Review

Pharmacological actions of *Uncaria* alkaloids, rhynchophylline and isorhynchophylline

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ABSTRACT

The pharmacological actions of *Uncaria* alkaloids, rhynchophylline and isorhynchophylline extracted from *Uncaria rhynchophylla* Miq Jacks were reviewed. The alkaloids mainly act on cardiovascular system and central nervous system including the hypotension, brachycardia, antiarrhythmia, and protection of cerebral ischemia and sedation. The active mechanisms were related to blocking of calcium channel, opening of potassium channel, and regulating of nerve transmitters transport and metabolism, *etc*.

INTRODUCTION

Gambirplant (Gouteng) is a traditional Chinese medicine which belongs to the plants of Rubinaceae genus. There were 34 gambirplant plants in the world distributed mainly in the torrid zone, and 14 kinds of gambirplant in south area of China, including provinces of Yunnan, Guangxi, Guizhou, Sicuan, Jiangxi, and Fujian, *etc*. Gambirplants used for the prescription of traditional Chinese medicine are mainly *Uncaria rhynchophylla* Miq Jacks, *Uncaria macrophylla* Wall, and *Uncaria sinensis* (Oliv) Havil, but *Uncaria sessilifructus* Roxb are also used some times[1]. Gambirplant in the prescription of traditional Chinese medicine was mainly used to treat ailments in the cardiovascular and central nervous systems, such as lightheadedness, convulsions, numbness, and hypertension, *etc*. It was reported[2] that the active pharmacological component was the alkaloids of *Uncaria rhynchophyllina*. The total alkaloid content in *Uncaria rhynchophyl-lina* is about 0.2 %, in which rhynchophylline (Rhy) is 28 %-50 %, isorhynchophylline (Isorhy) is 15 %. The other trace components include hirsutine, hirsuteine, corynantheine, dihydrocorynantheine, isocorynoxeine, akuammigine, geissoschijine, and methylethe[3-5]. The chemical structure of some alkaloids from *Uncaria rhynchophylla* Miq Jacks is shown in Fig 1. The pharmacological effects of Rhy and Isorhy were extensively studied, especially in the cardiovascular system.

TOTAL ALKALOID

The alkaloids, extracted from *Uncaria rhynchophyllina* Miq Jacks, are white crystals. The hypotensive effect was reported in 1970', and was used clinically[6-9]. The total effective rate of the alkaloid in the patients with mild to moderate hypertension was 83 %. The electrocardiogram (ECG) in one third of the patients with accompanied stress in left ventricle function become normal or nearly normal after the total alkaloid was administered. The early phase of hypotension (first 30 min) was mainly due to the decrease of peripheral vascular resistance after 15-30 mg of the al-

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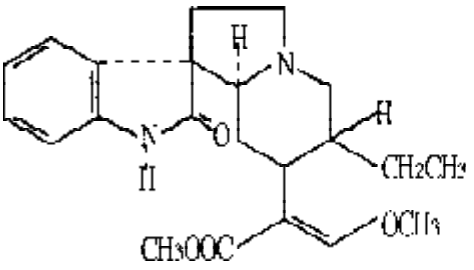
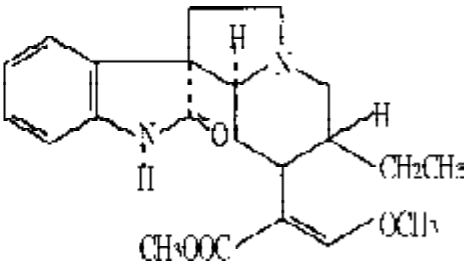
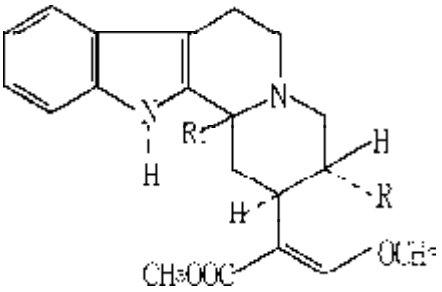


Rhynchophylline



Isorhynchophylline



	R	R_1
Hirsutine	$-CH_2CH_3$	beta-H
Corynantheine	$-CH=CH_2$	alpha-H
Hirsuteine	$-CH=CH_2$	beta-H
Dihydrocorynantheine	$-CH_2CH_3$	alpha-H

Fig 1. Chemical structure of Rhy and Isorhy and some minor components in *Uncaria rhynchophylla*.

kaloid were administered, one time per day. The subsequent sustained hypotensive effect was related with a decrease of cardiac output, which resulted from brachycardia and not from the inhibition of cardiac contractility.

