Rauwolfia Serpentina in the Treatment of High Blood Pressure

A Review of the Literature

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The root of the Rauwolfia serpentina Benth (N. O. Apocynaceae) has been in use in India for hundreds of years for a host of unrelated ailments. Since 1949, after the English publication of a clinical report by the author on Rauwolfia serpentina therapy in fifty cases of essential hypertension, the plant has gained universal acclamation as a useful therapeutic weapon in high blood pressure states. The whole subject of Rauwolfia serpentina therapy in hypertension has been reviewed up to the present time, including discussions on the history of the plant, its various species and types, nomenclature, geographic distribution, chemistry, pharmacologic actions and clinical studies, reported on the subject from all over the world.

The plant rauwolfia is named after the German doctor and traveller Leonhard Rauwolf, who in 1582 published an account of his many travels. Roots of the plant Rauwolfia serpentina (Benth) have been recognized in India and the Malay peninsula from ancient times as antidotes to the stings and bites of insects and poisonous reptiles. Mention of the plant is found in an old Hindu manuscript (1000 B.C.) as well as in the monumental works of Charaka (second century, A.D.), under the Sanskrit name of “sarpagandha.” It has also been used as a febrifuge, as a stimulant to uterine contractions, for diarrhea, dysentery, insomnia and insanity. For just over two decades, its clinical application has been extended with success to the treatment of high blood pressure.133

R. Serpentina or the serpentina plant is a large climbing or twining herb or shrub, belonging to the natural order Apocynaceae, and found in the Himalayas, Assam, Pegu, Java, Tenasserim, Bihar, Deccan peninsula and the Malay peninsula. It is variously known as sarpagandha (from ancient times), chandrika (Sanskrit), chota-chand (Hindi), chand (Bengali), dhan-murua or dhanbarua or pagla-kadawa (Bihar), chandra, chota-chand, karavi or harkai (Bombay), harkaya (Marathi), pata la garud or atalagandhi (Telegu), covanamiloori (Tamil), chuvanaavilpori (Malay) and as dhamnera or dhan-barua (Oriya).

Of the 130 odd species of rauwolfia, which are said to occur indigenously in the tropics, Youngken has given an excellent description of the following five, viz. R. serpentina, R. canescens, R. micrantha, R. densiflora, and R. perakensis. Eight species of rauwolfia grow in India; according to origin or source of supply, it is customary to recognize the Bengal, Bihar, Assam, Dehra Dun and Ceylon varieties of rauwolfia in the Indian market; these show considerable differences in quality and content of the therapeutic alkaloids. The most useful variety of rauwolfia from the therapeutic standpoint is R. serpentina, which grows to a height of one and one-half to three feet and has pinkish-white flowers.

Chemical Composition

Early researches suggested the presence in the R. serpentina plant of an alkaloid, which was provisionally named pseudobrucine. Since 1931, the chemical structure or composition of the plant has been the subject of investigation by numerous observers.

In 1891, Dymock, for the first time, detected the presence of an alkaloid and a yellow resin in the root of R. serpentina.

In 1931, Sen and Bose found two alkaloids in its root (the total alkaloid content being...
about 1 per cent of the dried root), in addition to fair quantities of resin and starch. Siddiqui and Siddiqui\textsuperscript{17} (1931) found, besides phytosterol, oleic acid and unsaturated alcohols, five alkaloids with different physical characteristics and molecular formulae, classified by them into two groups, viz., (1) the ajmaline group of three white crystalline weak bases, ajmaline (C\textsubscript{26}H\textsubscript{26}O\textsubscript{2}N\textsubscript{2}), ajmalinine (C\textsubscript{26}H\textsubscript{25}O\textsubscript{4}N\textsubscript{2}), and ajmalicine; and (2) the serpentine group of two yellow, crystalline stronger bases, serpentine (C\textsubscript{21}H\textsubscript{25}O\textsubscript{3}N\textsubscript{2}) and serpinine (C\textsubscript{26}H\textsubscript{29}O\textsubscript{3}N\textsubscript{2}).

