Review Article

Rauvolfia serpentina L. Benth. ex Kurz.: Phytochemical, Pharmacological and Therapeutic Aspects

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ABSTRACT

Rauvolfia serpentina is an important medicinal plant in the pharmaceutical world due to the presence of its immense therapeutic properties. The plant is known for curing various disorders because of the presence of alkaloids, carbohydrates, flavonoids, glycosides, phlobatannins, phenols, resins, saponins sterols, tannins and terpenes. The plant parts, root and rhizome have been used since centuries in Ayurvedic medicines for curing a large number of diseases such as high blood pressure, mental agitation, epilepsy, traumas, anxiety, excitement, schizophrenia, sedative insomnia and insanity. The plant contains more than 50 different alkaloids which belong to the monoterpenoid indole alkaloid family. The major alkaloids are ajmaline, ajmalicine, ajmalimine, deserpidine, indobine, indobinine, reserpine, reserpiline, rescinnamine, rescinnamidine, serpentine, serpentinine and yohimbine. *R. serpentina* is also known for its antimicrobial, antifungal, anti-inflammatory, antiproliferative, antidiuretic and anticholinergic activities. The herbal medicine is still the basis of primary health care for 75–80% of the world population because of its cultural acceptability, better compatibility with the human body and lesser side effects. Therefore, there is a need for us to search alternative, naturally available remedies for curing million's of people worldwide. Due to all these properties, the present review aims to evaluate the various pharmacological, phytochemical and therapeutic properties of *R. serpentina*.

Keywords: Antihypertensive, Herbal remedy, Indole Alkaloids, Medicinal plant, Reserpine.

INTRODUCTION

Increase in world population poses huge challenges to satisfy the need for food, shelter and cloth. There is a rise in demand for medicine, as millions of people are suffering from various types of diseases worldwide. There are several pharmaceutical formulations available commercially for the treatments of disorders but they are costly, not effective and show numerous toxic effects. Therefore, there is an urgent need for us to use an alternate, naturally available medications or herbal remedies which do not show any side effects. Over 80 % of world population are dependent on herbal medicine for its therapeutic effects and more than 800 plant species shows hypoglycaemic activity.[1] In India, various indigenous plants are used to cure disease, as nature has provided a perfect storehouse of remedies to cure all elements of humanity.[2] The medicinal plants show the presence of various chemical substances such as alkaloids, hydrogen, carbon, nitrogen, glycosides, volatile oils, fatty acids, resins, gums and tannins that are responsible for treating various diseases.[3-5]. According to WHO (World Health Organization), any plant or its parts containing substance that can be used therapeutically or can be used as raw material for chemical or pharmaceutical synthesis is classified as a drug.[6] Today about 300 species of medicinal and aromatic plants are used worldwide in the pharmaceutical, food, cosmetics and fragrance industries.[4,7,8] One of the medicinally important plant used for the purposes of obtaining drugs is *Rauvolfia serpentina.*

Rauvolfia serpentina L. Benth. Ex Kurz. is an evergreen, woody, glabrous and perennial shrub with maximum height upto 60 cm. The plant possess tuberous root with pale brown cork and elliptic to lanceolate or obovate leaves in whorls of three.[8] 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 Sri Lanka and is indigenous to India, Bangladesh and other regions of Asia.[9,10] The plant is commonly known as Sarpagandha, Chandrabagha, Snake root plant, Chotachand, Chandrika and Harkaya etc.[11] 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.[5,12] It has been used in India as a part of the Ayurvedic medical system for the treatment of various ailments.[13] In Ayurvedic medicines, the roots of *R. serpentina* is used as a remedy for curing hypertension, insomnia, mental agitation, gastrointestinal disorders, excitement, epilepsy, traumas, anxiety, excitement, schizophrenia, sedative insomnia and insanity.[12,14] In Siddha medicine, *R.* serpentina roots are used for curing hypertension-associated headache, dizziness, amenorrhea, oligomenorrhea and dysmenorrhea like

abnormalities. According to Rajendran and Agarwal (2007)[15], fruits and seeds have also been used for its medicinal or ethno botanical purposes by the ethnic tribes of Virudhungar district Tamil Nadu, India.

