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Effect of Umbelliferone on pharmacokinetic and pharmacodynamic parameters of Glibenclamide in Streptozocin induced diabetic rats

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ABSTRACT

The present investigation aims to determine the effect of Umbelliferone (UMB) on pharmacokinetic (PK) and pharmacodynamic (PD) parameters of Glibenclamide (GLB) in diabetic rats. Simultaneously, the effect was studied in normal rats. Diabetes in rats was induced by Streptazocin (STZ). The PK parameters are calculated in normal and diabetic rats. PD studies were performed only on diabetic rats. From the PK results, about 2.0-fold improvement in the oral bioavailability of GLB in diabetic rats was observed when treated with GLB in normal rats. A single-dose (SD) and multi-dose (MD) administration of GLB + UMB showed about 3.8 and 4.0-fold enhancement in oral bioavailability of GLB, respectively in the diabetic group compared with the normal GLB-treated group. Similarly, SD and MD of GLB + UMB showed 2.8-folds and 2.7-folds, respectively in diabetic rats when compared with SD and MD of GLB + UMB in normal rats. Further, the rate of clearance and also the volume of distribution significantly changed in diabetic rats. No significant differences were observed in the PK parameters of SD and MD of GLB+ UMB treated groups in diabetic rats. The blood glucose levels were significantly ($p<0.05$) reduced (12.0 and 13.5% after SD and MD of GLB + UMB treatment, respectively) compared to GLB alone treated diabetic rats during a period of 24 h were noticed from PD studies. The maximum reduction was observed at 2 h (44.3 and 45.6 % after SD and MD of GLB + UMB treatment, respectively) compared with standard GLB treatment (32.1%).
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Keywords: Glibenclamide, Umbelliferone, Streptazocin, Rats, Pharmacokinetics, Pharmacodynamics.

Introduction

Diabetes Mellitus (DM) is a metabolic condition characterized by hyperglycemia, or increased blood glucose levels that exceed the normal range[1]. Metabolic problems such as hyperglycemia, hyperinsulinemia, and hypertriglyceremia are associated with diabetes mellitus (DM), a chronic and complex systemic disease [2]. The number of people with DM has increased to around 422 million as of right now, and is expected to reach 592 million by 2035 due to the significant increase in the disease's incidence. Adults worldwide currently account for 8.5% of the prevalence, which is increasing more quickly in middle- and low-income nations[3]. Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are the two forms of DM, with T2DM accounting for around 95% of cases [4]. Absolute insulin insufficiency linked to the death of pancreatic cells characterizes type 1 diabetes (T1DM), whereas insulin resistance (IR) and insufficient insulin production are the primary causes of type 2 diabetes (T2DM)[5]. Numerous problems and damage to multiple organs can result from type 2 diabetes[6].

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Glibenclamide (GLB) is a sulfonylurea medication that is frequently used to treat type 2 diabetes. Its hypoglycaemic effect results from pancreatic β-cell activation, which increases endogenous insulin secretion. CYP2C9 in the liver completely absorbs and metabolizes GLB[7].

In underdeveloped nations, herbal medicines continue to be the primary source of concern for the majority of the population over their health[8]. To control diabetes mellitus, a variety of Indian medicinal plant herbs have been identified. The majority of people employ complicated mixtures of various chemicals as herbal remedies, which are thought to be an alternative therapy for diabetes. Interactions between pharmacokinetics (PK) and pharmacodynamics (PD) may arise from the mixture's putative active components as well as other constituents. There are reports that PK and PD interactions occur when herbal goods or medications are taken in conjunction with allopathic ones[9].

7-hydroxy coumarin popularly known as Umbelliferone (UMB). UMB showed a variety of benefits, including anti-diabetes, anti-cancer, anti-infection, anti-rheumatoid arthritis, neuroprotection, and alleviation of tissue damage in the liver, kidneys, and heart[10]. UMB regulates blood glucose and lipid metabolism in addition to improving insulin resistance, cardiac hypertrophy, tissue fibrosis, and the control of oxidative stress, inflammation, and apoptosis[11]. Therefore, the purpose of this study was to examine how UMB therapy affected the pharmacokinetics and pharmacodynamics of GLB in normal and diabetic rats.

