WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 7, 967-978. Review Article ISSN 2277– 7105

ROLE OF *RAUWOLFIA SERPENTINA* IN THE MANAGEMENT OF HYPERTENSION

Dr. Sumitra Devi Jajra*[1] and Dr. Sukhdev Rao[2]

[1]PG Scholar Dept. of Dravyaguna, Dr. Sarvepalli Radhakrishnan Rajasthan Ayurved University Jodhpur.

[2]PG Scholar Dept. of Anaesthesiology, Dr. S. N. Medical College Jodhpur Rajasthan, India.

Article Received on
12 April 2019,
Revised on 02 May 2019,
Accepted on 23 May 2019
DOI: 10.20959/wjpr20197-15170

***Corresponding Author**
Dr. Sumitra Devi Jajra
PG Scholar Dept. of Dravyaguna, Dr. Sarvepalli Radhakrishnan Rajasthan Ayurved University Jodhpur.

ABSTRACT

Sarpgandha (*Rauwolfia serpentina*) is an evergreen shrub that is a member of the **Apocynaceae** family. More than 100 species are included in the *Rauwolfia* genus, and they are native to tropical and subtropical regions of the world, including Europe, Africa, Asia, Australia, and the Central and South Americas. *Rauwolfia* serpentina is native to the moist, deciduous forests of Southeast Asia, including India, Burma, Bangladesh, Sri Lanka, and Malaysia. The plant usually grows to a height between 60 and 90 cm and has pale green leaves that are 7 to 10 cm long and 3.5 to 5.0 cm wide. The leaves are elliptical or lanceolate shaped and occur in whorls of 3 to 5 leaves. The plant has many shiny, black or purple, round fruits that are approximately 0.5 cm in diameter. It also has small pink or white flowers. The plant has a prominent tuberous, soft taproot that reaches a length between 30 and 50 cm and a diameter between 1.2 and 2.5 cm.

KEYWORDS: Sarpgandha (*Rauwolfia serpentina*) is Apocynaceae between 1.2 and 2.5cm.

INTRODUCTION

History and Folk Use

Rauwolfia serpentina was used in folk medicine in India for centuries to treat a wide variety of maladies, including snake and insect bites, febrile conditions, malaria, abdominal pain, and dysentery. It was also used as a uterine stimulant, febrifuge, and cure for insanity. The plant was mentioned in Indian manuscripts as long ago as 1000 BC and is also known as *sarpagandha* and *chandrika*. The genus *Rauwolfia* was named in honor of the 16th-century German physician Dr Leonhard Rauwolf, who studied plants while travelling in India.

Serpentina was selected for study due to its long, tapering, snake-like roots. The Indian political leader Mahatma Gandhi was known to employ *Rauwolfia*, reportedly using the root to make a tea that he consumed in the evening to help relax after a busy, overstimulated day.

The Indian physician Rustom Jal Vakil is considered responsible for introducing *Rauwolfia* to Western medicine. He collected data on patients treated with *Rauwolfia* for 10 years, from 1939 to 1949. In 1949, he published a watershed paper on the antihypertensive properties of *Rauwolfia serpentina* in the *British Medical Journal*. He presented his detailed results from treating 50 patients who had high blood pressure with the root of *Rauwolfia*. The results were remarkable and significant. By 1949, more than 90% of Indian physicians were using *Rauwolfia* in the treatment of high blood pressure. After Vakil's original paper, more than 100 scientific articles were published throughout the world.

Chemical Composition

Rauwolfia contains many different phytochemicals, including alcohols, sugars and glycosides, fatty acids, flavonoids, phytosterols, oleoresins, steroids, tannins, and alkaloids. The most important alkaloids found in the plant are indole alkaloids, with more than 50 of those alkaloids having been isolated in the plant Indole alkaloids are a group of nitrogenous compounds that are derived from the amino acid tryptophan. They share a common 5 and 6 carbon heterocyclic ring structure with 1 nitrogen molecule.

