HYPOTENSIVE PRINCIPLES FROM PLANTS†

Shinji Funayama and Hiroshi Hikino*

Pharmaceutical Institute, Tohoku University, Aoba-yama, Sendai, Japan

Abstract — This review article summarizes our knowledge regarding the structure, occurence and activity of known substances showing hypotensive activity in the plant kingdom.

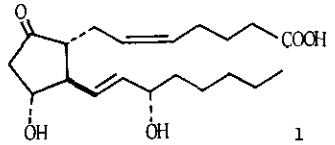
1. Introduction

The discovery of physiologically active principles in crude drugs originating from plants and animals began with the isolation of morphine from opium by Sertürner at the outset of the 19th century. At that moment, it became clear that the therapeutic effects of crude drugs are effected by chemical substances present in them, and scientists acquired the conception of active principles of crude drugs. Since then, the active principles of a large number of crude drugs have been identified but there are numerous crude drugs whose active principles have not yet been elucidated, although their activities have been substantiated. The purpose of this review article is to survey the structure, occurrence and activity of hypotensive principles of the crude drugs of plant origin and, hopefully, to stimulate continuing interest in this field.

The impossibility of covering all papers published in this field compelled us to limit ourselves mainly to those referred to in *Chemical Abstracts*.

2. Fatty acids

Since the water extract of a red alga, *Gracilaria lichemoides* (Gracilaceae), showed potent anti-hypertensive activity when dosed *i.v.* to pentobarbitone-anesthetized hypertensive rats, it was subjected to a sequence of chromatographic separations, guided by the hypertensive rat bioassay, to yield the anti-hypertensive prostaglandin E_2 (1) and the inactive prostaglandin $F_{2\alpha}$.[1]



1

† Dedicated to Professor Tetsuji Kametani on the occasion of his retirement from Pharmaceutical Institute of Tohoku University.

3. Amino acids, peptides and proteins

3-1. Amino acids

There are in plants, various amino acids in which those reported as hypotensive principles are restricted to non-protein amino acids.

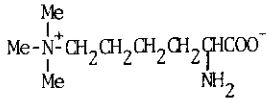
γ-Aminobutyric acid (GABA, 2) is biosynthetically formed by decarboxylation of glutamic acid

$$H_2NCH_2CH_2CH_2COOH \qquad 2$$

and had already been synthesized as early as the end of the last century. The presence of this amino acid in the vegetable kingdom was first detected in 1941 by Dent[2] in an extract of *Solanum tuberosum* (Solanaceae) by means of two-dimentional paper partition chromatography. Steward[3] later isolated this substance and unambiguously identified it. In the 1950's, GABA suddenly came into the limelight when it was established that it existed in the brain tissues of animals including humans.[4] At present, it is recognized as having wide physiological activity, including hypotensive and diuretic effects,[5-7] and is particulary being watched with interest as an inhibitory transmitter.[8-10]

Meanwhile, it has been revealed that GABA is widely distributed in the vegetable kingdom. Thus, in 1962, Durand et al.[11] isolated GABA as the hypotensive principle from the leaves of *Artocarpus altilis* (Moraceae) and *Piper amalgo* (Piperaceae). Recently, Hikino et al.[12] identified GABA as the hypotensive principle of the oriental medicine "ōgi", prepared from the roots of *Astragalus* and *Hedysarum* plants (Leguminosae), and determined its concentration in a number of samples in connection with the evaluation of the quality of the crude drug. As a result it was revealed that the hypotensive activity of various samples of "ōgi" showed a good correlation with the content of GABA. Quite recently, Funayama and Hikino[13] demonstrated that one of the active principles of the crude drug "shōriku", the roots of *Phytolacca esculenta* and *P. japonica* (Phytolaccaceae), was also GABA.

Since the crude drug "kombu" prepared from a seaweed, *Laminaria japonica* (Laminariaceae), and allied plants, is widely used for hypotensive purposes in the folkloric medicine of Japan, Kameda[14] examined the clinical utility of "kombu" (the blades) and found that oral administration of a hot water extract to patients with essential hypertension elicited a significant hypotensive effect with no appreciable side effects. From *Laminaria angustata* was isolated a basic amino acid, laminine (trimethyl-(5-amino-5-carboxypentyl)-ammonium, 3)[15] the oxalate of which was shown by Ozawa et al.[16] to exhibit a weak hypotension in urethane-anethetized rabbits (20 mg/kg, *i.v.*).



3

3-2. Peptides

Knowledge on peptides showing hypotensive activity is limited to that purified from *Daemia extensa* (Asclepiadaceae). This peptide when hydrolyzed afforded lysine, serine, glutamic acid, glycine, proline, tyrosine, valine and leucine. Administration of the peptide to cats and dogs produced a hypotension at doses of 1-2 mg/kg, *i.v.*, while increase of the dose to 4 mg/kg brought about an abrupt fall of the blood pressure followed by death.[17]

3-3. Proteins

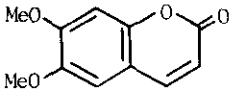
During the course of a search for hypotensive substances in nature, Honda *et al.*[18] found that the water extract of "bai-kisei", a fungus (Polypolaceae) parasitic on the trunks of *Prunus mume* (Rosaceae), exhibited a significant hypotension. Fractionation by monitoring hypotensive

activity using spontaneous hypertensive rats, furnished an active substance whose administration at a dose of 3 mg/kg, *i.v.* induced a marked blood pressure fall. The active substance was revealed to be a glycoprotein.

4. Phenylpropanoids

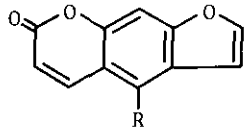
4-1. Coumarins

In 1972, Jamwal *et al.*[19] isolated scoparone (4) from the aerial part of *Artemicia scoparia (Compositae)* and found that it exhibited hypotensive activity as well as tranquilizing activity in laboratory animals.



4

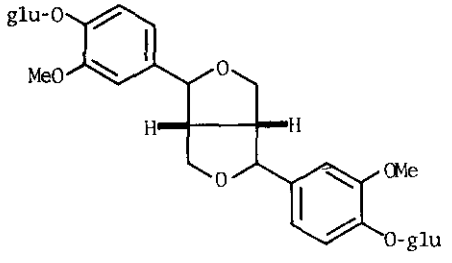
Prior to this, in 1963, Tatsuno et al.[20] described the remarkable hypotensive potency of an extract of the leaves of *Ficus carica* (Moraceae) in rabbits, dogs and cats. Later, in 1969, Triveri *et al.*[21] reported that an extract of the leaves of *F. racemosa* caused a slight initial fall in blood pressure, followed by a slight increase, and then a secondary fall. The latter action was not blocked by pretreatment with atropine (2 mg/kg). Furthermore, Isomura *et al.*[22] carried out a survey of the hypotensive principles of the leaves of *F. carica* and isolated psoralen (5) and bergapten (6) as the active principles, which mediated a blood pressure fall at a dose of 6 mg/kg, *i.v.*



5: R = H
6: R = OMe

4-2. Lignans

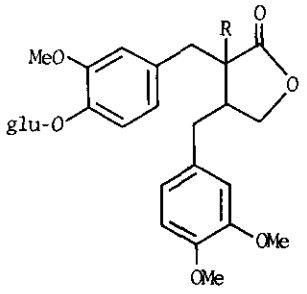
The oriental medicine prepared from the stem barks of *Eucommia ulmoides* (Eucommiaceae) is called "tochū" and has been used as a tonic in China. In 1956, Kin *et al.*[23] observed that dosing of the hot water extract of the leaves of this plant (5-8 g/kg, *i.p.*) to hypertensive dogs induced a blood pressure fall as well as a decrease of the heart rate. Shortly thereafter, Chien[24] found the water extract of "tochū" to produce a hypotension in rabbits which was inhibited by pretreatment with atropine but not affected by treatment with adrenaline and cocaine. Sih *et al.*[25] later fractionated the ethanol extract of "tochū" by monitoring the hypotensive activity in hypertensive rats and identified the active principle to be (±)-pinoresinol diglucoside (7) which induced a blood pressure fall on administration to hypertensive rats at doses of 30-100 mg/kg, *i.v.*



7

Funayama[26] observed hypotension when the 50% ethanol extract of "tochū" from China was dosed to urethane-anesthetized rats (65 mg/kg, *i.v.*), but no hypotension when the extracts of "tochū" from Vietnam and Burma were administrated.

