**Introduction**

Nature is the world's best medicine. Most of the bioactive components present in the natural plants and food may delay or prevent the onset of many diseases such as cancers, diabetes and arthritis etc. It has been reported since long about the medicinal potency of herbal plants. Many herbs used for medical purposes come from common plants only. There are times when it might be smarter to use an herbal remedy than pharmaceuticals because natural medicine offers a safer alternative. We should respect the power that many natural plants can have on our health. In fact, many pharmaceutical drugs are based on the synthesized versions of naturally occurring compounds found in plants. In recent years, interest in herbal medicine has skyrocketed leading to a greater scientific interest in the medicinal use of plants. Many research studies and clinical trials have shown that plants are capable of treating disease and improving health, often without any significant side effects. By keeping the above mentioned points in mind, it is good to know about a single plant in detail that helps to focus on future study about the plant with novel technology. With the advent of genomics, proteomics, glycomics and metabolomics and with major advances in techniques for analyses (e.g. surface-enhanced laser desorption ionization time-of-flight mass spectrometry), chemical synthesis and high-throughput screening of active compounds, there is an unprecedented opportunity to evaluate and explore the huge medicine chest that is embedded in herbs. So, this review consolidated most of the scientific reports available for *Rhazya stricta* Decne (*R. Stricta*), an arid plant available and grown a lot in Middle East countries.

**Conclusion:** This review consolidated the main phytochemical and pharmacological activity reported on *R. Stricta*. Based on this review, we concluded that there is a lacuna of research on other aspects of *R. stricta* such as toxicology, safety and genomic studies. More intricate studies are needed for other pharmacological activity also for reaching precise conclusion. As there is a need for developing new drug, this plant may act as a potent source for promising lead molecule in support of upcoming researchers.

**Keywords:** *Rhazya stricta*, phytochemicals, pharmacological, alkaloids.

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**Abstract**

Objective: Medicinal plants with its numerous bioactive compounds such as alkaloids, flavonoids, phenolics, etc., are nature's gift to the world. It is time to revisit our thinking towards natural remedies to find useful natural products with interdisciplinary approach. Conventional allopathic drugs prescribed for the treatment of diseases are associated with numerous side effects and so there is a need for valuable, safe and superior drugs for different ailments. Considering *Rhazya stricta* plant, there is a large scope for scientific evaluation based on the active principles it possess as per different scientific reports. This plant has extraordinary medicinal potential to hit upon new chemical leads for pharmaceutical use. The research work done with this plant by various scientists should be appreciated. The main aim of this article is to review most of the scientific reports available for *Rhazya stricta* Decne (*R. Stricta*), an arid plant available and grown a lot in Middle East countries. Conclusion: This review consolidated the main phytochemical and pharmacological activity reported on *R. Stricta*. Based on this review, we concluded that there is a lacuna of research on other aspects of *R. stricta* such as toxicology, safety and genomic studies. More intricate studies are needed for other pharmacological activity also for reaching precise conclusion. As there is a need for developing new drug, this plant may act as a potent source for promising lead molecule in support of upcoming researchers.

**Keywords:** *Rhazya stricta*, phytochemicals, pharmacological, alkaloids.
scientist Abu Bakr Mohammed bin Zakariya Al-Razi, known in Europe mostly under the Latinized name of Rhazes (Batanouny et al., 1999). The plant is a glabrous erect shrub, about 90 cm high (Jafri, 1966), with a smooth central stem and dense semi-erect branches (Western, 1989); leaves alternate, 6 to 10 × 1 to 2 cm, elliptic–lanceolate, thick or leathery, sessile, turning yellow with age; flowers white in short branched cymes; fruit pale yellow follicles; seeds shortly winged (Jafri, 1966). Some research proceedings mentioned *R. stricta* as an evergreen poisonous shrub, has covered large hilly areas of Pakistan. *R. stricta* like other weeds compete with the main crops for nutrients and other resources and hamper the healthy growth ultimately, reducing the yield both qualitatively and quantitatively (Khan et al., 2011).

