

## Effect of curcumin on the contraction of isolated goat uterus

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### ABSTRACT

**Background:** The aim of the study was to investigate the effect and mechanism of action of curcumin on potassium chloride (KCl) induced contraction of isolated goat uterine tissue.

**Methods:** KCl induced contraction in the presence and absence of log doses of curcumin were obtained with the help of force transducer and student physiograph. Also, the effect of glibenclamide (K<sup>+</sup>ATP channel blocker) and methylene blue v (nitric oxide blocker) on the contractility of uterus tissue in presence of curcumin was recorded. Wilcoxon Signed Rank test was used for statistical analysis. The percentage inhibition of height and area under curve were calculated.

**Results:** There was decrease in the height of KCl induced contraction in the presence of curcumin 4 μM (p value 0.046) 40 μM (p value=0.028) and 400 μM (p value=0.028). There was reduction in area under curve of KCl induced contraction in presence of curcumin 4 μM (p value=0.463) 40μM (p value=0.027) and 400 μM (p value=0.028). There was decrease in the height (p value=0.046) and significant decrease in area (p value=0.046) of KCl induced contraction in the presence of curcumin 100 μM and glibenclamide. There was decrease in height (p value=0.027) and area (p value=0.028) of KCl induced contraction in the presence of curcumin 100 μM and methylene blue.

**Conclusions:** Curcumin causes relaxation of goat uterus. Since methylene blue and glibenclamide were not able to reverse the inhibition produced by curcumin it implies curcumin may not act via the nitric oxide pathway nor does it interact with K<sup>+</sup>ATP channels to relax the uterus.

**Keywords:** Curcumin, Contraction, Goat, Uterus, Physiograph

### INTRODUCTION

Turmeric (*Curcuma longa*) is a spice, used widely in India. The bright yellow color of turmeric comes from curcuminoids, of which curcumin (diferuloylmethane) is the principle and most active constituent. Curcumin has a wide spectrum of action which includes anti-inflammatory, antioxidant, anti-carcinogenic, anti-mutagenic, anticoagulant, anti-fertility, antidiabetic, antibacterial, antifungal, antiprotozoal, antiviral, anti-fibrotic, antivenom, anti-ulcer, hypotensive and hypercholesteraemic activities. It is also found to be a safe compound.

Curcumin has shown to cause relaxation of various types of smooth muscles such as Guinea pig ileum, rat uterus and rat aorta.<sup>3-5</sup> The mechanism of this action of curcumin is not known. In a study done by Gilani et al (2005), an extract of turmeric relaxed the contractions in isolated rabbit jejunum. In rabbit tracheal preparation there was inhibition of contraction. In anesthetized rats there was variable responses on blood pressure with a mixture of weak hypertensive and hypotensive actions.<sup>6</sup>

Conventional tocolytic agents e.g. (β<sub>2</sub>-adrenoceptor agonists, calcium channel antagonists, prostaglandin synthesis inhibitors) are associated with serious

cardiovascular, metabolic and neuromuscular side effects hindering their clinical use. The effectiveness of oxytocin antagonists is not proven.<sup>8</sup>

If curcumin inhibits contracted uterus, this drug may find use in the treatment of clinical conditions that require relaxation of the uterus like dysmenorrhea and premature labour.

