Effect of Ayuraved Siriraj Herbal Recipe "Wattana" on Gastric Emptying Rate

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ABSTRACT

Background: Wattana, an herbal recipe from Ayuraved Siriraj, has been used as an analeptic remedy, enhancing fitness, anti-aging, increasing appetite and attenuating abnormal gastric motility since 1982. One of the factors that induce abnormal gastric motility is delayed gastric emptying rate (GER).

Objective: To evaluate the effect of Wattana on GER in healthy volunteers.

Methods: Seventeen healthy male volunteers (age 26.76 ± 1.16 years, body mass index (BMI) 20.30 ± 0.43 kg/ m^2; mean ± SEM) were studied on two separate days, with a wash out period of at least one week. After an overnight fast, each subject consumed 3 tablets of Wattana or placebo with 150 ml water, 10 minutes before drinking 15 g glucose in 150 ml water. Then 1 g paracetamol with 150 ml water was consumed 20 minutes after that. Blood samples were collected 11 times in three hours (at 0, 15, 30, 45, 60, 75, 90, 105, 120, 150 and 180 minutes) for gastric emptying evaluation. The feeling of hunger, fullness, abdominal discomfort, bloating, and nausea were assessed by visual analog scale (VAS). Serum paracetamol concentrations were analyzed, mean serum paracetamol concentrations, peak serum concentrations (C_{max}), time to peak serum concentrations (T_{max}) and area under the serum paracetamol concentration-time curve (AUC) and VAS score were determined.

Results: Mean serum paracetamol concentrations after Wattana consumption tended to be higher than after placebo. There was no significant difference in T_{max}, AUC and VAS score between Wattana or placebo consumption. However, C_{max} after Wattana was significantly higher than placebo (p = 0.044). It was noticed that all volunteers felt sleepy after Wattana consumption.

Conclusion: Wattana showed no effect on gastric emptying rate, but tended to increase the paracetamol absorption in the small intestine. A sedating effect of Wattana was noted.

Keywords: Ayuraved Siriraj, herbal recipe Wattana, gastric motility, gastric emptying, paracetamol absorption test

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INTRODUCTION

Nowadays, traditional herbal medicine is becoming more popular as an alternative treatment for gastrointestinal symptoms. Ayuraved Siriraj herbal recipe Wattana has been used for the treatment of gastrointestinal symptoms since 1982[1]. This recipe has also been used as an analeptic, enhancing fitness, anti-aging, attenuating abnormal gastric motility or dyspepsia and increasing appetite by Ayuraved Siriraj Clinic. The recipe consists of 15 herbal components: Pepper *(Piper nigrum Linn)*, Krachai *(Boesenbergia pandurata (Roxb.) Schltr.)*, Nutgrass/ Haew muu *(Cyperus rotundus Linn.)*, Boraphet *(Tinospora crispa Miers ex Hook.f. & Thoms.)*, Sa maw Thai/ Chebulic mytabulans *(Terminalia chebula Retz)*, Jet punk kee *(Cladogynos orientalis Zipp. Ex Span.)*, Thao wan prieng *(Derris scandens Benth.)*, Kho khlan/ Fishberry *(Anamirta cocculus (Linn.) Wight et Arnott)*, Ma khum kai *(Drypetes roxburghii Wall)*, Kha ton/ Cinnamon *(Cinnamomun siamense Craib)*, Asafoetida *(Ferulaa assa-foetida Linn.)*, Bael fruit *(Aegle maemelos (Linn.) Corr.)*, Kot hua bua *(Conioselinum univitatum Trucz.)*, Costus *(Saussurea lappa Clark.)* and Soften tendons *(Cryptolepis buchanani Roem. & Schult.)*[1].

According to the Thai herbal principle, many components of this recipe such as Asafoetida *(Ferulaa assa-foetida Linn.)*, Jet punk kee *(Cladogynos orientalis Zipp. Ex Span.)*, Nutgrass/ Haew muu *(Cyperus rotundus Linn.)*, Pepper *(Piper nigrum Linn.)*, and Kha ton/ Cinnamon *(Cinnamomun siamense Craib.)* are hot spicy herbs,[1] and are considered to have benefits of attenuating dyspepsia or abnormal gastric motility and increasing appetite.

