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Review Article **Zoology**

Burden of Diabetes and Role of Medicinal Plants in Its Treatment

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Abstract

Diabetes is a growing health concern worldwide and now emerging as an epidemic world over. Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia or increased blood glucose levels, resulting from insufficient or inefficient insulin secretion, with alterations in carbohydrate, protein and lipid metabolism. Type-2 diabetes is the most prevalent form, of the total diabetics about 90% have type-2 diabetes, which is characterized by post-prandial hyperglycaemia (increase in blood sugar level after a meal). Many medicinal plants are reported to have insulin-mimetic effect, modulation of insulin secretion and inhibition of carbohydrate digesting enzymes. The currently available anti diabetic agents include sulfonylureas, thiazolidinediones and alpha glucos idase inhibitors and are widely used to control the hyperglycemia. These drugs fail significantly to alter the course of diabetic complications. They have limited use because of undesirable pathological conditions and high rates of secondary failure. This it is essential to look for more effective antidiabetic agents with fewer side effects. Traditional medicinal plants having anti diabetic properties can be a useful source for the development of safer and effective oral hypoglycaemic agents. More than 350 traditional plants are used in the treatment of diabetes mellitus, which have been recorded. Only a small number of these have received scientific and medical evaluation to assess their efficacy. However, plant remedies are the mainstream of treatment in underdeveloped regions. This review focuses on diabetes mellitus and the role of plants in the treatment of diabetes mellitus.

Keywords: Diabetes mellitus, Metabolic disorder, chronic hyperglycemia, Insulin, Carbohydrate.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder, resulting from insulin deficiency, characterised by abnormal increase in the blood sugar level, altered metabolism of carbohydrates, protein and lipids and an increased risk of vascular complications [1][11][12][13]. Since ancient times, plants have been an exemplary source of medicine. Ayurveda and other Indian literature mentioned the use of plants in treatment of various human ailments. In India, indigenous plant remedies have been used in the treatment of Diabetes mellitus since the time of Charaka and Sushruta (6th century BC) [1]. Plants have always been an exemplary source of drugs and more than 80% of the currently available drugs have been derived directly or indirectly from them. Medicinal plants have the advantage of having no or only few side effects. Some of them are being used in traditional systems of medicine from hundreds of years in many countries of the world. Metformin is an oral anti-diabetic drug used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM) patients. Metformin is now believed to be the most widely prescribed anti diabetic drug in the world; it was first derived from a medicinal plant *Galega officinalis*, which was historically used for treatment of diabetes in medieval Europe [2]. There are many anti-diabetic plants which might provide useful sources for the development of drugs which can be used in the treatment of diabetes mellitus. The literature on medicinal plants with anti-diabetic activity is vast, so a few commonly used plants have been discussed here.

What is Diabetes?

Diabetes mellitus is a complex metabolic disorder resulting from either insulin insufficiency or insulin dysfunction. The disease is primarily classified into insulin-dependent diabetes mellitus (type 1 diabetes, IDDM), non- insulin-dependent diabetes mellitus (type 2 diabetes, NIDDM) and Gestational

diabetes mellitus (GDM). The prevalence of NIDDM is increasing globally. Of the total diabetics, about 90% have NIDDM [3, 14, 15], which is characterized by post-prandial hyperglycaemia (PPHG) and associated with post-prandial oxidative stress. PPHG (increase in blood sugar level after a meal) plays an important role in the development of NIDDM, as well as in complications associated with the condition, including micro-vascular and macro vascular diseases.

Most of the food we eat is broken down into simple sugar glucose, which is the main source of fuel to get energy for the body. After digestion the glucose reaches our blood stream where it is available for the cells to utilize for energy, but insulin is needed for the uptake of glucose into the cells. Insulin is a hormone secreted by the pancreas; it has to be secreted in adequate amount to transport glucose from blood into different cells of the body. If the insulin is not produced sufficiently or the produced insulin does not work efficiently, the glucose is not taken into the body, remains in the blood. This makes rise in blood sugar level causes hyperglycaemia. If a diabetic person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger) [4, 14, 16].

