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Original Article

PRENATAL DEVELOPMENTAL TOXICITY STUDY OF POLYPHENOLS-BASED STANDARDIZED CINNAMON BARK EXTRACT IN RATS

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ABSTRACT

Objective: To evaluate developmental toxicity of the polyphenol-based standardized cinnamon bark extract (IND02) during the gestational period in pregnant rats using "Organization for Economic Co-operation and Development" (OECD) Test No. 414.

Methods: Pregnant female rats were daily administered IND02 via gavage (125, 250, or 500 mg/kg) from Gestational Days (GD) 05 to GD19, except for the Vehicle Control (VC) group. On GD20, the dams underwent cesarean section, and observations were made of the uteri and fetuses of the dams.

Results: Prenatal oral administration of IND02 during gestation period in female rats did not show detrimental effects on maternal (body weight, uterine weight, uterine morphology, and gross pathology) or fetal development parameters (crown-rump length, sex ratio, and occurrence of anomalies) compared with VC, indicating normal fetal development. A few skeletal and visceral malformations that were noted were infrequent, incidental, and without toxicological significance.

Conclusion: Prenatal oral exposure of rats to IND02 did not result in developmental toxicity (fetotoxicity or teratogenicity). "No-Observed-Adverse-Effect Level" (NOAEL) and "Human Equivalent Dose" (HED) of IND02 in rats at prenatal oral exposure was more than 500 mg/kg/d and 4.86 g/d respectively.

Keywords: Cinnamon bark, Developmental toxicity, Polyphenols, Prenatal exposure, Standardized extract

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INTRODUCTION

Recently, the prevalence of chronic non-communicable diseases with multimorbidity has necessitated intricate and long-term treatment plans with multiple medications [1, 2]. Herbal medicines, phytonutrients, and nutraceuticals are becoming increasingly recognized as complementary and alternative therapies for managing chronic diseases and maintaining healthy lifestyles [3-6]. Concurrently, consistent quality and standardization of natural products are crucial to guarantee their quality, efficacy, and safety [7]. Therefore, regulatory bodies worldwide have insisted on appropriate toxicity assessments before human use to protect public health.

Polyphenols, a category of bioactive compounds with phenolic structures found in plants, have garnered growing attention owing to their potential health advantages, including beneficial effects against chronic conditions such as hypertension, diabetes, obesity, cancer, and neurodegenerative diseases [8, 9].

Polyphenols extracted from cinnamon bark (*Cinnamomum zeylanicum,* Family: Lauraceae) have been reported to reduce hyperlipidemia [10], have neuroprotective activity in traumatic brain injury [11], and anti-inflammatory effects [12] in animal studies. In clinical settings, cinnamon-derived polyphenols are effective in reducing hyperlipidemia and dyslipidemia [13, 14], glycemic indices [14], insulin resistance [15], inflammatory markers [16], and chemotherapy-induced side effects [3].

In the last decade, a "polyphenol-based standardized cinnamon bark extract" (IND02) has demonstrated efficacy in animal models of asthma [17, 18], allergic rhinitis [19], and arthritis [20, 21]. In addition, the clinical efficacy of IND02 supplementation has been reported to alleviate chemotherapy-induced side effects [3], seasonal allergic rhinitis [22, 23], and coronavirus disease 19 [24].

Moreover, IND02 has been reported to be safe and well tolerated without adverse clinical events [3, 22-24]. In addition, IND02 showed robust safety during acute and subacute (90 d repeated dose) oral administration, without mutagenicity and carcinogenicity [25]. In addition, toxicity studies on unstandardized cinnamon bark extract (aqueous) revealed No-Observed-Adverse-Effect-Level (NOAEL) of 500 mg/kg/d [26].

However, the toxicity assessment of IND02 exposure during pregnancy has not yet been reported. Pregnancy is considered a separate physiological state, as it induces hormonal, immunological, and metabolic changes that significantly impact maternal health and fetal development [27-29]. The gestational period of organogenesis is particularly important when improper drugs or supplements pose substantial risks to the fetus, leading to maternal complications and adverse fetal outcomes [30]. Thus, a separate prenatal toxicity assessment of IND02 exposure during the gestational period is necessary for safe human use.

