Blood plasma levels of anterior pituitary hormones of rabbits after apricot seed exposure *in vivo*

Adenohypofyzárne hormóny krvnej plazmy králikov po expozícii marhuľových semien *in vivo*

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Abstract

The present study describes possible changes in plasma levels of anterior pituitary hormones induced by bitter apricot (*Prunus armeniaca L.*) seeds in young female rabbits *in vivo*. *Prunus armeniaca* L. is an important medicinal edible plant species commonly known as “apricot”. The apricot is a member of the *Rosaceae* and subfamily *Prunoideae*. It is one of the most delicious and commercially traded fruits in the world. Apricot kernel is the inner part of the seed of the apricot fruit. The kernel is used to produce oil and other chemicals used for medicinal purposes. The seeds are potentially useful in human nutrition and for treatment several diseases especially cancer. In the present study apricot seeds were mixed with feed at different doses 0, 60, 300, 420 mg*kg^{-1} of body weight. ELISA was used to determine the levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PRL). 58-days application of apricot seeds did not affect the concentration ($P \geq 0.05$) of PRL, LH in blood plasma. Significant ($P \leq 0.01$) inhibition of FSH levels induced by the seeds was found at the dose of 420 mg*kg^{-1} but not at 60 and 300 mg*kg^{-1} of body weight. These results are suggesting that the natural substances present in apricot seeds may be involved in mechanisms of ovarian folliculogenesis.

Keywords: amygdalin, follicle stimulating hormone, luteinizing hormone, prolactin

Abstrakt

Táto štúdia popisuje možnú zmenu koncentrácie hormónov adenohypofýzy u mladých samíc králikov, vyvolanú biologickou aktivitou horkých marhuľových semien *(Prunus armeniaca L.)*. *Prunus armeniaca L*. je jedlý liečivý druh všeobecne známy ako "marhuľa". Marhuľa obyčajná patrí do čeľade *Rosaceae* a podčeľade *Prunoideae*. Reprezentuje jedno z najchutnejších a komerčne ľahko dostupných ovocných druhov na svetovom trhu. Marhuľové semeno je vnútorná časť jadra marhúľ. Semeno sa využíva na výrobu oleja a iných chemických zlúčenín, ktoré našli uplatnenie v medicíne. Semená sú potenciálne vhodné pre ľudskú výživu a na liečbu mnohých ochorení najmä nádorov. V predloženej štúdii boli marhuľové semená pridané do krmiva v rôznych dávkach 0, 60, 300, 420 mg*kg^{-1} telesnej hmotnosti. Následne bola na stanovenie folikulostimulačného (FSH), luteinizačného hormónu (LH) a prolaktínu (PRL) použitá ELISA metóda. 58-dňová aplikácia marhuľových semien nemala vplyv (P≥0.05) na koncentráciu PRL, LH v krvnej plazme. Významná (P≤0.01) inhibícia uvoľňovania FSH bola indukovaná pri dávke 420 mg*kg^{-1} živej hmotnosti marhuľových semien. Tieto výsledky naznačujú, že prírodné látky prítomné v semenách marhúľ, by mohli byť zapojené do mechanizmov ovariálnej folikulogenézy.

Kľúčové slová: amygdalin, folikulostimulačný hormón, luteinizačný hormón, prolaktín

Introduction

The apricot, *Prunus armeniaca L*., is a member of the *Rosaceae*, subfamily *Prunoideae*. These orange coloured fruits are one of the first signs of summer. Apricot fruit quality is associated with attributes such as appearance, texture, taste and colour. The fruit has distinctively delicious taste, appealing smell, and varying colours from yellow to orange with a reddish random overlay. In the middle of the apricot is a large pit. Apricot seeds are generally exported to European countries and used especially in medicine, cosmetic and oil production (Gezer, 2002). Durmaz and Alpaslan (2007) mentioned that apricot seeds are added to bakery products (as whole seeds or ground) in retail bakeries and also consumed as appetizers. Apricot seeds, particularly rich in lipid and protein, are potentially useful in human nutrition (Femenia et al., 1995; Alpaslan et al., 2006) along with significant amounts of oil fiber (Abd el-aal et al., 1986; Hacisefero et al., 2007) high antioxidant and antimicrobial activities (Yigit et al., 2009). Sweet apricot seeds contain more oil than bitter and such oleic acid and linoleic acid correspond to approximately 92 g*100 g^{-1}of the total fatty acids present in apricot seed. Apricot seeds contain the cyanogenic glycoside (CGs) amygdalin depending on the variety and environmental effects. Apricot kernels contain approximately 20-80 μmol*g^{-1} of amygdalin, and it is very high (5.5 g*100 g^{-1}) in bitter apricot cultivars while it is not detected in the sweet ones (Femenia et al., 1995). CGs are natural plant toxicants (Bolarinwa et al., 2015). The genetic control of cyanogenesis has no unique mechanism. The plants show variation in the amount of the produced hydrocyanic acid (HCN). The generation of hydrocyanic acid HCN from

