Zhu et al. 2008	Not stated	Multi-center, randomized, control study	Medilac-S or Bifico; orally	2 capsules t.i.d. (3.0×10^9 cfu bacteria/day; 3.0×10^8 cfu R0179/day); 2 weeks	158 patients with IBS-diarrhea divided in 2 groups of 79	All groups combined: 101 M / 57 F; 44 ± 12 yrs (18-65 yrs)	Evaluate the efficacy and safety of Medilac-S and BIFICO	No severe adverse events were reported; 3 cases of mild adverse events (2 headache and 1 low back pain cases)
Liang. 2009	Mar 2006 to Sep. 2007	Randomized with active control	Medilac-S and Levofloxacin or Medilac-S or Lvofloxacin orally.	1 capsule t.i.d. (1.5×10^9 cfu bacteria/day; 1.5×10^8 cfu R0179/day); 3-5 days	173 patients with acute diarrhea (60 in the combined treatment group, 55 in Medilac-S group and 58 in Levofloxacin group)	All groups combined: 68 M / 105 F; 28-60 yrs	Observe the effect of combination of Medilac-S and levofloxacin capsule in the treatment of acute infectious diarrhea	Not stated
Liu et al. 2009	Sep. 2006 to Mar. 2007	Randomized with active control	Triple therapy (esomeprazole, clarithromycin, and amoxicillin) or triple therapy + Medilac-S; orally	1 capsule t.i.d. (1.5×10^9 cfu bacteria/day; 1.5×10^8 cfu R0179/day); 2 weeks	80 patients with peptic ulcer and 120 patients with chronic gastritis randomly divided in 2 groups of 100 people	All groups combined: 109 M / 91 F; 44.30 ± 9.33 yrs	Observe the eradication rate and side-effect of triple therapy on anti-*Helicobacter pylori*	Reduction of the adverse reactions of the treatment when using Medilac-S
Qin and Bai. 2009	Aug. 2007 to Feb. 2008	Randomized with active control	Medilac-S alone (A) or Trimebutine maleate alone (B)or combination of both; orally (C)	1 capsule t.i.d. (1.5×10^9 cfu bacteria/day; 1.5×10^8 cfu R0179/day); 2 weeks	86 patients with diarrhea-predominant IBS (respectively 32, 28 and 26 in groups A,B,C)	All groups combined: 42 M / 44 F; 41.0 ± 45 yrs (19-66 yrs)	Evaluate the efficacy of combination of Medilac-S with Trimebutine Maleate for diarrhea-predominant IBS	No side effects were reported in the Medilac-S alone group
Sun 2009	Not stated	Randomized with active control	Medilac-S, and mesalazine vs. mesalazine only; orally	2 capsules t.i.d. (3.0×10^9 cfu bacteria/day; 3.0×10^8 cfu R0179/day); 12 weeks	92 patients with mild to moderate ulcerative colitis (44 patients in the treatment group and 48 in control)	All groups combined: 42 M / 50 F; 41 ± 12 yrs	Improvement of mesalazine treatment of ulcerative colitis	No serious adverse reactions were reported

Tang et al. 2009	Jan. 2007 to Dec. 2007	Randomized with active control	Medilac-S and Liuwei-anxiao or liuwei anxiao alone; orally	1 capsule t.i.d. (1.5×10^9 cfu bacteria/day; $1.5x10^8$ cfu R0179/day); 4 weeks	65 patients with functional constipation (33 in combination therapy group and 32 in control group)	11 M / 21 F; 18-69 yrs	12 M / 21 F; 18-67 yrs	Evaluate the efficacy and safety of Medilac-S and Liuwei—Anxiao capsules in patients with functional constipation	No intervention-related adverse reactions were reported
Zhang et al. 2009	Sep. 2007 to Apr. 2008	Randomized with active control	Medilac-S and pinevarium bromide or pinevarium bromide alone; orally	1 capsule t.i.d. (1.5×10^9 cfu bacteria/day; $1.5x10^8$ cfu R0179/day); 4 weeks	60 patients with IBS-diarrhea divided in 2 groups of 30	11 M / 19 F; 36 ± 13 yrs (22-63 yrs)	10 M / 20 F; 36 ± 15 yrs (20-66 yrs)	Evaluate the clinical efficacy of pinaverium bromide alone or combination with Medilac-S in relieving symptoms in patients with IBS-D	No intervention-related adverse reactions were reported
Lee *et al.*, 2010	Not stated	Prospective, randomized, controlled and investigator blinded	Medilac-DS or placebo; orally. 2 doses of sodium phosphate for both groups, just before colonoscopy; orally	1 capsule t.i.d. (3.0×10^9 cfu/day); 2 weeks	104 patients with constipation (51 in treatment group and 53 in control) and 107 patients with normal bowel movement (53 in treatment group and 54 in control)	48 M / 5 F; 42.2±11.7 yrs in the constipation group 50 M / 4 F; 41.7±10.8 yrs in the normal bowel group		Evaluate the clinical efficacy of sodium phosphate in combination with Medilac-S in relieving symptoms in patients with IBS-D	No related adverse reactions were reported
Luo, Hou & Ma. 2011	2005 to 2009	Randomized with active control	Stilamin or Stilamin and Medilac-S; orally.	1 capsule t.i.d. (1.5×10^9 cfu bacteria/day; 1.510^8 cfu R0179/day); 5-10 days	80 patients with severe acute pancreatitis, 35 in Stilamin treated group and 45 in the combined treatment group	All groups combined: 46 M / 34 F; 28-78 yrs		Study the clinical efficacy of Stilam in combination with Medilac-S in treatment of severe acute pancreatitis	Not stated