**Folklore claims for medicinal use**

*R. stricta* is a medicinal plant used in folk medicine to treat diseases such as diabetes mellitus, fever, sore throat, and syphilis (Adam, 1998; El-Ghonemy, 1993). It's used in the treatment of diseases like boils, eruptions, red sore, infected and swollen eyes, skin rashes, colic and stomach pain etc. It is also used as a general coolant and is famous for treating jaundice, anemia like symptoms in pregnant women and problems associated with child development, also effective for treatment of gastrointestinal parasites, such as round worm and flat worms. It is also used for drying up haemorrhoids (Ahmad et al., 2007). Leaves and roots are useful for moth blisters, dysentery, jaundice (Tareen et al., 2010), diabetes, general debility, chronic rheumatism and tumour (Qureshi et al., 2012). Extract of leaves is prescribed in folkloric medicine for the treatment of various disorders such as diabetes, sore throat, helminthiasis, inflammatory conditions and rheumatism (Mohammed N Baeshen et al., 2015). It is widely used in traditional medicine as a reputed tonic and curative for rheumatic pain, sore throat, syphilis, diabetes, helminthiasis, inflammatory conditions, fever and other diseases (Ali et al., 1995; Ali et al., 1998).

**Documented Phytochemicals-Brief Note**

*R. stricta* is an important medicinal species that is rich in alkaloids containing mostly anticancer alkaloids and few non alkaloidal compounds (Gilani et al., 2007). Over 100 alkaloids have been isolated from *R. stricta*, but the pharmacological activities are known for only a few of these compounds. It is an important medicinal species used in indigenous medicinal herbal drugs to cure various diseases in South Asia and the Middle East (Gilani et al., 2007). Most of the activities of the plant reside in its alkaloidal fractions (Khan et al., 2012). A few flavonoids have been isolated and their structures and stereochemistry are characterized (Ali et al., 2000b). The leaves of the plant contain alkaloids with β-carboline nucleus namely akuammidine, rhazinilam and tetrahydrosecamine (Bashir et al., 1994). The *R. stricta* leaves have been shown to contain flavonoids, glycosides, triterpenes, tannins, volatile bases and probably other substances (Ahmed et al., 1983; Baeshen et al., 2010).

**Review report submitted by different groups**

Gilani et al. (2007) reviewed the phytochemical, pharmacological and ethnobotanical studies of *R. stricta*. They reported phytochemical and pharmacological aspects of the species have been investigated by many research groups but pharmacological activities are evaluated only for a few of the isolated alkaloids from *R. stricta*. There is a particular need for ethnobotanical studies of *R. Stricta* in various regions of Middle Eastern countries and in South Asia where the species grows. Gilani et al. (2007) concluded that more ethnomedical and pharmacological studies are recommended for *R. stricta* with the ultimate goal of benefiting local communities in regions where this plant grows. This should be accomplished by sharing knowledge and also through the manufacture of herbal drugs from *R. stricta*'s active chemical constituents following the World Health Organization's guidelines for safety and efficacy.

Khan et al. (2012) reviewed the phytochemistry, biological and pharmacological activities, and ethno medicinal uses of *R. stricta*. Appreciable pharmacological and biological activities are mainly due to the presence of more than 100 alkaloids and a few non alkaloids in the plant. They reviewed that phytochemicals in the plant have been reported to exhibit ambulatory, antifungal, antimicrobial, antioxidant, endogenous monoamine oxidase (MAO) A and B inhibitory and herbicidal activities. Those phytochemicals also showed effects on arachidonic acid (AA) metabolism, blood pressure, central nervous system (CNS), immunity, smooth muscles and glucose homeostasis. Sarfaraz Khan et al. (2012) suggested doing more research work for exploring its medicinal importance due to its richness of phytochemicals. *R. stricta* has immense potential as an antimicrobial; therefore, such studies are highly suggested for research activity.

Ali et al. (2000b) reviewed the phytochemical, pharmacological and toxicological properties of the medicinal plant *R. Stricta*. Other than alkaloids they reported the presence of few flavonoids also. However, they reported that the biological activity of these compounds has not been studied clearly. *R. Stricta* alkaloids which cause depression of the central nervous system and hypotension have not been explored completely. Extracts of *R. stricta* appear to have low toxicity also, so it's inadvisable to be used by pregnant women.
Baeshen et al. (2015) reviewed the therapeutic potential of folkloric medicinal plant *Rhazya stricta* in detail and reported that extract contains alkaloids, glycosides, flavonoids, tannins and triterpenes. They stated that several preclinical studies reported that the leaves extract causes sedation, analgesia, anti cancer, decreases motor activity and have anti-depressant, antioxidant activity, complex effect on brain endogenous monoamine oxidase activity and central mediated hypotension. The genotoxicity of *Rhazya stricta* leaves was demonstrated by Baeshen and colleagues in a battery of tests. They also demonstrated the effect of *Rhazya stricta* in insulin insensitivity, MDRs (multi-drug resistant organisms), cardiovascular diseases, obesity and some other ailments. They revealed that their research group is presently involved in extensive studies on the whole genome of *Rhazya stricta* which may lead to future Natural Products Genomics and PDT (Phytodynamic Therapy).