Scientists have been working on the phytochemical analysis of the plant due to its medicinal importance. It has been used as anthelmintic and anti-hypertensive drugs. It is used as an antidote against snake bite and bites of other poisonous insects. In diarrhoea, dysentery, cholera, fever, opacity of the cornea and central epilepsy and ecbolic *R. serpentina* also played an important role.[10,16] The plant is known to cure various circulatory disorders due to the presence of alkaloids.[17] The root juices or extract is used to treat liver and abdomen pain, various gastrointestinal disorders and to expel intestinal worms from the childrens.[18-20] Mao et al. (2009) [21] have reported the plant as a function of the ethnobotanical wealth of north east India. The plant also shows the use by local people of Eastern Ghats, Uttar Pradesh, Karnataka and Bangladesh against snake bite.[22] The roots and leaf buds are crushed with milk, made into a paste and used externally on the affected areas.[23,24] The other diseases such as pneumonia, malaria, body aches, eczema, burns, menstrual disorders, scabies, skin cancers, asthma, respiratory problems, eye inflammation, spleen diseases and fever can also be cured using *R. serpentina*.[19,20,25-30] The present review work emphasizes on the potential of *R. serpentina* as antifungal, anti-inflammatory, antioxidant, antiproliferative, anticancerous, antidiuretic, antifibrillar, antiarrhythmic, anticholinergic, antidysentry, antidiarrhoeal antihypotensive, anticontractile, antidiuretic, sympathomimetic, and tranquillizing agent.[31-36]

PHYTOCHEMICAL CONSTITUENTS

Rauvolfia serpentina has been a prevailing field of research for decades and several workers have explored this area due to its phytochemical properties.[5,10-12,29] The various phytochemical compounds or secondary metabolites present in *R. serpentina* include alkaloids, phenols, tannins and flavonoids.

Alkaloids

Alkaloids are 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 isolated alkaloids and their synthetic derivatives are used as medicinal agents for their analgesic, antispasmodic and bactericidal effects.[37] The alkaloids obtained from the root extract acts directly on central nervous system and thereby reduces 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.[38] The various alkaloids identified in *Rauvolfia* (Figure 1) include ajmaline, ajmalimine, ajmalicine, deserpidine, indobine, indobinine, reserpine, reserpiline, rescinnamine, rescinnamidine, serpentine, serpentinine and yohimbine etc.[39,40]

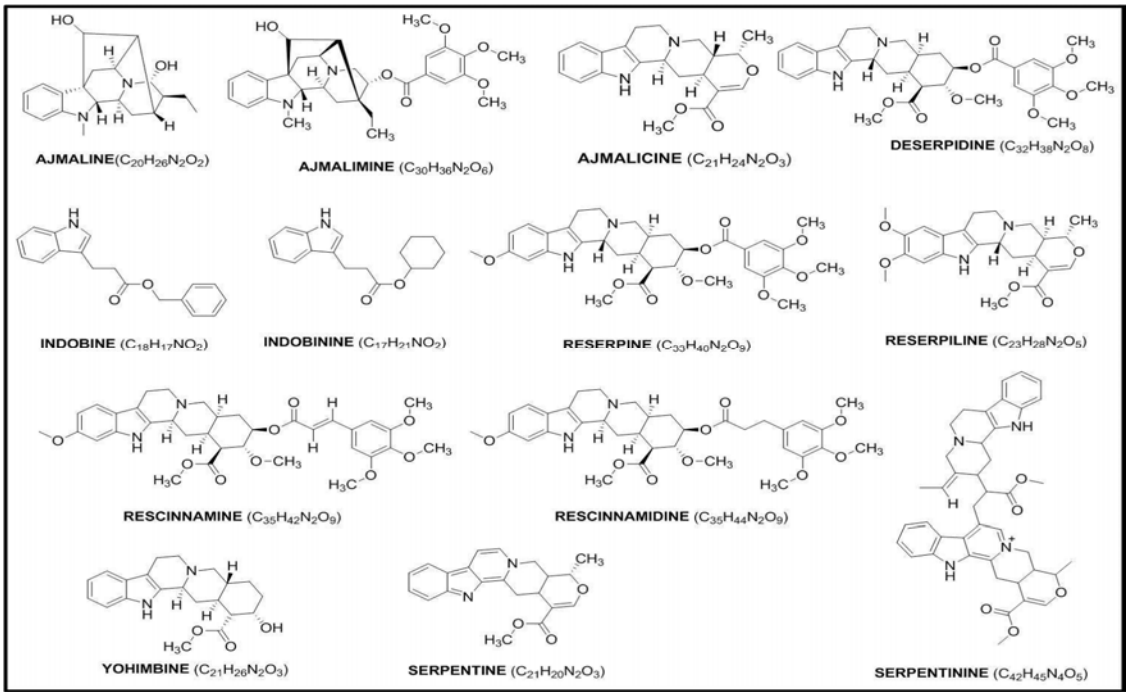

Figure 1: Chemical structures of some alkaloids present in *Rauvolfia serpentina*.