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The pathophysiology of dyspepsia is still unclear. Previous studies showed that dyspepsia can be caused by gastric motor abnormality, such as delayed gastric emptying.[2] Gastric emptying rate (GER) is the rate at which a meal leaves the stomach into the small intestine (cal/min, ml/hr).[3] Various factors both endogenous and exogenous control gastric emptying. The interactions of nerve and hormones influence gastric emptying together with volume, pH, and nutrient content of the meal.[4,5]

Scintigraphic method is the gold standard to assess the gastric emptying rate, however, this method has limitations, as it is expensive, requires special instruments, and involves radiation exposure.[6,7] The paracetamol absorption test is an indirect method for the assessment of gastric emptying. It is simple, noninvasive, economical, safe and has significant correlation with the scintigraphic method though with less accuracy.[6]

Wattana has been used in the form of tablets (100 mg of herb per tablet of 200 mg). The usual dosage is 3 tablets before meal 3 times/ day[1]. Though Wattana has been used for the treatment of gastrointestinal tract symptoms for nearly 30 years, there is little evidence-based information of the effect of this recipe on gastric emptying rate. The aim of the present study was to investigate the effect of Ayuraved Siriraj herbal recipe Wattana on gastric emptying rate in healthy male volunteers by a paracetamol absorption test.

MATERIALS AND METHODS

Subjects

Seventeen healthy male subjects, age 26.76 ± 1.16 years, BMI 20.3 ± 0.43 kg/ m^2 participated in the study. Each participant completed a medical interview, underwent a physical examination and an initial laboratory screening before enrollment. No subject had a history of ongoing gastrointestinal disease or surgery, significant respiratory or cardiac disease or was taking medication known to affect gastrointestinal function. The protocol was approved by The Siriraj Institutional Review Board (EC number: 445/2551), and each subject gave written inform consent.

Protocol

Each subject was studied on two occasions separated by an interval of more than 7 days in randomized double-blinded order. In each study, following an overnight fast, an intravenous cannula was inserted into an antecubital vein for blood sampling. Each subject consumed three tablets of Wattana or placebo (3 x 200 mg/ tablets, Lot no. 30808-022-0955, Center of Applied Thai Traditional Medicine, Siriraj Hospital, Thailand) together with 150 ml water, then 15 g glucose in 150 ml water was consumed 10 minutes later. Twenty minutes later, 1 g paracetamol[6,8] (2 x 500 mg/ tablets Tylenol, Thailand) with 150 ml water was given and blood samples were collected at t0, 15, 30, 45, 60, 75, 90, 105, 120, 150 and 180 minutes for gastric emptying evaluation. The cannula was flushed with 10 ml 0.9% NSS, after each sample was taken. Blood samples were dispensed into clot blood tubes (5 ml/ tube). The subject's blood pressure and pulse rate were recorded at each interval together with the VAS for their gastrointestinal feelings. At 180 minutes after Wattana or placebo consumption, the intravenous cannula was removed. Subjects were assessed for their vital signs at regular intervals and closely observed for any adverse drug reaction for two more hours. Blood samples were centrifuged at 3,000 rpm for 10 minutes (Nahita, Model 2610). Serum paracetamol concentrations were analyzed by Automate AxSYM using FPIA principle (Siriraj Poison Control Center, Siriraj Hospital, Thailand)[9] for gastric emptying evaluation.

Measurement

Gastric Emptying

Gastric emptying rate was assessed by paracetamol absorption test in 180 minutes. Serum paracetamol concentrations were measured using fluorescence polarization immunoassay (FPIA) principle. Mean serum paracetamol concentrations, C_{max}, T_{max} and AUC were evaluated after consuming Wattana or placebo. C_{max}, and T_{max} can be read or recorded directly from data. The AUC was calculated by using SPSS statistics 17.0 program.

Visual analog scale

The visual analog scale (VAS) scores from the feeling of hunger, fullness, abdominal discomfort, bloating, and nausea after receiving Wattana and placebo were recorded. The VAS is a simple method to assess the intensity of sensations and feelings. The VAS is a straight 100 mm horizontal line.[10] It was used to ask the volunteers how they felt about the state of hunger, fullness, abdominal discomfort, bloating or nausea, grading from 0 (no hunger, fullness, abdominal discomfort, bloating or nausea) to 10 (extreme feeling of hunger, fullness, abdominal discomfort, bloating or nausea).