**Pharmacological Activities**

**Antihyperglycemic Studies**

The leaves extract of *R. stricta* have been used for the treatment of diabetes mellitus (Western, 1989; Gonemi, 1992). The beneficial effect of *R. stricta* in diabetes was studied by oral administration of the decoction to streptozotocin-induced diabetic rats under different experimental conditions. The results showed no improvement in glucose homeostasis (Wasfi et al., 1994). In another experiment, *R. stricta* leaf extract administrated sub chronically for 28 days (0.5 to 2 g/kg, p.o.) to streptozotocin-diabetic rats showed no effect on either plasma glucose or insulin concentrations (Tanira et al., 1996a). In the report of Ali et al., it was show that oral doses of the leaf extract (0.5, 2 and 4 g/kg) reduced the plasma glucose and increased insulin levels at 1 and 2 h following administration to diabetic rats (Ali et al., 2000b). From these research studies, it is clear that a conspiracy still remains in the antidiabetic activity of *R. stricta*.

**Antihypertensive Studies**

Lyophilized aqueous extract of *R. stricta* caused an inconsistent effect on heart rate, and a dose-dependent decrease in mean blood pressure (MBP) of urethane-anesthetized rats (Tanira et al., 1996). The maximum reduction amounted to 40% and the alkaloidal fraction was found to be the most effective in this action. Tanira et al. (2000) reported that using preparations such as frank pithed rat, and spinalized rats, it was found that the extract acts centrally, rather than peripherally, to reduce blood pressure. Recently, the alkaloidal fraction was injected into the cerebral ventricles (i.c.v.), and results were similar to those obtained from the i.v. injection (Khan et al., 2012).

**Immunological Studies**

The possibility that some of the folklore claimed therapeutic actions of the plant extract may be due to immunomodulatory capacity and it was tested in peritoneal macrophage-derived cytokines in mice. Each mouse received an alkaloidal fraction of *R. stricta* and peritoneal cells were isolated, cultured and assayed for IL-1 alpha and TNF alpha using an Enzyme Linked Immunosorbent Assay (ELISA) technique. The alkaloidal fraction of *R. stricta* significantly increased the production of these two proinflammatory cytokines (Tanira et al., 1998).

**Effect on arachidonic acid (AA) metabolism**

Rhazimine alkaloid isolated from *R. stricta* leaves has been studied to describe the effect on AA metabolism in human blood. It has dual and selective inhibitor effect on platelet activating factor (PAF)-induced platelet aggregation and AA metabolism in vitro (Saed et al., 1993). These effects might provide additional beneficial anti-inflammatory and anti-PAF effects by comparison with classical non steroidal anti-inflammatory drugs (Saed et al., 1993). Lyophilized and butanol extracts of *R. stricta* shown significance reduction in carrageenan-induced inflammation in the rat paw edema test, and decrease rectal temperature of pyrexic rats. Activity-guided fractionation indicated that the potency of anti inflammatory action was about one tenth of the standard anti-inflammatory drug phenylbutazone (Wasfi et al., 1994; Tanira et al., 1996).

**Antioxidant Studies**

Iqbal et al. (2006) reported the presence of high amount of phenolic content and antioxidant potential in the methanolic extract of *R. stricta* leaves. The ethanolic extract of *R. stricta* fruit has shown significant lipoxygenase and acetylcholine esterase activities (Sultana and Khalid, 2010). The plant extract have shown good antioxidant activity in the animal models of diseases (Ali et al., 1998). The leaf extract *R. stricta* showed prominent dose dependent effect on reduced glutathione (GSH), lipid peroxidation (LP) and ascobic acid (AA) concentrations in the liver and kidneys of rats. It was concluded that the *R. stricta* extract, at some of the doses used, has antioxidant actions (Ali et al., 2000).

