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Scientific Validation of the Antidiabetic Effects of *Syzygium jambolanum* DC (Black Plum), a Traditional Medicinal Plant of India

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Abstract

Background: In spite of the tremendous progress achieved in medical sciences in the last century, the management of diabetes mellitus, a disease as old as mankind, is poor. Diabetes is currently the world's largest endocrine disorder, and estimates are that it affects almost 5% of the population. Ayurveda, the Indian traditional system of medicine, is one of the world's oldest systems to have documented the diagnosis and treatment of diabetes.

Methods: Experimental studies performed in accordance with the modern medicine principles have shown that some of the medicinal plants and polyherbal preparations made using the plants used in Ayurveda are effective in preventing both hyperglycemia and its complications. *Syzygium jambolanum* (Syn *Syzygium cumini, Eugenia cumini, Eugenia jambolana*), commonly known as black plum and originally indigenous to India, is one of the important antidiabetic plants.

Results: Jamun has been used in various complementary and alternative systems of medicine and, before the discovery of insulin, was a frontline antidiabetic medication even in Europe. The brew prepared by boiling the Jamun seeds in boiling water has been used in the various traditional systems of medicine in India.

Conclusions: This review includes the validated antidiabetic effects of Jamun and some of its compounds. Emphasis is also placed on addressing the various mechanisms of action contributing to the pharmacological effects and the aspects that need future investigations for Jamun to be of clinical use.

Introduction

Diabetes mellitus (DM), which is the leading metabolic disorder of the endocrine system globally, is one of the world's oldest diseases and is mentioned in ancient literatures.[1–4] DM is caused by inherited and/or acquired deficiency or inadequate secretion of the hormone insulin (type I or insulin-dependent DM) or due to an inadequate response of target cells to insulin (type II or non–insulin-dependent DM) or by a combination of these factors that ultimately culminates in hyperglycemia. The currently available therapeutic options, especially for the non–insulin-dependent DM, such as oral hypoglycemics, and insulin, have limitations of their own and are expensive. In milieu of these observations, many people rely upon alternative and complementary medicine for management of diabetes, and many plants have been observed to be useful.[1–4]

Literature study suggests that of the many plants studied, *Syzygium jambolanum* (Syn *Syzygium cumini, Eugenia cumini, Eugenia jambolana*) or black plum in English is arguably one of the most highly studied plants. Historically, the Jamun tree was exclusive to the Indian subcontinent but is currently found growing throughout the Asian subcontinent, Eastern Africa, South Africa, Madagascar, and in the warmer regions of the United States in states such as Florida.[2] The fruits are the most important plant part, and many of the colloquial names such as Java plum, Portuguese plum, Malabar plum, black plum, Indian blackberry, jaman, jambu, jambul, and jambool are attributed to the tree due to this.[3] The colloquial names of Jamun in various countries are listed in Table 1. In India there are two morphotypes of Jamun, the Kaata Jamun, which are small and acidic to taste, and the Ras Jaman, which are oblong, dark purple, or bluish, with pink, sweet fleshy pulp and small seeds (Fig. 1).[2]

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Table 1. Different Vernacular Names of *Eugenia jambolana* in India and Other Southeast Asian Countries

Language	*Names*
Scientific name	*Syzygium jambolanum, Eugenia cumini, Syzygium cumini, Eugenia jambolana*
English	Jaman, black plum, damson plum, duhat plum, Indian blackberry, jambolan, jambolan plum, Java plum, Malabar plum, Portuguese plum, black plum, black plum tree, Indian blackberry, jambolan, jambolan-plum, Java plum, malabar plum, Portuguese plum
Indian languages	
Assamese	*jamu, kala jamu*
Bengali	*kala jam*
Gijrati	*Jambu, jaambu*
Hindi	*Jamun, duhat, jam, jaman*
Kannada	*Nerale hannu*
Konkani	*jambul*
Malayala	*kaattucaampa, njaaval, njaara, perinjaara*
Manipuri	*gulamchat, jam*
Marathi	*jambool*
Mizo	*hmuipui*
Nepalese	*jamunu, phanrir*
Oriya	*jamkoli*
Pali	*Jambu*
Prakrit	*Jambulo, jammulo*
Punjabi	*Jaman*
Sanskrit	*Jambu, jambulah, meghamodini*
Tamil	*kottai-nakam, naval*
Telugu	*Neredu*
Urdu	*Jaman*
Other languages	
Burmese	*thabyay-hypyoo*
Filipino	*duhat, lomboi*
French	*Jamélongue*
Javanese	*Duwet, jamblang*
Khmer	*pring bai*
Malay	*jambolan, jambulana, jiwat, obah*
Nepali	*Jamun*
Sinhala	*jambu, jambul, madan, naval*
Swahili	*msambarau, mzambarau*
Thai	*hakhiphae, wa*
Tibetan	*dzam-bu*
Vietnamese	*trâm môc, vôi rung*

