

A Review of the Ethnopharmacology, Phytochemistry and Pharmacology of *Rauwolfia tetraphylla*

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Abstract:- Human civilization was encountered by many insults in the form of diseases since the day of evolution. In ancient times, natural products were used as the main source of remedies to overcome the aforesaid situation. The availability of growing body of literature on the medicinal properties of the plants belonging to the family *Apocyanaceae* is grabbing attention towards its further research. *Rauwolfia tetraphylla* is one of the plant of this family having many therapeutic benefits holds an important position in Indian traditional system of medicine. The plant commonly known as “Devil-pepper” widely used among south Indian tribes due to their ethnobotanical significance. Hence, present article reviews about updated information on various ethnopharmacological activities of *R. tetraphylla* owing to their medicinal importance.

Keywords:- *Rauwolfia Tetraphylla*, Ethnopharmacological, Antioxidant Activity, Anticancer Activity, Reserpine

I. INTRODUCTION

Products from natural origin are estimable sources of novel structures for the ambition of drug development. Identification of plant products for their therapeutic application continues to be a growing interest from ancient time to till now [1]. Use of herbal medication is known as

alternative therapy against several diseases having plentiful advantages over synthetic drugs like decreased adverse effects, cost effective, easily accessible and improved compatibility [2].

Rauwolfia tetraphylla (Synonym- *Rauwolfia canescens*, *Rauwolfia heterophylla*, *Rauwolfia hirsuta*) commonly known as Devil pepper, Be still tree, milkbush, wild snake root, American serpentwood in english, Barachandrika, chandrabhaga in hindi, pampukaalaachchedi in tamil, pampumkolli, Kattamalpori in malayalam, Papataku in telugu, bar chandrika, gandhankuli in bengali, patalagarudi in odia and sarpanasini in sanskrit belongs to family Apocyanaceae is a species facing extinction being native to West Indies and now cultivated commercially in many countries such as India, Pakistan, Sri Lanka, Bangladesh, Nepal, and Myanmar and often cultivated as garden plants. Distribution of the plant in India includes several states such as West Bengal, Karnataka, Odisha, Bihar, Andhra Pradesh, Tamilnadu and Kerala. *R. tetraphylla* having illustrious therapeutic potential described in ancient literature triggers the widely practice in traditional system of medicine. The plant contains alkaloids such as reserpine, rauvolschine, ajmalicine, ajmaline, canescine, pseudoyohimbine, and yohimbine. *R. tetraphylla* contains a number of chemicals and several studies carried out on the plant have revealed various pharmacological activities [3-15].



Fig 1:- A- Fruiting stem, B- Whole plant of *Rauwolfia tetraphylla*

II. BOTANICAL CHARACTERIZATION

R. tetraphylla (Figure 1) synonym *R. canescens* is a pubescent, ever-green shrub with woody stem and reaching a height of 4-6 feet. Leaves are unequal, 5-9 x 3-4 cm, elliptic-ovate, acute at apex, pubescent and usually found in whorls of 4. Flowers are cream colored, about 5mm across, found in terminal corymbose cymes. Calyx lobes are short, ciliate and round. Corolla is white in color, approximately 3mm long, lobes and tubes are short. Drupes are ovoid, 2-seeded, 5-10mm across, smooth, jointed to the top, purple when ripe. Flowering occurs throughout the year [10,16,17].

III. TRADITIONAL USES

Plants are an integral component of traditional medicine. Throughout world, whole plants or certain parts of the plants have been widely used to cure several diseases and disorders either in single or polyherbal formulations. Plant based medicines are cheaper, usually devoid of side effects (that are associated with the use of modern medicines like antibiotics and anticancer agents), confer multifold beneficial effects and are locally available [18-26].

The plant *R. tetraphylla* possesses a range of ethnobotanical applications in various countries across the world as indicated by several studies. The latex from the plant is reported to be cathartic, emetic, and expectorant besides its use in the treatment of dropsy. The juice prepared from the fruit is used as a substitute for ink. Leaf juice is used in eye troubles and decoction prepared from leaves is used for toothache. Root is reported to have antihypertensive, sedative, hypnotic effect. Paste prepared from roots is useful in stomach pain and snake bite [5,27,28,29].

R. tetraphylla is one among the various ethnomedicinal plants being used by amerindian communities of Caribbean basin [30]. The roots of the plant are used in nervous disorders and insomnia in Gopalganj district of Bihar, India [31]. Whole plant as well as different parts such as root, fruit and leaves of *R. tetraphylla* are widely used in traditional medicine (in various forms such as paste, powder, decoction and juice), particularly snake bite. In Bagota, Colombia, the plant is used as an antidote and for blood pressure [32].

