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Effects of Cabergoline on Embryo Growth: Macroscopic and Molecular Findings

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ABSTRACT

Background: Prolactin is a neurohypophyseal hormone that plays a major role in behavior, growth, and angiogenesis. CAB suppresses the effects of PRL by targeting the D2R. In this study, we used in silico and in vivo approaches to examine the side effects of CAB using chicken as a model.
Methods: Thirty fertilized eggs were equally divided into three groups: one control and two experimental groups treated with CAB at doses of 0.5 mg/kg and 1 mg/kg, respectively. After 18 days of experiment, embryo weight, average body length, chorioallantoic vessels length, and relative *PRL* gene expression were analyzed. Also, prolactin-protein interaction and functional pathways regulated by PRL and associated proteins were investigated using the STRING database.
Results: Macroscopic analysis showed a significant increase (17.54 ± 0.28) and decrease (12.92 ± 0.38) in weight in the 0.5 mg/kg and 1 mg/kg groups, respectively, as compared to the control. A significant reduction in body size and an increase in chorionic vessel development were observed only in the 0.5 mg/kg group. *PRL* expression levels significantly decreased in both CAB-treated groups. In silico analysis revealed PRL interactions with INS and POMC proteins, which are conserved between *H. sapiens* and *G. gallus*.
Conclusion: Our findings indicate that CAB not only reduces prolactin levels but also affects fetal weight and body size. ***DOI: 10.61882/ibj.4987***

Keywords: Cabergoline, Chorioallantoic membrane, Prolactin

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INTRODUCTION

Prolactin is a steroid hormone produced by the pars nervosa of the neurohypophysis. In addition to inducing lactation, PRL has shown a wide range of functions. The release of neurotransmitters from the pituitary terminals of hypothalamo-hypophyseal tracts supports a basal release of PRL. Estradiol hormones, stress, and pregnancy increase PRL secretion through the production of encephalins, while short-loop feedback and dopamine play essential roles in modulating PRL secretion[1]. PRL is present in the blood of mammalian fetuses during the second half of gestation. This lactogenic hormone contributes to chondrogenesis, the maturation of the hypothalamus and olfactory bulb, and the development of the pancreas[2].

List of Abbreviations:
CAB: cabergoline; **cDNA:** complementary DNA; **D2R:** dopamine d2 receptor; ***G. gallus***: *Gallus gallus*; ***H. sapiens***: *Homo sapiens*; **POMC:** pro-opiomelanocortin; **PPIN:** Protein-Protein Interaction Network; **PRL:** prolactin; **qRT-PCR:** quantitative real-time PCR

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During pregnancy, encephalin levels peak, whereas dopamine secretion reaches its lowest levels[3].

In vitro and in vivo studies, conducted over the past two decades, have demonstrated that the D2R mediates the dopaminergic inhibition of PRL[4,5]. Dopamine receptors are members of the well-known family of G protein-coupled receptors and are categorized into two main groups: D1 and D2 receptors. D1 receptors stimulate the activation of the adenylyl cyclase enzyme, whereas D2 receptors inhibit its activity. Anatomically, D2Rs are located in various brain regions, including the pituitary gland, olfactory tubercle, ventral tegmental area, and striatum. Indeed, D2R signaling antagonizes the downstream of adenyly cyclase activity. Lactotrophic cells in the pituitary gland, which produce and secrete PRL, also express D2Rs[6]. Activation of D2R by dopamine inhibits PRL production, leading to the elevated PRL levels (prolactinoma)[7].

CAB is a dopamine agonist derived from the ascomycete *Claviceps* spp., a type of fungal ergot with a tetracyclic ergoline skeleton[8]. CAB, chemically known as 1-[(6-allylergolin-8ß-yl)-carbonyl]-1-[3-(dimethylamino) propyl]-3-ethylurea, acts as a D2R agonist in central nervous system. Thus, CAB has been prescribed for various psychiatric and neurological disorders[9]. Generally, the use of dopamine agonists is prohibited, especially during the second and third trimesters of pregnancy. However, a 2014 cohort study involving pregnant women found no significant association between the administration of dopamine agonists and low birth weight or birth defects. Nonetheless, an increased risk of preterm birth and pregnancy loss was reported[10]. Despite these findings, the mechanisms underlying these outcomes have been poorly understood.