Pancreatic α-amylase is a key enzyme in the digestive system and catalyses the initial step in hydrolysis of starch to a mixture of smaller oligosaccharides. These are then acted on by αglucosidases and further degraded to glucose which on absorption enters the blood-stream. Degradation of this dietary starch proceeds rapidly and leads to elevated PPHG (post-prandial hyperglycemia). PPHG can be controlled by delaying the absorption of carbohydrates from the gastrointestinal tract by inhibiting digestive enzymes. Foodstuffs which are rich in phenolic compounds are known to inhibit digestive enzymes, most of the phenolics of millets (finger millet or ragi) and grains are concentrated in the seed coat5. Many plants (Indian gooseberry, guava, and pomegranate), vegetables (cauliflower, garlic, onion) and leafy vegetables (amaranth, punarnava) are reported to have hypoglycaemic activities. An herbal formulation containing the three medicinal fruits *Phyllanthus emblica* (Amla), *Terminalia belerica* (Bibhitaki) and *Terminalia chebula* (Haritaki) named Triphala (Sanskrit, tri = three and phala = fruits), is traditionally used medicine for the treatment of diabetes.

Types of Diabetes [6]

- **Type 1 Diabetes** is called as insulin-dependent diabetes mellitus (IDDM), immune-mediated or juvenile-onset diabetes. It is caused by an autoimmune reaction where the body's defense system attacks the insulin-producing cells. This disease can affect people of any age, but usually occurs in children or young adults. People with this form of diabetes need injections of insulin every day in order to control the levels of glucose in their blood.
- **Type 2 Diabetes** is called as non-insulindependent diabetes mellitus (NIDDM), and accounts for at least 90% of all cases of diabetes. It is characterized by insulin resistance and relative insulin deficiency, either of which may be present at the time that diabetes becomes clinically manifest. The diagnosis of NIDDM usually occurs after the age of 40 but can occur earlier, especially in populations with high diabetes prevalence. It is characterized by insulin resistance and impaired beta cell function.
- **Gestational Diabetes** (GDM) is a form of diabetes consisting of high blood glucose levels during pregnancy. It develops in one among 25 pregnancies worldwide and is associated with complications in the period immediately before and after birth. GDM usually disappears after pregnancy but women with GDM and their offspring are at an increased risk of developing NIDDM later in life. Approximately half of women with a history of GDM go on to develop type 2 diabetes within five to ten years after delivery.
- **Specific Types of Diabetes** due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation).

Diabetes Complications [4, 5]

Diabetes mellitus (DM) is the commonest endocrine disorder that affects more than 100 million people worldwide (6% of the population) and in the next 10 years it may affect about five times more people than it does now (WHO, 1992, ADA, 1997). In India, the prevalence rate of diabetes is estimated to be 1–5% [1]. Complications are the major cause of morbidity and mortality in DM.

One of the long-term complications of NIDDM is hypertension or high blood pressure. Hypertension and NIDDM are interrelated metabolic disorders. Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and is a leading cause of chronic renal failure. Though pathophysiology of diabetes remains to be fully understood, experimental evidences suggest the involvement of free radicals in the pathogenesis of diabetes and more importantly in the development of diabetic complications. Free radicals are capable of

damaging cellular molecules, DNA, proteins and lipids leading to altered cellular functions. Many recent studies reveal that antioxidants capable of neutralizing free radicals are effective in preventing experimentally induced diabetes in animal models as well as reducing the severity of diabetic complications. For the development of diabetic complications, the abnormalities produced in lipids and proteins are the major etiologic factors. In diabetic patients, extra-cellular and long lived proteins, such as elastin, laminin, and collagen are the major targets of free radicals. These proteins are modified to form glycoproteins due to hyperglycemia. The modification of these proteins present in tissues such as lens, vascular wall and basement membranes are associated with the development of complications of diabetes such as cataracts, microangiopathy, atherosclerosis and nephropathy. During diabetes, lipoproteins are oxidized by free radicals. As diabetes is a multifactorial disease leading to several complications, and therefore demands a multiple therapeutic approach.