All parts of the plant, including the stem and leaves, contain indole alkaloids, but they are found in highest concentration in the bark of the root. The identified indole and 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 exact concentration of alkaloids varies. One study found that the yield of total alkaloids ranged from 0.8% to 1.3% of the dry weight of the plant. Another study put the total yield of alkaloids between 0.7% to 3.0% of the root content. The maximum alkaloid content detected in regenerated roots was 3.3%. Other species in the *Rauwolfia* genus have been used in place of *Rauwolfia serpentina*, including *Rauwolfia vomitoria* and *Rauwolfia caffra* from Africa and *Rauwolfia heterophylla* and *Rauwolfia tetraphylla* from Central and South America.

Woodson et al. found that the species of the same genus contained variable quantities of indole and indole alkaloids and could be used as suitable alternatives to *Rauwolfia serpentina*.

Reserpine

Reserpine is one of the major alkaloids of the plant. The reserpine content has been found to be highest in the root and lower in the stems and leaves. Scientists have believed it to be the most prevalent indole alkaloid in the plant; however, different assays have challenged that assertion. The concentration of reserpine in the plant has been found to vary from 0.03% to 0.14% of the dry weight of the plant. The same study found that the reserpine content of the root varied from 0.038% to 0.14% in different plants. In one study, the reserpine content was 33 mg of 496 mgs of total alkaloids per gram of root. In another study of the *Rauwolfia* root, reserpine content was 0.955 mg/g. Other alkaloids in the plant have also been identified to have biochemical medicinal actions, including canescine, deserpidine, recanescine, and rescinnamine.

Pharmacology

Reserpine is the most widely studied alkaloid found in *Rauwolfia serpentina*. The first modern paper on reserpine was published in 1931 in the *Indian Medical Journal* by Sen and Bose. It was first isolated and used by Robert Wallace Wiggins in 1950.

In 1952, CIBA Labs (now Novartis) in Switzerland published the first complete report on the chemistry and pharmacology of reserpine. Also in 1952, isolated reserpine was introduced as the drug Serpasil for the treatment of hypertension, tachycardia, and thyrotoxicosis.

Reserpine has been classified as an indole alkaloid. It is a white-to-yellow powder that becomes darker when exposed to light. It is odorless, insoluble in water, slightly soluble in alcohol, and freely soluble in acetic acid. It has a chemical formula of C33H40N209, a molecular mass of 609 g, and a bitter taste.

After oral ingestion, the bioavailability of reserpine has been determined to be between 50% and 70%, although most studies have indicated it to be approximately 50%. Absorption is fairly rapid, occurring between 1 and 2 hours after oral ingestion, although slower absorption of between 2 and 4 hours has been reported.

Reserpine is widely distributed throughout the body to the brain liver, spleen, kidney, and adipose tissue. Other studies have shown that reserpine is also widely distributed to red blood cells and peripheral neurons. It has been found to be present in breast milk and to cross the placenta and blood-brain barrier. Its initial half-life in the blood has been observed to be 4 to 5 hours. Its elimination half-life has been determined to be between 45 and 168 hours in plasma. Its relatively long elimination half-life is believed to be due to its binding to proteins and red blood cells. Hepatic metabolism accounts for approximately 62% of the degradation of reserpine, whereas kidney elimination accounts for less than 8%. Most of the elimination of it occurs through fecal excretion. Between 30% and 60% of eliminated metabolites have been found in reserpine itself.

Mechanism of Action

The mechanism of action of reserpine is well researched and well documented. Reserpine binds to protein receptors called *vesicular monamine transporters (*VMATs) in the organelle membranes of specialized secretory vesicles of presynaptic neurons. Reserpine prevents intracellular neurotransmitters from binding to VMAT proteins and stops secretory vesicles from uptaking neurotransmitters.

Ultimately, use of reserpine provides that no or few neurotransmitters are released from the presynaptic neuron. As a result, no or only slight promulgation of the nerve impulse occurs in the postsynaptic neuron.

