www.ijarp.com ISSN 2456-9992 Page: 01-15

International Journal Advanced Research Publications

Review Article

Volume: 02
Issue: 04

# RAUWOLFIA IN THE TREATMENT OF HYPERTENSION

*[1]Mr. Arun Pal, [2]Mr. Awan Kumar Pandey (Assistant Professor)

India.

**Article Received: 03 March 2026, Article Revised: 21 March 2026, Published on: 11 April 2026**

***Corresponding Author: Mr. Arun Pal**

India.

DOI: https://doi-doi.org/101555/ijarp.9486

## ABSTRACT

Rauwolfia serpentina is considered a safe and efficacious remedy for the management of hypertension. The plant was extensively utilized by numerous physicians across India during the 1940s and subsequently gained global recognition in the 1950s, including in the United States and Canada. However, its use declined due to reported adverse effects, such as depression and concerns regarding carcinogenicity.

In this review, the author critically evaluates the scientific literature related to the application of Rauwolfia in the management of hypertension. The discussion encompasses the plant's botanical characteristics, chemical composition, and pharmacological properties, while presenting a well-documented mechanism of action of its active constituents. Special emphasis is placed on its therapeutic role in controlling elevated blood pressure. Furthermore, the medical applications of the plant are analyzed, with a critical assessment of its side effects, toxicological profile, and potential carcinogenic risks.

The author challenges the purported association between Rauwolfia and cancer risk, highlighting the significance of appropriate dosage and patient screening to reduce the likelihood of depressive side effects. The review concludes with a recommendation for the use of low-dose Rauwolfia (LDR) in selected hypertensive patients. The plant thus offers clinicians a safe and effective complementary option alongside conventional antihypertensive medications.

Rauwolfia serpentina is an evergreen shrub belonging to the dogbane family, Apocynaceae. The genus Rauwolfia comprises over 100 species distributed across tropical and subtropical regions worldwide, including Europe, Africa, Asia, Australia, and Central and South America. Rauwolfia serpentina is indigenous to the humid, deciduous forests of Southeast Asia, particularly in India, Myanmar, Bangladesh, Sri Lanka, and Malaysia.

The plant typically attains a height of 60–90 cm and bears light green leaves measuring 7–10 cm in length and 3.5–5.0 cm in width. These leaves are elliptical to lanceolate in shape and arranged in whorls of three to five. The plant produces numerous glossy, black or purplish, spherical fruits approximately 0.5 cm in diameter, along with small pink or white flowers. It possesses a well-developed, tuberous, soft taproot, extending 30–50 cm in length and 1.2–2.5 cm in diameter.

**History and Folk Use**

Rauwolfia serpentina has been employed in traditional Indian medicine for centuries to manage a broad spectrum of ailments, including snake and insect envenomation, febrile illnesses, malaria, abdominal discomfort, and dysentery. It has also been utilized as a uterotonic agent, antipyretic, and remedy for mental disorders. Historical references to the plant date back to around 1000 BC in ancient Indian texts, where it is commonly referred to as *sarpagandha* and *chandrika*.

The genus *Rauwolfia* was named in honor of the 16th-century German physician Leonhard Rauwolf, who documented plant species during his travels in India. The species name *serpentina* was chosen due to the plant's long, tapering, snake-like roots.

The prominent Indian leader Mahatma Gandhi was known to use Rauwolfia, reportedly preparing a decoction from its root and consuming it in the evening to promote relaxation after a demanding day.

The Indian physician Rustom Jal Vakil is credited with introducing Rauwolfia into Western medical practice. Over a decade (1939–1949), he systematically documented clinical outcomes in patients treated with the plant. In 1949, he published a landmark study in the *British Medical Journal* highlighting its antihypertensive efficacy. His research included detailed observations of 50 patients with elevated blood pressure treated using Rauwolfia root, yielding highly significant results. By that time, over 90% of physicians in India had adopted Rauwolfia for hypertension management. Following Vakil's pioneering publication, more than 100 scientific papers were published globally on this plant.

