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Phytochemical, pharmacological and therapeutic aspects of Rauwolfia serpentina L. Benth. ex-Kurz

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ABSTRACT

Various parts of this plant, especially the root and rhizome, have been used since ancient times in the treatment of many diseases such as hypertension, mental disorders, epilepsy, stroke, anxiety, insomnia, schizophrenia and insanity. More than 50 alkaloids are found in this plant, which mainly fall in the monoterpenoid indole alkaloid class. These major alkaloids include compounds such as reserpine, serpentine, ajmaline, ajmalicine, deserpidine, resinamine and yohimbine, which are considered extremely active and useful from the medicinal point of view. Additionally, the plant contains bioactive compounds such as alkaloids, carbohydrates, flavonoids, glycosides, tannins, phenols, saponins, and sterols, which make it have anti-inflammatory, antimicrobial, antifungal, antidiuretic, and anticholinergic properties. According to the World Health Organization, even today about 75–80% of the world's population depends on herbal medicines for primary health care. This is mainly due to the cultural acceptability of these medicines, natural availability, biocompatibility with the human body, and fewer side effects.

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

Introduction

Today's world is facing the challenge of a rapidly growing population, which has resulted in the difficulty in fulfilling the basic needs of food, shelter and clothing. In addition, millions of people suffer from a variety of diseases, which has led to a significant increase in the demand for medicines. However, many of the currently available medicines are expensive, have limited efficacy and sometimes toxic effects, which further complicate the health of patients. In such a situation, it has become necessary to look at naturally available alternative therapies and herbal remedies. These medicines are not only accessible and affordable, but also have minimal or no side effects. By combining traditional knowledge and modern research, we can develop safer, more effective and sustainable health solutions that will prove helpful in the long-term well-being of humanity. More than 80% of the global population is still dependent on herbal medicines for primary health care, mainly due to their curative effects, accessibility and fewer side effects. Of the thousands of plants used in traditional medicine, scientific research has confirmed hypoglycaemic activity (ability to lower blood sugar) in more than 800 plant species. (1) Various indigenous medicinal plants have been used in India since ancient times for the treatment of diseases. Indian traditional systems of medicine are based on the belief that nature itself is the perfect healing system. Nature has provided mankind with a rich storehouse of essential elements for the prevention of every disease and disorder of life. (74) Medicinal plants contain various bioactive chemical compounds that are responsible for their medicinal properties. These include alkaloids, glycosides, volatile oils, fatty acids, resins, gums and tannins. Elements such as hydrogen, carbon and nitrogen are also structurally important in them. These compounds exhibit anti-inflammatory, antibacterial, antidiabetic, analgesic and immune-enhancing properties, making them helpful in the treatment of various diseases.(2-4) According to the World Health Organization (WHO), any plant or any part thereof is considered as a drug if it contains a substance that can be used therapeutically

or which can be used as a raw material for drug manufacture.(5) Today, around 300 medicinal and aromatic plant species are widely used in the pharmaceutical, food, cosmetic and perfume industries worldwide. These plants play an important role as natural ingredients in various products. (3) One of the medicinally important plants used to obtain medicines is Rauwolfia serpentina.

Rauwolfia serpentina (Rauwolfia serpentina L. Benth. ex-Kurz) is an evergreen, perennial, woody shrub with a maximum height of up to 60 cm. This plant belongs to the Apocynaceae family and has a tuberous root with light brown cork. Its leaves are oval, lanceolate or obovate in shape in whorls of three. It is mainly found in tropical and subtropical regions and many species are found in India, Bangladesh, Sri Lanka, Burma and Indonesia. It is commonly known by names like Sarpagandha, Chandrabhaga, Chhotachand, Chandrika and Harakaya. Its roots, leaves and sap are very important medicinally. It contains large amount of secondary metabolites like indole alkaloids, which are mainly stored in the roots and rhizomes. In the Ayurvedic system of medicine, the roots of Rauwolfia serpentina are used to treat hypertension, insomnia, mental agitation, epilepsy, anxiety, schizophrenia, and other mental disorders. In Siddha medicine it is used for the treatment of gynaecological problems such as headache, dizziness, amenorrhea, oligomenorrhea and dysmenorrhea. According to Rajendran and Agarwal (2007), the tribal communities of Virudhunagar district of Tamil Nadu also use its fruits and seeds for medicinal and ethnobotanical purposes. (10) This plant holds a very important place in traditional medicine and is also useful for modern drug research.