In 1932, two Dutch chemists, Van Italie and Stenhauer\textsuperscript{97} isolated three alkaloids similar in formula or structure to the ajmaline, ajmalinine and serpinine of Siddiqui and Siddiqui\textsuperscript{17,98}. They named their first alkaloid, rauwolfin (C\textsubscript{25}H\textsubscript{26}O\textsubscript{2}N\textsubscript{2}).

In 1939, Siddiqui\textsuperscript{99} reported that the only two alkaloids obtained from the Dehra Dun variety of R. serpentina differed from those of the Bihar variety in their chemical structure and melting points and named them iso-ajmaline or neoajmaline. In 1941, Mookherjee\textsuperscript{100} isolated an alkaloid from R. canescens, and named it rauvoseline (C\textsubscript{21}H\textsubscript{26}O\textsubscript{3}N\textsubscript{2}). Muller, Schlittler and Bein,\textsuperscript{92} in 1952, isolated a new alkaloid, reserpin, from R. serpentina, with an empirical formula of C\textsubscript{33}H\textsubscript{40}O\textsubscript{9}N\textsubscript{2}. In 1953, Chowdhury and Ghosh\textsuperscript{101} isolated yet another alkaloid, hypotensin, from the serpentina root.

Other alkaloids of R. serpentina more recently isolated and described are, sarpagine (C\textsubscript{19}H\textsubscript{22}O\textsubscript{2}N\textsubscript{2}), isolated and described by Stoll and Hofmann\textsuperscript{102} (1953), raupine (C\textsubscript{26}H\textsubscript{26}O\textsubscript{2}N\textsubscript{2}), by Bodendorf and Eder\textsuperscript{13} (1953), rauhimine (C\textsubscript{21}H\textsubscript{26}O\textsubscript{2}N\textsubscript{2}), and iso-rauhimine (C\textsubscript{21}H\textsubscript{26}O\textsubscript{2}N\textsubscript{2}) by Hofmann\textsuperscript{67} (1954), substance I (C\textsubscript{22}H\textsubscript{28}O\textsubscript{4}N\textsubscript{2}) and substance II (C\textsubscript{23}H\textsubscript{28}O\textsubscript{4}N\textsubscript{2}) by Popelak and associates\textsuperscript{106} (1953) and reserpinine (C\textsubscript{19}H\textsubscript{26}O\textsubscript{3}N\textsubscript{2}) by Schlittler and associates\textsuperscript{108} (1954).

**Pharmacologic Effects**

The pharmacologic actions of the R. serpentina root and of its individual alkaloids have been investigated from time to time.

On the basis of experiments on frogs, Siddiqui and Siddiqui\textsuperscript{17} (1931) showed that while the ajmaline group acts as a general depressant to the heart, respiration and central nervous system, the serpentine group causes paralysis of respiration, depression of nerves and stimulation of the heart. Sen and Bose\textsuperscript{111} (1931) reported a small drop of blood pressure, a depression of the heart muscle, respiratory stimulation and relaxation of smooth muscles, in cats and other animals, after the administration of R. serpentina alkaloids. Roy\textsuperscript{104} (1931) described dulling of sensations, sluggish reflexes and sleep after large doses and death from respiratory failure after lethal doses. In 1933, Chopra and associates,\textsuperscript{24} working with the total alkaloids of R. serpentina described valuable sedative, hypnotic and hypotensive properties.

In 1940, Hamet\textsuperscript{65} observed, for the first time, the sympathicolytic activity of alkaloids, particularly, ajmaline and rauwolfin, isolated from R. serpentina (Benth), and remarked on the hypotensive action of several of the alkaloids.