**Chemical Composition**

Rauwolfia serpentina contains a diverse array of phytoconstituents, including alcohols, carbohydrates, glycosides, fatty acids, flavonoids, phytosterols, oleoresins, steroids, tannins, and alkaloids. Among these, alkaloids represent the most pharmacologically significant

group, particularly the indole alkaloids, of which more than 50 have been isolated from the plant.

Indole alkaloids are nitrogen-containing organic compounds biosynthesized from the amino acid tryptophan. Structurally, they possess a characteristic heterocyclic ring system composed of fused five- and six-membered rings containing one nitrogen atom.

These alkaloids are distributed throughout the plant, including stems and leaves; however, their highest concentration is found in the root bark. Identified indole alkaloids include ajmalidine, ajmaline, ajmalinine, ajmalicine, aricine, canescine, coryanthine, deserpidine, isoajmaline, isoserine, isoserpiline, lankanescine, neoajmaline, papaverine, raubasine, raucaffricine, rauhimbine, rauwolfinine, recanescine, rescinnamine, reserpiline, reserpine, reserpinine, sarpagine, serpentine, serpentinine, thebaine, yohimbine, and yohimbinine.

The concentration of total alkaloids varies depending on factors such as plant part and growth conditions. Studies have reported alkaloid yields ranging from approximately 0.8% to 1.3% of the plant's dry weight, while other findings suggest a range between 0.7% and 3.0% in root material. The highest alkaloid content observed in regenerated roots has been reported at 3.3%.

Other species within the *Rauwolfia* genus have also been utilized as substitutes for *R. serpentina*, including *Rauwolfia vomitoria* and *Rauwolfia caffra* from Africa, as well as *Rauwolfia heterophylla* and *Rauwolfia tetraphylla* from Central and South America. Research indicates that these related species contain varying levels of indole alkaloids and may serve as viable alternatives to *R. serpentina*.

**Reserpine**

Reserpine is one of the principal alkaloids present in Rauwolfia serpentina. Its concentration is highest in the root, while comparatively lower levels are observed in the stems and leaves. It has long been regarded as the predominant indole alkaloid in the plant; however, subsequent analytical studies have questioned this assumption.

The proportion of reserpine in the plant varies, typically ranging from 0.03% to 0.14% of the plant's dry mass. Similar variability has been observed in the root, where concentrations range between 0.038% and 0.14% across different samples. In one investigation, reserpine accounted for 33 mg out of 496 mg of total alkaloids per gram of root, whereas another study reported a concentration of 0.955 mg/g in Rauwolfia root.

In addition to reserpine, several other alkaloids present in the plant exhibit noteworthy biological and therapeutic activities, including canescine, deserpidine, recanescine, and rescinnamine.

**Pharmacology**

Reserpine is the most extensively researched alkaloid derived from *Rauwolfia serpentina*. The earliest modern scientific report on reserpine was published in 1931 in the *Indian Medical Journal* by Sen and Bose. It was later isolated and utilized therapeutically by Robert Wallace Wiggins in 1950.

In 1952, CIBA (now Novartis) published the first comprehensive report detailing the chemistry and pharmacological properties of reserpine. In the same year, purified reserpine was introduced into clinical practice under the trade name Serpasil for the management of hypertension, tachycardia, and thyrotoxicosis.

Chemically, reserpine belongs to the class of indole alkaloids. It appears as a white to pale yellow crystalline powder that darkens upon exposure to light. It is odorless, poorly soluble in water, slightly soluble in alcohol, and readily soluble in acetic acid. It possesses a molecular formula of $C_{33}H_{40}N_2O_9$, a molecular weight of approximately 609 g/mol, and a characteristically bitter taste.

Following oral administration, the bioavailability of reserpine ranges between 50% and 70%, with most studies indicating an average of around 50%. Gastrointestinal absorption is relatively rapid, generally occurring within 1–2 hours, although delayed absorption (2–4 hours) has also been reported.

