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Mini Review

Prospective Applications of the Medicinal Desert Plant *Rhazya stricta* in Green Chemistry Genomics and Agriculture Biotechnology: Mini Review

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Abstract

The medicinal desert shrub *Rhazya stricta* is a member of the *Apocynaceae* family. This plant is a local shrub, which mostly found around and within the valleys in desert lands. *R. stricta* was one of the famous medicinal plants in traditional and folkloric medicine. As well as to its medicinal properties, it's also a promising plant in the field of bioengineering and the future of genetically modified corps according to its resistance biotic and biotic stress factors and its survival in the harsh desert conditions. The plant was used over history in many nations and prescribed to treat many infections, inflammations, and diseases. On the basis of various experimental validations, it's been found that *R. stricta* has various chemotherapeutic properties such as, anti-cancer, anti-diabetic, and antibacterial effects, including. Future studies must concentrate on the chemo informatics, bioengineering, natural product genomics and metabolomics of the plant. It can be concluded that *R. stricta* is wealth resource for many cosmetic and pharmaceutical products and a solution for genetic modification of many corps according to its resistant genes to biotic and abiotic conditions.

Keywords: *Rhazyastricta*; Chemoinformatics; Bioengineering; Genomics; Bioinformatics; Metabolomics

Introduction

Natural medicine has been used for many decades to treat diseases, but for years the biologically active molecules and plant-derived drugs have been discussed and their mechanism of action. Rhazya stricta is a toxic, small, erect and glabrous classic shrub. It is one of the major medicinal shrubs in the Arab Peninsula desert, including the Kingdom of Saudi Arabia (KSA) used in herbal medicines to cure different diseases [1]. The term of Rhazya derived from the name of a Muslim scientist Abu Bakr Mohammed bin Zakariya Ar-Razi (925) and in Europe, this is known as Rhazes (in Latin) [2]. It is also known as "Harmal" and "Rangobul" in Arabic and Urdu respectively. The plant is used in the cure of various disorders Inflammation, skin diseases, stomach diseases, cancer, diabetes, etc [3]. It has several medicinal applications including cure syphilis, chronic rheumatism, and body ache. A dried, fresh powder obtained from leaves of *Rhazya stricta* is used for wound infection on the face. Fresh leaves, branches and paste of soaked seed are used in foot burning, orthodontics and heartburn respectively.

The leaves of *R. stricta* contain alkaloids, glycosides, triterpene and tannins 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 [3]. More than hundreds of alkaloids have been isolated and characterized from *R. stricta* leaves [4] stems, roots and legumes [5]. Still, a large number of alkaloids from *R. stricta are* not commercially available and their isolation is a challenging and time-consuming process. Khan et al demonstrated that organic alkaloid extracts of *Rhazya stricta* were showing the antibacterial property towards MERSA, and

transmission electron microscopy was showing the Rhazya extract disrupt the cell membrane of MERSA.

In this study the antibacterial property was demonstrated by the well plate methods, the measured the size of the zone it was 9-16mm in range. Khan et al demonstrated that organic alkaloid extracts of *Rhazya stricta* were showing the antibacterial property towards MERSA, and transmission electron microscopy was showing the Rhazya extract disrupt the cell membrane of MERSA. In this study the antibacterial property was demonstrated by the well plate methods, the measured the size of the zone it was 9-16mm in range. The organic alkaloid extract of *R. stricta* was the most effective against *E. Coli* and MRSA, resulting in cell membrane disruption visible with transmission electron microscopy [6].

Genotoxicity is also one of the key characteristics that make it important as therapeutic shrubs after the antibacterial activity of Rhazya. When Baeshen et al administered a whole aqueous and alkaloid extract of Rhazya to rats by oral gavage the DNA damage was showing in RAPD. In finally the results were showing the genotoxicity and clasto genicity in rat leukocytes. In this context, *Rhazya stricta* Improves key biochemical parameters in mammals Baeshen et al found that alkaloids are isolated from R's aqueous and chemical extracts. Strict therapy has the potential to reduce triglycerides without affecting the function of the liver and kidneys [7].