In 1934, Koike[27] found that arctiin (8) isolated from the seeds of *Arctium lappa* (Compositae) exhibited a slight hypotensive activity in rabbit (50-200 mg/kg, *i.v.*). Tracheloside (9), isolated from the leaves and stems of *Trachelospermum asiaticum* (Apocynaceae), was also shown to exhibit hypotensive activity in rabbit (2 mg/kg, *i.v.*).[28]

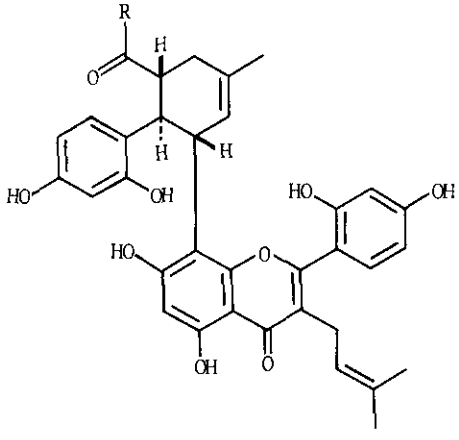


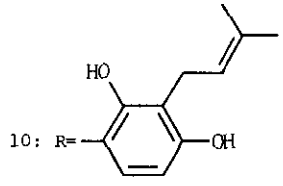
8: R=H
9: R=OH

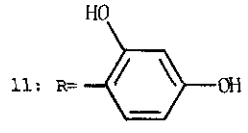
5. Flavonoids

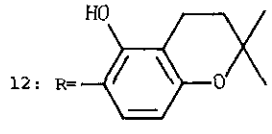
5-1. Flavones

The crude drug "sōhakuhi", the root barks of *Morus* plants (Moraceae), was shown by a number of pharmacological investigations to induce a hypotensive effect. Nevertheless, no hypotensive principle was isolated except for Tanemura's pharmacological examination of a hypotensive principle which, however, was not chemically characterized.[29] Quite recently, Oshima *et al.*[30-32] found that a marked hypotension was induced when the methanol extract was administered to urethane-anesthetized rat. By fractionation of the extract, while monitoring hypotensive activity of the fractions, they obtained three isoprenoid flavone derivatives, moracenin A, B and C (10-12), dosing of which at a dose of 5 mg/kg, *i.v.* to urethane-anesthetized rats produced a significant hypotension.







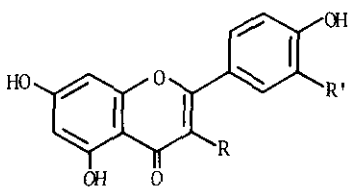


5-2. Flavonols

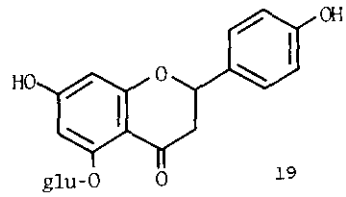
The leaves and "kaki-shibu" (the astringent juice of the immature fruits) of *Diospyros* plants (Ebenaceae) have been employed as a hypotensor in the folkloric medicine of Japan. In 1956, Yamashita[33] reported that clinical administration of the leaves of *D. kaki* (10 mg/kg, *p.o.*, for 1 week) resulted in hypotension in 9 patients out of 13. Its activity was ascribed to ascorbic acid which is contained in large quantities in the leaves although the presense of other essential hypotensive principles was suggested. Funayama and Hikino[34] noticed a significant hypotension with the methanol extract of the leaves of *D. kaki* and fractionated it, monitoring for hypotensive

activity against urethane-anesthetized rats, to obtain astragalin (13) and isoquercitrin (14) as the active principles.

Other examples of flavonol glycosides which act as hypotensive principles in plants are quercitrin (15), from the stems and leaves of *Crusea calocephala* (Rubiaceae), which exhibited a similar hypotensive activity to that produced by compound 48/80 in dogs,[35] hyperoside (16), from the leaves of *Crataegus monogyna* (Rosaceae), which showed an intense hypotension at a dose of 10 mg/kg, *i.v.* in cats,[36] and rutin (17), from the flowers of *Sophora japonica* (Leguminosae), which induced a raise followed by a fall of the blood pressure in rabbits.[37] However, concerning the effect of rutin on the blood pressure, there is a report by Kato[38] in which it is concluded that rutin does not affect the blood pressure of rabbits. Funayama[26] also observed no apparent effect of rutin on the blood pressure of urethane-anesthetized rats at a dose of 10 mg/kg, *i.v.* *Helichrysum arenarium* (Compositae) is known to contain astragalin (13), apigenin (18) and naringenin 5-glucoside (19), and Szadowska[39] obserbed that fractions containing any of these flavonol glycosides exhibited a hypotensive action in dogs.



13: R=O-β-glu, R'=H
14: R=O-β-glu, R'=OH
15: R=O-rham, R'=OH
16: R=O-gal, R'=OH
17: R=O-rut, R'=OH
18: R=R'=H



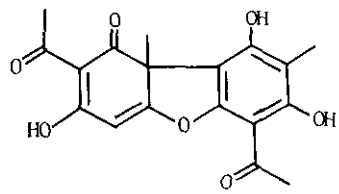
19

5-3. Miscellaneous

Flavonoids in the water extracts and the diluted ethanol extracts of the rhizomes of *Cyperus rotundus* (Cyperaceae),[40] total flavonoids from *Euphorbia seguieriana* (Euphorbiaceae),[41] total flavonoids from the leaves of *Aesculus hippocastanum* (Hippocastanaceae)[42] and total flavonoids from *Scutellaria orientalis* (Labiatae)[43] are known to produce hypotensive effects in laboratory animals.

6. Polyphenols

Usnic acid (20), isolated from *Usnea longissima* (Usneaceae), was shown to induce hypotensive activity in rabbit (*i.v.*).[44]



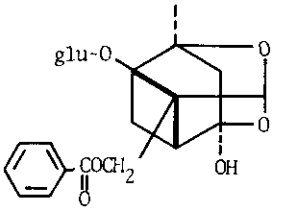
20

Other polyphenols exhibiting hypotensive activity are the polyphenol fraction of the roots of *Potentilla erecta* (Rosaceae),[45] polyphenols of the rhizomes of *Cyperus rotundus* (Cyperaceae),[40] polyphenols from the pollen of *Gossypium indicum* (Malvaceae)[46] and a polyphenol from every part of *Eucalyptus robusta* (Myrtaceae).[47] The extract of *E. robusta* (20 mg/kg) induced a strong and prolonged hypotension and its active principle was reported to be a tannin of moleculer weight of *ca.* 4000 which was unstable under basic conditions and underwent facile oxidation.[47]

7. Terpenoids

7-1. Monoterpenoids

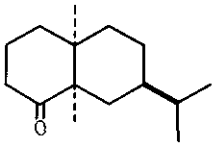
Paeoniflorin (21), the main component of the oriental medicine "shakuyaku", the roots of *Paeonia albiflora* (Ranunculaceae), was found to elicit a weak blood pressure fall in guinea pigs.[48]



21

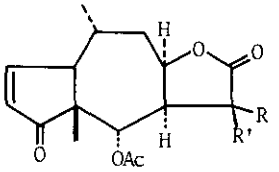
7-2. Sesquiterpenoids

The crude drug "kanshōkō", prepared from the roots of *Nardostachys jatamansi* (Valerianaceae), has been utilized as a stomachic, a sedative and a perfumery. The essential oil from the crude drug when dosed at 0.1-1.0 mg/kg, *i.v.* to dogs, induced a long-lasting hypotension.[49] From this essential oil, valeranone (22) was isolated as the hypotensive and sedative principle.[50,51]



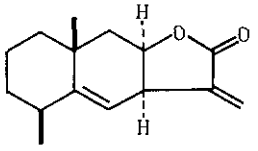
22

In 1974, List[52] isolated from the flowers of *Arnica montana* (Compositae) four bitter principles of which helenalin acetate (23) and dihydrohelenalinacetate (24) were found to show hypotensive activity (0.33 mg/kg, *i.v.*).

