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REVIEW

Rauwolfia serpentina: A Potential Plant to Treat Insomnia Disorder

Soumi Paul[1] · Sivasudha Thilagar[1] · Gayathri Nambirajan[2] · Abbirami Elangovan[1] · Dinesh Kumar Lakshmanan[1,3] · Guna Ravichandran[1] · Abirami Arunachalam[1] · Selvakumar Murugesan[1]

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Abstract

The global economic burdens of chronic degenerative diseases are a primary worldwide concern for nutraceutical-pharmaceutical researchers. Insomnia is a potential risk factor of such medical conditions with a complex two-way association and multi-folding associated financial debts. The long-term insomnia treatments by synthetic hypnotics produce side-effects-addictions-abuses. Thus, today, alternative therapies are getting promoted for safe treatment, and phytopharmaceuticals' use is one such. *Rauwolfia serpentina* (Indian Snakeroot) is such potential phytopharmaceuticals' source to treat insomnia, well-recognized for therapeutic applications, making traditional beverages. Its diverse alkaloids are responsible for many notable pharmacological activities, especially the active root-alkaloid reserpine. Even psychopharmacological researches principally described reserpine for sedation. But, later studies concluded reserpine is a tranquilizer, not a sleep-promoter. Such monotherapeutic approaches, a few controversial reserpine therapy reports, and reluctance from evolving modern science to strategically explore the traditional medicinal knowledge eventually shadowed sleep-promoting researches on *R. serpentina*. This review, relying on the well-researched traditional-scientific data, suggested root-based monotherapeutic approaches with *R. serpentina* need revisions treating insomnia.

Keywords *Rauwolfia serpentina* · Indian Snakeroot · Insomnia · Nutraceuticals · Phytopharmaceuticals

1 Introduction

Insomnia is an exponentially growing sleep disruptive medical condition of this century, a threat to our physiological and psychological well-being. Sleep disparity even got recognized as a global epidemic by the World Health Organization (WHO). One-third of an average human life got occupied by sleep. In healthy human sleep, 4–6 repetitive and alternative events of non-rapid eye movement (NREM) and rapid eye movement (REM) sleep in one sleep cycle work synergistically to restore the energy of both body and mind. NREM sleep (deep sleep) helps in active physiological healing, REM sleep (active sleep) restores psychological strength [1]. Hence, a sleep-disruptive disorder like insomnia acts as a stressor for both our physiological and mental health. Clinically, insomnia got defined as a poor sleep state (increased sleep-latency and decreased sleeping-time) of people despite a favorable sleeping environment, resulting in daytime impairments which could be chronic (insomnia symptoms three nights/week for ≥ 3 months), or short-term/acute (insomnia symptoms three nights/week for < 3 months) in nature [2].

Individuals suffering from any disease, aged populaces, and women are more prone to suffer from insomnia and related comorbidities. According to a community-based cross-sectional study of Taylor et al. [3], patients with the following medical conditions tend to show more frequency of chronic insomnia: neurological disorders (66.7%), breathing disorders (59.6%), gastrointestinal issues (55.4%), chronic pain (48.6%), cardiac diseases (44.1%), hypertension (44.0%), urinary problems (41.5%), and cancer (41.4%). Similarly, chronic insomnia patients showed a higher prevalence of the following diseases compared to the normal sleepers: chronic pain (50.4%), hypertension

✉ Sivasudha Thilagar
sudha@bdu.ac.in; sudacoli@yahoo.com

[1] Department of Environmental Biotechnology, School of Environmental Sciences, Bharathidasan University, Tiruchirappalli, Tamil Nadu 620024, India

[2] Department of Microbiology and Biotechnology, Bharath University, Selaiyur, Chennai, Tamil Nadu, India

[3] Department of Biotechnology, Bannari Amman Institute of Technology, Sathyamangalam, Tamil Nadu, India

(43.1%), gastrointestinal diseases (33.6%), breathing problems (24.8%), heart diseases (21.9%), urinary diseases (19.7%), and neurological diseases (7.3%). Lind et al. [4] reported genetically, women (59%) inherit insomnia more than men (38%). A cross-sectional survey of insomnia from seventy-one primary health centers of Kerala, India, on elderly primary care patients (1,574 valid respondents of 68.6 years mean age) showed 11.8% of elderly attendees had clinical and 30.4% with sub-clinical insomnia. Aged women (55.5%) reported clinical and sub-clinical insomnia most. Even the patients with clinical insomnia reported experiencing anxiety, depression, and somatization; sub-clinical insomnia stated low life satisfaction [5]. Reportedly, 9% (703 million) of the world population aged ≥ 65 years, and by 2050 it got estimated to rise as high as 16% (1.5 billion) [6]. Hence, insomnia and its related chronic comorbidities on this elderly population are already a matter of concern for nutraceutical-pharmaceutical research sectors and industries globally. Lack of governmental focus, media awareness on sleep debt, and its consequences lead to its negative reflection in policy-making. Hence, eventually, the economic burden of countries at the cost of sleep also increases. Sleep debts increase the risks of road accidents, industrial accidents, medical mishappenings, reduced academic or professional productivity [7].