In hypertensive rats, the total alkaloid at a dose of 50 $mg \cdot kg^{-1} \cdot d^{-1}$ was administered by intra-gavage for 20 d, the maximal decrease of blood pressure by 24 mmHg was observed at d 15 and the blood pressure remained at normal level for 5 d. In anesthetized cats, treatment with the alkaloid 20 mg/kg iv, decreased the blood pressure by 13.9 %-23.2 %, and the hypotensive effect was maintained for 3 h. In a hemodynamic study in anesthetized dogs, the treatment with alkaloid 20 mg/kg iv reduced the mean blood pressure for less than 5 min. However, the decrease of heart rate lasted for more than 30 min[10-12].

In experimental rabbits, the total alkaloid can inhibit sino-atrial node and ectopic pacemaker, delay the conduction between atrial-ventricule and intraventricule. ECG of rats was affected by the alkaloid. The interval of P-R, P-P, Q-T, and QRS waves were elongated markedly that was similar with the effects of class III antiarrhythmics, such as amiodarone. The alkaloid can inhibit arrhythmia induced by aconitine, calcium chloride, and barium chloride in rats and dogs, respectively, even arrhythmia of ventricular fibrillation induced by calcium chloride 150 mg/kg iv in 10 s[13]. In the arrhythmia induced by barium chloride, the alkaloid can normalize the cardiac rhythm, however, S wave was deepened, QRS wave was widened, and P wave was lost or reversed after the alkaloid was given. These changes of ECG in the arrhythmia model of barium chloride can be completely arrested by phenytoin[13-15], which acts by opening of potassium channel. These evidences indicated that the active mechanism of the alkaloids on myocardial electrophysiology was not the same with phenytoin.

The total alkaloids can inhibit the neuropotential and block nerve impulse conduction[13]. The inhibitive effect of the total alkaloid on toad sciatic nerve action potential was similar to quinidine. It was supposed that effect of the alkaloid resulted from block of Na^+ channel. Kuramochi *et al* reported that the Gouteng alkaloids induced endothelium-dependent and -independent relaxations in the isolated rat aorta[12]. Other evidence, including experiments of toad sciatic nerve, rabbit vertebral canal infiltration, mice sole infiltration, forearm skin test of human, also suggested that the alkaloid can block esthesia impulse conduction[16,17]. The blocking effect of the alkaloid on nerve conduction could last for 90-150 min. However, the alkaloids were not yet considered as the local anesthetics.

RHYNCHOPHYLLINE

The hypotensive effect of Rhy was also observed by Zhang and colleagues in 1978[4]. The peculiarity of Rhy was that renal blood flow was not significantly interfered upon lowering of blood pressure[18,19]. The decrease of renal blood flow is one of the serious side effects for many antihypertensive drugs, which can induce decrease of glomerular clearance rate and increase of renin secretion. Renin-angiotensin-system is one of the important factors contributing to hypertension. Although the effect of Rhy on the renin secretion remained unclear, the consequence of Rhy on the renal blood flow ought to be considered as an advantage.

The cardiovascular effects of Rhy was supposed due to calcium channel block. In an experiment with guinea pig, Rhy inhibited the left atrium post-rest potential enhancement and staircase phenomenon[20]. The post-rest potential enhancement induced by auxo-frequency stimulation is the characteristic of Ca^{2+} influx increase, and the calcium antagonists, such as verapamil, can reverse the staircase phenomenon. In isolated strips of rabbit aorta, Rhy inhibited $^{45}Ca^{2+}$ influx induced by K^+ 40 mmol/L. Effects of Rhy on the $^{45}Ca^{2+}$ influx and efflux induced by noradrenaline were small[21]. In another experiment using isolated rabbit aorta, Rhy inhibited the contraction induced by noradrenaline in both normal calcium and calcium-free medium[22]. Otherwise, although direct evidence that Rhy inhibited aortic contraction induced by caffeine is still absent, hirsutine, another indole alkaloid extracted from *Uncaria rhynchophylla* Miq Jacks, posseses similar pharmacological effects with Rhy. When hirsutine 30 mmol/L was added before caffeine treatment, the agent slightly but significantly reduced the caffeine-induced contraction. When added during Ca^{2+} loading, hirsutine definitely augmented the contractile response to caffeine. These results suggest that hirsutine inhibits Ca^{2+} release from the Ca^{2+} store and increases Ca^{2+} uptake into the Ca^{2+} store, leading to a reduction of intracellular Ca^{2+} level. It is concluded that hirsutine reduces intracellular Ca^{2+} level through its effect on the Ca^{2+} store as well as through its effect on the voltage-dependent Ca^{2+} channel[22]. The vasodilative effect of Rhy was mainly due to the dysfunction of Ca^{2+} transport, including influx of extracellular calcium and release of intracellular calcium by blocking the voltage-dependent calcium channel and the receptor-regulation calcium channel.

