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ANTIHYPERGLYCAEMIC AND HYPOLIPIDEMIC STUDIES OF THREE MEDICINAL PLANTS ON ALLOXAN-INDUCED DIABETIC RATS

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ABSTRACT

Ethanolic extracts of *Canarium schweinfurthii* stem bark and *Senna alata* leaf, and aqueous extract of unripe *Carica papaya* fruit, at two different doses (150, 400 mg/kg), were evaluated for antihyperglycaemic and hypolipidemic effects on alloxan-induced diabetic rats following daily oral administration for 28 days. While antihyperglycaemic effect was lacking in *Senna alata*, it was persistent ($P<0.05$) in *Canarium schweinfurthii* and *Carica papaya*. The activity was comparable to that of chlorpropamide at 100 mg/kg. All three extracts significantly ($P<0.05$) attenuated all lipid parameters, except HDL-cholesterol which increased significantly in rats treated with *Senna alata* and *Carica papaya* extracts without any appreciable weight gain. Hypolipidemic effect is reported for the first time for *Canarium schweinfurthii* stem bark. Signs of toxicity included renotoxicity by *Canarium schweinfurthii* and *Carica papaya* extracts which was typified by marked vascular congestion with extensive areas of intraparenchyma and glomerular haemorrhage. Further congestion of lungs with extensive harmorrhage in *Carica papaya*-treated rats and intraparenchyma haemorrhage of the heart of *Senna alata*-treated animals were also evident. This study though supports folkloric usage of the three plants in the traditional management of diabetes and related conditions may not be safe for long term usage until evaluated for further toxicity studies.

Keywords: *Canarium schweinfurthii; Senna alata; Carica papaya; antihyperglycaemic activity; hypolipidemic activity; alloxan-induced rats.*

INTRODUCTION

Diabetes is a serious disease characterized by multiple complications. The prevalence of diabetes for all age-groups worldwide is projected to rise from 171 million in 2000 to 366 million in 2030[1]. Pawpaw, *Carica papaya* L. (Caricaceae) is one of the most widely used remedies for the treatment of diabetes mellitus[2]. It is native to tropical America as a fast growing, short-lived tree with a very straight trunk up to 7.62 m. It is widely grown for the edible fruit and for the protein-digesting enzyme, papain, which is extracted from the fruit. The fruit has been studied for its anthelmintic[3] and abortifacient[4] properties. *Carica papaya* and *Senna alata* L. (Legiminosae) are among the principal antidiabetic plants included in recent surveys in Nigeria[5,6].

The bush candle tree, *Canarium schweinfurthii* Engl. (Burseraceae) is a large forest tree to 40 m. high, occurring throughout West Africa, and extending to East and Central Africa with very slight blunt buttresses[2]. Cut bark copiously exudes gum which solidifies to a whitish resin. Bark decoction is drunk as a remedy for pulmonary and stomach complaints. Information is scanty on pharmacological properties of *Canarium schweinfurthii*. Apart from the antioxidant and antimicrobial[7], and analgesic[8] activities of the Central African Republic species, only one report appeared on antidiabetic activity in streptozotocin-induced diabetic rats from a Cameroonian species[9].

Hypoglycaemic activity of many plants has been investigated[10-13], and potential remedies have been identified. Nevertheless, the search for more potent and tolerable antidiabetic agents is on the increase. The present study was undertaken to evaluate the antihyperglycaemic and hypolipidemic effects of ethanolic extracts of *Canarium schweinfurthii* stem bark and *Senna alata* leaf, and *Carica papaya* fruit juice aqueous extract on alloxan-induced diabetic rats in a chronic model experiment.

MATERIALS AND METHODS

Plant material and extraction

Fresh samples of *Canarium schweinfurthii* stem bark were collected from trees growing in Onigambari Forest Reserve, PSP 81, Oyo State, while *Senna alata* leaves were harvested along Lagos/ Benin expressway in the neighbourhood of the University (OOU) in Sagamu, Ogun State. Fresh samples of unripe *Carica papaya* fruit were bought from a local market. Plants were

