

Original Article

Vasculoprotective and vasodilatation effects of herbal formula (Sahatsatara) and piperine in spontaneously hypertensive rats



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ABSTRACT

Background: The herbal formula (Sahatsatara, STF), the Thai traditional poly-herbal recipe, has been used for treatment of muscle pain, anti-flatulence and numbness on hands and feet, with the caution when used in hypertensive patients. However, there is no scientific evidence to prove its effects on cardiovascular system. Piperine is the proposed major active compound in STF. It is shown to have antihypertensive effect in the L-NAME-induced endothelial dysfunction rats.

Purpose: This study investigated the pharmacokinetics, mechanism of action, as well as the hemodynamic and vasoactive effect and toxicity of STF and piperine using spontaneously hypertensive rats (SHR) and normal Wistar rats (NWR).

Methods: The amount of piperine in STF was measured by ultra performance liquid chromatography (UPLC). SHR and NWR were gavaged with piperine (50 mg/kg/day) or STF (100, 300, or 1000 mg/kg/day) alone or together with L-NAME (in drinking water) for 28 days. Hemodynamic effects were monitored by noninvasive tail cuff every 7 days. Vasorelaxation effect on the thoracic aorta in organ chamber was observed through force transducer at the end of the experiment. Biochemical parameters for kidney and liver toxicity were measured. In addition, pharmacokinetic study was performed using non-compartment analysis.

Results: The amount of piperine in STF was 1.29% w/w. Both STF and piperine did not affect blood pressure and heart rate in both SHR and NWR. Interestingly, STF and piperine increased acetylcholine-induced vasorelaxation of isolated thoracic aorta and have vasculoprotective effect in nitric oxide (NO) impaired rats. No liver or kidney toxicity was found in this study. Non-compartment pharmacokinetic analysis showed that the time to reach maximum concentration (T_{max}) of plasma piperine after administration of piperine and STF were 3.9 and 1.7 h, respectively. This result suggested that piperine in the recipe had better absorption than the pure standard piperine.

Conclusions: STF had no effect on blood pressure in both SHR and NWR. However, it was able to relax isolated thoracic aorta and had the potential for vasculoprotective effect in hypertensive and NO impaired condition. The effects of STF were comparable to those of piperine.

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Introduction

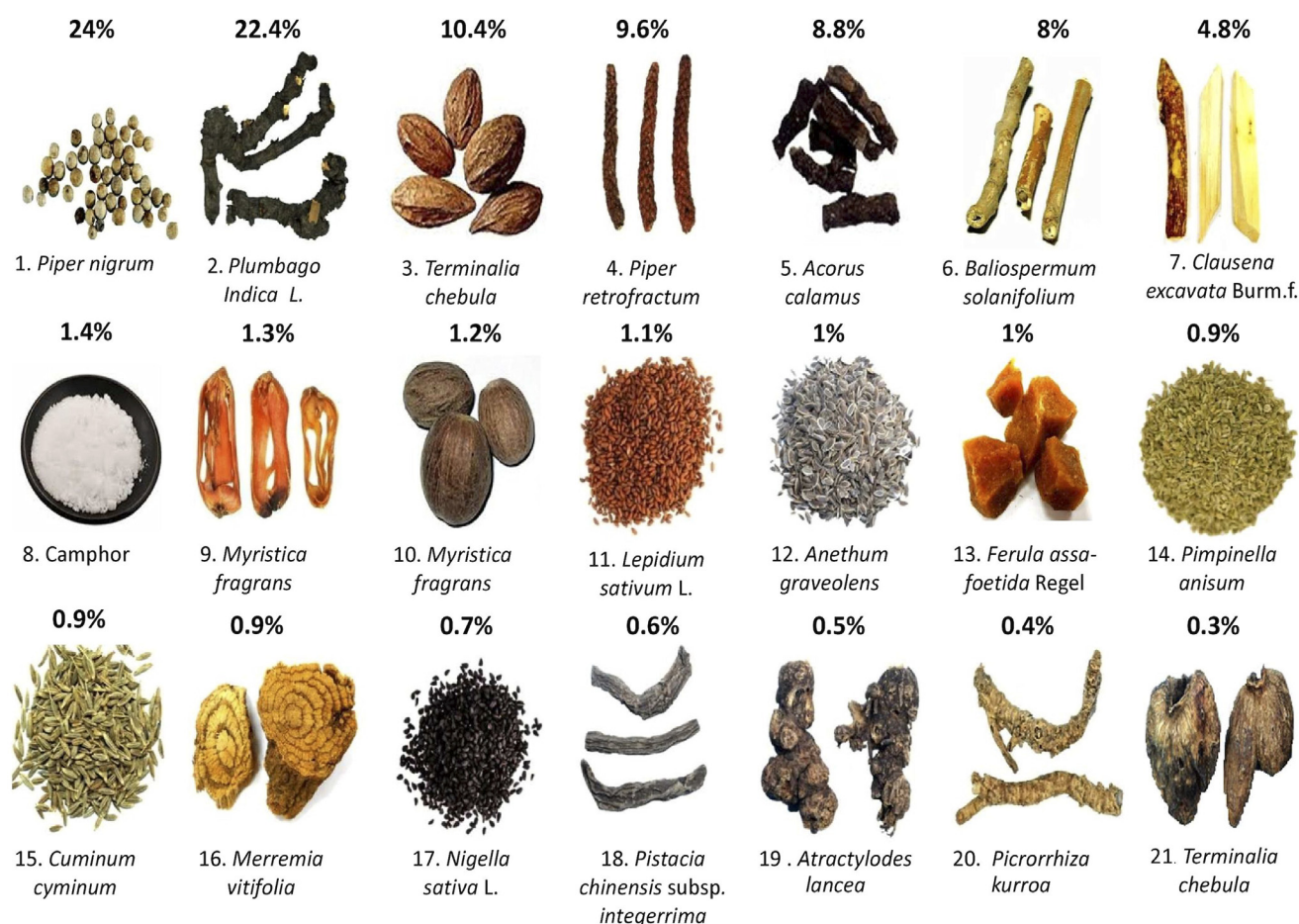
Currently, the number of people interested in natural products is increasing worldwide. Thai herbal Sahatsatara formula (STF) is a