Brachycardia and cardiac contractility repression induced by Rhy were observed[23]. In the experiments of myocardial electro-physiology, Rhy decreased the zero phase elevation velocity (V_{max}) and amplitude of action potential in a concentration-dependent manner while the sinus rhythm was slowed significantly[24]. A direct evidence of Rhy blocking calcium channel came from the study by Wang and colleagues, in which Rhy 10 μmol/L and 50 μmol/L reduced verapamil-sensitive Ca^{2+} inward current by 60 % and 80 % on the myocyte, respectively, without affecting the voltage-dependency of the maximal activation of Ca^{2+} current. It indicated that the effect of Rhy on the activation of Ca^{2+} channel was voltage-independent[24]. A parallel result was also observed on the neurons[25-27]. Effect of Rhy on potassium channel was studied by Kaili and colleagues, in which Rhy 30, 45, and 60 μmol/L decreased the open time, but increased the open probability of calcium-activated potassium channels in concentration-dependent manner in isolated rat pulmonary artery smooth muscle cells[28]. Theses results indicated that the electrophysiological effects of Rhy resulted from the blockade of calcium channel and sodium chanel, and opening of potassium channel, respectively. Furthermore, Zhu *et al* reported that Rhy did not antagonize the heart rate increase induced by atropine or isoprenaline[29]. It was proposed that the brachycardia and cardiac contractility repression effects of Rhy was not related with the block of muscarinic receptor or beta-adrenergic receptor.

Rhy inhibited rabbit platelet aggregation induced by arachidonic acid (AA), collagen, and ADP, and reduced the thromboxane B_2 (TXB_2) generation in platelet rich plasma (PRP) induced by collagen but failed to reduce TXB_2 generation that induced by AA. Rhy suppressed malondialdehyde (MDA) formation in platelet suspension stimulated by thrombin, inhibited the platelet factor 4 (PF4) release. It did not alter intraplatelet cAMP concentration. Rhy 10-20 mg/kg iv showed a significant inhibition on venous thrombosis and cerebral thrombosis in rats[29-31].

Rhy can relieve contraction of respiratory tract smooth muscle and uterus smooth muscle induced by agonist[32], in which a mechanism of calcium channel blocking was also proposed.

In the prescriptions of traditional Chinese medicine for treatment of convulsion, epilepsy, eclampsia, and cerebral apoplexy, *Uncaria rhynchophylla* is always included as an essential herb ingredient. In our and other laboratories, a significant sedative effect of Rhy

was observed. However, no hypnosis was observed while it was used alone. It inhibited the epileptic seizure in rats model induced by chemicals. In an experiment of animals, Rhy reduced the spontaneous motor activity and enhanced the sedative and hypnotic effects of sodium pentobarbital in mice. In a cultured brain slices of rats, Rhy increased the 5-HT content in the hypothalamus and cortex, but reduced the dopamine (DA) concentrations in the cortex, amygdala, and spinal cord. Rhy promoted the release of endogenous DA from hypothalamus, cortex, amygdala, and spinal cord. The release of 5-HT was increased in cortex and amygdala, and was decreased in hypothalamus slice. However, Rhy inhibited the release of both 5-HT and DA evoked by high potassium[4,29]. In our laboratory, a significant protective effect on cerebral ischemia in mice and rats was observed (data not shown). The active mechanisms of Rhy on central nervous system is to be further studied, including the transmitters metabolism and ions channel modulation. In the model of ischemia-reperfusion of rat brain, Kaili *et al* reported that the expression of nitric oxide synthase was increased in cortex and hippocampus[26]. We have reported that Rhy can protect neurons from damage induced by dopamine, which behaves as a free radical at higher concentration[34]. Taken together, calcium channel blockade, transmitters metabolism modulation, anti-free radicals, as well as an amelioration of hemorrheology may be involved in the central nervous system protection.

ISORHYNCHOPHYLLINE

The cardiovascular effects of Isorhy, such as calcium channel blockade, were similar to that of Rhy. The available evidence has shown that the cardiovascular effects of Isorhy, including the hypotension in conscious rats, anesthetized dogs, renal hypertensive rats, the negative chronotropic effect and negative inotropic effect, were due to the calcium channel blockade[35-41]. However, the potency and duration of the effects of Isorhy was higher than those of Rhy. In anesthetized rats, Isorhy decreased blood pressure by 42.0 % (Rhy by 32.1 %, and total alkaloid by 21.3 %)[31-33]. In anesthetized thoracotomized dogs, Rhy (5 mg/kg, iv) reduced the mean arterial pressure by 9 mmHg, whereas Isorhy (1 mg/kg, iv) reduced the mean arterial pressure by 26.9 mmHg[18]. Another difference between Rhy and Isorhy is that Isorhy does not show ganglion blocking effect. In our previous study, Isorhy did not block nictitating membrane contraction induced by stimulating collum sympathetic nerve, and it did not decrease blood pressure when it was injected in cerebral ventricle[38]. The reason for these difference is not clear and warrants further studies.

In preparing traditional Chinese medicine decoction, *Uncaria rhynchophylla* should be added last when the herbs of the prescriptions were decocted. In our recent study, we found that when Isorhy was dissolved in solutions for one week, a significant part of Isorhy was converted to Rhy (to be published). The instability of Isorhy may be the partial explanation that *Uncaria rhynchophylla* should be added last.

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