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Therapeutic Potential of the Folkloric Medicinal Plant *Rhazya stricta*

Mohammed N Baeshen[1,3]*, Raziuddin Khan[2], Roop S Bora[2] and Nabih A Baeshen[2]

[1]*Department of Biological Sciences, Faculty of Sciences, University of Jeddah, Saudi Arabia*
[2]*Department of Biological Sciences, Faculty of Sciences, King Abdulaziz University, Jeddah, Saudi Arabia*
[3]*Center of Nanotechnology, King Abdulaziz University, Jeddah, Saudi Arabia*

Abstract

Medicinal plants assumed principle role in folkloric medicine throughout history. They have been the subject of many recent studies for the evaluation of what have been ascribed to them of medicinal properties by means of modern techniques. For example *Rhazya stricta* decne of the Apocynaceae family is a widely distributed plant in Saudi Arabia. Extract of its leaves is prescribed in folkloric medicine for the treatment of various disorders such as diabetes, sore throat, helminthiasis, inflammatory conditions and rheumatism. The extract contains mainly alkaloids, glycosides, flavonoids, tannins and triterpenes. Several studies on rats and mice reported that the leaves extract causes sedation, analgesia, decreases motor activity and has anti-depressant, anti-oxidant activity, complex effect on brain endogenous monoamine oxidase activity and central–mediated hypotension. Moreover, some studies ascribed anticancer activities to indole alkaloids of *Rhazya stricta*. The genotoxicity of *Rhazya stricta* leaves was demonstrated by Baeshen and colleagues in a battery of tests. We also demonstrated various therapeutic properties of *Rhazya stricta* for the treatment of cancer, insulin insensitivity, MDRs (multi-drug resistant organisms), cardiovascular diseases, obesity and some other ailments. We are currently having collaboration with some international institutes in the United States and Europe for extensive studies on the whole genome of *Rhazya stricta* which may lead to future Natural Products Genomics and PDT (Phytodynamic Therapy).

Introduction

Folkloric medicinal herbs are generally used in folk medicine and are considered as a key resource of novel drugs. For centuries, it has been exploited for treating and curing various human and animal ailments. There are varieties of medicinal plants species that have yet to be discovered in ecologically diverse areas such as Saudi Arabia peninsula. A large number of these plants grow under adverse weather conditions, which makes their genomes remarkably unique. Furthermore, the evolutionary selection pressures undergone by these desert herbs over thousands of years give rise to "survival molecules" and metabolites.

Rhazya stricta is an evergreen, toxic shrub, small, erect and glabrous [1-4]. It is a significant medicinal plant used in herbal drugs to cure various ailments in Afghanistan, India, Iran, Iraq, Pakistan, Qatar, Saudi Arabia and United Arab Emirates (UAE) [5-7]. The genus Rhazya belongs to the order Gentianales, family Apocynaceae [5,7] and subfamily Rauwolfioideae [1-3]. Rhazya species was termed after the name of a Muslim scientist Abu Bakr Mohammed bin Zakariya Ar-Razi (925) and it is known in Europe mostly under the Latinized name of Rhazes [8]. It is also called as "Harmal" in Arabic, "Rangobul" in Urdu, Vergalum, Ganderi in Pushto [5,9]. Different parts of the plant have been used in traditional medicines against various ailments such as diabetes, foot burning, skin diseases, stomach pain etc. The plant is used in UAE, mostly in the form of decoctions, for various ailments that include anti-pyretic, cancer, diabetes mellitus, helminthiasis, inflammatory conditions, rheumatism, sore throat, stomach diseases, and skin diseases [4,5,7,10,11]. In the non-urban area of Saudi Arabia, the leaves of *R. stricta* are used in folk medicine as a treatment for syphilis [9], chronic rheumatism, and body pain [4]. Powder of dried fresh leaves is used for acne and pimples of face. Fresh leaves are kept in shoes and put under feet for treating foot burning. Branches are used as toothbrush for teeth ache [12]. The paste of soaked seeds with butter is used for achenes and the treatment of the heat burns [13].

