

Peganum harmala Chemical Compounds and Its Pharmacological Effects

Jawad Aliyar

jawad.aliyar@yahoo.com

Habibullah Paiz

Ibrahim Darwish

Ghazni University, Afghanistan

Muhammad Hussain Neda

Kabul Education University, Afghanistan

Abstract: *Peganum harmala* plant has been used in traditional Afghan medicine as a medicine in various fields. This plant contains important alkaloids such as Harmalin, Harmin, Harman, etc. The results of previous studies have shown that different concentrations of the mentioned alkaloids are used in the treatment of various diseases, including inhibition of cancer cells, diabetes, control of bacterial and fungal diseases, etc. In this article, after reviewing the definition, history of use, classification of important *Peganum harmala* alkaloids and their effective chemical compounds, we will further investigate its pharmacological effect as an important medicinal plant. In this review study, the search among the international indexes of Google Scholar, Scopus, Web of Science, Pubmed and Magiran was evaluated without year restrictions and with the keywords of *Peganum harmala* plant, alkaloid, chemical compounds and pharmacology and related articles. The findings of this research showed that *Peganum harmala* plant extract is much more effective in preventing the progression of cancer cells than its other pharmacological effects, and a lot of research can be done on it in the future studies in the field of cancer treatment methods. The *Peganum harmala* plant "Peganum harmala" is considered one of the important medicinal plants that, having valuable alkaloids from the beta-carboline family, produces an effective substance against cancer cells that is effective in the treatment of cancer cells. On the other hand, other pharmacological effects of this plant have caused it to be used in the treatment and control of many diseases such as high blood pressure, diabetes, bacterial and fungal infections, and even Parkinson's.

Keywords: Peganum harmala, alkaloids, chemical compounds and pharmacology.

1. Introduction

Peganum harmala plant with the scientific name *Peganum harmala* and the English name African rue belongs to the Zygophyllacea family. This plant is a native

plant that grows in most parts of the world, including Africa, Mediterranean regions, Europe, Asian countries, including Turkey, Iraq, Iran, and Afghanistan [1], [13], [16]. This plant has been used as an important medicine in various fields since long time in traditional medicine [1], [3], [5]. The history of medicine and treatment in Iran and Afghanistan goes back to the Aryan era, around 7000 years before Christ, as well as the first writings and prescriptions obtained from medicinal plants in important civilizations of the world such as Iran, Afghanistan, Egypt, the Middle East, ancient Greece, India and China dates back to 3000 BC. The biggest and most famous people who took the initiative to publish and compile herbal medicine as a codified science are Hippocrates because of his writings and especially his medical oath, as well as Avicenna, the author of the book (Law in Medicine), which includes information on the recognition of disease and how to treat them is considered one of the reference books of medical science. One of the most important medicinal plants, which has been studied a lot on its active ingredient, is *Peganum harmala*. Avicenna writes in his book about *Peganum harmala* that its solution is useful for joint pain and also causes heart palpitations [7]. In folk medicine from *Peganum harmala* to cure cancer, diabetes, asthma, colic, dysmenorrhea, fever, bladder stones, hysteria, jaundice, laryngitis, malaria [23]. It is used for Parkinson's and rheumatism [7]. The use of this plant in different countries is different according to their customs, for example, in India, *Peganum harmala* is used to treat syphilis and in North Africa, it is used to reduce fever. In Egypt, this plant is used in the treatment of infectious diseases and microbicide [7]. In the Second World War, harmine alkaloid found in *Peganum harmala* was used as a real serum [7]. In the Middle East, as well as in India and Africa, this plant has also been used for abortion [5]. In Afghanistan, this plant is also widely used as a popular medicinal plant to reduce blood sugar, invigorate, remove bladder stones, and in new researches to inhibit cancer cells [8], [10].

2. Methodology

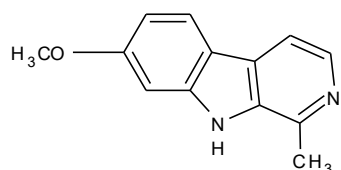
I have reviewed a number of papers in different web pages such as Google Scholar, Scopus, Web of Science, and Pubmed, and retrieved the data from those sources.

