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Attenuation of Reproductive Dysfunctions by Hydroethanolic Leaf Extract of *Fleurya aestuans* in Diabetic Rats

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Diabetes mellitus produces excessive reactive oxygen species (ROS) in the male gonads resulting to impairments of steroidogenesis and spermatogenesis. *Fleurya aestuans* is an extremely basic plant with therapeutic properties but it's frequently viewed as a weed in Nigeria. The present study therefore attempts to examine the effects of the hydroethanolic leaf extract of *Fleurya aestuans* on reproductive dysfunctions of diabetic rats. The rats were randomly assigned into seven groups of five rats each. Diabetes was induced in all the test groups 2-7 by intra-peritoneal injection of 150mg/kg bwt of alloxan monohydrate. Rats of the first group served as control and were only allowed rat feed and tap water ad libitum. Rats of the second group served as alloxan only group (ALXOG) and received 150mg/kg bwt of alloxan monohydrate. The third, fourth and fifth groups served as low dose extract group (LDEG), medium dose extract group (MDEG) and high dose

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extract group (HDEG) and received 50, 75 and 200mg/kg bwt of the extract respectively. Rats of the sixth group served as positive control group 1 (PCG1) and received 600mg/kg bwt of glibenclamide while rats of the seventh group served as positive control group 2 (PCG2) and received 100mg/kg bwt of tetrahydroxyflavone. Both extract and drugs were administered orally using oral gavage. The results indicated that the extract significantly reduced ($p<0.05$) blood glucose levels (203.10±0.10, 136.06±0.06, 111.01±0.01, 106.01±0.08) in contrast to group 2 (399.02±0.02, 277.02±0.02, 291.02±0.02, 383.01±0.00). In addition, the extract significantly improved ($p<0.05$) conceptive hormones, sperm parameters, SOD, CAT and GSH parameters. Our study confirmed that the leaf extract of *Fleurya aestuans* can be utilized in the correction of male reproductive dysfunction mediated by diabetes.

Keywords: Fleurya aestuans; hyperglycemia; conceptive hormones; wistar rodents.

1. INTRODUCTION

Elevated blood glucose levels or hyperglycemia is a classical sign and manifestation in individuals with diabetes mellitus. This issue produces excessive reactive oxygen species (ROS) prompting some malicious impact on some organ-system, like the eye, pancreas and kidneys [1]. Diabetes mellitus isn't just common in Nigeria yet its poor management is the main source of diabetic hitches like retinopathy, neuropathy, nephropathy and cardiovascular illnesses.

Past examinations uncovered that DM antagonistically influences the male gonads bringing about debilitation of steroidogenesis, spermatogenesis and sperm properties [2]. Diabetic men and animal models have been accounted for to be fruitless or barren based on impotency, regressive discharge of sperm, and hypogonadism. DM may influence male reproductive capacities because of demunition in male sexual drive and conceptive hormones, expanded germinal epithelial cell exhaustion, Sertoli cell vacuolization, variability in sperm quality, modified spermatogenesis and histomorphological changes in the testicles [3,4]. This could be mediated through hormonal modifications in the hypothalamic-pituitary-testicular axis or through the direct interactions of insulin with the testicles and sperm cells, as both the testicles and sperms themselves produce insulin. Insulin articulation in the testicles additionally is by all accounts influenced by diabetes [5].

Orthodox anti-diabetic agents, for example, glibenclamide are regularly utilized for diabetic treatment and management. Be that as it may, these medications have been accounted for to have numerous antagonistic impacts, for instance, increased prevalence of cardiovascular and gastrointestinal infections [6,7].

