Journal of Elementology ISSN 1644-2296

Markiewicz, W., Markowska-Buńka, P., Burmańczuk, A., Formella, A. and Jaroszewski, J. (2026)
'Effect of chrysin on the contractile activity of porcine uterine smooth muscle',
Journal of Elementology, 31(3), 623-632,
available: https://doi.org/10.5601/jelem.2026.31.2.3886

RECEIVED: 18 May 2026
ACCEPTED: 21 July 2026

ORIGINAL PAPER

Effect of chrysin on the contractile activity of porcine uterine smooth muscle*

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Abstract

Chrysin is a naturally occurring flavonoid with a wide range of biological activities. However, little is known about its effect on female reproductive function, particularly on uterine contractility. The aim of the present study was to evaluate the effect of chrysin on the contractile activity of porcine uterine smooth muscle collected from cyclic and early pregnant gilts. The experiment was performed on two groups of animals (n=6 per group): cyclic gilts in the luteal phase of the estrous cycle (days 12-14) and early pregnant gilts (days 12-16 of gestation). Uteri were collected immediately after slaughter, placed on ice, and myometrial strips were isolated from the middle part of the uterine horns. The strips were mounted in organ baths containing Krebs-Ringer solution. After an equilibration period of 60-90 min, the tissues were exposed to increasing concentrations of chrysin (10^{-13}-10^{-3} M) at 15-min intervals. Chrysin increased contraction amplitude while reducing contraction frequency and resting tension in a concentration-dependent manner, with cyclic gilts responding at lower concentrations than early pregnant gilts. These findings indicate that chrysin modulates porcine myometrial activity in a complex manner. The observed responses may involve nitric oxide release and modulation of calcium-dependent signaling pathways. In conclusion, chrysin significantly affects uterine smooth muscle contractility in pigs and may be considered a potential natural modulator of myometrial function.

Keywords: chrysin, flavonoid, porcine myometrium, uterine contractility

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* This work was funded by the Department of Pharmacology and Toxicology, Faculty of Veterinary Medicine University of Warmia and Mazury, Olsztyn, Poland.

INTRODUCTION

Flavonoids are a diverse group of low-molecular-weight polyphenolic compounds widely distributed in the plant kingdom. They have attracted considerable attention because of their broad spectrum of biological activities, including antioxidant, anti-inflammatory, antibacterial, and antitumor effects (Duarte et al. 2001, Huang et al. 2013, Xiao et al. 2014, Zhu et al. 2014, Kasala et al. 2015). One such flavonoid is chrysin (5,7-dihydroxyflavone), which occurs naturally in *Passiflora caerulea*, honey, propolis, *Radix Scutellariae*, and edible mushrooms such as *Pleurotus ostreatus* (Mani, Natesan 2018, Naz et al. 2019).

Chrysin has been reported to exert neuroprotective, hepatoprotective, nephroprotective, and reproductive effects (Ciftci et al. 2012, Sultana et al. 2012, Ciftci and Ozdemir 2013, Kandhare et al. 2014, Shen et al. 2015, Aksu et al. 2016). In the male reproductive system, it improves testicular morphology, sperm quality, and testosterone production and exhibits steroidogenic and anti-aromatase properties, suggesting a role in the regulation of reproductive function (Campbell, Kurzer 1993, Sanderson et al. 2004, Jana et al. 2008, Altawash et al. 2017).

Despite these documented biological activities, little is known about the influence of chrysin on the female reproductive tract, particularly on uterine contractility. This issue is of potential importance because preterm labour remains a serious clinical problem, affecting approximately 5-10% of human pregnancies worldwide (Motazedian et al. 2010). Although several pharmacological agents are used to inhibit uterine contractions, their efficacy is often limited, and their use may be associated with adverse effects. Therefore, natural compounds such as flavonoids may represent promising modulators of myometrial activity.

Given the lack of data concerning the effect of chrysin on uterine smooth muscle, the aim of the present study was to evaluate the effect of chrysin on the contractile activity of porcine myometrium collected from cyclic and early pregnant gilts. The results may provide a basis for further studies on the role of flavonoids in the regulation of uterine contractility.

