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A Review: Use of Rauwolfia Serpentina for Antihypertensive Activity

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Abstract: ***The root of sarpgandha is a species of flowering plant in the family Apocynaceae has been traditionally used in Ayurveda for many years to treat the variety of diseases of that at been traditionally apper to bear little similar to one another. Rauwolfia Serpentina is a safe and effective treatment of hypertension. This author reviews the scientific literature with regard to the use of Rauwolfia and the treatment of hypertension. Much smaller dose of reserpine is required to obtain the antihypertensive activity. The present review focuses mainly on chemical composition, pharmacology, mechanism of action, side effect and toxicity and antihypertensive effect of Rauwolfia alkaloids. The plant provide clinician with a safe and effective adjunct to high blood pressure.***

Keywords: *reserpine, hypertension, serpgandha, rauwolfia serpentina*

1. Introduction

Rauwolfia serpentine is the dried root of rauwolfia serpentine (linne) bentham ex kurz.(family: *Apocynaceae*). It is an erect shrub that grows 1 meter in the height and has cylendric stems. These stem have pale bark and consist of light colored viscous latex. [1,2]

Rauwolfia Serpentine L. Benth. Ex Kurz. Is an evergreen, woody, glabrous and perennial shrub with maximum height upto 60 cm. The plant posses tuberous root with pale brown cork and elliptic to lanceolate. [3] The plant belongs to the family *Apocynaceae* and occurs in habitats of tropical and subtropical regions. The family includes 50 species, distributed worldwide in the region of the Himalayas, Indian peninsula, Burma, Indonesia and Shri Lanka and is indigenous to India, Bangladesh and other regions of Asia.[4] The plant is commonly known as *Sarpgandha, Chandrabagha, Snake root plant, ChotaChand, Chandrika and harkaya* etc. [5] The roots, leaves, and juice are of medicinal importance and have attracted the attention of practitioners of indigenous system of medicine, as it contain a large number of secondary metabolites (N containing indole alkaloids) localized mainly in the roots and rhizomes. It has been used in India as a part of the ayurvedic medical system for the treatment of various aligments.

Scientist have been working on the phytochemical analysis of the plant due to its medicinal importance. It has been used as anthelmentic and antihypertensive drugs. It is used as an antidote against snake bite and bite of other poisonous insects. In diarrhea, dysentery, cholera, fever, opacity of cornea and central epilepsy and ebolic *R. serpentine* is known to cure various circulatory disorders deu to the presence of alkaloids. [6] the room juices or extract is used to treat liver and abdominal pain, various gastrointestinal disorders and to expel intestinal worms from the childrens. [7] Mao et al. (2009) have reported the palnt as a function of the ethnobotanical wealth of north east India. The plant also shows the use by local people of Eastern Ghats, Utter Pradesh, Karnataka and Bangladesh against snake bite. The roots and leaf buds are crushed with milk, made into a paste and used externally on the affected areas. The other diseases such as pneumonia, malaria, body aches, eczema, burns, menstrual disorders, scabies, skin cancer, asthma, respiratory problems, eye inflammation, spleen diseases and fever can also be cured using *R. Serpntina*.

2. Chemical Composition

Rauwolfia contains many different phytochemicals, including alcohols, suger and glycosides, fatty acids, flavonoids, phytosterols, oleoresins, steroids, tannins and alkaloids. The most important alkaloid found in the plant are indole alkaloids, with more than 50 of those alkaloids having been is lated in the plant.[8]

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.[9]

All part of the plant, including the stem and leaves, contain indole alkaloids, but they are found in highest concentration in the bark of the root. [11] The the identified indole alkaloid include ajmalidine, ajmaline, ajmalinine, ajmalicine, aricine, canescine, coryanthine, deserpidine, isoajmaline, isoserine, isoserpiline, lankanescine, raucaffricine, rauhimbine, rauwolfinine, recanscine, rescinamine, reserpiline, reserpine, reserpinine, thebaine, yohimbine, and yohimbinine. [11, 12]

The exact concentration of alkaloids varies. One study concentration of alkaloids varies. One study found that the yield of total alkaloid ranged from 0.8% to 1.3% of the dry weight of the plant. [10] Anather study put the total yield of alkaloids between 0.7% to 0.3% of the root content. [4] The maximum alkaloid content detected in regenerated root was

3.3%. [12] Other species in the Rauwolfia genus have been used in place of *R. Serpentina*, including Rauwolfia vomitoria and rauwolfia caffra from Africa and Rauwolfia heterophylla and Rauwolfia tetraphylla from central and south America. Woodson et al [11] found that the species of the same genous contained variable quantities indole and indole alkaloids and could be used as sutaible alternatives to *R. Serpentina*.

Pharmacology

Reserpine is the most widely studied alkaloid found in *R. Serpentina*. The first modern paper on reserpine was published in 1931 in the Indian medical Journal by sen and bose.[14] It was first isolated and used by Robert Wallace wigging in 1950.