Hanifi et al.	2012	Randomized, double blind, placebo controlled	*B. subtilis* R0179 and placebo	$0.1x10^9$ cfu/day, $1x10^9$ cfu/day, $10x10^9$ cfu/day,	81 healthy patients 18-50 years old, 61 in combined treatment groups 20 in placebo.	9M, 11F; 23 years (20-46)	$0.1x10^9$ cfu/day, 8M, 13 F; 23 yrs (20-49)	Safety study	1 adverse event unrelated to the bacteria (hypertension)
							$1x10^9$ cfu/day, 12M, 8F; 22 yrs (20-31)		
							$10x10^9$ cfu/day, 10M, 10F; 23 yrs (19-46)		

t.i.d: Three times a day

In 2018, a new systematic literature search was conducted on Medilac-S containing $5x10^7$ cfu *B. subtilis* R0179 per capsule to evaluate the safety and efficacy in a Chinese population with ulcerative colitis (Sohail et al. 2018). Fifty-three clinical trials with a total of 3984 participants were identified and included in the review. The primary outcome was the induction of clinical remission and the secondary outcomes included changes in Sutherland index, endoscopic and histological scores, proportion of reported clinical symptoms and adverse events (AEs).

All studies contained a control arm providing only conventional oral medication (aminosalicylates) and a treatment arm providing the same conventional medication with MedilacS®. Treatment periods ranged from 4 to 96 weeks. Twelve studies included a third study arm which was not incorporated into the study analysis as a comparator because it incorporated the use of a different product, an herbal remedy and/or an enema (Chen et al.2017, Liu 2014, Qin 2015, Tan et al. 2008, Tang et al. 2008, Xu and Cui 2009, Yang et al. 2008, Zhang et al. 2010, Zhu et al. 2013, Zhuo et al. 2016). Nine studies included a post-treatment follow-up period of 8, 26, or 52 weeks to track the maintenance of symptom remission (Chen 2007, Jiang 2013, Li et al. 2006, Liu and Yao 2012, Miao 2014, Qin et al. 2010, Wang 2013, Xiao 2014, Zeng 2008), and one study, Wang et al. 2016, evaluated the maintenance of remission alone. Study characteristics and outcomes are presented in Table 18.

Table 18 : Characteristics of included studies

Trial Reference	Participant evaluated	Medication	Dose	*B. subtilis* dose	Treatment duration week	Follow-up period week	Outcome analyzed
Xiang and Feng 2006	46	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	4	NR	1, 4, 6
Li et al. 2006	50	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	12	26	1, 5
Wang and Lui 2007	36	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	4	NR	1, 6
Chen 2007	47	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	12	26	1, 4, 5, 6
Yang et al. 2008	52	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	4	NR	1
Yuan et al. 2008	40	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	¨12	26	1,4, 6
Zeng 2008	49	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	12	NR	1,5
Tan et al. 2008	20	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	4	NR	2,3,6,7
Tang et al. 2008	104	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	4	NR	1
Guo and Sun 2009	92	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	12	NR	1,6
Liu et al. 2009	43	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	8	NR	1,6
Xu and Cui 2009	56	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	4	NR	1
Qin et al. 2010	20	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	4	NR	3,7
Qin et al. 2010	64	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	8	26	5,6
Zhang et al. 2010	54	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	12	NR	1
Li 2011	62	Mesalazine	60 mg/d		12	NR	1
Lu and Lei 2011	132	Olsalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	12	NR	1,6
Gu 2012	62	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	12	NR	1,6
Liu and Yao 2012	139	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	Unknown	Unknown	1,5
Meng 2012	90	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	8	NR	1,2
Jiang 2013	110	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	16	52	1,5,6
Li 2013	124	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	12	NR	1,6
Wang 2013	84	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	16	52	1,5
Zhang 2013	78	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	4	NR	1,4,6
Zhang 2013	68	Olsalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	12	NR	1,6
Zhu et al. 2013	44	Olsalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	96	NR	2,3

Chen 2014	100	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	6	NR	1,4
Jin et al. 2014	226	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	12	NR	1,6
Li 2014	147	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	4	NR	1
Liu 2014	62	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	4	NR	1,2,3
Liu and Li 2014	101	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	6	NR	1,2,4
Miao 2014	72	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	8	26	1,5,6
Shen 2014	96	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	6	NR	1,4,6
Tan et al. 2014	20	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	4	NR	2,3,6,7
Wang and Li 2014	100	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	8	NR	1,2
Xiao 2014	63	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	8	8	5,6
Xu 2014	60	Basalazide	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	12	NR	1,4,6
Yang 2014	80	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	Unknown	NR	1
Duan et al. 2015	64	SASP	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	4	NR	2,3,6,7
Qin 2015	56	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	8	NR	4
Su 2015	120	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	12	NR	1,6
He et al. 2016	52	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	12	NR	1,6
Li et al. 2016	100	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	8	NR	1,4,6
Liang et al. 2016	92	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	16	NR	1
Luo 2016	56	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	8	NR	1,4,6
Wang et al. 2016	65	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	26	NR	5,6
Zhang et al. 2016	70	Mesalazine	60 mg/day		12	NR	1
Zhang et al. 2016	60	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	12	NR	1
Zhao and Zhang 2016	62	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	24	NR	1
Zheng et al. 2016	118	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	4	NR	1,6
Zhuo et al. 2016	40	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	8	NR	1,3,6
Bu et al. 2017	68	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	16	NR	1,6
Chen et al. 2017	68	Mesalazine	$3x10^9$ cfu/d	$0.3 x10^9$ cfu/d	8	NR	1,6,7

Outcomes analyzed: (1) Clinical Efficacy; (2) Histological Assessment; (3) Endoscopy Assessment; (4) Clinical Symptoms; (5) Maintenance of Remission; (6) Adverse Events; (7) Sutherland Index. NR: Not reported. SASP: Sulfasalazine.

As indicated in blue lines in Table 18, 30 RCTs reported adverse events affecting 2430 participants, 1195 in the control group and 1235 in the treatment group. A meta-analysis including these 30 RCTs was completed and represented in the figure below, which shows that the proportion of individuals in the treatment arms reporting adverse events is estimated to be 72% of the proportion of individuals reporting adverse events in the control arms.

