

# Evaluating the therapeutic efficiency and drug targeting ability of alkaloids present in *Rauwolfia serpentina*

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## Abstract

*Rauwolfia serpentina* is reported in an Ayurvedic medicinal system for centuries, for the treatment of various ailments such as snakebites, insomnia, hypertension, and insanity. Scientific evaluation of these documents can be valuable for finding new potential use in neurological disorders. The work presents the brief overview of *R. serpentina* including a description of the plant, its active chemical constituents and pharmacological properties with the major emphasis on cardiovascular and central nervous system disorders. This review compiles information available in the scientific literature from databases such as Science Direct, PubMed, India bioscience.org, Herbs - Medicinal plant usage and Identification Database, Database on medicinal plants used in Ayurveda and Siddha, Missouri Botanical Garden, National Medicinal Plants Board, and the International Plant Names Index. Information gathered from the literature has shown that the alkaloids are the major constituents of the plant imparting various pharmacological properties. Reserpine, the Indole alkaloid, is the most active compound of *R. serpentina*. The plant is known to possess antidiarrheal, antimicrobial activity apart from using it for the treatment of circulatory disorders, rheumatism, hypertension, insanity, epilepsy, and leaves are used in the removal of opacities of the cornea. Research shows that *R. serpentina* is a potential source of compounds pertaining medicinal applications. It provides an interesting subject in the search for new drugs of natural origin.

**Key words:** Reserpine, alkaloids, hypertension, neuropsychiatry disorders, vasodilatation

## INTRODUCTION

India has a rich heritage of traditional Ayurvedic medicine, and a recent surge in the demand for plant-derived drugs has gained momentum. Plants have played a significant role in maintaining human health and improving the quality of human life for thousands of years.<sup>[1]</sup> The World Health Organization estimated that <80% of the world's population relies on traditional medicine for their primary health-care requirement most of them are derived from plant extracts or their active components. Herbal remedies and herbal drugs playing a key role in curing central nervous system (CNS) disorders.<sup>[2]</sup> There are certain potential herbal medicines specifically for CNS disorders which exhibit a pharmacological potency and clinical efficacy of synthetic drugs in neurological disorders. *Rauwolfia serpentina* is reported as an Ayurvedic medicine which is also named Sarpgandha or Chandra which refers to use as an antidote for snakebite.<sup>[3]</sup> It is one of the first neuroleptic compounds that are used in the history of medical science.<sup>[4]</sup> The plant's more formal introduction is attributed to physicians:

Bose and Sen, (in 1931 paper) "*R. serpentina*, a new Indian drug for insanity and high blood pressure"<sup>[5]</sup> which was published in Indian medical journal. However, it soon became apparent that it could cause depression and even suicides. Therefore, because of the side effects, the use of drug for antipsychotics was eclipsed especially by chlorpromazine.

As reported in the ancient Ayurvedic literature, *R. serpentina* has been used for the treatment of skin cancer, eczema<sup>[6]</sup> psychosis phenomenon, hysterical neurosis, and high blood pressure, schizophrenia, and angiospastic attacks due to peripheral vascular disorders.<sup>[7]</sup> This paper summarizes the knowledge on pharmacological properties, major chemical constituents, therapeutic actions, presymptomatic studies,

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**Received:** 04-05-2017

**Revised:** 06-06-2017

**Accepted:** 23-06-2017

safety and this paper summarizes the knowledge on pharmacological properties, major chemical constituents, therapeutic actions, pre symptomatic studies, possible mode of action and safety of *R. serpentina* which is of historical interest drug.<sup>[8]</sup>

In modern medical science, its active constituent is used effectively as commercial drugs. It is one of the essential compounds; Reserpine is used as an antihypertensive, anthelmintic drug.<sup>[9]</sup> It plays an important role in dysentery, ebolic, fever, diarrhea, cornea's opacity, and epilepsy.<sup>[10]</sup> It is used to treat high blood pressure,<sup>[11]</sup> arrhythmia,<sup>[12]</sup> breast cancer, cardiovascular diseases,<sup>[13]</sup> hypertension,<sup>[14]</sup> mental disorders,<sup>[15]</sup> and leukemia.<sup>[16]</sup> Due to the presence of Alseroxylon alkaloid (fat soluble, extracted from roots), it is known to cure many circulatory disorders.<sup>[17]</sup> The root extract or decoction extracts is known to treat and relieves the abdomen, liver pain, and gastrointestinal disorders. The leaves, flower buds, and roots are dried and crushed into milk, and the crude paste is used externally on affected areas to treat burns, body aches, eczema, and scabies.<sup>[18]</sup>