CGs is a two step process (Vetter, 2000). Kernels of the wild apricot contain a high concentration of HCN (200 mg*100 g^{-1}), whereas domestic bitter apricot cultivars contain relatively low levels of HCN (11.7 mg*100 g^{-1}) (Stoewsand et al., 1975). Amygdalin can be hydrolyzed to form glucose, benzaldehyde and hydrocyanic acid. Enzymatic release of cyanide occurs in the presence of β-glucoronidase, an enzyme found in the human intestine (Strugala et al., 1995). On average, apricot seeds contain approximately 0.5 mg of cyanide (Femenia et al., 1995). The use of apricot seeds for human nutrition is limited because their content of the toxic, CGs (amygdalin) accompanied by minor amounts of prunasin. Amygdalin, can be used for an effective prevention and treatment of human cancer (Gomez et al., 1998). However, the Food and Drug Administration (FDA) has not approved amygdalin as a cancer treatment owing to insufficient clinical evidence of its efficacy and potential toxicity (Chang et al., 2006; Kwon et al., 2010). The seed oil has been used to treat tumors, ulcers (Rieger, 2006) well as in cosmetics and as a pharmaceutical agent (laxative and expectorant). In very small amounts, the toxic hydrogen cyanide present in bitter apricot kernels has been prescribed for asthma, cough and constipation. Apricot seeds paste can heal vaginal infections (Chevallier, 1996). Anterior pituitary hormones play a key role in reproductive physiology (Bugbee et al., 1931). Gonadotropin-releasing hormone (GnRH) binds to gonadotropes to stimulate synthesis and secretion of two glycoprotein hormones: follicle stimulating hormone (FSH) and luteinizing hormone (LH) by the anterior pituitary (Gromoll et al., 2003; Müller et al., 2004a; 2004b; Scammell et al., 2008). Female fertility depends on the precise execution of ovarian development, regulated allocation and maturation of oocytes, and the proliferation and differentiation of the surrounding somatic cells that occur during folliculogenesis (Elvin et al., 1998). FSH and LH are known collectively as gonadotrophins and control reproductive functions and sexual characteristics. Prolactin (PRL) stimulates the breasts to produce milk. This hormone is secreted in large amounts during pregnancy and breast feeding, but is present at all times in both men and women (Rogers et al., 2011). The aim of study was to examine whether apricot seeds are able to cause changes in blood plasma levels of anterior pituitary hormones of rabbits.

Materials and methods

Animals

Young female rabbits, meat line P91 Californian rabbits (n=32) from the experimental farm of the Animal Production Research Centre Nitra (Slovak Republic), were used in this experiment. The rabbits were 98 days old and housed in individual flat-deck wire cages under temperature 20-24°C, humidity 55% ± 10% and constant photoperiod of 12 hours of daylight. Institutional and national guidelines for the care and use of animals were followed appropriately, and all experimental procedures were approved by the State Veterinary and Food Institute of Slovak Republic, no. 3398/11-221/3 and Ethic Committee.

Apricot seeds

Overall 32 experimental animals were randomly divided into the four groups, leading to 8 rabbits in each group. The control group was fed a commercially available feed without apricot seeds while the three experimental groups received daily doses 60, 300, 420 mg*kg^{-1} of body weight of crushed apricot seeds mixed with feed during 58 days.

Analysis of blood plasma

Venous blood from *vena auricularis* was collected into EDTA-treated tubes. Blood plasma was separated from whole blood by centrifugation at 3000 rpm for 10 min. at 20°C. The clear supernatant (plasma) was then separated from the pellet and kept frozen until analysis. During the experiment, blood collections were carried out to control the health of offspring.