Rauwolfia serpentina is attracting the attention of scientists due to its medicinal properties and extensive phytochemical analysis is being done on it. It is used as anthelmintic, antihypertensive, and antidote for snake and poisonous insect bites. Rauwolfia serpentina is also used in the treatment of diarrhea, dysentery, cholera, fever, corneal opacity, central epilepsy and ecbolic actions (inducing uterine contractions).(6-11) The alkaloids present in Rauwolfia serpentina are responsible for its important medicinal properties, which help in the treatment of various circulatory disorders.(12) The root juice or extract is used to treat liver and stomach pain, gastrointestinal disorders and to remove intestinal worms in children.(13-15) Mao et al. (2009) reported Rauwolfia serpentina under the ethnobotanical wealth of North East India. The plant is also used by local people of the Eastern Ghats, Uttar Pradesh, Karnataka and Bangladesh to treat snake bites. (16,17) The roots and leaf buds are ground with milk to make a paste, which is applied externally on the affected area. This traditional treatment is believed to be helpful in reducing the effects of snake venom. Other diseases such as pneumonia, malaria, body pain, eczema, burns, menstrual disorders, itching, skin cancer, asthma, respiratory problems, eye inflammation, spleen diseases and fever can also be cured using R. serpentina. (14,15,19-24)

The present review work highlights several medicinal properties of Rauwolfia serpentina, which include antifungal, anti-inflammatory, antioxidant (reduces oxidative stress), antiproliferative (inhibits cell growth), anticancer, antidiuretic (reduces urinary secretions), ant fibrillar (reduces fever), antiarrhythmic (controls irregular heartbeats), anticholinergic (blocks nerve signals), antidysentery (prevents diarrhea), antidiarrheal (reduces diarrhea), antihypotensive (reduces blood pressure), anticontractile (inhibits muscle contractions), sympathomimetic (activates sympathetic nervous system), tranquilizing agent. This plant is extremely important in pharmacology due to its multifaceted biological activities.

PHYTOCHEMICAL CONSTITUENTS

Rauwolfia serpentina has been an important subject of scientific research for decades. Its medicinal importance is attributed to its diverse phytochemical compounds or secondary metabolites. The main phytochemical components include alkaloids, phenols, tannins, flavonoids. Due to the presence of these compounds, Rauwolfia serpentina is recognized as an important medicinal plant in both traditional and modern systems of medicine.

Alkaloids

Alkaloids are an important group of organic compounds containing a heterocyclic nitrogen ring. These compounds are produced primarily by plants and are estimated to be produced by about 10% of plant species as secondary metabolites. Their main function is to protect against herbivores and pathogens. The total alkaloids in the root of Rauwolfia serpentina range from 0.7% to 3.0%, with the major active component being reserpine (about 0.1%), a potent indole alkaloid. This alkaloid lowers blood pressure by acting on the central nervous system, making it more

effective than other antihypertensive drugs. Based on structure, alkaloids are divided into three main classes. 1. Weakly basic indole alkaloids 2. Alkaloids with intermediate basicity 3. Strong anhydronium base alkaloids |38 The various alkaloids identified in Rauwolfia (Figure 1) include ajmaline, ajmalimine, ajmalicine, deserpidine, indobine, indobinine, reserpine, reserpilin, resinamine, resinamidine, serpentine, serpentine and yohimbine etc. Among all these, resperine is the main alkaloid which shows a large number of clinical applications. (27,28) Along with resperine, yohimbine, serpentine, deserpidine, ajmalicine and ajmaline are used to treat hypertension and breast cancer.

Reserpine

Reserpine is a pure crystalline single alkaloid, first isolated in 1952 from the roots of Rauwolfia serpentina. It is a weak tertiary base and is found in the oleoresin fraction of the roots. And is useful in the treatment of hypertension, cardiovascular diseases and neurological diseases. (30,31) The antihypertensive (blood pressure lowering) properties of the roots of Rauwolfia serpentina are mainly attributed to the alkaloid called reserpine.