All parts of the Jamun, and the seeds in particular, have a long history of medicinal use in the various traditional and folk systems of medicines. The fruits are considered to be tonic, astringent, carminative, and useful in spleen diseases. The fruits and seeds are also used to treat pharyngitis and ringworm infection. The fruits are acrid and sweet, cooling, dry, and astringent to bowels.[2] Seeds are astringent, diuretic, and stop urinary discharge.[2] The various medicinal properties are attributed to the presence of myriad phytochemicals in the fruit and are listed in Table 2. Jamun is useful in the management of diabetes in various traditional (such as Ayurveda, Unani, Siddha, Srilankan, Tibetan, and homeopathy) and folk systems of medicine.[1–6] The method of preparation and use in the Ayurvedic, folk, and homeopathic systems of medicine are listed in Table 3.

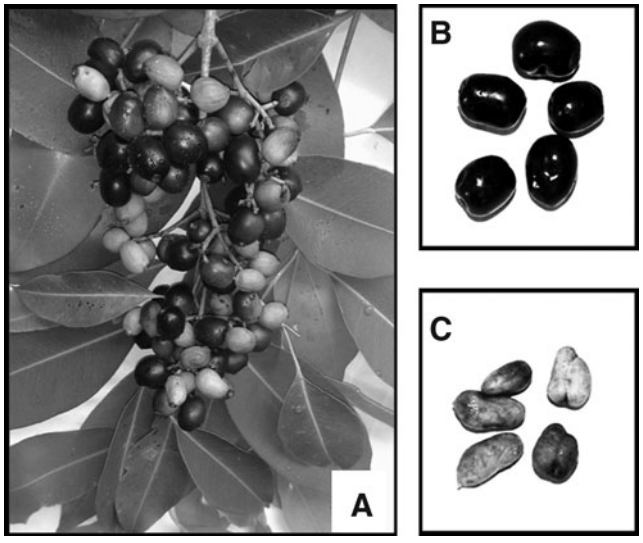

FIG. 1. Photograph of Jamun fruits **(A, B)** and seed **(C)**.

Antidiabetic Effects of Jamun: Preclinical Observations

Innumerable preclinical studies in the recent past have shown that the seed of Jamun possesses antihyperglycemic effects in both types 1 and 2 models of DM in rodents.[7–16] Studies with alloxan-induced diabetic rabbits have shown

Table 2. Phytochemicals Present in the Jamun Plant

Plant part	*Chemicals present*
Stem bark	Friedelin, friedelan-3-α-ol, betulinic acid, β-sitosterol, kaempferol, β-sitosterol-D-glucoside, gallic acid, ellagic acid, gallotannin, and ellagitannin and myricetine[2,4]
Leaves	β-Sitosterol, betulinic acid, mycaminose, crategolic (maslinic) acid, n-hepatcosane, *n*-nonacosane, *n*-hentriacontane, noctacosanol, *n*-triacontanol, *n*-dotricontanol, quercetin, myricetin, myricitrin and the flavonol glycosides myricetin 3-*O*-(4′-acetyl)-α-L-rhamnopyranosides[2,4]
Flowers	Oleanolic acid, ellagic acids, isoquercetin, quercetin, kampferol and myricetin[2,4]
Fruit pulp	Anthocyanins, delphinidin, petunidin, malvidin-diglucosides[2,4,40]
Seeds	Jambosine, gallic acid, ellagic acid, corilagin, 3,6-hexahydroxy diphenoylglucose, 1-galloylglucose, 3-galloylglucose, quercetin, β-sitoterol, 4,6-hexahydroxydiphenoylglucose[2,4]
Essential oil	α-Terpeneol, myrtenol, eucarvone, muurolol, α-myrtenal, 1,8-cineole, geranyl acetone, α-cadinol and pinocarvone[2,4a]