Diabetes and Insulin

Even insulin therapy does not reinstate a permanent normal pattern of glucose homeostasis, and carries an increased risk of atherogenesis and hypoglycemia1. Regardless of the type of diabetes, patients are required to control their blood glucose with medications and/or by adhering to an exercise program and a dietary plan. Insulin therapy by injection is given to those with IDDM and also to some patients with NIDDM when oral hypoglycaemic drugs fail to lower blood glucose. Due to modernization of lifestyle, NIDDM is becoming a major health problem in developing countries. Patients with NIDDM are usually placed on a restricted diet and are instructed to exercise, the purpose of which primarily is weight control. If diet and exercise fail to control blood glucose at the desired level, oral antidiabetic medication is prescribed. Several plants have been reported for their insulin stimulation and mimetic activities (Table 1).

Table 1: Some important medicinal plants with anti-diabetic properties [6, 8, 9]

SL No.	Botanical Name	Beneficial Effects
1	*Aloe vera*	Hypoglycemic, wound healing in diabetics
2	*Punica granatum*	Antioxidant, anti-hyperglycemic effect
3	*Boerhaavia diffusa*	Increases plasma insulin concentration and insulin sensitivity
4	*Azadirachta indica*	Hypoglycemic, reduces peripheral utilization of glucose and glycogenolytic effect
5	*Caesalpinia bonducella*	Hypoglycemic, insulin secretagogue, hypolipidemic activity
6	*Ficus benghalensis*	Hypoglycemic, hypolipidemic, inhibits insulinase activity from liver and kidney, Insulin mimetic activity
7	*Glycyrrhizae radix*	Hypoglycemic activity
8	*Syzigium cumini*	Hypoglycemic, anti-oxidant activity, αglucosidase inhibitory activity
9	*Momordica charantia*	Insulin mimetic activity
10	*Phyllanthus emblica*	Decreases lipid peroxidation, antioxidant, hypoglycemic
11	*Trigonella foenumgraecum*	Hypoglycemic activity, stimulates insulin release by islet cells
12	*Pterocarpus marsupium*	Hypoglycemic, insulinogenic-enhance insulin release
13	*Amaranthus caudatus*	Hypoglycaemic activity
14	*Swertia chirayita*	Stimulates insulin release from islets
15	*Terminalia bellerica*	Hypoglycemic, antioxidant, hypolipidemic activity
16	*Terminalia chebula*	Hypoglycemic, antioxidant, hypolipidemic activity
17	*Tinospora cordifolia*	Anti-hyperglycemic, stimulates insulin release from islets
18	*Gymnema sylvestre*	Stimulation of repair or regeneration of beta cells, anti-hyperglycemic effect, hypolipidemic

Synthetic Drugs and Herbal Medicine

Oral antidiabetic agents exert their effects by various mechanisms:

1. Stimulation of β-cells in the pancreas to produce more insulin (sulfonylureas and meglitinides),
2. Increasing the sensitivity of muscles and other tissues to insulin (thiazolidinediones),
3. Decreasing gluconeogenesis by the liver (biguanides), and
4. Delaying the absorption of carbohydrates from the gastrointestinal tract (α-glycosidase inhibitors) [6].

A major effort was directed toward discovery of novel antidiabetic agents, which resulted in the discovery of several patented compounds namely cryptolepine, maprouneacin, 3β, 30-dihydroxylupen20 (29)-en-2-one, harunganin, vismin, and quinines [7]. Galegine was isolated as an active antihyperglycemic

agent from the plant *Galega officinalis* L. used ethnomedically for the treatment of diabetes. Galegine provided the template for the synthesis of metformin and opened up interest in the synthesis of other biguanidine-type antidiabetic drugs [2]. Since the hydrolysis of dietary carbohydrates such as starch is the major source of blood glucose, it is believed that the inhibition of the carbohydrate hydrolytic enzymes may be a promising strategy for the management of NIDDM. Phytochemicals such as phenolics with strong antioxidant properties have been reported to be good inhibitors of the enzymes linked to NIDDM. Phenolic extracts of plants were found to be effective inhibitors of intestinal α-glucosidase and are being used to control NIDDM. Some polyphenolic compounds from plants are known to cause insulin like effects in glucose utilization in mammals. Aloe vera, bitter gourd, guduchi, *Gymnema sylvestre* (gudmar), neem, methi, *Syzygium cumini* (jamun) and pomegranate etc. are some most commonly used plants which have anti-diabetic properties [7, 8]. Several mechanisms have been investigated to explain the antihyperglycemic action of medicinal plants, which include modulation of insulin secretion, insulinmimetic effect and inhibition of intestinal glucosidase activity [7, 9]. Some important commonly used medicinal plants having anti-diabetic properties and their beneficial effects are presented in Table 1.