Amongst all, resperine is the principle alkaloid which shows large number of clinical applications.[41,42] Along with resperine, yohimbine, serpentine, deserpidine, ajmalicine and ajmaline are used to treat hypertension and breast cancer.[43,44]

Reserpine

It is a pure crystalline single alkaloid, derived from the roots of *Rauvolfia* and was first isolated in 1952.[45] 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.[46,47] The antihypertensive properties of *Rauvolfia* 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.[48,49] 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 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 decline of catecholamine. It interferes with the function of autonomic nervous system by depleting the transmitter substance from the adrenergic neurons and possibly by activating the central parasympathetic system.[50-52] 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 increase of urinary metabolites.[53]

Ajmaline

The compound was first isolated by Salimuzzaman Siddiqui in 1931 from the roots of *R. serpentine.* He named it ajmaline, after Hakim Ajmal Khan, one of the most illustrious practitioners of Unani medicine in South Asia.[54,55] 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.[56] 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 *Rauvolfia* alkaloid to patients with this type of arrhythmia is known as the "Ajmaline Test".[57,58] It has been reported to stimulate respiration and intestinal movements. The action of ajmaline on systemic and pulmonary blood pressure is similar as of serpentine.[42]

Ajmalicine

Alkaloid, ajmalicine have a large number of applications in the treatment of circulatory diseases, especially in providing relief to normal cerebral blood flow. It affects the function of smooth muscle, prevent strokes and helps in lowering blood pressure.[39] An estimated 3500 kg of ajmalicine is isolated annually from either *Rauvolfia* or *Catharanthus* spp. by pharmaceutical industries for the treatment of circulatory diseases. The synthetic pathway starts with geraniol through iridodial and irdotrial by the synthesis of loganin, which on oxidation converts loganin into secoloanin. This helps the tryptamine to form corynanthe type nucleus that results in the formation of ajmalicine.[41,59] The ajmalicine is derived from tryptophan which is converted to tryptamine via secologanin, strictosidine and cathenamine. Reduction of cathenamine to ajmalicine is facilitated by enzyme NADPH and tryptophan decarboxylase (TDC). Decarboxylase might be the key enzyme involved in the synthesis of ajmalicine in *Rauvolfia*.[60]

Serpentine

Serpentine, a type II topoisomerase inhibitor, exhibits antipsychotic properties.[61,62] The enzyme peroxidase (PER) is responsible for oxidation of ajmalicine to serpentine by catalyzing bisindole alkaloid localized in the vacuole.[41]

Rescinnamine

Rescinnamine, a purified ester alkaloid of alseroxylon fraction in species of *Rauvolfia*; related chemically and pharmacologically to reserpine with similar uses. Investigated in 1950's and used for the treatment of hypertension as an antihypertensive agent. It is clinically a less potent alkaloid than reserpine and not so effective in lowering blood pressure.[63] Rescinnamine inhibits angiotensin converting enzyme, peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II which stimulates aldosterone secretion by the adrenal cortex. Firstly it inhibits the Angiotensin Converting Enzyme (ACE) and then blocks the conversion of angiotensin I to angiotensin II. Inhibition of ACE results in decreased plasma angiotensin II. As angiotensin II is a vasoconstrictor and a negative-feedback mediator for renin activity, its lower concentration results in a decreasing in blood pressure and stimulation of baroreceptor reflex mechanisms, which ultimately results in decreased vasopressor activity and aldosterone secretion.[64]

Deserpidine

Deserpidine is an ester alkaloid isolated from *Rauvolfia.* It differs from reserpine only by means of absence of a methoxy group at C-11, which is synthesized from reserpine. It is used mainly for its antipsychotic and antihypertensive properties. It is capable of reducing high blood pressure by controlling nerve impulses along various nerve pathways. As a result, they act on the heart and blood vessels to lower blood pressure and also for

the relief of psychotic behaviour. Deserpidine also binds and inhibits the angiotensin converting enzyme and competes with angiotensin I for binding at the angiotensin-converting enzyme. It also blocks the conversion of angiotensin I to angiotensin II. [65]