Distribution

Rhazya stricta Decne is found in the sandy plains of Saudi Arabia and several other regions of the world [4]. It is abundantly found in Western Asia from Yemen to Saudi Arabia and also to the North Western parts of various regions of Pakistan and India [10,11]. This plant species is one of the famous plants that grow in Saudi Arabia and is considered one of the most precious medicinal plants that are found in the most desert areas in the Arabian Peninsula. *Rhazya stricta* grows in depressions with silt and sandy soils [14]. Yaghmoor et al., in 2015 reported that it is increased in abundance along gradient of sand.

Phytochemistry

The leaves of *R. stricta* contain alkaloids, glycosides, triterpenes and tannins [4] and it is known to be a rich source of indole alkaloids. Indole alkaloids exhibit various biological activities such as antihypertensive, antimicrobial and antitumor properties and also shown as central nervous system stimulants [4]. Phytochemical analysis has identified more than 100 alkaloids [7]. These alkaloids have several pharmacological properties. More than 100 alkaloids have been isolated and characterized from *R. stricta* leaves [7] stems, roots and legumes [15]. Still, a large number of alkaloids from *R. stricta* are not commercially available and their isolation is challenging and time consuming process. To overcome this problem, *Rhazya stricta* alkaloids were fractionated by MPLC (medium pressure liquid chromatography), TLC (Thin layer liquid chromatography) and HPLC (high performance liquid chromatography), and subjected to GC-MS for characterization of purified compounds [2]. GC-MS is a useful technique which can be used for the identification and quantification of alkaloids and non-alkaloids from *Rhazya stricta* extract. Recently, Akhgari et al. analysed the alkaloid of hairy root cultures by HPLC and UPLCMS (ultra-performance liquid chromatography-mass spectrometry),

***Corresponding author:** Baeshen MN, Department of Biological Sciences, Faculty of Sciences, University of Jeddah, Saudi Arabia, Tel: +9665036745; E-mail: mnbaeshen@kau.edu.sa

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and identified five indole alkaloids. Most of the alkaloids, identified by HPLC, mainly accumulated in hairy roots [3]. Table 1 represent examples for some important compounds in *R.* stricta, their formulae and medical importance obtained from some preferred literature (Table 1).

Biological and Pharmacological Activities

Antimicrobial activities

Only few studies have been conducted so far to show antimicrobial activities of *R. stricta* extracts. A microbiological study based on epidemiological survey was conducted in which, *Rhazya stricta* leaves extract showed antibacterial growth effect of on the locally meningococcal isolates [16]. Another important study from our laboratories demonstrated the anti-microbial activity of *Rhazya stricta* extract on various lethal and antibiotic resistant pathogens such as ESBL and other MDR pathogens and thus suggested the potential application of *Rhazya stricta* extract as an alternative therapeutic medicine to control the infection caused by these antibiotic resistant pathogens [17]. Another study revealed that the ethanolic extract of