**Herbicidal Activity**

Kamel and Al-Mutlaq, proved that *R. stricta* extract has herbicidal activity by inhibiting the growth of wild radish without affecting the biological processes in the plant (Kamel and Al-Mutlaq, 2004).

**Effect on Smooth Muscles**

The lyophilized extract of *R. stricta* has been tested and proved that it has relaxing effect on the isolated intestinal muscles of the rats (Tanira et al., 1996) because it increases...
the production of proinflammatory cytokines (Tanira et al., 1998). This plant is having highest antispasmodic drug potential character that will help in folk medicinal use of the plant (Ali et al., 2000b).

**As Food supplements: d-tocopherol & c-tocopherol, feed stock, minerals**

*R. stricta* seed oil d-tocopherol and c-tocopherol, is potentially useful in food and pharmaceutical applications but the safety of this oil must be tested before use for human nutrition (Imededdine et al., 2016). *R. stricta* oil which is a potential source of d-tocopherol is useful for the prevention, delay, or treatment of chronic and acute diseases (Imededdine et al., 2016). Nutritive analysis of *R. stricta* revealed that the plant is a good source of minerals necessary for maintenance of normal physiological parameters (Baloch et al., 2016). They also reported that the plant is a rich source of iron, zinc, sodium, potassium, magnesium and calcium which make it drug of choice in the management of anemia, dysentery and jaundice and related bone disease (Baloch et al., 2016). A recent study by Imededdine et al. (2016) showed that *R. stricta* seeds are a source of unsaturated oil which can be used as a feedstock for biodiesel production.

**Hypotriglyceridemic and hypocholesterolemic effect**

Marked hypotriglyceridemic and hypocholesterolemic effect of the plant is reported and it may have therapeutic implications on patients with hypertriglyceridermia and hypercholesterolemia (Baeshen et al., 2005). More research work is needed to explore possible mechanisms of action of *Rhusia stricta* leaves in human cardiovascular disorders. The aqueous extract of the *R. stricta* leaves significantly decreased concentrations of TGs, LDL-c, cholesterol, uric acid and creatinin, but increased concentration of HDL-c. It triggered all these activities without affecting liver enzyme activities or kidney functions. These findings may have a positive impact on the cardiovascular patients and may provide a new therapeutic strategy to reduce hypertriglyceridermia (Baeshen et al., 2005). Additionally, the extract significantly decreased concentrations of triglycerides, low density lipoprotein, cholesterol, uric acid and creatinine, without affecting liver or kidney functions in rats (Baeshen et al., 2010).

**Genotoxicity and antigenotoxicity Effect**

Genotoxic effect of *R. Stricta* was perceived by cytogenetical and molecular assays against wide range of cell types including Saccharomyces cervisae (Baeshen et al., 2005) and the primary culture of human lymphocytes (Baeshen et al., 2009). *R. stricta* extractions not showed any mutagenicity effect on the battery of Salmonella typhimurium mutant tests strains TA98TA79a, TA100, TA102 and TA1535. Comet assay results showed genotoxicity effect of the *R. stricta* and its extract produced significant effects on comet percent and the mean tail moment value in single. *R. stricta* extract increased the cytochrome p450 1A1 concentration in mice liver. However, more work is needed, with the growing interest of the world in complementary and alternative medicines applications, to investigate possible mechanisms of action of *R. stricta* leaves using the same method of extraction that have been used by humans in the folk medicine (Almostady et al., 2015). Baeshin et al., 2009 reported that *R. stricta* leaf extract have strong mutagenic activities as compared with the potent chemical mutagenic agent NTG (Baeshin et al., 2009). Their study showed that the increase in concentration of leaf extract and exposure time led to a decrease in survival percentage and an increase in auxotrophic mutation percentage by linear regression calculation method.

**Cytotoxic and anticancer Activity**

Zaman, 1990 reported that *R. stricta* plant having cytoxic activity against the cell cultures human carcinoma MCF-7 cells. Cytotoxic action is mainly by the reduction in cell proliferation. Depending on extract’s type and concentration there are different antiproliferative profiles of *R. stricta* (Zaman, 1990). Antiproliferative effect proved against MCF-7 and MDA-MB-231 cells effectively with the ethanol extract of Harmal. They potentially inhibited cellular growth and colony formation of human breast cancer cell lines, MCF-7 and MDA-MB-231, in a dose- and time dependent manner (El-Awady et al., 2015). Furthermore, it induced sequences of events marked by apoptosis, accompanied by a loss of cell viability, chromatin condensation, DNA fragmentation and proteolytic cleavage of poly (ADP-ribose) polymerase. Harmal dependent apoptotic mechanisms involved an increase in the Bax:Bcl-2 ratio and down-regulation of all c-myc, human telomerase reverse transcriptase, and cyclin D1 proteins (Baeshen et al., 2012).