Even the popular sleep-promoting drugs like benzodiazepines, ramelteon, zolpidem treat mild-chronic insomnia globally for a short-term period. The long-term use of these produces varying degrees of side effects (dizziness, depression, loss of orientation, headache, aggression, memory impairment), addiction, and abuse of these hypnotics. These are the reasons why today's functional food, superfood, whole food, and phytopharmaceutical industries seeking remedies from components of natural origin for health benefits. Even the growing numbers of health-conscious consumers are increasing the demands for organic foods, drugs, personal care goods in the market. Therefore, the number of researches to find such potential components from natural resources and scientifically prove their health benefits are also inclining. Herbal plants are one of the leading natural resources to get such potential compounds for therapeutic profits as they possess secondary metabolites/organic compounds (terpenes, phenolics, polyketides, alkaloids) to combat various diseases, including treating sleep-related disorders. The addition of herbal extracts in food products is already a well-known health-giving way. WHO classified plants or plant parts used for pharmaceutical synthesis as drugs [8]. Even the traditional Indian medicinal literature Charaka Samhita and Sushruta Samhita mentioned such dietary consumption and therapeutic applications to treat sleep-related diseases like insomnia [9]. Medicinal herbs, *Hypericum perforatum* L. (St John's wort), *Valeriana officinalis* L. (Valerian), *Humulus lupulus* L. (Hops), *Scutellaria lateriflora* L. (Blue Skullcap), *Piper methysticum* G.Forst. (Kava Kava), *Melissa officinalis* L. (Lemon Balm), *Eschscholzia californica* Cham. (California poppy), etc. are some globally well-known potential herbal sources to treat insomnia either in combination with other plant extracts or alone.

The herb *Rauwolfia serpentina* (L.) Benth. ex Kurz (Indian Snakeroot), well-known as Sarpagandha, is a historically favored native South and East Asian plant with many notable therapeutic uses since the pre-Vedic era. The plant has customary use of its root in tea preparation and root powder consumption with milk to calm nerves, promote sleep [10]. Its root cork has uses in preparing traditional rice-based-beverage among the north Bengal tribal folks of West Bengal, India [11]. These Ayurveda, Siddha, and Unani medicinal systems mentioned the medicinal use of *R. serpentina* for therapeutic benefits. The Macassar folks of Indonesia, the Mech community of Eastern Nepal, Madhupur people from Bangladesh said ethnomedicinal uses of this plant. The tribal people of state Madhya Pradesh, India and livestock farmers of district Nawalparasi, Central Nepal mentioned about its ethnoveterinary uses. This whole plant and plant parts separately, especially using Sarpagandha roots, are extensively mentioned in ancient medicinal documentation and folklore for treating fever, snake bites, cardiovascular disorders, hypertension, gastrointestinal diseases, schizophrenia, epilepsy, insomnia, insanity [11, 12]. It was popularly known as 'Pagal ki Jaddi-buti' among Bihar folks for its effective local use to treat psychosis [13]. This plant proved its therapeutic claims via positive outcomes in pharmacological activities. These are cardiovascular, gastrointestinal, anti-poisonous, anti-oxidant, anti-bacterial activities [14]. This plant is also extensively studied for its sedative activity. Mid-twentieth century, when the alkaloid reserpine got declared as an active constituent of this plant, it was assumed to produce sleep as well. However, later it was proved to act as a tranquilizer that keeps the body inactive without promoting sleep. Future studies even restricted its use to a low dose for its adverse side effects. Even reserpine started to get prescribed combined with other drugs. Henceforth, the monotherapeutic psychopharmacological approaches (primarily root-derived alkaloid reserpine-based), controversial cases of adverse reports, and the consequential reluctance of evolving modern biomedical science work in co-operation with traditional medicinal knowledge gradually shadowed further scientific psychopharmacological researches on *R. serpentina*. Thus today, it is vital to connect those conventional records and psychopharmacological research reports on *R. serpentina*, which indicated that this plant is a potential natural source to treat insomnia, explain possible scientific approaches towards this herb to prove its anti-insomniac efficacy.

This piece of writing reviews the presently available literature on *R. serpentina* for its folk uses, phytochemistry, and pharmacological benefits based on well-researched scientific evidence. Besides, this current paper specifically focused on elucidating the local dietary consumption, medicinal uses, and pharmacological studies on *R. serpentina* as a sedative and the future scopes of scientific works on it to treat insomnia.