ELISA (Enzyme linked immunosorbent assay)

Quantification of anterior pituitary hormones (FSH, LH and PRL) after apricot seeds supplementation was performed by ELISA. ELISA assays (Dialab, Wiener Neudorf, Austria) were performed according to the manufacturer's instructions and the colour intensity was inversely proportional to the concentration of hormones in the sample.

Statistical Analysis

Analysis of substances was performed in duplicate. The significance of differences between the control and experimental groups was evaluated by One-Way ANOVA (Dunnett´s multiple comparison test) using the statistical software GraphPad Prism 3.01 (GraphPad Software Inc., San Diego, CA, USA). The data are expressed as means ± SEM. Differences were compared for statistical significance at the p-level less than 0.05 ($P \leq 0.05$).

Results

The effect of short-term application of apricot seeds on plasma levels of anterior pituitary hormones: FSH, LH, PRL were evaluated in this study. Plasma levels of FSH, LH, PRL during 58-days feeding period of apricot seeds to experimental young female rabbits were assessed in this *in vivo* study (Figs.1-3). Statistically significant differences ($P \leq 0.01$) were recorded in the case of FSH level. FSH level in blood plasma was significantly ($P \leq 0.01$) inhibited by the highest dose of apricot seeds compared to control group without supplementation (Fig. 1). On the other hand the plasma levels of LH and PRL were not affected by apricot supplementation in comparison to control animals (Figs. 2-3).

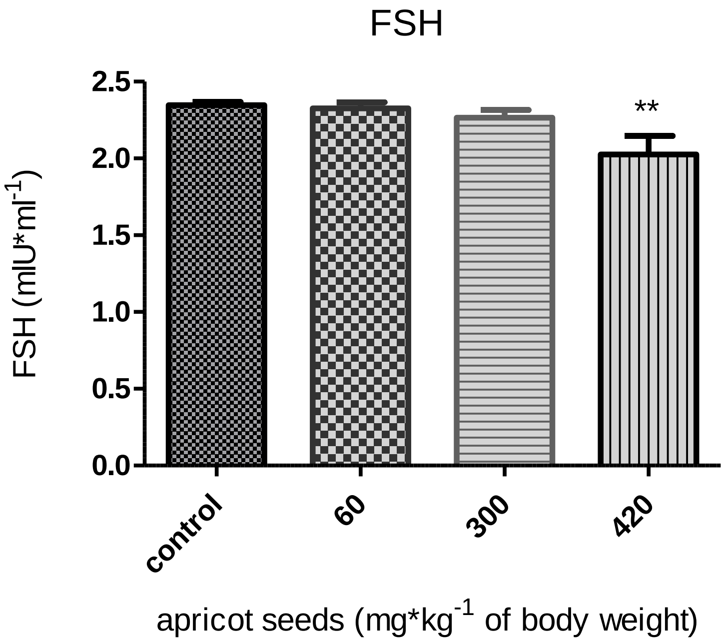

Figure 1. The plasma levels of FSH after oral treatment of apricot seeds. The control group (control) represents a group of rabbits without application of seeds. Experimental groups with apricot seeds at the doses 60, 300 and 420 mg*kg^{-1} of body weight. **Significance of (P≤0.01) differences between control and experimental groups. The data are expressed as means ± SEM. ELISA.

Obrázok 1. Koncentrácie FSH v krvnej plazme králikov po perorálnom podaní marhuľových semien. Kontrolná skupina (kontrola) reprezentuje skupinu králikov bez prítomnosti marhuľových semien v krmive. Experimentálne skupiny reprezentujú skupiny králikov s marhuľovými semenami v dávkach 60, 300 a 420 mg*kg^{-1} živej hmotnosti. **Signifikantné zmeny medzi kontrolou a experimentálnymi skupinami. Údaje sú vyjadrené ako priemer ± SEM ELISA.

