Drugs of the Future 1999, 24(8): 877-882

CCC: 0377-8282/99

Review Article

Alkaloids of Chinese Aconitum plants

Xing-Wang Wang and Hong Xie

Shanghai Institute of Cell Biology, Chinese Academy of Sciences, 320 Yue-Yang Road, Shanghai 200031, P.R. China

CONTENTS

Introduction

In Chinese traditional medicine, *Aconitum* plants have been frequently used as a component of numerous prescriptions used for the treatment of cold- and dampness-induced ailments, rheumatoid arthritis and various types of pain including migraine, swelling induced by trauma and fracture, facial paralysis, *etc*. In the early 1950s, phytochemists in China began to study the active principle in *Aconitum* plants. Since then, the screening of these plants for a wide range of biological activities continues and many alkaloids have been isolated from plants of the *Aconitum* genus (1). Pharmacological studies show that at very low doses, many alkaloids from these plants exhibit analgesic, antiinflammatory, immunomodulating, antiarrhythmic, antithermic, as well as local anesthetic activities, without obvious toxicity. Some of the alkaloids have completed preclinical testing and are now in clinical trials for the treatment of various types of pain and rheumatoid arthritis.

The present paper briefly describes the source and chemistry, pharmacological actions, pharmacokinetics, toxicity and clinical effects of alkaloids of Chinese *Aconitum* plants.

Source and chemistry

There are about 170 species of plants of the *Aconitum* genus throughout China, found mainly in provinces located in the southwest and northwest. More than 40 *Aconitum* species have been reported to be used medicinally for various ailments and about 20 species have been scientifically tested in China. In the past decades, Chinese chemists have extracted, isolated and identified more than 150 types of alkaloids from these plants, including known alkloids and some new ones. Among them are 3-acetylaconitine, bulleyaconitine A, *N*-deacetylranaconitine, *N*-deacetylfinaconitine, penduline, beiwutine, nagarine, 3-*O*-acetylbeiwutine, karakomine, *N*-deacetyllappaconitine, 3,15-diacetylbenzoylaconine, polyschistine A-D and others (2-4). In addition, 3-*O*-acetylbeiwutine can also be obtained by chemical transformation from beiwutine (5) and 3-acetylaconitine can be semisynthesized from yunaconitine (6).

Chemically, most of the alkaloids of *Aconitum* plants are diterpene compounds which can be divided into two classes: C19 and C20. Other nonditerpene alkaloids such as guan-fu bases and higenamine are also present in plants of the *Aconitum* genus (7). The chemical structures of some alkaloids are shown in Figure 1. Generally, the diterpene alkaloids of the C19 type are more bioactive and more toxic than those of the C20 type and the nonditerpene alkaloids.

Pharmacological actions

In therapeutic doses, the alkaloids in Chinese *Aconitum* plants exhibit various pharmacological activities which have attracted many Chinese researchers.

Analgesic

The analgesic action of many *Aconitum* alkaloids has been investigated in detail using such methods as acetic acid-induced writhing, hot plate test, formaldehyde-elicited continuous pain stimuli in mice and tail-flick response to light irradiation in rats. The analgesic effects of these compounds are summarized in Table I. Some alkaloids (*e.g*, bulleyaconitine A) had more potent analgesic effects than morphine and aspirin (8), and the duration of effect of bulleyaconitine A and 3-acetylaconitine was longer than that of morphine. Lappaconitine, 3-acetylaconitine and *N*-deacetyllappaconitine potentiated the analgesic action of morphine, an effect which was reversed by naloxone. However, naloxone did not affect