Two isoforms of vesicular transport proteins are called *VMAT1* and *VMAT2*. VMAT1 is mainly found in the neuroendocrine cells of the peripheral nervous system, particularly in the chromaffin granules in the adrenal medulla, sympathetic neurons, and platelets. VMAT2 is mainly found in the brain, sympathetic nervous system, mast cells, and cells containing histamine in the gut and pancreas. Reserpine has an affinity for VMAT2 that is 3 times greater than its affinity for VMAT1. It has a strong affinity and binds almost irreversibly to specific receptors on VMAT, particularly VMAT2.

***Rauwolfia* and Hypertension**

In 1949, Vakil reported on a study of 50 patients with essential hypertension who were treated with *Rauwolfia*. In that study, 85% of patients experienced a drop in systolic blood pressure, and 81% of patients experienced a drop in diastolic blood pressure.

In 1952, Vida in Germany and Austria reported a blood pressure drop in 25 patients with hypertension. Arnold and Bach showed a good response in 37 of 50 patients in whom systolic pressure dropped an average of 30 mm Hg and diastolic pressure dropped 15 mm Hg. In 1953, Meissner reported *Rauwolfia* to be effective in 90% of a study's participants, with a lowering of systolic blood pressure between 15 and 40 mm Hg. In 1953, Loffler in Switzerland reported a lowering of blood pressure in 51 Swiss workers with hypertension. In 1954, Goto in Japan reported lower blood pressure in 12 of 15 patients with hypertension. In 1954, Doyle and Smirk in Zealand reported that reserpine produced a striking fall in blood pressure within 4 to 6 hours of administration. It has been further reported that *Rauwolfia* was the best hypertensive remedy used in India throughout the 1950s. It was reported to be used by 90% of all physicians or more than 60 000 doctors throughout the country. One manufacturer claimed to have sold 94 million tablets of the dried root in 1954, and it was exported to more than 17 countries throughout the world.

In 1952, a purified, standardized, isolated alkaloid extract called alseroxylon was introduced in the United States. The active ingredients of the purified extract were a mixture of reserpine and rescinnamine. In this study, 346 patients with hypertension were treated on an outpatient basis in public and private hospitals. Participants' original blood pressures were greater than 150/100 mm Hg on admission. During the control period, patients received a placebo. A consistent decrease in blood pressure readings of greater than 20 mm Hg was observed in patients treated with the alseroxylon extract.

A *Rauwolfia* product called Serpina was given to more than 100 patients for periods of 1 month to 1 year. In the study, a daily dose of 1 to 3 Serpina tablets was well tolerated. Its action was slow to appear, ranging from 3 to 6 days, and it disappeared 7 to 21 days after stopping the drug. It did not produce any serious side effects. The product caused sedation and usually improved sleep, although it could occasionally cause nightmares in some people, and it could cause bradycardia and nasal congestion in some patients. It apparently was not habit forming, and its administration could be stopped easily for several days to relieve any uncomplicated side effects. It promoted a moderate hypotension, particularly in labile patients with hypertension and tachycardia, and it appeared to have a sympatholytic effect but did not produce postural hypotension. It appeared to be more effective in young, neurotic hypertensive patients with tachycardia that in those with long-established, fixed hypertension with organic, vascular disease. Thirty-nine patients with an average blood pressure reading of

192/122 mm Hg and a pulse of 82 were treated with Serpina alone. The average blood pressure dropped to 165/95 mm Hg and the average pulse was 70. In 13 of 39 patients, blood pressure was controlled, returning to a normal reading of lower than 150/90 mm Hg.

In a clinical trial of *R serpentina* in essential hypertension, Vakil treated 50 patients with initial blood pressures greater than 160/95 mm Hg. The study included 30 males and 20 females ranging in age from 39 to 76 years. Thirty-nine of 48 patients who completed the study showed a drop of both systolic and diastolic blood pressure at 1 week after starting the medicine. After 4 weeks of taking the medicine, systolic blood pressure dropped between 2 and 54 mm Hg for those patients. 22 of 47 patients (1 dropped out of the study) showed a moderate drop in systolic blood pressure, from 10 to 24 mm Hg. Thirteen of the 47 patients showed a marked drop in systolic blood pressure of greater than 25 mm Hg, and 38 of the 47 patients showed a drop in diastolic blood pressure of between 4 and 34 mm Hg, with an average drop of 11 mm Hg. Twenty-seven patients showed a moderate drop of diastolic blood pressure of between 5 and 14 mm Hg, and 7 patients showed a drop greater than 15 mm Hg. The hypotensive action of the drug was perceptible at 2 weeks after stopping the drug in 91% of patients and at 4 weeks after discontinuing the drug in 75% of patients. No serious adverse side effects were noted.