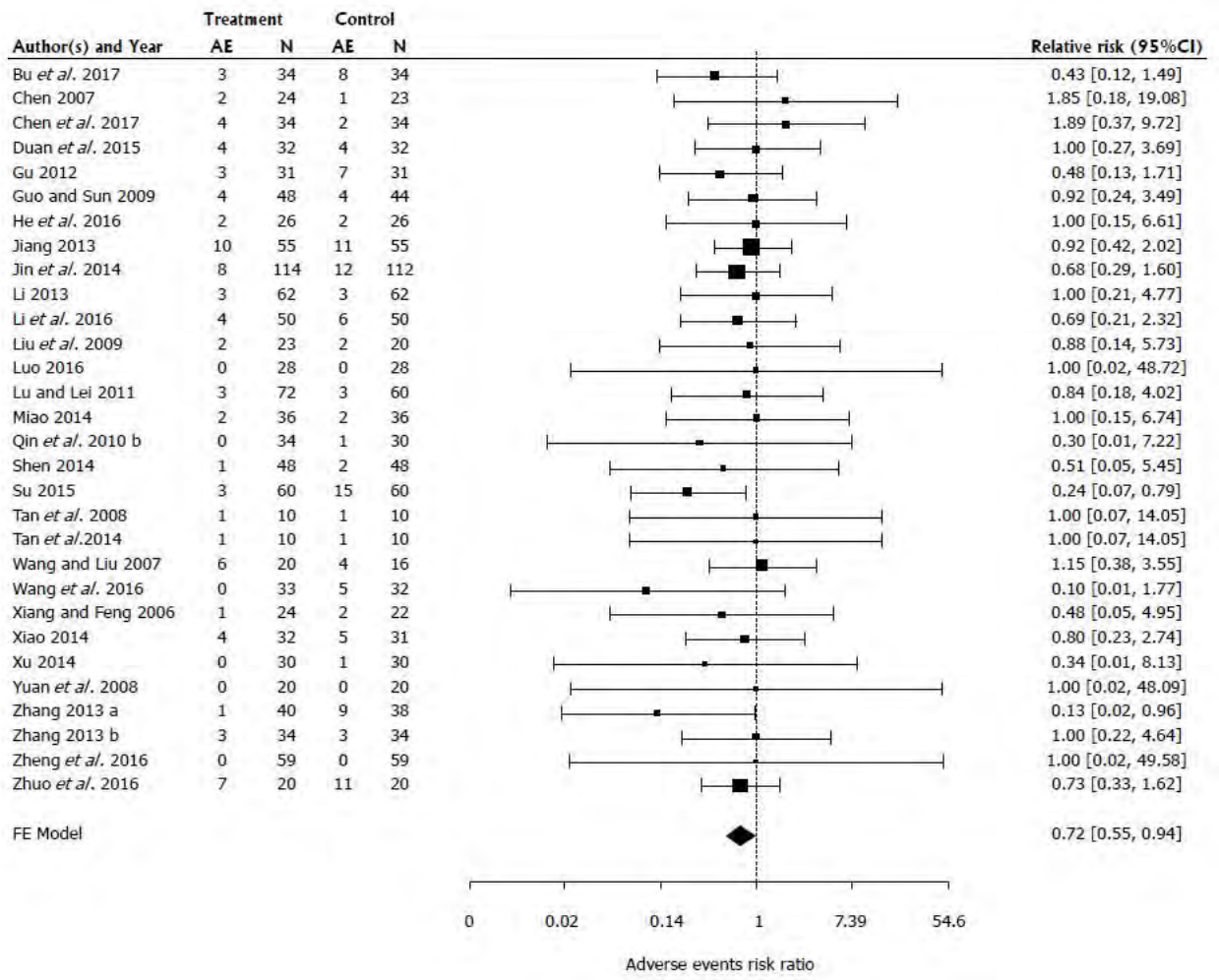

Figure 10: Forest plots of the results of fixed effects meta-analysis with 30 studies evaluating the effect of Medilac-S® in combination with conventional drug therapy on number of participants reporting adverse events.

"AE" is the number of participants reporting adverse events within a study and "N" is the total number of participants within the study. The relative risk (RR) and its 95% CI for each study are listed on the right-hand side of the graph. The 95% CI for the estimated mean RR for each concomitant drug therapy category is shown as a shaded diamond with the endpoints of the diamond being the CI endpoints. The vertical dashed line at 1 indicates a RR of 1, which occurs when there is no observed difference in AEs between the treatment and the control.

Overall, the studies show that Medilac-S® (*B. subtilis* R1079 and *E. faecium* R0026) is safe, with no reports of serious adverse events. Rather, the results highlighted that the incorporation of Medilac-S® with SASP and other aminosalicylates (mesalazine, olsalazine, balsalazide) reduced the risk of AEs, suggesting the role of selected bacteria in the prevention of AEs associated with anti-inflammatory drug use. In summary, the absence of any reports of adverse events attributable to the administration of $3.0x10^8$ cfu of *B. subtilis* R0179 per day to these vulnerable individuals provides strong evidence of the safety of this strain.

In 2019, a study (Culpepper et al. 2019) was published using *B. subtilis* R0179 in otherwise healthy obese participants to determine if the strain could have an effect on fecal or plasma bile acids due to its bile salt hydrolase activity. This study included 3 different strains of bacteria, including *B. subtilis* R0179 at $2.5x10^9$

cfu per day, in healthy people between the ages of 35 and 65, with a waistline over 102 cm for males and 88 cm for females. This was a double-blind, randomized, cross-over, controlled trial. In total, 35 people took *B. subtilis* R0179 for 6 weeks during the trial. The study design involved a 1-week lead-in period, followed by either bacteria or placebo for 6 weeks, followed by a 3-week washout, then a 1-week lead-in period, another 6-week intervention period with the opposite intervention, followed by a final 1-week washout period. Stool and blood samples were taken at the end of the first lead-in week, the end of the first intervention period, the end of the washout, and the end of the opposite intervention period. Gastrointestinal Symptom Rating Scale questionnaires and International Physical Activity questionnaires were taken weekly throughout the trial, and a daily questionnaire determining intake of the treatment product, number of stools, adverse events, and daily alcohol consumption was performed.