The leaves of *R. tetraphylla* are used ethnomedicinally by Peasant community of San Jacinto, Northern Colombia to relieve tension [33]. Roots are used in high blood pressure and mental disorders in Coimbatore district, Tamilnadu, India [34]. The leaves and roots are used against nervous disorders, anxiety, excitement, cough and fever in Barpeta district, Assam, India [35]. Roots are used for treating nervous disorders in Villupuram district, Tamil Nadu, India [36].

The Nyishi tribe of Arunachal Pradesh, India uses roots of the plants as anthelmintic, antidote to snake bite and to cure vomiting, insomnia, insanity, blood pressure, malaria [37]. The leaves are used traditionally for treating eczema in Tamil Nadu, India [38]. The leaves and fruits are used against snake bite in Thiruvannamalai district, Tamil Nadu, India [39]. In Odisha, India, the leaves and roots are used to treat stomachache [40]. Roots and whole plant of *R. tetraphylla* are used to increase uterine contraction, as anthelmintic and to treat skin diseases and hypertension in South West Bengal, India [41]. In Midnapore district, West Bengal, India, the roots are used as sedative, hypnotic and for hypertension. Leaf juice is used for the purpose of removal of opacities of cornea of eyes [42]. The whole plant and root or *R. tetraphylla* are used in the treatment of impotency and to increase libido in Greater Naogaon district, Bangladesh [43]. The plant is used as an antidote to poison in Rajshahi district, Bangladesh [44]. In Chuadanga and Jhenaidah districts of Bangladesh, different parts i.e. leaf, stem and root are used in snake bite and as snake repellent [45]. In Vizianagaram district of Andhra Pradesh, India the plant is used to treat blood pressure [46]. In Chittagong, Bangladesh, the leaves and roots are used against high blood pressure [47]. Various parts such as seed, leaf and root of *R. tetraphylla* are used to treat snake bite in Kancheepuram district, Tamil Nadu, India [48]. The roots are used to treat mental disorders and high blood pressure in Erode district, Tamil Nadu, India [49].

IV. PHYTOCHEMISTRY

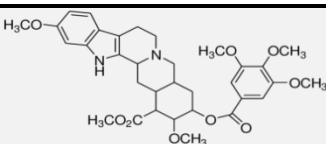
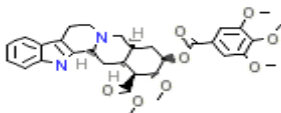
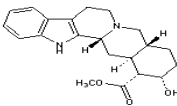
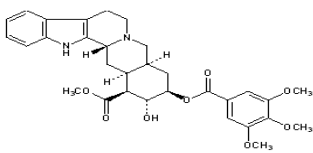
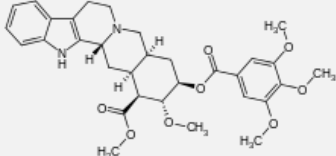
Plants produce a range of chemicals that can be divided into two categories viz. primary and secondary metabolites. These chemicals are known as phytochemicals and most of the secondary metabolites (with complex chemical composition), for e.g., alkaloids, terpenes and polyphenolic compounds, exert multifold effects on the health of human beings besides conferring resistance to plants that produce

them against insects, pathogens and herbivores. Secondary metabolites in plants are restricted in distribution within the plant kingdom i.e. some metabolites are present in only one plant species or in a related group of species. Metabolic pathways such as shikimic acid pathway, malonic acid pathway and mevalonic acid pathway are responsible for synthesis of secondary metabolites in plants [50-58]. Due to advancements in chromatographic and spectral methods, a vast number of plant secondary metabolites have been identified and their structures are proposed [59-65].

R. tetraphylla is shown to contain a myriad of secondary metabolites, particularly alkaloids. Reserpine is an important alkaloid found in *R. tetraphylla*. With the help of chromatographic and spectral analyses, many secondary compounds have been isolated from different parts of *R. tetraphylla* and their structures have been elucidated. Klohs et al. [66] isolated reserpine from roots of *R. tetraphylla*. Stoll and Hofmann [67] isolated two alkaloids canescine and pseudoyohimbine from the roots of *R. tetraphylla*. Two ester alkaloids, named as raunescine and isoraunescine, have been isolated from *R. tetraphylla* [68]. An alkaloid designated as Recanescine (that lack the methoxyl group in the C-II position of reserpine) with sedative and hypotensive property was isolated from *R. tetraphylla* [69,70]. An alkaloid designated as heterophyllin was isolated from roots of *R. tetraphylla* [71]. Raunescine (renamed as canembine), an alkaloid, was isolated from roots of *R. tetraphylla* [72]. An alkaloid pseudoreserpine possessing hypotensive and sedative activity

was isolated from the root of *R. tetraphylla* [73]. Djerassi et al. [74] elucidated the structures of two alkaloids from root of *R. tetraphylla* i.e. tetraphylline and tetraphyllicine. Belikov [75] isolated alkaloids namely ajmaline, ajmalieine, aricine, reserpiline, α -yohimbine, sarpagine and reserpine from roots and epigeal parts of *R. tetraphylla*.