Another study was designed to evaluate various effects of oral reserpine on a group of hypertensive individuals in an outpatient clinic. Reserpine from CIBA Pharmaceuticals was given in a dosage of 20 mg twice per day to 15 individuals who had initial blood pressures between 160/98 and 240/150 mm Hg. For those patients, systolic blood pressure dropped an average of 30.7 mm Hg and diastolic blood pressure dropped an average of 19 mm Hg. Some patients reported transient nausea, fainting, and dyspnea. The researchers concluded that the drug was a useful and potent agent in some patients with severe as well as mild hypertension.

A Cochrane Database Review was undertaken to investigate the dose-related effects of reserpine on blood pressure, heart rate, and withdrawals due to adverse effects. The review examined medical databases that included Central, EMBASE, and MEDLINE. The study selected only truly randomized, controlled trials (RCTs) for review that compared reserpine monotherapy to placebo or no treatment in patients with primary hypertension. Four RCTs were found to meet inclusion criteria. None of the trials reported any withdrawals due to adverse effects. The authors concluded that reserpine was effective in reducing systolic blood pressure to the same degree as other first-line antihypertensive drugs; however, they could

not make definite conclusions regarding the dose response pattern because of the small number of included trials. They suggested that more RCTs were needed to assess the effects of reserpine on blood pressure and to determine the dose-related safety profile before the drug could be widely recommended as a primary antihypertensive drug. Reserpine is also one of the few antihypertensive drugs that have been shown to produce a reduction in mortality in RCTs.

Other Medical Uses

Rauwolfia has been studied for the treatment of mental diseases, including schizophrenia and bipolar disorder, epilepsy and seizures, and of insomnia and sleep problems.

One study found *Rauwolfia* to be effective in the treatment of anxiety. All forms of *Rauwolfia* were used in that study, including reserpine, alseroxylon, and the whole root, and all gave the same results in the control of overt anxiety in ambulatory patients.

Rauwolfia has been studied as a treatment for autistic children between the ages of 3.5 and 9 years. Another study found it to be effective in treatment of delirium tremens in alcohol and drug addicted patients. The researchers in that study observed a noted decrease in agitation, excitement, and acute hallucinatory episodes.

One study found that *Rauwolfia* treated migraine headaches effectively, with a noted improvement in quality of life and a decrease in pain. Another study used *Rauwolfia* to treat angina pectoris in patients with coronary artery disease, finding a decrease in angina symptoms and a prolonged therapeutic effect. One-half of the patients in that study went on to develop normal electrocardiograms.

In another study, *Rauwolfia* was studied to examine its benefits in improving pruritic and psychogenic dermatosis. It has also been reported to improve psoriatic outbreaks.

Side Effects and Toxicology

Adverse side effects of reserpine include lethargy, sedation, psychiatric depression, hypotension, nausea, vomiting, abdominal cramping, gastric ulceration, nightmares, bradycardia, angina-like symptoms, bronchospasm, skin rash, itching, galactorrhea, breast enlargement, sexual dysfunction, and withdrawal psychosis in 1 case. The most common side effect noted in all patients was nasal congestion, occurring in 5% to 15% of all patients. After several months of use, mental depression can occur and may persist. With extremely large

doses, Parkinson-like symptoms, extrapyramidal reactions, and convulsions can occur. Allergic reactions to *Rauwolfia*, including asthma, are rare.