The chemical form of reserpine is 3,4,5-trimethyl benzoic acid ester of reserpic acid, which is an indole derivative of the 18-hydroxy yohimbine type. This compound acts on the central nervous system, thereby calming the nerves and effectively controlling blood pressure. Therefore, reserpine is considered to be the main active component of Rauwolfia's medicinal power and plays an important role in the treatment of cardiovascular and mental diseases. It interferes with the function of the autonomic nervous system by reducing transmitter substances from adrenergic neurons and possibly activating the central parasympathetic system. (32-33) These substances are mostly involved in controlling heart rate, cardiac contraction and peripheral resistance. Reserpine also has a significant effect on 5-hydroxytryptamine (5-HT or serotonin). It releases 5-HT from all tissues where it is normally stored, such as the brain, intestines and blood platelets. As a result, serotonin levels in the body decrease and its metabolism increases. This change is reflected as an increase in the amount of 5-HT metabolites (such as 5-HIAA) in the urine, which is also considered an indicator of the biological activity of reserpine. Due to this effect, reserpine is used not only for hypertension but also for some mental disorders

Ajmaline

This compound, called ajmaline, was first isolated from the roots of Rauwolfia serpentina in 1931 by Salimuzzaman Siddiqui. It was named in honor of Hakim Ajmal Khan, a famous Unani physician of South Asia. (34,35) Ajmaline is an important class I antiarrhythmic agent, used in the diagnosis and distinction between subtypes of Brugada syndrome (an inherited heart disorder). [36] These agents are mainly classified into four major groups based on their mechanism of action, i.e. sodium channel blockade, beta-adrenergic blockade, repolarization prolongation and calcium channel blockade. It acts primarily as a sodium channel blocker. Its effect is immediately evident when given intravenously (intramuscular or intravenous), making it suitable for diagnostic purposes. Administration of Rauwolfia alkaloids to patients with this type of arrhythmia, known as the "ajmaline test", (37,38) shows that ajmaline stimulates the respiratory system and intestinal activity. Its effects on systemic and pulmonary blood pressure are similar to those of serpentine.28]

Ajmalicine

Ajmalicine is an important alkaloid used in the treatment of circulatory diseases. It is particularly helpful in improving blood flow to the brain. Ajmalicine prevents stroke by affecting the smooth muscle function. It also helps in lowering blood pressure. (26) Annually about 3500 kg of ajmalicine is isolated from Rauwolfia and Catharanthus species, which are used by the pharmaceutical industry. Synthesis of ajmalicine begins by the iridodial and iridotrial pathway from geraniol. Geraniol is synthesized as loganin, which is converted to secologanin after oxidation. This synthesis aids in the formation of the corynanth type nucleus of tryptamine, resulting in the formation of ajmalicine. (27,39) Ajmalicine is derived from tryptophan, which is converted to tryptamine via secologanin, strictosidine, and cathanamine. The conversion of cathenamine to ajmalicine is facilitated by the enzymes NADPH and tryptophan decarboxylase (TDC). Decarboxylase may be the enzyme playing a key role in the synthesis of ajmalicine in Rauwolfia.

Serpentine

Serpentine, a topoisomerase type II inhibitor, has antipsychotic properties. (40,41) The conversion of ajmalicine to serpentine occurs by an oxidation process involving the enzyme peroxidase (PER). This enzyme catalyzes the bisindole alkaloid located in the vacuole. This reaction results in the oxidation of ajmalicine to form serpentine. [27]

Rescinnamine

Resinamine is a purified ester alkaloid obtained from the alseroxylon fraction of Rauwolfia species. It is chemically related to reserpine and has similar medicinal uses. It was used as an antihypertensive agent in the 1950s. It is used in the treatment of hypertension, but is a less potent alkaloid than reserpine. It is not as effective in lowering high blood pressure. (42) Resinamine inhibits the angiotensin converting enzyme, peptidyl dipeptidase, which catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II, which stimulates aldosterone secretion by the adrenal cortex. It first inhibits angiotensin converting enzyme (ACE) and then prevents the conversion of angiotensin I to angiotensin II. Inhibition of ACE results in a decrease in plasma angiotensin II. Since angiotensin II is a vasoconstrictor and a negative-feedback mediator for renin activity, its decreased concentrations result in decreased blood pressure and stimulation of the baroreceptor reflex mechanism, ultimately resulting in decreased vasopressor activity and aldosterone secretion.43

Deserpidine

Deserpine is an ester alkaloid derived from the Rauwolfia plant. It differs from reserpine only by the absence of a methoxy group at C-11. It can also be synthesized from reserpine. The major effects of deserpine are antipsychotic and antihypertensive. It regulates nerve impulses, thereby helping to lower blood pressure. It is also helpful in calming psychological disorders. Deserpine binds to angiotensin-converting enzyme (ACE) and competitively binds with angiotensin I. This results in inhibition of the formation of angiotensin II, which is helpful in lowering blood pressure. (44)