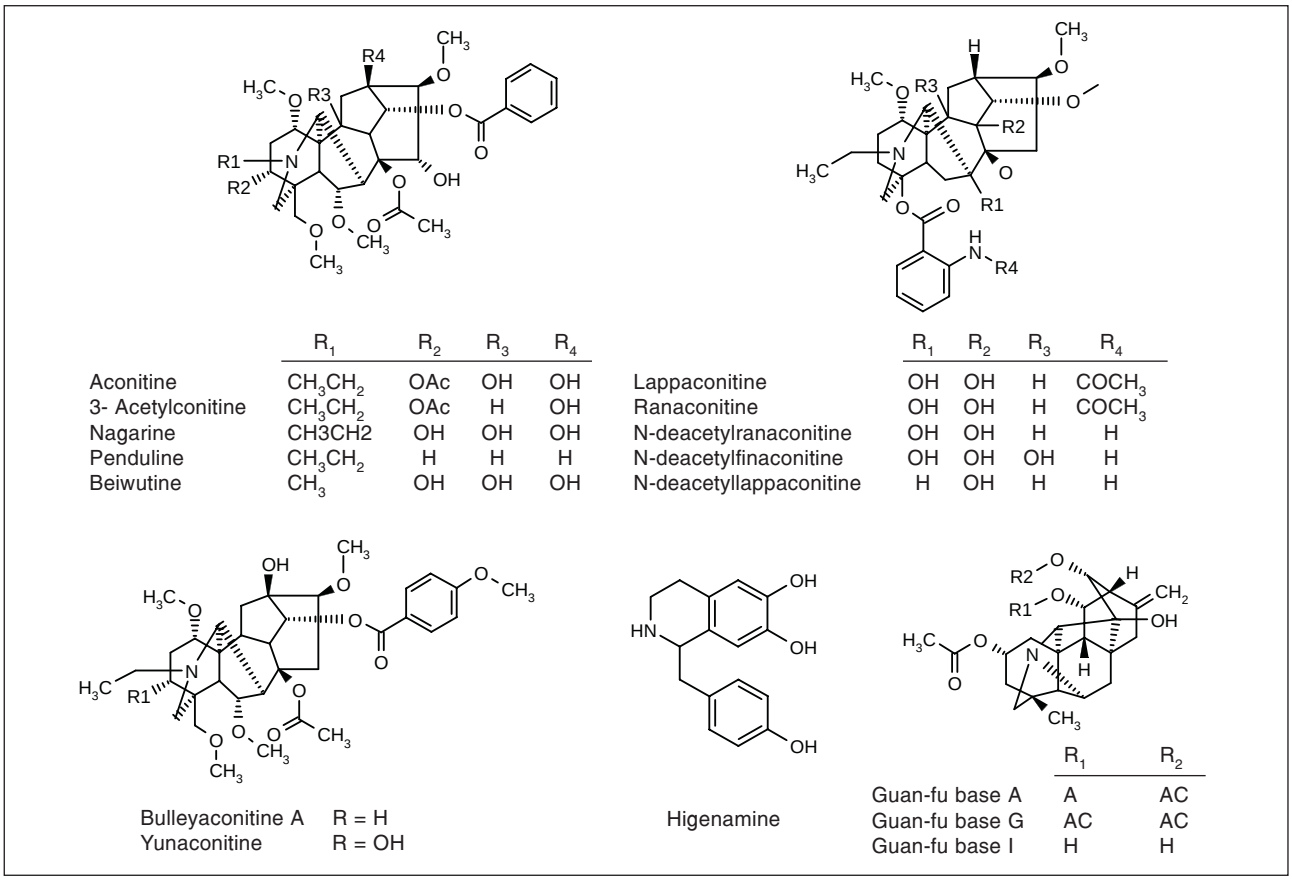

Fig. 1. Chemical structures of alkaloids from Chinese *Aconitum* plants.

the analgesia induced by these alkaloids (9-11). The analgesic actions mediated by 3-acetylaconitine, bulleyaconitine A and lappaconitine could be abolished by reserpine and were enhanced by elevation of brain 5-HT or norepinephrine. Analgesia induced by these three compounds was also found to be attenuated or augmented by administration of chemicals related to brain monoamines. These results indicate that the central catecholaminergic and serotonergic systems are involved in the modulation of analgesia induced by the alkaloids (12, 13).