3. Classification of Alkaloids in *Peganum harmala*

Peganum harmala plant contains important alkaloids, which include: harmaline, harmine, harmalol [16], harmol, tetrahydroharmine and opoid [12], as well as substances including: Paganin, isopaganin, dopamine, gamma-aminobutyric acid, 5-hydroxytryptamine, benzodiazepine, imidazoline [5]. and also aromatic aldehydes such as benzaldehyde, methoxybenzaldehyde, 4-methoxybenzaldehyde and 3-methoxybenzaldehyde [30]. The important alkaloids of *Peganum harmala* are found in different parts of the plant such as seeds, roots, stems, leaves and even flowers. [17], [26]. But most of the storage of important alkaloids, including harmine and harmaline,

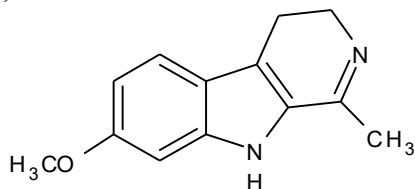
is in *Peganum harmala* seeds [17]. The most important feature of *Peganum harmala* alkaloids is that they belong to the beta carboline family [3]. Here we discuss the formulation of the important alkaloids of *Peganum harmala* [11], [12], [20].

a) Harmine:



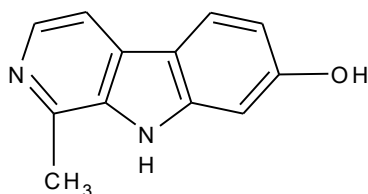
7-methoxy-1-methyl-9h- pyrido(3,4-b) indole [35].

b) Harmaline:



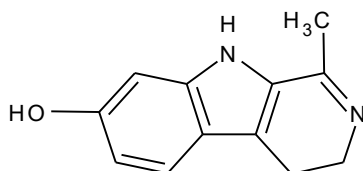
7-methoxy-1-methyl-3,4- dihydro-b-carboline [35].

c) Harmol:



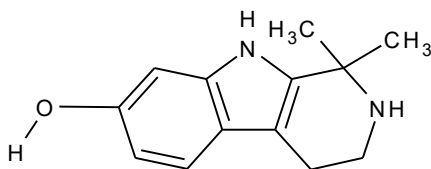
7-hydroxy-1-methyl-9h- dihydro-b-carboline [36].

d) Harmalol:



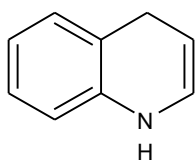
7-hydroxy-1-methyl-9h- dihydro-b-carboline [36].

e) Tetrahydroharmine:



7-methoxy-1-methyl-1,2,3,4- tetrahydro-b-carboline [37].

f) Kynuramine:



4-hydroxyquinolin [38].

g) In addition to these, there are other compounds called Imidazolin and Opioid-banzodiazepine in *Peganum harmala* extract.

Investigations have shown that the amount of two important alkaloids of *Peganum harmala*, harmine and harmaline, is the highest in the seeds and roots, and there is a small amount in the flowers [12].

Table 1

The amount of alkaloids in different parts of the body of *Peganum harmala* plant [12].

Alkaloids	Root	Stem	Leaves	Flovers	Seeds	%age
Harman alkaloids (Harmine)	+	+	-	-	+	3-2.5 %
Harmaline	+	+	-	-	+	3-2.5%
Dehydroharmine	+	+	-	-	+	3-2.5%
Quinazoline derivative de vasicine (Peganine)	-	+	-	+	+	3-2.5%
2,3-trimethylene 4 quinazoline	-	-	-	-	-	3-2.5%
1,2,3-hydroxytrimethylene quinazoline (Harmalol)	-	+	-	-	+	3-2.5%
Harmaline β carboline	-	-	-	-	+	3-2.5%
Harmaline	-	-	-	-	+	3-2.5%
Pegamine	+	+	+	-	+	-
Vasicinones	+	+	+	-	+	-

4. Betacarbolines Family

Beta-carbolines are one of the most important synthetic substances of plants, which include the structure of two indole B¹ [19]. Nearly 26 types of betacarboline have been found to be effective in the treatment of cancer cells [22]. For example, Harmin, Harman, and Noorharman, which are alkaloids found in *Peganum harmala*, belong to this family, and one of their obvious effects is to destroy cancer cells [22]. Beta-carbolines are found in medicinal plants such as *Peganum harmala*, *Eurycoma logifolia* and *Banisteria cappi* [5]. In addition to beta-carbolines, quinazolines are another group of important chemical compounds found in *Peganum harmala* alkaloids that cause many pharmacological effects [5].

5. Examining the Pharmacological Effect of *Peganum harmala* Alkaloids on Cancer Cells

5.1. The Effect of *Peganum harmala* Alkaloids on Cancer Cells

A lot of research has been done in recent years on the effects of *Peganum harmala* extract on cancer cells, all of which confirm the anti-cancer and inhibitory effects of the alkaloids in *Peganum harmala* extract. The important alkaloids of *Peganum harmala*, including harmine and harmaline, and its other alkaloids have anti-cancer properties because they belong to the beta-carboline family. In a study conducted on acute leukemia cancer cells, it has been shown that the toxicity level of *Peganum harmala* alkaloid derivatives, namely harmine and harmaline, decreases and depends on the amount (dose) and growth time of cancer cells. Therefore, the use of these alkaloids prevents the growth of K562 erythroid leukemia cells by preventing DNA² synthesis and cell division, and the harmine present in these compounds prevents the