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authenticated at the herbarium of the Forestry Research Institute of Nigeria (FHI), Ibadan or Department of Botany, Obafemi Awolowo University, Ile-Ife (UHI) (voucher nos: *Senna alata* FHI 107161 and *Canarium schweinfurthii* UHI 4638A; *Carica papaya* UHI 14729). *Canarium schweinfurthii* stem bark and *Senna alata* leaves were separately cut into pieces, sun dried at ambient temperature and ground into coarse powder using a milling machine (Philips, MK-2815). 500 g each of *Senna alata* and *Canarium schweinfurthii* were macerated with 95% ethanol for a week and filtered. Further maceration of the marc for 5 days produced additional filterate which were combined and concentrated *in vacuo* to yield residues (*Senna alata* 17.8%; *Canarium schweinfurthii* 7%). Dried residues were reconstituted with normal saline for administration purpose. *Carica papaya* fruit was peeled, seeds removed and pulp cut into pieces which was homogenized in water, in the ratio of 1:25 with an electric blender (Philips, MK-2815) to produce a stock concentration of 40 mg/ml. This was then refrigerated in stopper bottle for screening.

Animals

Albino Wister rats of either sex weighing between 125-275 g were sourced from the colony breed of the Department of Physiology and Pharmacology, University of Ibadan, Ibadan, Oyo state. Rats were kept in cages at the animal house of Faculty of Pharmacy (OOU, Nigeria) under standard conditions, and fed with standard animal pellets (Livestock Nigeria PLC) and water *ad libitum*. These normoglycaemic rats were divided into five groups (A-E) of eight animals each.

Ethical clearance

The experiment was performed with the permission of the University's Animal Ethical Committee, and in accordance with approved institutional and national guidelines for the care and use of laboratory animals. The authors declare no conflicting interest in this work.

Phytochemical screening

Plant extracts were separately screened for secondary metabolites as previously described[14]. Saponins, tannins, cyanogenetic glycosides and cardiac glycosides were detected in *Canarium schweinfurthii*, while *Senna alata* yielded anthraquinones, cyanogenetic glycosides and alkaloids. *Carica papaya* also yielded saponins and cardiac glycosides. Apart from saponins and cardiac glycosides detected in *Canarium schweinfurthii* and *Carica papaya,* tannins and cyanogenetic glycosides were further detected in *Canarium schweinfurthii*. The presence of anthraquinones, cyanogenetic glycosides and alkaloids were identified in the extract of *Senna alata.*

Antihyperglycaemic activity

Animals were fasted for 18 h. (but allowed access to water) before induction of hyperglycaemia, which was accomplished by intraperitoneal injection of 180 mg/kg of alloxan monohydrate (Sigma, UK) according to Gbolade *et al*.[13]. Animals were fed *ad libitum* 1 h. after alloxanisation. Fasting blood glucose (FBG) was monitored before and after alloxanisation from samples collected by amputation of the tail tip under mild anaesthesia. The blood was dropped onto LibertyR dextrostix (AgaMatrix, Inc, USA) reagent pad and values read using the micro processor digital LibertyR blood glucometer (AgaMatrix Inc, USA). The diabetic state of the animals was assessed by measuring FBG 48 h. after alloxanisation, and rats with significant hyperglycaemia i.e. FBG beyond 150 mg/dl were selected for the study and divided into five groups A-E of eight animals each.

Experimental doses of 150 mg/kg and 400 mg/kg were selected for comparative purpose from previous studies on *Canarium schweinfurthii* [9] and *Carica papaya* [15] based on documented LD_{50} (> 2000 mg/kg), implying that the chosen doses are in the safety region. These doses of the aqueous filtrate of each extract were fed orally to separate groups A and B rats respectively. Group C animals received 100 mg/kg chlorpropamide (reference drug, positive control, Pfizer-Nigeria) while normal saline (1 ml/kg) was fed into both the negative alloxanised control group D and normoglycaemic group E. The FBG was monitored in all these groups at 0 h. prior to treatment with test agents, and after 7, 14, 21, 28 days of administration of a daily dose of each extract and control drugs (with feeding).