Further studies found that the analgesic action of 3,15-diacetylbenzoylaconine was abolished or reduced by reserpine, diethyidithiocarbamate, phenoxybenzamine and yohimbine, although prazosin and propranolol had no effect. It is suggested that the analgesia mediated by the compound may be related to α_2-adrenoceptors of the central noradrenergic system (14). In contrast, the analgesic action of lappaconitine was reduced with calcium chloride treatment and augmented by ethylene glycol tetraacetic acid. The calcium antagonists nifedipine and verapamil partially reversed the calcium-antagonistic effect on analgesia induced by lappaconitine (15). Electrolytic or kainic acid lesion experiments showed that superspinal sites, especially the periaqueductal gray and nucleus raphe magnus, are involved in lappaconitine- and *N*-deacetyllappaconitine-induced analgesia (16).

In contrast to the central analgesic effect of opiates, tolerance did not develop when mice were repeatedly injected with 3-acetylaconitine, bulleyaconitine A and lappaconitine. Moreover, abstinence syndrome was not observed after sudden withdrawal of the alkaloids and upon nalophine challenge. No physical dependence on the alkaloids was observed in rats and monkeys. Footshock-induced analgesia showed a cross-tolerance to morphine-induced analgesia, whereas lappaconitine and *N*-deacetyllappaconitine had no such effect. These results indicate that lappaconitine, bulleyaconitine A, 3-acetylaconitine and *N*-deacetyllappaconitine belong to the nonnarcotic class of analgesics (11, 17).

Antiinflammatory

Some *Aconitum* alkaloids have been identified as having antiinflammatory effects in several animal models of inflammation (6, 8, 9, 18-22).

In ovalbumin- and formaldehyde-induced paw swelling in rats, aconitine (0.05 mg/kg) and 3-acetylaconitine (0.05 mg/kg) had equivalent or slightly stronger antiinflammatory effects as compared to sodium salicylate (200 mg/kg). *N*-Deacetylaconitine had significant inhibitory effects on various acute inflammation models of

Table I: Analgesic effects of Aconitum *alkaloids in mice.*

Alkaloid	ED_{50} (mg/kg s.c.) Hot plate	Writhing
Aconitine	0.13	0.06
3-Acetylaconitine	0.16	0.16
Lappaconitine	5.60[+]	3.50
Ranaconitine	0.04	4.20
Yunaconitine	0.09	0.04
Bulleyaconitine A	8.60	0.05
N-Deacetylaconitine	NT	2.30
N-Deacetyllappaconitine	7.10[*]	2.30
N-Deacetylranaconitine	NT	8.60
N-Deacetylfinaconitine	NT	8.60
Avadharidine	NT	52.20
Lycoctonine	NT	144
Penduline	0.94	0.89
Mesaconitine	0.07	0.04
Beiwutine	0.15	0.06
Songoline	100[++]	NT
Neoline	150[++]	NT
Denudatine	50[++]	NT
Deoxyaconitine	0.90	0.48
Hypaconitine	0.65	0.31
Nagarine	NT	0.14
Morphine[**]	5.70	0.80
Aspirin[**]	626	195
3,15-Diacetylbenzoylaconine	3.50	2.76

NT: not tested; [*]formaldehyde test; [**]reference compound; [+]effective dose; [++]ineffective dose.

exudation and edema, and also had a higher therapeutic index than 3-acetylaconitine, as demonstrated by weaker action and lower toxicity. Aconitine, 3-acetylaconitine and *N*-deacetylaconitine had no effect on the proliferation of late-phase inflammation. Lappaconitine and *N*-deacetyllappaconitine exhibited significant antiinflammatory action on rat paw swelling induced by ovalbumin and carrageenin and suppressed inflammatory granuloma caused by cotton pellets; the antiinflammatory action of these compounds was independent of the adrenal glands. Among the known alkaloids, yunaconitine was identified as having the strongest antiinflammatory action, being about 5-10 times more potent than 3-acetylaconitine and having a larger therapeutic index. Yunaconitine inhibited inflammatory exudation, edema, granuloma and leukocyte migration. Its antiinflammatory effects were independent of the pituitary-adrenal cortex system. Guan-fu base A (98 mg/kg i.p.) had similar antiinflammatory effects as sodium salicylate (400 mg/kg). The antiinflammatory mechanisms of action of higenamine, the main crude drug used by doctors of traditional Chinese medicine for the treatment of rheumatic diseases, may be related to its scavenging of free radicals and inhibition of lipid superoxidation.