Therefore, present study's objective was toxicity assessment of IND02 on prenatal oral exposure to female rats during gestational stages on physiological outcomes of dams and fetuses.

MATERIALS AND METHODS

Animals

Fifty-five male and 110 female nulliparous Sprague-Dawley rats (aged 11-12 w) were bred in the animal house facility of Bioneeds India Pvt. Ltd. (Bangalore, India) and used after a 5 d acclimatization period to the experimental room conditions in polypropylene cages and a stainless-steel wire lid with a ratio of one male to two females to allow mating. The housing conditions included a temperature of 19.9-23.6 °C, relative humidity of 51-68%, a 12 h: 12 h light-dark cycle, and 12-15 air changes per hour, fed with rodent feed (Nutrilab®, Provimi Animal Nutrition India Pvt. Ltd., Bangalore, India) and ad libitum filtered water.

The material

The material, IND02, was provided by Indus Biotech Limited (Pune, India). The IND02 sample had a total polyphenol content of 67.91%, as determined by high-performance liquid chromatography [17]. Previously, IND02 was found to be safe until oral exposure to 500 mg/kg for a 90-day repeated dose treatment and was reported as a NOAEL [25]. Therefore, 125 mg/kg and 250 mg/kg (i. e., one-quarter and half of 500 mg/kg), and the highest dose of 500 mg/kg were

selected, based on the guidelines of the "Organization for Economic Co-operation and Development" (OECD) Test No. 414 [31].

IND02 was insoluble in distilled water. Therefore, a fresh uniform suspension in 0.5% carboxymethyl cellulose sodium salt of IND02 was prepared daily to limit the volume to 10 ml/kg. IND02 or vehicle was administered to the respective groups of female rats in two equally divided doses, 7±1 h apart.

Method

The present study was performed as per test no. 414 (Prenatal Development Toxicity Study) of OECD [31] and "Principles of Good Laboratory Practices" [C(97) 186/Final] in compliance with "Organization for Economic Co-operation and Development (OECD). The study protocol received approval by the "Institutional Animal Ethics Committee" of Bioneeds India Pvt., Ltd. Bangalore, India (No: BIO-IAEC 986). During the study, each female rat was examined each morning during a pregnancy test with samples of the vaginal plug and smears. On confirmed pregnancy, that is, the presence of sperm in the vaginal plug and/or smear, confirmed pregnancy (gestation) and day was considered as Gestation Day 0 (GD0). On GD0, the rats were housed as single in cages for assignment to one of the four treatment groups. Each rat was administered vehicle or IND02 daily at 125, 250, or 500 mg/kg/day to the IND02-125, IND02-250, and IND02-500 groups, respectively, from GD5 to GD19. The process and observations were performed as outlined in the OCED Test No. 414 [31].

The following outcome measures were recorded during maternal examination of dams: clinical signs, mortality, percentage of confirmed pregnancies, body weights, food consumption, and number of rats per group on GD0. GD3, GD5, GD8, GD11, GD14, GD17, GD19, and GD20, with body weight changes and daily food consumption per dam and per kg, respectively.

Uterine observations of pregnant rats were recorded as per method previously reported [32]. The calculation of pre-implantation and post-implantation losses were done as follows: pre-implantation loss = [(no. of corpora lutea−no. of implantations)/no. of corpora lutea]×100, and post-implantation loss = [(no. of implantations−no of live fetuses)/no. implantations]×100 [33]. All live fetuses were checked for external defects. Skeletal malformations (or variations) and visceral abnormalities (and variations) were examined after grouping the fetuses into half of each number as per reported procedures [32].

Statistical analysis

Data are shown as mean±standard deviation (SD). The outcomes were analyzed based on nature, that is parametric (gestational body weight, gravid uterine weight, food consumption, fetal weight, fetal crown-rump length, implantation losses, live/dead fetuses) with One-Way Analysis Of Variance (ANOVA) with Dunnett's test, non-parametric (numbers of corpora lutea, implantations, litters, fetuses and early resorptions, sex ratio or incidences of malformations and variations) by Kruskal–Wallis test with Mann–Whitney test or frequency (pregnancy status, survival status of the dam, number of fetuses with male/female or live/dead fetuses per dam, and occurrence and resorption number) by chi-square test. Comparisons between IND02-treated and v/s VC were made. Differences were considered statistically significant at $P<0.05$.