Fraction	Compound	Formula	Source	Biomedical Importance	Reference
Alkaloids	15β-hydroxy vincadifformin	$C_{21}H_{26}N_2O_3$	Leaves	-	Atta-ur-Rahman et al. (1988b), Fatima (1988)
	dl-1-(oxo-3,4-thero-3,4,5-trihydroxy-1- pentyl) βbcarboline	$C_{16}H_{16}N_2O_{14}$	Cultured cell clumps	Cytotoxic activity	Abdel Moty et al. (1997);Ali et al (2000)
	16-epi-Z-isositsirikine	$C_{20}H_{22}N_2O_2$	Leaves	Antineoplastic activity	Mukhopadhyay et al. (1983)
	Akuammidine,	$C_{21}H_{24}N_2O_3$	Leaves	Antimicrobial	Bashir et al. (1994); Fatima (1980); Zaman (1990)
	Aspidospermiose	$C_{24}H_{32}N_2O_5$	Leaves	-	Habib-ur-Rehman and Atta-ur-Rahman (1996)
	(+)-Aspidospermidine	$C_{19}H_{26}N_2$	[1]Leaves [2]Ariel part	-	[1]Habib- UR- Rehman (1987); [1]Fatima (1980). [2]Abdbl-Mogib et al. (1998)
	Bhimberine-N-oxide	$C_{21}H_{26}N_2O_4$	-	-	Qureshi (1991)
	Bhimberine	$C_{21}H_{26}N_2O_3$	-	-	Qureshi (1991)
	Bis-Strictidine	$C_{38}H_{48}N_4$	Leaves	-	Habib-UR- Rehman (1987); Qureshi (1991)
	Condylocarpine	$C_{20}H_{22}N_2O_2$	Fruit	-	Qureshi (1991)
	Didemethoxycarbonyl-tetrahydrosecamine	$C_{38}H_{52}N_4$	Root	Cytotoxic activity	Mukhopadhayay et al., (1981)
	Rhazimine	$C_{21}H_{22}N_2O_3$	Leaves	Arachidonic acid metabolism inhibitor	Atta-ur-Rahman and Khanum, (1984); Saeed et al., (1993)
	Rhazimanine	-	Leaves	Antimicrobial	Bashir et al., (1994)
	Rhazinilam	$C_{19}H_{22}N_2O$		Cancer chemotherapy	Banerji et al., (1970)
	Sewarine	$C_{20}H_{22}N_2O_3$	Leaves and roots	Cytotoxic activity against Eagle's KB carcinoma of the nasopharynx in a cell culture model	Siddiqui et al., (1966); Ahmad et al., (1970) and (1971); Mukhopadhayay et al., (1981)
	Stemmadenine	$C_{21}H_{26}N_2O_3$	Leaves	Antimicrobial activity against *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans*	Mariee et al., (1988); Qureshi (1991)
	Strictanol	$C_{19}H_{26}N_2O$	Leaves	Antimicrobial activity against *E. coli* and *P. aeruginosa*	Bashir et al. (1994)
	Tetrahydrosecaminediol	-	Leaves	Antimicrobial	Bashir et al. (1994)
	Tetrahydrosecaminediol diacetate	-	-	Cytotoxic	Mukhopadhayay et al. (1981)
	Vallesiachotamine	$C_{21}H_{22}N_2O_3$	Leaves and roots; Callus	Cytotoxic activity	Pawelka and Stockigt (1986)
	Tetrahydrosecamine	$C_{42}H_{56}N_4O_4$	Leaves and roots	Cytotoxic activity against Eagle's KB carcinoma of the nasopharynx in a cell culture model	Evans et al. (1968);Mukhopadhayay et al. (1981)
	Vincadine	$C_{21}H_{28}N_2O_2$	Fruit	-	Atta-ur-Rahman and Malik (1985)
Non-Alkaloids	3a-hydroxy-ursane-5-ene	$C_{30}H_{50}O$	Fruit	-	Sultanaa and Khalid (2010)
	9-octadecenoic acid-20,30-dihydroxy propyl ester	$C_{21}H_{40}O_4$	Root	-	Atta-Ur-Rahman et al., 2008
	Hexadecanoic acid-20,30-dihydroxy propyl ester	$C_{19}H_{38}O_4$	Root	-	Atta-Ur-Rahman et al., 2008
	b-Sitosterol	$C_{29}H_{50}O$	Root	-	Zaman (1990)
	Oleanolic acid	$C_{30}H_{48}O_3$	Fruit	Antibacterial, Lipoxygenase and Acetylcholinesterase activities.	Sultanaa and Khalid (2010)
	Rhazianoside A	$C_{34}H_{42}O_{21}$	-	-	Zaman (1990)
	Rhazianoside B	$C_{34}H_{42}O_{21}\cdot 3H_2O$	-	-	Zaman (1990)
	stigma sterol	$C_{29}H_{48}O$	Fruit	-	Sultanaa and Khalid (2010)
	Ursolic acid	$C_{30}H_{48}O_3$	Root	-	Zaman (1990)

Table 1: Some isolated compounds from *Rhazya stricta*.