Oviparous species have long provided an advantage for studying early life and developmental biology[11]. The patterns of gene expression, organogenesis, and growth in avian embryos are well characterized, making them a valuable model to assess direct drug toxicity effects without interference with maternal metabolism[12]. However, physiological differences have limited biomedical research in birds. Notably, unlike mammals, PRL is responsible for brooding behavior in fowl[13]. Bana et al. administered the dopamine receptor agonist, ergocryptine salt, to hens to investigate PRL-related genes. They found a strong relationship between D2R activation and decreased PRL secretion[14], confirming similarities in the protein signaling cascade within the dopamine-PRL pathway. Due to ethical restrictions prohibiting drug experimentation on human fetuses, the chick embryo model serves as an ideal system to study the adverse effects of drugs. Therefore, the current study aimed to evaluate, for the first time, the effects of CAB on chick embryo development.

MATERIALS AND METHODS

Chicken embryo preparation

A total of 30 fertile chicken eggs (Ross 308) were incubated at a relative humidity of 60% at 37.5 ºC. The eggs were randomly assigned to three experimental groups: (1) 10 embryonated eggs treated with phosphate-buffered saline (control group), (2) 10 embryonated eggs treated with CAB (Iran Hormone Pharmaceutical Co., Karaj, Iran) at a dose of 0.5 µg/kg of egg weight, and (3) 10 embryonated eggs treated with CAB at a dose of 1 µg/kg of egg weight. In all the groups, a treatment volume of 0.5 mL/egg was administered via direct injection into the yolk sac on day four of incubation, following standard techniques[15]. After treatment, the embryos were re-incubated and allowed to develop until day 18, when they were evaluated macroscopically. The study workflow is shown in Figure 1.

Macroscopic analysis

The average weight of the eggs and embryos, as well as the body length (in mL), was calculated for each group. Body weight was measured using a digital scale, while body length was determined with a digital caliper, measured from the anterior border of the head to the tip of the tail, including the uropygial gland. Additionally, chick embryos were evaluated for the angiogenic activity of the chorioallantoic membrane[16].

Molecular analysis

RNA extraction

Molecular analysis was performed on pituitary gland samples to assess the expression of the PRL gene. Briefly, 1 mg of pituitary tissue was homogenized, and 1 mL of cold QIAzol lysis reagent (Qiagen, USA) was added. The mixture was vortexed and incubated at room temperature for 5 min. Afterwards, 0.2 mL of chloroform (Merck, Germany) was added to the tubes, which were then inverted several times and centrifuged at 10956 ×g at 4 °C for 15 min. The supernatant was transferred to a new microtube, followed by the addition of 1 mL of absolute cold ethanol (Merck) and 2 µL of glycogen (20 mg/mL, ABM Inc., Canada). After centrifugation, the RNA pellet was washed with 75% ethanol and centrifuged again. The pellet was air-dried and dissolved in 100 µL of DEPC-treated water (Cinnagen, Iran). The extracted RNA samples were stored at -70 °C until further processing[17].

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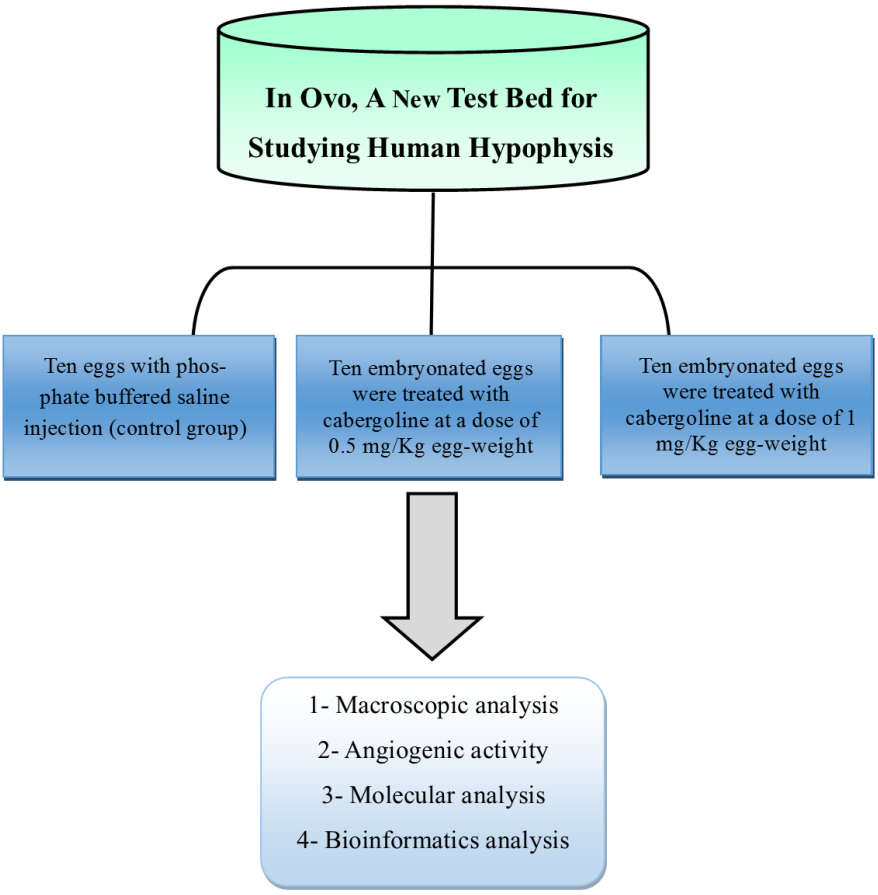