Adequate doses of reserpine that produce decreased blood pressure will not cause reserpine-induced gastric ulcerations. Reserpine has been observed to cause a slight edema in some patients. Possible interactions with other drugs include cardiac glycosides, ephedra, alcohol, antipsychotic drugs, barbiturates, digoxin, diuretics, ephedrine, levodopa, monamine oxidase inhibitors, propranolol, stimulant drugs, and tricyclic antidepressants. *Rauwolfia* may interact with the following lab tests, including tests for corticosteroids, bilirubin, catecholamines, gastric acidity, norepinephrine, prolactin, thyroxine, and vanillylmandelic acid.

From 1959 to 1960, 151 cases of toxicity were reported in the United States from consuming *Rauwolfia*, and only 4% of these cases were in adults. Nausea, vomiting, hypotension, sedation, and coma have been described by patients. Also symptoms of bradycardia and facial flushing were reported. Psychiatric depression was most common with doses of reserpine of greater than 0.5 mg per day and was significantly decreased in a daily dose of less than 0.25 mg of reserpine. Between 1962 and 1965, 225 reports of accidental ingestion were reported in the United States. Three cases were reported of children between the ages of 30 months and 4 years who ingested reserpine in doses as high as 25 mg. All cases were resolved.

An association does not appear to exist between reserpine and cancer. No increased risk of birth defects has been shown in female humans who consumed reserpine at any time during their pregnancy. No mutagenic, genotoxic, or recombinogenic effects of reserpine have been demonstrated.

CONCLUSIONS

Based on a review of the literature, *Rauwolfia* appears to be a safe and effective treatment for hypertension when used in appropriate low doses. An equivalent dose of pure *Rauwolfia* alkaloids, also known as alseroxylon extract or pure reserpine, can also be used to treat hypertension. The author has found that LDR can be safely recommended to patients who have been screened to be of benefit from the treatment. The total daily dose of *Rauwolfia* should be lower than 500 mg of root and, in most cases, can be less than 250 mg per day. The dosage of purified alkaloid-alseroxylon extract should be lower than 5 mg per day and, in most cases, is less than 2.5 mg per day. The reserpine dose should be lower

than 500 µg per day and, in most cases, lower than 250 µg per day. An equivalent tincture dose should be based on the strength of the tincture. For instance, the dose of a 1:5 tincture would be 0.5 mL, equalling 100 mg of crude root, whereas in a standard dropper, 15 drops would equal 1.0 mL.

REFERENCES

1. Endress ME, Bruyns PV. A revised classification of the Apocynaceae s.l. Bot Rev., 2000; 66(1): 1–56. [Google Scholar]
2. Vakil RJ. Rauwolfia serpentina in the treatment of high blood pressure: a review of the literature. Circulation, 1955; 12(2): 220–229. [PubMed] [Google Scholar]
3. US Dept of Agriculture. Rauvolfia L. Germplasm Resources Information Network Web site. [Accessed August 2014]. http://www.ars-grin.gov/cgi-bin/npgs/html/genus.pl?10272. Published, March 14, 2003.
4. Brijesh KS. Rauwolfia: cultivation and collection. Biotech Articles Web site.[Accessed September 25, 2014]. http://www.biotecharticles.com/Agriculture-Article/Rauwolfia-Cultivationand-Collection-892.html. Published May 23, 2011.
5. Yarnell E, Abascal K. Treating hypertension botanically. Altern Complement Ther., 2001; 7(5): 284–290. [Google Scholar]
6. Tyler VE, Brady LR, Robbers JE. Pharmacognosy. 9th ed. Philadelphia, PA: Lea & Febiger, 1988; 222–225. [Google Scholar]
7. Jerie P. Milestones of cardiovascular therapy, IV: reserpine [in Czech] Cas Lek Cesk, 2007; 146(7): 573–577. [PubMed] [Google Scholar]
8. Isharwal S, Gupta S. Rustom Jal Vakil: his contributions to cardiology. Tex Heart Inst J., 2006; 33(2): 161–170. [PMC free article] [PubMed] [Google Scholar]
9. Verma KC, Verma SK. Alkaloids analysis in root and leaf fractions of sarpaghanda (Rauwolfia serpentina) Agric Sci Dig., 2010; 30(2): 133–135. [Google Scholar]
10. Leete E. The biogenesis of the Rauwolfia alkaloids, I: the incorporation of tryptophan into ajmaline. J Am Chem Soc, 1960; 82(24): 6338–6342. [Google Scholar]
11. Ruyter CM, Akram M, Illahi I, Stöckigt J. Investigation of the alkaloid content of Rauwolfia serpentina roots from regenerated plants. Planta Med., 1991; 57(4): 328–330. [PubMed] [Google Scholar]
12. Woodson RE, Youngken HW, Schlittler E, Schneider JE. Rauwolfia: Botany, Pharmacognosy, Chemistry and Pharmacology. Boston, MA: Little, Brown and Company, 1957; 32–33. [Google Scholar]