The study demonstrated that there were no differences among groups (all bacteria vs. all placebo) in safety outcomes, and no effects were seen on white blood cell numbers or percentages, as reported by the authors. Nausea, vomiting, or stomach upset were similar between bacterial and placebo groups. One participant taking *B. subtilis* R0179 (n=35) reported a headache, versus 9 participants in the placebo group (n=114).

No differences were seen in blood glucose, insulin, or blood lipids between the groups and the pooled placebo. A trend showing an increase in ApoB100 was seen in the *B. subtilis* R0179 group when compared to the pooled placebo. There was no interaction between *B. subtilis* R0179 and plasma deconjugated bile acids, but a *post hoc* analysis determined that if the subjects were stratified according to BMI, there was an interaction between *B. subtilis* R0179 and the sum of plasma deconjugated secondary bile acids in participants with BMI>30. In addition, supplemental published materials indicated that there was some effect on the glycine-coupled bile acids that were tested in the plasma of individuals, whereas there was no change in concentrations of taurine-coupled bile acids.

6.4.1.3. Studies with *Bacillus subtilis* strains other than R0179

As the use of *B. subtilis* is widespread, there have been studies with other strains consumed as a component of natto and a few studies done with other strains. GRAS notifications to the FDA for *B. subtilis* strains and by-products of these strains have been accepted, including GRN 476, 592, 831, 905, and more. The use and safety of *B. subtilis* strains and other bacilli have been reviewed in Sanders et al. (2003), and Hong et al. (2005). These reviews did not reveal any cases of infection due to the ingestion of *B. subtilis*, although a product, Enterogermina®, containing four strains of *B. clausii,* had some reports of infection due to this microorganism. Also, a product with a *B. cereus* strain, mislabelled as *B. subtilis* in a product called Bactisubtil®, caused three cases of diarrhea (reviewed in Hong et al. 2005). The reviews urged caution and recommended an individual approach when assessing the clinical outcome and safety of strains of *B. subtilis*.

6.4.1.4. Conclusions from Studies in Adults

According to the Hanifi et al. (2015) safety study, which was conducted to determine the safety status of the strain *Bacillus subtilis* R0179 individually and in a higher concentration, the daily consumption of this strain is safe and well tolerated in healthy individuals up to $1.0x10^{10}$ cfu/day. This was also supported by

data from Culpepper et al. (2019), which studied the effects of *Bacillus subtilis* R0179 in healthy overweight individuals at $2.5x10^9$ per day. No adverse effects were seen.

Additionally, based on clinical data with Medilac-S and Medical- DS products (containing $1x\ 10^7$ and $1x10^8$ cfu of *Bacillus subtilis* R0179 per capsule, respectively), the absence of any reports of adverse events attributable to the administration of $3.0x10^8$ cfu *Bacillus subtilis* R0179/day in severely compromised and vulnerable individuals provides strong evidence of the safety of this strain in adults for its intended use in a healthy population.

- Tompkins et al. (2010), including 3347 patients (1948 patients with the bacterial treatment), suffering from medical conditions, including acute or chronic diarrhea, acute pancreatitis, irritable bowel syndrome, constipation, ulcerative colitis, peptic ulcers and *H. pylori* infections, cirrhosis, and antibiotic-associated diarrhea, concluded that the product is safe, with no reports of serious adverse events
- Sohail et al. (2018), reporting on 30 RCTs on ulcerative colitis with reported adverse events which included 2430 participants (1235 in the treatment group), highlighted that the incorporation of Medilac-S® with SASP and other aminosalicylates (mesalazine, olsalazine, balsalazide) reduced the risk of AEs, resulting in the absence of any reports of adverse events attributable to the administration of $3.0x10^8$ cfu of *Bacillus subtilis* R0179

Studies from other strains of *B. subtilis* have demonstrated safety of use in food and have been represented by no-question letters in response to GRAS notices to the FDA for similar uses.

In conclusion, given the safety of intake of $3.0x10^8$ and $1.0x10^{10}$ cfu/day of the bacterial strain *Bacillus subtilis* R0179 in severely vulnerable and healthy individuals, respectively, it has been shown to be safe for use in adults.

6.4.2. Studies in Children and Infants

6.4.2.1. Studies of other formulations containing *Bacillus subtilis* R0179

In China and Korea, *B. subtilis* R0179 is found in combination with *E. faecium* R0026 and a variety of vitamins and minerals in a product called Medilac-Vita ("妈咪爱"), Medilac-bebe, or Mamiai (Mother's Love). The products are detailed below:

Medilac-Vita ("妈咪爱", sold as Mamiai in China)

Active Ingredients; 1 g contains:

- Bacterial culture: 37.5 mg (*S. faecium* $1.35X10^8$ cfu, *B. subtilis* $1.5X10^7$ cfu)
- Thiamine HCl: 0.5 mg
- Riboflavin: 0.5 mg
- Pyridoxine HCl: 0.5 mg
- Ascorbic acid: 10 mg
- Nicotinamide: 2.0 mg
- Cyanocobalamin: 1.0 mg (0.1%)
- Calcium lactate: 20 mg (as Ca 2.6 mg)
- Descote zinc oxide 50%: 2.5 mg (as Zn 1.0 mg)

Dosing:

- 3~12 months: 0.5 g
- 1~2 years: 1 g
- Children over 3 years: 1~2 g
- Administer the above dosage 1~2 times a day dissolved in water, milk, baby food