Yohimbine

Yohimbine is a major alkaloid derived from Rauwolfia species and some other plants. It is used as a selective alpha-adrenergic antagonist or alpha-blocker in blood vessels for the treatment of erectile dysfunction. It dilates blood vessels and increases blood flow to the penis, which helps improve erectile function. (45) Yohimbine is a major alkaloid that antagonizes α2A-adrenergic receptors. It acts on the receptors to relax smooth muscles, thereby dilating blood vessels and lowering blood pressure. It has also been identified as a potential treatment for diabetes in animal and human models, as it may affect insulin secretion. Additionally, yohimbine also helps in dilation of the pupils of the eye (mydriasis) by increasing the activity of certain neurotransmitters. (46)

Phenols

Phenols are secondary plant metabolites found mainly in herbs, shrubs, vegetables, and trees. (47,48) Their presence protects plants from insects and pathogens, as they are toxic to their growth. (73) Rauwolfia serpentina contains high amounts of polyphenolic compounds, which show it to have antidiabetic, hypolipidemic properties. (24,49) In medicine, it is used as an expectorant and emulsifying agent. The presence of phenolic compounds indicates that it can be used as an anti-microbial agent.

Tannins

The tannins found in Rauwolfia serpentina exhibit potent antioxidant activity due to the presence of compounds such as gallic acid and digallic acid. (50) The astringent properties of tannins help speed wound healing and inflamed mucous membranes. Due to these properties, traditional healers in southeastern India use this plant to treat various skin diseases, wounds, burns, and inflammatory disorders. (25,51) Additionally, tannin-rich plants are also used in traditional medicines to stop bleeding, reduce diarrhea, and protect against infections.

Flavonoids

The flavonoids found in Rauwolfia serpentina are powerful water-soluble antioxidants that prevent oxidative cell damage by neutralizing free radicals in the body. This property makes them effective as anticancer agents. (52,53) Flavonoids act in the intestinal tract and help reduce the risk of heart disease. Their anti-inflammatory properties make them useful in inflammatory diseases such as arthritis, lung inflammation, and skin disorders. For this reason, flavonoids are used as important components in herbal medicine for the treatment of various diseases. (4,54)

Saponins

Saponins are glycosides of the triterpene and sterol classes and are found in more than 70 plant families. Their properties include water foaming, hemolytic activity, ability to bind to cholesterol, and bitterness. (55) Saponins have the property of coagulating red blood cells. The high content of saponins in Rauwolfia serpentina is useful in stopping bleeding and wound healing. (25)

Mineral composition

Rauwolfia contains many macro and micro-nutrients, the most important of which is calcium.[51] The high calcium content of R. serpentina helps in stopping bleeding and healing wounds, as calcium aids in blood clotting. Additionally, the plant is low in sodium, which is beneficial for individuals with high blood pressure, as high sodium intake increases blood pressure.[56] Also, the presence of zinc may be helpful in diabetes management, as zinc plays an important role in improving problems associated with insulin deficiency. Rauwolfia serpentina is an important herb, known not only for its various bioactive compounds but also as an excellent source of nutrients. The plant contains high amounts of essential vitamins such as ascorbic acid (vitamin C), riboflavin (vitamin B2), thiamine (vitamin B1), and niacin (vitamin B3).[57]

Ascorbic acid plays an important role in the normal functions of the body and especially in the wound healing process. This vitamin is essential in the synthesis of collagen, which is essential for the formation of intercellular substances such as bone matrix, tooth dentin, and other connective tissues. Ascorbic acid deficiency disrupts the normal formation of these tissues, slowing wound healing and leading to various tissue pathologies.[54]

The rich nutrient profile of Rauwolfia serpentina gives it special importance in herbal medicine. The plant is a rich source of phytochemicals, minerals, and vitamins, making it a potential medicinal source for the treatment of many diseases. The nutrients and bioactive compounds found in it help strengthen the body's immune system, improve metabolism, and treat a variety of diseases, such as hypertension, diabetes, and circulatory disorders. [4,25]

Moreover, various extracts of this plant are used in both traditional and modern systems of medicine, ensuring that Rauwolfia serpentina is an important herb not only for its medicinal properties but also from a nutritional point of view. The presence of vitamins and phytochemicals in this plant makes it helpful in improving overall health, indicating its growing importance in the field of herbal medicine.