Thai herbal Sahatsatara formula; UPLC, ultra high performance liquid chromatography; UV, ultraviolet; v/v, volume by volume; WKY, Wistar Kyoto rat.

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Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; C, degrees celsius; eV, electron-volts; G, gram; GMP, good manufacturing practice; h, hour; Kg, kilogram; L, liter; L-NAME, N^ω-nitro-L-arginine methyl ester hydrochloride; LOD, limit of detection; LOQ, limit of quantitative; μ, micro; mM, millimolar; Mg, milligram; min, minute; ml, milliliter; mm, millimeter; mmHg, millimeter of mercury; MS, mass spectrometry; m/z, mass to charge ratio; MTBE, Methyl tert-butyl ether; N, number of observation; nm, nanometer; NO, nitric oxide; NWR, normal wistar rat; %, percentage; QTOF, quadrupole-time-of-flight; R², coefficient of determination; RSD, relative standard deviation; RT, retention time; sec, second; SEM, standard error of mean; SHR, spontaneously hypertensive rat; STF,



Source: Department of Applied Thai Traditional Medicine, Faculty of Medicine Siriraj Hospital

Fig. 1. Percentage of twenty-one components in Thai herbal Sahatsatara formula (STF) in Thailand National List of Herbal Medicinal Products.

mixed powder of 21 components (National Drug Committee, 2011), shown in Fig. 1. This recipe has been prescribed by Thai traditional practitioners for more than 30 years and has been included in Thailand National List of Herbal Medicinal Products since AD 2011. STF is a pungent taste drug used for relief of muscle pain, flatulence and numbness on hands and feet. According to Thai traditional medicine theory, these conditions are caused by wind obstruction in parts of the body and pungent taste drug enhances wind and fire elements, causing blood and wind distribution comparable to enhancing blood circulation in western medicine. Previous *in vitro* study shows STF ethanolic extract has inhibitory effects on nitric oxide (NO) production, cyclooxygenase 2 (COX-2), and oxidative stress (Kakatum et al., 2012; Sakpakdeejaroen and Itharat, 2013). Subsequently, clinical study showed that STF relieves shoulder and neck pain (Nootim et al., 2013). In addition, eight components of STF have hemodynamic and vasodilatation effects, namely *Piper nigrum L.* (Taqvi et al., 2008), *Terminalia chebula Retz.* (Singh et al., 2010), *Acorus calamus L.* (Agarwal et al., 1956; Dandiya and Cullumbine, 1959; Shah, 2009), *Lepidium sativum Linn.* (Maghrani et al., 2005), *Ferula assa-foetida L.* (Fatehi et al., 2004), *Nigella sativa Linn.* (Ali and Blunden, 2003; Dehkordi and Kamkhah, 2008; Tahir et al., 1993), *Atractylodes lancea Thunb. DC* (Plengsuriyakarn et al., 2012) and *Picrorrhiza kurroa Royle ex Benth.* (Bäumer et al., 2007). Despite presence of such data, there is no scientific evidence for the effects of STF on hemodynamics as a combination as it has been prescribed. Moreover, the traditional medicine theory states that patients with hypertension should use this medication with

caution due to concerns regarding high blood pressure after administration (National Drug Committee, 2011), however, this caution has no scientific evidence.

Black pepper (*Piper nigrum L.*) is the most prominent component in STF. It contains piperine as an active compound. Piperine is also found in some other components of STF, and therefore is proposed as the most abundant active compound of STF. Prior study revealed that piperine caused vasodilatation effect in rat aorta (Taqvi et al., 2008). In addition, piperine is also shown to attenuate hypertension in N^{ω} -nitro-L-arginine methyl ester hydrochloride (L-NAME) induced hypertensive rat (Hlavackova et al., 2011; Kumar et al., 2010). In order to substantiate the current clinical contraindication regarding hypertensive patients, the hemodynamic changes and vasoactive activities, and mechanism of action of STF were investigated compared to piperine in spontaneously hypertensive rat (SHR). Furthermore, the amount of piperine in rat plasma was measured for pharmacokinetic study using ultra performance liquid chromatography (UPLC) technique.

Materials and methods

Materials and reagents

STF powder was obtained from Herbal Medicines and Products Manufacturing Unit, manufactured under GMP by Ayurved Siriraj, Center of Applied Thai Traditional Medicine (CAITM), Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand (GMP

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