2 Morphology and Agri-Botany

The 74 accepted plants under the genus *Rauwolfia* (Gentianales: Apocynaceae) got distributed in the tropical climates of Asia, Africa, South America, and diverse oceanic islands [15]. The plant *Rauwolfia serpentina* (L.) Benth. ex Kurz syn. *Ophioxylon sepentinum* L. propagated globally in the tropical Indian regions, Bangladesh, Bhutan, Nepal, Pakistan, China, Sri Lanka, Myanmar, Indonesia, Malaysia, Laos, Thailand, Vietnam. In India, all over the country, it is found in the foothills of the Himalayas at an elevation of 1000 m and above, deciduous moist forests of the Eastern and Western Ghats, near lower Gangetic regions, Andaman islands [12, 16]. Such wide distribution of this plant and its various medicinal uses among the folks gave it many vernacular identities such as Sarpagandha, Nakuli, Sugandha, Sarpasugandha, Naganadha, Chandrika, Dhavalavitapa, Chandramarah, Raktapatrika (Sanskrit); Chandra, Gandharasna, Nakuli (Bengali); Arachoritita (Assamese); Bhungmaraja (Arunachal Pradesh); Dhan-Barua, Dhavalbarua, Chandamarva, (Oriya); Nakulikanda, Chota-chand, Chandrabhaga, Rasnabheda (Hindi); Chevanamalpodi, Sarppaganti (Tamil); Patalaguni, Patala garuda, Sarpagandhi (Telugu); Keramaddinagaddi, Sutranabhi (Kannada); Amalpori, Chuvannavilpori (Malayalam); Harkaya, Mungusabel, Aakayi, Saapand (Marathi); Amelpodee (Gujarati) [12, 14]. The extensive studies on anti-hypertensive, nootropic properties of *R. serpentina* root in western medicine gave it recognition as Serpentine root, Rauvolfia root [14].

R. serpentina is an evergreen, perennial, glabrous, woody, erect undershrub (Fig. 1). The roots are aromatic, long, fleshy, rarely branched, cork grayish-yellow to pale brown colored. The stem is cylindrical of about one-meter height. Leaves are ecliptic-lanceolate or obovate-acuminate, slender with tapering base, occur in 3–4 whorls, rarely opposite, dark green upside and pale green below. Flowers are irregular corymbose cymes, laid out in bunches, white–pink–red in color. The inflorescence appears as red pedicels-calyx and white corolla. The Indian climate permits flowering during the tenure of March to May. The fruits are drupes, single-didymous, green when unripe, and shining purplish-black to black when ripe, ovoid seeds [16, 17]. This plant usually grows under the shades of moist deciduous forest trees, swampy localities of India. But over-exploitation for pharmaceutical benefits, indiscriminate collection by locals, difficulty in the cultivation of this plant pose threats to its existence in the wild [12]. It led the International Union for the Conservation of Nature and Natural Resources (IUCN) to place *R. serpentina* in the IUCN Red List. The taxonomic hierarchy and conservation status of the plant got mentioned in Table 1.

3 Traditional Uses

The plant *R. serpentina* is a popular herb for its dietary consumption of root/root-powder with tea, milk for soothing nerves [10, 18]. Biradar et al. [10] mentioned the consumption of 1 g root powder of *R. serpentina* with 250 ml of sweetened goat milk after/before meal for treating insomnia. The tribal folks of Himalayan Tarai of northern Bengal use *R. serpentina* root skin to grow bitterness in the starter Ranu Dabai of traditional rice-based beverage Jhara and other rice beers. Even the sufficient production of *R. serpentina* could surpass *Coccinia grandis* use in preparing the starter of local fermented food products [11]. *R. serpentina* is equally well-known for its folk medicinal applications in traditional medicine systems since the pre-Vedic time. In Ayurveda, *R. serpentina* got popularly mentioned as Sarpagandha in the ancient documentations. The ancient literature, Charaka Samhita mentioned this plant as 'Nakuli' (a synonym of Sarpagandha), which got used as a constituent of herbal formulation named 'Vachadi Yoga,' an effective anti-poisoning agent. Ekasar Gana (Susruta Kalpa) claimed *R. serpentina* as anti-poisonous, got used to treating rat poisoning. Vrindamadhava mentioned its use for the aliment of 'Visuchika' means cholera. Scriptures of Shodhal recognized Sarpagandha as 'Vatavyadhinashini,' indicates its usefulness to treat neuromuscular disorders [12–14, 19]. Siddha mentioned ethnomedicinal use of *R. serpentina* roots to treat high blood pressure, cephalalgia, head spinning, menstruation-related disorders (amenorrhea, oligomenorrhea, dysmenorrhea). Unani system of medicinal application talked about *R. serpentina* as a potential diuretic agent [14]. Besides, folklore also mentioned the therapeutic values of this plant to treat wounds, fever, coughs, pneumonia, malaria, worm infestation, snake and insect bites, constipation, labor pain during childbirth, ulcer, cataract, anxiety, depression, insomnia, schizophrenia, epilepsy, insanity [12].

Rauwolfia serpentina already got coined as a 'wonder herb' for its diverse health-giving uses across the nations. But this review focuses on the elucidation of its importance to treat insomnia.