[a]Shafi PM, Rosamma MK, Jamil K, Reddy PS. Antibacterial activity of *Syzygium cumini* and *Syzygium travancoricum* leaf essential oils. Fitoterapia 2002;73:414–416.

that ethanolic extract of the seeds was effective in decreasing hyperglycemia in the subdiabetic and mildly diabetic rabbits, but was ineffective against the severely diabetic rabbits. Administering the extract (100 mg/kg body weight) orally to the subdiabetic rabbits for 1 day, mildly diabetic for 7 days, and severely diabetic rabbits for 15 days showed significant decrease in the fasting blood glucose during glucose tolerance test. Additionally, reduction in the levels of glycosylated hemoglobin and a concomitant increase in the concentration of serum insulin, in the levels of glycogen in liver and muscle were also observed. The histopathological studies of liver, pancreas, and aorta in alcoholic extract–treated diabetic groups showed almost normal appearance.[8]

The flavonoid-rich extract obtained from seeds of Jamun is also observed to be an efficient antihyperglycemic agent in streptozotocin-induced diabetic rats.[16] *In vitro* study validated that culturing pancreatic cells with flavonoids stimulated a 16% release in insulin, thereby confirming its ethnomedicinally presumed secretagogue effects. The extract also possessed hypolipidemic action and decreased the levels of low-density lipoprotein (LDL), triglycerides, and increased the high-density lipoprotein (HDL) levels over untreated diabetic rats.[16] Sharma et al.[17] purified hypoglycemic principles from Jamun seeds, and one such principle (LH II) when administered to diabetic rabbits at a dose of 10 mg/kg decreased the fasting blood glucose at 90 minutes, 7th day, and 15th day. Treating severely diabetic rabbits with LH II drastically decreased the levels of glycosylated hemoglobin and concomitantly increased the plasma insulin levels. Studies with cultured pancreatic islets have also shown a threefold increase in insulin levels as compared to untreated animals, validating the observations seen in the diabetic rabbits. A significant increase in the activity of key enzymes of glycolysis, decrease in the activity of key enzymes of gluconeogenesis and increase in the liver and muscle glycogen content were also observed.[17] The rate of glycogen biosynthesis and levels of glucose homeostatic enzymes (glucose-6-phosphatase, hexokinase) were also enhanced when compared with the diabetic cohorts.[16]

Jamun seed and pulp extract stimulated the release of insulin from the cultured Langerhans cells from both normal and diabetic rats, with better effects seen in the cells from the normoglycemic animals.[7] The pulp and seed extracts were also found to inhibit the hepatic and renal insulinase activity in a concentration-dependent manner.[7] In addition to decreasing hyperglycemia and hyperinsulinemia, animal studies have also shown that Jamun seeds prevented the diabetes-induced secondary complications such as nephropathy, neuropathy,[18] gastropathy,[18] diabetic cataract,[13] and also decreased peptic ulcer diseases.[19] These properties are useful in the management of the hyperglycemia-induced complications and in improving the quality of life of the patients.

The alcoholic extract of Jamun is shown to restore serum aspartate aminotransferase and alanine aminotransferase activities and serum urea, total protein, and albumin concentrations in streptozotocin diabetic rats, in a dose- and duration-dependent manner. These observations suggest

Table 3. Method of Preparing *Eugenia jambolana* Medication to Treat Diabetes in Various Systems of Medicine

System of medicine	*Method of preparation*
Ayurveda and various Indian folk systems	The powder of Jamun fruits is boiled in 10 parts of water until the volume reduced to 1/4th of the original. Once cooled, the supernatant is decanted and taken.[a]
Homeopathy	Classically the mother tincture of *Syzygium jambolanum* is prepared by suspending the powder in 5 volumes of absolute ethanol and thoroughly mixed. The whole mass is kept in a glass-stopped bottle in a cool dark place for 15 days. The clear tincture is decanted and the residual substance is strained and added to the previously decanted tincture. It is then filtered and stored in a glass-stopped phial.[b]