Materials and Methods

Sample collection

Glibenclamide and Glimepiride (internal standard) were obtained from Sigma Aldrich, Hyderabad, India. Umbelliferone was purchased from Yucca Chemicals Pvt Ltd, Wadala, Mumbai, Maharashtra, India.on 09/08/2022. Methanol (HPLC grade), Acetonitrile (HPLC grade), and potassium dihydrogen phosphate (AR grade), were purchased from Merck Pvt. Ltd., Mumbai. Streptozocin (STZ) was purchased from Hi Media Chemicals, Mumbai, India. Double distilled water was collected from Millipore water system (Direct-Q-UV-3). Chemicals used were of analytical grade.

Experimental animals

Prior to the investigation, all experimental animals were reviewed and approved by the Institutional Animal Ethical Committee (IAEC), UCPSc, Kakatiya University, Warangal, India (06/ IAEC /UCPSC/KU/2022). Male albino Wistar rats weighing 180±30 g was purchased from Vyas labs, Hyderabad, India. The animals were housed in standard polypropylene cages and maintained under standard laboratory conditions (12 h light and dark cycle at an ambient temperature of 25 ± 5^0C; 35-60% of relative humidity). The animals were fed with standard rat pellet diet and water *ad libitum.*

Experimental design

Induction of diabetes

Diabetes was induced in overnight-fasted rats by administering single intraperitoneal (i.p) injection of freshly prepared streptozotocin 60 mg/kg bw in 0.1 M citrate buffer (pH 4.5) in a volume of 0.5 ml/kg/bw, the induction of diabetes was confirmed by measuring fasting blood glucose level on the fifth day of STZ administration. Rats with fasting blood glucose level of more than 250 mg/dl were considered as diabetics and used for the experiment. After 72 h the blood samples were collected by retro orbital puncture and Plasma was analyzed for glucose levels. Rats with blood glucose levels of 250 mg/dL were considered as diabetic and used for the study[12].

Pharmacokinetic study

The PK study was conducted in normal and diabetic rats. After overnight fasting, the rats were randomly divided into three groups (each group contains 6).

PK Study designed as follow:

Single dose and multi dose interaction study in normal rats

Group I (control) was administered with GLB (10 mg/kg body wt. po), suspended in 0.5% sodium CMC[13].

Group II was pretreated with Umbelliferone (40mg/Kg Po)[14] followed by Glibenclamide (10mg/kg/po) for single dose interaction study (SDI)

Group III was pretreated with UMB (40 mg/kg/po) for 7 days and on the 8thday treated with UMB followed by GLB (10 mg/kg) which is known as multiple dose interaction study (MDI)[15].

Single dose and multi dose interaction study in diabetic rats

Group I (control) was administered with a single dose of GLB (10 mg/kg body wt. po) suspended in 0.5% sodium CMC.

Group II was pretreated with a single dose of UMB (40mg/Kg Po) followed by GLB
(10mg/kg/po).

Group III was pretreated with UMB (40 mg/kg/po) for 7 days and on the 8th day treated with
UMB followed by GLB (10 mg/kg) which is known as multiple dose interaction study
(MDI)[16].

Blood samples (about 0.5 mL were collected at predetermined time intervals from retro-orbital vein puncture using heparinized capillary tubes[17]. Plasma samples were separated after centrifugation at 8000 rpm for 15 min and the samples were stored in freezer at -20^0 C further analysis[18].

HPLC analysis

GLB concentrations were estimated in Plasma by RP- HPLC with slight modification by earlier reported methods. The analysis was performed using ultrafast Liquid Chromatography (Shimadzu, Kyoto, Japan) system with gradient capillary binary pump (LC-20AD) and the analytical column C18 (2), 250 × 4.6 mm, 5 µ particle size (Luna 5 µ, Phenomenex). The column effluent was measured with a UV-Visible dual wavelength absorbance detector (SPD-M20A) at 254nm. The mobile phase is composed of methanol, acetonitrile, and potassium dihydrogen phosphate buffer (20mM, pH 4.5) in a 50:20:30 v/v/v ratio, given isocratically at a flow rate of 1.5mL/min[19].