R. serpentina in pharmacology

Rauwolfia serpentina is extremely important in the medicinal world due to the various alkaloids found in the oleoresin fraction of the roots. Its alkaloids have proven useful in treating diseases such as heart disease, hypertension, arrhythmias, mental diseases, breast cancer, and human promyelocytic leukemia. [23,29,58-63]

Reserpine, its major alkaloid, affects the concentration of amino acids and hormones in the brain. It alters the levels of glycogen, acetylcholine, GABA, nucleic acids, and anti-diuretic hormone. The effects of reserpine include respiratory inhibition, muscle excitability, myosis, pupillary dilatation, temperature control, and increase in gastric acidity.[4]

The extract of R. serpentina in the Unani formulation Pitkriya capsule is used for various therapeutic actions such as sedative, diuretic, nerve calming, anesthetic, etc. Its pharmacological activities include anticholinergic, hypotensive, anticontractile, relaxant, hyperthermic, antidiuretic, sympathomimetic, hypnotic, vasodilator, antifungal, and anti-arrhythmic properties. [23,64,65] Major medicinal properties of Rauwolfia: 1. Action on vasomotor center: Lowers blood pressure and increases vasodilation. 2. Depressant effect on brain: Calms the nervous system. 3. Sedative effect on gastric mucosa: Stimulates intestinal plain muscles. 4. Stimulates bronchial muscles.[7]

R. serpentina as a medicinal herb and therapeutic agent

Rauwolfia serpentina is a valuable medicinal plant with a wide range of therapeutic activities. It is mainly effective in the treatment of mental disorders such as hypertension, schizophrenia, epilepsy, insomnia, anxiety and insanity. It is also used as a powerful sedative and hypnotic. (7,67) The roots of this plant are rich in medicinally important indole alkaloids (such as reserpine). Extracts of the root are used for diarrhea, dysentery, intestinal disorders and as anthelmintic. In combination with other plants, it is useful in the treatment of cholera, abdominal pain and fever. (12) Rauwolfia root induces uterine contractions, so it has also been recommended for use in labor. Its incomplete hypoglycemic effects have also been observed in patients with diabetes and hypertension. The juice of the leaves is used for corneal opacity, while the juice of tender leaves and roots is helpful in treating liver diseases, stomach pain, dysentery and intestinal worms. Its extract is also used in serious diseases like cancer. (14,68)

Prostate cancer

Prostate cancer is a leading cause of death in men, and modern treatments such as chemotherapy/radiotherapy offer limited survival benefits. (67) Natural products have played an emerging role as a major source of identification of bioactive compounds in cancer treatment. Various parts of Rauwolfia serpentina have been traditionally used to treat fever, liver disorders, bowel diseases and mental disorders.(68) Alstonine, a beta-carboline alkaloid obtained from its root bark, has been found to be effective in inhibiting tumor growth.(69) Research has found that this plant affects gene expression, DNA damage and cell signaling pathways on prostate cancer cells in in vitro and in vivo models, thereby establishing its anti-cancer potential.(70)

Mental illness, schizophrenia, high blood pressure and other diseases

The root of Rauwolfia serpentina is used in traditional and modern medicine for hypertension, mental agitation, insomnia and as a sedative. (9,18) The root extracts have been found to be highly effective for hypertension and have been adopted by the medical fraternity worldwide. The alkaloids obtained from this plant have a direct effect on blood pressure and are used in the manufacture of many medicines.

Additionally, the use of R. serpentina has been found to be helpful in the treatment of fever, malaria, eye diseases, pneumonia, asthma, AIDS, headache, skin diseases and spleen disorders. Its multifaceted medicinal effects make it an important herbal medicine source. (13,14,19,71,72,73)

CONCLUSION

In the current global scenario, many people are suffering from chronic and complex diseases due to climate change and environmental imbalance. In these situations, the need for herbal medicines has become more important than ever, which are culturally acceptable, biocompatible with the body and have fewer side effects.

In this context, the roots of Rauwolfia serpentina (R. serpentina) are emerging as a highly promising herbal option in the pharmaceutical world. The bioactive chemical compounds such as alkaloids, phenols, flavonoids, etc. found in its roots make it useful in the treatment of various diseases.

This review work provides an in-depth understanding of the following therapeutic potentials of R. serpentina:

Antioxidant, Anticancer, Antidiuretic, Antiarrhythmic, Antidysentery & antidiarrheal, Antihypotensive, Anticontractile, tranquilizing agent Based on these properties, R. serpentina emerges as a holistic, natural and effective medicinal solution, especially in areas where allopathic therapy may be limited or ineffective.

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