Gestational Diabetes Review: Maternal-fetal Comorbidities and Treatment with Medicinal Plants

Saulo José de Lima Júnior[1], Tatyanne Milhomens Soares[1],
Vanderson Ramos Mafra[1], Sara Falcão de Sousa[1*],
Jaqueline Cibene Moreira Borges[1], Natallia Moreira Lopes Leão[1],
Andreisa Prieb[1], Yara Silveira[1], Christiane Rodrigues de Paula Marques[2],
Nayanne Deusdará Escobar[1], Marco Túlio Borges Sousa[1],
Thalita Melo França Costa[1], Taciano Peres Ferreira[3]
and Janne Marques Silveira[1]

[1]*University of Gurupi, Av. Rio de Janeiro, Nº 1585 - St. Central, Gurupi, 77403-090, Tocantins, Brazil.*
[2]*AVM Educational, Edifício Carmo - 5th floor, R. do Carmo, 07 - Centro, Rio de Janeiro, 20011-020, RJ, Brazil.*
[3]*Environmental Chemistry Collegiate, Federal University of Tocantins, Chácara 69-72 Rua Badejos, Lote 7 no number - Jardim Sevilha, Gurupi, 77404-970, Tocantins, Brazil.*

Authors' contributions

This work was carried out in collaboration among all authors. Author SJLJ designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors TMS and SFS managed the analysis of the study. Author SFS managed the literature research. All authors read and approved the final manuscript.

Review Article

ABSTRACT

Gestational Diabetes is a condition characterized by hyperglycemia that provides a drop-in insulin performance in its appropriate receptors by hormones secreted by the placenta and fetus. The main fetal comorbidities are macrosomia, growth disorder, and congenital and maternal anomalies in gestational diabetes, preeclampsia, vascular injury, and post-gestational diabetes. This study

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Corresponding author: E-mail: sarafalcao@unirg.edu.br;

addressed the possible treatments with medicinal plants in gestational diabetes. Medicinal plants that have the diabetic purpose were researched, however, many pregnant women use and do not know the effects that can happen for the fetus and also for itself, the plants used for this work is not satisfactory for pregnant women with diabetes, but for non-diabetics, some are beneficial for treating this pathology. It becomes necessary for people to know the effects of plants that are used to treat certain types of diseases because most often in great excess can be fatal. All of them presented satisfactory results in a study for diabetes mellitus in non-pregnant patients, but the study presented by Cow's Paw (*Bauhinia forficata* l.) in pregnant rats with diabetes showed harmful results in embryo implantation and there was no glycemic control, which leads us to investigate further under the use of all plants in the treatment of gestational diabetes.

Keywords: Gestational diabetes comorbidities; fetal risk factors; treatments with medicinal plants.

1. INTRODUCTION

A woman's pregnancy is the most important phase in her life and a phase that occurs intense changes in her body, mainly physiologically, being a period of several endocrine-metabolic modifications [1] while the placenta and fetus secrete several hormones for maternal circulation such as human placental lactogen (hPL), human chorionic gonadotropin (hCG), human chorionic adrenocorticotrophin (hCACTH), estrogen and progesterone that occurs in the second trimester of pregnancy, which provides a drop-in insulin performance in its appropriate receptors [2] whose some systems of the organism are overloaded causing it to fail to meet adequate maternal and fetal needs [1].

Gestational Diabetes (GD) is a condition characterized by hyperglycemia, that is, it causes an increase in blood glucose levels, this disease reaches approximately 4% in all pregnancies and is recognized during pregnancy, usually at the first prenatal visit. In some cases, the pregnant woman acquires diabetes during pregnancy and after childbirth she cures, in other cases, the woman already has some type of diabetes before she even becomes pregnant, and if treated from the beginning is not at risk of the child being born with malformation [3].

The incidence of malformations varies from 2 to 4 times higher in the general population than in the population studied, while malformations are 7 to 10 times more frequent in newborns (NB) of diabetic mothers, evidenced by the increase in glycated hemoglobin (HbA1ac) at conception and initial pregnancy, particularly when levels 8 to 12 standard deviations above the average of non-diabetic pregnant women [4].