Diabetes and Diet

The uncontrolled diabetes can lead to long-term organ damage, resulting sometimes in heart disease, stroke, vision loss, kidney failure, foot amputation or death, studies show. The diet frequently recommended for people who suffer from diabetes is one that is high in dietary fibre, especially soluble fibre, but low in fat (especially saturated fat) and sugar. Highly processed, calorie-dense, nutrient depleted diet leads to exaggerated increase in blood glucose and lipids that induces immediate oxidative stress [5, 10, 13-15].

A statement of American Diabetes Association recommended the medical nutrition therapy (MNT) for diabetics. MNT is important in preventing diabetes, managing existing diabetes, and preventing, or at least slowing, the rate of development of diabetes complications. MNT is an integral component of diabetes self-management at all levels of diabetes prevention [4]. The MNT recommendations include [4]

(a) Energy Balance, Overweight and Obesity:

- In overweight and obese insulin resistant individuals, modest weight loss has been shown to reduce insulin resistance. Thus, weight loss is recommended for all overweight or obese individuals who have or are at risk for diabetes.
- For weight loss, either low-carbohydrate or low-fat calorie-restricted diets may be effective in the short-term (up to 1 year).
- For patients on low-carbohydrate diets, monitor lipid profiles, renal function, and protein intake (in those with nephropathy) and adjust hypoglycaemic therapy as needed.
- Physical activity and behaviour modification are important components of weight loss programs and are most helpful in maintenance of weight loss. (b) Primary prevention of diabetes
- Among individuals at high risk for developing NIDDM, structured programs emphasizing lifestyle changes that include moderate weight loss (7% body weight) and regular physical activity (150 min/week) with dietary strategies including reduced calories and reduced intake of dietary fat can reduce the risk for developing diabetes and are therefore recommended.
- Individuals at high risk for NIDDM should be encouraged to use dietary fiber (14 g fiber/1,000 kcal) and foods containing whole grains (one-half of grain in take).

Inhibition of pancreatic α-amylase could result in the abnormal bacterial fermentation of undigested carbohydrates in the colon and therefore mild αamylase inhibition activity is useful. Plant derived compounds are reported to have strong inhibitory activity against α-glucosidase and mild α-amylase inhibition. High fibre content may further improve the satiating effect of the diet and a diet rich in soluble fibre, including oat bran, legumes, barley and most fruits and vegetables, has the most beneficial effect on blood lipids and blood pressure levels 10. Pulses are important in the diet as their effect on blood glucose is less than that of most other carbohydrate containing foods.

Green leafy vegetables rich in fiber help to lowering down the blood sugar levels and thus are healthy.

Burden of Diabetes in India

In India, the burden of diabetes has been increasing steadily since 1990 and leaps and at a faster pace from the year 2000. Figure 1 shows the increasing trend in diabetes prevalence in India during the past decade in India as per International Diabetes Federation [17]. The prevalence of diabetes in India has risen from 7.1% in 2009 to 8.9% in 2019.