RESULTS

Maternal observations

All pregnancy data, such as confirmed pregnancy, pregnancy rate, body weight, and food consumption in IND02-treated groups (vs. VC) rats, showed no significant changes, except for a decrease in body weight on GD20 in the IND02-500 group (Table 1).

Table 1: Effects of IND02 on maternal outcomes

Outcome	VC	IND02-125	IND02-250	IND02-500
Pregnancy data				
No. of rats examined	25	25	25	25
No. of rats with confirmed Pregnancy	22	22	21	23
Pregnancy Rate (%)	88	88	84	92
Maternal data				
Body weight (g) at GD5	253.98±14.53	246.47±15.28	250.83±16.30	246.60±13.81
Body weight (g) at GD20	351.91±24.50	334.00±27.21	344.44±38.81	323.72±35.78*
Food Consumption (g/dam/d)	19.36± 2.02	17.75± 2.00	18.39± 2.84	17.53± 2.47
Food Consumption (g/kg/d)	64.95± 5.71	62.68± 6.67	63.12± 6.92	62.74± 5.67

Value are expressed as Mean±SD, VC-Vehicle control, GD-Gestational Day. *P<0.05 (v/s VC), n=25

Table 2: Effects of IND02 on reproductive outcomes

Outcomes	VC	IND02-125	IND02-250	IND02-500
Uterine observations				
Number of Females with confirmed pregnancy	22	22	21	23
Gravid uterus weight (g)	70.98±13.32	66.08±18.71	68.24±20.65	52.79±21.78*
Corpora Lutea (no)	12.00±2.73	11.41±3.07	11.33±3.88	9.39±4.02
Implantation per dam (no)	12.00±2.73	11.18±3.33	11.33±3.88	9.35±4.06
Litter observations				
Male/female sex ratio (no)	1.40±0.90	1.28±0.86	1.06±0.45	1.56±1.66
Litter size (no)	11.77±2.56	10.95±3.21	10.95±3.57	8.83±3.81*
Live fetuses per dam (no)	11.77±2.56	10.95±3.21	10.90±3.55	8.74±3.82*
Dead fetuses per dam (no)	0.00±0.00	0.00±0.00	0.05±0.22	0.09±0.29
Early resorptions per dam (no)	0.23±0.69	0.23±0.53	0.62±0.97	0.78±1.38
Late resorptions per dam (no)	0±0	0±0	0±0	0±0
Pre-implantation loss (%)	0.00±0.00	26.77±25.00	0.00±0.00	16.67±0.00
Post-implantation loss (%)	11.27±7.56	9.34±4.04	14.16±6.43	22.12±12.00
Live male fetuses (no)	6.23±2.00	5.86±2.87	5.52±2.36	4.70±2.53*
Live female fetuses (no)	5.55±2.09	5.09±1.48	5.38±1.66	4.04±2.18*
Fetal weight per dam (g)	3.75±0.34	3.79±0.45	3.74±0.41	3.73±0.39
Male fetal weight per dam (g)	3.89±0.36	3.89±0.44	3.90±0.39	3.87±0.40
Female fetal weight per dam (g)	3.59±0.33	3.63±0.46	3.59±0.42	3.57±0.39
Fetal crown rump length per dam (mm)	36.68±1.91	36.56±1.73	36.48±2.35	36.31±1.61
Male fetal crown rump length per dam (mm)	37.12±1.95	36.95±1.26	37.12±1.73	36.98±1.63
Female fetal crown rump length per dam (mm)	36.14±2.10	36.21±2.03	35.99±2.56	35.51±1.92

Value are expressed as mean±standard deviation (SD), *P<0.05 (v/s vehicle control, VC), n= Number of females with confirmed pregnancy

Embryo-fetal observations

As shown in

Table 2, the reproductive system-related outcomes during embryo-fetal examination did not show statistical significance between the groups, except for decreased values of gravid uterus weight (P<0.05), litter size (P<0.05), and live fetuses in male or female rats (P<0.05) in the IND02-500 group (v/s VC).

