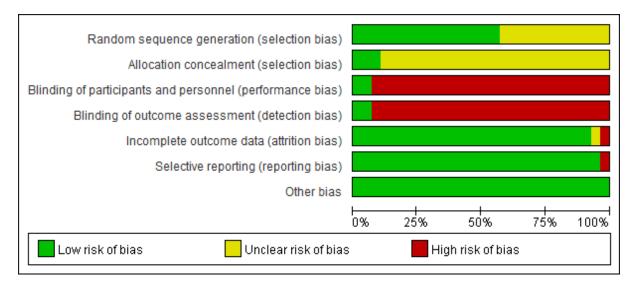
# SUPPLEMENTARY INFORMATION

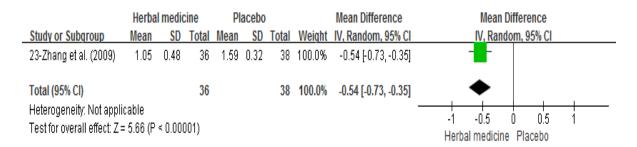
# TITLE: Herbal Medicine for Adult Patients with Cough Variant Asthma: A Systematic Review and Meta-analysis

(List available Supplementary Information items in the following order)

Figure S1- Risk of bias graph



**Figure S2-** Forrest plot of CD4+/CD8+ ratio



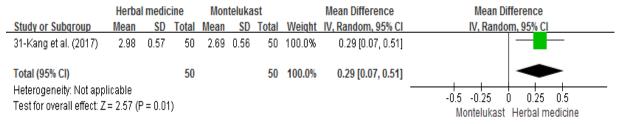
**Figure S3-** Forrest plot of Forced Expiratory Volume in One Second (FEV1)

# A Herbal Medicine versus Montelukast

# $(1) \text{ FEV}_1 (\%)$

	Herbal	medic	ine	Montelukast Mean Diff		Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
27-Zhang et al. (2014)	90.67	4.2	24	87.83	4.6	24	100.0%	2.84 [0.35, 5.33]	-	
Total (95% CI)			24			24	100.0%	2.84 [0.35, 5.33]	•	
Heterogeneity: Not applicable Test for overall effect: Z = 2.23 (P = 0.03)								-10 -5 0 5 10		

## (2) FEV<sub>1</sub> (L)



# B Herbal Medicine versus ICS plus Bronchodilator

# (1) $FEV_1$ (%)

	Herba	al medio	cine	ICS plus Bronchodilator		ICS plus Bronchodilator Mean Differe				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
42-Zhao et al. (2015)	89.7	6.9	43	83.6	7.2	40	31.3%	6.10 [3.06, 9.14]	_ <del>-</del>		
44-Sun et al. (2016)	79.9	4.3	32	76.5	3.3	32	47.8%	3.40 [1.52, 5.28]	<del>-   -</del>		
46-Lu et al. (2016)	96.55	15.68	40	92.72	12.2	40	11.4%	3.83 [-2.33, 9.99]	<del></del>		
49-Lu et al. (2017)	95.16	13.21	30	96.66	13.91	30	9.5%	-1.50 [-8.36, 5.36]			
Total (95% CI)			145			142	100.0%	3.83 [1.55, 6.10]	•		
Heterogeneity: Tau² = 1.90; Chi² = 4.66, df = 3 (P = 0.20); I² = 36%  Test for overall effect: Z = 3.30 (P = 0.0010)  ICS plus Bronchodilator Herbal medicine											

### (2) FEV<sub>1</sub>(L)

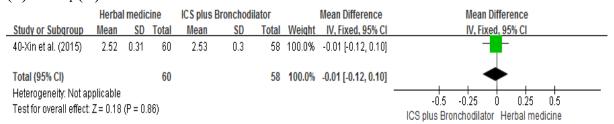


Figure S3 – A and B, Forrest plot of Forced Expiratory Volume in One Second (FEV1).