¹ -Benzopyrole

² -Deoxyribonucleic acid

activity of topomerase 1 enzyme [10]. In another study conducted in 2007 on leukemia cells, the effects of *Peganum harmala* alkaloids along with (all-transretinoic acid) ATRA, vitamin D3 and arsenic trioxide [19], were investigated on cancer cells. ATRA is a well-known differentiator in the treatment of cancer cells [10]. Studies have shown that ATRA and vitamin D3 differentiating factors direct malignant and immature myeloid cells to differentiate into neutrophils and monocytes and show the anti-leukemic effects of plant alkaloids [10], [20]. In another research conducted on Pc12, B65, B19 cancer cells, the extract of *Peganum harmala* seeds, especially the beta-carbolines in *Peganum harmala* seeds, were used against these cells. In this research, Xanthomicrol and noscapine, which is an alkaloid extracted from Opium, and its interaction with these alkaloids in *Peganum harmala*, were used against Pc12 and 65B cells. The results showed that harmaline present in *Peganum harmala* extract has little toxicity on animals and humans, and on the other hand, it shows strong inhibitory effects against cancer cells [21]. In a study conducted in 2004 on the effects of beta-carbolines in *Peganum harmala* dry seed extract, the results showed that beta-carbolines inhibit cancer cells in mice by inhibiting DNA synthesis and helix DNA intercalate and inhibiting DNA topomerase 1 and 2 [23]. According to the results of the investigation, the mechanism of action of beta-carbolines is not as clear as other anti-cancer alkaloids such as camptothecin, vincristine and ellipticin, but through apoptosis, inhibition of DNA topomerase 1 and 2 takes place [23]. In another study, the extract of *Peganum harmala* plant was effective on cancer cells (med-vcp), (mekcarcinoma-med), (sarcoma med-vcp), the results showed the death of cancer cells 48 to 72 hours after the effect of this alkaloid. Yes, it confirms. In this study, the mechanism of effect of *Peganum harmala* alkaloids is its inhibitory effect on DNA and ANA synthesis through the inhibition of topomerase 1 enzyme and the inhibitory effect on cyclin kinase (CDKS)³ in the G1⁴ phase of cell divisions [5]. In another study, thiourea was used to cause cancer cells in mice, and then *Peganum harmala* alkaloids were used to affect these cells and several indicators were examined [1]. The effect of *Peganum harmala* on cancer cells in thyroid cells, the effect of *Peganum harmala* on liver enzymes (ALK⁵, BILL⁶ AST⁷, ALT⁸) and the effect of *Peganum harmala* on cancer cells in leukemia, which in all cases were met with the inhibitory effect of the compounds in *Peganum harmala* on these cancer cells. These compounds, in addition to beta-carbolines, contain phenolic flavonoids that have antioxidant effects and prevent the occurrence of free radicals and the creation of cancer cells [39]. And finally,

³ - Cyclin-dependent kinases

⁴ - First gap

⁵ - Anaplastic lymphoma kinase

⁶ - Bilirubin Total

⁷ - Association of Surgical Technologists

⁸ - Alanine Transaminase

in the recent studies in 2010, the alkaloids in *Peganum harmala* were used against laryngeal and hep-2 cells, the method was that when cancer cells were identified in mice and were progressing. The methanolic extract of *Peganum harmala* plant, whose main alkaloid was harmalol, was used in different doses, and the results indicated that the dose of 312 mcg/ml of the extract had a significant inhibitory effect on cancer cells compared to other doses in other treatments [16].

5.2. Disinfection and Antimicrobial Effects of *Peganum harmala*

Since ancient times and in ancient medicine, the antiseptic effects of *Peganum harmala* have been used on bacterial diseases [7]. In many researches that have been conducted in recent years, the antibacterial and anti-inflammatory role of *Peganum harmala* has been proven [28]. In 2011, *Peganum harmala* methanolic extract extracted from roots, stems, seeds, leaves and even flowers was used against human pathogenic bacteria and also the synergistic effect of these alkaloids with antibiotics against bacteria was investigated [17]. In this research, 4 different doses of methanolic extract of alkaloid were affected on gram positive bacteria including *Bacillus anthracis* and gram negative bacteria including *Pseudomonas aeruginosa* and in the next step the synergistic effect of *Peganum harmala* alkaloids on kinetic antibiotics including new and biotic, colistin and Kar nilisin and their effects on bacteria were investigated. The data analysis showed that the combination of *Peganum harmala* extract with antibiotics has a significant control effect against gram positive and negative bacteria, also the results showed that the antibacterial effect of the extract of different parts of the *Peganum harmala* plant has better results on gram positive bacteria, compared to Gram-negative bacteria [17]. In another research conducted in 2007 on *Peganum harmala* alkaloids, harman, harmine and harmalol obtained from the extract of this plant were effective on *Streptococcus*, *Escherichia coli* and *Staphylococcus aureus* bacteria, and after 24 hours of incubation at 37 degrees, the colonies were investigated. The results of the data analysis indicated that the alkaloids in *Peganum harmala* extract had a strong toxic effect on bacteria and stopped the growth of their colonies [31], [36].