Reserpine has been classified as an indole alkaloid. It is 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 acitic acid. It has chemical formula$C^{33}H^{40}N^{209}$, a molecular mass of 609 g, and bitter taste.

In 1952, CIBA Labs (now Novartis) in Switzerland published the first complete report on the chemistry and pharmacology of reserpine. [14] Also in 1952, isolated reserpine was introduced as the drug serpasil for the treatment of hypertension, tachycardia, and thyrotoxicosis.

Reserpine is widely distributed throughout the body to the brain, liver, sleen, kidney and adipose tissue. [15] Other studies have shown that reserpine is also widely distributed red bood cell and peripheral neurons. It has been found to be present breast milk and 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 protein and blood cells. Hepatic metabolism account for approximately 62% of the degradation of reserpine, where as kidney elimination accounts for less that 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 bind to protein receptors called *vesicular monamine transporters* (VMATs) in the organelle membranes of specialized secretory vesicles of presynaptic neurons. [19,20] Reserpine prevents intracellular neurotransmitters from binding to VMAT proteins and stops secretory vesicles from uptaking neurotransmitters. [21]

Ultimately, use of reserpine provide that no or few neurotransmitter 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 protein 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 platlets. 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 VMAT1.[22,23] It has strong affinity and bind almost irreversibly to specific receptors on VMAT, particularly VMAT2.[21]

Rauwolfia and Hypertension

In 1949, Vakil reported on a study of 50 patients with essential hypertension who were treat with *Rauwolfia*.[26] In that study, 85% of patients experienced a drop in systolic blood pressure, and 81% patient experienced a drop in diastolic blood pressure.

In 1952, Vida in Germany and Australia reported a blood pressure drop in 25 patient with hypertension .[26] Arnold and Bach showed a good response in 37 and 50 patientsin whom systolic pressure droped an average of 30mm Hg and diastolic pressure droped 15mm Hg.[26] In 1953, Meissner reported Rauwolfia to be effective in 90% of a study participant, with a lowering of systolic blood pressure between 15 and 40 mm Hg.[26] 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 patient with hypertension. In 1954, Doyle and smirk in Zealand reported that reserpine produced a striking fall in blood pressure within 4 to 8 hours of administration. It has been further reported that Rauwolfia was the best hypertensive remedy used in India throughout the 1950s.[26] it was reported to be used by 90% of all physicians or more than 60,000 doctors throughout the country.[26] one manufacturer claimed to have sold 94 million tablets of dryed root in 1954, and it was exported to more than 17 countries throughout the world.

In a clinical trial of *R. serpentina* in essential hypertension, Vakil treated 50 patients with initial blood pressure greater than 160/95 mm Hg.[26] The study included 30 male and 20 females ranging in age from 39 to 76 years. Thirty-nine of 48 patients whocomplited the study showed a drop of both systolic and diastolic blood pressure at 1 weak after starting the medicine. After 4 weak taking medicine, systolic blood pressure droped between 2 to 54 mm Hg for those patients.22 to 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 patient showed a drop in diastolic blood pressure of between 4 to 34 mm Hg. With an average drop of 11 mm Hg. Twenty-seven patient showed a moderate drop of diastolic blood pressure of between 5 and 14 mm Hg, and 7 patient showed a drop greater than 15 mm Hg. The hypertensive action of drug was perceptible at 2 weeks after stopping the drug in 91% of patients and at 4 weeks after discounting the drug in 75% of patients. No serious adverse side effects were noted.

Side effect and Toxicology

Adverse side effect 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.[17] after

several month of use, mental dipression can occure and may persist. With extreamly large doses, Parkinson-like symptoms, extrapyramidal reactions, and convulsion can occure. Allergic reactions to Rauwolfia, including asthma, are rare.

Adequate doses of reserpine that produce decreased blood pressure will not cause resepine include gastric ulcerations. [37]nReserpin has been observed to cause a slight edema in some patients. [38] possible interaction with other drug include cardiac glycosides, ephedra, alcohol, antipsychotic drug, barbiturates, diauretics, ephedrine, levodopa, monamine oxidase inhibitors, propranolol, stimulant drug, and tricyclic antidepressants. Rauwolfia may interact with the following lab tests, including tests for corticosteroids, bilirubin, catecholamines, gastric acidity, norepinephrine, prolactine, thyroxine, and vanillymandelic acid.[37]

3. Conclusion

Based on the review of the literature, rauwolfia appears to be the safe and effective treatment of hypertension used in appropriate low doses. These review is prove to be true in case of sarpgandha as reserpine has reprted also human population have developed a drug resistance resulting in discontinuation of reserpine in hypertension management whereas sarpgandha root is still in wide use. 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 the LDR can be safly recomonded to patient who have been screened to be of benefit from the treatment.

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