Reserpine demonstrates extensive distribution throughout the body, including the brain, liver, spleen, kidneys, and adipose tissue. It is also distributed to erythrocytes and peripheral neurons. Additionally, it is capable of crossing the placental barrier and the blood–brain barrier, and has been detected in breast milk.

Pharmacokinetic studies indicate that the initial half-life of reserpine in the bloodstream is approximately 4–5 hours, while its elimination half-life ranges from 45 to 168 hours in plasma. This prolonged elimination is attributed to its strong binding affinity to plasma proteins and red blood cells.

Metabolism primarily occurs in the liver, accounting for nearly 62% of its biotransformation, whereas renal excretion contributes less than 8%. The majority of the drug and its metabolites are eliminated via fecal excretion. It has been observed that approximately 30% to 60% of the excreted metabolites are present in the form of unchanged reserpine.

**Mechanism of Action**

Reserpine has a well-established and extensively studied mechanism. It acts by binding to vesicular monoamine transporters (VMATs), which are protein carriers located on the membranes of intracellular storage vesicles within presynaptic neurons. By attaching to these transporters, reserpine inhibits the uptake and storage of neurotransmitters such as norepinephrine, dopamine, and serotonin into synaptic vesicles.

As a consequence, intracellular neurotransmitters are depleted, and their release into the synaptic cleft is markedly reduced or prevented. This leads to diminished transmission of nerve impulses to the postsynaptic neuron, resulting in decreased sympathetic activity.

Two main isoforms of vesicular transporters exist: VMAT1 and VMAT2. VMAT1 is primarily localized in neuroendocrine cells of the peripheral nervous system, including adrenal medullary chromaffin cells, sympathetic neurons, and platelets. In contrast, VMAT2 is predominantly found in the central nervous system, sympathetic neurons, mast cells, and histamine-containing cells of the gastrointestinal tract and pancreas. Reserpine exhibits approximately threefold greater affinity for VMAT2 compared to VMAT1 and binds strongly, almost irreversibly, particularly to VMAT2 receptors.

**Rauwolfia and Hypertension**

Rauwolfia serpentina has been extensively investigated for its antihypertensive properties, with numerous clinical studies demonstrating its efficacy.

In 1949, Rustom Jal Vakil reported a clinical study involving 50 patients with essential hypertension treated with Rauwolfia. The results showed that 85% of patients experienced a reduction in systolic blood pressure, while 81% showed a decrease in diastolic pressure.

Subsequent international studies further supported these findings. In 1952, Vida reported reductions in blood pressure among 25 hypertensive patients in Germany and Austria. Similarly, Arnold and Bach observed significant improvement in 37 out of 50 patients, with an average reduction of 30 mm Hg in systolic and 15 mm Hg in diastolic pressure. In 1953, Meissner documented effectiveness in 90% of study participants, reporting systolic reductions ranging from 15 to 40 mm Hg. Additional studies by Loffler (Switzerland), Goto (Japan), and Doyle and Smirk (New Zealand) also demonstrated substantial antihypertensive effects, with rapid onset of action observed within 4–6 hours in some cases.

During the 1950s, Rauwolfia was considered one of the most widely used antihypertensive agents in India, reportedly prescribed by over 90% of physicians, representing more than

60,000 practitioners. It was also commercially successful, with millions of tablets distributed globally.

In 1952, a standardized alkaloid extract known as alseroxylon was introduced in the United States. This preparation, containing reserpine and rescinnamine, was evaluated in 346 hypertensive patients. A consistent reduction in blood pressure exceeding 20 mm Hg was observed in treated individuals compared to placebo.