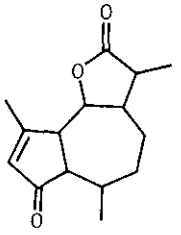


23: R,R'=CH_2
24: R=Me, R'=H

Alantolactone (25, 20 mg/kg, *i.v.*), isolated from the roots of *Inula helenium* (Compositae),[53] and carpesialactone (26, *i.v.*), isolated from the seeds of *Carpesium abrotanoides* (Compositae),[54] were also reported to cause hypotensive effects on urethane-anesthetized rabbits.



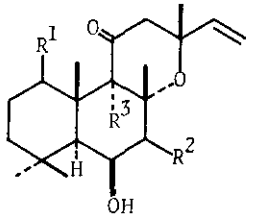
25



26

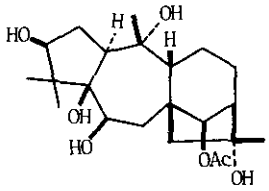
7-3. Diterpenoids

The diterpenoides (27-29) and coleonol (30), isolated from *Coleus forskohlii* (Labiatae), were reported to possess hypotensive activity.[55,56]

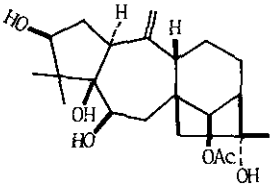


27: R^1=H_2, R^2=α-H,β-OH, R^3=H
28: R^1=α-OH,β-H, R^2=α-H,β-OAc, R^3=OH
29: R^1=α-OH,β-H, R^2=α-H,β-OH, R^3=OH
30: R^1=α-OH,β-H, R^2=α-OAc,β-H, R^3=OH

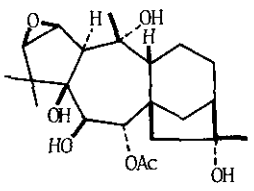
Certain species of the Ericaceae family are well kown to be toxic and often cause livestock loss. The toxic principles of these plants have now been determined to be diterpenic polyalcohols. It was revealed that certain ericaceous toxins constitute one of the most toxic groups of compounds of plant origin.[57] On the other hand, *Rhododendron* leaves have been employed as a cure for hypertension in the folk medicine of Japan. Actually, grayanotoxin I (31) and IV (32) were found to show hypotensive activity.[58] Since *Rododendron* leaves contain some ericaceous toxins, their repeated dosage may cause side effects. In fact, an instance of human poisoning was recorded in Japan in which long-term ingestion of the leaves of a *Rhododendron* species for hypotensive purposes produced toxic symptoms.[59] Lyoniatoxin (33), isolated from the leaves of an other ericaceous plant, *Lyonia elliptica* var. *elliptica* was shown to produce hypotensive activity in urethane-anesthetized rabbits (0.375 mg/kg, i.v.).[60]



31



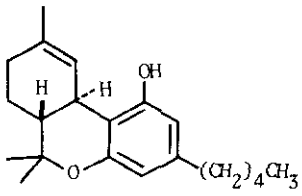
32



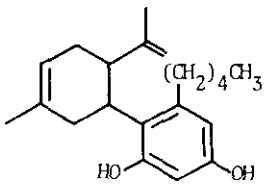
33

7-4. Cannabinoids

Cannabis plants (Moraceae) are famous for containing the cannabinoids which proved to have hypotensive activity in laboratory animals. For example, tetrahydrocannabinol (34) was reported to exhibit a transient weak hypertension followed by a lasting hypotension in urethane-anesthetized rats, and to show hypotension in barbital-anesthetized animals.[61,62] In this connection, Adams *et al.*[63] reported that the abnormal cannabidiol (35) induced a significant blood pressure fall in dogs, while the closely related analog, cannabidiol, elicited no effect on the blood pressure of dogs.



34

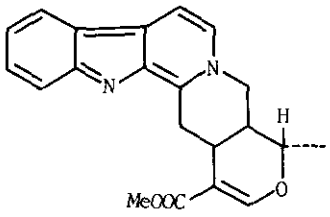


35

8. Alkaloids

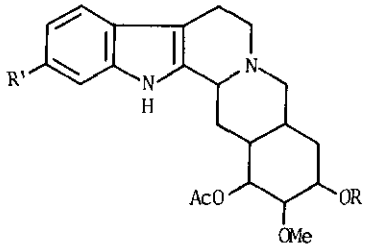
8-1. Indole alkaloids

The roots of *Rauwolfia serpentina* (Apocynaceae) have long been used in folkloric medicine in India. In the 1930's, an extract was reported to possess the tranquilizing effect as well as the hypotensive effect.[64] In 1943, Chopra *et al.*[65] reported the hypotensive activity of the total alkaloids and the component alkaloid, serpentine (36), in chloral hydrate-anesthetized cats. Since the isolation by Müller *et al.*[66] of reserpine (37), which induced a similar hypotension to that produced by the extract, the crude drug and reserpine became important for clinical use in the



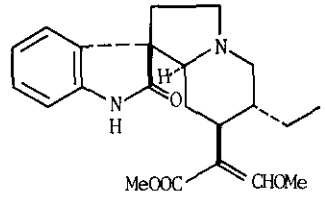
36

treatment of high blood pressure. From the crude drug was isolated other alkaloids, rescinnamine (38) and deserpidine (39), showing hypotesive activity.[64]



37: R=3,4,5,-trimethoxybenzoyl, R'=OMe
38: R=3,4,5,-trimethoxycinnamoyl, R'=OMe
39: R=3,4,5,-trimethoxybenzoyl, R'=H

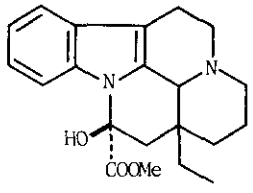
The oriental medicine "chōtō-kō", the stems and hooks of *Uncaria sinensis* and *U. rhynchophylla* (Rubiaceae), has been utilized as a sedative and an analgesic. Rhynchophylline (40), one of the



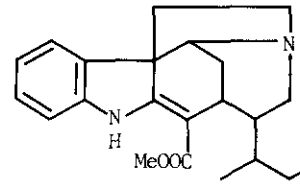
40

main alkaloids in the latter species, was revealed to show significant hypotensive action in rabbits which was not inhibited by vagotomy or pretreatment with atropine.[67,68]

On the basis of the observation that the total alkaloids of the aerial part of *Vinca* plants (Apocynaceae) exhibited hypotensive activity at doses of 0.1-20.0 mg/kg, in anesthetized cats and non-anesthetized rabbits.[69] Kaczmarek *et al.*[70] demonstrated vincamine (41) to be an active principle of *Vinca minor* in 1962. Later, vinervinine (42), another constituent of this plant,



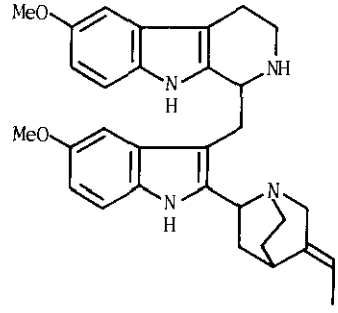
41



42

was also revealed by Karmukov *et al.*[71] to have a hypotensive activity similar to that of acetylcholine.