Fig. 1 Morphology of *Rauwolfia serpentina*

Table 1 Taxonomic hierarchy and conservation status of *Rauwolfia serpentina*

Rank	
Kingdom	Plantae
Phylum	Angiospermae
Subphylum	Eudicotidae
Class	Asterids
Order	Gentianales
Family	Apocynaceae
Genus	*Rauwolfia*
Species	*serpentina*
Botanical name	*Rauwolfia serpentina* (L.) Benth. ex Kurz
Conservation Status	Endangered (EN)

3.1 Earliest Ethnomedicinal Recognition of *R. serpentina* to Treat Insomnia

The plant got mentioned for its nerve relaxing activity first in the ancient literature Susruta Samhita (fifth century B. C.—second century A. D.). Aparajit Gana (Susruta Uttartantra) introduced its use to treat psychosis [12, 13, 20]. Among the different vernacular names of this plant which depict its various therapeutic aspects names such as Chandrika (Sanskrit), Chandra (Bengali), Chota-chand (Hindi) refer to the 'moon' and the use of this plant to treat 'moon's disease or lunacy' [21]. In modern medical terms, such vernacular names of *R. serpentina* indicate its use to treat psychotic or central nervous system (CNS) disorders, including 'Anidra/Nidranasha' means insomnia.

3.2 Tribal and Traditional Medicinal Uses of *R. serpentina* to Treat Insomnia

Since the pre-Vedic and Vedic periods, this plant's root got extensively used for health benefits [12]. Later on, the ethnobotanical documentation on *R. serpentina* folk use for sleep-promoting purposes confirms its applications to treat insomnia. The Chatra block in the Sonbhadra district of state Uttar Pradesh and the Chhatarpur district tribes of state Madhya Pradesh are using *R. serpentina* for treating

insomnia [11, 22]. The plant also got popularly known as a potential hypnotic agent among the people of state Bihar [13]. Later, *R. serpentina* also got reported as one of the many significant plants obtained from the Suhelwa Wildlife Division, Balarampur district of Uttar Pradesh by the Tharu tribe, ethnotherapeutically used for treating sleep disparity [23]. The tribal (Santal, Munda, Oraon, Lodha, Sabar) and non-tribal (Rajbongshi, Hindus, Muslims, other minorities) communities at the ethnomedicinally active Dakshin Dinajpur district of state West Bengal reported keeping the leaves (2–3) of the herb under the pillow to reduce insomnia [24]. In the traditional medicine system, Ayurvedic preparations such as Sarpagandha Ghanvati, Sarpagandha Churna, Sarpagandha Yoga, Maheshvari Vati, Nidrakar Bati, Vedic Calm containing this herb in part or whole have got suggested as remedies for insomnia [12, 25–27]. The Unani formulation, Pitkriya capsule, known for containing arsol (*R. serpentina*), which got mentioned to exhibit nervine properties [11].

3.3 Miscellaneous Nervine Reports on *R. serpentina*

Apart from the tribal use of *R. serpentina* to promote sleep, miscellaneous reports on this plant mentioned inducing sleep among the sufferers are also present. The practice of making crying babies asleep by allowing them to have breast milk where breasts got smeared with the *R. serpentina* root-paste, reported from certain parts of India [13, 28]. Even the distinguished Indian political leader Mahatma Gandhi used *R. serpentina* root while making evening tea for fetching relaxation after a busy day [18, 29].

4 Phytochemistry

4.1 Secondary Metabolites

The phytochemical analyses of *R. serpentina* revealed that the plant is a rich source of secondary metabolites like phenols, flavonoids, alkaloids, and it also contains other such metabolites like saponins, tannins, terpenes, steroids, reducing sugars, fatty acids. However, *R. serpentina* is well-studied for its claimed therapeutic benefits of indole alkaloid constituents, especially the alkaloid reserpine [17, 18]. The whole plant got reported to contain such alkaloids, but root cork reported the highest percentage of indole alkaloids, including reserpine. Even the total alkaloid and reserpine yield of the plant root recorded to vary depending on the geographical location and season of the collection [17, 18, 30]. But a study on the mother tinctures made from wild and cultivated varieties of *R. serpentina* reported no significant differences in their physicochemical parameters [31].

Scientific studies isolated greater than 50 indole alkaloids from *R. serpentina*. This alkaloid is one of the largest groups of nitrogenous secondary plant metabolites that originate from the amino acid tryptophan precursor with an indole moiety in its construction [17, 18]. The plant exhibits three types of such alkaloids of weakly basic (Reserpine, Rescinnamine, Deserpidine), intermediate basicity (Reserpiline, Ajmaline, Isoajmaline), and strong anhydronium basic (Serpentine, Serpentinine, Alstonine) nature (Fig. 2) [8]. Other than these three types *R. serpentina* reported alkaloids such as Ajmalimine, Ajmalicine, Indobine, Indobinine, Rescinnamidine, Yohimbine,