[a]Nadkarni AK. Indian Materia Medica, 3rd ed. Mumbai, India: Popular Press Ltd., 1976:1308–1315.
[b]Mandal PP, Mandal B. A Text Book of Homoeopathic Pharmacy. 1st volume, 1st ed. 1972.

that Jamun is useful in preventing structural and functional impairment of liver and kidney in diabetes. The beneficial effects of Jamun in 500 mg/kg dose in streptozotocin diabetic rats were comparable to that of glibenclamide (300 μg/kg), a standard oral hypoglycemic drug used in clinical practice.[20] Studies have also shown that mycaminose (50 mg/kg) isolated from the seeds of Jamun produced significant reduction in blood glucose level against the streptozotocin-induced diabetes in rats.[21]

Administration of different doses of alcoholic and aqueous extracts of Jamun seed to the fructose-induced type 2 diabetic rats was observed to cause concentration-dependent beneficial effects. Feeding fructose for 15 days increased the serum glucose, insulin levels, and the triglyceride levels marginally when compared with the normal controls.[22] Treatment with 400 mg per day of aqueous extracts of Jamun for 15 days substantially prevented hyperglycemia and hyperinsulinemia induced by a diet high in fructose, suggesting it to be of use in type 2 diabetes.[22]

Human Trials on Antidiabetic Effect of Jamun

With regard to human studies, there have been very few studies on human volunteers in the post-1945, era and some have been promising. Srivastava et al.[23] administered 4–24 g of the seed powder to 28 patients with diabetes and observed a reduction in the mean fasting and postprandial blood sugar levels. Later, Kohli and Singh[24] have also observed that administering 12 g of the Jamun seed powder in three divided doses for 3 months to 30 patients with "uncomplicated" non-insulin-dependent DM caused a moderate hypoglycemic effect. The effect of Jamun was comparable to that of chlorpropamide. Jamun was shown to ameliorate polyurea, polyphagia, weakness, and weight loss. In this study, no side-effects were observed, and this may be possibly due to the fact that the powder was administered three times daily.[24]

Recently, in an open-labeled, randomized, parallel-designed controlled study 15 patients who had type 2 DM and who were freshly diagnosed, Sahana et al.[25] observed that administering the standardized seed powder caused a significant decrease in the fasting blood sugar, insulin resistance, and increase in HDL cholesterol at the end of the third month (when compared to the baseline). However, there was no significant reduction in the postprandial blood sugar and glycosylated hemoglobin at the end of the third and sixth months, when compared to the baseline. Furthermore, there was no change in the levels of triglycerides, total cholesterol, and LDL.[25]

Mechanisms of Action

DM is a multifactorial disorder involving genetic influence and effects of environmental factors. Type 1 DM involves a genetic basis with autoimmune destruction of pancreatic islet β-cells triggered by viral infections. Type 2 DM has the involvement of many genes and multiple environmental factors. Insulin resistance, decreased insulin sensitivity, impaired glucose uptake, hyperglycemia, and dyslipidemia are the biochemical features of type 2 DM. The long-term complications of DM include retinopathy, neuropathy, and nephropathy. Various mechanisms have been proposed for the antidiabetic actions of Jamun. These include stimulation of pancreatic insulin secretion,[7,14,17,26–28] restoration of β architecture,[7,8,28] reduction of oxidative stress and antioxidant action,[10,11,29] and amelioration of dyslipidemia,[15,16,28] Other mechanisms suggested are inhibition of the human peroxisome proliferator-activated receptor γ,[30] upregulation of the glucose transporter GLUT-4,[31] rise in cathepsin-B activity,[7] inhibition of extrahepatic insulinase activity, development of insulin-positive cells from the pancreatic duct epithelial cells,[32] and increasing glycogen content in liver and muscle.[7,8,15] Jamun also caused an increase in the activity of key enzymes of glycolysis and a decrease in the activity of important enzymes of gluconeogenesis.[17]

Jamun Stimulates Pancreatic Insulin Secretion, and Restores and Regenerates β -Cell Architecture (Secretagogue Effect)