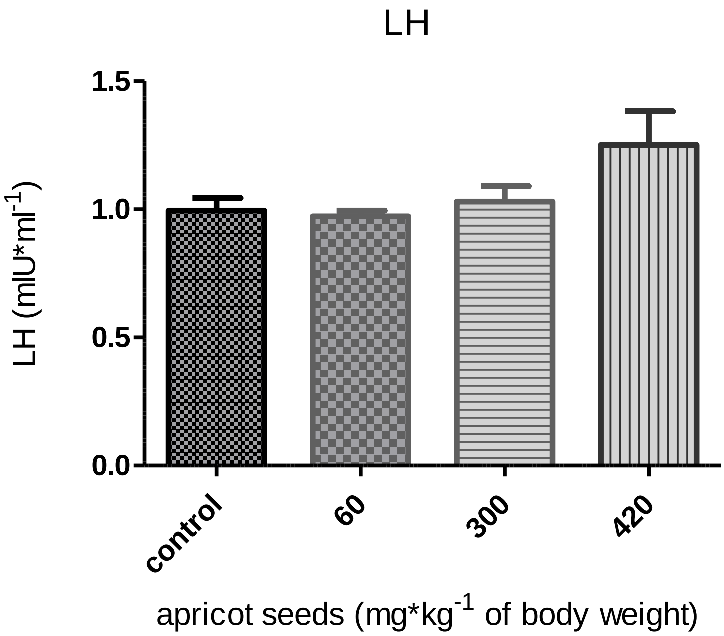

Figure 2. The plasma levels of LH after oral treatment of apricot seeds. The control group (control) represents a group of rabbits without application of seeds. Experimental groups with apricot seeds at the doses 60, 300 and 420 mg*kg^{-1} of body weight. The data are expressed as means ± SEM. ELISA.

Obrázok 2. Koncentrácie LH v krvnej plazme králikov po perorálnom podaní marhuľových semien. Kontrolná skupina (kontrola) reprezentuje skupinu králikov bez prítomnosti marhuľových semien v krmive. Experimentálne skupiny reprezentujú skupiny králikov s marhuľovými semenami v dávkach 60, 300 a 420 mg*kg^{-1} živej hmotnosti. Údaje sú vyjadrené ako priemer ± SEM. ELISA.

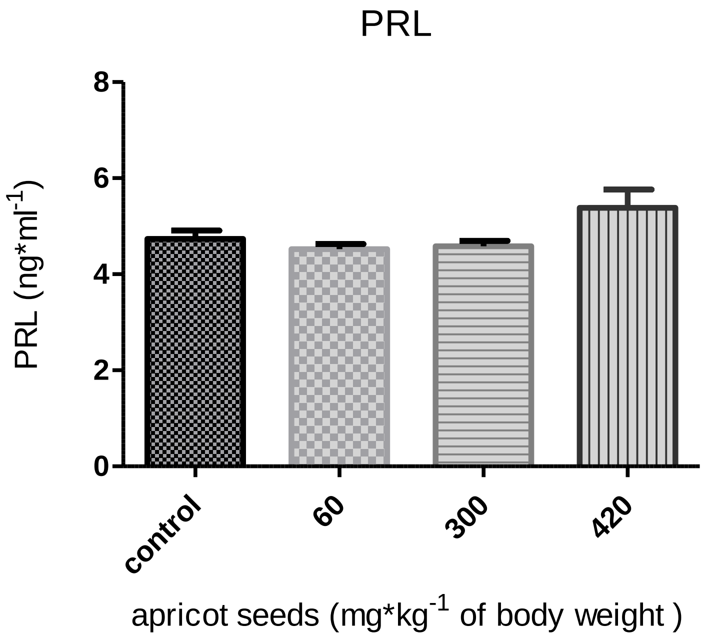

Figure 3. The plasma levels of PRL after oral treatment of apricot seeds. The control group (control) represents a group of rabbits without application of seeds. Experimental groups with apricot seeds at the doses 60, 300 and 420 mg*kg^{-1} of body weight. The data are expressed as means ± SEM. ELISA.

Obrázok 3. Koncentrácie PRL v krvnej plazme králikov po perorálnom podaní marhuľových semien. Kontrolná skupina (kontrola) reprezentuje skupinu králikov bez prítomnosti marhuľových semien v krmive. Experimentálne skupiny reprezentujú skupiny králikov s marhuľovými semenami v dávkach 60, 300 a 420 mg*kg^{-1} živej hmotnosti. Údaje sú vyjadrené ako priemer ± SEM. ELISA.