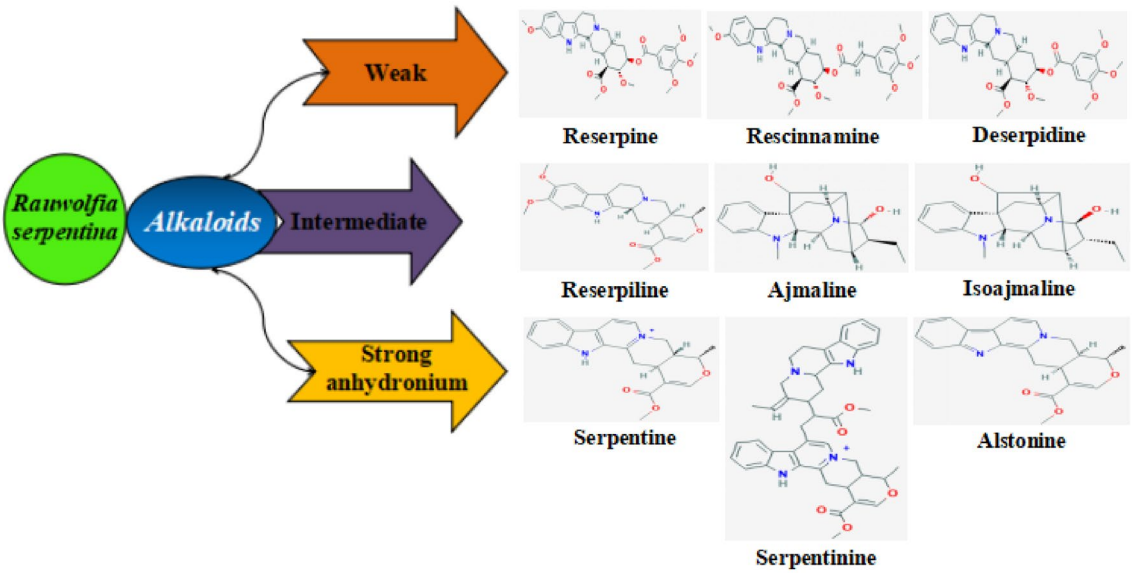

Fig. 2 Chemical structures of three types of alkaloidal basicities in *Rauwolfia serpentina*

Serpentine, Serpentinine, Chandrine, Renoxidine, Reserpinine, Sarpagine, Neoajmaline, Rauwolscine, Serpinine, 3-epi-a-Yohimbine. The plant also reported steroids β-Sitosterol along with its dehydro derivative [30].

4.2 Minerals and Vitamins

The minerals and vitamins reported from *R. serpentina* play a significant part in its pharmacological activities with its recorded secondary metabolites. The herb is a good source of macroelement calcium (Ca); microelements like zinc (Zn), iron (Fe); and vitamins like ascorbic acid ($C_6H_8O_6$), riboflavin ($C_{17}H_{20}N_4O_6$), thiamine ($C_{12}H_{17}N_4OS^+$) [17].

5 Pharmacology

The multipotent therapeutic benefits of the wonder plant *R. serpentina* got initial attention for pharmacological studies back in the twentieth century. Henceforth, the significant outcomes in pharmaceutical-clinical studies made this plant a promising source of natural drugs. *R. serpentina* showed the following diverse pharmacological activities: anti-oxidative, anti-inflammatory, anti-bacterial, anti-fungal, anti-venomous, gastroprotective, hypolipidemic, hypoglycemic, hepatoprotective, antidiabetic, cardioprotective, anti-hypertensive, neuroprotective, nerve-regenerative, sedative, anti-prostate cancerous (Fig. 3) [8, 14, 17, 30].

Though scientific literature reported such multifunctional properties, this review focuses on the sedative pharmacological studies on *R. serpentina that would contribute* to insomnia treatment.

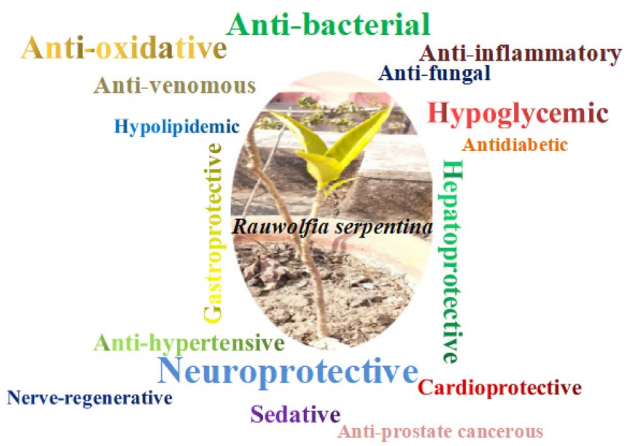

Fig. 3 Pharmacological attributes of *Rauwolfia serpentina*

5.1 Earliest Introduction of *R. serpentina* as a Sedative in Science

Georg Eberhard Rumphius, aka Rumpf, also sometimes known as the 'Pliny of India,' appointed by the Dutch East India Company to document significant plants on the then island of Amboina (now Eastern Indonesia), first illustrated the plant *R. serpentina* as *Radix mustelae* in *Herbarium Amboinense* (1741), based on the folklore of its consumption by mongoose before attacking poisonous snakes. Later, the entire genus was renamed *Rauwolfia* by Linnaeus (4th edition of the *Species Plantarum*), honoring the 16th-century German botanist Leonhart Rauwolf. [13, 21, 32]. During the documentation of *R. mustelae*, Rumpf noted the use of this herb to calm nerves [32]. Monachino [21] even mentioned *R. serpentina* root demand in India for almost two decades before its recognition by the Western pharmaceuticals, where a single production firm claimed to sell over 50 million dried root tablets.