Along with other potential approaches, the anti-cancerous property of Rhazya is a novel potential in the field of medical science. Various studied has been done in this field, regarding the justification of this point Baeshen et al demonstrates that the aqueous extract of *Rhazya stricta* obtained from leaves induced DNA damage, cell death, cytotoxicity. This concludes that the extract has anti-cancerous and mutagenicity property [3]. *Rhazya stricta* crude extract has property has induced apoptosis [8]. Indole alkaloids (tetrahydro sycamine and swearing) have great potential regarding anti-cancer activity [10]. Rhazinilam is isolated alkaloid compounds from Rhazia stricta have great importance regarding various cancerous cell line at very low concentration [9,10] *Rhazya stricta* has a property of anticancer and antioxidant. In concern with cancer, breast cancer is a big issue. Every year it is spreading very rapidly and a prime cause of cancer death among women. In this regard, Baeshen et al reveal the anti-human breast cancer activity in Rhazya using *in vitro* methods. Ethanolic extract of *Rhazya stricta* inhibits the human breast cancer cell line MCF-7 and MDA-MB-231. They define the apoptosis by the loss of cell viability, proteolytic cleavage of polymers and chromatin condensation. They demonstrate that Bax/Bcl-2 ratio, low expression of human telomerase transcript and gene of cyclin D1. On behalf of above results *Rhazya stricta* showing anti human breast cancer activity [1]. Baeshen et al. demonstrated successfully the potential of Harmal's anti-cancer activity against human breast cancer cells *in vitro* and the mechanism of its activity. In which they found that the ethanol extract of Harmal potently inhibited the cellular growth of human breast cancer cell lines, MCF-7 and MDA-MB-231, in a dose-time dependent manner. 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. From these results, we conclude that Harmal exerts anti-proliferative action on breast cancer cells through apoptosis induction, and that it may be a potentially effective chemo preventive or therapeutic agent against breast cancer [1].

Combine effect of crude alkaloid (CAERS) and flavonoid (CFEZO) extracts prepared from medicinal herbs, *Rhazya stricta* and *Zingiber officinale*, respectively, on the growth of human GBM cell line, U251 induced apoptosis. Combination of *Rhazya stricta* and *Zingiber officinale* has potential to induce apoptosis mediated by PARP-1 cleavage, down regulation of cyclin D1 and I creased the expression of p53 and p21 [11].

Rhazya has anti-cancer properties as well as anti-diabetic properties. Rhazya has anti-diabetic potential along with anticancer as well. Baeshen et al show that alkaloids, flavonoids, tannins, and *Rhazya stricta* triterpene extract contain anti-diabetes mellitus properties. They also show that the leaf extract of Rhazya, when administered orally to streptozotocin-treated rats, increases the level of insulin and reduces the level of plasma glucose [1,3,4,12,13]. Ali et al. reveal that the stringent Rhazya also has an impact on CNS. High dose of Rhazya showed the CNS depressing property as different researchers conclude that this depressing property may be caused by the presence of β-carboline ring in the molecules obtained from Rhazya extract [14,15]. This study is an attempt to gather Rhazya data that have been grown in KSA. As far as our knowledge is concerned, however, there are few literary works related to studying Rhazya as a Mini Review.

Future prospects of Rhazya Molecules

Faisal et al have demonstrated that a chloroform extract of *Rhazya stricta* has potential in neurodegenerative diseases. It helps in neuronal differentiation at the initial stage. Pleuripotency markers (TRA-1-60, Klf4, Oct4, Sox2) were showing the down regulation under the treatment of alkaloid extract [16]**.** Nano formulation is also important steps to control the pathogenic microbes in this context Ahmed et al demonstrated the gold nano particles by the leaves of *Rhazya stricta* Decne was effective against *Leishmania Tropica* and *Staphylococcus aureus* [17]**.** The ability of humans and other mammalian species to combat a wide array of potentially invasive bacterial species depends, in part, on diverse cellular and humoral antibacterial innate immune systems [24].