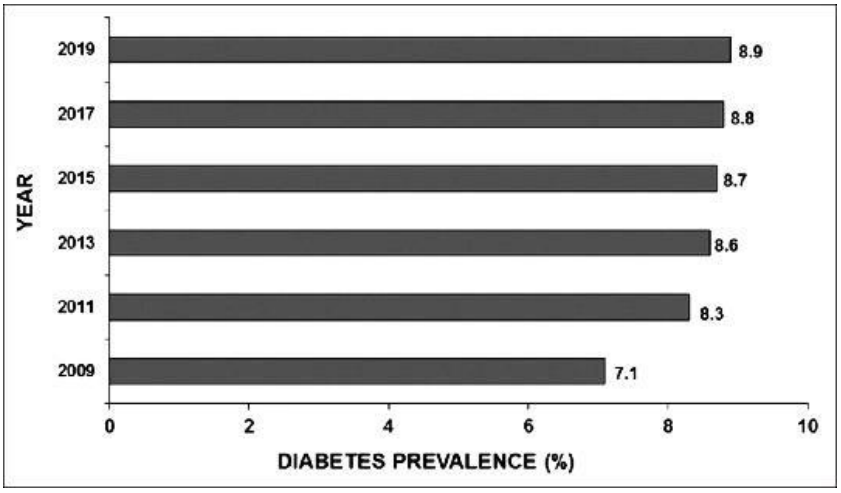

Figure 1: Trends in diabetes prevalence during the past decade in India

Table 2 [17] provides the burden of diabetes in India at a glance. Currently, 25.2 million adults are estimated to have IGT, which is estimated to increase to 35.7 million in the year 2045. India ranks second after China in the global diabetes epidemic with 77 million people with diabetes. Of these, 12.1 million are aged >65 years, which is estimated to increase to 27.5 million in the year 2045. It is also estimated that nearly 57% of adults with diabetes are undiagnosed in India, which is approximately 43.9 million. The mean healthcare expenditure on diabetes per person is 92 US dollars, and total deaths attributable directly to diabetes account for 1 million.

Table 2: Burden of Diabetes / Pre-diabetes in India [17]

	Year	
	2019	**2045**
Impaired Glucose Tolerance (estimates) [20-79 years]		
Number of People (million)	25.2	35.7
Rank	4	3
Diabetes (estimates) [20-79 years]		
Prevalence (%)	8.9	-
Age adjusted prevalence (%)	10.4	-
Number of People (million)	77.0	134.2
Rank	2	2
Diabetes (estimates) [>65 years]		
Number of People (million)	12.1	27.5
Rank	3	2
Undiagnosed Diabetes (estimates)		
Prevalence (%)	57.0	-
Number of People (million)	43.9	-
Rank	2	-
Healthcare Expenditure on Diabetes		
Mean expenditure per person with diabetes (USD)	92.0	-
Deaths related to Diabetes		
Total Deaths (million)	1.0	-

The report on the state-level disease burden in India stated that the percent change in diabetes prevalence among all ages in India from 1990 to 2016 was 64.3%, while the age-standardized prevalence was 29.3% [18]. The India State- Level Disease Burden Initiative Diabetes study collaborators [19] reported that the prevalence and number of people with diabetes in India increased from 5.5% and 26.0 million in 1990 to 7.7% and 65.0 million in the year 2016. According to this report, Tamil Nadu had the highest prevalence in 2016, followed by Kerala, Delhi, Punjab, Goa, and Karnataka.

The National Family Health Survey, four survey conducted in 15 Indian states/union territories during the year 2014–2015, reported that Andaman and Nicobar Islands had the highest prevalence of diabetes (26 and 14.5% among men and women, respectively), while Haryana had the lowest prevalence of diabetes (8.2%) for men and Bihar (6.1%) for women. The prevalence was higher in urban than in rural areas. The

recent Secular Trends in Diabetes in India study which assessed the change in diabetes prevalence between 2006 and 2016 in urban and rural areas of Tamil Nadu reported that the prevalence of diabetes increased from 18.6% in 2006 to 21.9 in 2016 in the city, while in the smaller towns, it increased from 16.4 to 20.3, and in the periurban villages, from 9.2 to 13.4, respectively.

Apart to from the rising prevalence of diabetes in India, the incidence of diabetes is also rising steadily, with a fast transition from euglycemia to pre-diabetes and diabetes. In India, very few longitudinal studies have been conducted to assess the incidence of diabetes and pre-diabetes. In the Chennai Urban Population Study cohort, diabetes and pre- diabetes incidence rates were reported to be 20.2 and 13.1 per 1000 person-years, respectively, while the follow-up study conducted in the Chennai Urban Rural Epidemiology Study (CURES) cohort reported the incidence rates of diabetes, pre-diabetes, and any dysglycemia to be 22.2, 29.5, and 51.7 per 1000 person-years, respectively. The conversion rate to diabetes was reported to be 19.4% among those with normal glucose tolerance and 58.9% among those with pre-diabetes. Diabetes incidence was reported to be 78.9 per 1000 person-years among those with Pre-diabetes [20].