Fig. 1. Study workflow.

Primer design

The software Oligo 7 (Molecular Biology Insights, Inc., Cascade, CO, USA) was utilized to design primers for the *PRL* and *ß-actin* genes[18]. The specificity of the designed primers was confirmed using the NCBI-BLAST tool. The sequences of the primers are listed in Table 1.

cDNA synthesis and real-time PCR

The quality of the extracted RNA was assessed using a NanoDrop (Eppendorf, Germany) by measuring the optical density at 260/280 nm. Single-stranded cDNA was synthesized using a commercial kit (Thermo Scientific, USA) following the manufacturer's protocol. Each reaction mixture contained 1 µg of RNA, 1.25 µL of random hexamer primers, 7.5 µL of 5× RT buffer, 2.5 µL of 10 mmol/L dNTPs, 1.25 µL of 200 U reverse transcriptase enzyme, 1.25 µL of 20 U RNase inhibitor, and 2.5 µL of nuclease-free water[19]. The qRT-PCR reactions were performed in a 13 µL total volume using the DNA Master SYBR Green I Mix (7 mmol/L; Yektatajhiz, Tehran, Iran). The mixture consisted of 4 mmol/L nuclease-free water, 1 mmol/L of mixed forward and reverse primers specific to each gene, and 1 mmol/L of synthesized cDNA. The qRT-PCR cycling program consisted of 40 cycles with the following steps: an initial extension for 2 min at 95 °C, five denaturation steps at 95 °C for 5 seconds, an annealing step at 60 °C for 30 s, and an extension at 72 °C for 10 seconds[20].

Table 1. Primers used in this study

Gene	Primer sequences	Size (bp)
	Forward: 5'- AATAGTTGGGCGGGTTCATTC -3'	
	Reverse: 5'- ATGGATTAGGCGGCACTTCA -3'	
	Forward: 5'- TATTGCTGCGCTCGTTGTTG-3'	
	Reverse: 5'- ACCAACCATCACACCCTGAT-3'	

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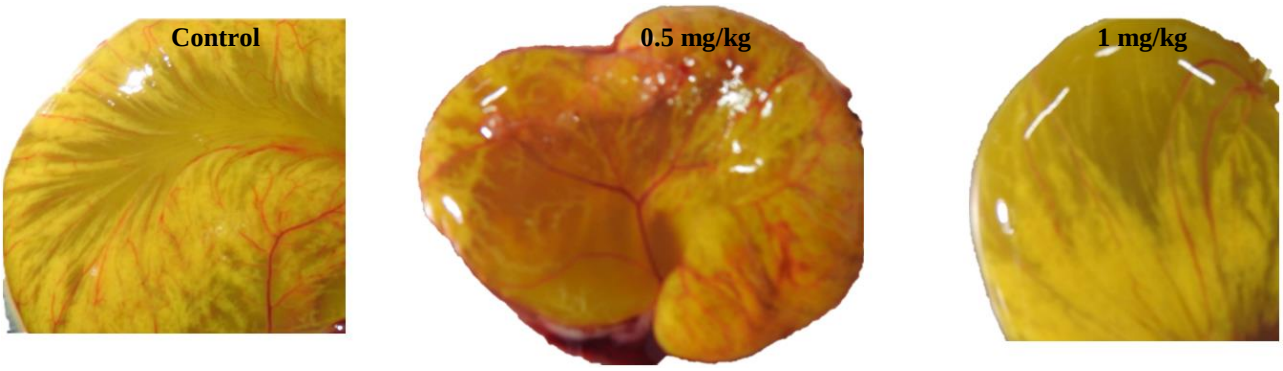

Fig. 2. Angiogenic activity. The angiogenic activity was higher in the 0.5 mg/kg CAB-treated group compared to the control and 1 mg/kg group.