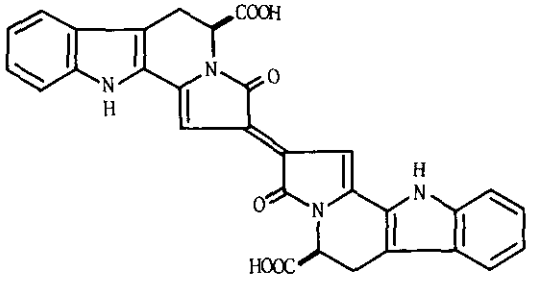
The stem and root barks of *Cinchona* plants (Rubiaceae) are particularly well-known sources of alkaloids which have use in medicine. Cinchophyllamine (43) obtained from the leaves of a species, *C. ledgeriana*, was shown to possess hypotensive activity.[72]



43

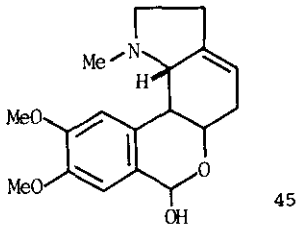
The roots, stems, leaves and fruits of *Clerodendron trichotomum* (Verbenaceae) have been used in folklore medicine as a remedy for high blood pressure and rheumatism in China. From this plant,

trichotomine (44) was isolated as a hypotensive principle.[73] The same alkaloid was also obtained from *Premna microphylla* (Verbenaceae).[73]

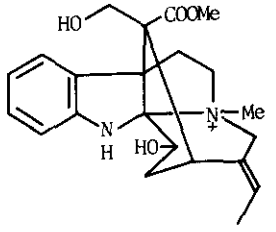


44

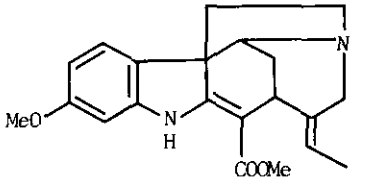
There are, in addition to the above-mentioned indole alkaloids, analogs which were also revealed to have hypotensive activities. Examples include lycorenine (45) from the bulbs of *Lycoris radiata* (Amaryllidaceae),[74] echitamine (46) and echitamidine (47) from the stem barks of *Alstonia boonei* (Apocynaceae),[75] and harman (48) and harmine (49) from various plants.[76,77]



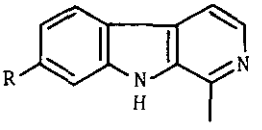
45



46



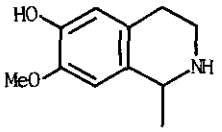
47



48: R=H
49: R=OMe

8-2. Isoquinoline alkaloids

It was reported that, in the treatment of hypertension, administration of salsoline (50, 30 mg/kg, *p.o.*), isolated from *Salsola richteri* (Chenopdiaceae), induced a blood pressure fall within 30-60 min, the effect being maintained for 2-3 hr.[78]



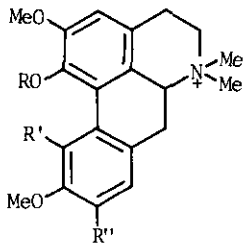
50

From the roots of *Aristolochia deblis* (Aristolochiaceae), magnoflorine (51) was isolated as a hypotensive principle.[79]

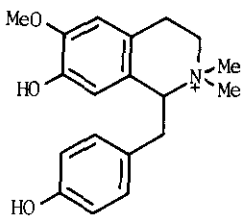
Because magnoflorine (51) is widely distributed in *Magnolia* plants (Magnoliaceae),[80] this alkaloid may contribute to the hypotensive activity of the ethanol extract of the leaves of *M. gradiflora*[81] and *M. denudata*[26] in laboratory animals.

In the genus, *Magnolia*, other alkaloids, magnocurarine (52) and salicifoline (53) are also known as hypotensive principles.[82]

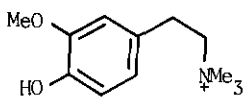
On the other hand, laurifoline (54) and menisperine (55), isomers of magnoflorine (51), were reported to be the hypotensive principles of *Cocculus* plants (Menispermaceae).[82]



51: R=R"=H, R'=OH
54: R=R'=H, R"=OH
55: R=Me, R'=OH, R"=H

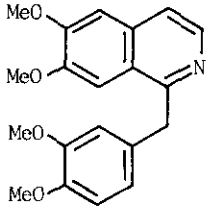


52

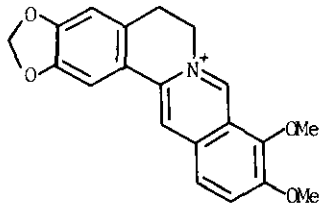


53

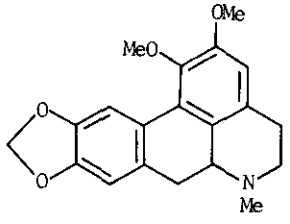
Papaverine (56) from the milky exudate of the incised, unripe capsules of *Papaver somniferum* and related plants (Papaveraceae),[83] berberine (57) from the rhizomes of *Coptis japonica* (Ranunculaceae)[84] and many other plant sources, domestine (58) from the seeds and nandenine (59) from the stem and root barks of *Nandia domestica* (Nandinaceae),[85,86] lycoramine (60) from the bulbs of *Lycoris radiata* (Amaryllidaceae),[87] dauricine (61) and epistephanine (62) from the rhizomes of *Menispermum dauricum* (Menispermaceae),[88] insularine (63) from the roots of *Cissampelos insularis* (Menispermaceae),[88] liensinine (64) from the embryo of *Nelumbo nucifera* (Nymphaceae),[89] tetrandrine (65) from the roots of *Stephania tetrandra* (Menispermaceae),[90] thalirevolutine (66) and thalirevoline (67) from the roots of *Thalictrum revolutum* (Ranunculaceae),[91] and sinomenine (68) from the rhizomes of *Sinomenium* plants (Menispermaceae)[92] were also reported to produce a blood pressure fall in laboratory animals.



