

## Original Article

# Effect of different curcumin dosages on human gall bladder

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Our previous study demonstrated that curcumin, an active compound of *Curcuma xanthorrhiza* and *C. domestica*, produces a positive cholekinetic effect. A 20 mg amount of curcumin is capable of contracting the gall bladder by up to 29% within an observation time of 2 h. The aim of the current study was to define the dosage of curcumin capable of producing a 50% contraction of the gall bladder, and to determine if there is a linear relationship between doubling the curcumin dosage and the doubling of gall bladder contraction. A randomised, single-blind, three-phase, crossover-designed examination was carried out on 12 healthy volunteers. Ultrasonography was carried out serially to measure the gall bladder volume. The data obtained was analysed by analysis of variance (ANOVA). The fasting volumes of gall bladders were similar ( $P > 0.50$ ), with  $17.28 \pm 5.47$  mL for 20 mg curcumin,  $18.34 \pm 3.75$  mL for 40 mg and  $18.24 \pm 3.72$  mL for 80 mg. The percentage decrease in gall bladder volume 2 h after administration of 20, 40 and 80 mg was  $34.10 \pm 10.16$ ,  $51.15 \pm 8.08$  and  $72.25 \pm 8.22$ , respectively, which was significantly different ( $P < 0.01$ ). On the basis of the present findings, it appears that the dosage of curcumin capable of producing a 50% contraction of the gall bladder was 40 mg. This study did not show any linear relationship between doubling curcumin dosage and the doubling of gall bladder contraction.

**Key words:** curcumin, dosages, gall bladder, Malaysia.

## Introduction

Medicinal plants containing curcumin as an active compound, such as *Curcuma longa* and *C. xanthorrhiza* (known as 'jamu'), are traditionally consumed by Indonesian people for their health benefits, especially in pregnant women. The crude *curcuma* species is believed to give beneficial effects in the treatment of jaundice (as cholagogum) and hepatic diseases. Our previous study demonstrated that curcumin, an active compound of *C. xanthorrhiza* and *C. domestica*, produces a positive cholekinetic effect. A 20 mg amount of curcumin is capable of contracting the gall bladder by up to 29% over a 2 h observation time.<sup>1</sup> Further dosage-response studies are needed to determine the optimal dosage of curcumin that is able to induce a 50% contraction of the human gall bladder.

The finding that curcumin causes contraction of the gall bladder indicates that this chemical may be useful in preventing gall bladder stone formation, and may be used clinically to enhance biliary flow or to push out biliary sludge in the gall bladder. It is possible that curcumin is capable of being used as a cholekinetic agent, and that gall bladder contraction of more than 29% could be reached. The present study was therefore carried out in order to determine a dosage capable of producing gall bladder contraction of around 50% and to define whether there is any linear relationship between the doubling of curcumin dosages and the doubling of gall bladder contraction.

Various studies have been conducted to define a suitable cholecystokinetic agent for preventing the formation of gall bladder stones in patients with high risk, for example, those in sepsis, long standing fasting periods or receiving total parenteral nutrition. Erythromycin,<sup>2,3</sup> fatty meals<sup>4,5</sup> and amino acids<sup>6</sup> have also been shown to stimulate gall bladder contraction with different mechanisms.

## Materials and methods

This study was conducted as a randomised, single-blind, three-phase, crossover design with a wash-out period of one week. The participants were 12 healthy volunteers (eight men and four women) aged 20 to 50 years (mean  $\pm$  SD  $30.45 \pm 5.37$  years) with weights ranging from 45 to 65 kg (mean  $\pm$  SD  $54.72 \pm 5.25$  kg) and heights ranging from 150 to 168 cm (mean  $\pm$  SD  $159 \pm 6.36$  cm). All subjects gave their informed written consent to participate in the study. The study protocol was approved by the Dean of the School of Medicine and the University Research Committee of

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University of Sumatera (Institutional Ethics Committee), Medan, Indonesia. All subjects were evaluated for general good health on the basis of medical history, physical examination, laboratory tests and ultrasonography of the upper abdomen. None of them had a history or clinical evidence of hepatobiliary or gastrointestinal disease or operations. None of the subjects took any regular medication (including 'jamu' and oral contraceptive pills) for at least 7 days prior to the study, nor were they permitted to have fatty meals before the study. The subjects were all in good health, with no jaundice and unpalpable liver and spleen. Bilirubin, Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT), alkaline phosphates, cholesterol, albumin and globulin levels were normal. Ultrasonography of the upper abdomen showed normal liver, gall bladder and biliary tract. The subject who had the ellipsoid form of gall bladder was able to participate in this study.<sup>7</sup>

The curcumin (C<sub>21</sub>H<sub>20</sub>O<sub>6</sub>) used in this study was purchased from Merck Schudhardt (Munich, Germany). The single oral dosage of curcumin or placebo (amylum; Shanghai, Java, Indonesia) was swallowed with 100 mL water.