Diabetes in Jammu & Kashmir

Diabetes, a growing health challenge of the 21st century, is a serious long-term condition and one of the chronic non-communicable diseases (NCDs). Diabetes care in Jammu and Kashmir continues to be a challenge for the primary care physicians/endocrinologists as urbanization continues to predict a steep rise in disease prevalence over the next few years. Rapid urbanization with increasing addiction on e-gadgets and sedentary lifestyle contribute significantly to this epidemic with a commensurate upward trend in the prevalence of pre-diabetes. Recently our group has published a study wherein we found 11.6% of population had Pre-diabetes. The prevalence of diabetes mellitus was 6.3% in general population and (1.3%) in tribal population of same geographical area of Jammu and Kashmir. The astonishing observation that we made was that 96% individuals with Diabetes mellitus/Pre-diabetes were undiagnosed. These nerve- racking percentages can be attributed to lack of awareness and scarcity of trained manpower cum health care facilities.

Access to diabetes care is lacking in this region owing to several problems; lack of appropriate facilities for diabetes care, an inadequate infrastructure, scarcity of trained healthcare personnel etc. Diabetic people require access to affordable holistic medical care and support for management, treatment and to avoid related complications. Over 422 million people worldwide have diabetes, the majority living in low-and middle-income countries, and 1.5 million deaths are directly attributed to diabetes each year. Covid19 epidemic infection has further frightened and harmed people with diabetes and posed an additional major health threat. Emerging data reported that COVID-19 is common in patients with diabetes, hypertension, and cardiovascular disease (CVD). Understandably, prevalence of diabetes in patients with COVID-19 varies by region, age and ethnicity. Nearly 40% of people who have died from Covid-19 were patients with diabetes. The government and current public health system need to hand in hand and promote access to diabetes care.

There are evidences of gaps and challenges in the care of people with diabetes. The stand out areas includes lack of diabetes educators, education programs and fragmented care. Furthermore, the COVID-19 epidemic poses a challenge to combat diabetes and its complications. Though, there has been an outpouring of support from medical personnel and others on the front lines for those afflicted. The diabetes community urgently needs immediate access to affordable diabetes care. It is imperative that the healthcare sector is equipped with trained diabetes educators to assist endocrinologists, diabetologists for delivering quality care for patients with diabetes and its management. Alongside, virtual interactions can be used to guide the care of patients, providing remote access to ones who may be otherwise inaccessible.

Future Directions

Although many plant species have been validated for their anti-diabetic properties and related complications, there is a need for modern research in the identification of phytochemical compound (s), their target (s) and their modes of action and combination therapy of plant pro-ducts with synthetic drugs. To make the therapy cost-effective, extensive clinical studies for long-term side-effects are a must. A large-scale production of quality plant material and innovative procedures to easily consume these medicinal plant species have to be further validated.

November 14, World Diabetes Day (WDD**)**, a globally celebrated event was created in 1991 by International Diabetes Federation [IDF] and the World Health Organization in response to growing epidemic of diabetes and escalating health threat posed by diabetes. November 14th marks the birthday of the gentleman who co-discovered insulin, F. Banting in 1922 with Charles Best.

CONCLUSION

Diabetes is a growing health concern worldwide and now emerging as an epidemic world over. The management of diabetes is still a major challenge. Thus there is great demand for research on natural products with anti-diabetic properties. Numerous studies have confirmed the benefits of medicinal plants with anti-hyperglycemic effects in the management of diabetes mellitus. Diabetes is an

important human ailment afflicting many from various walks of life in different countries. In India it is proving to be a major health problem, especially in the urban areas. Though there are various approaches to reduce the ill effects of diabetes and its secondary complications, herbal formulations are preferred due to lesser side effects and low cost.

CONFLICT OF INTEREST

Authors declare they have no conflict of interest.

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