13. Panwar GS, Guru SK. Alkaloid profiling and estimation of reserpine in Rauwolfia serpentina plant by TLC, HP-TLC and HPLC. Asian J Plant Sci., 2011; 10(8): 393–400. [Google Scholar]
14. Hareesh Kumar V, Nirmala, Shashidhara S, Rajendra CE. Reserpine content of Rauwolfia serpentina in response to geographical variation. Int J Pharm Biosci, 2010; 1(4): 429–434. [Google Scholar]
15. Deshmukh SR, Ashrit DS, Patil BA. Extraction and evaluation of indole alkaloids from Rauwolfia serpentina for their antimicrobial and antiproliferative activities. Int J Pharm Pharm Sci., 2012; 4(5): 329–334. [Google Scholar]
16. Friedli GL. Indole alkaloids. Friedli Enterprises Web site. [Accessed September 25, 2014]. http://www.friedli.com/herbs/phytochem/alkaloids/alkaloid5.html.
17. Reserpine. International Programme of Chemical Safety Web site. [Accessed September 25, 2014]. www.inchem.org/documents/pims/pharm/reserpn.htm.
18. Armstrong WP. Major types of chemical compounds in plants and animals, II: phenolic compounds, glycosides and alkaloids: indole alkaloids. In: Armstrong WP, editor. Wayne's Word: An On-Line Textbook of Natural History. San Marcos, CA: Palomar College, 2005. [Accessed January 22, 2015]. http://waynesword.palomar.edu/chemid2.htm#alkaloids. [Google Scholar]
19. Schuldiner S, Liu Y, Edwards RH. Reserpine binding to a vesicular amine transporter expressed in Chinese hamster ovary fibroblasts. J Biol Chem., 1993; 268(1): 29–34. [PubMed] [Google Scholar]
20. Qu L, Akbergenova Y, Hu Y, Schikorski T. Synapse-to-synapse variation in mean synaptic vesicle size and its relationship with synaptic morphology and function. J Comp Neurol, 2009; 514(4): 343–352. [PubMed] [Google Scholar]
21. Gopalakrishnan A, Sievert M, Ruoho AE. Identification of the substrate binding region of vesicular monoamine transporter-2 (VMAT-2) using iodoaminoflisopolol as a novel photoprobe. Mol Pharmacol, 2007; 72(6): 1567–1575. [PubMed] [Google Scholar]
22. Wimalasena K. Vesicular monoamine transporters: structure-function, pharmacology, and medicinal chemistry. Med Res Rev., 2011; 31(4): 483–519. [PMC free article][PubMed] [Google Scholar]
23. Eiden LE, Schäfer MK, Weihe E, Schütz B. The vesicular amine transporter family (SLC18): amine/proton antiporters required for vesicular accumulation and regulated exocytotic secretion of monoamines and acetylcholine. Pflugers Arch, 2004; 447(5): 636–640. [PubMed] [Google Scholar]