Three diameters (length, width and depth) of the gall bladder were measured by ultrasonography to calculate its volume. The ultrasound machine used was a real-time system model SSH140A (Toshiba, Shimoishigami Ottawara, Japan) with a 3.75 MHz convex sector transducer similar to the one used in other studies.<sup>8,9</sup>

The transducer was placed in a sagittal plane in the right upper quadrant of the supine subject with the left lateral decubitus 45-degree position. Each subject was required to hold a maximum deep thoracic inhalation for maximal visualisation of the gall bladder, and for standardisation of gall bladder measurements.<sup>10</sup> The photograph of the gall bladder was taken when the greatest size of the gall bladder was obtained. The image was then frozen on the oscilloscope screen and the greatest length of the gall bladder was meas-

ured on screen with a previously standardised electronic caliper. The transducer was then rotated 90 degrees to obtain the image of the short axis of the gall bladder with the greatest transverse (width) and anteroposterior (depth) dimensions.

After an overnight fast, the length, width and depth of gall bladder were measured at 8.00 AM (as zero time) and then at 0.5, 1.0, 1.5, and 2.0 h after administration of 20, 40 or 80 mg of curcumin. The gall bladder volume (GV; measured in mL) was calculated using an ellipsoid method.<sup>9,11</sup>

$$GV = 0.52 \times \text{length} \times \text{width} \times \text{depth}$$

To express the gall bladder contraction, it was recorded as the percentage reduction in gall bladder volume (%GV) compared to the fasting gall bladder volume (GV<sub>0,0</sub>)

$$\%GV = [(GV_{0,0} - GV_t)/GV_{0,0}] \times 100\%$$

where GV<sub>0,0</sub> = fasting gall bladder volume and GV<sub>t</sub> = gall bladder volume at the time measured. If gall bladder reduction was observed it was noted as positive contraction and *vice versa*.

Data obtained were expressed as mean ± standard deviation and statistically analysed by analysis of variance (ANOVA), with *P*-values less than 0.05 regarded as statistically significant.

## Results

The fasting gall bladder volumes before taking 20 mg curcumin (17.28 ± 5.47 mL), 40 mg curcumin (18.37 ± 3.75 mL) and 80 mg curcumin (18.24 ± 3.72 mL) were not statistically different (*P* > 0.50; Table 1). After curcumin was administered at the three different doses, gall bladder volume was reduced over the 2 h observation time (Table 1; Fig. 1). A significant difference in gall bladder volume (*P* < 0.05) was also observed between the three groups 1 h after curcumin administration (Table 2).

**Table 1.** Gall bladder volume after administration of 20, 40 and 80 mg doses curcumin

Dosage (mg)	Gall bladder volume (mL) at					<i>P</i> -value
	0.0 h	0.5 h	1.0 h	1.5 h	2.0 h	
20	17.28 ± 5.47	14.12 ± 4.57	13.79 ± 3.36	12.49 ± 3.62	11.20 ± 3.17	>0.10
40	18.34 ± 3.75	14.60 ± 3.37	12.49 ± 1.88	11.40 ± 2.25	8.92 ± 1.87	<0.01
80	18.24 ± 3.72	15.64 ± 2.75	10.97 ± 3.20	7.72 ± 2.62	4.79 ± 1.83	<0.01
<i>P</i> -value	>0.50	>0.50	>0.20	<0.01	<0.01	

**Table 2.** Percentage gall bladder contraction after administration of 20, 40 and 80 mg curcumin

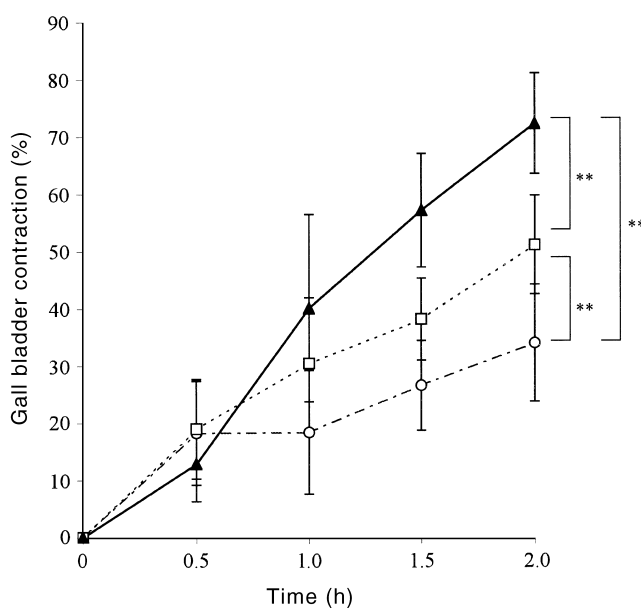
Dosage (mg)	Time (h)				<i>P</i> -value
	0.5	1.0	1.5	2.0	
20	18.35 ± 9.12	18.48 ± 10.72	26.67 ± 7.78	34.10 ± 10.16	<0.01
40	18.85 ± 8.58	30.62 ± 11.25	38.23 ± 7.21	51.15 ± 8.08	<0.01
80	12.92 ± 6.49	40.21 ± 16.16	57.28 ± 9.82	72.25 ± 8.22	<0.01
<i>P</i> -value	>0.20	<0.01	<0.01	<0.01	