Harmal extract Rhazimanine hinders metastasis and encourages apoptosis by down regulating Bcl-2 gene *in vitro* in breast cancer as well as in colon cancer, which is mediated by inhibition of NFkB and

activator protein-1. *Rhazya stricta* extract also exhibit antioxidant, inhibits colony-formation capacity and cell cycle custody. Many researchers use these Rhazya stricta compounds as a novel potential anti-tumor agent in different treatments for cancer [16,18,19].

To understand the chemical /physiochemical properties of Rhazia stricta molecules which obtain from extract will open the new vista of Rhazya compounds for their biological activity. In this regard, we predict the biological activity of a modified Rhazya compound using different commercial / public domain sarwar that may increase compound activity. Scientific community trying to identify molecules founds in Rhazya extract and study of molecules considered as future prospects of *Rhazya stricta* target and drug classification based using the commercial and public domain [20]. Swiss Target Prediction [21]. In hopes of creating better access to protein crystallization, researchers are doing to develop algorithms and hardware devices [22].

The discovery of Rhazya as therapeutic potential for various diseases since more than 100 alkaloids and non-alkaloids have been reported, but still we are not able to understand the uses of these compounds as a drug. Keeping with the view of the above facts various research groups trying to utilize the identified Rhazya compound as a modified form using various Chemo informatics techniques and predicts the biological activity of new compounds. Site-driven mutagenesis based on polymerase chain reaction (PCR) is an invaluable technique to alter genes and therefore the structure and activity of individual proteins in a systematic manner, opening up opportunities to investigate protein structure-function relationships, enzyme specificity and selectivity, or protein engineering [23].

Rhazya stricta is easily available in Arabia and South Asia and act as folk medicines so it is worth to understand at the level of the chemical, computational and synthetic point of view. Baeshen et al work on known compounds of antimicrobial Rhazia, namely Tetrahydrosecamine, Rhazimanine, Akuammidine and Stemmadenine (Tables 1- 4).

Using different Chemo informatics tool targets of antimicrobial compounds in human cells will predict and study most similar drugs. In our computational information focus on Yohimbin compound because in our selected antimicrobial compound Yohimbin is the highly similar drug for the entire compound. [20–21] Tetra hydrosecamine were targeting 73% membrane receptor, 13% enzymes (Acetylcholinesterase and Cholinesterase) while 13% target were showing unclassified. Tetra hydrosecamine is also showing similarity with Bacampicillin: It's a pro drug of ampicillin used by oral administration, absorbed in the gastrointestinal tract and hydrolyzed by the action of esterases in the intestinal wall. It has an antibacterial property using the mechanism to inhibit the biosynthesis of cell wall. It's applicable in the treatment of urinary tract and respiratory tract infections. In this context computational drug classification on the basis of drug similarity, maybe Tetra hydrosecamine has also the same mechanism of action of antimicrobial. Tetrahydrosecamine has also similarity with Pivampicillin and Pivmecillinam both have antimicrobial activity using the mechanism action of inhibition of cell wall synthesis [24].

Conclusion

Rhazya stricta is folk medicinal herbs have various pharmacological significance. In the past people were using as directly herbs, parts leaves, root and stem. In the present the chemical molecules of the herbs obtained after isolation and extraction of alkaloid and non-alkaloid have various biological activities (antimicrobial, antioxidant, antifungal, anti-inflammatory, hypertension, metabolic and CNS). In the future may be the scientific community need to change the native alkaloid structure using various server studies described in this article. Tables 1-4 reveals that the natural occurring Indole alkaloids possess not only those characteristics which are reported, but also, they have a various target prediction and drug (FDA approved) similar by chemo informatically. In this context, the researcher will design the new drugs based on Indole alkaloids of a slight modification of the side chain of Rhazya stricta's heterocyclic compounds, perhaps this new drug design that will invade the different diseases in the future. We have suggested from this current report that strict crop promotion and marketing of Rhazya throughout the world may prove to be an invaluable alternative non - conventional medicinal sources.