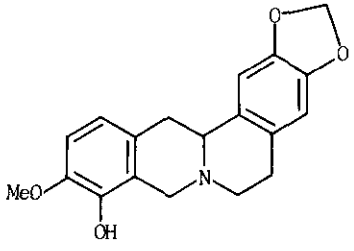
56



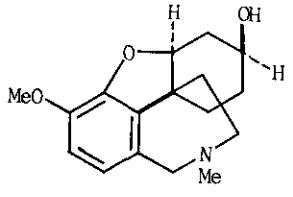
57



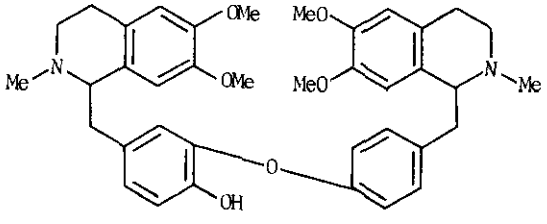
58



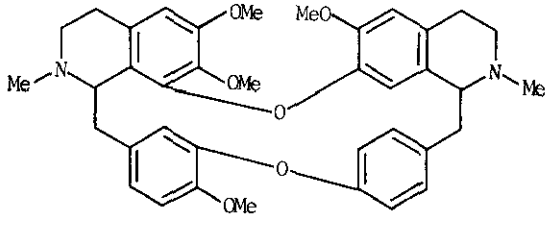
59



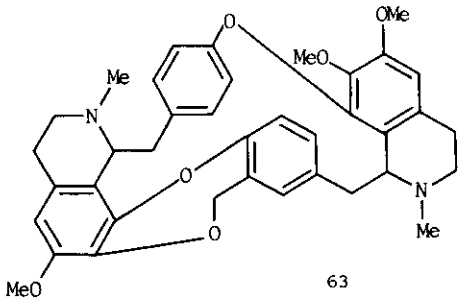
60



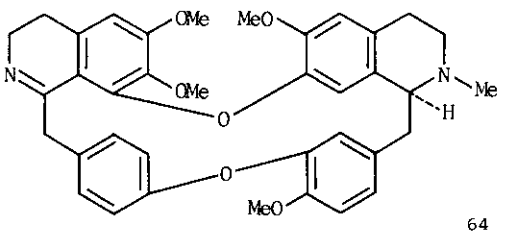
61



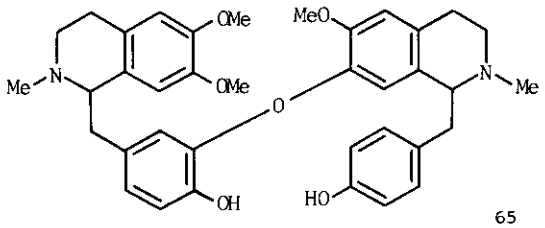
62



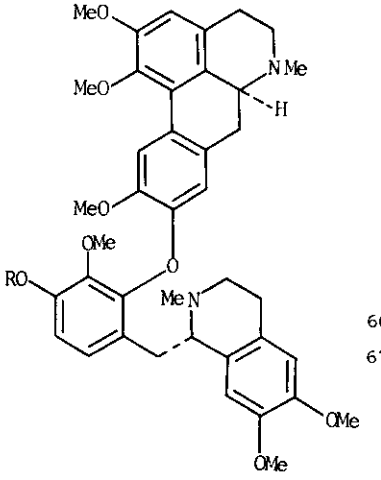
63



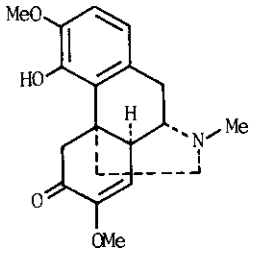
64



65



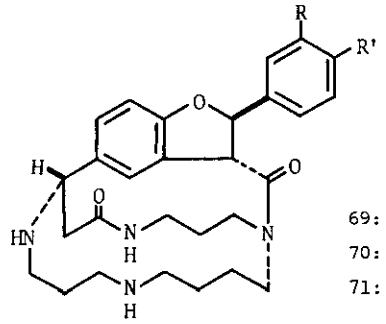
66: R=Me
67: R=H



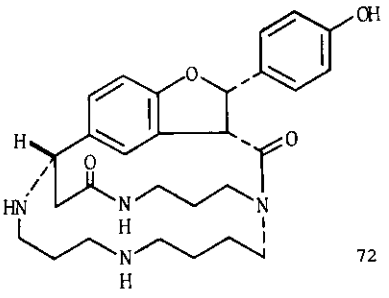
68

8-3. Spermine alkaloids

The oriental medicine "mao-kon", the underground part of *Ephedra* plants (Ephedraceae), is said to possess therapeutic effects opposite to those of "mao", the aerial part of *Ephedra* plants, which contains alkaloids of the ephedrine series. In 1925, Fujii[93] found that the ethanol extract of "mao-kon" elicited a significant hypotension in urethane-anesthetized rats, while that of "mao" exerted a remarkable hypertesion, and obtained an alkaloid from the roots responsible for the hypotensive activity which, however, was not characterized chemically. Quite recently, Tamada *et al.*[94-96] isolated three macrocyclic spermine alkaloids, ephedradine A, B and C (69-71) as the



69: R=H, R'=OH
70: R=OMe, R'=OH
71: R=R'=OMe

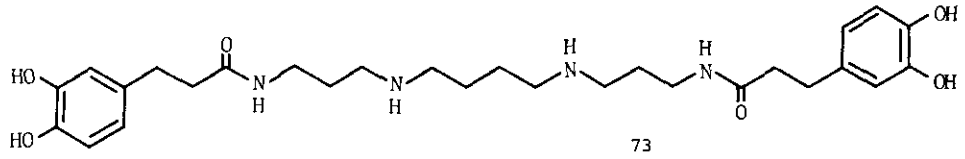


72

hypotensive principles from "mao-kon". Determination of the concentrations of the ephedradines in various samples indicated that the content varies significantly depending on the samples.

Because aphelandrine (72) isolated from the roots of *Aphelandra squarrosa* and several other *Aphelandra* species and of *Encephalosphaera lasiandra* (Apocynaceae) is apparently the C-2 epimer of ephedradine A (69),[97] the hypotensive activity of aphelandrine (72) is of particular interest.

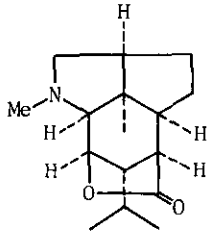
The root barks of *Licium chinese* (Solanaceae) are materials for the crude drug "jikoppi" which has been utilized as an antipyretic and a tonic in oriental medicine. Funayama *et al.*[98] isolated a spermine alkaloid, kukoamine A (73), which showed hypotensive activity.



73

8-4. Terpenoidal Alkaloids

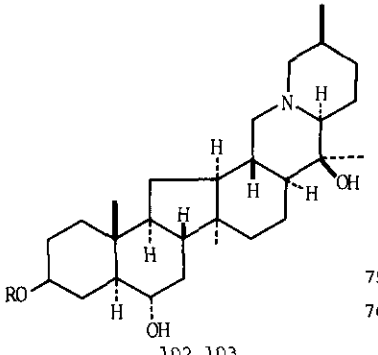
Dendrobine (74), isolated from the herbs of *Dendrobium nobile* (Orchidaceae), was shown to induce marked hypotension when injected at a dose of 2 mg/kg, *i.v.* in urethane-anesthetized rats.[26]



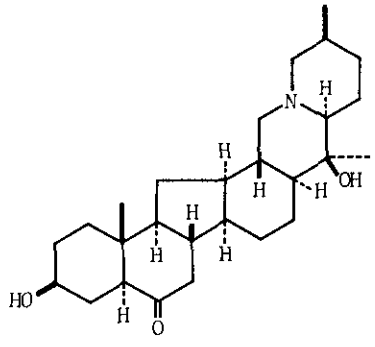
74

8-5. Steroidal alkaloids

From the crude drug "baimo", prepared from the bulbs of *Fritillaria verticillata* var. *thunbergii* (Liliaceae), an intense hypotensor, peimine (75) and its glucoside peiminoside (76) were obtained.[99,100] Imperialine (77), isolated from the bulbs of *F. eduardi*, was also reported to exhibit hypotensive activity at doses over 10 mg/kg.[101]

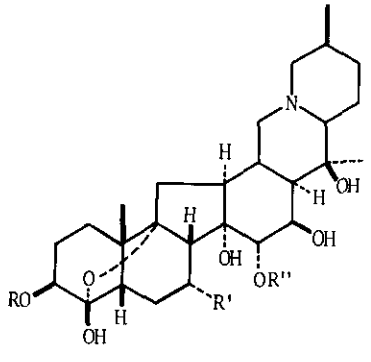


75: R=H
76: R=glu



77

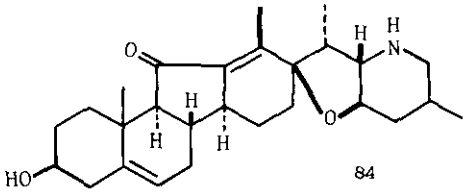
Kupchan *et al.*[102,103] identified the hypotensive principles of *Zygadenus venenosus* (Liliaceae) as veratroylzygadenine (78), vanilloylzygadenine (79), protoveratridine (80), neogermitrine (81),



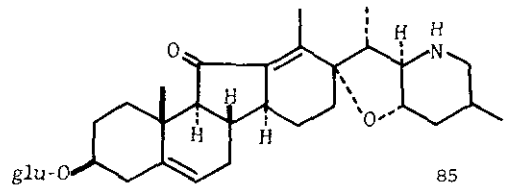
78: R=3,4-dimethoxybenzoyl, R'=R"=H
79: R=3-methoxy-4-hydroxybenzoyl, R'=R"=H
80: R=$COCH(CH_3)CH_2CH_3$, R'=OH, R"=H
81: R=Ac, R'=OAc, R"=$COCH(CH_3)CH_2CH_3$
82: R=Ac, R'=OH, R"=$COCH(CH_3)CH_2CH_3$
83: R=H, R'=OAc, R"=$COCH(CH_3)CH_2CH_3$

germidine (82) and neogermidine (83).

