

The Use of *Rauwolfia serpentina* in Hypertensive Patients

Ritu Soni¹, Sakshi Jaiswal², Jyoti Kiran Bara³, Dr. Parul Saksena⁴
Department of Biotechnology, Sri Sathya Sai College Bhopal, Madhya Pradesh, India

Abstract: The root of *Sarpagandha* is a species of flowering plant in the family Apocynaceae has been traditionally used in Ayurveda for many years to treat a variety of diseases that at first thought appear to bear little similarity to one another. These include insanity, epilepsy, insomnia, hysteria, eclampsia and hypertension. On reflection, however, these various diseases could have a common denominator if they were all relieved symptomatically by a sedative or a 'relaxing' drug such as *Rauwolfia*. In the fifty decade, its root gained popularity for its effect on hypertension. The alkaloid found in its root is attributed to anti hypertensive pharmacological action. Thus, initially serpentine was isolated with an objective of predictable and better efficacy in the management of hypertension. Ayurveda believes in use of whole herb because of apparent benefits over the extract. The whole herb has many components which can: (1) Help in biotransformation into pharmacologically active forms (2) Enhance bioavailability (3) Reduce the possible side effects (4) Help in smooth excretion and (5) Prevent development of possible drug resistance. This hypothesis is proved to be true in case of *Sarpagandha* as Reserpine has reported many ADRs and also human population have developed drug resistance resulting in discontinuation of Reserpine in hypertension management whereas *Sarpagandha* root is still in wide use. The article will review the concepts of whole herb and its extracts, published information in this regard in order to draw a possible suggestive conclusion for safe and effective use of *sarpagandha*.

Keywords: hypertension, *sarpagandha*, reserpine, *Rauwolfia serpentina*.

I. Introduction

Sophisticated advancements in chemistry combined with changing pattern of consumer preference have revolutionized the chemical maneuvering of medicinal herbs. Semi purified / purified chemical derivatives of herbs like extracts, fractions, isolates are being preferred over the whole herb for therapeutic uses. As a logical spin off, this also has thrown up a debate, if these chemical derivatives are medicinally better than the herb. In addition to the classical support for the use of whole herb, many recent research findings also indicate that extracts are always not necessarily better medicinal substance than the whole herb as in case of root of *sarpagandha* (*Rauwolfia serpentina*) whole herb and its alkaloid reserpine in the management of hypertension and other CNS diseases. [1]

About Drug *Sarpagandha*

Sarpagandha (*Rauwolfia serpentina*) is a species of flowering plant in the family Apocynaceae. About 80 alkaloids are isolated from *Rauwolfia* species among them reserpine is most important principal active constituent. Reserpine is most important principal active constituent. [1]

Ayurvedic pharmacodynamics – Rasa- Tikta, Guna – Ruksha, Virya- Ushna, Vipak – Katu, Doshkarma- Kaphavatsamak. [1]

Therapeutic uses - The drug *Sarpagandha* is cardiodepressant, hypnotic and sedative. It is used in hypertension, insomnia, sexual aggression and vertigo. The drug is much used in schizophrenia and conditions involving influence of evil spirits (*bhutawadha*). The classical text of Indian medicine mention about drug, *Sarpagandha* is included in *Aparajit Gana* which is indicated in mental disorder (*susruta uttarantra* 60/47). *Sarpagandha* is also included in *Ekasar Gana* (*susruta kalpa* 5/84) useful against *visha* and for treatment of *musaka visha* (*susruta kalpa* 7/29). Also use in treatment of *Visuchika* (*vrindamadhava* 6/26). In modern era *Sarpagandha* is used as an effective Antihypertensive and it is WORLD'S FIRST ANTIHYPERTENSIVE DRUG. [1]