MATERIALS AND METHODS

Animals

The study was conducted on two experimental groups of gilts (n=6 per group). The first group consisted of cyclic gilts aged 6-7 months, weighing 120-130 kg, in the luteal phase of the estrous cycle (days 12-14), as confirmed by ovarian morphology (Akins and Morrissette 1968). The second

group included early pregnant gilts with a body weight similar to that of cyclic gilts on days 12-16 of gestation, in which pregnancy was confirmed by flushing the uterine horns with phosphate-buffered saline (PBS, pH 7.4) to recover embryos. The selection and insemination procedures for these gilts were described previously by Kaminski et al. (2018).

Preparation of myometrial strips for contractility measurements

Uteri were collected from all animals immediately after slaughter. All procedures involving animals, including insemination and animal handling, were conducted in accordance with the ethical standards of the Local Ethics Committee in Olsztyn, Poland, which approved the study protocol (Decision No. 91/2011/DTN). The biological material used for contractility measurements was obtained post mortem from slaughterhouse animals; therefore, no separate ethical approval was required for the ex vivo experiments. Myometrial strips were prepared as previously described (Markiewicz et al. 2012). Briefly, the uteri were placed on ice and myometrial strips (3×5 mm) were excised from the middle part of the uterine horns. The strips were washed in saline and mounted between two stainless steel hooks in an organ bath (Schuler Organ Bath type 809, Hugo Sachs Elektronik, Germany) under a resting tension of 10 mN. The tissues were maintained in 5 mL of Krebs-Ringer solution (KRS) of the following composition (mmol L^{-1}): NaCl, 120.3, KCl, 5.9, $CaCl_2$, 2.5, $MgCl_2$, 1.2, $NaHCO_3$, 15.5, and glucose, 11.5, at 37°C and pH 7.4. Throughout the experiment, the solution was continuously aerated with a gas mixture of 95% O_2 and 5% CO_2. Contractile activity of the myometrial strips was measured using force transducers (HSE F-30 type 372) connected to a bridge coupler (type 570). The recordings were collected using a Hugo Sachs Elektronik system with HSE-ACAD/W software.

Experimental design

Recording was started after an equilibration period of 60-90 min. Tissue viability and responsiveness were verified by acetylcholine (ACh, 10^{-6}-10^{-4} M) administration at the beginning of the experiment. Subsequently, the strips were exposed to increasing concentrations of chrysin (10^{-13}-10^{-3} M) at 15-min intervals. Chrysin (CHR, purity > 98%, Sigma-Aldrich, Germany) was initially dissolved in dimethyl sulfoxide (DMSO) to obtain a 10^{-1} M stock solution, and further dilutions were prepared in KRS. At the end of the experiment, ACh was administered again to confirm tissue viability. Only strips showing less than a 20% difference between the responses to ACh at the beginning and at the end of the experiment were included in the statistical analysis. This criterion was applied to ensure sustained tissue viability and experimental consistency throughout the study. Between successive treatment periods, the tissue chambers were washed three times with 15 mL of incubation solution at 10-min intervals.

Statistical analysis

The following contractility parameters were analysed: resting tension (mN), frequency (number of contractions per 15 min), and amplitude (mN), defined as the difference between the minimum and maximum force during a contraction. Values recorded during the 15 min preceding chrysin administration were taken as 100% (baseline). Post-treatment values were expressed as percentages of baseline (mean ± SD, n=6). Differences within and between groups were analysed using one-way ANOVA followed by Bonferroni's post hoc test (GraphPad Prism 3.1, GraphPad Software, San Diego, CA, USA). A value of $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

To the best of our knowledge, this is the first study evaluating the effect of chrysin on the contractile activity of porcine uterine smooth muscle. Representative recordings showing the effect of chrysin on myometrial contractility in cyclic gilts in the luteal phase (days 12-14 of the estrous cycle) and early pregnant gilts (days 12-16 of gestation) are presented in Figure 1.