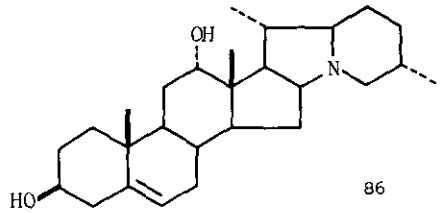
Total alkaloids contained in the roots and rhizomes of *Veratrum viride* (Liliaceae) were once employed clinically in treatment of high blood pressure. In the total alkaloids, there are jervine (84), pseudojerine (85), rubijervine (86), cevadine (87) and germitrine (88) besides the aforementioned neogermitrine (81) and germidine (82).[104,105]



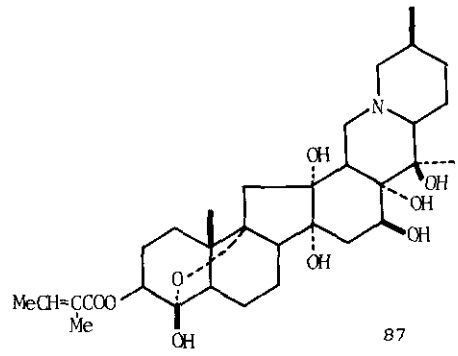
84



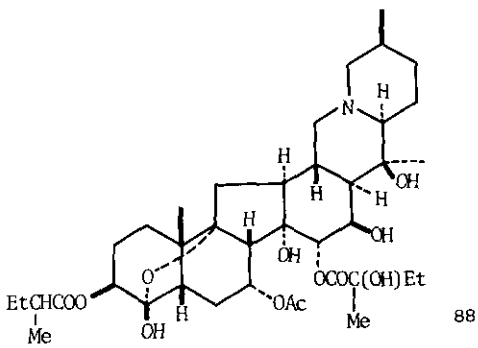
85



86

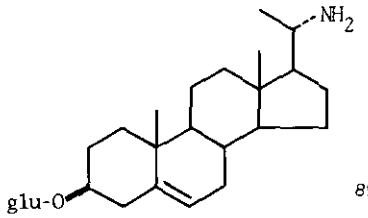


87



88

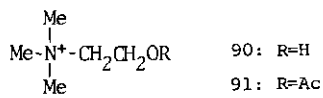
Further, from the roots of *Conopharyngia pachysiphon* (Apocynaceae) was isolated 20α-amino-3β-hydroxy-5-pregnene β-D-glucoside (89) which, on administration to dogs (*i.v.*), produced a hypotension as well as a decrease of respiration rate.[106]



89

8-6. Miscellaneous alkaloids

The water and ethanol extracts of the flowers, seeds or herbs of *Capsella bulsa-patris* (Cruciferae) were found to produce a significant fall of the blood pressure of rabbits when dosed *i.v.*, the active principles being elucidated as choline (90) and acetylcholine (91).[107]

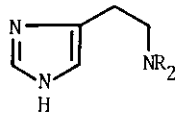


90: R=H

91: R=Ac

The water extract of the leaves of *Olea europaea* (Oleaceae) was observed to induce a hypotension in cats and rabbits when administered *i.v.*, the activity also being due to choline (90).[108]

A remarkable blood pressure fall elicited by *i.v.* administration of the diluted ethanol extract of the crude drug "shōriku" to rabbits was observed by Maeda[109] as early as 1922. Quite recently, Funayama and Hikino[13] fractionated the 50% ethanol extract of the crude drug, monitoring the hypotensive activity and, as a result, obtained histamine (92) and GABA (2) as the active principles.



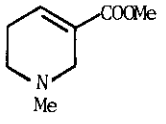
92: R=H
93: R=Me

The crude drug "ne-kombu", described previously, was assessed with a blood pressure test to reveal that *i.v.* dosing to urethane-anesthetized rats of the 50% ethanol extract of a commercial preparation exhibited a marked hypotension. Funayama and Hikino[110] carried out a survey for a substance responsible for its hypotensive activity and identified histamine (92) to be the active principle.

As mentiond above, the astringent juice of the immature fruits ("kaki-shibu") of *Diospyros* plants (Ebenaceae) had been employed as a hypotensor in the folkloric medicine of Japan. In 1940, Ishihara[111] suggested the active principle to be histamine (92) because of its chemical and physico-chemical properties and of disappearance of the activity on treatment with histaminase.

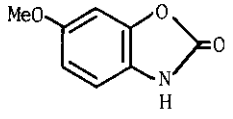
Further, N^{α},N^{α}-dimethylhistamine (93) was obtained as the hypotensive principle from the seeds of *Casimiroa edulis* (Rutaceae).[112]

Arecoline (94), isolated from *Areca catechu* (Palmae), was reported to exhibit hypotensive activity in cats, rabbits and dogs.[113]

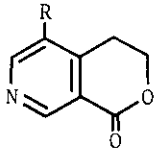


94

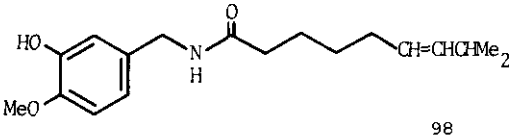
There are some other hypotensive principles known: coixol (95) from the roots of *Coix lacryma-jobi* var. *ma-yuen* (Gramineae),[114] gentianine (96) and gentianadine (97) from the herbs of *Swertia chirata* (Gentianaceae),[115,116] capsaisin (98) from the fruits of *Capsicum* plants (Solanaceae),[117,118] loberine (99) from the herbs of *Lobelia inflata* (Campanulaceae)[119] and matrine (100) from the roots of *Sophora angustifolia* (Leguminosae).[120]