In 1941 and 1942, Chopra and his associates\textsuperscript{84, 37} reported exhaustively on the pharmacological and toxic effects of R. serpentina root extracts as well as of individual alkaloids; in their experience, while the total alkaloids, alcoholic extracts and serpentine, particularly the last, possess valuable hypotensive properties, ajmaline and serpentinine are hypertensive drugs. Bhata and Kapur\textsuperscript{12} (1944) reported, after the administration in animals of the two alkaloids, isoajmaline and neoajmaline, stimulation followed by depression of the central nervous system, and lowering of the blood pressure in intact, spinal and decerebrate animals, with or without experimentally induced hypertension. In 1944, Gupta, Kahali and Dutt\textsuperscript{55} found that the crude resin isolated by Dynoek in 1891, also possessed the sedative and hypnotic properties of the serpentina root. Chakravart\textsuperscript{17} (1952) and Mukherjee\textsuperscript{31} (1953) described the sympathicolytic effects of the alkaloid rauvoseline, isolated from R. canescens (Linn).

Muller and associates\textsuperscript{82} (1952) and Bein\textsuperscript{8} (1953), on the basis of animal experiments, found the new alkaloid reserpin to possess marked and long-lasting hypotensive, vasodepressor and sedative-hypnotic properties. In
1953, Dasgupta and associates\textsuperscript{31} described the sympatholytic activity and adrenergic blocking activity of the purified total alkaloids and the oleoresinous fraction of \textit{R. serpentina}. In their opinion, the hypotensive action of the root is only partly due to the sympatholytic effect, other factors like peripheral vasodilation being also concerned. Chowdhury and Ghosh\textsuperscript{29} (1953) reported the hypotensive effects of a new alkaloid, hypotensin, isolated from the root.

On the basis of experimental and clinical studies, the root of \textit{R. serpentina} is said to have the following pharmacologic attributes.\textsuperscript{192} (1) By action on the vasomotor center, it leads to generalized vasodilatation, with a lowering of blood pressure. (2) By depressant action on the cerebral centers, it soothes the general nervous system.\textsuperscript{143} (3) It exerts a sedative action on the gastric mucosa and a stimulating action on the plain musculature of the intestinal tract. (4) It stimulates the bronchial musculature.

\textbf{Clinical Studies}

Until the year 1949, in spite of many notable clinical and pharmacologic contributions on the subject in India, interest in \textit{R. serpentina} therapy had remained strictly localized to that country.

When, in 1949, the author\textsuperscript{192} published in England the first clinical report on \textit{R. serpentina} therapy to appear outside of India, interest in the subject soon became international. Since that time, contributions, both clinical and pharmacologic, on the subject of \textit{R. serpentina}, have been literally pouring forth from different countries of the world.

\textbf{Earlier Indian Contributions}

Although the therapeutic value of \textit{R. serpentina} in cases of insanity, particularly when associated with maniacal tendencies, was recognized in 1931 by Sen and Bose\textsuperscript{111} and subsequently confirmed by Ghosh in 1940, the first mention in the literature of its value in human cases of hypertension was in 1940, when Vakil\textsuperscript{103} made the following allusion to the subject: “After a trial of this preparation, one finds it useful in a percentage of cases of hypertension only; the indications and suitability of the case for the drug have not as yet been worked out.”

A vague reference to the use of a tincture or alcoholic extract of the root of \textit{R. serpentina}, in cases of high blood pressure, was made in 1942 by Paranjpe.\textsuperscript{95} He claimed improvement, without any statistical support, in most cases of hypertension; the hypotensive action was said to be particularly gratifying in elderly subjects and in the case of the diastolic pressure.

In 1942, Bhatia,\textsuperscript{11} after employing \textit{R. serpentina} in the treatment of cases of high blood pressure, both with and without renal damage, reported it as a useful and well-tolerated hypotensive remedy.