## METHODS

This experimental study was conducted in the animal laboratory of the Christian medical college, Vellore, after obtaining approval by the institutional animal ethics committee and institutional research committee. The study was done over a period of 3 months (April 2011 to July 2011). The chemicals, curcumin and glibenclamide was obtained from sigma Aldrich. Methylene blue was obtained from Fisher scientific (Qualigens, Mumbai, India). Goat uterus was transported from the local slaughter house in aerated Dejalon's solution at room temperature at a pH of 7.2. The composition of Dejalon's solution is (NaCl 153.85 mM, KCl 5.64 mM, CaCl<sub>2</sub> 0.55 mM, MgSO<sub>4</sub> mM, NaOH 12.5 mM and Glucose 2.78 mM. Solution was aerated with oxygen and maintained at 35°C. In the laboratory, one horn of the uterus muscle measuring 10 mm in length was dissected, suspended on a tissue holder and placed in a 20 ml organ bath filled with Dejalon solution. Suture was connected to a force displacement transducer and resting tension was adjusted to 1 gram. The tissue was made to contract using KCl. The findings were recorded using student physiograph purchased from Inco Biodevices, Ambala, India. Curcumin and glibenclamide was diluted with ethanol. The agonist was left in contact with tissue for a period of 90 sec, after which 3-4 times washes with Dejalon solution was given. After getting a standard contraction relaxation curve, tissue was incubated with curcumin for 10 minutes after which KCl was added. For each tracing a contact time of 90 sec was given after which uterus muscle strip was washed 3-4 times. The mechanism of action of curcumin was investigated using glibenclamide (potassium channel blocker) and methylene blue (nitric oxide blocker). After getting a standard contraction relaxation curve with KCl, tissue was incubated with glibenclamide for 5 min followed by curcumin for 10 minutes after which KCl was added. The same procedure is followed to find if methylene blue will reverse the relaxant effect of curcumin on KCl induced contraction. Samples taken from 6 goats were studied. The graphs obtained in the experiment was scanned to create jpeg picture files and then pixels were calculated using computer software image tool version 3 (university of Texas health sciences centre at St. Antonio, Texas, USA).

### Statistical analysis

Wilcoxon paired signed-rank test (non-parametric test) was used for statistical analysis since the variables showed a non-normal distribution and the comparison was made

between paired observations. A p-value of <0.05 was considered to imply significance. Measurements of KCl induced contractions were taken as the 100% and the measurements with KCl with curcumin±other agents were expressed as percentage with respect to KCl-induced contractions i.e.

$$\left[ \frac{\text{KCl} + \text{curcumin}}{\text{KCl}} \right] \times 100$$

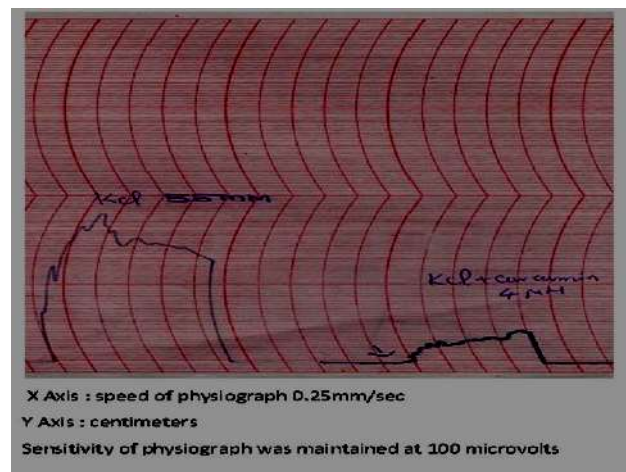
The percentage of inhibition was calculated using the formula  $100 - \left[ \frac{\text{KCl} + \text{curcumin}}{\text{KCl}} \right] \times 100$ .<sup>9</sup>

## RESULTS

One of the contraction relaxation curves obtained by using the student physiograph administration of KCl and KCl in the presence of curcumin is shown in Figure 1.

As we can see in Table 1, the ethanol which was used for dissolving the curcumin powder did not affect the height or area of KCl induced contractions. From these results it is evident that curcumin can inhibit the contractions of isolated goat uterus produced by KCl. Increasing log doses of curcumin show increased inhibition of these contraction. The height of the contractions as well the area under curve is decreased. There was difference in the height of potassium chloride (55 mM) induced contraction in the presence of curcumin 4 μM (p value=0.046) 40 μM (p value=0.028) and 400 μM (p value=0.028). There was a difference in area of potassium chloride induced contraction in the presence of curcumin 4 μM (p value=0.463) 40 μM (p value=0.027) and 400 μM (p value=0.028).