## DESCRIPTION OF THE PLANT

*R. serpentina* belongs to the family Apocynaceae.<sup>[19]</sup> The genus name was selected in honor of Dr Leonhard Rauwolf, a 16<sup>th</sup>-century German botanist, Physician and explorer, who reported this plant as a potential source of therapeutic alkaloid.<sup>[14]</sup> The discovery of genus *Rauwolfia* dates back to the 16<sup>th</sup> century and around 130 species are known till now among which the most useful variant available in India of commercial importance is *R. serpentine*.<sup>[20]</sup>

*R. serpentina* is a climbing evergreen, perennial shrub grows up to a height of 60 cm and has cylindrical stem.<sup>[21]</sup> Its roots are tuberous with pale brown cork. Plant leaves are in whorls of three, elliptic to lanceolate or obovate, base tapering, and slender. Flowers are in many irregular corymbose cymes.<sup>[22]</sup> Its fruits are Drupe, single or two-fold, shining black, the inflorescence with red pedicels and calyx and white corolla. Corolla is longer than calyx, tube slender, swollen a little above the middle, three-lobed, and elliptic-oblong. The flowering time is from March to May in Indian conditions.<sup>[23]</sup>

The root occurs as segments, subcylindrical to tapering, tortuous or curved, rarely branched, occasionally bearing twisted rootlets, which are larger, more abundant, and more rigid and woody on the thicker parts of the roots. Root odor is indistinct, earthy, reminiscent of stored white potatoes, and the taste is bitter. Bark separates easily from the wood on scraping. The wood is hard and of relatively low density.<sup>[10,24]</sup> Figure 1 depicts the various parts of the plant. The plant inhabits the hot and humid regions of South and South-East Asian countries mainly Ceylon, Burma, Indonesia, and India. In India, it is widely distributed in the tropical Himalayas,



**Figure 1:** Images of *Rauwolfia serpentina*, showing various parts (a) *R. serpentina* whole plant, (b) flower sproutings, (c) dried seed, (d) dried roots

Sikkim, North Bihar, Assam, and Deccan Peninsula. It is also found in the lower hills of Gangetic Plains, Eastern and Western Ghats and Andamans. It is mostly found in moist deciduous forests at altitudes ranging from sea level to an altitude of 1200 m high.<sup>[25]</sup>

Distinctly, focusing on the root extract of *R. serpentina*, which possesses high therapeutic properties and is potent in treating chronic hives, malnutrition, that was earlier unresponsive to high energy diets or high proteins.<sup>[8]</sup> The other effective remedial properties are in treating and relieving conditions such as - Hysteria, Urticaria, and instant lowering of high blood pressure.<sup>[26]</sup> Furthermore, these roots contain a high quantity of starch, resin and some micronutrients such as - phosphate, silicate, manganese, potassium carbonate, and traces of iron.<sup>[27]</sup> The phytochemical content of roots is Reserpine, serpentine, reserpiline, ajmalicine, ajmaline, aricine, ajmalimine, deserpidine, corynanthine, rescinnamidine, rescinnamine, isoreserpiline, isoreserpine, indobinine, indobine, yohimbine, serpentine apart from these contents there are various indole alkaloids that are identified in the roots, namely, isorauhimbic acid, yohimbic acid, N(b)-methylajmaline, 3 hydroxysarpagine, and N(b)-methylisoajmaline. The most potent and essential ingredient found in *R. serpentina* roots is "reserpine."<sup>[28]</sup> Harisaranraj evaluated the chemical composition, minerals and vitamins of *R. serpentina*. Tables 1-3 provide a brief description of the chemical composition.<sup>[29]</sup>

The plant is enriched with vitamins, particularly, ascorbic acid (vitamin acid), which was found to be  $44.03 \pm 0.20$  mg/100 g in *R. serpentina*. Other vitamins were also found to be present in the plant, namely, riboflavin, thiamine, and niacin.<sup>[30]</sup> The plant may be an antimicrobial agent because of the presence of phenolics compound in it. Phenols are responsible for the antioxidant properties of the plant.<sup>[31]</sup> Alkaloids and its derivatives are used as medicinal agents because of their antispasmodic, analgesic, and bactericidal effects.<sup>[32]</sup> They

**Table 1:** Phytochemical composition of *R. serpentine* (expressed as mg/100 g dry wt.)

Phytochemicals	<i>R. serpentine</i>
Phenols	1.86±0.11
Flavonoids	1.72±0.11
Alkaloids	1.48±0.02
Tannins	0.51±0.20

*R. serpentine*: *Rauwolfia serpentina***Table 2:** Macro and microelement composition of *R. serpentine* (expressed as mg/100g dry wt.)