A new sarpagine-type alkaloid, named as N (α)-Demethylacedine, was isolated from stem bark of *R. tetraphylla* [76]. By high-performance thin-layer chromatography (HPTLC) analysis, reserpine and ajmalicine were identified in root of *R. tetraphylla* [77]. Quercetin was identified in the leaves of *R. tetraphylla* by HPTLC analysis [78]. Alkaloids 10-methoxytetrahydroalstonine, isoreserpiline, α -yohimbine, reserpiline was isolated from chloroform fraction of *R. tetraphylla* leaves by pH-zone-refining fast centrifugal partition chromatography [79]. Six indole alkaloids viz. isoreserpiline, 10-methoxytetrahydroalstonine, 11-demethoxyreserpiline, 10-demethoxyreserpiline, α -yohimbine and reserpiline have been identified from leaves of *R. tetraphylla* [80]. A new labdane diterpene characterized as 3 β -hydroxy-labda-8(17),13(14)-dien-12(15)-olide (Figure 2) was isolated from air-dried stems and branches of *R. tetraphylla* [81]. The study by Panda et al. [82] revealed a varying concentration of reserpine in different parts of *R. tetraphylla*. Root was shown to contain high concentration of reserpine followed by stem and leaf.

PHYTOCONSTITUENT	STRUCTURE	MEDICINAL USES	REFERENCE
RESERPINE		Sedative and hypotensive activity	Klohs et al., 1957
CANESCINE		Antihypertensive agent	Stoll and Hofmann et al., 1955
PSEUDYOYOHIMBINE		Antihypertensive, Treatment of prostate and aphrodisiac activity	Stoll and Hofmann et al., 1955
RAUNESCINE		Tranquilizing activity	Hosansky and Smith et al., 1955
RECANESCINE		Antihypertensive and sedative	Slater et al., 1955 Neuss et al., 1955

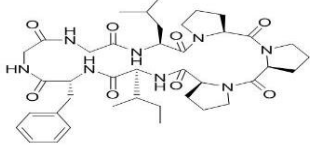
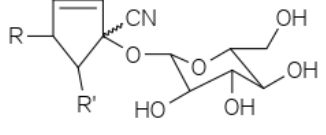
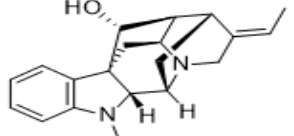
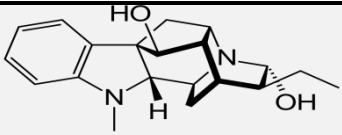
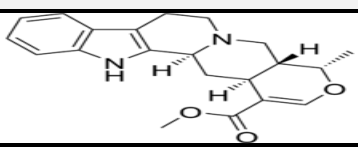
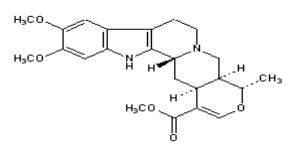
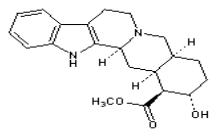
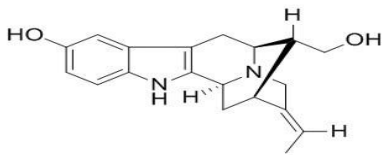
HETEROPHYLLIN		Antiplasmodial, antitrypanosomal, and cytotoxic activities	Hochstein et al., 1955
TETRAPHYLLINE		Antianxiety activity	Djerassi et al., 1957
TETRAPHYLLICINE		Central tranquilizing and prolonged hypotensive activity	Djerassi et al., 1957
AJMALINE		Antiarrhythmic activity	Belikov et al., 1969
AJMALICINE		Antihypertensive activity	Belikov et al., 1969
RESERPILINE		Hypotensive and antimicrobial activity	Belikov et al., 1969
A-YOHIMBINE		Increase libido and antianxiety activity	Belikov et al., 1969
SARPAGINE		Antiarrhythmic, antihypertensive and antimicrobial activity	Martinez et al., 1989

Table 1:- Phytoconstituents and their uses of *R. Tetraphylla*

V. PHARMACOLOGICAL ACTIVITIES

Due to the presence of diversified phytoconstituents (most importantly alkaloids) *R. tetraphylla* acquires several distinctive pharmacological properties. Numerous reported activities are listed below.