Indication:

- Anorexia, dyspepsia, intestinal putrefaction, loose feces, constipation, nutritional disorders (weaning period, children of unbalanced diet)

Medilac-Bebe

Active Ingredients; 1 g contains:

- Bacterial culture: 62.5 mg (*S. faecium* 2.25X10^8 cfu, *B. subtilis* 2.5X10^7 cfu),
- Thiamine: HCl 0.3 mg
- Riboflavin: 0.2 mg
- Pyridoxine HCl: 0.3 mg

Dosing:

- 3~12 months: 0.5 g
- 1~2 years: 1 g
- Children over 3 years: 1.5 g
- Administer the above dosage q.i.d. dissolved in water, milk, baby food

Indication:

- Anorexia, dyspepsia, intestinal putrefaction, loose feces, constipation, nutritional disorders (weaning period, children of unbalanced diet)

A search of the Chinese scientific literature in http://www.wanfangdata.com/coj/advanced_search.asp or http://scholar.google.com or for these terms (i.e. Medilac-Vita, Mamiai or "妈咪爱") indicates that there have been more than 100 clinical studies in children and infants (primarily neonates). In their review of use of microorganisms in China, Wang and Zheng (2009) reported 112 articles for Medilac-vita (Mamiai) as of December 2007; however, they did not mention terms such as constipation, eczema, etc. The actual number of articles may well be over 220. These numbers indicate that Medilac-Vita is the most studied such product in China and perhaps all the world. Generally, these 112+ studies can be categorized as:

1. Prevention and treatment of neonatal and breast-milk jaundice (hyperbilirubinemia);
2. Prevention and treatment of seasonal (autumnal) influenza, primarily rotaviral in origin;
3. Treatment of infantile constipation;
4. Miscellaneous uses such as eczema treatment, digestion aids, etc.

The specific contribution of the *B. subtilis* R0179 to effectiveness in these studies is difficult to assess due to the complex nature of the test articles (i.e., the combination of two strains with vitamins and

minerals). These studies are frequently compounded by the combination of the bacterial strain with traditional Chinese therapies or with conventional medications in the treatment of the condition. In a few papers Medilac-Vita is presented as the conventional medication and other therapies are compared to it, thus showing that its use is accepted as routine practice in hospitals in China. Wang and Zheng (2009) reported nine studies that had a safety component and only one paper reported nausea and gastrointestinal reactions, which may well not be attributable to *B. subtilis* R0179.

A search of the scientific literature (e.g., http://www.druglib.com/drugindex/adverseeventreport/) for pharmacovigilance on this product did not reveal any reports of death, injury, or infection in neonates and infants. The distributor of the product in China and Korea, Hanmi Pharmaceutical Co. Ltd., did not receive any serious adverse event reports or complaints regarding this product.

Table 19 summarizes 30 published studies in which Medilac-Vita (Mamaia) was administered to infants at doses providing *B. subtilis* R0179 at a range of $1.5x10^7$ to $9.0x10^7$ cfu/day. A total of 3,619 infants was enrolled in these studies, with approximately 1890 receiving the test formulation. Some of the studies enrolled healthy infants in order to investigate prophylactic effects, but in most of the research the enrolled infants were suffering from diarrhea (idiopathic, rotaviral, or antibiotic-associated), constipation, infantile bilirubinemia or frank jaundice, or dysentery. The duration of administration was most often under a week, but several studies had longer durations up to 2 weeks. In none of the studies was any adverse effect observed that could reasonably be believed to be attributable to the treatment. As was the case with the studies in adults, the absence of any adverse effects due to administration of up to $9.0x10^7$ cfu *B. subtilis* R0179/day in these clinical trials with vulnerable infants indicates that this bacterial strain poses little risk of harm under the intended conditions of use.

Table 19. Clinical Studies in children, infants, and newborns.

Study ID	Start and end dates	Design Control type	Treatment; route	Dose, regime, and duration.	Total enrolment	Control gender M/F Age	Treated gender M/F Age	Primary objective(s)	Averse events
Zhang et al. 2000	May 1999 to May 2000	Randomized with control	Mamiai; orally	0.5g bid ($1.5x10^8$ cfu bacteria/day; $1.5x10^7$ cfu R0179/day); 24-72 hrs.	132 cases of neonatal children with diarrhea (74 in the treatment group and 58 in the control group)	31 M / 27 F; 9-28 days	44 M / 30 F; 6-28 days	Explore Mamiai treatment efficacy and mechanism of neonatal diarrhea	Not stated
Ye 2001	May 1998 to May 2000	Randomized with control	Cefoperazone (injected) and Mamiai (orally)	< 1 yr: 1g/d ($1.5x10^8$ cfu bacteria/day; $1.5x10^7$ cfu R0179/day) 1 - 3 yrs: 1g bid ($3.0x10^8$ cfu bacteria/day; $3.0x10^7$ cfu R0179/day) > 3 yrs: 1g or 2g bid or tid ($3.0x10^8$ cfu bacteria/day; $3.0x10^7$ cfu R0179/day to $9.0x10^8$ cfu bacteria/day; $9.0x10^7$ cfu R0179/day); duration not stated	100 children with acute dysentery (50 in each group)		All groups combined: 69 M / 31 F; 6 months to 12 yrs	Efficacy of Mamiai and Cefoperazone treatment of children with acute dysentery	Occasional skin rashes, elevated aminotransferases (probably not linked with Miamiai); were restored after withdrawal to normal
Lu and Song 2003	Not stated	Randomized with active control	Mamiai; orally	< 1 yr: 0.5g tid ($2.25x10^8$ cfu bacteria/day; $2.25x10^7$ cfu R0179/day) 1 - 4 yrs: 1g tid ($4.5x10^8$ cfu bacteria/day; $4.5x10^7$ cfu R0179/day) > 4 yrs: 2g tid ($3.0x10^8$ cfu bacteria/day; $3.0x10^7$ cfu R0179/day); 3 to 5 days	204 children with constipation (112 in the treatment group and 92 in the control group)		All groups combined: 124 M / 80 F; 62 aged 3 to 6 mo 72 aged 1 to 4 yrs 70 aged 5 to 14 yrs	Efficacy of Mamiai treatment of constipation	Not stated
Tang 2003	Sep. 2000 to Sep. 2001	Randomized with control	Mamiai and Ribavirin; orally	< 1 yr: 0.5g tid ($2.25x10^8$ cfu bacteria/day; $2.25x10^7$ cfu R0179/day) > 1 yr: 1g tid ($4.5x10^8$ cfu bacteria/day; $4.5x10^7$ cfu R0179/day); 4.6 ± 1.3 days	110 infants and children with viral enteritis (60 in the treatment group and 50 in the control group)	27 M / 23 F; Infants and young children	32 M / 28 F; Infants and young children	Efficacy of Mamiai and Ribavirin treatment of infant viral enteritis	No intervention-related adverse reactions were reported