In this investigation we present a new therapeutic plant – *Fleurya aestuans,* which may have some beneficial effects on diabetes and its related complications. In Nigeria, *Fleurya aestuans* is an incredibly fundamental plant, where it is often seen as a weed. Extracts of *Fleurya aestuans* leaves have been utilized by traditional medicine practitioners as infertility and infection medicines. This concentrate additionally shows antifungal and antiviral activity [8]. A past report detailed the defensive impact of methanolic concentrate of *Fleurya aestuans* on indomethacin-initiated kidney impairment in male Wistar rodents [9]. The methanol extract has been accounted for its ameliorative impacts in diabetic animal models [10,11]. A new report from our center by Charles et al., [12], demonstrated the use of *Fleurya aestuans* leaves in the correction of low sexual drive and hormonal disequilibrium caused by lead acetate in female Wistar rats.

Notwithstanding, the impact of this extract on diabetes mediated reproductive dysfunction in male humans and animal models have not been accounted for. Hence, this examination endeavors to explore the impacts of hydroethanolic leaf extract of *Fleurya aestuans* on reproductive functions of alloxan-induced diabetic rats.

2. MATERIALS AND METHODS

2.1 Collection and Identification of Plant Material

Fresh leaves of *Fleurya aestuans* were harvested from University of Port-Harcourtand its environs and verified by a plant taxonomist, of the Department of Plant Science and Biotechnology, University of Port Harcourt. The plant was given herbarium number of: UPH/P/263.

2.2 Preparation of Extract

Fleurya aestuans leaves were collected; foreign materials were eliminated, dried at room temperature for one week and powdered mechanically. 690 g of the dry powdered leaves were de-fatted and sequentially extracted in 400ml of water-ethanol mixture (30:70) for 72 hours in an extraction jar using a sohxlet apparatus. The extract was concentrated through the use of a rotary evaporator, to yield the crude extract. The yield of the extract obtained was stored in a household refrigerator at 4^{o}C till further use.

2.3 Quantitative and Qualitative Phytochemical Analysis

The quantitative and qualitative phytochemical analysis of the extract was performed according to the methods of Sofowara [13] with slight modifications. The analysis of phytochemical was performed on a BUCK M910 Gas chromatography equipped with a flame ionization detector using the method of [14].

2.4 Induction of Diabetes

Using the method of Mbaka et al., [15], diabetes was induced by intraperitoneal injection of alloxan monohydrate 150 mg/kg after an overnight fast. The blood glucose levels (BGL) were monitored daily using accucheck glucometer and test strips. Rats with blood sugar level greater than 200 mg/dl were categorized as diabetic and were used for the study [16].

2.5 Lethality Test

Using the technique of Lork [17] the lethal dose (LD_{50}) of *Fleurya aestuans* extract (FAE) did not produce any signs of toxicity in rats even up to the dose of 4600 mg/kg.

2.6 Experimental Design

A total of 35 Wistar rats weighing between 193.9 - 210.5 g obtained from the animal house, Madonna University Elele, Nigeria were used for the study. The rats were housed in wire meshed cage under standard conditions (temperature 25-29°C and natural dark/light cycle and fed with a standard rat pelleted diet and tap water ad libitum. The animals were given a period of two week for acclimatization. After acclimatization the rats were randomly divided into seven [7] groups of five [5] five rats each. The rat groups were treated as follows:

Group 1 (Control group) were only allowed rat feed and tap water ad libitum for 28 days.
Group 2 (ALX only group) were only treated with alloxan (ALX) orally.
Group 3 (Low dose extract group) were orally administered 50 mg/body weight of *Fleurya aestuans* leaf extract for 28 days.
Group 4 (Medium dose extract group) were orally administered 75 mg/body weight of *Fleurya aestuans* leaf extract for 28 days.
Group 5 (High dose extract group) were orally administered 200 mg/body weight of *Fleurya aestuans* leaf extract for 28 days.
Group 6 (Positive Control group 1) were orally administered 600 mg/body weight of glibenclamide for 28 days.
Group 7 (Positive Control group 2) were orally administered 100 mg/body weight of tetrahydroxyflavone (THF) for 28 days.