Chemist & Ayurvedist Perspective

When a chemist picks up an herb, his default reductionist approach makes him to assume that the active ingredient(s) is/are responsible for the pharmacological effects of the herb. Therefore, a chemist tries to identify the active ingredient(s) and endeavours to bring the identified ingredient to an optimum concentration with a tenet to pronounce the effects in a consistent manner. But, an Ayurvedic expert sees both the herb and the individual as whole systems comprising up of many components, which produce the ultimate effects in an interactive mode rather than summation mode. The fundamental assumption is that "whole is not equal to the sum of the component". [1],[2]

II. Phytochemical Constituents

Rauwolfia serpentina has been a prevailing field of research for decades and several workers have explored this area due to its phytochemical properties. The various phytochemical compounds or secondary metabolites present in *R. serpentina* include alkaloids, phenols, tannins and flavonoids[2].

Alkaloids

Alkaloids are a large group of organic molecules which contain a heterocyclic nitrogen ring. These are brought about by different organisms such as animals and microbes, but a particularly diverse array of alkaloids is produced by plants. Approximately 10 % of plant species are believed to produce alkaloids as secondary metabolites, where they work predominantly in providing defence against herbivores and pathogens. Pure isolate alkaloids and their synthetic derivatives are used as medicinal agents for their analgesic, antispasmodic and bactericidal effects. The alkaloids obtained from the root extract act directly on the central nervous system and thereby reduce blood pressure as compared to other blood-pressure lowering agents. *R. serpentina* root is reported to contain 0.7 – 3.0 % of total alkaloids and about 0.1% of the active principle reserpine which is an indole alkaloid, present in the root. Hence, root biomass production of this plant could be of economic importance. On the basis of the structure there are three types of alkaloids namely, weak basic indole alkaloids, alkaloids of intermediate basicity and strong anhydronium bases. The various alkaloids identified in *Rauwolfia* include ajmaline, ajmalimine, ajmalicine, deserpidine, indobine, indobinine, reserpine, reserpiline, rescinnamine, rescinnamidine, serpentine, serpentinine and yohimbine etc.[2]

Reserpine

It is a pure crystalline single alkaloid, derived from the roots of *Rauwolfia* and was first isolated in 1952. It is a relatively weak tertiary base occurring in the oleoresin fraction of the roots and is useful in the treatment of hypertension, cardiovascular diseases and neurological diseases. The antihypertensive properties of *Rauwolfia* roots are attributed to reserpine (3,4,5-trimethyl benzoic acid ester of reserpic acid, an indole derivative of 18-hydroxy yohimbine type). It is the most prominent of all alkaloids and used mainly as a natural tranquillizer. Reserpine is now being utilized as a tool in physiologic studies of body functions and in pharmacological studies. The antihypertensive actions of reserpine are due to its depressant action on the central nervous system (CNS) and peripheral nervous system by binding to catecholamine storage vesicles present in the nerve cell. This prevents the normal storage of catecholamines and serotonin in the decline of catecholamine. It interferes with the function of the autonomic nervous system by depleting the transmitter substance from the adrenergic neurons and possibly by activating the central parasympathetic system. These substances are mostly involved in controlling heart rate, cardiac contraction and peripheral resistance. It also helps in sedation and lowering of blood pressure, especially in cases of hypertension exacerbated by stress and sympathetic nervous system activity. Reserpine causes the release of 5-hydroxytryptamine (5-HT) from all tissues in which it is normally stored and results in an increase of urinary metabolites.[3],[4]

Ajmaline

The compound was first isolated by Salimuzzaman Siddiqui in 1931 from the roots of *R. serpentina*. He named it ajmaline, after Hakim Ajmal Khan, one of the most illustrious practitioners of Unani medicine in South Asia. Derived from roots of *R. serpentina* as a class I antiarrhythmic agent, it is highly useful in diagnosing Brugada Syndrome (hereditary cardiac disorder), and differentiating between subtypes of patients with this disease. These agents are primarily classified into four major groups on the basis of their mechanism of action i.e. sodium channel blockade, beta-adrenergic blockade, repolarization prolongation and calcium channel blockade. Ajmaline is a sodium channel blocker that shows instant action when given intravenously, which makes it ideal for diagnostic purposes. The administration of *Rauwolfia* alkaloid to patients with this type of arrhythmia is known as the "Ajmaline Test". It has been reported to stimulate respiration and intestinal movements. The action of ajmaline on systemic and pulmonary blood pressure is similar to that of serpentine.[4]