Table 1: *Rhazya stricta* antimicrobial compound 'Tetra hydro secamine' target prediction and drug similarity [21].

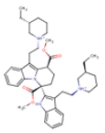
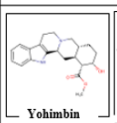
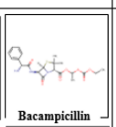
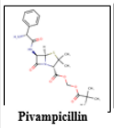
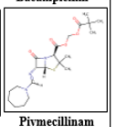
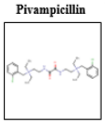
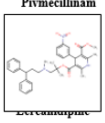
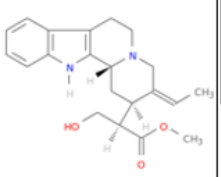
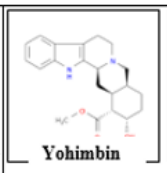
Name of molecules (Antibacterial)	Input Structure	Most similar drug	Drug predicted target
Tetrahydrosecamine	 Tetrahydrosecamine	 Yohimbin  Bacampicillin  Pivampicillin  Pivmecillinam  	Target / Target Class: Mu-type opioid receptor – Membrane receptor; Delta-type opioid receptor – Membrane receptor; Kappa-type opioid receptor – Membrane receptor; Nociceptin receptor *(by homology)* – Membrane receptor; Cholinesterase *(by homology)* – Enzyme; Acetylcholinesterase – Enzyme; Translocator protein *(by homology)* – Unclassified; Microtubule-associated protein tau – Unclassified; D(2) dopamine receptor – Membrane receptor; D(3) dopamine receptor – Membrane receptor; 5-hydroxytryptamine receptor 6 – Membrane receptor; 5-hydroxytryptamine receptor 2A – Membrane receptor; 5-hydroxytryptamine receptor 2C *(by homology)* – Membrane receptor; 5-hydroxytryptamine receptor 2B – Membrane receptor; Adenosine receptor A3 – Membrane receptor

Table 2: *Rhazya stricta* antimicrobial compound 'Rhazimanine' target prediction and drug similarity [20].

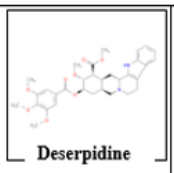
Rhazimanine ($C_{21}H_{26}N_2O_3$)



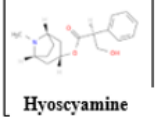
Rhazimanine



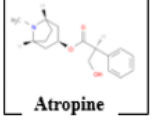
Yohimbin



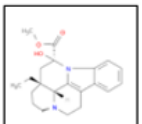
Deserpidine



Hyoscyamine



Atropine

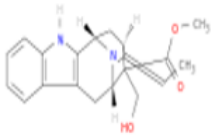


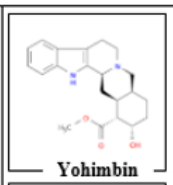
Vincamine

14 targets of Rhazimanine		
S.No	Predicted targets ordered by prediction score	E-Value
1.	Alpha-2b adrenergic receptor	3.463E-2
2.	Alpha-2a adrenergic receptor	2.599E-1
3.	Alpha-2c adrenergic receptor	3.157E 0
4.	Cytochrome P450 2D6	2.231E 2
5.	Alpha adrenergic receptor (1a and 1d)	1.499E 2
6.	Adrenergic receptor alpha-1	1.392E 2
7.	Voltage-gated L-type calcium channel alpha-1C subunit	4.812E 1
8.	Adrenergic receptors; alpha-1 A & B	3.179E 2
9.	Serotonin 2b (5-HT2b) receptor	4.425E 2
10.	Serotonin 6 (5-HT6) receptor	3.604E 2
11.	Dopamine receptors; D2 & D3	5.190E 2
12.	Dopamine receptors; D3 & D4	4.919E 2
13.	Adenosine receptors; A1 & A3	5.223E 2
14.	Serotonin 1a (5-HT1a) receptor	6.177E 2