Bioinformatic analysis

The PPIN analysis helps in understanding the functions and evolutionary characteristics of proteins[21,22]. In this study, the PRL protein was submitted to the STRING database to construct a PPI network and identify related pathways[23-25].

Statistical analysis

Differences in *PRL* gene expression were assessed using the Relative Expression Software Tool (REST 2009, Qiagen). Statistical analyses were conducted using SPSS 20.0 and GraphPad Prism 8.0 software. A *p* value less than 0.05 was considered statistically significant.

RESULTS

Macroscopic analysis

We assessed the average egg weight, embryo weight, and body length in three groups: control and 0.5 mg/kg, and 1 mg/kg of CAB. There were no significant differences in average egg weight among the groups. However, we observed a significant decrease in the average embryo weight in the 1 mg/kg group compared to both the control and 0.5 mg/kg groups ($p < 0.01$). Conversely, the 0.5 mg/kg group had a significantly higher average embryo weight than the control and 1 mg/kg groups ($p < 0.05$). Furthermore, the analysis of the average body length showed a significant decrease in the 0.5 mg/kg group when compared to the control and 1 mg/kg groups ($p < 0.05$; Table 2).

Angiogenic activity analysis

The analysis of angiogenic activity in the chorioallantoic membrane revealed an increase in angiogenesis in the 0.5 mg/kg group compared to both the control and 1 mg/kg groups (Fig. 2). As shown in Figure 3, some placentas from embryos treated with both doses of CAB exhibited hemorrhagic foci. In contrast, no hemorrhages were observed in the placentas of embryos in the control group. Accordingly, the incidence of hemorrhage was significantly higher in the treated groups compared to the control group ($p < 0.05$).

PRL expression pattern

The qRT-PCR was performed to assess the relative expression of the *PRL* gene in the control, 0.5 mg/kg, and 1 mg/kg groups. The results showed that *PRL* expression was significantly reduced in both treatment groups compared to the control group ($p < 0.001$). However, there was no statistically significant difference in *PRL* gene expression between the 1 mg/kg and 0.5 mg/kg CAB-treated groups (Fig. 4).

Bioinformatics analysis

The results from the STRING database showed that the PRL protein directly interacts with the following proteins in *G. gallus*: GRH, PRLR, GH, VIP, LOC417800, TRH, POMC, TSHB-2, FSHB, and POU1F1. In *H. sapiens*, PRL interacts with INS, POMC, STAT5A, GH2, ERBB4, JAK2, LEP, PRLR, and HBEGF. Figure 5 depicts the PIN. Pathway analysis for *G. gallus* revealed that PRL and its associated

Table 2. The average egg weight, embryo weight, and body length in the study groups

Parameters	Control	0.5 mg/kg	1 mg/kg
Egg weight (g)	40.76 ± 0.7	42.56 ± 0.67	40.14 ± 1.4
Embryo weight (cm)	15.64 ± 0.41	17.54 ± 0.28*	12.92 ± 0.38**
Embryo size (mm)	76 ± 1.4	63.50 ± 0.7*	74 ± 8.4*