Discussion

Previous studies examined the effects of natural compounds on different parts of animal reproductive system (Kolesárová et al., 2012a; 2012b; 2011; Tanyildizy and Bozkurt, 2004; Yasui et al., 2003). However, much interest has shown in recent years to control fertility by using plants (Ros et al., 2003). Apricot kernels may be used to treat any type of symptoms that invigorate the blood menstrual disorders and cancer disease (Moss, 2005). In the present *in vivo* study, possible response of rabbit plasma levels to apricot seeds was examined. This study is suggesting that plasma levels of anterior pituitary hormones PRL, LH did not statistically (P≥0.05) differ after oral application of apricot seeds at the doses 60, 300, 420 mg*kg^{-1} of body weight, compared to the hormone levels of animals in the control group. However, plasma levels of FSH were significantly (P≤0.01) decreased by apricot seeds at the highest dose (420 mg*kg^{-1} of body weight) compared to the control group. Previously, the possible effects of apricot seeds, during 28 days oral applications, on plasma levels of anterior pituitary hormones in female rabbits were described by Michalcová et al. (2016). The results indicated no significant (P≥0.05) differences in the case of PRL and LH levels but significant (P≤0.05) decrease of FSH levels induced by seeds at the doses 300, 420 mg*kg^{-1} of body weight. Nevertheless, this analysis was performed after 28 days application of apricot seeds and female rabbits were only 40 days old. Both studies suggest a possible effect of higher doses of apricot seeds on the plasma levels of FSH in rabbits. With regard to reproduction, a previous study showed that Japanese apricot (*Prunus mume*) extract improved the egg quality of hens (Itami et al., 2005). Amygdalin is one of the cyanogenic glycosides found, for example, in apricots (Bolarinwa et al., 2014). The possible effects of amygdalin and its combination with the mycotoxin deoxynivalenol (DON) on the steroid hormone secretion (progesterone and 17-β-estradiol) by porcine ovarian granulosa cells were examined. The progesterone secretion by porcine ovarian granulosa cells was not affected by amygdalin in comparison to the control. However, the highest dose of amygdalin 10000 μg*ml^{-1} caused a significant stimulation of the 17-β-estradiol release. A combination of amygdalin with DON significantly (P<0.05) increased the progesterone release at all concentrations. Similarly, a stimulatory effect of amygdalin co-administered with DON was detected with respect to the 17-β-estradiol secretion at the highest dose 10000 μg*ml^{-1} of amygdalin and 1 μg*ml^{-1} of DON. Noticeable differences between the effects of amygdalin alone and its combination with DON on the progesterone release were detected. In contrast, no differences between the stimulatory effects of amygdalin and its combination with DON on the 17-β-estradiol synthesis by porcine granulosa cells were observed. Findings from this *in vitro* study did not confirm the expected protective effect of amygdalin on mycotoxin induced reprotoxicity. The results indicate that the stimulatory effect of amygdalin combined with DON on the progesterone release was clearly caused by the DON addition, not by the presence amygdalin per se. On the other hand, the stimulation of 17-β-estradiol production was solely caused by the presence of amygdalin addition. Their findings suggest a possible involvement of both natural substances into the processes of steroidogenesis and appear to be endocrine modulators of porcine ovaries (Halenár et al., 2015). Londonkar et al. (2013) have suggested that administration of ethanol extract of *Portulaca oleracea L* may block ovulation by inhibiting cyclooxygenase activity, alters estrous cycle with a prolonged diestrous, increases the uterine muscle weight and ovary weight and may cause anti-ovulation effect. The estrogenic activity of the ethanol extract of *P. Oleracea L* might be due to the presence of flavonoids, which possess estrogenic activity, thus their study supports that pharmacological basis of *P. oleracea L* extract can be used for further development of contraceptive agent without side effect and cost effect. There are also varieties of apricot seeds that are reported to be edible and used for treatment (Dai and Mumper 2010).

Conclusions

Findings from this experiment indicate that selected doses of apricot seeds (60, 300, 420 mg*kg^{-1} of body weight) did not significantly (P≥0.05) affect the plasma levels of LH and PRL. However, plasma level of FSH was significantly (P≤0.01) decreased by apricot seeds at the highest dose 420 mg*kg^{-1} but not at 60 and 300 mg*kg^{-1} of body weight. These results indicate that the natural substances present in apricot seeds may be involved in mechanism of ovarian folliculogenesis

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