Optimal pancreatic β-cell function is essential for the regulation of glucose homeostasis, and its impairment leads to the development of diabetes. Studies have shown that the administration of Jamun restored the architecture of the pancreatic β-cell,[7,8,28] increasing plasma insulin levels by converting proinsulin to insulin possibly through pancreatic cathepsin B, and/or its secretion.[33] Jamun extract is also shown to inhibit insulinase activity in the liver and kidney (which are the main sites for insulin breakdown), thereby suggesting that its protective effects are also mediated by the extrapancreatic pathways.[7,15,16,28] Phytochemical examinations have confirmed that Jamun contains flavonoids and other polyphenolics, and it is possible that these compounds could act separately or synergistically to cause the hypoglycemic effect. To substantiate this, flavonoids are shown to regenerate the damaged pancreatic β-cells in diabetic animals.[34] Anthocyanins, the natural colorants, have also been shown to stimulate insulin secretion from rodent pancreatic β-cells *in vitro*.[35]

Jamun Reduces the Oxidative Stress and Improves Antioxidant Status

Persistent hyperglycemia in patients with diabetes leads to generation of oxidative stress due to auto-oxidation of glucose, and nonenzymatic glycosylation of body proteins and the polyol pathway. The auto-oxidation of glucose involves spontaneous reduction of molecular oxygen to superoxide and hydroxyl radicals, which are highly reactive and interact with all biomolecules. They also accelerate the formation of advanced glycation endproducts and impair synthesis, regeneration, and functioning of antioxidants. Together, these mechanisms contribute to the secondary complications observed in diabetes.[36]

The antioxidant effects of the ethanolic extract of the fruit pulp, kernel, and seed coat in various *in vitro* assays (DPPH, OH, and O_2^-) with gallic acid, quercetin, and trolox as reference molecules.[37] It was observed that in the DPPH scavenging assay, the kernel extract was better than the seed coat and pulp extract, but less than the reference molecules. However, in the superoxide radical scavenging activity, the kernel extract was six times more effective than trolox and three times more effective than catechin.[37]. In the hydroxyl radical scavenging assay, the kernel extract was comparable to the effect of catechin.[37]

The methanol-formic acid (9:1) extract of the fruit,[38] the hydroethanolic extract of the seed,[39] and anthocyanin-rich

fruit peel extract[40] have all been reported to be potent free-radical scavengers in the DPPH• scavenging assay. The hydrolyzable and condensed tannins in the fruit are also reported to possess antioxidant activity in the DPPH radical-scavenging and FRAP assays.[41] The organic extract of the leaf (methanol-dichloromethane extract) as well as the hydroethanolic extract of the seed is reported to be a scavenger of nitric oxide *in vitro*.[42]

The fruit skin of Jamun possesses antioxidant effects, as confirmed by results from the hydroxyl radical-scavenging assay, superoxide radical-scavenging assay, DPPH radical-scavenging assay, and lipid peroxidation assay with egg yolk as the lipid-rich source.[43] The anthocyanin-rich fruit peel extract is also observed to be an effective reducing agent.[40] Additionally, Bajpai et al.[44] have also observed that the hydromethanolic extract of the Jamun seed was effective in scavenging (90.6%) free radicals as evaluated in the auto-oxidation of β-carotene and linoleic acid assay. Animal studies have also shown that administering Jamun decreased the levels of lipid peroxides in the stomach of animals subjected to ulcerogenic treatments[19] in the brain, liver, kidneys, and serum of diabetic animals.[9–11]

Jamun Improves Glucose Utilization and Maintains Glucose Homeostasis

In the postprandial state, insulin promotes the uptake of glucose by tissues, glycolysis, oxidation, and glycogenesis. Studies suggest that administering Jamun increases glycogen content in the liver and muscle cells of diabetic animals[7–12,15,16,28] and increases the activities of enzymes crucial for glycogenesis, glycolysis, and concomitantly decrease enzymes involved in gluconeogenesis.