Taken together, the *Aconitum* alkaloids exhibited potent antiinflammatory effects on exudation and edema in early-phase inflammation and some compounds were also able to suppress late- phase inflammation. Their antiinflammatory effects were independent of the pituitary-adrenal cortex system, thus differing from conventional steroidal antiinflammatory agents.

Immunomodulating

The inflammatory process *per se* is considered to be an immunological response. Inflammation may be the initiation or latest manifestation of immunological responses. Many mediators and modulators of the inflammatory process also mediate and modulate immunological responses. Therefore, it is important to study the effects of antiinflammatory agents of natural origin on immune function. This work is now being carried out in China.

Aconitine was found to significantly increase IFN-γ-induced peritoneal macrophage Ia expression in normal mice. Moreover, the corticosterone-inhibited expression in "Yang-deficient" mice was also enhanced by aconitine treatment. These results suggest that the compound could enhance the antigen-presenting ability of macrophages and promote the immune response (23).

Yunaconitine also had immunomodulatory effects in addition to analgesic and antiinflammatory activity (24). When excised heart tissue of newborn mice was transplanted into ear pinna of adult mice, yunaconitine markedly prolonged the survival time of allografts, its effect being comparable to that of the immunosuppressant, prednisolone. Inhibition of delayed-type hypersensitivity was also observed in rats administered the compound. In experiments in mice, yunaconitine had no effect on serum hemolysin and IgG levels, but decreased plaque-forming cell counts in spleen. The compound also increased serum total complement as well as the phagocytic activity of the reticuloendothelial system in mice, which is considered to be beneficial in the clearance of pathogenic antigens (Table II).

Antiarrhythmic

Results from animal studies suggest that guan-fu base A, G and I have antiarrhythmic activity (25-27). These compounds were shown to counteract choroform-induced ventricular fibrillation in mice and increase the dose of beiwutine necessary for inducing cardiac arrhythmias in anesthetized rats. In isolated guinea pig hearts, guan-fu base A and G antagonized electrically induced ventricular fibrillation, reduced heart rate, prolonged P-R and QRS intervals and prolonged the functional refractory period in isolated left atria.

Lappaconitine at low doses decreased heart rate, increased P-R interval, prevented barium chloride-induced arrhythmia and increased the dose of ouabain required to induce arrhythmia. In addition, low doses of lappaconitine had significant antagonistic effects on arrhythmia induced by 3-acetylaconitine without affecting the analgesic action of the compound (28, 29). Low doses of aconitine antagonized the T inversion caused by calcium chloride, in addition to antagonizing the initial elevation and subsequent depression of the ST segment induced by posterior pituitary preparations in rabbits (30). Using the cell-attached configuration of the patch-clamp technique, the single channel activities of L-type calcium

Table II: Immunomodulating activity of yunaconitine (YAC, i.p.) in mice.

Group	Dose (μg/kg)	Heart Survival (days)	DTH	Complement	Phagocytic index
Control	-	8.7	3.5	55	3.56
YAC	5	NT	1.7	NT	NT
YAC	10	NT	0.6	NT	NT
YAC	20	NT	NT	65	3.63
YAC	50	10.3	NT	66	4.40

NT: not tested; DTH: delayed-type hypersensitivity.

Table III: Anesthetic effects of Aconitum *alkaloids on sciatic nerve block in mice.*

Alkaloid	IC_{50} (mg/kg)
Aconitine	0.007
3-Acetylaconitine	0.003
Lappaconitine	0.040
Ranaconitine	0.100
Yunaconitine	NT
Bulleyaconitine A	0.003
N-Deacetylaconitine	0.076
N-Deacetylranaconitine	0.100
N-Deacetylfinaconitine	0.102
N-Deacetyllappaconitine	0.076
Avadharidine	1.000^{+}
Lycoctonine	1.000^{+}
Penduline	0.105
Mesaconitine	0.004
Beiwutine	0.050^{+}
Songoline	17.400
Neoline	20.000^{+}
Denudatine	20.000^{+}
Deoxyaconitine	0.011
Hypaconitine	0.016
Nagarine	0.010^{+}
Cocaine*	0.250