Minerals	<i>R. serpentine</i>
Macroelements	
Calcium	0.32±0.10
Phosphorus	0.18±0.22
Magnesium	0.10±0.20
Potassium	0.04±0.11
Sodium	0.02±0.10
Microelements	
Zinc	5.38±0.11
Iron	1.85±0.20

*R. serpentine*: *Rauwolfia serpentina***Table 3:** Vitamin composition of *R. serpentine* (expressed as mg/100g dry wt.)

Vitamins	<i>R. serpentine</i>
Ascorbic acid	44.03±0.20
Riboflavin	0.42±0.10
Thiamine	0.18±0.02
Niacin	0.02±0.10

*R. serpentine*: *Rauwolfia serpentina*

show marked physiological activity when administered to animals. Flavonoids are the free radical scavengers and water soluble antioxidants which have strong anticancer activity and prevent oxidative stress to the cells. Further, the flavonoids in the intestine decrease the risk of heart diseases.<sup>[33]</sup> Flavonoids have antioxidant and anti-inflammatory activities which are used in the treatment of diseases in herbal medicine.<sup>[34]</sup>

Tannins, on the other hand, have peculiar properties and increase the healing of inflamed mucous membrane and wounds. The lower sodium content of the plant is an added advantage because of the direct relationship between hypertension and sodium intake in humans.<sup>[35]</sup> The plant plays an important role in the management of diabetes because of the presence of zinc.<sup>[36]</sup> The plant is a good source of riboflavin, niacin, ascorbic acid, and thiamin.<sup>[37]</sup> Due to the presence of ascorbic acid in the plant, it is used in herbal medicines to treat many diseases.<sup>[38]</sup> Lack of ascorbic acid hinders the normal synthesis of intercellular substances in

the body, which includes, tooth dentin, collagen, and bone matrix.<sup>[39]</sup> Ascorbic acid is essential for body's performance.<sup>[40]</sup> Anemia, weakening of the endothelial wall of capillaries and pain in the joint can be related to the association of normal connective tissue metabolism and ascorbic acid.<sup>[41]</sup>

## MEDICINALLY ACTIVE CHEMICAL CONSTITUENTS OF *R. SERPENTINE*

Reserpine, the major pure crystalline alkaloid isolated from root, stem and leaves of the plant, is the most active compound of *R. serpentine*.<sup>[42]</sup> It is an indole alkaloid, and chemically it is 11, 17  $\alpha$ -Dimethoxy-18  $\beta$ -[(3,4,5-Trimethoxybenzoyl) Oxy]-3  $\beta$ , 20  $\alpha$ -yohimban-16  $\beta$ -carboxylic acid methyl ester.<sup>[43]</sup> The concentration of reserpine varies from 1.7% to 3.0% depending on geographical location and the season of plant collection with December being the favorite month for maximum alkaloid yield.<sup>[44]</sup>

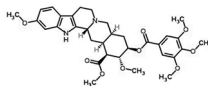
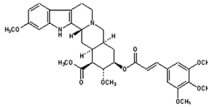
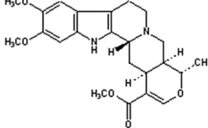
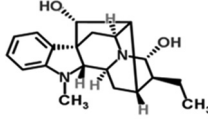
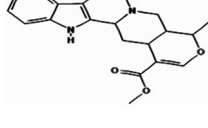
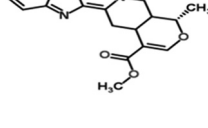
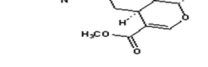
The age of the plant has no effect on the percentage of alkaloid content. It contains not <0.15% of reserpine - rescinnamine group alkaloids, calculated as reserpine. Apart from reserpine, other minor alkaloids present in the plant are ajmalicine, ajmaline, isoajmaline, chandrine, rauwolfinine, renoxidine, rescinnamine, reserpiline, sarpagine, tetraphyllicine, and yohimbine.<sup>[45,46]</sup> The root contains ophioxylins, resin, starch, and wax.<sup>[20]</sup> The whole root contains over 50 alkaloids.<sup>[47]</sup> These alkaloids are categorized based on basic strength and solubility in organic solvents as shown in Table 4.