5.2 Indian Scientific Community Studying the Sedative Activity of *R. serpentina*

A seminal paper presented by Gananath Sen and Karthick Chander Bose (1931) first reported the use of 20–30 grains of *R. serpentina* powder twice a day that produced hypnotic symptoms along with treating high blood pressure and violent symptoms [32]. K. C. Bose noted every minute therapeutic detail of *R. serpentina* in *Pharmacopoeia Indica* (1932), disclosing the clinical potential of this herb. Following his work, Ram Nath Chopra and his team in the Calcutta School of Tropical Medicine studied and reported the nervine property *R. serpentina* root crude extracts in 1933. Later, pharmacologist Bishnupada Mukerjee from the same team held the oleoresin fraction of the plant for its sedative nature. The human administration of crude extracts on the patients of Carmichael Hospital for Tropical Diseases significantly potentiated sedation. The controlled human trialing of the same alcoholic extracts on 26 men, 14 women with catatonia at Ranchi Institute of Neuro-Psychiatry and Allied Sciences, India (1935) efficiently calmed nerves [33]. Gupta et al. [34], through their case notes on patients suffering from various mental disorders, strongly confirmed the potentiality of standardized *R. serpentina* root alcoholic extract to prolong the sleep duration, saying, "*Rauwolfia serpentina* never failed to induce sedation and sleep." But it is also important to note that they used the standardized extract instead of root powder to avoid great respiratory depression. Besides, they mentioned that the alcoholic extract was more sedative than the total alkaloid itself. Despite all, the presence of root alkaloids (1.21–1.367%) redirected the research work, and therefore Gupta et al. [35] considered alcoholic extracts of roots containing ~ 0.57% alkaloids for clinical trials. The

failure of alkaloids to produce marked sedative action shifted the focus on non-alkaloidal substances, especially oleoresin, and reported the 95% alcohol-soluble resin fraction to show the desirable sedative activity in experimental animals. Even the Bengal Chemical manufactured Ralfen, a standardized extract of *R. serpentina*, was available at the Indian market by 1949 to treat insomnia [33]. The Himalaya Drug Company marketed the Sarpagandha as Serpina in India [21], which is still sold at the market to treat anxiety and hypertension.

5.3 Occidental Science Discovering the Sedative Activity of *R. serpentina*

Rauwolfia serpentina root extract as a potential hypnotic agent made its way in European and American clinical applications by the mid-twentieth century [21]. Müller et al. [36] reported for the first time the sedative component from the oleoresin fractions of the herb root and demanded that it is an alkaloid responsible for the prolonged sedative activity, they named it as reserpine. In November 1953, Ciba Pharmaceuticals first commercialized *R. serpentina* root extract as Serpasil, a tranquilizing and anti-hypertensive drug, with reserpine as its active component. In the same year, American pharma company Bristol Myers Squibb marketed Raudixin tablets containing the powdered-root of *R. serpentina* [21]. Even Kline [37] confirmed the sedative effects of the plant among patients suffering from various kinds of psychosis, saying, "… *Rauwolfia* will reduce anxiety and obsessive compulsive drives, and will overcome excessive inhibition and reticence." But it is important to note that not all patients equally responded to the sedative action of *R. serpentina*. The heavy, vivid dreaming of the patients got also reported. Yet, the identification of reserpine as the most active component redirected the research on *R. serpentina* alkaloid-based. Following this direction, Pletscher et al. [38] examined the serotonin (5-hydroxytryptamine/5-HT) level with reserpine use and reported 5-HT depletion. Based on the evidence of 5-HT loss from the hypothalamus and hypothalamus also has the highest concentration of noradrenaline (NA), the reserpine effect on NA got tested in cats [39]. The study reported reserpine (0.4 mg/Kg) to deplete the NA concentration from the cat hypothalamus. *R. serpentina* has been studied from various perspectives to provide a scientific road map on how this plant exerts action on the CNS. One group of researchers demonstrated reserpine as the active part of the root powder, and another group argued that total alkaloids are more potent in exerting sedation than the reserpine itself. One such was by Frommel and Gold [40], who explained the total alkaloids of the plant potentiated barbiturate-induced and pentothal-induced sleep more effectively than the reserpine itself. Another scientific community believed reserpine as a tranquilizer and not a sleep-inducer. The report published by Rinaldi and Himwich [41] was one such kind where it clearly explained that the reserpine acts as a tranquilizer, mentioning, "Unlike barbiturates, it renders patients less active without inducing sleep. This action, peculiar to reserpine, has been called a tranquilizing effect. Evidence that this state of quiescence is distinctly different from sedation induced by barbiturates is revealed by the fact that, in monkeys, reserpine does not produce an electroencephalographic picture of sleep." It is significant to note from this report on the effect of reserpine on the mesodiencephalic activating system (MDAS) that although reserpine showed alerting patterns in MDAS, the same certainly does not indicate the cause of sleeplessness. Hence, reserpine is neither a sleep-inducer nor causes insomnia. Extensive studies on the sedative alkaloidal components of *R. serpentina* root shifted focus to rescinnamine as well [42]. However, further studies proved it weaker in action than reserpine, and it is now known to treat hypertension only. Likewise, studies on different alkaloids of this herb found the therapeutic potential of each of them. When the potentiality of individual alkaloids or total alkaloids could not match the known level of sedation produced by *R. serpentina* (as mentioned since the pre-Vedic time) and reserpine got reported for promoting depression-suicide attempts [43], the historically popular plant like this one gradually lost its importance with the progress of time.