Serpentine

Serpentine, a type II topoisomerase inhibitor, exhibits antipsychotic properties. The enzyme peroxidase (PER) is responsible for the oxidation of ajmalicine to serpentine by catalyzing bisindole alkaloid localized in the vacuole.[4]

Phenols

Phenols are the secondary plant metabolites widely distributed in the plant kingdom, mainly in herbs, shrubs, vegetables and trees. The presence of phenols is considered toxic for the growth and development of various pests and pathogens. Presence of a high quantity of total polyphenolic compounds in *R. serpentina* shows significant antidiabetic and hypolipidemic properties. In medicine, it is used as an expectorant and emulsifying agent. The presence of phenolic compounds indicates this can be used as an anti-microbial agent.[5],[6]

Tannins

The oxidation inhibiting activity of tannin is due to the presence of gallic acid and diagallic acid. Tannins have astringent properties, they hasten the healing of wounds and inflamed mucous membranes. Thus, explain the use of *R. serpentina* in treating many disorders by traditional medicine healers in South eastern India [4],[6].

Flavonoids

These are potent water-soluble antioxidants and free radical scavengers, which prevent oxidative cell damage and have strong anticancerous activity. Flavonoids in intestinal tract also lower the risk of heart disease. As antioxidants, flavonoids provide anti-inflammatory activity used for the treatment of diseases in herbal medicine. [7]

Saponins

Saponins are glycoside of both triterpenes and sterols and have been detected in over 70 families of plants. Some of the characteristics of saponins include formation of foams in aqueous solutions, hemolytic activity, cholesterol binding properties and bitterness. Saponin has the property of coagulating red blood cells. The high saponin content of *Rauwolfia serpentina* substantiates the use of this extracts to stop bleeding and in treating wounds. [7],[8],[27]

***R. serpentina* in Pharmacology**

R. serpentina holds an important position in the pharmaceutical world due to the presence of various alkaloids in the oleoresin fraction of the roots. Alkaloids of this plant have a great medicinal importance to treat cardiovascular diseases, high blood pressure, hypertension, arrhythmia, various psychiatric diseases, mental disorders, breast cancer, human promyelocytic leukemia like diseases. Reserpine is the main alkaloid that shows highly complex pattern of activity mainly variation of amine concentration in brain. It is responsible for influencing the concentration of glycogen, acetyl choline, γ -amino butyric acid, nucleic acids and anti-diuretic hormone. The effects of reserpine include respiratory inhibition, stimulation of peristalsis, myosis, relaxation of nictating membranes and also influences temperature regulating centre. It increases the volume and free acidity of gastric secretion. The Pitkriya capsule (Unani formulation) contains arsol (*R. serpentina*) which acts as Musakkin-wo-Munawwim (sedative and hypnotic), Mudir (Diuretic), Musakkin-e- Asab (nervine sedative) and Mukhaddir (anesthetic). Its various pharmacological activities include anticholinergic, hypotensive, anticontractile, sedative, relaxant, hyperthermic, antidiuretic, sympathomimetic, hypnotic, vasodilator, antiemetic, anti-fibrillar activity tranquilizing agent, anti-arrhythmic, antifungal and nematocidal. *R. serpentina* is believed to have following pharmacological attributes: (1) By the action on vasomotor centre, as it leads to generalized vasodilatation by lowering blood pressure. (2) By depressant action on the cerebral centres as it soothes the general nervous system. (3) It exerts a sedative action on the gastric mucosa and shows stimulating action on the plain musculature of the intestinal tract. (4) It also stimulates the bronchial musculature. [9],[10]