Commercially available preparations of *R. serpentina* generally contain 0.15-0.25% active alkaloids (reserpine and rescinnamine) by weight. Reserpine is most commonly used alkaloid for treating mild to moderate essential hypertension<sup>[48]</sup> and is approved by FDA (1953) as an antihypertensive drug molecule. Besides this, reports have shown its effects against *Staphylococcus aureus*<sup>[49]</sup> and a potential commercial antipsychotic drug.<sup>[50]</sup> Moreover, other alkaloids have also been reported for treatment of hypertension and other cardiac disorders.<sup>[51]</sup> Ajmaline (known by trade names Aritmina, Ritmos, Gilurytmal) is used as an antiarrhythmic agent (class 1a).<sup>[52]</sup> It is used to lower the ST elevations in patients suffering from Brugada syndrome.<sup>[53]</sup> This compound was named after Hakim Ajmal Khan, a Unani medical practitioner from South Asia.<sup>[54]</sup> It is found in *Catharanthus roseus*<sup>[55]</sup> and most species of *Rauwolfia* genus but its concentration is too low when extracted from the root part and also its bioavailability is lesser<sup>[56]</sup> hence, a semisynthetic propyl derivative called prajmaline was developed that had a better absorption and bioavailability as compared to Ajmaline.<sup>[57]</sup>

## MECHANISMS OF ACTION

On the basis of experimental and clinical studies, the root of *R. serpentina* attributed to many pharmacological actions.<sup>[58]</sup>

**Table 4:** Properties of major alkaloids present in *R. serpentina*<sup>[62]</sup>

Alkaloid	Molecular formula	Nature	Chemical structure	Functions	Melting point
Reserpine	$C_{33}H_{40}N_2O_9$	Indole alkaloid, soluble in chloroform		Antipsychotic antihypertensive	264.5°C
Rescinnamine	$C_{35}H_{42}N_2O_9$	Weakly basic Indole Alkaloids		Antihypertensive	238°C
Reserpiline	$C_{23}H_{28}N_2O_5$	Indoline Alkaloids of intermediate basicity		Antihypertensive	207°C
Ajmaline	$C_{20}H_{26}N_2O_2$	Alkaloid, miscible in water		Antiarrhythmic	158°C
Ajmalicine	$C_{21}H_{24}N_2O_3$	Indoline Alkaloids		Vasodilator	250°C
Serpentine	$C_{20}H_{21}N_2O_3$	Basic anhydronium alkaloids		Tranquilizer	153°C
Alstonine	$C_{21}H_{20}N_2O_3$	Indole alkaloid		Antipsychotic	348°C

It leads to generalized vasodilation acting directly on the vasomotor center, resulting in lowering of blood pressure. It's been also reported for depressant action on the cerebral centers, it exerts a sedative action<sup>[59]</sup> on the gastric mucosa and a stimulating action on the plain musculature of the intestinal tract.<sup>[22]</sup> It stimulates the bronchial musculature. The principal action of the drug appears to be an alteration of the sympathetic-parasympathetic balance by the partial suppression of sympathetic predominance at the hypothalamic level.<sup>[60]</sup>

Ajmaline, another alkaloid isolated from *Rauwolfia* has a potent antiarrhythmic effect and lowering of blood pressure. Studies have shown that ajmaline specifically depresses intraventricular conduction, suggesting this would be particularly effective in the treatment of re-entrant ventricular arrhythmias. In one study of 100 patients with essential hypertension, it was determined that serum cadmium levels were 643% higher and serum zinc levels 28% lower in

hypertensives when compared with normotensive controls. When the patients were put on ajmaline, blood pressure was lowered significantly. It also appeared to decrease the elevated serum cadmium levels in these individuals.<sup>[61]</sup>