Extraction of GLB Plasma samples:

About 100 µL of Plasma sample, added 100 µL of Glipizide at concentration of 25 µg/mL as IS and then added 100 µL of cold acetonitrile as precipitating agent and vortexed for 1 min and further centrifuged at 13000 g for 15 mins. The supernatant was transferred into a clean labelled tube and was stored at -20ºC further analysis. The resultant samples were reconstituted in 200 µL of mobile phase and about 20 µL were injected into HPLC for analysis of GLB[20].

Calculation of PK parameters.

Non compartmental pharmacokinetic analysis is performed using Kinetica TM software (version 4.4.1, Thermo Fisher Scientific Corporation, USA). The PK parameters like C_{max}. T_{max}, AUC_{total}, $t_{1/2}$, MRT, V_d and clearance were calculated.

Pharmacodynamic (PD) study

PD studies were conducted in diabetes induced rats. After overnight fasting the diabetic rats were randomly divided in to 5 groups containing six rats in each group. The single dose and multi-dose treatment given for the rats was as follows:

Group I: Control (diabetic control)

Group II: GLB (10mg/kg/po) 8 days per orally suspended in 0.5% sodium CMC.

Group III: Administered UMB (40mg/Kg/Po) suspended in 0.8 ml of DMSO for 8 days

Group IV: pretreated with UMB (40 mg/Kg/Po) followed by GLB (10mg/kg/po) for single dose interaction study

Group V: pretreated with UMB (40 mg/Kg/Po) for 7days on 8th day UMB followed by GLB (10mg/kg/po) for multiple dose interaction study

Blood samples were withdrawn from the retro-orbital plexus of the rats at 0,0.5,1, 2, 4, 6, 8, 12 and 24 h after the treatment[16]. The samples were analyzed for blood glucose using glucose oxidase-peroxidase (GOD-POD) method. The mean blood glucose levels and percentage reduction in blood glucose levels were determined and applied for statistical studies.

Statistical analysis

All the PK and PD Parameters were expressed as mean ±SD. The data were statistically evaluated using Student's unpaired t-test using Graph pad prism 5.03.2011 software. Values corresponding to ($p<0.05$) were considered as significant.

Results and Discussion

The diabetes in rats was induced by streptozotocin. During the induction, the weight of the rats was reduced. The rats with more than 250 mg/dL of glucose level were considered diabetic and used for the studies.

PK study in normal and STZ induced diabetic rats.

The PK studies of GLB, GLB+UMB after a SD and MD oral administration was conducted in normal and diabetes induced rats. The mean Plasma concentration and time profiles of GLB and GLB with UMB in normal and diseased rats were showed in Figure 1 and 2 respectively. The calculated PK parameters of normal and diseased treated rats are presented in Table 1 and Table 2, respectively.

PK parameters in normal rats: From the results, C_{max}, t_{max}, AUC_{tot}, $t_{1/2}$ and MRT in normal rats was 3.8±0.5 µg/mL,2.0h, 10.4 ±1.5µg/mL 2.5 ±0.37h and 3.6 ±0.5 h, respectively in GLB treated group.

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GLB plus UMB SD treated group, no significant difference ($p<0.05$) was observed in C_{max} (3.5±0.7 µg/mL) and t_{max} (2.0 h) compared with GLB treated group. But, about 1.3-folds increment ($p<0.05$) in the AUC_{tot} (14.0 µg/mL.h), $t_{1/2}$ (3.2 h) and MRT (4.6 h) was observed compared with GLB group. In case of GLB plus UMB MD treated group, similar PK profile behavior was observed like GLB plus UMB SD treated group. But, 1.5-folds increment ($p<0.05$) in the AUC_{tot} (15.1 µg/mL.h), $t_{1/2}$ (3.7 h) and MRT (5.2 h) was observed in comparison with GLB treated group comparison with GLB treated group.