*$p < 0.05$; **$p < 0.01$ compared to the control group

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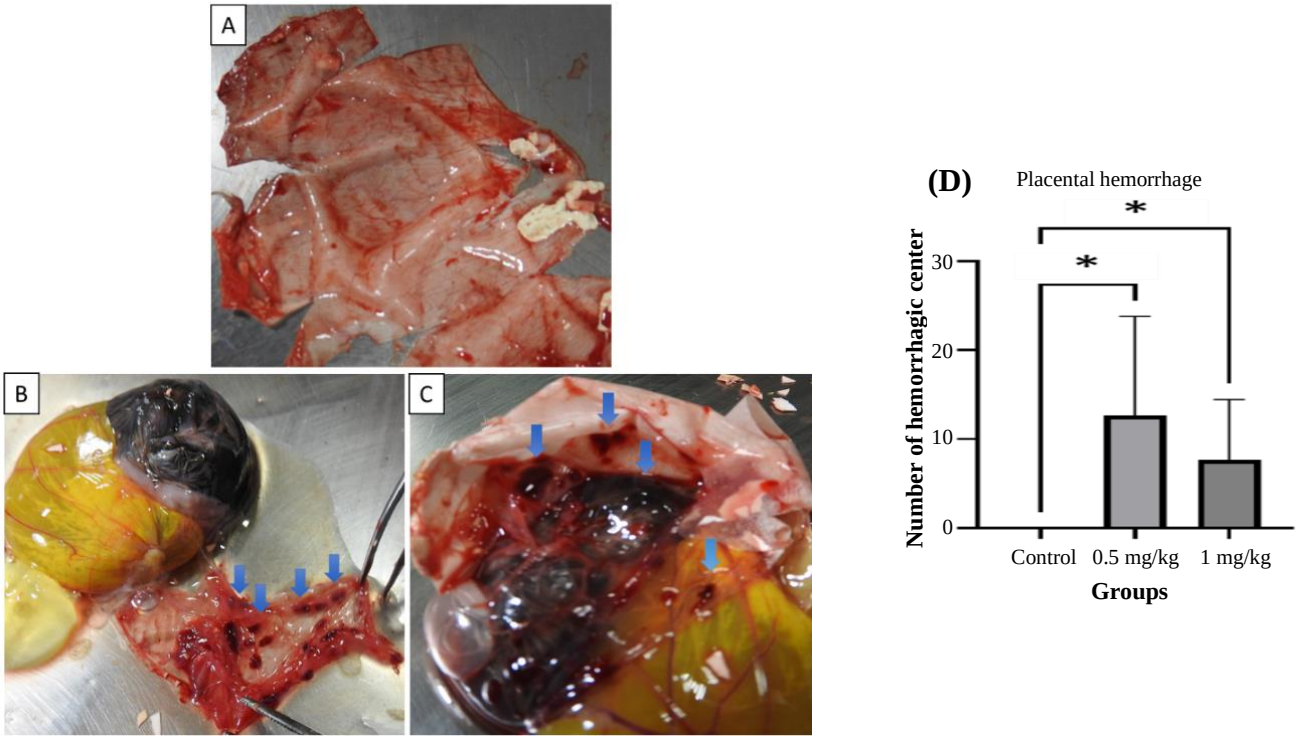

Fig. 3. Health status of the chorioallantoic membrane. (A) Normal appearance of the placenta in the control group; (B) presence of hemorrhage foci (arrows) in the membrane in the 0.5 mg/kg CAB-treated group; (C) blood pool and hemorrhagic foci (arrows) observed in the placenta in the 1 mg/kg CAB-treated group; (D) Comparing the number of hemorrhagic foci across different groups. Hemorrhage increased in both the 0.5 and 1 mg/kg groups compared to the control ($^{*}p < 0.05$).

proteins are involved in several pathways, including PRL receptor signaling, Class A/1 (rhodopsin-like receptors), hormone ligand-binding receptors, growth hormone receptor signaling, and glycoprotein hormones pathways. In *H. sapiens*, PRL and its associated proteins are engaged in Th17 cell differentiation, cytokine-cytokine receptor interaction, Th1 and Th2 cell differentiation, adipocytokine signaling, and neuroactive ligand-receptor interactions. The top five KEGG pathways are presented in Table 3.

DISCUSSION

Excess levels of PRL can lead to the development of prolactinoma, which accounts for approximately 40% of all hypophysis tumors. The most commonly observed clinical manifestations entail gonadal dysfunction, which results in infertility in both males and females. Macroprolactinomas are less common than microprolactinomas and tend to occur more frequently in men than women. In men, the most significant symptom is the reduced libido, often underestimated by patients. These symptoms can considerably affect the quality of life and should not be overlooked[26]. Historically, surgical resection or irradiation were the primary treatments for prolactinomas before the widespread use of dopamine agonists. Today, dopamine agonists are the first-line and preferred treatment, and surgery or radiotherapy are reserved for patients who do not respond to, or cannot tolerate, pharmacological therapy[27].