Ajmaline group acts as a general depressant to the heart but has been reported to stimulate respiration and intestinal movements while serpentine group causes paralysis of respiration, depression of the nerves, and stimulation of the heart.<sup>[62]</sup> Rauwolfinine has hypotensive properties on the autolysis of rat brain and liver tissue.<sup>[63]</sup> Isoajmaline and neoajmaline causes lowering of blood pressure in intact, spinal and decerebrate animals with or without experimentally induced hypertension.<sup>[64]</sup> It is also reported for the enhanced glucose tolerance in Wister mice, methanolic root extract of *R. serpentina* shows significant antidiabetic, antiatherogenic, and hypolipidemic effects in alloxan-induced diabetic mice which could be due to the presence of total flavonoids [Table 5].<sup>[9,65]</sup>



**Table 5:** Detailed pharmaceutical information of different constituents of *R. serpentina* plant

Name of compound	Category of drug	Bioavailability	Patent information	Generic name/brand name
Ajmaline (C <sub>20</sub> H <sub>26</sub> N <sub>2</sub> O <sub>2</sub> )	Indole alkaloids antiarrhythmics (class I and III) antiarrhythmic agent, cardiovascular system, membrane transport modulators, secologanin tryptamine alkaloids, sodium channel blocker, voltage-gated sodium channel blocker	50%	U.S. Patent US4175078, issued on May 1975. <sup>[66]</sup> The patent covers Ajmaline derivatives: Cardenolide and Bufadienolide and the process of production The derivatives produce two therapeutically important effects: Tonicizing cardiac's activity Relieving Cardiac arrhythmia	Generic name Ajmaline (OS: DCF, JAN) Rauwolfia (IS) Ajmalina (PH: F.U. IX) Ajmaline (PH: BP 1980, JP XVI) Ajmalinum (PH: Ph. Helv. VI) Brand name Gilurytmal
Reserpine (C <sub>33</sub> H <sub>40</sub> N <sub>2</sub> O <sub>9</sub> )	Indole alkaloids antihypertensive agent, adrenergic uptake inhibitor, antipsychotic agent, hypotensive agent, membrane transport modulator, neurotransmitter agent (OCT2 substrates)	50%	U.S. Patent US 2788309 An issued on 9 April, 1957. <sup>[67]</sup> The patent covers composition for reserpine for parenteral administration	Brand name Demi-Regroton, Regroton Diuretic Ap-Es, Serathide, Ser-Ap-Es, Serpazide Hydropres-25, Hydroserpine 1, Hydroserpine, Hydropres-50 Salutensin, Salutensin-Demi
Rescinnamine (C <sub>35</sub> H <sub>42</sub> N <sub>2</sub> O <sub>9</sub> )	Alkaloid angiotensin converting enzyme inhibitor cardiovascular system indoles antihypertensive agent yohimbine indole alkaloid	0	U.S. Patent US 3898215 A issued on 5 August, <sup>[68]</sup> 1975 The patent covers rescinnamine-like compounds and a process for producing the same.	Generic names: Rescinnamina (OS: DCIT) Rescinnamine (OS: BAN, DCF, JAN) 3,4,5- Trimethoxycinnamic acid ester of methyl reserpate (IS: WHO) Reserpyletrimethoxycinnamate (IS) BRAND NAME Tsuruselpi S

## **R. SERPENTINA AND NEURODEGENERATIVE DISEASES (NDD)**

The main strategy against Alzheimer's disease (AD) is the inhibition of acetylcholine esterase (AChE). In addition to currently approved drugs, many phytochemicals derived from the plant are used for the treatment of NDD. Apart from NMDA antagonist memantine, the only approved drugs for the treatment of AD are rivastigmine, galantamine, and donepezil till 2014.<sup>[69]</sup> Inhibition of AChE is known to be a promising strategy for treatment of Parkinson's disease, glaucoma, dementia, myasthenia gravis in addition to AD. Various plant species from worldwide have been screened for the AChE activity.<sup>[70]</sup> Formation of reactive oxygen species, reactive nitrogen species is another important neurotoxic pathway in AD, which leads to neuronal injury and death.<sup>[71]</sup>

Various plant species are used by the ayurvedic system of medicine since 4000 years for the treatment of CNS disorders and to improve cognitive function and memory. Mathew *et al.* conducted a study wherein *R. serpentina* was used to screen anti-cholinesterase and antioxidant activity.<sup>[72]</sup> The results revealed that *R. serpentina* showed high antioxidant activity with IC<sub>50</sub> of 96 ± 7.8 µg/ml using DPPH assay<sup>[73]</sup> and IC<sub>50</sub> for AChE inhibitor was 22 ± 4.9 µg/ml using Ellman's colorimetric methodology.<sup>[70]</sup> Thus, *R. serpentina* was an effective candidate as a source of antioxidants and AChE inhibitors.<sup>[74]</sup>