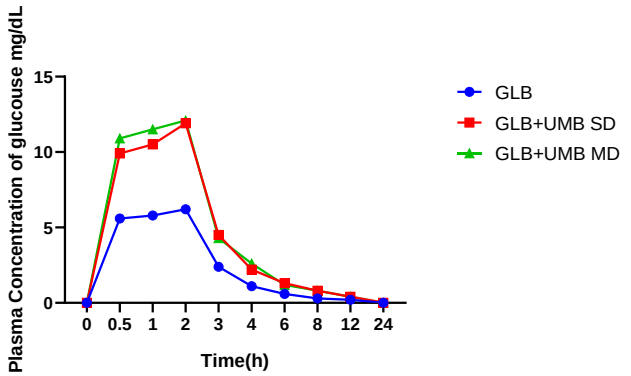

Figure 1: Pharmacokinetic parameters of Glibenclamide in different groups of normal rats (mean±SD, n=6)

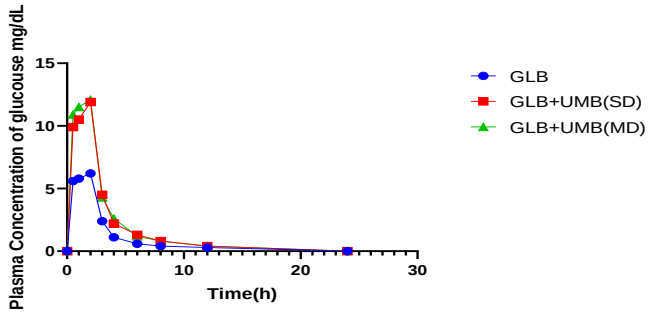

Figure 2: Pharmacokinetic parameters of Glibenclamide in different groups of Diabetic rats (mean±SD, n=6)

PK parameters in diabetic rats: In case of diabetic rats, C_{max}, t_{max}, AUC_{tot}, $t_{1/2}$ and MRT of GLB SD treated group was 6.2 ±0.5 µg/mL, 2.0 h, 20.8 ±1.5 µg/mL.h, 3.8 ±0.37 h and 3.5 ± 0.5 h, respectively. In GLB plus UMB SD treated group, no significant difference ($p<0.05$) was observed in t_{max} (2.0 h), $t_{1/2}$ and MRT compared with GLB treated group. But, about 1.9- folds increment ($p<0.05$) in the C_{max} (11.9 ±0.7 µg/mL) and 1.9-folds increment in the AUC_{tot} (39.4 µg/mL.h) was observed compared with GLB group. In case of GLB plus UMB MD treated group, similar PK profile behavior was observed like GLB plus UMB SD treated group. But, 2.0-filds increment ($p<0.05$) in the C_{max} (12.1 ±0.7 µg/mL) and AUC_{tot} (41.2µg/mL.h) was observed in comparison with GLB treated group.

PK parameters comparison in normal vs disease rats: From the comparison of PK parameters of GLB treated between normal and disease treated rats were showed 1.6, 2.0, and 1.5-folds enhancement in the C_{max}, AUC_{tot} and $t_{1/2}$, respectively of the diabetic group. Diabetic group GLB plus UMB SD treated group showed 3.4, 2.8 and 1.1-folds enhancement in the C_{max}, AUC_{tot} and $t_{1/2}$, respectively. Similarly, GLB plus UMB MD treated group showed 3.4 and 2.7-folds enhancement in the C_{max} and AUC_{tot}, respectively. In case of GLB plus UMB SD and MD treated diabetic rats group showed 3.1, 3.8, 1.4 and 3.2, 4.0, 1.4-folds enhancement in the C_{max}, AUC_{tot} $t_{1/2}$, respectively compared with normal rats GLB treated group. But the t_{max} in both normal and diabetic rats was found to be 2 h. This indicates that the coadministration of UMB does not alter the absorption of the GLB. In comparison to normal rats, there was 38.05% increments in the oral bioavailability of GLB in diabetic rats when pretreatment with UMB.

The significant change in the PK parameters might be due to the alteration in the metabolism of GLB or increased absorption of the drug or both. The variation in PK parameters C max, AUC_{tot}, and $t_{1/2}$ and MRT may be due to inhibition of drug metabolizing enzyme CYP2C9 in the liver microsomes. Previous reports indicated that the hepatic protein expression of CYP2C9 was decreased in diabetic rats which leads to the slower clearance of GLB and other diabetic drugs in diabetic rats compared to the normal rats[19,20,21].