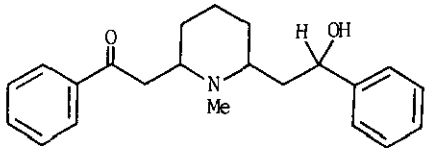
95



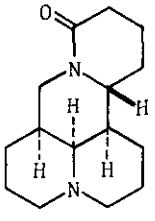
96: R=CH=CH$_2$
97: R=H



98



99



100

References

1. R. P. Gregson, J. F. Marwood and R. J. Quinn, *Tetrahedron Letters*, 1979, 4505.
2. C. E. Dent, W. Stepka and F. C. Steward, *Nature*, 1947, 160, 682.
3. F. C. Steward, J. F. Thompson and C. E. Dent, *Science*, 1949, 110, 439.
4. K. A. C. Elliott and H. H. Jasper, *Physiological Reviews*, 1959, 39, 383.
5. H. Takahashi, M. Tiba, M. Iino and T. Takayasu, *Jap. J. Physiol.*, 1956, 5, 334.
6. H. C. Stanton, *Arch. Int. Pharmacodyn. Ther.*, 1963, 143, 195.
7. Y. Yamaguchi and S. Omata, *Shindan to Chiryō*, 1955, 43, 1017.
8. H. Takahashi, *Igaku no Ayumi*, 1960, 32, 735.
9. D. R. Curtis and J. C. Watkins, *Pharmacological Reviews*, 1965, 17, 347.
10. D. R. Curtis, A. W. Duggan, D. Felix and G. A. R. Johnston, *Nature*, 1970, 226, 1222.
11. E. Durand, E. V. Ellington, P. C. Feng, L. J. Haynes, K. E. Magnus and N. Philip, *J. Pharm. Pharmacol.*, 1962, 14, 562.
12. H. Hikino, S. Funayama and K. Endo, *Planta Medica*, 1976, 30, 297.
13. S. Funayama and H. Hikino, *Lloydia*, 1979, 42, 672.
14. J. Kamda, *Fukushima Igaku Zasshi*, 1960, 10, 251.
15. T. Takemoto, K. Daigo and N. Takagi, *Yakugaku Zasshi*, 1964, 84, 1176.
16. H. Ozawa, Y. Gomi and I. Otsuki, *Yakugaku Zasshi*, 1967, 87, 935.
17. B. J. R. Ghatak and N. N. De, *J. Sci. Ind. Research*, 1961, 20, 51 [*Chem. Abstr.*, 1961, 55, 16774].
18. S. Honda, K. Kakehi, S. Komiya, K. Okamoto, H. Miyake, Y. Iizuka and T. Murakami, " The 100th Annual Meeting of the Pharmaceutical Society of Japan", Tokyo, April 1980, Abstr., p. 224.
19. K. S. Jamwal, M. L. Sharma, N. Chandhoke and B. J. R. Ghatak, *Indian J. Med. Res.*, 1972, 60, 763 [*Chem. Abstr.*, 1972, 77, 160212].
20. cf. K. Akamatsu, "Wakan-yaku", Ishiyaku-shuppansha, Tokyo, 1970, p. 512.
21. C. P. Trivedi, S. Shinde and R. C. Sharma, *Indian J. Med. Res.*, 1969, 57, 1070 [*Chem. Abstr.*, 1969, 71, 59418].
22. A. Isomura, M. Nagai, Y. Ishidate, T. Inoue and S. Yanagiura, *Shoyakugaku Zasshi*, 1975, 29, 147.
23. K. C. Kin and K. S. Ting, *Acta Physiol. Sinica*, 1956, 20, 247 [*Chem. Abstr.*, 1957, 51, 15788].
24. T. H. Chien, *Jap. J. Pharmacol.*, 1957, 6, 122 [*Chem. Abstr.*, 1958, 52, 3158].
25. C. J. Sih, P. R. Ravikumar, F. C. H. C. Buckner and H. J. Whitlock, *J. Am. Chem. Soc.*, 1976, 98, 5412.
26. S. Funayama, unpublished results.
27. H. Koike, *Nippon Yakubutsugaku Zasshi*, 1934, 17, 179.
28. cf. K. Akamatsu, "Wakan-yaku", Ishiyaku-shuppansha, Tokyo, 1970, p. 148.
29. I. Tanemura, *Nippon Yakurigaku Zasshi*, 1960, 56, 704.
30. Y. Oshima, C. Konno, H. Hikino and K. Matsushita, *Tetrahedron Letters*, 1980, 3381.
31. Y. Oshima, C. Konno, H. Hikino and K. Matsushita, *Heterocycles*, 1980, 14, 1287.
32. Y. Oshima, C. Konno, H. Hikino and K. Matsushita, *Heterocycles*, 1980, 14, 1461.
33. H. Yamashita, *Fukuoka Igaku Zasshi*, 1956, 47, 824.
34. S. Funayama and H. Hikino, *Chem. Pharm. Bull.*, 1979, 27, 2865.
35. R. M. Brooker and J. M. Eble, *Lloydia*, 1966, 29, 230 [*Chem. Abstr.*, 1966, 65, 15953].
36. N. Nikolov, P. Manolov and V. Ivanov, *Farmasiya* (Sofia), 1972, 22, 30 [*Chem. Abstr.*, 1972, 77, 9554].
37. R. Gakhniyan, *Farmasiya* (Sofia), 1961, 11, 27 [*Chem. Abstr.*, 1961, 55, 22582].

38. Y. Kato, *Nippon Yakurigaku Zasshi*, 1951, 47, 93.
39. A. Szadowska, *Acta Polon. Pharm.*, 1962, 19, 465 [*Chem. Abstr.*, 1964, 61, 1136].
40. B. A. Akperbekova and D. Y. Guseinov, *Azerb. Med. Zh.*, 1966, 43, 12 [*Chem. Abstr.*, 1966, 65, 20702].
41. V. I. Sila and T. T. Lavrushina, *Farm. Zh.* (Kiev), 1971, 26, 78 [*Chem. Abstr.*, 1972, 76, 135735].
42. M. Asano, C. Ohokubo and K. Kikuchi, *Koshu Eiseiin Kenkyu Hokoku*, 1972, 21, 20.
43. R. A. Akhundov, A. A. Nasudari and A. V. Reish, *Azerb. Med. Zh.*, 1977, 54, 15 [*Chem. Abstr.*, 1977, 87, 96003].
44. K. Mikoshiba, *Nippon Yakubutsugaku Zasshi*, 1933, 16, 100.
45. L. V. Selenina, R. N. Zozulya and T. N. Yakovleva, *Rast. Resur.*, 1973, 9, 409 [*Chem. Abstr.*, 1974, 80, 22614].
46. H. Antweiler and S. Pallade, *Ann. N. Y. Acad. Sci.*, 1974, 221, 132 [*Chem. Abstr.*, 1974, 81, 73058].
47. G. W. Read, G. S. Naguwa, J. J. Wigington and J. F. Lenny, *Lloydia*, 1970, 33, 461 [*Chem. Abstr.*, 1971, 75, 128342].
48. K. Takagi and M. Harada, *Yakugaku Zasshi*, 1969, 89, 893.
49. R. B. Arrora, K. P. Singh, P. K. Das and P. N. Mistry, *Arch. Int. Pharmacodyn.*, 1958, 113, 367 [*Chem. Abstr.*, 1958, 52, 12189].
50. R. B. Arrora and C. K. Arrora, *Proc. Intern. Pharmacol. Meeting* (Prague), 1963, 52 [*Chem. Abstr.*, 1965, 62, 2151].
51. H. Hikino, Y. Hikino, Y. Takeshita, K. Meguro and T. Takemoto, *Chem. Pharm. Bull.*, 1965, 13, 1408.
52. P. H. List and B. Friebel, *Arzneim.-Forsch.*, 1974, 24, 148.
53. S. Kuribayashi and N. Hara, *Nippon Yakubutsugaku Zasshi*, 1936, 22, 65.
54. Y. Ogawa, S. Takahashi and M. Kishigami, *Shionogi Kenkyusho Nenpo*, 1956, 6, 227.
55. S. V. Bhat, B. S. Balwa, H. Dornauer, N. J. Souza and H. W. Fehlhaber, *Tetrahedron Letters*, 1977, 1669.
56. J. S. Tandon, M. M. Dhar, S. Ramakumar and K. Venkatesan, *Indian J. Chem., Sect. B*, 1977, 15, 880 [*Chem. Abstr.*, 1978, 89, 24556].
57. H. Hikino, T. Ohta, M. Ogura, Y. Ohizumi, C. Konno and T. Takemoto, *Toxicol. Appl. Pharmacol.*, 1976, 35, 303.
58. S. V. Kuerten, S. A. D. Keller, P. Pachaly, F. Zymalkowski, G. Tauberger and M. Moussawi, *Arch. Pharm.*, 1971, 304, 753.
59. H. Hikino, Y. Ohizumi, C. Konno, I. Hashimoto and H. Wakasa, *Chem. Pharm. Bull.*, 1979, 27, 874.
60. Y. Suzuki, H. Takagi and N. Ikeda, *Takamine Kenkyusho Nenpo*, 1960, 12, 247.
61. M. D. Adams, J. T. Earnhardt, W. L. Dewey and L. S. Harris, *J. Pharmacol. Exp. Ther.*, 1976, 196, 649 [*Chem. Abstr.*, 1976, 84, 130421].
62. M. J. Hosko and H. F. Hardman, *Pharmacol. Marihuana*, 1976, 1, 239 [*Chem. Abstr.*, 1976, 85, 171691].
63. M. D. Adams, J. T. Earnhardt, B. R. Martin, L. S. Harris, W. L. Dewey and R. K. Razdan, *Experientia*, 1977, 33, 1204 [*Chem. Abstr.*, 1978, 88, 83357].
64. cf. M. Fujita, "Shoyakugaku", Nanzando, 1959, p. 92.
65. R. N. Chopra, B. C. Bose, J. C. Gupta and I. C. Chopra, *Indian J. Med. Research*, 1942, 30, 319 [*Chem. Abstr.*, 1943, 37, 2819].
66. J. M. Müller, E. Schlitter and H. J. Bein, *Experientia*, 1952, 8, 338.