2.7 Collection of Blood Samples

Rats were anaesthetized with chloroform at the end of 28 days and sacrificed by cutting through the jugular vein. Whole blood was collected into heparinized tubes and centrifuged at 3,000 rpm at 4°C for 15 min to collect the plasma.

2.8 Determination of Sperm Parameters

Sperm parameters (sperm count, motility, viability and morphology) were determined using hemocytometer and eosin stain respectively.

2.9 Determination of Serum Hormone Assays

Serum LH, FSH, testosterone and prolactin were analyzed by enzyme linked immunosorbent assay (ELISA).

2.10 Statistical Analysis

All values were represented as mean ± S.E.M and subjected to statistical analysis. Comparison was done using one – way analysis of variance (ANOVA). Values were considered significant when $P < 0.05$.

3. RESULTS

All Results Obtained from the study were presented in tables and expressed as mean plus/minus standard error of mean (M±S.E.M) as below.

Table 1. Values of blood glucose concentration of extract in diabetic rats

GROUPS	Day 0	Day 7	Day 14	Day 21	Day 28
1 (Control)	88.50±0.00	93.04±0.04	79.55±0.00	80.66±0.00	100.05±0.00
2 (ALX OG)	300.05±0.00[a]	399.02±0.02[a]	277.02±0.02[a]	291.02±0.02[a]	383.01±0.00[a]
3 (LDEG)	297.12±0.12	282.13±0.13	199.06±0.06[b]	205.02±0.02	180.12±0.12[b]
4 (MDEG)	295.01±0.08	246.09±0.09[b]	181.09±0.09[b]	150.04±0.04[b]	144.08±0.06[b]
5 (HDEG)	299.01±0.01	203.10±0.10[b]	136.06±0.06[b]	111.01±0.01[b]	106.01±0.08[b]
6 (PCG1)	301.01±0.01	233.06±0.06[b]	267.10±0.10	195.44±0.00	177.11±0.01[b]
7 (PCG2)	288.01±2.03	307.06±0.22	274.10±0.40	215.44±0.00	293.11±0.16[ab]

KEY: Values are presented as mean ± sem. n= 5. [a] = mean values are statistically significant compared to control, [b] = mean values are statistically significant compared to ALX treated groups

Table 2. Values of extract of *Fleurya aestuans* on male reproductive hormones in diabetic rats

GROUPS	LH (m/u/ml)	FSH (m/u/ml)	TEST (ng/ml)	PRL (ng/ml)
1 (Control)	2.02 ± 0.00	0.68± 2.09	1.59 ± 1.00	1.79 ± 0.04
2 (ALX OG)	0.30±0.02[a]	0.15±3.38[a]	0.83±0.20[a]	16.20±0.02[a]
3 (LDEG)	0.60 ± 2.00	0.39 ±2.15[b]	0.86 ± 0.00	9.95±2.02[b]
4 (MDEG)	0.80±2.00	0.31±1.99	0.80±0.20	9.45±0.05
5 (HDEG)	1.38±1.00[b]	0.52±1.99[b]	0.85±0.00	8.85±0.22[b]
6 (PCG1)	1.22± 0.00[b]	0.40 ± 1.24[b]	0.86±0.03	8.85±4.00[b]
7 (PCG2)	2.65± 0.00[b]	1.04±1.24[b]	0.89±0.31[b]	9.87±4.00

KEY: Values are presented as mean ± sem. n= 5. [a] = mean values are statistically significant compared to control, [b] = mean values are statistically significant compared to ALX treated groups