In another study by Saharia *et al.*, reserpine efficacy in the treatment of AD was evaluated.<sup>[75]</sup> They reported that AChE is responsible for increasing the reserpine mediated lifespan<sup>[76]</sup> and reduction in Aβ toxicity.<sup>[75]</sup> In *Caenorhabditis elegans* (an established model of AD), Aβ toxicity causes paralysis<sup>[75]</sup>

and is expressed in muscles. It was observed that reserpine alleviated pathogenesis of AD in model worms by delaying the paralysis mediated by A $\beta$  expression. Furthermore, there was not the significant alteration in the deposits of A $\beta$  *in vivo*. Reserpine was able to extend the lifespan and increased the stress tolerance in *C. elegans*. Hence, reserpine provides protection against AD pathogenesis in *C. elegans*.<sup>[77]</sup>

## DRUG TARGETS FOR ALKALOIDS PRESENT IN *R. SERPENTINA*

### Reserpine

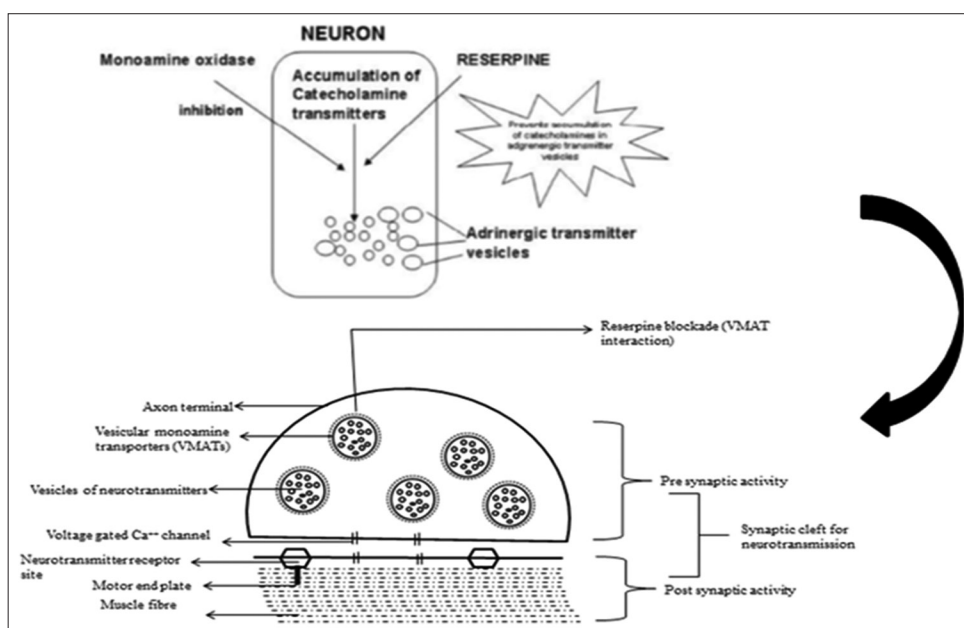
The antihypertensive property of *R. serpentina* is due to the presence of reserpine (3, 4, 5-trimethyl benzoic acid ester of reserpic acid, an indole derivative of 18-hydroxy yohimbine type).<sup>[78]</sup> It is the most significant of all alkaloids present in *R. serpentina* with good documentation about its therapeutic properties of being a natural tranquilizer and antihypertensive agent.<sup>[79]</sup> Physiologically, it binds with protein receptors vesicular monoamine transporters (VMATS) in membranes of specialized secretory vesicles of presynaptic neurons leading to pre synaptic closure of calcium-gated ion channels and preventing intracellular neuro transmitters from binding to VMAT proteins therefore, stopping secretory vesicles from up taking neurotransmitters [Figure 2].<sup>[80]</sup> Thus, causing a limited release of neurotransmitters from pre synaptic neurons subsequently, governing the nerve impulse transmission in postsynaptic neurons. Reserpine has the higher affinity for VMAT2 and binds irreversibly to their receptors.<sup>[81]</sup> It acts on both central and the peripheral nervous systems to deplete stores of neurotransmitters: Dopamine and nor epinephrine at central and peripheral synapses, epinephrine in the