NT: not tested; *reference compound; $^{+}$ineffective dose.

channels of ventricular myocardiocytes from neonatal rats were recorded before and after the addition of aconitine, with results demonstrating a blocking effect of the agent at low doses (31). However, high doses of lappaconitine and aconitine caused ventricular premature beats, ventricular tachycardia, ventricular fibrillation and cardiac arrest.

Miscellaneous

Some alkaloids of Chinese *Aconitum* plants, such as bulleyaconitine A, yunaconitine, lappaconitine and 3-acetylaconitine, were shown to possess antithermic effects in normothermic and pyrexial rodents (6, 8, 9, 18). Many alkaloids also had local anesthetic activity, as shown by sciatic nerve block in mice (8, 9, 32) (Table III).

Pharmacokinetics

Preliminary studies on absorption, distribution and excretion of bulleyaconitine A have been performed in rats after administration of [^{3}H]-bulleyaconitine A (8). The plasma concentration-time curve of the agent was shown to fit a three-compartment open model. Its half-life ($t_{1/2}$) was as follows: $t_{1/2\pi}$ = 2.87 min; $t_{1/2\alpha}$ = 11.6 min; $t_{1/2\beta}$ = 5 h. Volume of distribution was 1.79 l/kg and total plasma clearance rate was 4.12 ml/kg/min. After i.v. administration, high concentrations were found in the liver, kidney, lungs, spleen and heart; there was low distribution in the brain. Of the total dose, 46% was excreted from urine and 21.9% from feces within 6 days after administration.

Toxicity

Acute lethal doses (LD_{50}) of some of the *Aconitum* alkaloids are shown in Table IV. In rats, rabbits and dogs, continuous administration of bulleyaconitine A for 30 (rat) or 90 days (rabbit and dog) caused no significant drug-related changes in body weight and hematological tests. There was no liver or renal toxicity, and hereditary tests showed no mutagenic effects of the compound (8).

In clinical studies with bulleyaconitine A, there were no significant drug-related changes in liver and kidney

Table IV: Acute toxicity of Aconitum *alkaloids in mice.*

Alkaloid	LD_{50} (mg/kg s.c.)
Aconitine	0.31
3-Acetylaconitine	1.40
Lappaconitine	11.70
Ranaconitine	9.00
Yunaconitine	0.37
Bulleyaconitine A	0.92
N-Deacetylaconitine	36.40
N-Deacetylranaconitine	27.50
N-Deacetylfinaconitine	>50.00
N-Deacetyllappaconitine	36.40
3,15-Diacetylbenzoylaconine	21.68
Avadharidine	45.90
Lycoctonine	>500.00
Penduline	3.90
Mesaconitine	0.16
Beiwutine	0.39
Songoline	>300.00
Neoline	>400.00
Denudatine	207.00
Deoxyaconitine	2.80
Hypaconitine	2.80
Nagarine	1.22
Guan-fu base A	582.20 (i.p.)
Guan-fu base G	185.50 (i.p.)

Table V: Clinical effects of bulleyaconitine A on various types of pain.

Pain	Patients	Response Rate (%)
Periomitis	197	92.4
Rheumatism	442	91.3
Benign joint	71	100.0
Lumbago	134	99.3
Toothache	62	100.0
Postoperative	154	79.9

function, hematological tests, urinalysis and electrocardiogram in most patients. Abstinence syndrome was not observed after sudden withdrawal of the agent. The most common side effects were nausea and dizziness; mild cutaneous allergic reactions occurred in some patients (8).

Clinical effects

Some of the *Aconitum* alkaloids, such as 3-acetylaconitine, bulleyaconitine A, lappaconitine and guan-fu base A, are under clinical investigation to evaluate their efficacy.