Hypolipidemic activity

Lipid parameters such as total cholesterol (TC) and triglycerides (TG), as well as high density lipoprotein (HDL)-cholesterol and low density lipoprotein (LDL)-cholesterol were determined according to method of Sophia and Manoharan[12]. Blood samples were collected from the heart of all treated rats after day 28 of antihyperglycaemic experimentation under mild anaesthesia with diethyl ether vapour, and transferred into lithium heparin bottle. Lipid analyses were done using a Hitachi Biochemical analyzer 902 (Germany) and TC, TG and HDL-cholesterol values read off, while LDL-cholesterol was calculated from the formula[12]:

LDL cholesterol = total cholesterol – HDL + (TG/5)

At the end of the experiment, animals were sacrificed and the heart, lung, liver and kidney were isolated and preserved in formalin for histological analyses by conventional technique.

Determination of packed cell volume (PCV)

Blood was withdrawn from the cut end of sterilized tail using heparinised capillary tube. Tubes were sealed at one end and spunned at 12,000 rpm for 5 min. in a micro-haematocrit centrifuge (Hawksley, MK-5). PCV was read off using the haematocrit reader.

Statistical analyses

The Statistical Package for Social Sciences (SPSS) 10.0 was used for data entry. All values in the test were presented as mean±SEM (standard error of mean). Statistical differences between the means of the various groups were evaluated by one-way analysis of variance (ANOVA) and tested at 0.05 level of significance. The results were considered statistically significant if the P values were 0.05 or less.

RESULTS

Effect on blood glucose

Elevated levels of FBG at 0 h. after alloxanisation (i. e. post-induction) beyond baseline values, is an indication of hyperglycaemia in experimental rats (Table 1). At tested doses of 150 mg/kg and 400 mg/kg, *Canarium schweinfurthii* ethanolic extract significantly reduced alloxan-induced hyperglycaemia in rats after 28 days to almost preinduction values (108.4-112.2 mg/dl), and unripe *Carica papaya* fruit extract produced significant ($P < 0.05$) reduction from 199.6 mg/dl to 99.5 mg/dl when compared with diabetic and normoglycaemic controls. There was no significant variation in the hypoglycaemic index (defined as percentage decrease in FBG with reference to post-induction values, i.e. at 0 h.). Both doses of *Canarium schweinfurthii* appeared equipotent in hypoglycaemic index (61-74.5% decrease in FBG) in a non-dose dependent manner throughout 28 days, and *Carica papaya* (21.0-50.2% decrease in FBG) from day 14 to day 28. On the other hand, *Senna alata* ethanolic leaf extract produced a transient fall in FBG (7.6–9.3% reduction) in 7 days at both doses, which was not sustained. Subsequent rise in FBG till day 28 portends possible toxicological implication for *Senna alata* in diabetes therapy which connotes unsuitability as a natural product hypoglycaemic agent. Expectedly, diabetic and normoglycaemic control animals fed with 1 ml/kg normal saline did not record appreciable changes in FBG levels.

Senna alata at 150 mg/kg and 400 mg/kg, gave persistent and significant ($P<0.05$) reductions in weights of animals, 26.3-33.6% and 37.9-54.8% respectively from day 14 to day 28 with reference to baseline value (249.3-303.1 g). Furthermore, antihyperglycaemic actions of *Canarium schweinfurthii* (baseline weight 207.2-237.4 g)*, Carica papaya* (baseline weight 185.9-212.9 g) and chlorpropamide were not accompanied by significant changes in the weights of rats when compared with normoglycaemic animals. The PCV of diabetic rats treated with similar doses of the three extracts did not change significantly when compared with their respective baseline values (*Canarium schweinfurthii* 30.2-32.2%; *Carica papaya* 30.9-31.9%; *Senna alata* 30.1-33.7%).

Effect on lipid parameters

Treatment of diabetic rats with *Canarium schweinfurthii* extract resulted in significant lowering ($P<0.05$) in levels of lipid parameters like total cholesterol and LDL-cholesterol at both doses, and in total triglyceride only at the higher dose, 400 mg/kg after 28 days (Table 2). Attenuation ($P<0.05$) was observed in only LDL-cholesterol level by 41.2% at 150 mg/kg of *Carica papaya*-treated animals, and total cholesterol, total triglyceride and LDL-cholesterol levels by 42.9-92.8% ($P<0.05$) at higher dose, 400 mg/kg when compared with their respective baseline (pre-induction) values. *Senna alata* was also efficient in attenuating ($P<0.05$) all lipid parameters except HDL-cholesterol at 400 mg/kg. *Carica papaya* and *Senna alata* also significantly increased HDL-cholesterol by 35.1% at 150 mg/kg and 54.7% at 400 mg/kg, respectively. Hypolipidemic effect of these three plants was not comparable to that of chlorpropamide.