Yohimbine

A pharmacologically well characterized alkaloid Yohimbine, is used as a selective alpha-adrenergic antagonist or alpha-blocker in the blood vessels for the treatment of erectile dysfunction It dilates blood vessels and increases blood flow in the penis, which helps in improving erectile function.[66-69] Yohimbine was also explored as a remedy for diabetes in animal and human models carrying polymorphisms of the α_{2A}-adrenergic receptor gene. Antagonism at these receptors relaxes smooth muscle and lowers blood pressure. It works by increasing certain chemicals in the body, which dilates the pupils of the eye. [70]

Phenols

Phenols are the secondary plant metabolites widely distributed in the plant kingdom mainly herbs, shrubs, vegetables and trees.[71,72] The presence of phenols is considered toxic for the growth and development of various pest and pathogens.[73] Presence of high quantity of total polyphenolic compounds in *R. serpentina* shows significant antidiabetic and hypolipidemic properties.[30,74] In medicine, it is used as an expectorant and emulsifying agent. The presence of phenolic compounds indicates that this can be used as anti-microbial agent.

Tannins

The oxidation inhibiting activity of tanni is due to the presence of gallic acid and diagallic acid.[75] Tannins have stringent 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.[33,76]

Flavonoids

These are potent water-soluble antioxidants and free radical scavengers, which prevent oxidative cell damage and have strong anticancerous activity.[77,78] 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.[5,79]

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.[80] Saponin has the property of coagulating red blood cells. The high saponin content of *Rauvolfia serpentina* substantiates the use of this extracts to stop bleeding and in treating wounds.[33,81]

Mineral composition

Rauvolfia is also known to contain a large number of macro and micro-nutrients and the most abundant macro nutrient is calcium.[76] The potential of *R. serpentina to* stop bleeding and its use in treating wounds can be due to its high calcium content, as it helps in blood coagulation. *R. serpentina* contains low sodium content that can be an added advantage due to the direct relationship of sodium intake with hypertension in human.[82] The presence of zinc shows that plant can play valuable roles in the management of diabetes, which result from insulin malfunction.[76]

The plant *R. serpentina* is also an excellent source of ascorbic acids, riboflavin, thiamin and niacin.[83] Ascorbic acid is vital for body performance as it plays an important role in normal wound healing[79], and lack of it impairs the normal formation of intercellular substances throughout the body (including collagen, bone matrix and tooth dentine). The *R. serpentina* is used in herbal medicine as a potential source of useful drugs for the treatment of many diseases as it is a rich source of phytochemicals, minerals and vitamins.[5,33]

***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[84], high blood pressure[85], hypertension[43], arrhythmia[86], various psychiatric diseases[87], mental disorders[88], breast cancer[89], human promyelocytic leukemia[29] 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, g-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.[5] The Pitkriya capsule (Unani formulation) contains arsol (*R. serpentina*)[90] 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, vasodialater, antiemetic, anti-fibrillar activity tranquilizing agent, anti-arrhythmic, antifungal and nematocidal.[29,91] *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.[12]

R. serpentina as a medicinal herb and therapeutic 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.[12,92] 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)[17] 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 anathematic. 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)[30] showed therapeutic effects of *Rauvolfia* 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.[93] *Rauvolfia'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.[19] The extract is also utilized to treat cancer which is one of the leading cause of death and other diseases mentioned below.

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 ß-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 ascitic cells.[96] 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.[97]

Mental illness, schizophrenia, high blood pressure and other diseases

The root of the plant is used in high blood pressure, mental agitation, insomnia and sedative.[14,24] 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[18], malaria[19], eye diseases[19], pneumonia[25], asthma[98], AIDS[99], headache[99] skin disease[100] and spleen disorder.[101]

CONCLUSION

Worldwide large number of peoples are suffering from several chronic diseases, due to significant variation in the climate and environment. To cure large number of people there is an urgent need for an herbal drug that can be utilized to treat various diseases with better cultural acceptability, compatibility with the physical body and lesser side effects. Thus, to fulfil this requirement *R. serpentina* is a promising herbal option in the pharmaceutical world due to the presence of significant chemical compounds in roots. The present review work will shed new insights on the potential of *R. serpentina* as antioxidant, anticancerous, antidiuretic, antiarrhythmic, antidysentry, antidiarrhoeal antihypotensive, anticontractile, and tranquillizing agent.

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