Statistical analysis

All data were shown as mean plus and minus standard error of sample mean. Shapiro-Wilk test was used to test the data distribution both in placebo and Wattana sets. Wilcoxon's signed ranks test was used to compare the data sets with non-normal distribution. Pair t-test was used to compare data with normal distribution, and $p < 0.05$ was considered statistically significant.

RESULTS

The demographic data of all subjects have been presented in Table 1 including the age, body weight, height, body mass index together with physical examination and blood chemistry.

Gastric emptying rate

Mean serum paracetamol concentrations after consuming Wattana tended to be higher than placebo, but there was no statistically significant difference (Fig 1). T_{max} and the $AUC_{0\text{-}180min}$ curves after Wattana compared to placebo, showed no statistically significant difference (Table 2, $p = 0.831$, $p = 0.287$ respectively). C_{max} after Wattana was higher than after placebo (Table 2, $p = 0.044$).

Visual analog scale

There was no difference in the feeling of hunger, fullness, abdominal discomfort, bloating, and nausea after Wattana compared to placebo (Fig 2).

DISCUSSION

This present study is the first randomized controlled trial to evaluate the acute effect of Ayuraved Siriraj herbal recipe Wattana on gastric emptying rate by paracetamol absorption test in healthy volunteers.

TABLE 1. The demographic data and clinical laboratory of 17 volunteers (mean ± SEM, n = 17).

Age (yr)		26.76 ± 1.16	
Weight (kg)		59.95 ± 1.70	
Height (cm)		171.68 ± 1.26	
BMI (kg/ m^2)		20.3 ± 0.43	
Physical examination	SBP (mmHg)	117.12 ± 1.92	
	DBP (mmHg)	76.59 ± 1.99	
	Pulse (beats/ minute)	71.53 ± 1.68	
Clinical Laboratory	Glucose (mg/ dl)	86.29 ± 1.70,	(Normal value 74 - 100)
	BUN (mg/ dl)	12.59 ± 0.62	(7.0 - 20.0)
	Creatinine (mg/ dl)	0.95 ± 0.03	(0.5 - 1.5)
	Total bilirubin (mg/ dl)	0.76 ± 0.09	(0.3 - 1.2)
	AST (U/ L)	27.65 ± 6.68	(0 - 37)
	ALT (U/ L)	21.59 ± 2.57	(0 - 40)
	ALP (U/ L)	64.71 ± 4.14	(39 - 117)
	Hemoglobin (g/ dl)	14.32 ± 0.30	(12.0 - 18.0)
	Hematocrit (%)	43.23 ± 0.73	(37 - 52)

(SBP = systolic blood pressure, DBP = diastolic blood pressure)

The paracetamol concentrations in this present study showed that C_{max} after Wattana consumption was significantly higher than placebo. This can be caused by 2 possible mechanisms: 1) Wattana increases the small intestinal absorbent capability or 2) Wattana affects the metabolism of paracetamol such as in the liver.

Previous studies suggested that the delayed or decreased absorbent capability in the small intestine could occur as a result of a decrease in gut permeability or a reduction in concentration gradient of substances across the gut wall induced by alteration in portal blood flow.[11] Also the difference in individuals' first pass hepatic metabolism of drugs may cause misinterpretation in serum paracetamol concentration.[12] Further studies are needed for clarification of the exact mechanism.

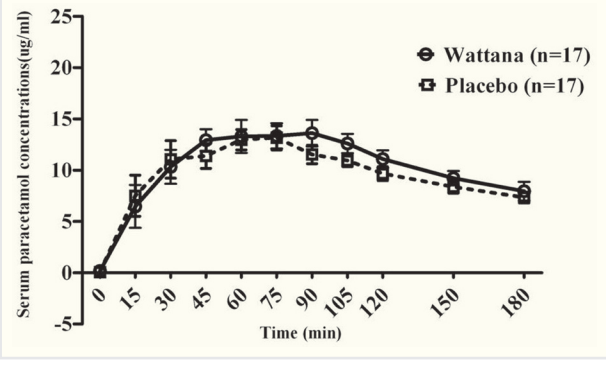

Fig 1. Mean serum paracetamol concentrations in 180 minutes after consumption of Wattana (⊖) or placebo (⊡) (mean ± SEM, n = 17)