adrenal glands, and serotonin (5-HT) in the CNS<sup>[82]</sup> and its higher doses cause a low release of neurotransmitters. This compound also damages the intracellular vesicles in which neurotransmitters are stored permanently, leading to spillage of neurotransmitters inside the neuron which are destroyed by monoamine oxidase. It is also used to treat symptoms of dyskinesia in patients suffering from Huntington's disease<sup>[83]</sup> by depleting catecholamine stores within the peripheral vascular adrenergic nerve endings, thus indirectly acting sympathomimetics and are unable to trigger the release of catecholamine.<sup>[84]</sup> The reserpine-induced catecholamine release increases sensitivity to the effects of direct-acting sympathomimetics.<sup>[85]</sup> It has sedative and tranquillizing effects, as it depletes catecholamine from the CNS.

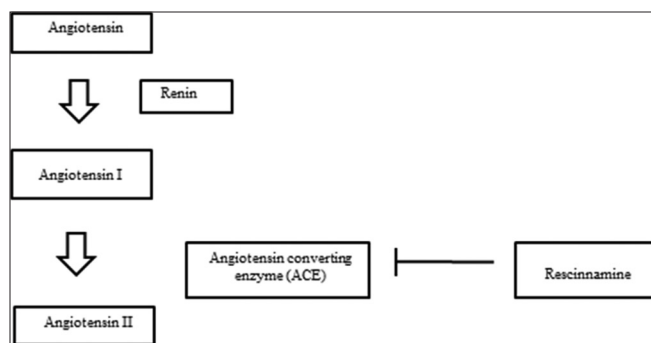
The tranquillizing effects of *R. serpentina* can result from the depletion of amino stores in the CNS; by depressant action on the cerebral centers, it relaxes the general nervous system.<sup>[86,87]</sup> Thereafter, effect of reserpine in the vasomotor center causes diminished reflex in vasomotor responses leading to generalized vasodilatation, with a lowering of blood pressure.<sup>[86]</sup>

### Rescinnamine

Rescinnamine binds and inhibits angiotensin converting enzyme and competes with Angiotensin I thus, blocking the conversion of Angiotensin I-II.<sup>[88]</sup> Angiotensin II is a negative feedback mediator of renin activity and a vasoconstrictor [Figure 3].<sup>[89]</sup> Therefore, rescinnamine helps in lowering the concentration of angiotensin II therefore, decreasing the blood pressure and stimulation of baroreceptor reflex mechanisms, leading to decreased aldosterone secretion and vasopressor activity.<sup>[90]</sup>



**Figure 2:** Schematic representation of reserpine neural mechanism at neuromuscular junction



**Figure 3:** Role of rescinamine in inhibiting angiotensin-renin system

### Reserpiline

It is a 10, 11 dimethoxy stereo isomer of Ajmalicine. It has an amorphous base and is extracted out from *R. serpentina* after extracting ajmalicine. Isoreserpiline and reserpiline coexist. It is useful extract for the treatment of psychosis. It increases the binding affinity for dopaminergic-B2, muscarinic and serotonergic receptors.<sup>[91]</sup>

### Ajmaline

Ajmaline is an antiarrhythmic agent (Class I) that acts by altering the shape and threshold of the cardiac action potential. It blocks sodium channel and a very short half-life makes it a very suitable drug for acute intravenous treatments. The mechanism of action of Ajmaline is that it depresses intraventricular conduction.<sup>[92]</sup> It leads to prolongation of P-Q interval, Q-T interval, QRS complex, and widening of R wave.<sup>[93]</sup> It does not deplete catecholamine content of heart, has a negative inotropic effect<sup>[94]</sup> and sympatholytic activity. Cellular stimulation was observed in the heart muscle of guinea pigs that received therapeutic ajmaline.<sup>[95]</sup> The drug is very famous in some countries for the treatment tolerated monomorphic ventricular tachycardias and atrial fibrillation in patients with the Wolff-Parkinson-White syndrome.<sup>[96]</sup> It has also been used as a drug to challenge the conduction system of the heart in cases of syncope and bundle branch block. It is used to diagnose Brugada disorder (genetic cardiac syndrome) and helps to distinguish the subtypes between patients with the syndrome.<sup>[97]</sup> On the basis of the molecular mechanism, these agents are classified into four groups, i.e. beta-adrenergic blockage, sodium channel blockade, calcium channel blockade, and repolarization prolongation.<sup>[98]</sup> It is reported to stimulate intestinal movements and respiration. Its action on pulmonary and systemic blood pressure is similar to that of serpentine.<sup>[43]</sup>