Malformations and variations of fetus

None of the malformations or variations were statistically significant between the IND02 and VC groups as shown in Table 3. A few variations and malformations during the skeletal examination are presented in Table 3. No sign of abnormalities or alterations was found in external, visceral, or skeletal examinations of fetuses, any litter of dams, or visceral examinations of the soft visceral tissue at any dose. As presented in Table 3, lateral ventricular dilation anomalies were noted in one fetus each from the VC, IND02-125, and IND02-500 groups, and in two fetuses from the IND02-250 group. Right kidney renal pelvic dilation (slight) was noted in three fetuses from the VC and IND02-125 groups, two fetuses from the IND02-250 group, and four fetuses from the IND02-500 group. Left kidney renal pelvic dilation (slight) was noted in one fetus each from the VC and IND02-125 groups and in two fetuses each from the IND02-250 and IND02-500 groups. Due to the absence of dose or treatment dependencies, these are considered incidental, unrelated to the treatments, and not significant.

Table 3: Effects of IND02 on malformations and variations of fetus

Outcomes	VC	IND02-125	IND02-250	IND02-500
Total No. fetuses (litters) examined				
External	259 (22)	241 (22)	229 (21)	201 (23)
Visceral	124 (22)	114 (22)	108 (21)	92 (23)
Skeletal	135 (22)	127 (22)	121(21)	109 (23)
External malformations	0 (0)	0 (0)	0 (0)	0 (0)
Visceral malformations				
Lateral ventricular dilation	1 (1)	1 (1)	2 (2)	1 (1)
Visceral Variations				
Right Kidney Renal pelvis Dilation	3 (3)	3 (3)	2 (2)	4 (4)
Left Kidney Renal pelvis Dilation	1 (1)	1 (1)	2 (2)	2 (2)
Skeletal Variations – *Sternum-Poor Ossification*				
Sternum No. 1-	1 (1)	0 (0)	0 (0)	0 (0)
Sternum No. 2	1 (1)	0 (0)	0 (0)	1 (1)
Sternum No. 4	0 (0)	0 (0)	1 (1)	0 (0)
Sternum No. 5	11 (7)	10 (4)	11 (7)	11 (7)
Sternum No. 6	7 (4)	12 (6)	18 (8)	20 (8)
Skeletal Variations-*Fore Limb*				
Metacarpal No. 5-Poor Ossification	1 (1)	3 (2)	0 (0)	0 (0)
Skeletal Variations-*Thoracic Vertebrae*				
No. 10-Asymmetric Bi-lobed	0 (0)	1 (1)	0 (0)	0 (0)
No. 11-Asymmetric Bi-lobed	1 (1)	1 (1)	2 (2)	1 (1)
No. 12-Asymmetric Bi-lobed	1 (1)	1 (1)	3 (3)	1 (1)
No. 13-Asymmetric Bi-lobed	3 (3)	1 (1)	0 (0)	1 (1)
Skeletal malformations-*Thoracic Vertebrae*				
No. 10-Split	1 (1)	0 (0)	0 (0)	0 (0)
No. 11-Split	1 (1)	0 (0)	1 (1)	0 (0)
No. 12-Split	1 (1)	0 (0)	1 (1)	1 (1)
No. 13-Split	0 (0)	1 (1)	1 (1)	0 (0)
Skeletal malformations-*Fore Limb*				
Absent Phalanx No. 3 and 4 (Bilateral)	9 (8)	12 (7)	12 (7)	15 (6)*