Table 3. Values of sperm parameters of extract in diabetic rats

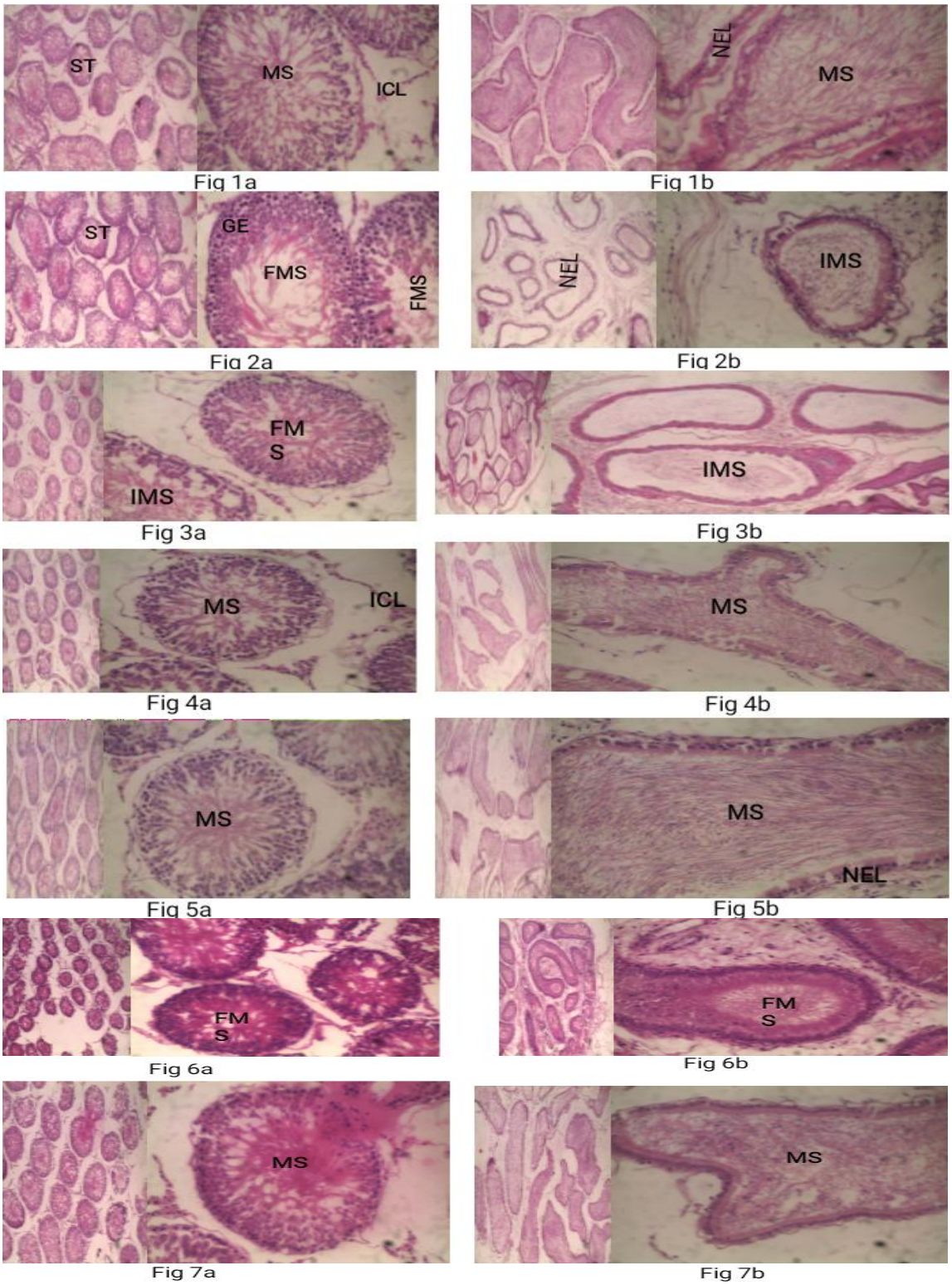
Groups	Control	ALXOG	LDEG	MDEG	HDEG	PCG1	PCG2
Appearance	Milky	Milky	Milky	Milky	Milky	Milky	Milky
Volume (ul)	0.3±0.00	0.2±0.03	0.2±0.01	0.3±0.00	0.3±2.00	0.2±0.03	0.2±0.00
pH	8.0±0.05	8.0±0.00	8.0±3.00	8.0±0.00	8.0±0.00	8.0±0.00	8.0±0.02
Viability (%)	90±4.00	70±1.00[a]	70±2.00	80±3.00[b]	80±0.00[b]	75±0.00	70±2.00
Viscosity	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Sperm count	800±0.50	400±0.10[a]	500±0.40	600±0.00[b]	900±0.40[b]	500±0.20	550±0.60[b]
Normal (%)	90±0.00	70±0.03[a]	75±0.00	80±0.04[b]	80±0.00[b]	75±0.00	75±0.09
Abnormal (%)	10±0.02	30±0.00[a]	20±0.03[b]	25±0.00	25±0.02	20±0.00[b]	25±0.04
Active (%)	80±0.00	65±2.00[a]	70±0.03	80±5.00[b]	85±0.00[b]	65±2.00	75±0.00[b]
Sluggish (%)	5±0.04	10±0.00	10±0.00	10±0.01	15±0.00[b]	10±0.04	10±0.00
Dead	10±0.00	25±0.00[a]	20±0.02	10±0.00[b]	10±0.05[b]	15±0.00[b]	25±0.07