The present study did not find any difference in T_{max} or $AUC_{0\_180\ min}$ after consumption of Wattana compare to placebo, and this may be because T_{max} and $AUC_{0\_180\ min}$ are influenced by many factors such as gastric emptying, rate of drug absorption in the small intestine, drug distribution and rate of drug elimination.[13]

Wattana is usually prescribed for the middle aged or elderly individuals in order to promote good health and appetite[1], but in this present study, the subjects were young adults with the age between 26.76 ± 1.16 year. Age difference might be one of the factors affecting the response to the Wattana recipe. However, the result from this present study can be the baseline information of the effect of Wattana on gastric emptying rate in humans, only in those who are healthy young males. Further studies should be performed in the elderly or patients with gastrointestinal symptoms. (of both sexes)

Another important factor involved in any herbal recipe action and effects is the dosage and duration of the drug consumption. In this present study, only a single dose of Wattana was evaluated. Most herbal recipes are in the form of crude plants and when ingested need longer time to accumulate and reach the threshold of response compared to chemically synthetic modern drugs. This preliminary study suggested that a larger sample size should be tried, the longer period and different dosages of drug administration should also be examined (in both sexes).

This present study found that 3 tablets of Wattana exerted obvious acute sedating effect on all volunteers. They all felt sleepy and some fell asleep. A previous study found that sleep delayed gastric emptying rate,[14] and this acute sedating effect of Wattana may influenced gastric

TABLE 2. Cmax, Tmax, and AUC0-180 min after consumption of Wattana or placebo (n = 17, median (range)).

	Wattana	Placebo	p - value
C_{max} (µg/ ml)	18.87 (11.33 - 35.19)	14.14 (9.61 - 31.36)	0.044*
T_{max} (min)	60 (15.0 - 90.0)	60 (15.0 - 150.0)	0.831
$AUC_{0-180\ min}$	1,777.73 (1,317.08 - 2,872.80)	1,734.15 (1,005.75 - 3,264.90)	0.287

(C_{max} = peak serum paracetamol concentrations, T_{max} = time to peak serum paracetamol concentrations, AUC = area under the serum paracetamol concentration-time curve, * $p < 0.05$ comparing Wattana to placebo (Wilcoxon's signed ranks test))