Another formulation, Serpina, was administered to over 100 patients for durations ranging from one month to one year. Daily doses of 1–3 tablets were generally well tolerated. The onset of action was gradual (3–6 days), and effects persisted for 7–21 days after discontinuation. While no severe adverse reactions were reported, mild effects such as sedation, improved sleep, occasional nightmares, bradycardia, and nasal congestion were noted. The preparation was non-habit forming and could be temporarily discontinued to alleviate minor side effects. It demonstrated moderate hypotensive activity, particularly in patients with labile hypertension and tachycardia, and exhibited sympatholytic properties without causing postural hypotension. Greater efficacy was observed in younger patients with neurogenic hypertension compared to those with long-standing vascular disease.

In a clinical trial involving 50 patients with baseline blood pressure above 160/95 mm Hg, Vakil reported significant reductions within one week of treatment initiation. After four weeks, systolic pressure decreased by 2–54 mm Hg, while diastolic pressure reductions ranged from 4 to 34 mm Hg. The antihypertensive effect persisted for weeks after discontinuation, with no serious adverse effects observed.

Another outpatient study evaluated oral reserpine in 15 hypertensive individuals receiving 20 mg twice daily. The results demonstrated average reductions of 30.7 mm Hg in systolic pressure and 19 mm Hg in diastolic pressure. Some participants reported mild, transient adverse effects such as nausea, fainting, and shortness of breath. Overall, reserpine was considered an effective therapeutic agent for both mild and severe hypertension.

A systematic review conducted by the Cochrane Collaboration assessed the dose-dependent effects of reserpine on blood pressure, heart rate, and treatment discontinuation due to adverse events. The review included randomized controlled trials comparing reserpine monotherapy with placebo. The findings indicated that reserpine effectively reduced systolic blood pressure to a degree comparable with other first-line antihypertensive agents. However, due to the limited number of high-quality trials, definitive conclusions regarding optimal dosing could not be established. The authors recommended further research to better define its safety and dose-response relationship.

Notably, reserpine remains one of the few antihypertensive agents demonstrated to reduce mortality in randomized controlled trials.

**Other Medical Uses**

Rauwolfia serpentina has been investigated for a variety of clinical applications beyond hypertension. It has shown potential in the management of psychiatric and neurological disorders, including schizophrenia, bipolar disorder, epilepsy, seizure conditions, insomnia, and other sleep-related disturbances.

Clinical studies have demonstrated its effectiveness in reducing anxiety. Various preparations of Rauwolfia—including Reserpine, alseroxylon, and whole-root formulations—have exhibited comparable efficacy in alleviating overt anxiety symptoms in ambulatory patients.

Rauwolfia has also been explored in pediatric populations, particularly in children aged 3.5 to 9 years with autism spectrum disorders. Additionally, it has been evaluated for the management of delirium tremens in individuals with alcohol or substance dependence, where it was associated with reductions in agitation, hyperexcitability, and acute hallucinations.

Further investigations have reported beneficial effects in the treatment of migraine, with improvements in both pain intensity and overall quality of life. It has also been used in patients with angina pectoris secondary to coronary artery disease, where it contributed to a reduction in anginal symptoms and demonstrated sustained therapeutic benefits. Notably, some patients exhibited normalization of electrocardiographic findings.

Dermatological applications have also been documented, including improvements in pruritic conditions and psychogenic dermatoses, as well as a reduction in psoriatic flare-ups.

**Side Effects and Toxicology**

Reserpine is associated with a range of adverse effects. Commonly reported reactions include fatigue, sedation, depressive symptoms, hypotension, nausea, vomiting, abdominal discomfort, gastric irritation or ulceration, nightmares, bradycardia, angina-like manifestations, bronchospasm, dermatological reactions (such as rash and pruritus), galactorrhea, gynecomastia, sexual dysfunction, and, in rare cases, withdrawal psychosis.

The most frequently observed adverse effect is nasal congestion, affecting approximately 5% to 15% of patients. Prolonged use over several months may lead to persistent depressive symptoms. At high doses, more severe neurological complications such as Parkinsonian features, extrapyramidal reactions, and seizures may occur. Allergic responses, including asthma, are infrequent.