KEY: Values are presented as mean ± sem. n= 5. [a] = mean values are statistically significant compared to control, [b] = mean values are statistically significant compared to ALX treated groups

Table 4. Values of leaf extract of *Fleurya aestuans* on oxidative parameters of diabetic rats

GROUPS	GSH (ug/ml)	CAT (u/g)	SOD (u/ml)	MDA (umol/ml)
1 (Control)	2.15 ± 0.04	4.75 ± 0.02	0.65± 2.02	0.27± 2.02
2 (ALX OG)	0.90±0.02[a]	1.15 ± 0.00	0.15±4.05[a]	0.67±4.05[a]
3 (LDEG)	0.98±2.02	3.28±0.00[b]	0.27±2.00	0.58±2.00
4 (MDEG)	0.95±0.05	3.75± 0.03[b]	0.25±5.10	0.60±5.10
5 (HDEG)	1.04±0.22[b]	2.88±0.02	0.31±0.00[b]	0.47±0.00[b]
6 (PCG1)	1.08±4.00[b]	4.15±1.01[b]	0.46±0.00[b]	0.42±0.00[b]
7 (PCG2)	1.02±4.00[b]	2.92±0.03	0.52±0.00[b]	0.38±0.00[b]

KEY: Values are presented as mean ± sem. n= 5. [a] = mean values are statistically significant compared to control, [b] = mean values are statistically significant compared to ALX treated groups



Figs. 1-7. Histology of the testes and epididymis

Key: ST= Seminiferous tubule, MS= mature spermatozoa, IMS= Immature spermatozoa, FMS= Few matured spermatozoa, NEL = Normal epithelia lining

The results of the photomicrographs of the rat's testes and epididymis stained with H & E dye at different magnifications (x125 and x600) were displayed in Fig. 1 to 7. Fig. 1a,b (control) contains mature spermatozoa in the lumen of the testis & epididymis. Fig. 2a,b (ALX only group) contains numerous immature spermatozoa in the epididymis & few matured spermatozoa in the testis. Fig. 3a,b contains mainly immature spermatozoa in the testis & epididymis. Fig 4-5a,b contains mainly mature spermatozoa in the testis & epididymal lumen. Fig. 6a,b (PCG1) contains few matured spermatozoa in the testis & epididymis. Fig. 7a,b (PCG2) contains matured spermatozoa in the testis & epididymis. The histological examination implies a remarkable inhibition of spermatogenesis in group 2 rats (ALX only group) which was ameliorated by the extract in the treatment groups.