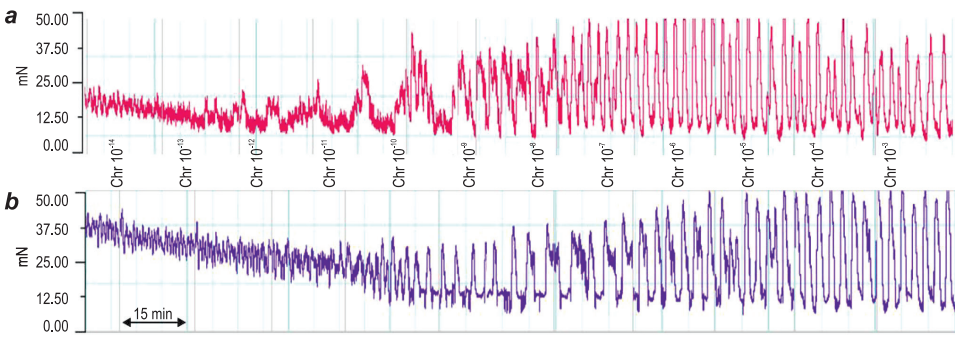

Fig. 1. Representative recordings of spontaneous contractile activity of porcine uterine smooth muscle obtained from cyclic gilts in the luteal phase (days 12-14 of the estrous cycle) – *a* and early pregnant gilts (days 12-16 of gestation) – *b*. Chrysin (Chr) was administered at increasing concentrations (10^{-13}-10^{-3} M) at 15-min intervals

Chrysin significantly affected all analysed parameters of myometrial contractility in both experimental groups (Figure 2). In cyclic gilts, chrysin significantly increased contraction amplitude over the tested concentration range (10^{-13}-10^{-3} M, $p<0.001$), whereas in early pregnant gilts a significant increase was observed from 10^{-12} to 10^{-3} M ($p<0.001$, Figure 2*a*). In contrast, contraction frequency decreased in both groups after chrysin treatment. In cyclic gilts, significant decreases were observed at concentrations of 10^{-9}-10^{-8} M ($p<0.01$) and 10^{-7}-10^{-3} M ($p<0.001$). In early pregnant gilts,