➤ Antimicrobial Activity:

A study was conducted on petroleum ether, ethyl acetate and chloroform extracts of dry fruits of the plant for determining antibacterial activity using agar diffusion method against eight bacterial species. The results indicated that the dry fruit extracts exhibited potential broad spectrum antibacterial activity [83].

The *In-vitro* antibacterial activity of ethanolic extracts of *R. tetraphylla* was assessed by disc diffusion method against pathogenic bacteria. The results indicated that inhibitory activity was comparable with standard antibiotic (ciprofloxacin) [84]. *R. tetraphylla* calli extract and leaves were tested for *In-vitro* antimicrobial activity using broth dilution method against pathogenic fungi and bacteria. The calli extract and leaves were extracted by petroleum ether, chloroform, benzene, methanol and absolute alcohol. The results indicated that the methanolic extract exhibited MIC of 0.5 to 100 mg/ml against pathogenic fungi and against bacterial pathogens have shown MIC of about 0.25 to 100 mg/ml [85]. The antimicrobial activity of *R. tetraphylla* ethanolic extract was determined against various fungi and bacteria. It was observed that the extract exhibited good

antimicrobial activity against *A.niger*, *E.aerogenes* and *E.coli* [86].

➤ *Anti-inflammatory Activity*

Anti-inflammatory activity was studied by orally administering various bark extracts of *R. tetraphylla* root using Carrageenan induced acute inflammation in rats and results have indicated good activity [87].

➤ *Anticancer Activity*

A study reported isolation and structure elucidation of 3 β -hydroxy-labda-8(17),13(14)-dien-12(15)-olide, new labdane diterpene. It was tested for anticancer and antitumor activity against breast cancer cell lines such as Michigan Cancer Foundation-7 (MCF-7), basal breast cancer cell line MDA-MB-468 and claudin-low cell line MDA-MB-231, human cancer cell lines such as KB cells a sub line of the ubiquitous KERATIN-forming tumor cell line HeLa, Human epithelial type 2 (Hep-2) cells, A549 and leukemic T cells. The labdane diterpene were found to show significant activity [88].

➤ *Anti-psychotic Activity*

The methanolic extracts of *R.tetraphylla* leaves were prepared and assessed for antipsychotic activity using female Swiss albino mice [89]. The antipsychotic activity was determined by amphetamine induced hyperactive mouse model in-vivo and against serotogenic (5-HT_{2A}) and dopaminergic (DA-D₂) receptors *in-vitro* [90]. Further safety and toxicity evaluation studies of *R. tetraphylla* leaves methanolic extracts on female Swiss albino mice at different doses (10, 100, 300 and 2000 mg/kg) and results indicated that methanolic extract is non toxic. The isolated alkaloids might serve as a promising lead structure in drug development for treating psychotic conditions in human [91].

➤ *Antioxidant Activity*

The antioxidant potential of five different species of Rauwolfia leaves (*R. serpentine*, *R. densiflora*, *R. tetraphylla*, *R. beddomei* and *R. micrantha*) from Western Ghats was investigated. The antioxidant activity was assessed using various in-vitro models like reducing power, 1, 1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity, total antioxidant capacity, and superoxide anion scavenging activity at different concentrations. *R. tetraphylla* have shown the highest concentration of Lycopene and β -carotene [92].

➤ *Antihypertensive Activity*

The roots were found to be useful in the treatment of cardiovascular diseases and hypertension [93].

➤ *Miscellaneous Activities*

The extract of *R. tetraphylla leaves* is useful in the treatment of diarrhoea, dysentery, cholera, eye disease, intestinal disorders and fever [94]. The decoction of the plant bark is useful in treatment of skin disease, chronic refractory and for destroying parasites whereas, the plant extract when mixed with castor oil is used for treatment of refractory ailments [95]. The roots are recommended to be used in resolving difficult cases of child birth as they induce uterine contraction [96].

VI. CONCLUSION

The traditional herbal medicine is considered as a prominent health care system and used for primary treatment in the developing countries. *R. tetraphylla* chemically reported to possess diverse group of bioactive compounds like alkaloids, flavonoids, phenols, tannins, terpenes and triterpenes. The plant has been used for therapy of the various ailments and the presence of above bioactive compounds in the plant can be attributed to their medicinal values. The various plant part extracts have been scientifically proven to possess the pharmacological activities namely – Antimicrobial, anti-inflammatory, antipsychotic, anticancer, antihypertensive, treatment of cholera, intestinal disorders, diarrhoea, dysentery, eye disease, fever and skin diseases. Hence, further research should be initiated in the isolation, characterization and pharmacological screening of isolated pure bioactive components of *R. tetraphylla*.

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