Effect on body organs

In this present investigation, we hereby further report histopathological condition caused by *Canarium schweinfurthii* and *Carica papaya* in treated rats after 4 weeks. Induced renotoxicity by these extracts was comparable to that of chlorpropamide, and it was characterized by marked vascular congestion with extensive areas of intraparenchyma and glomerular haemorrhage. Lungs of *Carica papaya*-treated rats also showed congestion with extensive haemorrhage, while intraparenchyma haemorrhage was characteristic of the heart of *Senna alata*-treated animals.

DISCUSSION

Canarium schweinfurthii and *Carica papaya* extracts are believed to elicit antihyperglycaemic action by the mechanism of stimulating beta cells leading to progressive increase in insulin secretion[16,17]. *Carica papaya* fruit contains phenolic compounds[18] which are known[10,19] to possess antioxidant and antidiabetic properties. Adeneye and Olagunju[15] had earlier reported preliminary hypoglycaemic and hypolipidemic effects of *Carica papaya* seed extract on normal rats. Antidiabetic activity of anthraquinone-containing plants has been linked to enhancement of insulin sensitivity and inhibition of á-glucoamylase activity[20], and control of oxidative stress[21], which may also contribute to the transient activity observed for the anthraquinone-producing *Senna alata* leaf extract[22]. Apart from essential oil constituents responsible for antibacterial activity[7], further research on *Canarium schweinfurthii* should unravel the active antihyperglycaemic principles.

Until now, we are not aware of any published information on antihyperglycaemic and hypolipidemic effects of *Senna alata* (syn. *Cassia alata*) which is one of the principal antidiabetic plants in Nigeria[5]. Information is also lacking on the hypolipidemic effect of *Canarium schweinfurthii.* Lack of antihyperglycaemic activity by *Senna alata* in diabetic rats is contrary to reports on other *Cassia* (syn. *Senna*) species, such as *Cassia auriculata* [23] and *Cassia glauca*[24] which have been shown to possess antihyperglycaemic activity in

Table 1: *Effect of plant extracts on blood glucose (mg/dl) of rats treated for 28 days*

Treatment and dose	Baseline	Post-induction	Day 7	Day 14	Day 21	Day 28
Diabetic rats + 100 mg/kg chlorpropamide	110.3±6.7	381.0±38.0	176.8±8.3* (-54.0%)[a]	155.0±11.9* (-59.3%)[a]	107.2±4.1* (-71.9%)	107.2±4.1* (-75.1%)
Diabetic rats + 1 ml/kg normal saline	105.7±3.5	292.9±19.3	219.4±8.8 (-24.1%)	224.0±8.8 (-23.0%)	-	-
Normoglycaemic rats + 1 ml/kg normal saline	133.0±0.4	134.5±0.5	137.0±0.4 (1.9%)	138.2±0.4 (2.8%)	138.2±0.4 (2.8%)	139.0±0.3 (3.3%)
Diabetic rats + 150 mg/kg CS extract	108.4±4.7	362.0±19.8	140.8±4.9* (-61.0%)[a,b]	119.9±3.9* (-66.8%)[a,b]	109.8±4.7* (-70.0%)	102.4±4.1* (-72.0%)
Diabetic rats + 400 mg/kg CS extract	112.2±4.6	411.4±26.0	135.3±2.9* (-67.1%)[a,b]	116.0±4.5* (-71.8%)[a,b]	112.7±5.8* (-72.6%)	105.0±6.9* (-74.5%)
Diabetic rats + 150 mg/kg CP extract	105.1±4.4	195.5±10.0	187.8±4.7* (-3.9%)[b]	154.4±7.1* (-21.0%)[b]	121.8±4.8* (-37.7%)[b]	111.0±5.0* (-43.2%)[b]
Diabetic rats + 400 mg/kg CP extract	110.1±3.9	199.6±15.3	187.4±4.1 (-6.1%)[a,b]	130.4±4.8* (-34.7%)[a,b]	118.9±4.5* (-40.4%)	99.5±7.2* (-50.2%)
Diabetic rats + 150 mg/kg SA extract	105.5±2.7	218.5±7.1	198.1±9.7* (-9.3%)[a,b]	300.4±5.0* (37.5%)[a,b]	392.5±2.5* (79.6%)[b]	-
Diabetic rats + 400 mg/kg SA extract	108.1±2.1	281.4±7.6	259.9±15.4* (-7.6%)[a,b]	483.3±10.4* (71.7%)[a,b]	498.7±1.2* (77.2%)[b]	498.3±1.2* (77.1%)[b]