6 Discussion

The negative cases of depression and suicidal attempts by reserpine usage, supported by the "catecholamine hypothesis of depression," adversely affected the sedative pharmacological studies on *R. serpentina*. In this regard, Healy and Savage [43] mentioned, **"**In these reports, it was recorded that 10–15% of hypertensive subjects taking reserpine became depressed. From four to 30 cases of depression were reported in samples of 39–195 subjects, with one or two individuals attempting or completing suicide." and argued those patients already had the earliest medical history of suffering depression. From the recent time, Jain and Murthy [32] also added the "…lack of intellectual support, and interactions, between the scientific community, and within psychiatry in the mid-twentieth century in India…" along with post-partition social disturbances in nations, the superiority of occidental science in psychiatry, as reasons, diluting the sedative medicinal value of *R. serpentina*.

Nevertheless, the nervine property of *R. serpentina* got strongly supported by Wilkins (1954), reporting an overall positive psychological improvement in his patients treated with *R. serpentina* [43]; Davies and Shepherd (1955) mentioned reserpine as an antidepressant [44]. Even from recent times, Douglas Lobay, a practitioner of naturopathic medicine in Kelowna, British Columbia, Canada to his experience

treating hypertension patients (with no history of depression, mental illness, anxiety, congestive cardiac failure, bradycardia, hypoadrenalism) mentioned low doses of *R. serpentina* root powder improved patients' sleep quality [18]. A polyherbal formulation Vedic Calm, containing *R. serpentina* as one of the ingredient plants, improved sleep duration in thiopental-induced sleeping time test [25]. Another south Asian herbal formulation Nidrakar Bati used *R. serpentina* root as one of the vital components that potentiated the pentobarbital-induced sleeping time test in mice [26]. The neurochemical paths to enhance sleep by these formulations are yet to be confirmed, yet their anti-insomniac efficacy positively draws attention towards the sedative potentiality of *R. serpentina*.

In this literature review, we observed that the individual alkaloid or even total alkaloid percentage do not match the very highlighted sedation ability of *R. serpentina*, as mentioned in the primeval documentations and early-late psychopharmacological researches. Therefore, future studies must consider evaluating different phytochemical aspects of *R. serpentina*, shifting focus from monotherapeutic alkaloidal approaches. *R. serpentina* can also produce sedation even without affecting the brain serotonin [45], must be considered as well. Considering these supportive early and now available scientific observations, the future sedative pharmacological works on *R. serpentina* to treat insomnia require to be revised.

7 Future Approaches with *R. serpentina* to Treat Insomnia

The monotherapeutic approaches towards *R. serpentina* gave the root-derived most active alkaloid, reserpine, significant attention in sedative pharmacological researches. Although further studies confirmed that reserpine is a tranquilizer that keeps the body inactive without promoting sleep. Reserpine exerts a tranquilizing effect by depleting the amino acids from its storage in the brain, which acts as nervine [17]. Even the cases of psychiatric depression by reserpine are only visible at higher dosages (> 0.5 mg/day) and are quite manageable by reducing its dosages at or below 0.25 mg/day [18]. Hence, it is clear that reserpine is a tranquilizer, not a sleep-promoter. Therefore, other possible phytochemicals of this plant could get studied in this regard. Scientific studies even mentioned the antipsychotic potential of deserpidine, serpentine, alstonine, and smooth muscle relaxing capability of yohimbine [8, 17, 32]. Jain and Murthy [32] mentioned the antipsychotic potential of alkaloids serpentine and alstonine on glutamate/serotonin receptor complex as new generation targets for antipsychotics. Micronutrients also play a part in the sedative property of plants. Especially, minerals such as Ca, Mg, and trace elements like Fe are evident to play significant roles in managing sound sleep. Ca is associated with the declination of sleep-latency and increase of more restorative sleep. Mg has a profound effect on increasing sleep duration or slow-wave sleep (SWS) or NREM sleep. Fe also acts quite similar to that of Mg by reducing night awakening events with increasing night time total sleep duration [46–48]. It is important to note that *R. serpentina* has already been reported these essential elements with high Ca concentration [8, 49]. Although no study yet correlated the mineral content to promote sleep by this plant. Therefore, micronutrients of *R. serpentina* could also play a part in its anti-insomniac activity. Besides, the traditional use of *R. serpentina* also said its leaves to treat insomnia, yet no pharmacological work to confirm that. Hence, future sedative pharmacological studies on *R. serpentina* could consider studying different sleep-promoting compounds from various plant parts. Plenty of evidence also recorded *R. serpentina* produced better sedation in standardized extract than in mono-compound-based alkaloidal approaches [33, 34]. Accordingly, it is necessary to find such strategies for this herb are suitable or not.