n= number of fetuses with defects (number of dams). *P<0.05, VC-Vehicle control

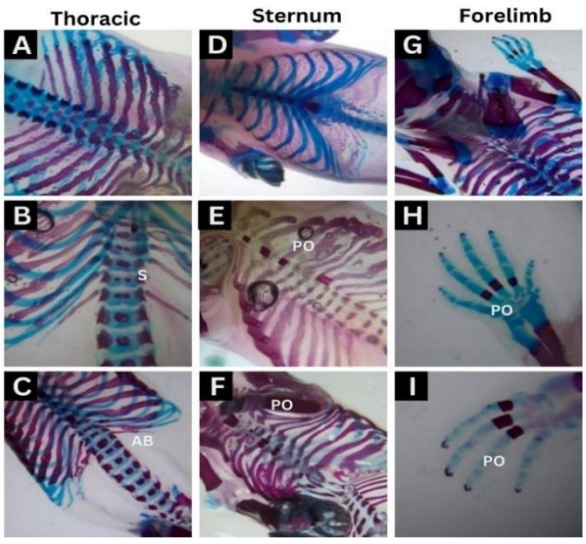

Fig. 1: The representative photos during skeletal examination of fetus: (A) Normal thoracic vertebrae (B) Thoracic vertebrae with Split (C) Thoracic vertebrae with asymmetric bilobed variation (D) Normal sternum (E and F) Sternum with poor ossification (G) Normal forelimb (H and I) Sternum with poor ossification. S–Split, AB–Asymmetric bilobed, PO–Poor Ossification

Skeletal examination

During the skeletal examination, IND02-500 group showed absent Phalanx No. 3 and 4 of forelimb, which is statistically significant (P<0.05 vs. VC), but that or none of the fetuses from the IND02 or VC showed significant or fatal malformations of teratological importance (Table 3). Representative sections from each group are presented in fig. 1. The few observed variations/malformations are known in the laboratory rodent population but do not affect fetal survival [34]. Therefore, these fetal malformations and variations were considered incidental without toxicological importance.

DISCUSSION

This study assessed the reproductive safety of IND02 in rats and their fetuses during prenatal exposure. No mortality or toxicity was observed with IND02 treatment. The anomalies detected were without dose-dependency or noticeable patterns and were typical for rats. These findings are incidental, indicating that IND02 does not adversely affect maternal health or fetal development.

The toxicity of plant-based natural extracts depends on their composition, authenticity, processing, dosage, duration, route of administration, and extractant solvents [35, 36]. Chemical marker-based standardization can help minimize adulteration and ensure batch-to-batch consistency, quality, and clinical efficacy of natural products [37]. Advanced instrumentation and technological identification of marker compounds are used for standardized natural product extracts to ensure consistent efficacy, quality, and safety [38]. Chemical standardization can also help reduce the risk of toxicity after toxicity assessment using internationally acceptable standardized protocols and guidelines [36]. Therefore, we used a standardized extract of cinnamon bark based on marker compound polyphenols and internationally accepted OECD guidelines relevant to prenatal developmental toxicity (Test No. 414) [31].

In this study, oral prenatal exposure to IND02 in pregnant female rats during gestation did not have or teratogenicity, or maternal or embryo-fetal toxicity up to 500 mg/kg/day, which is NOAEL. The "human equivalent dose" (HED) was calculated using the USFDA guidelines for the industry [39]. In the case of prenatal oral exposure to IND02, a dose of 4.86 g/day is HED (based on the NOAEL of IND02 = 500 mg/kg (assuming average human weight of 60 kg).

Recently, the prevalence of chronic autoimmune diseases has shown significant sex bias towards females owing to extensive stress or hormonal changes [40]. IND02 is promising nutraceutical ingredient for maintaining optimum immunity [41], especially against many autoimmune [3, 42] and inflammatory disorders [20, 21, 43]. This study is crucial towards development of IND02 as promising food-derived ingredient for supplements or complementary medicines for females.

CONCLUSION

The test material, prenatal oral exposure of IND02 in the gestational prenatal period in female rats, showed robust safety, with a NOAEL>500 mg/kg and safe HED>4.86 g/d. The robust safety as demonstrated by IND02 during prenatal exposure in rats, will be useful for risk assessment during regulatory processes or design of clinical studies towards safe dietary supplements or complementary medicines.

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AUTHORS CONTRIBUTIONS

PT and PD were involved in the conception and design of the study. PD was involved in project supervision and administration. All authors were involved in writing, reviewing, and approving the manuscript.

CONFLICT OF INTERESTS

This study was supported by Indus Biotech Limited, Pune, India, but had no role in the collection and analysis of data.

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