Therapeutic doses sufficient to reduce blood pressure are generally not associated with the development of gastric ulcers. Mild edema has been reported in some individuals. Reserpine may also interact with various medications, including cardiac glycosides, ephedra-containing products, alcohol, antipsychotics, barbiturates, digoxin, diuretics, ephedrine, levodopa, monoamine oxidase inhibitors, propranolol, stimulants, and tricyclic antidepressants.

Additionally, Rauwolfia preparations may interfere with several laboratory investigations, including assays for corticosteroids, bilirubin, catecholamines, gastric acidity, norepinephrine, prolactin, thyroxine, and vanillylmandelic acid.

Toxicity reports from 1959 to 1960 in the United States documented 151 cases associated with Rauwolfia ingestion, with the majority occurring in pediatric populations. Reported symptoms included nausea, vomiting, hypotension, sedation, coma, bradycardia, and facial flushing. Depression was most commonly observed at doses exceeding 0.5 mg/day, whereas significantly fewer cases were reported at doses below 0.25 mg/day. Between 1962 and 1965, 225 cases of accidental ingestion were reported, including pediatric exposures to doses as high as 25 mg; all cases resolved without long-term complications.

Current evidence does not support an association between reserpine use and carcinogenicity. No increased risk of congenital abnormalities has been observed in pregnant women exposed to reserpine. Furthermore, studies have not demonstrated mutagenic, genotoxic, or recombinogenic effects.

**Rauwolfia and Breast Cancer**

Concerns regarding a potential link between Rauwolfia or reserpine use and breast cancer emerged in the late 1960s and early 1970s following several case-control studies. However, subsequent re-evaluation of these studies revealed methodological limitations, particularly exclusion bias, where patients with cardiovascular disease were omitted from control groups.

Later analyses that corrected for such biases found no significant association between Rauwolfia use and breast cancer incidence. In comparative studies involving matched patient groups, the risk of developing breast cancer was found to be essentially equivalent between users and non-users of Rauwolfia-based treatments.

Additional investigations involving hypertensive patients treated either with Rauwolfia or alternative pharmacological therapies reported relative risk values close to unity, further supporting the absence of a causal relationship.

Although reserpine has been shown to elevate prolactin levels, studies comparing long-term users with non-users indicated only a moderate increase (approximately 50%). Researchers

concluded that such elevations, particularly in postmenopausal women, are unlikely to significantly influence breast cancer risk. Moreover, prolactin has not been definitively established as a contributing factor in human breast carcinogenesis.

**Rauwolfia and Depression**

The relationship between Rauwolfia serpentina and depression has been evaluated in clinical settings. A study conducted in an outpatient hypertensive clinic in Montreal (1954–1956) examined 296 patients, of whom 195 received Rauwolfia-based preparations and 101 served as controls without exposure to Rauwolfia.

Among those treated, 134 patients received Reserpine alone, while 61 patients were administered either whole-root preparations or the purified alseroxylon fraction. None of the control patients developed depression, whereas 30 out of 195 patients (approximately 15%) in the Rauwolfia-treated group reported depressive symptoms. The majority of these cases occurred in females, with ages ranging from 33 to 70 years (mean age: 52.7 years).

Of the patients who developed depression, 83% were receiving reserpine, while 17% were using either whole-root or alkaloidal extracts. The onset of depressive symptoms varied depending on the preparation:

- 2 weeks to 14 months (average 4.5 months) for reserpine,
- approximately 2.5–3 months for whole-root preparations, and
- about 5 months for alseroxylon.

Dosages associated with these outcomes included:

- 0.75–4 mg/day of reserpine (average 1.36 mg),
- 8–12 mg/day of alseroxylon (average 10 mg), and
- 150–200 mg/day of whole-root preparations (average 183 mg).

The severity of depression was graded on a scale of 1 to 4. Following discontinuation of therapy, 19 out of 30 patients recovered completely. Among these, 11 achieved full remission, 7 showed marked improvement, and 1 exhibited no change. Ten patients required hospitalization. Dose reduction in six cases resulted in complete recovery in four patients and partial improvement in the remaining two.