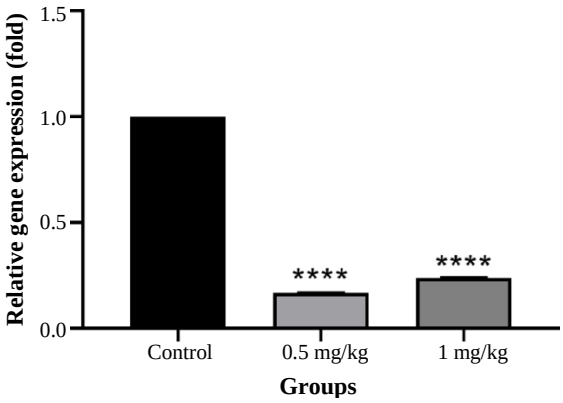

Fig. 4. The relative expression level of the *PRL* gene in the study groups. The housekeeping gene *β-actin* was used as an internal control for prolactin. The histogram shows a significant decrease in *PRL* expression level in both the 0.5 mg/kg and 1 mg/kg groups compared to the control group. ($^{****}p < 0001$).

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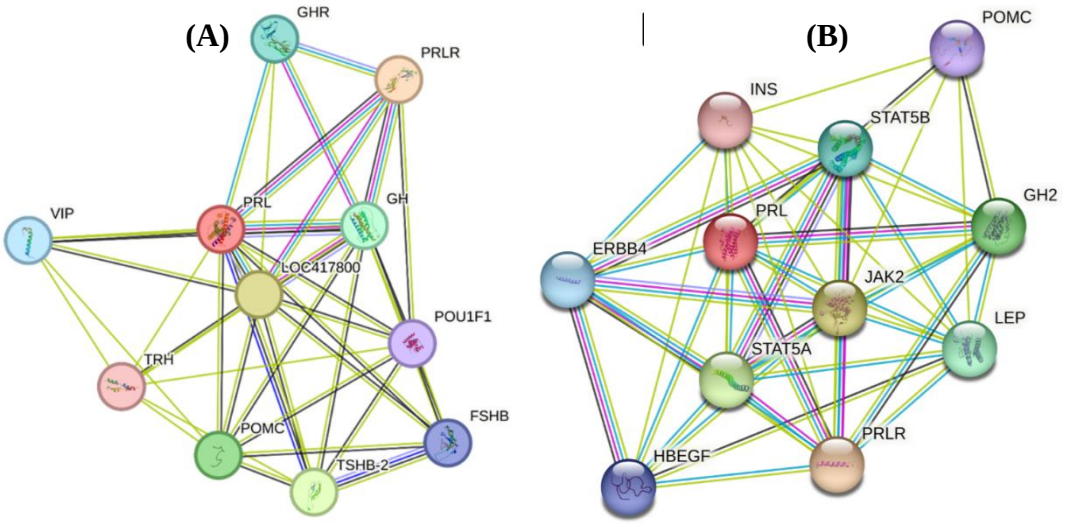

Fig. 5. PPIN of PRL and its associated proteins in (A) *G. gallus* and (B) *H. sapiens*.

In this study, increased angiogenesis in the chorioallantoic membrane, elevated embryo weight, and reduced average body length were observed in the chickens treated with 0.5 mg/kg of CAB compared to those treated with 1 mg/kg of CAB and the control group. In the 1 mg/kg of CAB group, embryo weight was significantly lower than that of the 0.5 mg/kg of CAB-treated and control groups. While there was no significant difference in body length between the 1 mg/kg and control group, the body length in the 1 mg/kg CAB-treated group was significantly greater than that in the 0.5 mg/kg group. In silico analysis showed interactions between PRL with INS and POMC in both *H. sapiens* and *G. gallus.* Notably, enhanced blood vessel formation was observed in the low-dose CAB group. PRL can either stimulate or inhibit vascular dilation, proliferation, and regression, depending on its molecular form. The full-length PRL protein promotes angiogenesis, while its proteolytic fragments, known as vasoinhibins, have vasoconstrictive and antiangiogenic properties[28,29]. Cockerill et al. reported that PRL administration did not affect blood vessel growth during the early stages of chorioallantoic membrane development[30]. Zimmermann et al. found that low doses of CAB did not inhibit angiogenesis in the rat endometrium[21], whereas high doses of dopamine receptor agonists exhibited antiangiogenesis effects in a mouse cancer model by internalizing VEGFR-2[32]. Both experimental groups showed significant weight loss in hatched chickens. Comparative PPI network analysis between humans and chickens confirmed the interactions between *PRL* and *INS* genes. Several observational clinical trials have reported that obesity reduces PRL responsiveness to INS[33]. Additionally, the PRL receptor type is expressed on adipocytes and β-cells, highlighting the role of PRL in peripheral