Correspondingly, there was marked increase in gall bladder contraction 1 h after administration of 20, 40 and 80 mg curcumin. This was indicated by the percentage of gall bladder volume reduced, that is,  $18.48 \pm 10.72$  for 20 mg curcumin,  $30.62 \pm 11.25$  for 40 mg curcumin and  $40.21 \pm 16.16$  for 80 mg curcumin ( $P < 0.01$  by ANOVA). The percentage decrease in gall bladder volume 2 h after curcumin administration was  $34.10 \pm 10.16$  for 20 mg curcumin,  $51.15 \pm 8.08$  for 40 mg curcumin and  $72.25 \pm 8.22$  for 80 mg curcumin, which was statistically significantly different ( $P < 0.01$  by ANOVA). This study did not show a linear relationship between the doubling of curcumin dosage and the doubling of gall bladder contraction. Instead, 40mg curcumin was able to produce a 50% contraction of the gall bladder, but doubling the curcumin dosage to 80 mg did not double gall bladder contraction to 100% (Figs 1,2). During this study and the following day, no side effects were reported by the participants.

### Discussion

The fasting gall bladder volumes demonstrated in the present study ( $\pm 17$  mL) were within the range of values reported by Everson *et al.* ( $16.7 \pm 2.5$  mL).<sup>12</sup>

This single-blind crossover study showed that a single oral dosage of 20, 40 and 80 mg curcumin stimulated contraction of the human gall bladder. Gall bladder volume was reduced over the 2 h time interval following curcumin administration (Fig. 1). In addition, there was a steady decrease in gall bladder volume over the same 2 h time interval. A significant difference ( $P < 0.01$ ) in gall bladder volume was observed between the three groups 1 h after drug administration (Table 1). It is worthwhile to note that



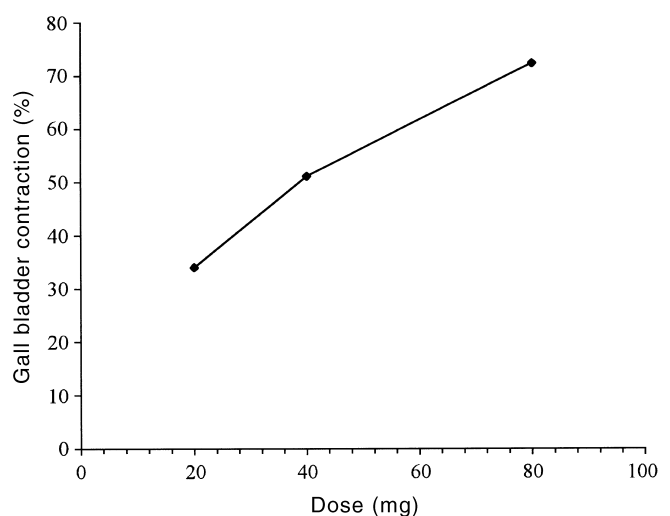
**Figure 1.** Percentage gall bladder contraction over time after administration of 20, 40 and 80 mg curcumin. (—○—) 20 mg curcumin; (··□··) 40 mg curcumin; (—▲—) 80 mg curcumin. \*\* $P < 0.01$ .

no side effects due to curcumin were reported by the participants of this study.

Curcumin dosages of 20, 40 and 80 mg are capable of contracting the gall bladder by 30, 50 and 70%, respectively. This study does not show a linear relationship between the doubling of curcumin dosage and gall bladder contraction. That is, 40 mg curcumin was able to contract the gall bladder by 50%, but doubling the curcumin dosage to 80 mg did not cause a corresponding doubling of gall bladder contraction to 100%. Other researchers have also stated that they could not cause contraction of the gall bladder by up to 100% using different cholekinetic agents. Cholecystokinin (CCK), fat and amino acids are only capable of contracting the gall bladder by 92, 85 and 80%, respectively.<sup>5,13,14</sup> Physiologically, the human gall bladder contracts and relaxes periodically.<sup>15</sup> This may explain the failure of curcumin, CCK, fat and amino acids to produce further reductions in gall bladder size, that is, up to 100%.