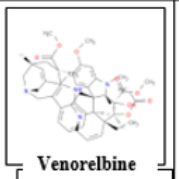
Table 3: *Rhazya stricta* antimicrobial compound 'Akuammidine' target prediction and drug similarity [21].

Akuammidine ($C_{21}H_{24}N_2O_3$)



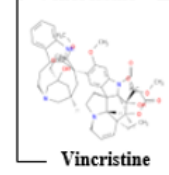


Yohimbin

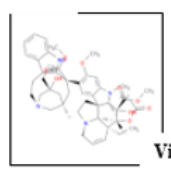


Venorelbine

Vinflunine



Vincristine

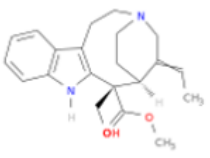


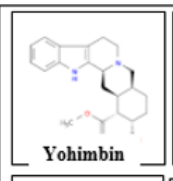
Vinblastine

Target	Target Class
Tyrosyl-DNA phosphodiesterase 1	Enzyme
Alpha-2A adrenergic receptor *(by homology)*	Membrane receptor
Alpha-2B adrenergic receptor *(by homology)*	Membrane receptor
Alpha-2C adrenergic receptor	Membrane receptor
D(2) dopamine receptor	Membrane receptor
5-hydroxytryptamine receptor 2A *(by homology)*	Membrane receptor
5-hydroxytryptamine receptor 2C *(by homology)*	Membrane receptor
5-hydroxytryptamine receptor 2B	Membrane receptor
D(3) dopamine receptor *(by homology)*	Membrane receptor
Sodium-dependent noradrenaline transporter *(by homology)*	Transporter
Sodium-dependent dopamine transporter *(by homology)*	Transporter
Cholinesterase	Enzyme
Acetylcholinesterase	Enzyme
Mu-type opioid receptor	Membrane receptor
Delta-type opioid receptor *(by homology)*	Membrane receptor

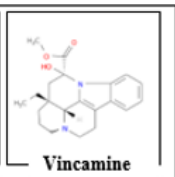
Table 3: *Rhazya stricta* antimicrobial compound 'Stemmadenine' target prediction and drug similarity [21].

Stemmadenine ($C_{21}H_{26}N_2O_3$)

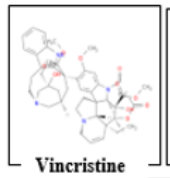




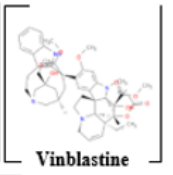
Yohimbin



Vincamine



Vincristine



Vinblastine

Vindesine

Target	Target Class
Cholinesterase	Enzyme
Acetylcholinesterase	Enzyme
Mu-type opioid receptor *(by homology)*	Membrane receptor
Delta-type opioid receptor	Membrane receptor
Kappa-type opioid receptor	Membrane receptor
Nociceptin receptor *(by homology)*	Membrane receptor
Complex	Ion channel
D(2) dopamine receptor	Membrane receptor
D(3) dopamine receptor *(by homology)*	Membrane receptor
5-hydroxytryptamine receptor 2A *(by homology)*	Membrane receptor
5-hydroxytryptamine receptor 2C *(by homology)*	Membrane receptor
5-hydroxytryptamine receptor 2B	Membrane receptor
Sigma non-opioid intracellular receptor 1	Membrane receptor
Alpha-2A adrenergic receptor	Membrane receptor
Alpha-2B adrenergic receptor	Membrane receptor

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