CS, Canarium schweinfurthii; CP, Carica papaya; SA, Senna alata
Values are expressed as mean±SEM, n=8
Values in parentheses represent % decrease (-) or increase (+) in parameter when compared with post-induction FBG
** - p<0.05 when compared with post-induction FBG for all treatment groups*
a - p<0.05 when % change in FBG extracts and chlorpropamide groups were compared with diabetic rats treated with normal saline
b - p <0.05 when % change in FBG in extract groups were compared with chlorpropamide group

Table 2: *Effect of Canarium schweinfurthii on lipid parameters of rats treated for 28 days*

Treatment and dose	Total cholesterol (mg/dl)		Total triglycerides (mg/dl)		HDL-cholesterol (mg/dl)		LDL-cholesterol (mg/dl)	
	Baseline	Day 28	Baseline	Day 28	Baseline	Day 28	Baseline	Day 28
Diabetic rats + 150 mg/kg CS extract	103.0±0.9	81.0±1.0* (-21.4%)	78.7±3.3	74.5±2.8 (-5.3%)	45.9±2.3	52.1±2.8* (13.5%)	41.7±2.7	12.4±2.9* (-70.3%)
Diabetic rats + 400 mg/kg CS extract	103.2±0.9	76.3±3.1* (-26.1%)	78.7±3.3	51.5±2.6* (-34.6%)	45.9±2.3	44.9±1.2 (-2.2%)	41.7±2.7	21.1±2.2* (-49.4%)
Diabetic rats + 150 mg/kg CP extract	103.2±0.9	101.8±0.5 (-1.4%)	78.7±3.3	76.0±1.4 (-3.4%)	45.9±2.3	62.0±0.7* (35.1%)	41.7±2.7	24.5±0.7* (-41.2%)
Diabetic rats + 400 mg/kg CP extract	103.2±0.9	58.9±1.5* (-42.9%)	78.7±3.3	34.0±4.3* (-56.8%)	45.9±2.3	49.4±0.8 (7.6%)	41.7±2.7	3.0±0.6* (-92.8%)
Diabetic rats + 150 mg/kg SA extract	103.2±0.9	88.3±0.1* (-14.4%)	78.7±3.3	37.3±1.2* (-52.6%)	45.9±2.3	71.0±1.2* (54.7%)	41.7±2.7	9.9±2.0* (-76.3%)
Diabetic rats + 100 mg/kg chlorpropamide	103.0±1.4	105.4±0.4 (2.3%)	80.7±5.4	83.0±1.7 (2.9%)	43.3±2.2	40.0±0.3 (-7.6%)	43.7±2.4	48.8±0.4 (11.7%)
Normoglycaemic rats + 1 ml/kg normal saline	104.6±1.7	102.0±0.4 (-2.5%)	81.8±6.3	76.4±1.6 (-6.6%)	42.4±0.9	46.8±1.9 (10.4%)	45.8±1.1	40.5±2.3 (-11.6%)

CS, Canarium schweinfurthii; CP, Carica papaya; SA, Senna alata
Values are expressed as mean±SEM, n=8; (-) represents dead animals at Day 28
Values in parentheses represent % decrease (-) or increase (+)
HDL= High density lipoprotein-cholesterol, LDL= Low density lipoprotein-cholesterol
** p<0.05 when lipid values in extract groups were compared with their baseline values*