24. Moyer JH, Dennis E, Ford R. Drug therapy (Rauwolfia) of hypertension, II: a comparative study of different extracts of Rauwolfia when each is used alone (orally) for therapy of ambulatory patients with hypertension. AMA Arch Intern Med., 1955; 96(4): 530–543. [PubMed] [Google Scholar]
25. Wilkins RW, Judson WE. The use of Rauwolfia serpentina in hypertensive patients. New Engl J Med., 1953; 248(2): 48–53. [PubMed] [Google Scholar]
26. Vakil RJ. A clinical trial of Rauwolfia serpentina in essential hypertension. Br Heart J., 1949; 11(4): 350–355. [PMC free article] [PubMed] [Google Scholar]
27. Bello CT, Turner LW. Reserpine as an antihypertensive in the outpatient clinic: a double-blind clinical study. Am J Med Sci., 1956; 232(2): 194–197. [PubMed] [Google Scholar]
28. Shamon SD, Perez MI. Blood pressure lowering efficacy of reserpine for primary hypertension. Cochrane Database Syst Rev., 2009; 4: CD007655. [PubMed] [Google Scholar]
29. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the hypertension detection and follow-up program, I: reduction in mortality of persons with high blood pressure, including mild hypertension. JAMA, 1979; 242(23): 2562–2571. [PubMed] [Google Scholar]
30. Healy D, Savage M. Reserpine exhumed. Br J Psychiatry, May, 1998; 172: 376–378. [PubMed] [Google Scholar]
31. Lowinger P. Rauwolfia serpentina in the control of anxiety. Psychiatr Q., 1957; 31(3): 445–453. [PubMed] [Google Scholar]
32. Lehman E, Haber J, Lesser SR. The use of reserpine in autistic children. J Nerv Ment Dis., 1957; 125(3): 351–356. [PubMed] [Google Scholar]
33. Avol M, Vogel PJ. Treatment of delirium tremens with reserpine (serpasil): a preliminary report. JAMA, 1955; 159(16): 1516–1520. [PubMed] [Google Scholar]
34. Friedman AP. The treatment of headache with reserpine. Ann N Y Acad Sci., 1955; 61(1): 276–280. [PubMed] [Google Scholar]
35. Lewis BI, Lubin RI, January LE, Wild JB. Rauwolfia serpentina in the treatment of angina pectoris. Circulation, 1956; 14(2): 227–232. [PubMed] [Google Scholar]
36. Ferrara RJ, Pinkus H. Alseroxylon in the treatment of pruritic and psychogenic dermatoses. AMA Arch Derm, 1955; 72(1): 23–28. [PubMed] [Google Scholar]
37. Therapeutic Research Facility. Natural Medicines Comprehensive Database Web site. [Accessed September 25, 2014]. www.naturaldatabase.com. Updated September 25, 2014.

38. Krogsgaard AR. The effect of reserpine on the electrolyte and fluid balance in man. Acta Med Scand, 1957; 159(2): 127–132. [PubMed] [Google Scholar]
39. Baumeister AA, Hawkins MF, Uzelac SM. The myth of reserpine-induced depression: role in the historical development of the monoamine hypothesis. J Hist Neurosci, 2003; 12(2): 207–220. [PubMed] [Google Scholar]
40. Weiss RF. Weiss's Herbal Medicine. New York, NY: Theime, 2001; 153–158. [Google Scholar]
41. Horwitz RI, Feinstein AR. Exclusion bias and false relationship and breast cancer. Arch Intern Med., 1985; 145(10): 1873–1875. [PubMed] [Google Scholar]
42. Aromaa A, Hakama M, Hakulinen T, Saxén E, Teppo L, Idä-Heikkilä J. Breast cancer and use of Rauwolfia and other antihypertensive agents in hypertensive patients: a nationwide case-control study in Finland. Int J Cancer., 1976; 18(6): 727–738. [PubMed] [Google Scholar]
43. D Lobay use of Rauwolfia in hypertension. https;//www.ncbi.nlm.nih.gov./pmc/articles/PMC4566472/
44. Ross RK, Paganini-Hill A, Krailo MD, Gerkins VR, Henderson BE, Pike MC. Effects of reserpine on prolactin levels and incidence of breast cancer in postmenopausal women. Cancer Res., 1984; 44(7): 3106–3108. [PubMed] [Google Scholar]
45. Lemieux G, Davignon A, Genest J. Depressive states during Rauwolfia therapy for arterial hypertension: a report of 30 cases. Can Med Assoc J., 1956; 74(7): 522–526. [PMC free article] [PubMed] [Google Scholar]