhibition Assay**

The results showed that RFE and UFE manifested inhibition of the alpha amylase enzyme assay. The results showed dose dependent inhibition of the alpha amylase

enzyme by the extracts and the acarbose, except below 6.25 mg/ml (Table 4). The UFE and RFE (at 25 mg/ml) showed percentage inhibition of 95.10 and 84.78%, respectively. The UFE seems to be mediating its effects by the inhibition of alpha amylase enzyme better than the RFE (Table 4).

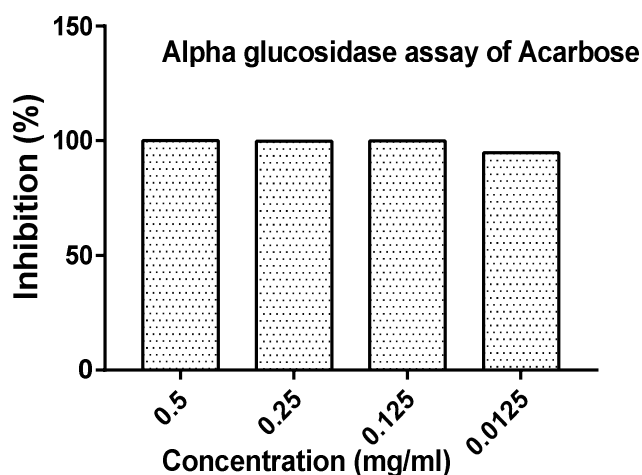


Fig. 2. Alpha glucosidase inhibition assay of acarbose

#### 4. DISCUSSION

In this study, the model of streptozotocin-nicotinamide model, as described by Furman [9] with little modifications was employed for the induction of diabetes (DM) in mice. This model is based on the fact that concurrent administration of nicotinamide with streptozotocin (STZ) affords partial protection of  $\beta$ -cells against STZ. As a result, it produces a pathological condition resembling insulin-deficient type II diabetes mellitus (T2DM), which is the more prevalent type of DM globally and often characterized by persistent hyperglycaemia associated with 60% loss of  $\beta$ -cell function. After successful induction of diabetes, in addition to hyperglycaemia, the diabetic mice on physical monitoring and observation manifested polydipsia, polyuria and polyphagia which are the initial triad symptoms of T2DM. At the end of treatment period, the results showed that both the extracts of ripe (RFE) and unripe (UFE) fruits of *S. grosvenorii* exhibited potent antidiabetic activity by gradual reduction of the fasting blood glucose of treated mice, while the UFE showed a more potent activity. In Traditional Chinese Medicine (TCM) the extract of ripe fruit of *S. grosvenorii* has been variously reported to possess antidiabetic or anti-hyperglycaemic effects with potentials to improve insulin resistance [12,6]. Ripening of fruits is an irreversible process that usually affect the phytochemical and biochemical contents as well as organoleptic properties of fruits making them very edible and palatable [13]. Interestingly, the phytochemical reports have shown seasonal variations in the constituents of ripe and unripe fruit which might affect their medicinal properties. Hence, reports have indicated that ripe fruits of

*Siraitia grosvenorii* contains mostly mogroside V, while unripe fruits contain mainly mogroside II [14,5]. Hence cucurbitane glycosides, known as mogrosides, are the major phytochemicals found in ripe fruit of *S. grosvenorii* extract (RFE) which confer overly sweet taste to the fruit and its extract, often making it 300 times sweeter than sucrose [12]. Mogrosides of *S. grosvenorii* have many components including mogrosides I to VI [8,5]. Among these mogrosides, mogroside II, triterpenoid saponin, is mainly found in the young unripe fruits with bitter taste while the rest are components of the ripe fruits responsible for their extremely sweet taste [8]. Also reports indicated that the antidiabetic effect for each of the mogrosides has been studied, except mogroside II [6,8]. Therefore, the antidiabetic activity of the UFE might be ascribable to mogroside II, the major phytochemical therein. Hence the better efficacy exhibited by the RFE could be due to its additional effects of various mogrosides and their metabolites particularly mogroside V [14,5]. Furthermore, RFE also contains flavonoids, phenolic acids and anthraquinones, while flavonoid kaempferol has also been isolated from UFE [14,12]. Phenolics, flavonoids and glycosides are various phytochemicals that have been reported as effective inhibitors of  $\alpha$ -glucosidase enzyme [15]. Moreover, the treated mice exhibited non-significant reduction in body weight, a feature that is commonly observed among T2DM patients known as muscle wasting. However, this could not be due to any form of toxicity from the extract since various reports have shown high margin of safety for extract and mogrosides of *S. grosvenorii* [12,14,16]. Furthermore, mogrosides have shown an estimated LD<sub>50</sub> greater than 10 000 mg/kg

[12,16], with no change in both organ and body weights of treated animals [5,16]. This study showed that the mechanism of antidiabetic activities of extracts of monk fruit could likely be via the inhibitory action on the carbohydrate metabolizing enzymes such as alpha glucosidase and alpha amylase enzymes located within the gastrointestinal small intestines. These carbohydrate metabolizing enzymes are responsible for the breakdown of carbohydrates to absorbable glucose molecules. The inhibitory activity against these enzymes is in corroboration with other published studies on the mechanism of antidiabetic effect of other medicinal plants [17-20]. Interestingly, new therapeutic interventions with respect to the treatment of diabetes were aimed at the inhibitory effects on the metabolizing enzymes responsible for the breakdown of carbohydrates such as alpha glucosidase, alpha amylase, and enzyme that metabolize glucagon-like peptides such as dipeptidyl peptidase IV enzyme (DPP-IV). Particularly, are the  $\alpha$ -glucosidase inhibitors such as acarbose that reduce the intestinal absorption of carbohydrates [11]. In all, the RFE and UFE exhibited good antidiabetic activities, with UFE being more potent than the more efficacious RFE. Efficacy is the ability of an agent to exhibit higher percentage pharmacological activity when compared with other agents at same dosage while potency is the ability of an agent to proffer better activity at lower concentration than others.

## 5. CONCLUSION

The ripe and unripe fruit extracts of *S. grosvenorii* exhibited antidiabetic activities, while the ripe fruit showed a better efficacious activity than the UFE which exhibited more potent antidiabetic effects. In addition, alpha glucosidase and alpha amylase enzymes inhibition might be one of the possible mechanisms of antidiabetic action of *S. grosvenorii*.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

All animal experiments were conducted in compliance with the national institute of health guidelines for care and use of laboratory animals (publication no. 85 – 23, revised 1985) and

approved by the Guangxi Institute of Botany's use of laboratory animals.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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