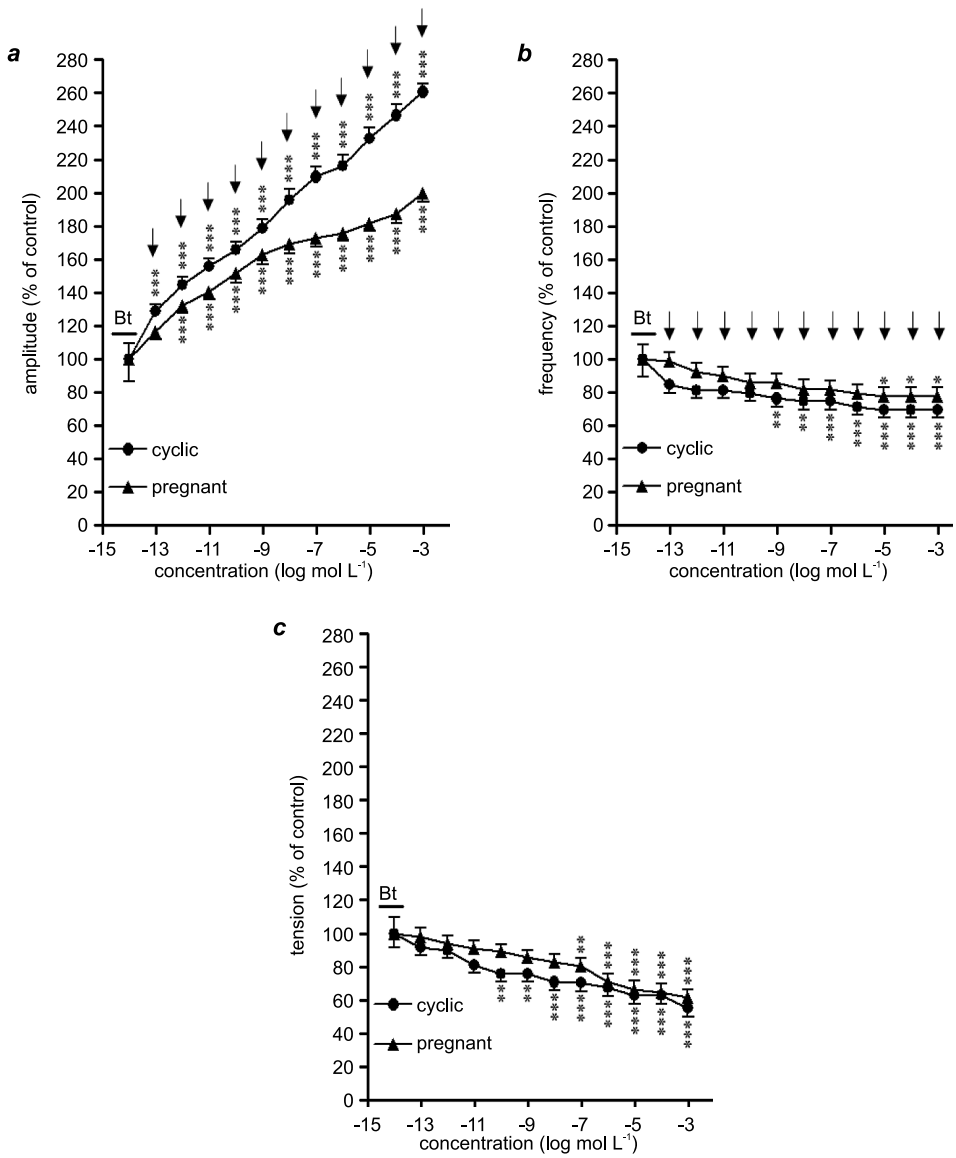

Fig. 2. Effect of chrysin on contraction amplitude (*a*), frequency (*b*), and resting tension (*c*) of porcine uterine smooth muscle obtained from cyclic gilts in the luteal phase (days 12-14 of the estrous cycle) (n=6) and early pregnant gilts (days 12-16 of gestation n=6). Results are expressed as percentages of baseline activity (mean ± SD) and were calculated 15 min after administration of increasing concentrations of chrysin (10^{-13}-10^{-3} M). Significant differences compared with baseline contractile activity before chrysin administration are indicated as follows: * p<0.05, ** p<0.01, *** p<0.001.

significant reductions were noted at concentrations of 10^{-5}-10^{-3} M ($p<0.05$, Figure 2*b*). Chrysin also significantly affected myometrial tension in both studied groups. In cyclic gilts, significant changes were observed at 10^{-10}-10^{-9} M ($p<0.01$) and 10^{-8}-10^{-3} M ($p<0.001$), whereas in early pregnant gilts significant effects occurred at 10^{-7} M ($p<0.01$) and 10^{-6}-10^{-3} M ($p<0.001$, Figure 2*c*). Overall, these findings may reflect a shift toward stronger but less frequent uterine contractions following chrysin administration.

The porcine uterus exhibits spontaneous contractile activity even in the absence of external neural or hormonal stimulation (Wray 1993). This activity depends on the electrophysiological properties of myometrial cells, which are responsible for force generation, propagation of action potentials, and regulation of uterine contractility (Young 2007). Intracellular Ca^{2+} plays a central role in the control of uterine contraction. An increase in cytoplasmic Ca^{2+} concentration activates the Ca^{2+} – calmodulin-myosin light chain kinase pathway, leading to phosphorylation of myosin light chains and initiation of contraction (Somlyo, Somlyo 1994, Wray 2007). In uterine smooth muscle, Ca^{2+} influx through voltage-dependent L-type calcium channels is considered the main source of activator Ca^{2+}, although release from intracellular stores also contributes to contractile regulation (Matthew et al. 2004, Wray et al. 2001, 2003).

Although no previous studies have described the effect of chrysin on uterine contractility, data from vascular smooth muscle suggest possible mechanisms underlying its action. In isolated rat thoracic aorta, chrysin and other flavones inhibited contractile responses to extracellular Ca^{2+} and reduced intracellular Ca^{2+} release induced by phenylephrine (Chan et al. 2000). Chrysin also relaxed noradrenaline-induced contractions in endothelium-intact rat aortic rings, and this effect was reduced after endothelium removal or L-NAME treatment, indicating the involvement of nitric oxide (Duarte et al, 2001, Oliveira et al, 2012). Other studies have suggested that the relaxant effect of chrysin may also involve inhibition of Ca^{2+} influx, reduction of intracellular Ca^{2+} release, and activation of the NO/cGMP signalling pathway (Chan et al. 2000, Duarte et al. 2001, Oliveira et al. 2012). Because Ca^{2+} influx through L-type calcium channels is essential for uterine contraction, inhibition of these channels together with activation of the NO/cGMP pathway may reduce intracellular Ca^{2+} availability, thereby contributing to the observed decrease in contraction frequency and resting tension despite the increase in contraction amplitude.