4. DISCUSSION

The utilization of plant assets in the management of diabetes is very much acknowledged presumably because of the counter hyperglycemic or reactive oxygen specie rummaging property of plant constituents. Therapeutic plants give better substitutes as they are less harmful, effectively accessible and moderate [18]. Be that as it may, much consideration has not been given to the impacts of DM on male conceptive functions and the utilization of phyto-constituents to oversee diabetes mediated reproductive dysfunctions, since most researchers' center at disposing the etiology of DM.

In this regard, the current examination was intended to screen the impacts of hydro-ethanolic leaf extract of *Fleurya aestuans* on reproductive dysfunctions of diabetic rodents.

Alloxan was utilized to stimulate diabetes in this investigation prompting a significant decrease in plasma conceptive hormones like LH, FSH and testosterone and semen parameters, for example, sperm count, sperm viscosity, percentage of normal and active sperms and sperm viability in the ALX only group when contrasted with the control rats.

The perception propose that the two most significant events in the testis - steroidogenesis and spermatogenesis were adversely influenced by ALX therapy. Reactive oxygen species (ROS) is at present viewed as the main source of debilitated testicular capacities in animals and human examinations. Reactive oxygen species (ROS) is currently regarded as the most important cause of impaired testicular functions in animal and human studies.

Similar examinations have reported significant diminution in testicular steroidogenesis and spermatogenesis in diabetic rodents [6,7]. This authenticates the discoveries of the current investigation.

Regardless, steroidogenesis; spermatogenesis and sperm related parameters were fundamentally improved in the experimental groups treated with hydroethanolic extract of the leaves of *Fleurya aestuans* in contrast to group 2 (ALX only group) of the current investigation.

Natural products and phytotherapy have been broadly embraced of late, likely due to the apparent adequacy comparative with present day drug prescriptions. This is conceivably a direct result of the different phytochemicals, which have various intercessions throughout treatment of diseased conditions.

In this investigation, the leaves of hydroethanolic extract of *Fleurya aestuans* have been exhibited to have various phytoconstituents, for example, narigenin, rutin, tetra-hydroxy-flavonone, catechin, phenol, resveratrol, steroids and so forth.

Consequently, the enhancements in steroidogenesis and spermatogenesis might be projected as a stimulatory effect by the phytochemicals present in the leaves of *Fleurya aestuans* extract on 3β-hydroxysteroid dehydrogenase (HSD) and 17β-HSD potentials; HPG-axis and marker chemicals (CYP11A1, 3β-HSD and 17β-HSD).

Comparable investigations utilizing unadulterated mixtures of plant have likewise been accounted for to enhance testosterone concentration in diabetic animal models. Rutin and quercetin was reported to enhance serum testosterone levels in T1 diabetic rats [19,20,21]. Naringenin was reported to expand serum testosterone levels in T1 diabetic rodents after 10 weeks of treatment [22]. Curcumin, a phenol, was reported to elevate serum testosterone levels in T1 diabetic rodents after two months of treatment [21]. Tetra-hydroxy-flavonone and catechin have anti oxidative stress property, consequently, decrease the oxidative free radicals related with DM conceptive dysfunctions [23,24]. It is proposed that an increase in steroidogenesis

helps in normal spermatogenesis for the production of normal and healthy spermatozoa. These findings concur with that of the current examination.

5. CONCLUSION

The study suggests the utilization of *Fleurya aestuans* leaves in reversing male reproductive dysfunctions mediated by diabetes. The prescription in human trial may be beneficial for patients with hyperglycaemia.

6. RECOMMENDATIONS

Molecular basis or molecular mechanisms of *Fleurya aestuans* should be demonstrated. Further examination on the potency of the leaves of this plant on other diseases should be conducted.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that International standard, rules and guidelines for use of laboratory animal for research were followed [25]. The research have been examined and approved by our institutional ethical committee with the reference number: UPH/CEREMAD/REC/MM78/052.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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