both normal and streptozotocin-diabetic animals. In addition, only hypoglycaemic and hypolipidemic effects of *Carica papaya* seeds in normal rats was reported[15]. In another study, Fakeye *et al.*[25] observed significant interactions of *Carica papaya* leaf extract with standard oral hypoglycaemic agents which produced variations in the onset of their hypoglycaemic activity. This approach may stimulate or enhance antidiabetic activity of the less active plants like *Senna alata* when co-administered, or improve the activity of the already active natural product hypoglycaemic remedies. Kamtchouing *et al*. [9] have earlier reported antidiabetic effect of *Canarium schweinfurthii* stem bark in streptozotocin-induced diabetic rats using a sub-chronic model without indicating any hypolipidemic effect. The present study, therefore, provides further information on the antihyperglycaemic effect of the three plants on the alloxan-diabetic rat model. However, antihyperglycaemic effect of *Canarium schweinfurthii* and *Carica papaya* plant extracts at both doses was comparable to that of standard drug, chlorpropamide at 100 mg/kg on days 21 and 28, and this is consistent with reports of Nagarajana *et al*.[26] and Gbolade *et al* [13], on appropriate plants. As expected, normal saline did not produce any hypoglycaemic effect in the extracts, thus leading to death of diabetic animals fed with normal saline (1 mg/ml) after 14 days.

The initial increase in weights of diabetic rats could be occasioned by an improvement in insulin secretion and glycaemic control. Weight reduction in *Senna alata*-fed rats, though an insignificant parameter[13], is consistent with reports of other workers[13,16,19] and may be attributed to excess breakdown of tissue proteins[12] or lipolysis. This observation may suggest usefulness of *Senna alata* in controlling weight in obese patients. The insignificant effect of *Canarium schweinfurthii* and *Carica papaya* on weight of animals may lend credence to safety in diabetes therapy. None of the three plant extracts had significant effect on PCV which suggests possible safety in traditional management of diabetes mellitus. Increase in PCV is suggested to be beneficial to recovery of animals from *in vivo* studies.[17, 27]

Hypercholesterolaemia and hypertriglyceridemia are reported phenomena accompanying alloxanisation of experimental animals[12,23,28]. Banerjee *et al*. [29] has reported lowering of cholesterol and triglycerides in triton-induced and high fat diet-induced hyperlipidemic rats treated with pawpaw extracts. The present study reports hypolipidemic activity of *Canarium schweinfurthii* for the first time. The significant reduction in alloxan-induced hyperlipidemia of all the three plant extracts investigated in this publication agrees with previous reports[16,23,30], and this supports their usefulness in therapy of hyperlipidemia-related conditions in traditional medicine. On the contrary, chlorpropamide-treated rats did not significantly change lipid parameters in all treatments. The goal of diabetes treatment with herbal remedies is to reduce the increased LDL-cholesterol and triglyceride, and to increase the decreased HDL-cholesterol[12,16], but only *Canarium schweinfurthii* extract did not significantly increase HDL-cholesterol among the three plants studied.

Hypolipidemic effect of plants has been linked with inhibition of endogenous synthesis of lipids probably by potentiating the secretion of insulin[12]. Other workers have documented reduction in plasma lipid levels in diabetic rats fed with plant extracts[16,25]. It is also reported that hyperlipidemia induces high damage[31], measurable by the changes on the liver weight, serum AST and ALT levels. Therefore, ability of plants to significantly reduce lipid levels is very important in diabetes therapy. Selective toxicity of the three plant extracts to heart, lung and kidney requires further confirmation by determining effect on relevant enzymes in the overall objective of drug discovery from plant sources. Renotoxicity observed for *Canarium schweinfurthii* and *Carica papaya* could be further substantiated by determining effect on kidney, heart and liver MDA levels, the inhibition of which has been shown to account for the significant antidiabetic effect of *Helichrysum plicatum*[19] in streptozotocin model. This would be significant in protection and alleviation of diabetic complications.

CONCLUSION

From these results, it can be concluded that *Senna alata* leaf lacked antihyperglycaemic activity, but possessed remarkable hypolipidemic activity against alloxan-induced hyperlipidemia in a chronic model which is being reported for the first time. This does not justify its traditional use as an antidiabetic remedy. Hypolipidemic effect of *Canarium schweinfurthii* is also being reported for the first time. Furthermore, *Canarium schweinfurthii* stem bark and *Carica papaya* juice extracts which both gave significant antihyperglycaemic and hypolipidemic activities in alloxan diabetic animals would be preferred natural products in the traditional management of diabetes and related diseases. The plants were also found to be selective in their toxicity to body organs which does not necessarily confer suitability on long term usage.

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