Wan & Lu 2003	Oct. 2002 to Feb. 2003	Random-ized with active control	Mamiai and Smecta; orally	< 1 yr: 0.5g tid ($2.25x10^8$ cfu bacteria/day; $2.25x10^7$ cfu R0179/day) > 1 yr: 1g tid ($4.5x10^8$ cfu bacteria/day; $4.5x10^7$ cfu R0179/day); 4.18 ± 1.2 days	136 children with diarrhea (68 in each group)	44 M / 24 F; 8 aged < 6 mo 35 aged 6 mo to 1 yrs 19 aged 1 to 2 yrs 6 aged 2 to 3 yrs	47 M / 21 F; 7 aged < 6 mo 39 aged 6 mo to 1 yrs 17 aged 1 to 2 yrs 5 aged 2 to 3 yrs	Mamiai and Smecta treatment efficacy in autumn and winter infant diarrhea	No side effects of the intervention were reported
Li, Gan, and Wu 2004	May 2003 to Aug. 2003	Random-ized with control	Mamiai; orally	0.5g bid ($1.5x10^8$ cfu bacteria/day; $1.5x10^7$ cfu R0179/day); 5 days	84 normal childbirths (44 in treatment group and 40 in control)	24 M / 20 F; Gestational age: 36 ± 3.5 w	21 M / 19 F; Gestational age: 37 ± 3.3 w	Study the clinical effect of Mamiai in neonatal jaundice	No side effects of the intervention were reported
Li, Wang, and Yan 2004	Jan. 2002 to Oct. 2003	Random-ized with control	Mamiai and Luminal; orally + photo-therapy	0.5g tid ($2.25x10^8$ cfu bacteria/day; $2.25x10^7$ cfu R0179/day); duration not stated	112 cases of full-term newborns with hyperbilirubinemia (58 in treatment group and 54 in control)	33 M / 21 F; Gestational age: 37.9 ± 1.6 w	34 M / 24 F; Gestational age: 38.3 ± 1.5 w	Evaluate the clinical effect of Mamiai on neonatal bilirubinemia	No side effects of the intervention were reported
Lui and Zhang 2004	Sep. 1997	Random-ized with control	Mamiai; orally	0.5g tid ($2.25x10^8$ cfu bacteria/day; $2.25x10^7$ cfu R0179/day); duration not stated	112 cases of normal full-term newborns (56 in each group)		All groups combined: 60 M / 52 F; Gestational age: 37 to 40 w in 94 cases, 41 w in 18 cases	Observe Mamiai on neonatal serum bilirubin metabolism	Not stated
Xu et al. 2004	Jan. 2001 to Jan. 2003	Random-ized with active control	Mamiai and Simotang; orally	0.5g tid ($2.25x10^8$ cfu bacteria/day; $2.25x10^7$ cfu R0179/day); duration not stated	150 children with neonatal hyperbilirubinemia (90 in the treatment group and 60 in control)	31 M / 29 F; 0.58-27 d (average 5.2 d)	44 M / 46 F; 0.87-28 d (average 5.5 d)	Observe Mamiai and Simotang effect on treatment of neonatal hyperbilirubinemia	No side effects of the intervention were reported
Yu 2004	Jan. 2000 to dec. 2003	With active control	Mamiai and Xiaoerhuaj; orally	1g tid ($4.5x10^8$ cfu bacteria/day; $4.5x10^7$ cfu R0179/day); duration not stated	98 cases of neonatal hyperbilirubinemia (50 in the treatment group and 48 in control)	23 M / 25 F; 1-9 d (average 4.2 ± 0.3 d)	26 M / 24 F; 1-8 d (average 5.5 ± 0.3 d)	Effect of Mamiai and Xiaoerhuaji in adjuvant treatment of neonatal hyperbilirubinemia	Not stated