\textbf{International Contributions}

In 1949, in England, Vakil\textsuperscript{192} reported the results of an extensive clinical trial of the dried root of \textit{R. serpentina} in 50 cases of essential, benign hypertension. Satisfactory drops of both systolic and diastolic blood pressure levels were observed in 83 per cent and 81 per cent of cases, respectively, after four weeks of therapy; it was concluded, on the basis of this study, that \textit{R. serpentina} has “a definite place in the treatment of high blood pressure.”

The following are among the most noteworthy of the international contributions on the subject.

\textbf{From the United States.} In 1953, after carrying out clinical trials in over 100 cases, over periods varying from one month to one year, Wilkins and Judson,\textsuperscript{148} found \textit{R. serpentina} useful in lowering high blood pressure levels, nonhabit forming, free of serious side effects, and applicable in most cases of hypertension. In the opinion of Wilkins,\textsuperscript{146-149} \textit{R. serpentina} is “a valuable addition to our armamentarium against hypertension,” possessing both symptom-relieving and hypotensive properties, especially in young labile hypertensives with sensitive nervous systems. Amongst side effects, he observed nasal stuffiness, a tendency to diarrhea, gain in body weight, nightmares and, on rare occasions, a sense of “depressed anxiety” or jitteriness. Optimal results were obtained with a dose of
100 to 125 mg. of crude root, administered one to three times a day.

In 1953 Ford and Moyer49, after subjecting 25 cases of essential hypertension to combined R. serpentina and hexamethonium therapy, were able to report (1) adequate reduction of pressure levels in a large number of cases, (2) fewer and milder side reactions than with hexamethonium alone, (3) adequate lowering of pressure even with suboptimal doses of hexamethonium and (4) better stabilization of pressure levels.

From England. In 1954, after a trial of R. serpentina, used in conjunction with veratrum viride, in 24 severely hypertensive patients, Joiner and Kauntze71 could not demonstrate either a good therapeutic response to the drug or evidence of synergistic action. Bradycardia and lowering of diastolic pressure were observed in some of their cases, while pruritus and urticaria were noted twice. In view of the acknowledged refractoriness of severe hypertensives to any form of therapy, the disappointing results obtained by these authors are not surprising.

From New Zealand. In 1954 Doyle and Smirk39 found reserpine, the alkaloid of R. serpentina, in large doses (2 to 3 mg., thrice daily), capable of inducing striking falls of blood pressure within four to six hours of administration; unpleasant reactions, like fatigue, drowsiness, depression, shivering, feeling of heat, conjunctivitis, restlessness, nausea, vomiting and diarrhea, were observed after larger doses of the drug. An additive effect was noted in some of the cases treated on combined reserpin-methionium therapy.