### Ajmalicine

Ajmalicine has application in the treatment of circulatory diseases by providing relief to normal cerebral blood flow. It effects in preventing strokes, lowering blood pressure,

and affects the function the function of smooth muscles.<sup>[99]</sup> Approximately, 3500 Kg of Ajmalicine is isolated from either *Rauwolfia* and *Catharanthus* spp. for the treatment of circulatory diseases.<sup>[100]</sup> The synthesis of Ajmalicine starts with geraniol through irdotrial and iridodial by the formation of loganin, which on oxidation converts loganin into secologanin.<sup>[101]</sup> This helps tryptamine to synthesise corynanthe type nucleus that results in the formation of ajmalicine.<sup>[102]</sup> The ajmalicine is derived from tryptophan which is converted to tryptamine via strictosidine, cathenamine, and secologanin.<sup>[103]</sup> The enzyme tryptophan decarboxylase and NADH reduces cathenamine to ajmalicine. The enzyme involved in the synthesis of ajmalicine is decarboxylase.<sup>[104]</sup>

### Serpentine

Serpentine is an inhibitor of topoisomerase (Type II) and has antipsychotic properties. For oxidation of ajmalicine to ajmalicine, an enzyme (PER) peroxidase<sup>[105]</sup> is responsible for it by catalyzing bisindole alkaloid localized in the vacuole.

### Side Effects

Orally, the roots of the plant may cause adverse reactions including nasal congestion, abdominal cramps, diarrhea, nausea, vomiting, anorexia, increased gastric acid secretion, drowsiness, fatigue, lethargy, slowed reflexes, and sexual dysfunction. Basically, the concomitant use of *R. serpentina* can increase the risk of bradycardia and arrhythmias. Although there are few reports in allergic responses from the use of plant root, it may precipitate asthma.

The dosage in larger amounts can precipitate mental depression and in extremely large amounts, Parkinson-like symptoms, extrapyramidal reactions, and convulsions may occur.<sup>[46,106]</sup> Recently, the studies are focused toward the high affinity of plant extract toward central  $\alpha_2$  and dopamine D2 receptors inducing hypolocomotion by nigral dopaminergic dysfunction producing an effect on peripheral movements, rearing, grooming, immobility, and defecation.<sup>[107]</sup> Hence, these intriguing findings will likely stimulate further interest in *R. serpentina*.<sup>[108]</sup> Some of the side effects of *R. serpentina* are faintness or drowsiness, lack of weakness or energy, inability to concentrate or mental depression, anxiety or depression, early morning sleeplessness, and impotence.<sup>[109]</sup>

## FUTURE PERSPECTIVE

Phytomedicine holds a great medical and public interest as a source of the novel lead compound and neutraceuticals for drug development. The roots of *R. serpentina* have been used for insanity and other illnesses such as vomiting, fever, and snakebites for more than 3000 years in Indian traditional medicine set up. Furthermore, it was the first reported antipsychotic drug but due to its side effects,

it was been withdrawn back from this use although, the intensive and systematic research is pending with this regard. Therefore, evolution of phytomedicine and plant-based chemical molecules needs more intense and multivariant research approaches, right from procuring and screening of plant extracts to phyto preparation and developing secured and efficient delivery system, till evaluating the safety and efficacy of the developed formulation. These targeted delivery systems will not only improve on the bioavailability of the phyto compounds, but their stability as well. Another approach to enhance the efficacy of these phytomedicine can be formulating them into nanoformulations or encapsulating them into nanoparticles or nanoemulsion forms, which is nowadays is a crucial field of nanomedicine.

## CONCLUSION

*R. serpentina* is well documented to exhibit potential medical values for treatment of hypertensive and neurological disorders. Extensive research has been carried out exploring its antihypertensive properties; however, limited literature is presently available on its neuropharmacological activities despite it being reported as the first neuroleptic compound. Although it was later reported for many CNS disorders, therefore *R. serpentina* covering the broad spectrum array of pharmacological activity proves to be an ideal therapeutic target for neurological disorders.

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**Source of Support:** Nil. **Conflict of Interest:** None declared.