Figure S4- Forrest plot of effective rate

#### A Herbal Medicine versus Placebo

	Herbal Me	dicine	Place	bo	Risk Ratio			Ris	k Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rar	ndom, 95% CI	
Wang et al. (2017)	25	40	7	32	100.0%	2.86 [1.42, 5.74]				
Total (95% CI)		40		32	100.0%	2.86 [1.42, 5.74]			•	
Total events	25		7							
Heterogeneity: Not applicable Test for overall effect: Z = 2.95 (P = 0.003)							0.001	0.1 Placeb	1 10 o Herbal Medic	1000

#### B Herbal Medicine versus Montelukast

	Herbal med	licine	ine Montelukast		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
25-Miao et al. (2012)	45	52	18	26	12.6%	1.25 [0.95, 1.65]	<del>  • </del>
26-Cong et al. (2013)	23	29	11	28	6.1%	2.02 [1.23, 3.32]	<del></del>
27-Zhang et al. (2014)	15	24	9	24	4.5%	1.67 [0.91, 3.04]	+
29-Wu et al. (2016)	30	40	25	40	11.7%	1.20 [0.89, 1.62]	<del>  •</del>
30-Yu et al. (2016)	23	30	13	30	6.9%	1.77 [1.12, 2.79]	
31-Kang et al. (2017)	44	50	22	50	10.6%	2.00 [1.44, 2.78]	
32-Sun et al. (2017)	37	49	21	49	9.5%	1.76 [1.23, 2.53]	
33-Teng et al. (2017)	23	30	13	30	6.9%	1.77 [1.12, 2.79]	<del>-</del>
34-Yan et al. (2017)	42	45	34	45	17.4%	1.24 [1.03, 1.48]	
35-Cao et al. (2018)	33	38	26	39	13.7%	1.30 [1.01, 1.68]	•
Total (95% CI)		387		361	100.0%	1.48 [1.29, 1.71]	•
Total events	315		192				
Heterogeneity: Tau² = 0.	02; Chi² = 16.	01, df=	9 (P = 0.0)	7); I² = 4	4%	-	0.5 0.7 1 1.5 2
Test for overall effect: Z =	= 5.47 (P < 0.0	Montelukast Herbal medicine					

### C Herbal Medicine versus ICS plus Bronchodilator

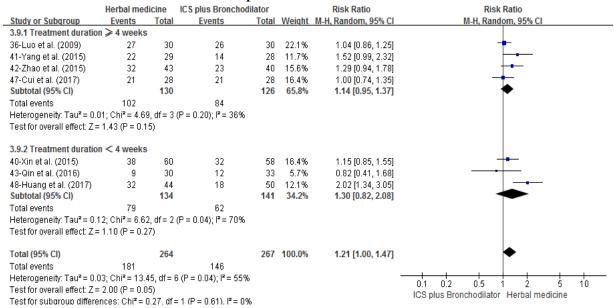


Figure S4 - A, B and C, Forrest plot of effective rate.

**Figure S5-** Sensitivity analyses of FEV1 (%) in Herbal Medicine versus ICS plus Bronchodilator

	Herb	Herbal Medicine ICS plus Br			ICS plus Bronchodilator Mean Difference		Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
42-Zhao et al. (2015)	89.7	6.9	43	83.6	7.2	40	48.6%	6.10 [3.06, 9.14]	-
46-Lu et al. (2016)	96.55	15.68	40	92.72	12.2	40	27.4%	3.83 [-2.33, 9.99]	+-
49-Lu et al. (2017)	95.16	13.21	30	96.66	13.91	30	24.0%	-1.50 [-8.36, 5.36]	-
Total (95% CI)			113			110	100.0%	3.66 [-0.58, 7.89]	•
Heterogeneity: Tau <sup>2</sup> = 7.19; Chi <sup>2</sup> = 4.03, df = 2 (P = 0.13); I <sup>2</sup> = 50%								-20 -10 0 10 20	
Test for overall effect: Z = 1.69 (P = 0.09)									ICS plus Bronchodilator Herbal Medicine