From Germany and Austria. After using R. serpentina in 25 cases, Vida138 in 1952 found it effective in all kinds of high blood pressure and superior to other hypotensive agents. Arnold3 (1952), regarded it as (1) the most effective soothing agent with a centrally effective component known for the autonomic nervous system and (2) a valuable hypotensive agent, particularly for cases of labile hypertension. Seliger110 (1952), after confirming Vakil’s work on the subject, recommended continuous R. serpentina therapy in the treatment of high blood pressure. Arnold and Boek1 (1953), obtained a good hypotensive response in 37 out of 50 cases of hypertension treated with R. serpentina. Cerebral arteriosclerosis and nephrosclerosis were regarded as contraindications. Lassitude was commonly noted as a side effect and orthostatic phenomena. From 1953, Sarre56 (1953) reported systolic pressure drops of over 30 mm. and diastolic drops of over 15 mm. in the great majority of his cases; headache and vertigo were constantly relieved and subjective improvement noted in almost all the cases. According to Newmayer94 (1953), R. serpentina is capable of lowering the systolic and diastolic pressures in most cases of labile hypertension, in a fair number of cases of fixed hypertension and in occasional cases of renal hypertension. The pressure effect was said to start gradually, attaining its maximum after two or three weeks; while nose blocking was common after therapy, symptoms akin to collapse were rarely observed. The bradycardia was found to be proportional to the degree of pressure drop. Kleinsoff and Wittig75-76 (1954), after using R. serpentina alkaloids in 84 classified cases of hypertension, reported a systolic response in about 40 per cent of cases. While subjective improvement occurred in about two-thirds of his cases, no alterations were observed in the eye grounds, electrocardiographic tracings and renal function tests. In 1953, Marx55 found the drug useful in all varieties of hypertension, including the nephrosclerotic and cerebral arteriosclerotic forms. He was greatly impressed by its sedative qualities. Meissner88 (1953) found it effective in 90 per cent of hypertensive cases, normal pressures being restored within three weeks in many cases. An average lowering of 40 mm. Hg of pressure was observed in cases of labile hypertension, of 28 mm. in fixed hypertension and of 15 mm. in renal hypertension. A good response was also noted in hyperexcitable and thyrotoxic individuals. Watschinger143 (1953) found it superior in many respects to the other better known hypotensive agents. Runck105 (1954) was impressed by both the hypotensive effect of the drug, as well as by the complete absence of toxic reactions. He advised a modification of dosage in cases of diabetes and
cerebral arteriosclerosis. Klausgraber (1953), in Vienna, tried the drug in 83 cases of hypertension of diverse types; some cases were associated with renal and cardiovascular complications. A satisfactory response of both systolic and diastolic pressures was obtained in 63 per cent of cases. Although all cases were subjectively improved, the electrocardiographic tracings, retinal fields, renal function tests and teleradiograms remained unaffected by the treatment.

From Switzerland. In 1953 Loffler and associates tried the alkaloid reserpin, isolated from R. serpentina by Swiss workers, in 51 cases of hypertension. Adequate falls of pressure were observed in only 14 cases and maintained for only 12 days in spite of continuation of therapy. Subjective improvement was reported in 16 cases, and side effects, including fatigue, depression, excitability, painful extremities, visual phenomena, miosis and dryness of mucous membranes only in cases treated with doses larger than 1.5 mg. per day.

From Japan. In 1954 Goto found the alkaloid reserpin effective in 12 out of 15 cases of hypertension. The hypotensive action was apparent three to seven days after initiation of therapy and maintained for 10 to 21 days after its suspension. Nose block and "pharyngeal bolus" were observed in three cases. On trying various combinations of R. serpentina with veratrum viride and Apresoline in 72 cases of hypertension, including 13 cases of renal hypertension, Goto obtained a hypotensive response of 30 mm. or over within a month of the initiation of therapy in 85 per cent of cases; this result was maintained for two to four months. Apart from occasional vertigo and conjunctivitis, there were no side-reactions.

From India. In 1952, Chakravarty and associates reported average systolic and diastolic pressure falls of 18.5 mm., and 16.4 mm., respectively, on the tenth day of R. serpentina therapy. Mazumdar and Mukherjee (1951) reported subjective improvement in all cases and a hypotensive response in 7 out of 12 cases of hypertension. Chowdhury and Ghosh (1953), found the alkaloid "hypotensin", isolated from R. serpentina in Calcutta, effective, even in small doses, in most cases of hypertension, and without ill effects. In 1953 Vakil reported a good hypotensive response to the alkaloid reserpine in 72 per cent of cases, and few side effects. The accidental administration of 10 times the therapeutic dose to one patient merely resulted in a transitory feeling of lassitude and vertigo.

Many more studies, hitherto unpublished, on the hypotensive action of R. serpentina root or of its individual alkaloids, either used singly or in combination with hypotensive agents like veratrum viride, hexamethonium and hydralazine, have been brought to light, recently, from various parts of the universe. The results are said to be uniformly good in mild and moderate cases of hypertension and devoid of any serious or toxic ill effects. As far as can be ascertained, the results obtained with individual alkaloids of R. serpentina have not differed materially from those obtained with the crude extracts of the root.