Pharmacodynamic study in diabetic rats.

In pharmacodynamic study the mean Plasma glucose levels were determined using glucose oxidase-peroxidase method and the percent glucose reduction at each time point were compared with 0 h (initial) mean glucose levels. The glucose levels of the study were shown in (Table 3 and 4) and Figure 3 and 4. The blood glucose levels were significantly ($p<0.05$) reduced (12.0 and 13.5% after SD and MD of GLB + UMB treatment, respectively) compared to GLB and UMB (group III) alone treated diabetic rats during a period of 24 h were noticed from PD studies. The maximum reduction was observed at 2 h (44.3 and 45.6 % after SD and MD of GLB + UMB treatment, respectively) when compared with standard GLB treatment (32.1%). Maximum hypoglycemic activity (8.7% reduction) was observed at 2 h in UMB treated group. The increased hypoglycemic activity with coadministration of GLB and UMB are compared with alone drug/UMB treated groups and suggested that enhanced glucose reduction activity of GLB in diabetic rats was only with pretreatment of UMB.

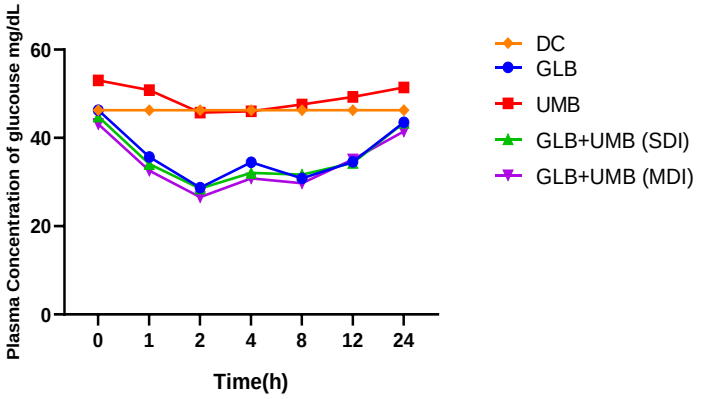

Figure 3: Comparison of mean Plasma glucose levels and percentage reduction of Plasma glucose levels in Normal rats (mean±SD, n=6)

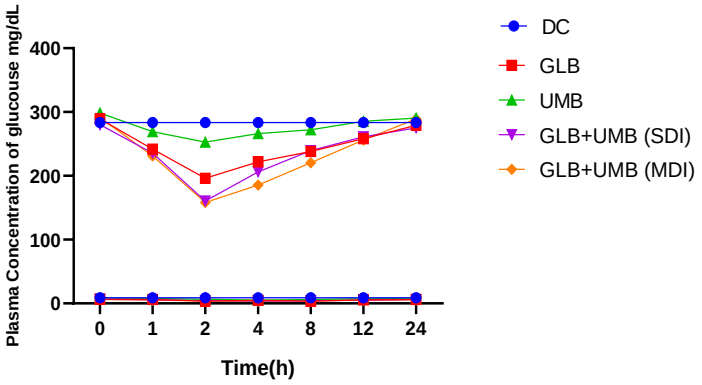

Figure 4: Comparison of mean Plasma glucose levels and percentage reduction of Plasma glucose levels in Diabetic rats (mean±SD, n=6)

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Table 1: Pharmacokinetic parameters of Glibenclamide in different groups of normal rats (mean±SD, n=6)

PK parameters	GLB	GLB+UMB (SDI)	GLB+UMB (MDI)
C_{max} (µg/mL)	3.81±0.60	3.51±0.71	3.60±0.82
T_{max} (h)	2.0	2.0	2.0
AUC_{tot} (µg.h/mL)	10.36±1.5	13.96±2.79**	15.05±3.46***
$T_{½}$ (h)	2.51±0.37	3.15±0.63	3.69±0.84
MRT (h)	3.58±0.57	4.56±0.91	5.20±1.19
CL (mL/h/kg)	0.96±0.14	0.70±0.14	0.66±0.15
Vd (mL/kg)	3.75±0.61	3.63±0.64	3.42±0.85
K_{el} (h^{-1})	0.26±0.03	0.21±0.04	0.18±0.04

*p < 0.05; **p < 0.01 considered as significant when compared with GLB control.
GLB – Glibenclamide; UMB – Umbelliferone.