Harmal has anticancer activity which could be attributed in part to its inhibition of proliferation and apoptosis induction of cancer cells through up-regulation and down-regulation of Bcl-2 proteins. Anticancer activity of *R. stricta* against Hepato-cellular carcinoma (HepG2) and the colon cancer (Caco cells) cell was reported. The results showed that extract produced a reduction in cell proliferation and showed different antiproliferative profiles regarding extract type and concentrations (El-Awady et al., 2015). This study inveterate the reports regard to natural products to be the most effective in terms of their ability to alter the function of proteins relevant to cancer, forever (Muhtasib, 2006). Medicinal plants have been curing various disorders.
in human being from the time immemorial, among the human diseases treated with medicinal plants more commonly is cancer (Koduru et al., 2007). *Rhazya stricta* treatment suppressed proliferation and colony formation and effectively induced morphological and biochemical features of apoptosis in U251 cells. Apoptosis induction was mediated by release of mitochondrial cytochrome c, increased Bax: Bcl-2 ratio, enhanced activities of caspase-3 and -9, and PARP-1 cleavage. *R. stricta* treatment decreased expression levels of nuclear NF-Bp65, survivin, XIAP, and cyclin D1 and increased expression level of p53, p21, and Noxa. This result provides a useful foundation for studying and developing novel chemotherapeutic agents for the treatment of GBM (Elkady et al., 2015).

Iqbal et al. (2006) proved that Harmal may be a good source of antioxidants. This fact deserves attention since considerable laboratory evidences from chemical, cell culture, and animal studies indicate that antioxidants may slow or possibly prevent the development of cancer (Kaefer and Milner, 2008; Liu, 2004). Based on the preceding information and lack of any reported scientific data elucidating the role of Harmal in prevention of human breast cancers, the impact of Harmal extracts on growth of breast cancer was also examined (Baeshen et al., 2012).

### Effect on Central Nervous System

Aqueous lyophilized leaves extract of *R. stricta* showed dose-dependent activities in antinociceptive tests and also they produced dose-dependent sedation effect, decreased motor activity, and impaired motor control (Ali et al., 1995). *R. stricta* has also CNS depressant effect due to present of b-carboline ring in some phytochemical constituents (Bashir, 1994 and Ali, 1995). Alkaloids present in the plant extract have the ability to reduce adrenaline concentration in the brain (Tanira et al., 1999).

### Antimicrobial Studies

Rucker et al. (1992); Murakami et al. (1993) reported the antimicrobial property of *R. stricta* glycosides and ensures its use as an anti-infective agent. Coumarin which is present in all plant extracts, are well known for its antitumor, antibacterial and anthelmintic properties. *R. stricta* antimicrobial efficacy against both bacteria and fungi revealed that plants have ability to kill or inhibit the growth of bacteria and fungi which experimentally support the use of this plant in traditional medicine by traditional healer (Reddy et al., 2016). Crude methanolic extract (CME) showed effective antileishmanial activity with ED50 14.93 μg/ml. Furthermore, the phytochemical analysis of CME and its fractions showed the presence of Alkaloids, Flavonoids, Phenols, Saponins and Diterpenes. The extract and fractions were also appreciating for further investigations in future (Muhammad et al., 2012).

### Conclusion

This review consolidated the main phytochemical and pharmacological activity reported on *R. stricta*. This review also revealed that *R. stricta* has immense pharmacological activity due to its richness of phytochemicals it possesses. There is a lacuna of research on other aspects such as toxicology and safety as well as intricate studies is needed for other activity also for reaching precise conclusion. Hence, further detailed research studies are recommended in various parts of the countries especially in Arabian cape where it grows, as the nature of phytochemicals and secondary metabolites composition in *R. stricta* plant varies from one region to another. As there is a need for developing new drug, this plant may act as a potent source for promising lead molecule in support of upcoming researchers. Further comprehensive study may still be necessary to elucidate the pharmacokinetics and pharmacodynamics behind the therapeutic action of this plant.

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