Rhazya fruit had antibacterial, lipoxygenase and acetylcholinesterase activities [18]. The chloroform and methanol extracts of the roots of *R. stricta*, showed antimicrobial and antifungal activities against *Aspergillus terreus, Aspergillus flavus, B. subtilis, C. albicans, E. coli, P. aeruginosa,* and *S. aurous,*. Tetrahydrosecamine, an alkaloid isolated from the plant confirmed broad spectrum antimicrobial activity (active against all pathogens except *E. coli*; MIC values 0.1 to 5.0 mg/ml). Similarly, another active component, Strictanol, was also found to be most active against *P. aeruginosa* and *E. coli* (MIC 0.5 mg/ml) [19]. In an antifungal study, five fractions such as Petroleum ether, carbon tetra chloride, chloroform, ethyl acetate and methanol were used. Among these, methanol and chloroform fractions showed significant antifungal activities. Petroleum ether and carbon tetrachloride fractions showed low activities against the fungal pathogens, while ethyl acetate fraction showed no activity at all [19].

Anticancer activity

R. stricta has been shown to possess anti-carcinogenic, anti-oxidant and free radical scavenging properties. Many indole alkaloids including vallesiachotamine, sewarine and tetrahydro secamine have been reported to exhibit cytotoxic activities. Tetrahydrosecaminediol and strictanol have also been shown as anticancer alkaloids [6]. Rhazinilam was isolated and characterized from *R. stricta*. Rhazinilam had been shown to have cellular activity similar to taxol. Rhazinilam was first synthesized by Smith and co-workers in 1973. *In vitro*, it showed inhibition of both microtubule assembly and enhanced the growth of abnormal tubulin spirals. Rhazinilam showed cytotoxicity toward several cancer cell lines at low micromolar range *in vitro* [20]. The leaves, flowers and fruit of *Rhazya stricta* are also used in joint infections and for cancer treatment [4]. Effect of *R. stricta* extract on root tip meristem of Allium cepa and the primary culture of human lymphocytes [4] verified pyknosis in Allium and necrosis in human lymphocytes which is an indication of anticancer activities of *R. stricta*. Baeshen and colleague studied the anticancer activity of *R. stricta* against human breast cancer cells [5]. It was found that ethanol extract of *R. stricta* inhibited cellular growth and colony formation of human breast cancer cell lines, MCF-7 and MDA-MB-231. It induced various aspects of apoptosis such as loss of cell activity, chromatin condensation, DNA fragmentation and proteolytic cleavage of poly (ADP-ribose) polymerase. *R. stricta* mediated apoptosis involved an increase in the Bax/Bcl-2 ratio and down-regulation of c-myc, human telomerase reverse transcriptase, and cyclin D1 proteins. Thus it can be concluded that *R. stricta* may be a valuable chemo-preventive or therapeutic agent for treatment of breast cancer.

Anti-diabetic activity

R. stricta leaves have been used for the treatment of diabetes mellitus [4,5,10,11]. Leaves extract of *R. stricta* contains the phytochemicals with anti-diabetic activities such as alkaloids, flavonoids, glycosides, triterpenes and tannins [4,7,9]. In one study, it was found that oral delivery of the leaf extract (0.5, 2 and 4 g/kg) decreased the plasma glucose level and enhanced insulin levels after administration to streptozotocin-treated rats. In another study the effect of different doses of Rhazya extract was analysed by administering the extract orally to the rats. This study analysed the effects of *Rhazya stricta* aqueous extract on adiponectin protein and insulin resistance. The data indicated a significant inverse correlation between adiponectin levels and insulin resistance after two weeks of treatment with Rhazya extract. There was a significant increase in adiponectin levels. Studies have indicated that polymorphisms at the adiponectin gene (exon 3) are predictors of adiponectin levels in blood. The effects of Rhazya aqueous extract to enhance the adiponectin levels concentrations could be a promising therapeutic strategy in treating diabetes [10,11].