Risk factors of GD include some racial groups, i.e., varies from region to region, also include advanced maternal age, overweight, obesity or excessive weight gain in current pregnancy, family history of diabetes in first-degree relatives, fetal or neonatal death, macrosomia, polycystic ovary syndrome, and short stature (less than 1.5 m) [5].

In Brazil, the Ministry of Health recommends that screening be performed immediately with the request for the fasting blood glucose test [5], and the OGTT test (oral glucose tolerance test) that aims to confirm this diagnosis [6].

Medicinal plants are being used more and more by humans for treatment for all types of diseases, these medicinal plants are understood by the population as herbal medicines. According to ANVISA (National Health Surveillance Agency), all medicine obtained from plant raw materials is herbal medicine, of course, analyzing its pharmacological properties, having a broad knowledge of its efficacy and safety for a qualified drug, because every plant has its risk of toxicity, so scientific studies are increasingly advanced [7].

2. LITERATURE REVIEW

2.1 Pathophysiology of Gestational Diabetes Mellitus (GDM)

A woman's pregnancy is the most important phase in her life and a phase that occurs intense changes in her body, especially physiologically. This pregnancy is the period of several endocrine-metabolic changes where some systems of the organism are overloaded causing it to fail to meet the adequate maternal and fetal needs [1].

In pregnancy, there are several changes concerning the glycemic control of women and it is in this period that a state of insulin resistance

is characterized. Glucose consumption by the embryo and fetus favors the event of glycemic modification where it helps to develop GDM [2].

Several hormones secrete both the placenta and the fetus that pass into the maternal circulation. Among the main hormones are human placental lactogen (hPL), human chorionic gonadotropin (hCG), human chorionic adrenocorticotropin (hCACTH), estrogen and progesterone that occurs in the second gestational trimester. These hormones provide a drop in insulin performance in its receptors, however, in healthy pregnant women there will be an increase in insulin production [2].

Due to the hyperplasia of β-pancreatic cells, in early pregnancy to an increase in insulin response, because this hyperplasia causes lipogenesis and gluconeogenesis that is the formation of new sugars. With this there is a large amount of glycogen, triglycerides, and proteins in the pregnant woman's body, causing her to develop healthily [8].

In the human body, there are two main types of tissues that make up the pancreas, divided into part exocrine by the antics that secrete pancreatic juice and endocrine composed of Langerhans islets formed by insulin-producing beta cells and glucagon-producing alpha cells. These are the main hormones that decrease the metabolism of sugar (glucose) of the human body, more specifically, in the blood [9].

Glucagon is a group that has 29 amino acids being a polypeptide hormone, in the islets of Langerhans have alpha cells, beta cells and delta cells, the alpha cells of this islet produces this hormone that has the most important role in instigating through the liver the production of energetic metabolites and also of raising the accumulation of glucose in the blood [10].

Gestational diabetes mellitus is determined as metabolic alteration that occurs in pregnant women who are at risk of the fetus being born with abnormality due to changes that occur throughout pregnancy, for this reason, and another the WHO (World Health Organization) recommends good follow-up throughout the pregnancy period, including prenatal care, feeding, exercise and if appropriate medications are necessary for pregnant women [3].

Hyperinsulinemia can be provoked during the pregnancy state of the woman who is determined by an increased amount of need and insulin resistance. When there is a partial deficiency or even a complete deficiency in the function of the islets of Langerhans, carbohydrate intolerance will occur in any severity, and this will determine that the woman has diabetes that will last for all pregnancy, it may happen that the woman no longer has this disease after childbirth, as it may also occur that she continues with diabetes [11].

A pregnancy with GDM can cause several risk factors for both the mother and the child, especially the child, including fetal macrosomia, which is overweight in the newborn, some metabolic complications such as hypoglycemia, hypocalcemia, hematological changes, such as bilirubinemia and polycythemia, and respiratory disorders, so qualified follow-up is required from the beginning [12].

2.2 Influence of Diabetes on Fetal Maternal Binomial

Pre-gestational diabetes, being DM1 or DM2, can progress worse perinatal outcome, its consequence arises in fertilization and implantation. It affects in particular, organogenesis, causing early abortion, a neonatal respiratory disorder, intrauterine death, malformations, macrosomia, and immaturity especially in cases that are not treated properly. Chronic complications occur as nephropathy and retinopathy can be complicated [4].