Thus, based on these available scientific data authors, suggest both phytochemical and micronutrient evaluation of standardized extract(s) from various plant parts of *R. serpentina* to find the right combination of components, related pathways to treat insomnia.

8 Side Effects, Toxicology, Drug Interactions, and Therapeutic Safety of *R. serpentina*

The therapeutic uses of *R. serpentina* for hundreds-thousands years in diet and various indigenous medicinal systems across the geographical borders confirm its well-established knowledge on medicinal efficacy. However, today, enhancement of nutraceutical-pharmaceutical uses require more data on the safe applications of their products. As of now, *R. serpentina* got commercially marketed as root powder for dietary consumption, tablets-homeopathic mother tinctures as pharmaceutical products for medicinal uses [50]. But, every individual has a unique medical background. The right dosages of *R. serpentina* therapeutic products and their combinations with other medicines are furthermore essential to know. To manage the severity of side effects and avoid any fatality.

The most common side effects of oral consumption of *R. serpentina* with reserpine as the main constituent are respiratory depression, dyspepsia, stomach ulcer, abdominal pain, vomiting, nausea, anorexia nervosa, bradycardia, arrhythmia, sleepiness, hyporeflexia, nephrotoxicity, galactorrhea, sexual inactivity [17, 18, 50, 51]. Even accidental ingestion of anti-hypertensive medicine containing reserpine by nine months old male dog reported *R. serpentina* toxicities like the human counterpart [52]. Mossoba et al. [51] reported the *R. serpentina* root methanolic extracts, containing major

phytochemicals ajmaline, serpentine, reserpine, showing dose-dependent (200 µg/ml and above) renal proximal tubule injury at in vitro HK-2 cell line screening. A few rare cases of asthma and slight edema got observed from *Rauwolfia* use. The increased reserpine dosages produced despondency and gradually developed seizures, extrapyramidal, Parkinson-like signs, which could continue with long-term use [17, 18]. The recent studies ahead are focused on the ability of the plant extracts towards causing hypolocomotion [17].

R. serpentina has possibilities of interactions with antipsychotic drugs, stimulant drugs, tricyclic antidepressants, monoamine oxidase inhibitors, diuretics, cardiac glycosides, alcohol. The herb even has chances of interactions with catecholamine, norepinephrine, corticosteroid, thyroxine, prolactin, gastric acid, bilirubin, vanillylmandelic acid lab tests [18].

The commonly reported toxicities of reserpine use by patients, even the mental depression, are significantly manageable when administered at lower doses. Reserpine therapy did not show any oncogenic effects. Despite no reports of fetal abnormalities due to reserpine use in pregnant women, its safety in pregnant ladies still needs to be verified [18].

The standardization of *R. serpentina* therapeutic products, drugs, and the knowledge on their interactions with other food products, medicines can positively maximize its therapeutic effectiveness for individuals tolerable to its use. In this regard, naturopathic physician, Lobay [18] even mentioned the preference of using encapsulated *R. serpentina* root powder combining with hawthorn, some other forms of Mg at low doses for effective treatment of hypertension. The side effects were mainly related to nasal congestion, diarrhea in patients excluded from mental depression, cardiovascular diseases, Addison's disease. Such use even got reported to improve the sleep quality of patients. It also combined well with diuretics, angiotensin-converting-enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARBs) with cautious usage along Beta-blockers, Ca channel blockers.

9 Conclusions

The importance of sound sleep in today's life when lifestyle disorders are exponentially increasing day by day is undeniable. The declination of sleep hours by 2 h every night for the past 50 years [53] is an alarm to draw our attention towards including insomnia as a serious health issue of this time. Seeking a safe remedy for its treatment is a must need. The use of herbal extracts in food products to enhance their therapeutic benefits is already a well-known methodology. The chemical profile of *R. serpentina* has already got researched well. However, further studies on the standardized extract(s) of different *R. serpentina* plant parts are needed to find the potential biocompounds for insomnia treatment. In this regard, the involvement of more efficient research techniques, solvent systems would benefit the identification of potential phytoconstituents. Subsequently, it would also help in knowing their molecular mechanisms of actions, right means of delivery. Studies are also required to understand the bioavailability of efficient biocompounds in adequate concentrations for achieving the target mechanisms upon human administration. Thus, the plant *R. serpentina* as a potential nutraceutical, phytopharmaceutical source to treat insomnia must consider all possible aspects and related technical necessities. Syncing traditional therapeutic knowledge with modern nutraceutical-pharmaceutical science to develop health-giving food products, drugs treating different health disorders is very much in demand for time.

Rauwolfia serpentina is a popular herb for thousands of years, crossing geographical barriers. The consumption of its root and root-powder with tea, milk along a daily diet for needed individuals is a convenient way to deliver its various health benefits of the nutrient-rich profile, especially in improving sleep. The dietary, nutraceutical, therapeutic advantages of this herb would contribute significantly to finding a holistic approach for treating insomnia.

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