***R. Serpentina* as a Therapeutic Herb and Medicinal Agent**

R. serpentina has an extensive spectrum of valuable therapeutic actions, mainly effective in the treatment of hypertension and psychotic disorders like schizophrenia, anxiety, epilepsy, insomnia, insanity, and also used as a sedative, a hypnotic drug. The plant is reported to contain a large number of therapeutically useful indole alkaloids and these alkaloids are largely located in the roots. Fabricant and Fransworth (2001) has emphasized the various ethnobotanical uses to cure various circulatory disorders. Extracts of the roots are valued for the treatment of intestinal disorders, particularly diarrhoea and dysentery and also as an anesthetic. Mixed with other plant extracts, they have been used in the treatment of cholera, colic and fever. The root was believed to stimulate uterine contraction and recommended for the use in childbirth. A study by Azmi and Qureshi (2012) showed therapeutic effects of *Rauwolfia* with incomplete hypoglycemic action in diabetic hypertensive patients. The juice of the leaves has been used as a remedy for the opacity of the cornea. *Rauwolfia*'s juice and extract obtained from the root can be used for treating gastrointestinal and circulatory diseases. The juice of tender leaves and root extract is used to treat liver pain, stomach pain, dysentery and to expel intestinal worms. [11],[12]

Prostate Cancer

Prostate cancer is considered to be major causes of cancer-related deaths among men. Modern techniques such as chemotherapy and radiotherapy have not provided significant survival benefits to patients with prostate cancer. 94 Natural products have proven to be a major resource for identification of bioactive compounds used in the treatment of a variety of ailments and diseases, including cancer as compared to chemotherapy and radiotherapy. Various parts of this plant have been used as a traditional medicine for centuries to treat a variety of ailments including fever, general weakness, intestinal diseases, liver problems and

mental disorders.⁹⁵ Extracts from the root bark of this plant are enriched with compounds of β -carboline alkaloid family of which the main constituent is alstonine. This compound has been previously reported to reduce tumour cell growth in mice inoculated with YC8 lymphoma cells or Ehrlich ascetic cells. The plant extract has anti-prostate cancer activity in both *in vitro* and *in vivo* model systems which, based upon analyses of gene expression patterns of treated prostate cancer cells, may be modulated by its effects on DNA damage and cell cycle control signalling pathways.[13],[14],[25]

Mental Illness, Schizophrenia, High Blood Pressure

The root of the plant is used in high blood pressure, mental agitation, insomnia and sedative. The root extract obtained is considered to be the best medicine for high blood pressure and has been adapted by the medical fraternity in most countries. The derived alkaloids have a direct effect on hypertension and are widely used in preparation of medicine. Extracts of *R. serpentina* is also helpful in curing other diseases such as fever, malaria, eye diseases, pneumonia, asthma, AIDS ,headache skin disease and spleen disorder.[15],[8]

III. Summary And Conclusion

Ayurveda believes in use of whole herb because of apparent benefits over the extract. The whole herb has many components which can(1) Help in biotransformation into pharmacoactive forms(2) Enhance bioavailability (3) Reduce the possible side effects(4) Help in smooth excretion and(5) Prevent development of possible drug resistance. These hypothesis is proved to be true in case of Sarpagandha as Reserpine has reported also human population have developed drug resistance resulting in discontinuation of Reserpine in hypertension management whereas Sarpagandha root is still in wide use. The authors suggest, it is prudent to use the whole herb for therapeutic applications, until and unless any chemical derivative is proved to be better than the whole herb. The authors do recognize the importance of chemical standardization of the herbs for quality assurance and strongly advocates for it. Finally, the objective of this article is not to show the extracts in a poorer light, but to critically evaluate the trend of chemically purifying herbs. Unfortunately, owing to lack of such assessments, extraction has become a fashion in herbal industry rather than a justified requirement.

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