According to reference [4], the incidence of malformations varies from 2 to 4 times higher in the general population than in the population studied, while malformations are 7 to 10 times more frequent in newborns (NB) of diabetic mothers, evidenced by the increase in glycated hemoglobin (HbA1ac) at the time of conception and initial pregnancy, particularly when levels 8 to 12 standard deviations above the average of non-diabetic pregnant women.

2.2.1 Fetal maternal comorbidities and fisk factors

Risk factors of GD include some racial groups, i.e., varies from region to region, also include advanced maternal age, overweight, obesity or excessive weight gain in current pregnancy, family history of diabetes in first-degree relatives, fetal or neonatal death, macrosomia, polycystic ovary syndrome, and short stature (less than 1.5 m) [5].

Even with all knowledge and understanding about Diabetes, the pregnant woman who has this disease has a high risk with many comorbidities, which needs to be inspected for the entire period of pregnancy and immediately, because the sooner she seeks to do all prenatal care correctly, she can avoid having serious serious problems due to metabolic alterations and hyperglycemia [13].

Gestational and fetal complications are immediate adverse effects that are during pregnancy and also late adverse effects, that is, it can progress during growth and development to the child, this child may have a high risk of obesity of type ll DM in his adult life, so all follow-up of physicians during pregnancy and of paramount importance, because it can prevent and prevent these risk factors [4].

In general gestational diabetes appears in the second half of pregnancy, with this, the risks of increased fetal malformations do not imply much, is more associated with the increase for macrosomia and neonatal complications and also other long-term complications that slow the psychomotor, obesity in the course of growth and also diabetes mellitus type ll [4].

According to reference [14], 243 patients were surveyed, about 26.3%, who presented complications during pregnancy with some occurrences of fetal malformations. These fetal malformations include brachycephalic, bilateral pyelectasis, hydrocephalus, hydronephrosis with multicystic kidneys, and absence of bladder, hydronephrosis with mega ladder, hydronephrosis with renal malformation, cleft palate, cardiac malformations, intraventricular communication, microcephaly, and encephalocele. Of these 243 patients, only 2 pregnant women had blood glucose above the reference value, one was found with 118 and the other with 226 mg/dL, thus evidencing the existence of pre-gestational diabetes. In the screening among this group studied, the mean fasting glycemia was < 110 mg/dL (18 patients) was 80.8, ranging from 66 to 97, which were performed around the 11th week of gestation.

Diabetes mellitus, being pre-gestational or gestational is the main factor for the pregnancy of a macrosomic fetus, however, maternal obesity predicted, excessive weight gain during pregnancy, post-dates, multiparity and maternal age greater than 35 years also influence this disorder. Diabetic mothers, because they manifest a greater supply of nutrients to the fetus, develop fetal macrosomia more easily [15]. The most common fatal complication in diabetic mothers is still fetal macrosomia, which is determined when the newborn is weighing more than 4,000 g. These complications have a huge risk for both mothers and the newborn, in diabetic mother's fetal macrosomia stimulates an increased risk of perineal laceration and a dystocic delivery where often it is forced to have a cesarean section. In newborns, the risks may occur intracranial hemorrhage, respiratory distress, neonatal hypoglycemia, shoulder dystocia, and even jaundice, this is immediate complications [16].

2.3 Laboratory Diagnostic Examination

It is recommended in Brazil by the Ministry of Health that screening should be performed immediately at the first prenatal consultation or in the first trimester of pregnancy, with the request

Table 1. Comorbidities and complications

Maternal changes	Gestational and fetal complications
Glycosuria	Abortion
Acute urinary infection	Late fetal deaths
Pyelonephritis	Changes in amniotic fluid volume
Vaginal candidiasis	Congenital anomalies
Obesity	Growth disorders
Vascular lesions	Macrosomia
Preeclampsia	Respiratory distress syndrome
	Neonatal hypoglycemia
	Hyperbilirubinemia
	Hypocalcemia
	Polycythemia
	Risk of diabetes in future life and congenital malformations

Adapted source reference [13]

for fasting glucose examination [5], the test performed in the diagnosis is that of fasting glycemia and the OGTT test (oral glucose tolerance test) that aims to confirm this diagnosis [6]. If the value obtained from fasting blood glucose at the first visit is the value ≥ 92 mg/dl and < 126 mg/dl is found in fasting plasma glucose, which is diagnosed with GDM, but these values should be confirmed at a second dosage [17].