The investigators concluded that while dosage plays a significant role in the development of depression, it is not the sole contributing factor. They emphasized the importance of

obtaining a comprehensive psychiatric history prior to initiating therapy and recommended maintaining reserpine doses below 0.75 mg per day.

**Author's Experience with Rauwolfia**

The author, with over two decades of clinical experience in naturopathic medicine, reports extensive use of Rauwolfia serpentina in the management of hypertension. Various combinations of herbal and mineral supplements have been utilized, with a preference for combining Rauwolfia with hawthorn and magnesium in the form of capsules, tablets, or tinctures. Encapsulated root powder is the preferred formulation.

Based on clinical experience involving more than 300 patients and over 80,000 prescribed capsules, the author typically limits the dosage to a maximum of 500 mg per day, most commonly prescribing 100 mg twice daily. In selected cases, doses of 300–400 mg per day are administered.

The concept of low-dose Rauwolfia (LDR) is strongly supported by the author, who reports consistent and sustained reductions in blood pressure. Observed outcomes include average decreases of 20–30 mm Hg in systolic pressure and 10–15 mm Hg in diastolic pressure. The therapeutic effect is considered comparable to that of standard first-line antihypertensive medications.

Rauwolfia has been used in combination with conventional drugs such as diuretics, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs). However, caution is advised when co-administered with beta-blockers or calcium channel blockers.

Most patients report improvements in well-being, reduced anxiety, and better sleep quality. Adverse effects have been minimal, with occasional reports of nasal congestion and mild gastrointestinal disturbances. Notably, no cases of depression have been observed in the author's practice, likely due to careful patient selection and screening.

The author emphasizes the importance of excluding patients with a history of depression or psychiatric illness. Additional caution is exercised in patients receiving antidepressant therapies, including selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and norepinephrine–dopamine reuptake inhibitors (NDRIs).

Rauwolfia is not recommended for patients with congestive heart failure, cardiac decompensation, bradycardia (heart rate below 60 beats per minute), or in frail elderly individuals. The author notes that Rauwolfia may reduce heart rate by approximately 10 beats per minute, which may not be beneficial in such populations.

Similarly, it is avoided in patients with suspected hypoadrenalism unless accompanied by elevated blood pressure, increased heart rate, and symptoms of nervous tension. Overall, the author expresses confidence in Rauwolfia as a highly effective natural therapeutic option for hypertension, considering it among the most reliable herbal remedies for managing elevated blood pressure.

## CONCLUSIONS

Based on a comprehensive evaluation of the available scientific literature, Rauwolfia serpentina appears to be a safe and effective therapeutic option for the management of hypertension when administered at appropriately low doses. Equivalent preparations containing purified Rauwolfia alkaloids, such as alseroxylon extract or Reserpine, have also demonstrated efficacy in reducing elevated blood pressure.

Clinical experience suggests that low-dose Rauwolfia (LDR) can be safely recommended for carefully selected patients following proper screening. The total daily dosage of Rauwolfia root should generally not exceed 500 mg and, in most cases, remains effective at doses below 250 mg per day.

For purified alkaloid preparations, including alseroxylon extract, the recommended daily dose should remain below 5 mg, with typical therapeutic doses being less than 2.5 mg per day. Similarly, the dosage of reserpine should not exceed 500 µg per day and is commonly maintained below 250 µg per day to minimize adverse effects.

When administered as a tincture, the dosage should be adjusted according to its concentration. For example, a 1:5 tincture preparation may be administered at a dose of approximately 0.5 mL, corresponding to about 100 mg of crude root material, while a standard dropper typically delivers 1.0 mL in approximately 15 drops.

Overall, careful dose optimization and patient selection are essential to maximize therapeutic benefits while minimizing potential risks associated with Rauwolfia therapy.

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