Present Day Status of R. Serpentina Therapy

In the short span of about 15 years that the dried root of R. serpentina has been on the market in India, this hypotensive remedy has gained such unprecedented popularity that the following statements can be made: (1) There is hardly one patient with high blood pressure in that country who has not been subjected at some time or another to its application. (2) In the experience of over 90 per cent of Indian doctors, as revealed by a questionnaire circulated by Vakil in 1949, R. serpentina is the best "hypotensive" remedy known. (3) One manufacturing firm alone claims to have sold, prior to the year 1954, over 98 million tablets of the dried root, of R. serpentina. (4) Shipments of the serpentina root in crude or tablet form have been sent from India to over 17 countries of the world within the last four years. (5) It is said to be prescribed by over 60,000 physicians at the present time.

R. Serpentina: Crude Extracts Versus Pure Alkaloids

For many years now, and particularly after the isolation of the alkaloid, reserpine, a strong
controversy has been raging between opposing schools of thought about the relative merits or superiority of the one form of *serpentina* preparation over the other.

The following arguments have been put forward in favor of the alkaloid: (1) Being a pure crystalline single alkaloid, it cannot produce undesirable effects from unknown alkaloids in the whole root. (2) Being a single known entity, results are likely to be more predictable. (3) Much smaller doses are required to obtain the same results. (4) According to some observers, it is a much more potent hypotensive agent.

Those who report favorably on the whole extract in preference to alkaloids support their claims with the following arguments: (1) The whole extract of *R. serpentina* contains not one but several proved alkaloids with hypotensive properties, ajmaline, serpinine and ajmalinine. According to those of this school of thought, the only pressure-raising alkaloid in the whole extract is serpinine, which is more than neutralized by the hypotensive alkaloids. (2) Alkaloids are not the only active constituents of *R. serpentina* root, the yellow resin fraction being also a highly active, sedative agent, as first noted by Dymock in 1891, and subsequently confirmed by Gupta, Kahali and Dutta. (3) Numerous authorities in the past have reported the therapeutic superiority of the crude extract. (4) The synergistic action of the total alkaloids eliminates danger of hypersensitiveness likely to develop from the use of single alkaloids.

**SUMMARIO IN INTERLINGUA**

Es presentate un revista del litteratura in re *Rauwolfia serpentina* como agente hypotensive, includente referentias a 151 distincte contributiones. Introductorimente le autor summarisa le historia ancian e plus recente del planta, su usos in medicina popular, su caracteristicas botanic, e su ecologia.

Receras chimic in re le agentes efficienc in *R. serpentina* es describite ab lor initio in le discoperta per W. Dymock in 1891 que le planta contine un alcaloide.

Le studio scientific del effectos pharmacologic de *R. serpentina* es traciate ab 1931 al presente.

Le nunc recognoscite usos del planta es enumere sequentemente: (1) Per ager super le centro vaso-motor, illo produce vasodilatation generalisate con resultant efectos hypotensive. (2) Per su action depressive super le centros cerebral, illo calma le systema nervose general. (3) Illo exercise un effecto sedative super le mucosa gastric e un action stimulante super le nonstriate musculatura del tubo digestive. (4) Illo stimula le musculatura bronchial.

Studies clinic ante le anno 1949 esseva restringite a India. A ille tempore le autor del presente articulo publicava un articulo in Anglaterra que initiava un longe serie de studios e reportos. Istos es summarisate in gruppos secundo le paises de lor origine. Le revista include contributiones ab le Statos Unite, Anglaterra, Nove Zelandia, Germania, Austria, Switza, Japon, e evidentemente India.

Le section concludente del articulo discute le stato presente del therapia a *R. serpentina*. Es presentate le major argumentos del autoritates qui prefere le extracto crude e le major argumentos de illes qui prefere le alcaloides in forma pur.

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