**Table S1-** GRADE evaluation of Herbal Medicine vs. Montelukast

Outcome	Absolute	Effect	Relative Effect	<b>Certainty of</b>		
	With	Without	(95% CI)	the Evidence		
	CHM	CHM	No. of	(GRADE)		
			Participants & Studies			
			MD 2.38			
LCQ	15.31	13.21	(1.32, 3.44)			
Scale from: 3 to 21 <sup>b</sup>	Average d	lifference:		$\oplus \oplus \bigcirc \bigcirc$		
Treatment duration:	2.38 point	ts higher	Based on data from	LOW <sup>1,2</sup>		
Range 2 to 4 weeks	(95% CI: 1		422 patients in 6			
	to 3.44 hig	her)	studies SMD -0.80			
COO			(-1.08, -0.51)			
CSS Scale from: 0 to 5 <sup>a</sup>			(1.00, 0.31)	$\Delta \Delta \Delta \Delta \Delta$		
Treatment duration:	_		Based on data from	0 $0$ $0$ $0$ $0$ $0$ $0$ $0$ $0$ $0$		
Range 2 to 8 weeks			454 patients in 6			
			studies			
	2.98	2.69	MD 0.29			
FEV <sub>1</sub> (L)	Average d	lifference:	(0.07 to 0.51)			
Treatment duration:	0.29 litres			$\oplus \oplus \bigcirc \bigcirc$		
Range 4 weeks		J	Based on data from 100 patients in 1	LOW 1,3		
	(95% CI: 0	•	study			
	to 0.51 hig	Í				
VAS	2.61	3.95	MD -1.34			
Scale from: 0 to 10 <sup>a</sup>	Average d		(-1.82, -0.86)	<b>0</b> 00		
Treatment duration:	1.34 point	ts lower	Based on data from	LOW 1,3		
Range 4 weeks	(05% CI: 1	.82 lower to	77 patients in 1	20 11		
	0.86 lower		study			
	78	50	DD 1 40			
	per 100	per 100	<b>RR 1.48</b> (1.29 to 1.71)			
Effective rate		e: 28 more	(1.2) (0 1./1)	⊕⊕○○ MODERATE <sup>1</sup>		
Treatment duration:	per 100 pa	atients	Based on data from			
Range 2 to 8 weeks	(95% CI: 1	5 to 38	748 patients in 10			
	`	00 patients)	studies			
The risk in the intervention of			interval) is based on the a	saymad midtain the comm		

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CHM, Chinese herbal medicine; CI, confidence interval; CSS, Cough symptom score; FEV<sub>1</sub>, forced expiratory volume-one second; LCQ, Leicester Cough Questionnaire; MD, mean difference; RR, risk ratio; SMD, standardised mean difference; VAS, Visual Analogue Scale.

- $a.\ Higher\ scores\ indicate\ more\ symptoms;\ b.\ Higher\ scores\ indicate\ less\ symptoms.$ 
  - 1. Unclear sequence generation and allocation concealment. Lack of blinding of participants and personnel;
  - 2. Considerable statistical heterogeneity;
  - 3. Small sample size.