Table 2: Pharmacokinetic parameters of Glibenclamide in different groups of Diabetic rats (mean±SD, n=6)

PK parameters	GLB	GLB+UMB (SDI)	GLB+ UMB (MDI)
C_{max} (µg/mL)	6.21±0.99	11.91±0.7	12.10±
T_{max} (h)	2	2	2
AUC_{tot} (µg.h/mL)	20.80±3.6	39.41±6.69*	41.19±9.23**
$T_{½}$ (h)	3.81±1.01	3.55±0.75	3.58±0.96
MRT (h)	3.49±0.79	3.58±0.81	3.69±1.2
CL (mL/h/kg)	0.48±0.12	0.35±0.16	0.24±0.63
Vd (mL/kg)	2.63±0.61	1.28±0.96	1.23±1.63
K_{el} (h^{-1})	0.16±0.32	0.18±0.61	0.17±0.69

*p < 0.05; **p < 0.01 considered as significant when compared with GLB diabetic.
GLB – Glibenclamide; UMB – Umbelliferone

Table 3: Comparison of mean Plasma glucose levels and percentage reduction of Plasma glucose levels in Normal rats (mean±SD, n=6)

Group no	Treatment	Dose (mg/kg)	Blood glucose levels (mg/dL) at different time points						
			0 h	1 h	2 h	4 h	8 h	12 h	24 h
I	NC	NT	86.23±5.98	85.61±6.54	87.51±5.78	85.94±5.24	86.37±7.21	87.53±5.83	86.51±6.85
II	GLB	10	85.61±6.98	65.18±6.13	53.51±3.91	63.5±5.41	57.30±4.35	64.00±5.13	80.80±6.23
III	UMB	40	98.61±7.39	95.06±6.58	86.16±5.30	88.25±3.81	90.16±4.99	92.61±5.89	96.15±6.65
IV	GLB+UMB (SDI)	10+40	83.18±6.51	62.28±5.86	53.72 ±3.31	59.91± 4.23	58.90±4.42	63.29±5.32	80.71±6.15
V	GLB + UMB (MDI)	10+40	80.15±6.12	59.95±5.19	50.19 ±2.95	57.54± 4.15	55.43 ±4.04	65.16±5.14	76.97±5.96

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Table 4: Comparison of mean Plasma glucose levels and percentage reduction of Plasma glucose levels in Diabetic rats (mean±SD, n=6)

Group no	Treatment	Dose (mg/kg)	Blood glucose levels (mg/dL) at different time points (h)						
			0 h	1 h	2 h	4 h	8 h	12 h	24 h
I	DC	NT	286.42± 7.25	285.27 ±6.56	285.64 ±7.85	286.28 ±5.76	285.12 ±7.61	287.56 ±7.52	286.65 ±5.62
II	GLB	10	289.24±6.86	241.90±6.24	196.20±3.45	221.95±4.85	238.30±4.91	258.13±5.65	279.17±6.15
III	UMB	40	283.64 ± 8.85	269.02 ± 7.86	258.94 ± 6.35	262.16±5.25	269.17±6.19	275.62±7.62	280.61±8.16
IV	GLB+UMB (SDI)	10+40	288.12±6.52	235.43±5.91	160.31±3.92	206.56± 4.42	239.59±4.32	261.24±5.09	275.12±6.12
V	GLB +UMB (MDI)	10+40	291.60±6.02	231.05±5.25	158.62±3.35	220.21± 4.02	239.52±4.37	256.17±5.25	289.23±5.92

Conclusion

The effect of UMB on pharmacokinetic and pharmacodynamic studies was studied. The UMB significantly enhances the oral bioavailability of GLB, when co-administered. The effect of UMB synergistically increases the Streptozocin-induced diabetic rats when compared with normal rats. The blood glucose levels also significantly reduced when pretreated with UMB than GLB alone treated diabetic rats. Hence, the combination has a beneficial result in diabetic condition, it requires additional studies to confirm the applicability of herbal-drug interaction in humans and conclude the mechanisms concerned.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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