Glibenclamide did not seem to affect the action of curcumin. The decrease in the height of potassium chloride induced contraction produced by 100 μM curcumin prevailed in the presence of glibenclamide (p value=0.046) and of area under curve (p value=0.046).



**Figure 1: KCl induced contraction of goat uterine tissue alone and in presence of curcumin.**

**Table 1: The inhibition of contractions by log doses of curcumin and that the inhibition is not reversed by glibenclamide or methylene blue.**

Variables	Median	Inter quartile range		P	Median percentage inhibition
		Q1	Q3		
KCl (Ht)	26.05	21.7	33.25	0.463	10.41
KCl+Ethan (Ht)	23.80	20.5	29.55		
KCl (area)	4.10	2.9	4.5	0.463	8.22
KCl+ethan (area)	3.67	2.7	4.60		
KCl (Ht)	30.40	22.4	37.32	0.046	43.87
KCl+Cur 4 $\mu$ M (Ht)	14.65	8.9	26.05		
KCl (area)	4.61	3	5.42	0.463	13.39
KCl+Cur 4 $\mu$ M (area)	1.71	1	4.74		
KCl (Ht)	25.80	24.5	30.82	0.028	77.36
KCl+Cur 40 $\mu$ M (Ht)	3.85	2.3	5.75		
KCl (area)	3.31	3.2	3.52	0.027	90.20
KCl+Cur 40 $\mu$ M (area)	0.12	0	0.29		
KCl (Ht)	26.35	25.4	28.72	0.028	91.33
KCl+Cur 400 $\mu$ M (Ht)	0	0	0		
KCl (area)	3.55	3.1	3.68	0.028	92.69
KCl+Cur 400 $\mu$ M (area)	0	0	0		
KCl (Ht)	27.30	22.7	29.32	0.046	48.98
KCl+Cur 40 $\mu$ M+Gly (Ht)	10.05	5.8	20.35		
KCl (area)	3.49	3	3.75	0.046	54.53
KCl+Cur 40 $\mu$ M+Gly (area)	0.95	0.4	2.55		
KCl (Ht)	23.30	23.2	30.67	0.027	74.83
KCl+Cur 40 $\mu$ M+methyl (Ht)	1.48	0	6.96		
KCl (area)	3.21	2.9	3.53	0.028	61.70
KCl+Cur 40 $\mu$ M+methyl (area)	0.59	0	2.34		

Methylene blue as well did not seem to affect the action of curcumin. The decrease in the height of potassium chloride induced contraction produced by 100  $\mu$ M curcumin (p value=0.027) and area (p value=0.345) was seen even in the presence of methylene blue.

## DISCUSSION

Similar to the findings of this study, Itthipanichpong et al had observed that the extract of curcuma longa inhibited the contractions of rat uterus produced by KCl.<sup>4</sup> Moreover in this study since we have used curcumin instead of crude extract, we can confirm that this relaxant effect is due to curcumin. Thaina et al, had worked on rat uterus inducing contractions with KCl and seen that extract of curcuma aeruginosa relaxed these contractions.<sup>10</sup> Propranolol was used to study this mechanism of action, but it did not reverse the effect of the extract, proving that curcuma may not act on beta receptors. Gilani et al had found that the crude extract of curcuma longa relaxed the KCl induced contractions of jejunum and trachea.<sup>6</sup> Also the contractions of aorta and atrial muscle suppressed by the extract was comparable with the relaxant effect of verapamil.

The limitation of this study is that we could not arrive at the mechanism of action of curcumin, though we established that there is relaxation of uterus.

## CONCLUSION

From all these findings, it is likely that curcumin cause relaxation of goat uterus. Since methylene blue and glibenclamide were not able to reverse the inhibition produced by curcumin it implies curcumin may not act via the nitric oxide pathway nor does it interact with K<sub>ATP</sub> channels to relax the uterus. Mechanism of relaxation of uterus by curcumin needs further investigation

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