Jamun Prevents Alterations in Glycation Status and Formation of Advanced Glycation End Products

Advanced glycation endproducts (AGES) generate reactive oxygen intermediates by autoxidation. AGES are responsible for diabetic microvascular and macrovascular complications. Studies have shown that the blood levels of glycated hemoglobin in experimental diabetic animals decreased on administering Jamun.[15–17,26] However, a similar observation was not observed in glycated hemoglobin levels in humans administered Jamun.[25] Levels of glycoconjugates such as protein-bound sialic acid, protein-bound fucose, and protein-bound hexosamines are known to increase with progression of diabetic complications. Diabetic rats showed increased or decreased levels of sialic acid, and increased levels of total hexoses, fucose, and hexosamines in plasma, liver, kidney, heart, and brain.[45] Treatment with Jamun bark extract was effective in restoring the levels of sialic acid, hexose, hexosamine, and fucose in plasma, liver, and kidney of diabetic rats.[45] The observed effect of Jamun bark extract on reversing the adverse effects of hyperglycemia provides an insight into the pathogenesis of diabetic complications, and may be used to advantage in therapeutic approaches.

Jamun Ameliorates Dyslipidemia in Diabetes

Dyslipidemia characterized by increased levels of triglycerides, total cholesterol, and LDL, and decreased level of HDL, is an important biochemical abnormality of DM.[22] Preclinical studies have shown that administering Jamun seeds and fruits decreased LDL cholesterol, triglycerides, and total cholesterol and increased HDL cholesterol in diabetic rats or rabbits.[6,15,16,22,26] In human studies, some observations suggest beneficial effects in amelioration of dyslipidemia,[6] while others have been contradictory.[25]

Jamun Inhibits α-Glucosidases

α-Glucosidase inhibitors (acarbose, miglitol, and voglibose), which inhibit the digestion of carbohydrates, are used to establish greater glycemic control over hyperglycemia in DM type 2, particularly with regard to postprandial hyperglycemia. *In vitro* studies by Ahmed et al.[46] have shown that the Jamun extract significantly inhibited the α-amylase, α-glucosidase, and sucrase activities in a dose-dependent manner. The heat treatment of the sample resulted in a significant increase in the α-amylase inhibitory activity of the sample, while a marginal increase in the α-glucosidase and sucrase inhibitory activities was observed. These findings emphasize that inhibition of carbohydrate hydrolyzing enzymes is one of the mechanisms through which Jamun exerts its hypoglycemic effect *in vivo*.[46]

Jamun Activates Peroxisomal Proliferator-Activated Receptors

The peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptor proteins important in the regulation of carbohydrate, lipid, and protein metabolism. They are expressed highly in the adipose tissue, and activation of PPARγ induces adipocyte differentiation and lipid accumulation by modulating numerous genes regulating adipogenesis, lipid uptake, and lipid metabolism.[47] Rau et al.[30] observed that Jamun activated both PPARα and PPARγ. Sharma et al.[15,16] observed that the hypoglycemic and hypolipidemic actions of Jamun were mediated through dual mechanisms by (1) upregulation of both PPARα and PPARγ up to about three- to fourfold (over control) and (2) their capacity to promote adipocyte differentiation. Together these observations clearly suggest the beneficial effects of Jamun.

Conclusions

Jamun has been used to treat diabetes for centuries, and scientific studies carried out in the past few decades have confirmed that the seed is the most effective and is useful in both insulin-dependent and non-insulin-dependent diabetes. Reports also suggest it to be effective in reducing the production of glucose, to increase utilization of glucose, and to be of use in preventing/retarding diabetic complications. Mechanistic studies indicate that Jamun possesses free-radical scavenging and antioxidant effects, prevents lipid peroxidation, regenerates the β-cells, prevents alterations in glycation status and formation of advanced glycation end-products, improves glucose utilization and maintains glucose homeostasis, activates PPARs, inhibits α-glucosidases, and ameliorates dyslipidemia. These activities are beneficial in reducing hyperglycemia and in preventing/reducing the secondary complications of diabetes. Although Jamun was propounded as an effective antidiabetic agent in both traditional and animal studies, the clinical trials performed with

small sample size have been inconclusive. The antidiabetic action of Jamun includes the combined effect of acarbose, insulin, lovastatin, and vitamin E. Future studies should be aimed at performing randomized double-blinded clinical studies with large sample size and standardized extract with suitable controls. The observation from these studies will help in understanding and validating the traditional observations.

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Disclosure Statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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