It is recommended by the Brazilian Federation of Associations of Gynecology and Obstetrics - FEBRASGO - (2012) that the glucose tolerance test (OGTT) be performed with care and with guidance on a diet with 250 g to 300 g of carbohydrates per day, which is about three days before the examination. The pregnant woman must be fasting from 8 to 12 hours one night before the test is performed, that is, that the examination will be performed the next day, these cares must be done to have an efficient reading of the results [6].

A very important study conducted in 2010 by HAPO (Hyperglycemia and Adverse Pregnancy Outcomes) surveyed 25,000 pregnant women to be able to observe blood glucose values by oral glucose tolerance test (OGTT) [18]. The OGTT is performed between the 24th and 28th weeks of pregnancy in all pregnant women who do not meet the criteria for the diagnosis of GDM [19].

The test is done with a solution of 75 g of glucose to obtain the values of each pregnant woman, the criteria for OGTT is at least a value greater than or equal to the fixed value, fasting the value should be ≥ 92, after 1 hour done the test the value will go to ≥ 180 and 2 hours later the value will go to ≥ 153, these values were established by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) in 2010 [19].

2.4 Treatments with Medicinal Plants

Medicinal plants are being used more and more by humans for treatment for all types of diseases, these medicinal plants are understood by the population as herbal medicines. According to ANVISA (National Health Surveillance Agency), all medicine obtained from plant raw materials is herbal medicine, of course, analyzing its pharmacological properties, having a broad knowledge of its efficacy and safety for a qualified drug, because every plant has its risk of

toxicity, so scientific studies are increasingly advanced [7].

Most often the population that uses medicinal plants for curative purposes of diseases does not know the proper care that must be taken from cultivation to the preparation that should be made, is not aware of the therapeutic action that that plant has, its toxicity, indications, and contraindications. Each plant has its theoretical value that benefits health as it also has values that can further harm the patient's health because as the plant has its ability to heal, it also has a great risk of intoxication if it does not know the correct form of proper preparation that should be done [20].

There are several plants popularly known for treating diabetes mellitus with little scientific research proving its effectiveness and being used in gestational diabetes. They are Jambolão *(Eugenia jambolana),* Pata de Vaca *(Bauhinia forficata l.),* Carqueja *(Baccharis trimera),* Melão de São Caetano *(Momordica charantia),* Oliveira *(Olea europaea),* Yacon *(Polymnia sonchifolia),* Hibisco *(Hibiscus rosa sinensis),* mangaba *(Hancornia speciosa)* [21].

2.4.1 Jambolão *(Eugenia jambolana)*

Eugenia jambolana is popularly known as jambolão or black olive, depending on the region in which it is located, and is used for certain therapeutic purposes [22]. It is a tree of Indian origin, belonging to the family of *Myrtaceae*, one of the most used plants for diabetes. Some authors have found that the leaf and seed of the jambolão have hypoglycemic action, that is, it can decrease the amount of glucose in the blood, besides, it has an antioxidant action [23].

Jambolão is used in folk medicine because it has medicinal properties for the benefit of health. It has anti-inflammatory properties from the stem of its bark, has properties that protect the formation of cancer and properties that control diabetes through the leaves of Eugenia jambolana [22].

2.4.2 Cow Paw (*Bauhinia forficata* L*.)*

Belonging to the family Leguminosae, the genus *Bauhinia* highlights about 300 species located worldwide in tropical areas [24]. *Bauhinia forficata L*. is a tree with arboreal or shrubby habit [25]. Its chemical composition is quite rich has tannins, terpenoids, saponins, trigonelline, some traces of phenols, alkaloids and flavonoids,

the latter having hypoglycemic action, there is already scientific evidence of this plant for diabetes treatment. The most used part of this plant is the leaves because it has the hypoglycemic properties, this has already been proven [26]. The cow's paw is of Origin of South America and can be found in some countries, including Brazil that extends more in the regions of Rio de Janeiro to the Rio Grande do Sul [24].