Yu et al. 2004	Jan. 2000 to Jan. 2003	Random-ized with active control	Mamiai and Smecta; orally	0.5g tid ($2.25x10^8$ cfu bacteria/day; $2.25x10^7$ cfu R0179/day); 5.19 ± 1.54 days	60 cases of neonatal hyperbilirubinemia (32 in the treatment group and 28 in control)	20 M / 8 F; 9 h to 29 d	19 M / 13 F; 10 h to 29 d	Effect of Mamiai and Smecta adjuvant therapy for neonatal hyperbilirubinemia	Few cases of constipation
Zhang 2004	Feb. 2003 to Jan. 2004	Random-ized with control	Mamiai; orally	0.5g bid ($1.5x10^8$ cfu bacteria/day; $1.5x10^7$ cfu R0179/day); duration not stated	60 cases of normal full-term newborns, breast-fed		Ratio M/F not stated; Age is not stated; Gestational age 38.5 ± 1.5 w	Effect of Mamiai on neonatal hyperbilirubinemia	Not stated
Chen and Wu 2005	Jun. 2000 to Dec. 2002	Random-ized with control	Mamiai and loperamide chloride; orally	< 2 yr: 0.5g bid ($1.5x10^8$ cfu bacteria/day; $1.5x10^7$ cfu R0179/day) > 2 yr: 1g bid ($3.0x10^8$ cfu bacteria/day; $3.0x10^7$ cfu R0179/day); 4.39 ± 1.2 days	96 hospitalized children with diarrhea (50 in the treatment group and 46 in the control group)	24 M / 22 F; 3 Mo to 3 yrs	24 M / 26 F; 3 Mo to 3 yrs	Efficacy of Mamiai combined with loperamide hydrochloride for the treatment of infantile diarrhea	No intervention-related adverse reactions were reported
Wu and yang 2005	Sep. 2003 to Apr. 2004	Random-ized with active control	Mamiai; orally	Dosage not stated; 6 days	60 children with rotavirus diarrhea (30 in each group)		Not stated	Effect of treating infant autumn diarrhea (rotavirus diarrhea) with Mamiai	Not stated
Qin et al. 2005	Not stated	With active control	Mamiai; orally	1g bid ($3.0x10^8$ cfu bacteria/day; $3.0x10^7$ cfu R0179/day); duration not stated	60 infants with rotavirus diarrhea (30 in each group)		All groups combined: 26 M / 34 F; < 6 months	Efficacy of Mamiai additionally with conventional medicine in the treatment of infantile rotavirus diarrhea	Not stated
Sun and Sun 2005	May 1998 to Sep. 2004	Random-ized with active control	Mamiai and Qinggan-lidan; orally	1g/d ($1.5x10^8$ cfu bacteria/day; $1.5x10^7$ cfu R0179/day; 6.45 ± 2.5 days	210 cases of neonatal hyperbilirubinemia in children (107 in the treatment group and 103 in the control group)	52 M / 51 F; 19 h to 31 d (average 5.7 d) Gestational age: 38 ± 4.9 w	52 M / 55 F; 20 h to 30 d (average 5.8 d) Gestational age: 38 ± 5.2 w	Investigate Mamiai and Qingganlidan treatment of neonatal hyperbilirubinemia clinical efficacy	Not stated

Zhou 2005	Jan. 2000 to Dec. 2003	Random-ized with active control	Mamiai, Simotang and Smecta; orally	0.5g bid ($1.5x10^8$ cfu bacteria/day; $1.5x10^7$ cfu R0179/day); duration not stated	96 infants with breast-milk jaundice (50 in treatment group and 46 in control	28 M / 18 F; Gestational age: 38.4 ± 0.7 w	26 M / 24 F; Gestational age: 38.1 ± 0.6 w	Efficacy of treatment of breast milk-jaundice with a combination of Mamiai, Smecta and Simotang	Not stated
Huang et al. 2006	Jan. 2005 to Nov. 2006	Random-ized with control	Mamiai; orally	< 1 yr: 0.5g bid ($1.5x10^8$ cfu bacteria/day; $1.5x10^7$ cfu R0179/day) 1 - 2 yrs: 1g bid ($3.0x10^8$ cfu bacteria/day; $3.0x10^7$ cfu R0179/day) 2 - 3 yrs: 1g bid or tid ($3.0x10^8$ cfu bacteria/day; $3.0x10^7$ cfu R0179/day or $4.5x10^8$ cfu bacteria/day; $4.5x10^7$ cfu R0179/day); 3 days	210 pneumonic infants in hospital (110 in the treatment group and 100 in the control group)		All groups combined: 134 M / 76 F; 1 to 36 months	Evaluate the preventive and treatment effects of Mamiai used in advance on pneumonic infants with secondary diarrhea	No intervention-related adverse reactions were reported
Bao & Huang 2006	Mar. 2005 to Nov. 2005	Random-ized with active control	Mamiai and Luminal; orally	Not stated	242 normal childbirths divided into intervention group (n=65) and 3 contrast groups mamiai alone (n=62), Luminal alone (n=55), no treatment (n=60)		All groups combined: ratio M/F not stated; The study was started just after birth of the infants	Evaluate the influence of applying Mamiai and Luminal in early stage for the incidence and the degree of neonatal jaundice	No side effects of the intervention were reported
Liang, Chen, and Li 2006	Not stated	With active control	Mamiai and simo decoction; orally	1.5g to 6g / day in three times ($2.25x10^8$ cfu bacteria/day; $2.25x10^7$ cfu R0179/day to $9.0x10^8$ cfu bacteria/day; $9.0x10^7$ cfu R0179/day); 2 weeks	86 children suffering from chronic idiopathic constipation		All groups combined: 46 M / 40 F; 6 months to 12 yrs	Efficacy of simo decoction and Mamiai on children with chronic idiopathic constipation	No significant adverse reactions were reported
Maio and Jia 2006	Oct. 2005 to Jan. 2006	No control	Mamiai and Yin Qi Huang; orally	0.5g bid ($1.5x10^8$ cfu bacteria/day; $1.5x10^7$ cfu R0179/day); duration not stated	60 infants diagnosed with breast milk jaundice		All groups combined: 32 M / 28 F; Infants of more than one month	Observe the curative effect of combined Yin Qi Huang and Mamiai in the treatment of the breast milk jaundice	No side effects of the intervention were reported
Pan 2006	Oct. 2004 to Feb. 2005	Random-ized with control	Mamiai and Ribavririn; orally	< 1 yr: 0.5g tid ($2.25x10^8$ cfu bacteria/day; $2.25x10^7$ cfu R0179/day) > 1 yr: 1g tid ($4.5x10^8$ cfu bacteria/day; $4.5x10^7$ cfu R0179/day); duration not stated	80 children with acute enteritis epidemic diarrhea (40 in each group)		All groups combined: 47 M / 33 F; 6 to 24 months	Efficacy of Mamiai and Ribavirin treatment of infantile autumn diarrhea	No intervention-related adverse reactions were reported
Wang and Bai 2006	Jun. 2005 to Dec. 2005	Random-ized with active control	Mamiai; orally + photother-apy	0.5g tid ($2.25x10^8$ cfu bacteria/day; $2.25x10^7$ cfu R0179/day); 5 days	67 infants with breast-milk jaundice (35 in the treatment group and 32 in the control group)		All groups combined: 39 M / 28 F; Gestational age: 38.5 ± 4.3 w Birth age: 15-38 d	Effect of Mamiai on lowering breast-milk jaundice	No side effects of the intervention were reported