Antioxidant action

R. stricta has been shown to have an antioxidant activity in rats, specially the leaf extract [9]. The methanolic extract of Harmal leaves exhibited the maximum total phenolic content and an antioxidant potential which was comparable with previously explored potent antioxidants [21]. The crude ethanolic extract of *R. stricta* fruits had also shown good lipoxygenase and acetylcholinesterase activities [18].

Effects on serum lipid profile

The Rhazya plant extract had been shown to be associated with increases in serum AST and LDH, elevated bilirubin and urea concentrations, and decreased total protein, albumin and calcium concentrations, leucopenia and anaemia [22]. In another study, the effect of oral administration of Rhazya leaves extracts on biochemical parameters such as liver enzyme functions and kidney functions, blood lipid profile in rats were analysed. It was observed that, aqueous extract of *R. stricta* leaves significantly reduced the concentrations of cholesterol, creatinin, uric acid, and TGs, LDL-c, but enhanced concentration of HDL-c. It induced these changes without affecting liver enzyme activities or kidney functions. These outcomes clearly indicated the positive impact of Rhazya extract on the cardiovascular system and hence it could be exploited as a new therapeutic strategy to control hypertriglyceridemia [10,11].

Hepatoprotective potential of R. stricta

Liver is known to be very prone to the damage due to adverse effects of drugs used for treatment of various diseases in human. Moreover, liver is also involved in the detoxication of several toxic compounds. Various medicinal plants are known to possess very potent hepatoprotective activity. Ali and colleague analysed the effect of lyophilized extract of *Rhazya stricta* in drug-induced- liver toxicity. Their data revealed significant improvement in the liver functions in Rhazya extract treated mice in which hepatotoxicity was induced with paracetamol. In another study, pretreatment with *R. stricta* aqueous extract protected the livers of treated mice against paracetamol induced hepatotoxicity [10,11].

Genotoxic and mutagenic action

Toxicity studies of *Rhazya stricta's* extract using *Saccharomyces cerevisiae* cells revealed that the extract has potent mutagenic and lethal activities. Frequency of auxotrophic mutants enhanced with increase in concentration or exposure time. Other studies have also indicated that extract of Rhazya leaves is a potent chemical mutagen for the induction of point mutations. Many previous studies have also demonstrated the cytotoxic activity of leaves extract of *Rhazya stricta* [23]. It was found that cytotoxic effect is associated with antitumor activity of the extract. Studies were conducted by Baeshen's team to analyse the mutagenic potential of Rhazya leaf extract by using the *S. cerevisiae* auxotrophic mutant test *Aspergillus terreus* [24] and also on different organisms and tissues. The cytogenetic and DNA integrity of human lymphocytes were studied after treatment with an aqueous extract of *R. stricta* leaves. Its effect were also analysed on *Allium cepa* root tip meristem [4,10,11].

Allelopathic activity

Allelopathy refers to the beneficial or harmful effects of one plant on another plant. Allelopathic potential of *R. stricta* using aqueous extract of leaves and stem was examined on seed germination and seedling growth of maize [25]. In another study of allelopathy the seedling of