Table 3. Pathway analysis of PRL and its associated proteins performed by the STRING database

ID	Term description	Proteins	*p* value
G. gallus			
GGA-1170546	PRL receptor signaling	GH, PRL	0.002
GGA-373076	Class A/1 (rhodopsin-like receptors)	TSHB-2, TRH, FSHB, POMC	0.002
GGA-375281	Hormone ligand-binding receptors	TSHB-2, FSHB	0.002
GGA-982772	Growth hormone receptor signaling	GH, PRL	0.002
GGA-209822	Glycoprotein hormones	TSHB-2, FSHB	0.0019
H. sapiens			
hsa04659	Th17 cell differentiation	STAT5B, STAT5A, JAK2	0.00072
hsa04060	Cytokine-cytokine receptor interaction	PRL, LEP, GH2, PRLR	0.00057
hsa04658	Th1 and Th2 cell differentiation	STAT5B, STAT5A, JAK2	0.00057
hsa04920	Adipocytokine signaling pathway	LEP, JAK2, POMC	0.00037
hsa04080	Neuroactive ligand-receptor interaction	PRL, LEP, GH2, POMC, PRLR	3.39E-05

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metabolism. Pirchio et al. demonstrated that CAB treatment improved lipid and gluco-insulin profiles and significantly decreased the prevalence of obesity and metabolic syndrome[34].

POMC is a precursor protein that is cleaved into alpha-melanocyte-stimulating hormone, adreno-corticotropic hormone, and beta-endorphin. In mammals, knockout or congenital mutations of the *POMC* gene are associated with obesity and weight gain. Experimentally produced Pomc$^{-/-}$ C57BL/6J mice exhibited lower corticosterone levels and significant weight loss[35]. Mankowska et al. identified a 14-base pair deletion mutation in *POMC* gene of 47 obese Retriever dogs[35]. Similar findings have also been reported in humans and pigs[37,38]. PRL is present in POMC-producing neurons, and changes in *POMC* mRNA expression in response to PRL suggest a direct regulatory role for PRL[37]. This pathway has also been validated in birds; in 1989, Buntin observed an altered food intake following intra-cerebral administration of PRL in doves and ring doves[40].

One of the key downstream signaling pathways of PRL is the JAK2/STAT5 pathway, which plays an important role in regulating glucose and lipid metabolism during embryonic development and fetal growth[41]. To date, no adverse effects from suppressing this pathway have been reported in humans. However, *STAT5* $^{-/-}$ mouse offspring exhibit severe growth retardation, anemia, and immune deficiencies[42]. *STAT5* is highly expressed in specific tissues, including the placenta, where it contributes to vascular development and maintains the nutrient supply to the fetus[43]. Based on these findings, it is plausible that CAB-induced suppression of PRL production could impair the formation of the fetal nutrient-supplying blood vessels or lead to recurrent hemorrhages, ultimately resulting in fetal growth restriction and low birth weight.

CONCLUSION

In light of previous human and animal studies, the use of CAB is not entirely without risks. The findings highlight the need for a detailed investigation into the signaling pathways associated with PRL in the developing fetus. Adverse effects observed after CAB administration in chicken embryos emphasize the importance of expanding these studies to laboratory rodents and conducting more comprehensive evaluations in pregnant mothers receiving this treatment. Based on the results of this in ovo study, CAB reduces the growth of chicken embryos, which it is associated with placental hemorrhage. Systemic biological analyses suggest that this growth inhibition may occur through the INS or POMC pathways within the embryo, as well as its impact on the JAK2/STAT5 signaling pathway in the placenta. These findings highlight the potential risks of CAB on embryonic development and underscore the urgent need for further investigation into its mechanisms and safety profile

DECLARATIONS

Acknowledgments

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Ethical approval

All the experimental procedures in this study were conducted in accordance with the local Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (ethical code: IR.SUMS.REC.1398.681). All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Consent to participate

Not applicable.

Consent for publication

All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions

GHD and JM: project administration and writing–original draft preparation; ZD: project administration and writing–original draft preparation, conceptualization, investigation, and methodology; AD: conceptualization, investigation, and methodology. All authors participated in writing, reviewing, and editing the work.

Data availability

All relevant data can be found within the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Supplementary information

The online version does not contain supplementary material.

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