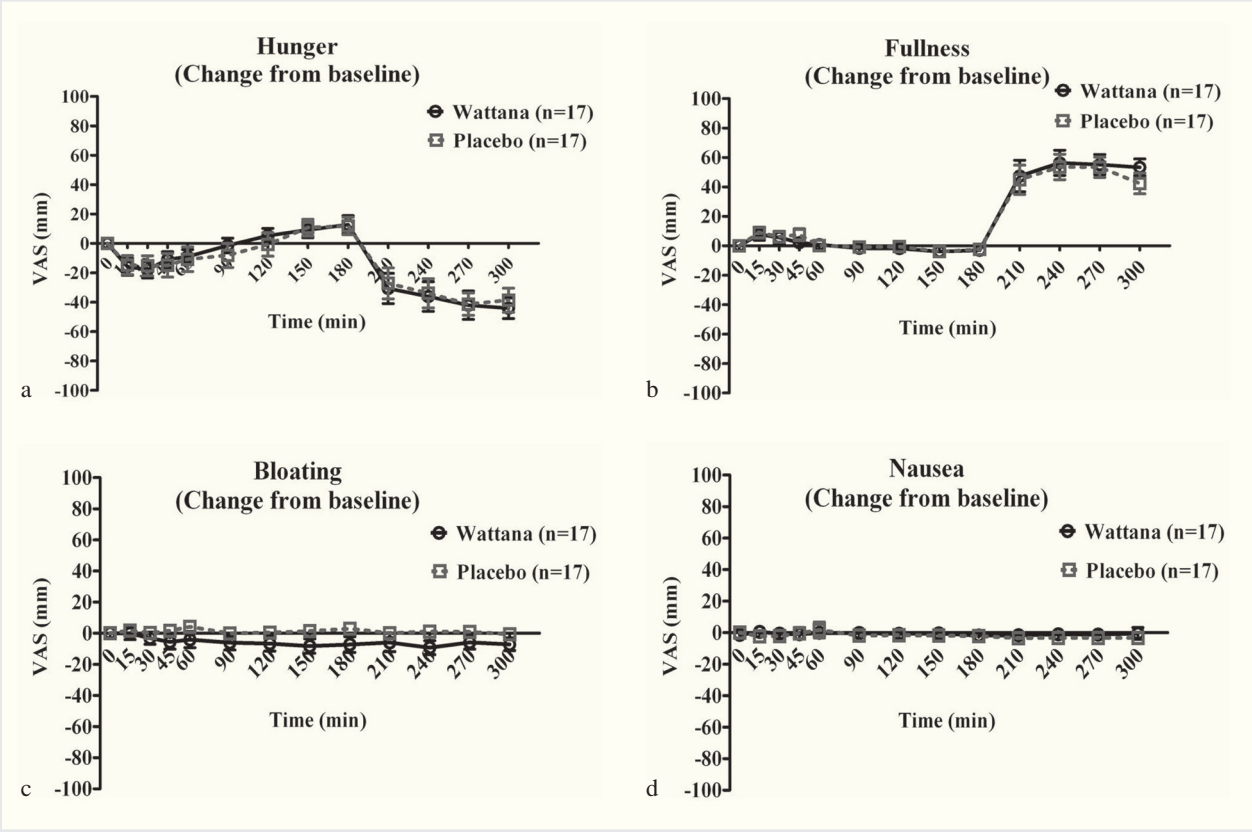

Fig 2. Visual analog scale of hunger (a), fullness (b), abdominal discomfort (c), bloating (d), and nausea (e) after Wattana (⊖) or placebo (⊟) consumption (mean ± SEM, n = 17) (change from baseline)

emptying or even intestinal motility. Furthermore, the sedating effect after wattana consumption may be caused by many herbs in Wattana such as Pepper *(Piper nigrum Linn)*, Nutgrass/ Haew muu *(Cyperus rotundus Linn.)*, Jet punk kee *(Cladogynos orientalis Zipp. Ex Span.)* which are known to have the benefit for sleep promotion.[1,15,16] These herbal components may cause sedation and make our volunteers to feel drowsy. The sedating and sleep promoting effect of Wattana should be further investigated and verified. Additionally, the diastolic blood pressure (DBP) was significantly lowered after Wattana consumption, while the systolic blood pressure (SBP) and pulse rate were not different compared to after placebo. Reduction of the DBP after Wattana consumption might be correlated to the sedation effect or the vasodilatory change in certain areas of the body including the splanchnic area, a hypothesis needing to be investigated. (Did you quantify the percentage of Diastolic Blood Pressure Reduction?) Although, the mechanism of Wattana in decreasing DBP is still unclear, it probably may be caused by Pepper *(Piper nigrum Linn)*, Krachai *(Boesenbergia pandurata (Roxb.) Schltr.)*, Boraphet *(Tinospora crispa Miers ex Hook.f. & Thoms.)*, Thao wan prieng *(Derris scandens Benth.)*, Kho khlan/ Fishberry *(Anamirta cocculus (Linn.) Wight et Arnott)*, Kha ton/ Cinnamon *(Cinnamomun siamense Craib)*, Bael fruit *(Aegle maemelos (Linn.) Corr.)*, Kot hua bua *(Coni-oselinum univitatum Trucz.)*, and Costus *(Saussurea lappa Clark.)* in this recipe, as they are known to have benefits for enhancing blood flow and hypotensive activity.[1,17-20] The reduction of DBP after Wattana consumption should be further examined.

Both pharmacokinetic and/or pharmacodynamic mechanisms have been considered to play an important role in herb-drug interactions, although the mechanisms for drug effect alteration remain to be determined. The clinical important of herb-drug interactions depends on various factors associated with the particular herb, drugs and patients.[21] In this present study, paracetamol may interact with any herb leading to a change in its pharmacokinetics. However, there has been no report about the interaction between Ayuraved Siriraj herbal recipe Wattana and paracetamol.

In summary, this present study was the first randomized controlled experiment which evaluated the effects of Ayuraved Siriraj herbal recipe Wattana on gastric emptying rate. A single dose of Wattana did not cause any apparent changes in gastric emptying rates, but slightly increased peak paracetamol concentrations which may be due to either augmented absorption in the small intestine or diminished drug elimination. Wattana also showed a sedating effect and a slightly lowering of diastolic blood pressure with no other acute adverse symptoms.

CONCLUSION

An acute 3-tablet dose of Wattana, an herbal recipe from Ayuraved Siriraj did not affect the gastric emptying rate but tended to increase the peak serum paracetamol concentrations and also showed sedating effect.

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