Wu and Sun 2006	Sep. 2002 to Feb. 2004	With control	Mamiai and 654-2-point injection; orally	< 1 yr: 0.5g bid ($1.5x10^8$ cfu bacteria/day; $1.5x10^7$ cfu R0179/day) 1 - 2 yrs: 1g bid ($3.0x10^8$ cfu bacteria/day; $3.0x10^7$ cfu R0179/day) 2 - 3 yrs: 1.5g bid ($4.5x10^8$ cfu bacteria/day; $4.5x10^7$ cfu R0179/day); duration not stated	74 cases of infant hospitalized with rotavirus diarrhea		All groups combined: ratio M/F not stated; Age is less than 3 yrs	Study therapeutic effect of combination treatment for infants with rotavirus gastroenteritis with 654-2-point injection and oral administration of Mamiai	Not stated
Huo 2007	Jul. 2004 to Apr. 2004	Case study, no control	Mamiai and Smecta; orally; + Rehydra-tion treatment	< 2 yr: 1g once or bid ($1.5x10^8$ cfu bacteria/day; $1.5x10^7$ cfu R0179/day or $3.0x10^8$ cfu bacteria/day; $3.0x10^7$ cfu R0179/day) > 2 yr: 1g or 2g once or bid ($1.5x10^8$ cfu bacteria/day; $1.5x10^7$ cfu R0179/day to $6.0x10^8$ cfu bacteria/day; $6.0x10^7$ cfu R0179/day); 3 to 7 days	43 children with antibiotic-associated diarrhea	Not applicable	24 M / 19 F; 4 Mo to 5 yrs	Efficacy of treatment of antibiotic-associated diarrhea with Smecta, Mamiai end rehydration	Not stated
Xie and Zhang 2007	Jan. 2004 to Dec. 2006	Random-ized with active control	Mamiai and decoction of four-drug juice; orally	0.5g bid ($1.5x10^8$ cfu bacteria/day; $1.5x10^7$ cfu R0179/day); 5 days	457 sick neonates with hyperbilimbinemia (229 in the treatment group and 228 in the control)	Ratio M/F not stated; 1-18 days (5.4 ± 0.7 d)	Ratio M/F not stated; 1-17 days (5.3 ± 0.8 d)	Observe the effect of Mamiai and decoction of four-drug juice in adjunctive treatment of hyperbilirubinemia in neonates	Not stated
Sheng, 2008	Jan. 2007 to Feb. 2008	Randomize d with control	Mamiai; orally	< 1 yr: 0.5g once or bid ($0.75*10^8$ CFU/d or $1.5*10^8$ CFU/d) 1 - 2 yrs: 1g once or bid ($1.5*10^8$ CFU/d or $3*10^8$ CFU/d) 2 - 3 yrs: 1g to 2g once or bid ($1.5*10^8$ CFU/d or $6*10^8$ CFU/d) 7 to 10 days	200 children with pneumonia and AAD (100 in each group)	51 M / 49 F; 32 aged 1.5 mo to 1 yr 68 aged 1 to 3 yrs	47 M / 53 F; 38 aged 1.5 mo to 1 yr 62 aged 1 to 3 yrs	Efficacy of treatment of infants with pneumonia secondary diarrhea with Mamiai	No adverse events
Xu 2008	Apr. 2002 to Apr. 2006	Random-ized with active control	Mamiai and Smecta; orally	0.5g tid ($2.25x10^8$ cfu bacteria/day; $2.25x10^7$ cfu R0179/day); duration not stated	60 infants diagnosed with breast-milk jaundice (40 in each group)	25 M / 15 F; 6-33 days	22 M / 18 F; 5-34 days	Efficacy of Mamiai and Smecta in the treatment of breast-milk infantile jaundice	No side effects of the intervention were reported
Zhu and Li 2008	Not stated	Randomize d with active control	Mamiai and Smecta; orally	0.5g tid ($2.25x10^8$ cfu bacteria/day; $2.25x10^7$ cfu R0179/day); duration not stated	96 cases of early neonatal hyperbilirubinemia (48 in each group)	All groups combined: 39 M / 28 F; Age is not stated		Efficacy of Mamiai and Smecta in the treatment of early neonatal hyperbilirubinemia	No side effects of the intervention were reported

Liu et al. 2010	Apr. 2007 to Oct. 2008	Random-ized with active control	Mamiai; orally + external application of potato slices / mashed potatoes	< 1 yr: 0.5g bid ($1.5x10^8$ cfu bacteria/day; $1.5x10^7$ cfu R0179/day) 1 - 2 yrs: 1g bid ($3.0x10^8$ cfu bacteria/day; $3.0x10^7$ cfu R0179/day); 3.5 ± 0.2 days	126 children with infant eczema (64 in treatment group and 62 in control)	37 M / 25 F; < 1 yr: 56 cases 1-2 yrs: 6 cases	41 M / 23 F; < 1 yr: 55 cases 1-2 yrs: 9 cases	Explore the clinical effect of oral Mamiai combined with external potato slices/mashed potato on infantile eczema	Not stated

b.i.d: Two times a day; t.i.d: Three times a day