**Table S2-** GRADE evaluation of Herbal Medicine vs. ICS plus Bronchodilators

Outcome	Absolute	Effect	Relative Effect	Certainty of	
	With	Without	(95% CI)	the Evidence	
	CHM	CHM	No. of Participants	(GRADE)	
			& Studies		
1.00	15.95	14.93	MD 1.02		
LCQ Scale from: 3 to 21 <sup>b</sup> Treatment duration:	Average d 1.02 point		(0.01, 2.05)	⊕⊕⊖⊖ LOW <sup>1,3</sup>	
Range 2 weeks	(95% CI: 0 2.05 higher		Based on data from 62 patients in 1 study		
CSS Scale from: 0 to 5 <sup>a</sup>			SMD -0.25 SD (-0.89, 0.39)	<b>0</b> 00	
Treatment duration: Range 4 to 8 weeks	-		Based on data from 369 patients in 5 studies	LOW 1,2	
	90.33	87.37	MD 3.83		
FEV <sub>1</sub> (%) Treatment duration:	Average d 3.83% hig		(1.55 to 6.10)	⊕⊕○○	
Range 2 to 12 weeks	(95% CI: 1 higher to 6 higher)		Based on data from 287 patients in 4 studies	LOW 1,3	
	2.78	3.48	MD -0.67	Ф000	
VAS Scale from: 0 to 10 <sup>a</sup>	Average d		(-1.80, 0.46)		
Treatment duration:	0.67 point	s lower	Based on data from	VERY	
Range 2 to 4 weeks	0.46 higher		281 patients in 4 studies	LOW 1,2,3	
	69	55	RR 1.21		
Effective rate	per 100 Difference	per 100 e: 14 more	(1.00 to 1.47)		
Treatment duration:	per 100 pa		Based on data from	⊕⊕⊖⊖ LOW <sup>1,2</sup>	
Range 2 to 8 weeks	(95% CI: 0 per 100 pat	to 26 more tients)	531 patients in 7 studies		

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CHM, Chinese herbal medicine; CI, confidence interval; CSS, Cough symptom score; FEV<sub>1</sub>, forced expiratory volume-one second; LCQ, Leicester Cough Questionnaire; MD, mean difference; RR, risk ratio; SMD, standardised mean difference; VAS, Visual Analogue Scale.

- a. Higher scores indicate more symptoms; b. Higher scores indicate less symptoms.
  - 1. Unclear sequence generation and allocation concealment. Lack of blinding of participants and personnel;
  - 2. Considerable statistical heterogeneity;
  - 3. Small sample size.

Table S3- GRADE evaluation of Herbal Medicine vs. Placebo

Outcome	Absolute	Effect	Relative Effect	Certainty of		
	With	Without	(95% CI)	the Evidence		
	CHM	CHM	No. of	(GRADE)		
			Participants & Studies			
CSS	2.35	3.5	MD -1.15			
Scale from: 0 to 5 <sup>a</sup> Treatment duration:	Average d 1.15 point		(-1.67, -0.63) Based on data from	⊕⊕⊕⊖ MODERATE <sup>1</sup>		
Range 2 weeks	(95% CI: 1 0.63 lower)	.67 lower to	72 patients in 1 study			
VA C	3.08	4.84	MD -1.76			
VAS Scale from: 0 to 10 <sup>a</sup>	Average d		(-2.66, -0.86)	$\oplus \oplus \oplus \bigcirc$		
Treatment duration:	1.76 point	s lower	Based on data from	MODERATE <sup>1</sup>		
Range 2 weeks	(95% CI: 2 0.86 lower)	.66 lower to	72 patients in 1 study			
	1.05	1.59	MD -0.54	$\Theta \oplus \Theta \bigcirc$		
CD4+/CD8+ ratio	Average d		(-0.73, -0.35)			
Treatment duration: Range 8 weeks	0.54 lower	r	Based on data from	MODERATE <sup>1</sup>		
range o weeks	(95% CI: 0 0.35 lower)	.73 lower to	74 patients in 1 study			
	63	22	RR 2.86			
Effective rate	per 100	per 100	(1.42 to 5.74)	⊕⊕⊕⊖ MODERATE <sup>1</sup>		
Treatment duration:	Difference per 100 pa					
Range 2 weeks	per 100 pa	11101118	Based on data from			
		00 patients)	72 patients in 1 study			

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CHM, Chinese herbal medicine; CI, confidence interval; CSS, Cough symptom score; MD, mean difference; RR, risk ratio; VAS, Visual Analogue Scale.

a. Higher scores indicate more symptoms.

<sup>1.</sup> Small sample size.