3-Acetylaconitine had potent analgesic activity and was effective in the treatment of several types of chronic pain (*e.g.*, periomitis, vertebral cervical disease, lumbago, leg pain) in a clinical trial in 1500 patients; overall response rates were 95-99% (11).

Bulleyaconitine A reduced inflammatory swelling, eased pain and improved function in patients with rheumatoid arthritis. In addition, laboratory results (*i.e.,* rheumatoid factor) for some patients were improved. Most patients in the active period of disease reported a satisfactory treatment effect. In 412 patients with rheumatism, total response rates of 91.6% were obtained (8). The compound was also effective in the treatment of various types of acute and chronic pain (Table V).

Lappaconitine has also been introduced into the clinic for the treatment of pain and clinical trials of the antiarrhythmic effects of guan-fu base A are currently under way (32).

Conclusions

The alkaloids from Chinese *Aconitum* plants are examples which demonstrate the role of traditional Chinese medicines in new drug development. In the past decades, Chinese pharmacologists, chemists and clinicians have extensively studied the chemical constituents, biological activities and clinical efficacies of these alkaloids (32). Some of the *Aconitum* alkaloids have the potential to be developed as new drugs for the treatment of various kinds of pain, inflammatory diseases and cardiac arrhythmias. However, at high doses, some of them (*e.g.*, aconitine, beiwutine, 3-acetylaconitine and lappaconitine) induce arrhythmias, a sign of severe toxicity. Therefore, it will be necessary to carefully monitor the doses administered in clinical practice to reduce toxicity. These alkaloids possess potent biological activities, indicating that it is possible to develop new and highly effective drugs by separating new components from the genus or reconstructing the structures of existing compounds.

References

1. Bai, D.L. *Traditional Chinese medicines and new drug development*. Pure Appl Chem 1993, 65: 1103-12.

2. Wang, Y.G., Zhu, Y.L., Zhu, R.H. *Alkaloids from Aconitum kusnezoffii*. Acta Pharm Sin 1980, 15: 526-31.

3. Huang, B.S., Wang, H.C., Lao, A.N. *Studies on the alkaloids from Aconitum karakolicum Rap*. Heterocycles 1991, 32: 2429-32.

4. Wang, H.C., Lao, A.N. *Studies on the alkaloids from Aconitum polyschistum Hand-Mazz*. Heterocycles 1988, 27: 1615-21.

5. Zhu, D.Y., Lin, L.Z., Cordell, G.A. *3-O-Acetylbeiwutine from Aconitum liaotungeuse.* Phytochem 1993, 32: 767-70.

6. Tang, X.C., Lin, Z.G., Cai, W., Chen, H., Shen, L. *Antiinflammatory effect of 3-acetylaconitine*. Acta Pharmacol Sin 1984, 5: 85-9.

7. Wang, F.P. *A review of the chemical studies on the alkaloids from Aconitum and Delphinium plants*. Acta Pharm Sin 1981, 16: 943-59.

8. Tang, X. C. *Bulleyaconitine A, a new analgesic and antiinflammatory agent*. New Drugs Clinic (China) 1986, 5: 120-1.

9. Tang, X.C., Zhu, M.Y., Feng, J., Wang, Y.E. *Studies on the pharmacological action of lappaconitine hydrobromide*. Acta Pharm Sin 1983, 18: 579-86.

10. Guo, X., Tang, X.C. *Lappaconitine and N-deacetyllappaconitine potentiate foot shock-induced analgesia in rats*. Life Sci 1991, 48: 1365-70.

11. Tang, X.C., Liu, X.J., Feng, J., Zhu, M.Y., Li, A.L. *Analgesic action and no physical dependence of bulleyaconitine A*. Acta Pharmacol Sin 1986, 7: 413-8.

12. Guo, X., Tang, X.C. *Effect of reserpine and 5-HT on analgesia induced by lappaconitine and N-deacetyllappaconitine*. Acta Pharmacol Sin 1990, 11: 14-8.

13. Lu, D.X., Guo, X., Tang, X.C. *Effect of monoamine transmitters on analgesia induced by 3-acetylaconitine*. Acta Pharmacol Sin 1988, 9: 216-20.