The name cow's paw is because of its shape on its leaves that look like the paw of a cow. The leaves and stem of this plant are widely used in folk medicine for the treatment of various diseases, mainly for diabetes, because it has hypoglycemic actions [27].

In addition to having hypoglycemic action through leaf infusion and which are used through Brazilian folk medicine, it has properties with diuretic, depurative, and tonic agents, besides helping to combat lymphatic filariasis and the reduction of glycosuria [28].

Table 2. Plant parts with medicinal properties

Part of the plant used	Medicinal properties
Stem bark	Anti-inflammatory
Leaves	Antidiabetics
Extract from leaves	Antiviral, antibacterial and antiallergic.
Extract from seeds	Antifungal and antibacterial
Fruits	Antioxidant, anti-inflammatory and hypoglycemic.

Adapted source reference [22]

Fig. 1. Fruits of Eugenia jambolana
Available:https://www.blackangelsl.net/2017/beneficios-e-propriedades-naturais-do-jambolao/

Fig. 2. *Bauhinia forficata* L. (Cow's paw)
Available:https://www.portaldoholanda.com.br/cura-pela-natureza/erva-medicinal-conhecida-como-pata-de-vaca-e-usada-no-combate-ao-diabetes

Fig. 3. *Baccharis trimera* (Carqueja)
Available:http://www.ufrgs.br/fitoecologia/florars/open_sp.php?img=5013

According to reference [29] confirmed in a study that the cow's paw did not have significant importance in pregnant rats with diabetes and glucose levels had no change, thus showing that pregnant rats with diabetes had no difference, on the other hand, it shows that in non-diabetic rats bauhinia extract forficata decreases embryo loss if the embryo has been implanted [29].

2.4.3 Carqueja (*Baccharis trimera*)

The carqueja belongs to the family Asteraceae, and have 433 species of the genus *Baccharis*, are mostly found in the south and southeast regions of Brazil and tropical, subtropical and temperate regions, their size is small about 4 m high 50 cm of perennials, are found in different ways such as subshrub shrubs, creepers trees [7].

Carqueja is the second plant that has the most citations for diabetes, its aqueous fraction presents an antidiabetic action that decreases the level of blood glucose for 7 days in treatment. *Baccharis* extract was used in a study with diabetic and non-diabetic mice for 7 days in treatments and concluded that the extract to be ingested twice a day for 7 days, presents a reduction in blood glucose, that is, it points to a potent antidiabetic activity [30].

2.4.4 Melon of são caetano (*Momordica charantia*)

It belongs to the family *Curbitaceace*, its flavor is quite bitter that it is found in leaves, stems, fruits, and also in another part of the plant. Many people have a different way of using this plant, some boil the leaves to use as an infusion, others cook the fruits along with food and others consume as a salad. The plant, the extract powder, and the fruit have actions that can treat various diseases, including diabetes [31].

The phytochemical composition of *Momordica charantia* is composed of saponins, steroids/triterpenes, flavonoids, and tannins. Diabetic people when they associate aqueous fruit extract with physical exercises tend to decrease blood glucose levels, all in a dose applicable to each type of diabetes [32].

Fig. 4. *Momordica Charantia* (Melon De São Caetano)
Available: https://olhares.sapo.pt/melao-de-sao-caetano-momordica-charantia-foto3292102.html

The hypoglycemic effect of this plant can be explained by various mechanisms of action, an increase in glucose in the liver, a reduction in gluconeogenesis; which is inhibited through the glucose-6-phosphatase enzyme and fructose-1,6- bisphosphatase, promotes the release of insulin in addition to potentiating its effect, all through Momordica Charantia, which in addition to providing all these effects among others can also increase the number of *β*-cells in the pancreas of diabetic animals [31].

2.4.5 Olive (*Olea europaea*)

Designated as Oliveira, *Olea europaea* belongs to the Family of Oleaceas and is a small perennial tree about 12 to 20 feet high, its bark is grayish and its branches rigid. It has green leaves, small flowers, and a purplish fruit called olives and it is through these fruits that the oil for olive oil production is extracted [31].

In addition to olive and olive oil, olive leaves allow their use for teas, as they are rich in hypoglycemic, antioxidant, anti-inflammatory, antimicrobial action among others [33].