Medical Condition	Extracts / Herbal Part used	Reference
Acne	**Aqueous extract from leaves powder**	Sultana et al. (2006)
Anti-inflammatory	**Alcoholic extract from leaves**	Tanira et al. (1996)
Antimicrobial activities	**Aqueous extracts from leaves**	Kabli et al., 2012;
Anti-pyretic	**Boiled aqueous extracts from leaves**	Miller and Morris (1988)
Foot burning	**Fresh whole leaves used in shoes**	Sultana et al. (2006)
Heat effects.	**Aqueous thick liquid from seeds**	Qureshi et al. (2007)
Helminthiasis in camels.	**Whole plant**	Tanira et al. (1996)
Mutagenic agent in *S. cerevisiae*	**Aqueous extracts from leaves**	Baeshin et al., 2005
Induce the chemopreven- tative Nqo1 enzyme through Nrf2-dependent mechanism	**Alkaloid fraction**	Gendy et al., 2012
In vitro mutagenic activities on human lymphocytes	**Aqueous extracts from leaves**	Baeshin et al.,2009a
In vitro Clastogenic activities on human lymphocytes	**Aqueous extracts from leaves**	Baeshin et al.,2009a
Help in reducing hypertriglyceridemia	**Aqueous extracts from leaves**	Baeshin et al.,2009b
Help in increasing levels of adiponectin concentrations	**Aqueous extracts from leaves**	Baeshin et al.,2010
Anti-Human breast cancer cell lines, MCF-7 and MDA-MB-231	**Aqueous extracts / Ethanol extract**	Baeshin et al., 2012
Genotoxicity /Clastogenicity in rat leukocytes	**Whole aqueous extract & alkaloid from leaves**	Baeshin et al., 2014
Rheumatism	**Whole plant**	Chopra et al. (1956)
Skin diseases	**[1]Tonic from Fruits / [2]Leaves**	[1]Ahmad et al. (2004); [2] Bashir et al. (1994)
Stomach disorders	**Whole plant**	Bashir et al. (1994)
Syphilis	**Bitter tonic from leaves**	Adam (1998)
Tooth ache	**Whole branches**	Sultana et al. (2006)
Tumour	**Leaves**	Jewers et al. (1980)
Urinary tract	**Whole plant**	Hassan (2006)
Vermifuge	**Leaves**	Al-Yahia et al. (1990)
Wounds	**Whole plant**	Khaksari et al. (2000)

Table 2: Medically importance of some *Rhazya stricta* extracts.

Vicia faba on treatment with *R. stricta* extracts showed different kinds of mitotic abnormalities and chromosomal aberrations [26].

Effect on cytochrome P450 enzyme

The alkaloid fraction of the *Rhazya stricta* was used to assess the microsomal activity of cytochrome P 450. The data suggested that Rhazya has the potential to interact with other drugs that are metabolized by cytochrome P450, when given concomitantly with it.

Larvicidal effect

The crude extracts of *R. stricta* exhibited growth inhibition properties against the fourth instar larvae of *Aedes aegypyti* [27]. Methanol and ether extracts of *R. stricta* showed acute and chronic toxic effects, respectively, on *Culex pipiens* mosquito larvae. Application of *R. stricta* and *C. procera* extracts applied to mosquito larval breeding sites may well provide an environmentally safe method for control of mosquito populations [5].

Effect on central nervous system

The effect of orally administered lyophilized aqueous extract of *R. stricta* leaves (2, 4 and 8 g/kg) on nervous system function was studied in mice. The extract showed significant dose-dependent effects in antinociceptive (reducing sensitivity to painful stimuli) tests [28]. The leaf extract also induced dose-dependent sedation, decreased motor activity and impaired motor control. Oral pre-treatment with *R. stricta* (8 g/kg) completely constrained the occurrence of aggressive behaviour in male mice. From the above observations, it was concluded that *R. stricta* also has anti- depressant properties [28]. It has also been suggested that the anti-depressing properties of *R. stricta* may be due to the presence of a beta-carboline ring in some chemical component [28].

Table 2 represents some medically importance of extracts derived from various part of *Rhazya stricta* (Table 2).

Conclusion

Rhazya stricta has been traditionally used for curing various ailments in many Middle East and South Asian countries. *Rhazya stricta* is known to be a rich source of several potent compounds including alkaloids with medicinal applications for treatment of various diseases such as diabetes, inflammatory diseases, sore throat, helminthesis, arthritis, infectious diseases and cancer. More than 100 alkaloids have been isolated and characterized from *Rhazya stricta*. Through chemical synthesis, various analogues of alkaloids with curative potential can be generated in sufficient quantities. Moreover, in recent years, availability of plant genomic data has improved tremendously due to the development of next-generation sequencing technologies. Genomic data that provide information regarding the metabolic pathways that are involved in synthesis of the alkaloids and other compounds with therapeutic potential is essential for the improvement and development of natural plant products as curative for treatment of various human diseases.

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