14. Zhang, H.L., Yang, Y.R., Wang, Y. et al. *Relationship between 3,15-diacetylbenzoylaconine-induced analgesia and central noradrenergic system*. Chin J Pharmacol Toxicol 1993, 7: 6-9.

15. Guo, X., Tang, X.C. *Effect of central Ca^{2+} on analgesic action of lappaconitine*. Acta Pharmacol Sin 1989, 10: 504-7.

16. Guo, X., Tang, X.C. *Roles of periaqueductal gray and nucleus raphe magnus on analgesia induced by lappaconitine, N-deacetyllappaconitine and morphine*. Acta Pharmacol Sin 1990, 11: 107-12.

17. Tang, X. C., Liu, X.J., Lu, W.H., Wang, M.D., Li, A.L. *Studies on the analgesic action and physical dependence of bulleyaconitine A*. Acta Pharmacol Sin 1986, 21: 886-91.

18. Lin, Z. G., Cai, W., Tang, X.C. *Antiinflammatory and analgesic action of yunaconitine*. Chin J Pharmacol Toxicol 1987, 1: 93-9.

19. Liu, J.H., Zhu, Y.X., Tang, X.C. *Antiinflammatory and analgesic activities of N-acetyllappaconitine and lappaconitine*. Acta Pharmacol Sin 1987, 8: 301-5.

20. Jiang, Y., Wu, H.Q., Liu, J.H. et al. *The pharmacological studies on guan-fu base A*. Chin Trad Herb Drugs 1987, 18: 23-6.

21. Song, D.J., Lu, M.W., Li, H.Q. et al. *Antiinflammatory, analgesic and antipyretic effect of deoxyaconitine*. Chin Pharmacol Bull 1987, 3: 157-61.

22. Zhang, J.J., Chen, W.W. *Protection of synovial fluid by higenamine*. Acta Pharmacol Sin 1985, 20: 423-6.

23. Ma, J., Lu, P.C., Makino, M. et al. *The effect of aconitine on Ia expression of peritoneal macrophages of mice.* Chin Pharmacol Bull 1997, 13: 341-4.

24. Li, X.Y., Jiang, K.M., Kin, Z.Y. *Immunomodulating action of yunaconitine*. Chin J Pharmacol Toxicol 1987, 1: 100-4.

25. Chen, W.Z., Dong, Y.L., Zhang, Y.F., Ding, G.S. *Antiarrhythmic effect of guan-fu base*. Acta Pharmacol Sin 1983, 4: 247-50.

26. Hou, D.H., Wu, L.Y., Xu, W.R., Liu, J.H. *Antiarrhythmic effect of guan-fu base G compared with guan-fu base A and I*. J China Pharm Univ 1987, 18: 268-72.

27. Wang, Y.P., Chen, W.Z., Sun, W.K., Wu, J.X. *Hemodynamic action of guan-fu base A in anesthetized rats*. Acta Pharmacol Sin 1992, 13: 231-4.

28. Wang, P.D., Ma, X.M., Zhang, H.L. et al. *Effect of lappaconitine on ECG in anesthetized rats and its antiarrhythmic action*. Chin Pharmacol Bull 1997, 13: 263-5.

29. Wang, P.D., Ma, X.M., Yatig, Y.R. et al. *Effect of lappaconitine on the toxicity and analgesic activity of 3-acetylaconitine in their combination*. Chin Pharmacol Bull 1993, 9: 382-5.

30. Liu, S.F., Yang, Y.Z. *The influence of total alkaloid of Aconitum kusnezoffii Reichb and aconitine on changes of ECG induced by several drugs*. Acta Pharm Sin 1980, 15: 520-5.

31. Chen, L., Ma, C., Cai, B.C., Lu, Y.M., Wu, H. *Single channel analysis of aconitine blockade of calcium channels in rat myocardiocytes*. Acta Pharm Sin 1995, 30: 168-71.

32. Zhu, D.Y., Bai, D.L., Tang, X.C. *Recent studies on traditional Chinese medicinal plants*. Drug Dev Res 1996, 39: 147-57.