The mechanism of action that is suggested for the Oliveira plant is that the release of insulin is potentiated induced by glucose and also an increase in peripheral glucose absorption. The mechanism of action of the Olive leaf resembles an antioxidant action [31].

2.4.6 Yacon (*Polymnia sonchifolia*)

Referring to the Family Compositae, and of origin of the Andes Andes and is known in Brazil as yacon potato, it has an enormous amount of oligosaccharides and fructans, a type of inulin, in its roots and is widely used by diabetic people. It is a tree that measures around 2.5 meters high and its tuberous roots weigh about 2 to 4 kg of the reserve. In its chemical composition, it exhibits phenolic compounds such as caffeic acid, ferulic acid, and chlorogenic acid, as well as flavonoids, such as quercetin [34].

Fig. 5. *Olea europaea* (Oliveira)
Available: https://www.researchgate.net/figure/Acebuchinas-los-frutos-del-acebuche-Olea-europea-varsylvestris_fig10_323476506

Fig. 6. *Polymnia sonchifolia* (Yacon)
Available:https://www.strangewonderfulthings.com/240.htm

Some authors describe that there is a reduction in blood glucose levels in diabetic rats, its action can be clarified through stimulating the pancreatic mechanism, regeneration, and protection of β cells [35].

2.4.7 Hisbico (*Hibiscus rosa sinensis*)

Hibiscus is part of the Malvaceae family and is a shrub, has more than 250 species and is native in tropical and subtropical regions. Hibiscus in many regions is eaten raw or cooked, besides having a therapeutic effect and widely used as food dyes [36].

Current research has shown that this plant has a variety of pharmacological action, an example is flowers that are rich in chemicals such as glycosides, vitamins, flavonoids, cyanides, riboflavin, among others that are responsible for these effects [36].

A study with rats showed a significant hypoglycemic effect so much that its effect was similar to that of glibenclamide which is a diabetes drug, but there are not as many scientific studies proving this study more is common diabetic pregnant women or not using plants that older

people indicate, but few people know their necessary pharmacological actions and their side effects leading to a risk of the toxic effect coming from the plant [36].

2.4.8 Mangaba (*Hancornia speciosa*)

The *Hancornia Speciosa* known as manga is a tree that is 2 to 10 meters high, reaching up to 15 meters depending on the region you are in, its flower and white color and has a good scent, its fruit, and rounded shape of yellowish color with some red spots and usually makeup about 2 to 15 seed in a single fruit [37].

Mangaba has been widely used by the food industry, is rich in vitamin C and folk medicine is used as a home remedy for some type of disease, for example, the bark of the stem of mangaba made in the infusion can be beneficial in the treatment of stomach disorders, gastric ulcers, and inflammatory diseases. The infusion of the mangabeira leaf serves to control chronic diseases such as hypertension, diabetes mellitus, and hypercholesterolemia. As the other plants still do not exist scientific studies that prove these pharmacological activities for

Fig. 7. *Hibiscus rosa sinensis* (Hibisco)
Available:https://blog.plantei.com.br/wp-content/uploads/2016/08/cuidados-com-hibiscos-5-768x566.jpg

Fig. 8. *Hancornia speciosa* (Mangaba)
Available:http://blogdarailda.blogspot.com/2012/03/suco-de-mangaba.html

pregnant women with diabetes, however, they use it even without having knowledge of its effects [37].

3. CONCLUSION

Gestational diabetes can progress worse perinatal outcome, its consequence arises in fertilization and implantation and affects in particular, organogenesis, causing early abortion, neonatal respiratory disorder, intrauterine death, congenital malformations, macrosomia, and immaturity. In the course of this study, it was possible to identify maternal-fetal comorbidities, which affect malformations more in newborns of diabetic mothers than the general population, however, risk factors such as obesity, late pregnancies, weight gain during pregnancy, family history, fetal death, macrosomia, which may influence maternal and fetal complications, requiring more detailed screening to ensure effective treatment for the population together with the basic health unit. The plants mentioned showed satisfactory results in research for diabetes mellitus in non-pregnant patients, but the study presented by Pata de Vaca (*Bauhinia forficata l.)* in pregnant rats with diabetes did not obtain beneficial but rather harmful results in embryo implantation, which leads us to investigate further under the use of all plants in the treatment of gestational diabetes.

CONENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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