In the present study, chrysin increased contraction amplitude but decreased contraction frequency and resting tension in both cyclic and early pregnant gilts. Moreover, the response to chrysin differed between cyclic and early pregnant gilts, suggesting that the physiological status of the uterus may influence sensitivity to chrysin. Differences in endocrine conditions and local regulatory factors between the luteal phase and early pregnancy may contribute to the observed variation in myometrial responsiveness.

The greater sensitivity of the myometrium from cyclic gilts, reflected by significant responses at lower chrysin concentrations, may be associated with differences in the endocrine environment between the luteal phase and early pregnancy. During early pregnancy, changes in progesterone and oestrogen concentrations, together with altered expression of receptors involved in the regulation of uterine contractility, may modify myometrial responsiveness to pharmacological agents. In addition, pregnancy – related adaptations in intracellular signalling pathways may contribute to the reduced sensitivity observed in early pregnant gilts.

At present, evidence regarding the effects of chrysin during pregnancy is very limited. Previous studies showed that chrysin did not affect ovarian aromatase activity or endometrial cell proliferation under some experimental conditions, and administration of chrysin to immature female rats did not induce uterine growth or modify oestrogen- or androgen-induced uterine growth (Pelissero et al. 1996, Edmunds et al. 2005, Saarinen et al, 2001). These observations suggest that the action of chrysin on reproductive tissues may be tissue-specific and dependent on physiological status.

Several limitations of the present study should be acknowledged. The experiments were performed using an in vitro organ bath model, which does not fully reflect the complex neuroendocrine regulation of uterine contractility in vivo. Furthermore, the present study focused on the functional effects of chrysin and did not investigate the molecular mechanisms underlying its action. Therefore, the proposed involvement of nitric oxide signaling and calcium-dependent pathways remains speculative and requires experimental confirmation.

In conclusion, chrysin significantly altered the contractile activity of porcine myometrium in both cyclic and early pregnant gilts. The observed increase in contraction amplitude accompanied by a decrease in contraction frequency and tension indicates that chrysin modulates uterine smooth muscle activity in a complex manner. These findings provide new information on the action of chrysin in the female reproductive tract and may serve as a basis for future studies investigating the molecular mechanisms of chrysin action, including the involvement of calcium channels, the NO/cGMP pathway, and hormone-dependent regulation of myometrial responsiveness. Furthermore, in vivo studies are required to evaluate the physiological relevance and potential therapeutic applicability of these findings.

CONCLUSIONS

This study provides the first evidence that chrysin modulates the contractile activity of porcine uterine smooth muscle and that its effects depend on the physiological status of the uterus. These findings expand current

knowledge of the biological activity of chrysin in the female reproductive tract and indicate that chrysin may represent a potential natural modulator of uterine contractility. Further studies are warranted to elucidate the underlying molecular mechanisms and to evaluate the physiological relevance and therapeutic potential of chrysin in vivo.

Limitations of the study

The present study has some limitations. Because the experiments were performed ex vivo on isolated myometrial strips, the findings cannot be directly translated to in vivo conditions. In addition, the mechanisms responsible for the observed effects of chrysin were not investigated and require further investigation.

Author contributions

W.M. – conceptualisation, data curation, investigation, methodology, formal analysis, writing – original draft preparation, writing – review and editing. A.F. – data curation, investigation, formal analysis, methodology. A.B. – methodology, writing. J.J.J. – conceptualisation, methodology, supervision. P.M.B.* – data curation, investigation, methodology, writing, writing – review and editing.

Conflicts of interest

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

The authors thank the University of Warmia and Mazury in Olsztyn for providing research facilities.

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