67. S. Akamatsu and T. Kunika, *Nippon Yakubutsugaku Zasshi*, 1928, 7, 35.
68. S. Machida, *Nippon Yakubutsugaku Zasshi*, 1930, 10, 53.
69. K. Rushinov, D. Zhelyazkov and V. Georgiev, *Izv. Inst. po Fiziol. Bulgar. Akad. Nauk*, 1962, 5, 271 [*Chem. Abstr.*, 1962, 57, 14391].
70. F. Kaczmarek, J. Lutomski and T. Wrocinski, *Biul. Inst. Roslin Leczniczych*, 1962, 8, 12 [*Chem. Abstr.*, 1963, 58, 10634].
71. A. G. Karmukov and K. S. Akhmedkhodzhaeva, *Farmakol. Alkaloidov Glikozidov*, 1967, 79 [*Chem. Abstr.*, 1969, 70, 2211].
72. A. Quevauviller, O. F. Blanpin, G. Sarrazin, P. Bourrinet and Y. Nakaji, *Ann. Pharm. Fr.*, 1969, 27, 397 [*Chem. Abstr.*, 1970, 72, 65061].
73. S. Iwadare, Y. Shizuri, K. Sasaki and Y. Hirata, *Japan. Kokai*, 1976, 76 41,415 [*Chem. Abstr.*, 1976, 85, 25376].
74. cf. K. Akamatsu, "Wakan-yaku", Ishiyaku-shuppansha, Tokyo, 1970, p. 562.
75. M. Kucera, V. O. Marquis and H. Kucerova, *Planta Medica*, 1972, 21, 343 [*Chem. Abstr.*, 1972, 77, 72587].
76. H. Raymond, *Compt. rend.*, 1945, 221, 387 [*Chem. Abstr.*, 1946, 40, 3761].
77. H. Raymond, *Compt. rend. soc. biol.*, 1941, 135, 328 [*Chem. Abstr.*, 1942, 36, 3265].
78. H. Wastl, *Hahnemannian Monthly*, 1946, 81, 243 [*Chem. Abstr.*, 1946, 40, 5147].
79. C. C. Chang, C. K. Wang, C. C. Li, I. T. Shao, Y. C. Pei, M. Y. Chiang, T. Li and T. C. Hsu, *Yao Hsueh Hsueh Pao*, 1964, 11, 42 [*Chem. Abstr.*, 1964, 61, 3590].
80. cf. J. S. Glasby, "Encyclopedia of the Alkaloids", Plenum Press, New York, 1975, p. 895.
81. O. I. Belova and Y. K. Nolle, *Apotechnoe Delo*, 1953, 2, 65 [*Chem. Abstr.*, 1953, 47, 8319].
82. K. Inoue, *Nippon Yakurigaku Zasshi*, 1957, 53, 797.
83. M. Barıéty and D. Khler, *Compt. rend. soc. biol.*, 1941, 135, 706 [*Chem. Abstr.*, 1945, 39, 5325].
84. K. Haneno, *Yakugaku Kenkyu*, 1960, 32, 836.
85. T. Shiina, *Yakugaku Zasshi*, 1927, 47, 529.
86. T. Shiina, *Chiba Igaku Zasshi*, 1926, 4, 870.
87. Y. Yamamoto and T. Takano, *Nichidai Igaku Zasshi*, 1952, 11, 92.
88. K. Horiuchi, *Nippon Yakubutsugaku Zasshi*, 1930, 10, 54.
89. cf. K. Akamatsu, "Wakan-yaku", Ishiyaku-shuppansha, Tokyo, 1970, p. 466.
90. S. Kubota, *Nippon Yakubutsugaku Zasshi*, 1931, 12, 338.
91. W. N. Wu, J. L. Beal and R. W. Doskotch, *Tetrahedron*, 1977, 22, 2919.
92. cf. K. Akamatsu, "Wakan-yaku", Ishiyaku-shuppansha, Tokyo, 1970, p. 436.
93. M. Fujii, *Manshu Igaku Zasshi*, 1925, 4, 56.
94. M. Tamada, K. Endo, H. Hikino and C. Kabuto, *Tetrahedron Letters*, 1979, 873.
95. M. Tamada, K. Endo and H. Hikino, *Heterocycles*, 1979, 12, 783.
96. C. Konno, M. Tamada, K. Endo and H. Hikino, *Heterocycles*, 1980, 14, 295.
97. P. Dätwyler, H. Bosshardt, H. O. Bernhard, M. Hesse and S. Johne, *Helv. Chim. Acta*, 1978, 61, 2646.
98. S. Funayama, K. Yoshida, C. Konno and H. Hikino, *Tetrahedron Letters*, 1980, 1355.
99. Y. Narumi, *Tohoku J. exp. Med.*, 1936, 28, 26.
100. cf. M. Konoshima, T. Sawada and K. Hata, "Shoyakugaku", Asakura Shoten, Tokyo, 1978, p. 258.
101. T. K. Saidokasymov and M. B. Sultanov, *Farmakol. Alkaloidov Glikozidov*, 1967, 138 [*Chem. Abstr.*, 1969, 70, 2218].
102. S. M. Kupchan and C. V. Deliwala, *J. Am. Chem. Soc.*, 1952, 74, 2382.

103. S. M. Kupchan and C. V. Deliwala, *J. Am. Chem. Soc.*, 1952, 74, 3202.
104. cf. "The Merck Index, 9th ed.", M. Windholz, S. Budavari, L. Y. Stroumtosos and M. N. Fertig (ed.), Merck & Co., Rahway, 1976, p. 1278.
105. S. M. Kupchan, *J. Am. Chem. Soc.*, 1959, 81, 1921.
106. D. Dickel, R. Lucas and H. B. Macphillamy, *J. Am. Chem. Soc.*, 1959, 81, 3154.
107. H. Boruttau and H. Cappenberg, *Arch. Pharm.*, 1921, 259, 33.
108. G. Samuelsson, *Farm. Revy*, 1951, 50, 229 [*Chem. Abstr.*, 1951, 45, 6304].
109. M. Maeda, *Tohoku Igaku Zasshi*, 1922, 5, 85.
110. S. Funayama and H. Hikino, *Planta Medica*, in press.
111. T. Ishihara, *Nippon Yakubutsugaku Zasshi*, 1940, 28, 134.
112. R. T. Major and F. Dürsch, *J. Org. Chem.*, 1958, 23, 1564.
113. cf. K. Akamatsu, "Wakan-yaku", Ishiyaku-shuppansha, Tokyo, 1970, p. 604.
114. cf. K. Akamatsu, "Wakan-yaku", Ishiyaku-shuppansha, Tokyo, 1970, p. 614.
115. S. K. Bhattacharya, S. Ghosal, R. K. Chaudhuri, A. K. Shigh and P. V. Sharma, *J. Pharm. Sci.*, 1974, 63, 1341.
116. F. S. Sadritdinov and N. Tulyaganov, *Farmakol. Alkaloidov Glikozidov*, 1967, 128 [*Chem. Abstr.*, 1969, 70, 2217].
117. J. Molnar and L. Gyorgy, *Eur. J. Pharmacol.*, 1967, 1, 86 [*Chem. Abstr.* 1967, 67, 10134].
118. A. Ueno, *Nippon Yakurigaku Zasshi*, 1971, 67, 572.
119. S. Utashiro, *Nippon Yakubutsugaku Zasshi*, 1941, 31, 34.
120. K. In, *Nippon Yakubutsugaku Zasshi*, 1928, 8, 42.

Received, 29th July, 1980