Marzio *et al.* investigated the effect of a graded dosage of intravenous CCK.<sup>13</sup> The maximum reduction in gall bladder volume was noted 15 min after the infusion started. At 0.002 International Dose Unit (IDU) CCK, a  $33 \pm 4\%$  reduction of fasting volume was reached. A dosage of 0.004 IDU gave  $56 \pm 7\%$  reduction, 0.008 IDU gave a  $77 \pm 4\%$  reduction, and with 0.016 IDU CCK, a reduction of  $92 \pm 5\%$  was achieved.

Sturdevant *et al.* studied the effect of graded dosages of intravenous OP-CCK (the C-terminal octapeptide of cholecystokinin) on human gall bladder volume in 18 healthy male subjects.<sup>16</sup> The 18 subjects were divided into six groups of three subjects each. Each group was studied at one of the following dosages: 2.5, 5, 10, 20, 40 or 80 ng/kg OP-CCK. A 20 ng/kg dosage of OP-CCK produced a mean peak decrease in gall bladder size of 44%. The 40 and 80 ng/kg dosages produced mean peak decreases of 33 and 28%, respectively. The 2.5, 5 and 10 ng/kg dosages produced similar mean peak decreases (11, 18 and 14%, respectively),



**Figure 2.** Percentage gall bladder contraction after administration of 20, 40 and 80 mg curcumin.

which were less than the mean peak decreases of the larger three dosages.

The effect of rapid intravenous infusions of amino acid solutions was studied by Zoli *et al.* in eight normal subjects.<sup>14</sup> Four dosages were tested (250, 125 and 50 mL over 5 min). Gall bladder emptying, as measured by ultrasound, depended on the amount of amino acid infused. The percentage of emptying produced was determined as 75% with 250 mL, 69% with 125 mL and 19% with 50 mL.

In order to confirm the benefit of a substance for diminishing the risk gall bladder stone development, Kakkos *et al.*<sup>2</sup> and Tsiaoussis *et al.*<sup>17</sup> found that 200 mg of intravenous the cholekinetic agent erythromycin (7 mg/kg body weight, administered intravenously) is capable of producing gall bladder contractions of 18.5 and 42%, respectively. Catnach *et al.*<sup>3</sup> and Arienti *et al.*<sup>18</sup> studied the effect of 500 mg oral erythromycin on gall bladder contraction during a fasting state. They reported 26 and 66% reductions in gall bladder fasting volumes, respectively, 2 h after erythromycin was administered. The maximal contraction effect of high-risk intravenous erythromycin 2 h after administration is not much different from that of 40 mg curcumin (51.15%), and is less than the effect of 80 mg curcumin (72.25%) demonstrated in this study (Table 1). This result indicates that curcumin might be useful as a cholekinetic agent, and therefore in preventing gall bladder stone formation.

Although curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), erythromycin (with the macrolide ring) and amino acids could all be used as compounds in preventing the development of gall bladder stones, it seems that the effects of these drugs on the gall bladder have no structure-activity relationships. However, it is known that consuming erythromycin in dosages for antimicrobial purposes will produce gastrointestinal side effects. In Indonesia, medicinal plants containing curcumin, such as cholagogum, have been used traditionally to prevent gall bladder stones.<sup>19</sup> In our study, no side effects were reported by the subjects who participated.

The findings of the present study are in agreement with those reported previously by Thamlikitkul *et al.*<sup>20</sup> This Thai study group treated their dyspepsia patients with two capsules of 250 mg *C. domestica val.* four times a day for 7 days. The dosage used in their study is therefore approximately 50 mg curcumin four times a day. Furthermore, they also mentioned that acute and subacute toxicity tests of *C. domestica val.*, carried out by the Division of Medical Research, National Institute of Health, Thailand, showed no toxicity.<sup>20</sup>

In order to study the effect of a drug and a cholekinetic agent on human gall bladder contraction, it is necessary to determine the residual gall bladder volume before administration of the drug. It seems that the optimal dosage of a cholekinetic agent is a dosage that is capable of contracting the gall bladder by 50%. In our study, we found that the optimal dosage of curcumin was 40%. Therefore, our next studies will be to determine the effect of single and multiple dosages of curcumin on human gall bladder, and to observe

the effect of a meal on the action of curcumin on human gall bladder using an oral dosage of 40 mg curcumin.

## Conclusion

No linear relationship was found between doubling of curcumin dosage and doubling of gall bladder contraction. The optimal dosage of curcumin capable of producing a 50% contraction was 40 mg.

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