5.3. Antifungal Effects of *Peganum harmala*

In many researches that have been conducted, the antifungal and antimicrobial effects of *Peganum harmala* have been confirmed, for example, in Ascension Arabia, the use of *Peganum harmala* against fungal infections is common [5]. Or, in a research conducted, the methanolic extract of *Peganum harmala* was tested on the fungi *A. ergillusniger*, *flavus*. and *candida albicans*, and its antifungal effect was proven with the agreement of the growth of these fungi [32].

5.4. *Peganum harmala* And Its Effects on A Cell

There are many sources that have confirmed the inhibitory effect of alkaloids in *Peganum harmala* extract on the growth of pathogenic cells. Among the researches that have been carried out is the use of *Peganum harmala* alkaloids against Leishmania,

the mechanism of the effect suggested by *Peganum harmala* alkaloids on Leishmania is the effect of harmaline on the inhibition of protein kinase C (PKC)⁹ enzyme in this parasite [5]. Also, in another research, it has been proven that the peganin in *Peganum harmala* extract, which is also a type of beta-carboline, has a very strong toxic effect on Leishmania (Leishmaniadonovani) [5]. Another parasite that is destroyed by *Peganum harmala* alkaloids is the bacterium that causes Mediterranean beach fever (Theileriosis). In this regard, a study has been carried out in Iran, which proves that the extract extracted from *Peganum harmala* at a dose of 5 mg / kg of body weight once a day for 5 days on cattle and sheep suffering from Mediterranean coast fever, has an effect. was given, causing signs of recovery to be observed in 78% [5]. In addition, the effect of *Peganum harmala* alkaloids on parasites has also been investigated and the results obtained show the inhibitory effect of this medicinal plant on parasites and also confirm the reduction of parasite resistance to nifurtimox, which is an anti-parasitic drug [5].

5.5. Effects On Insects

In many sources and also in traditional medicine, it is stated that *Peganum harmala* extract is a strong insect repellent [7]. In a series of researches, it has been found that the insect repellent effects of *Peganum harmala* are related to the beta carbolins present in this plant, which have strong inhibitory effects on insects in the larval stage. The extract of this plant has a very strong toxicity on the epithelial cells in the larvae, which eventually leads to the death of the larvae [5]. The next study investigated the toxicity effect of *Peganum harmala* alkaloids on the insect (*Tribolium castaneum*) and concluded that due to the death of larvae and the toxic effect of the extract of this plant on larvae, this plant can be used to control the population of harmful insects [7], [5]. *Peganum harmala* seeds powder is used as a local medicine in different parts of the world in the treatment of intestinal colic, in humans and even animals [5], [7]. The alkaloid effect of this plant is known as an antispasmodic in the treatment of intestinal diseases, and it is also possible that it is due to intestinal blockage in calcium channels [5].

5.6. Effects of *Peganum harmala* on Diabetes

One of the important effects of *Peganum harmala* plant is its effect on reducing blood sugar. The most important alkaloid that has an anti-diabetic effect in *Peganum harmala* is called harmine [5]. The mechanism of action of this alkaloid is that it regulates the lipid metabolism regulatory molecule (PPAR δ)¹⁰, which is the same mechanism of action of the anti-diabetic drug thiazolidinedinium, which inhibits the pathway (WNT)¹¹ [5]. In other experiments conducted in this field, different doses of

⁹ -Protein kinase C

¹⁰ -Peroxisome proliferator-activated receptor delta

¹¹ -A group of signal transduction pathways which begin with proteins that pass signals into a cell through cell surface receptors

Peganum harmala extract were administered to mice that had natural diabetes or were fed sucrose, and then their blood sugar levels were measured after 2 hours. The results showed that the blood sugar level of mice that received the extract of *Peganum harmala* plant was significantly reduced [20].

5.7. The Effect of *Peganum harmala* as Reducing Sensitivity to Painful and Inflammatory Stimuli

In traditional medicine, the anti-inflammatory and pain-relieving effects of *Peganum harmala* have been mentioned [7]. Many studies also confirm that the use of ethyl acetate of *Peganum harmala* extract and its formalin solution have a significant effect in reducing inflammation [5]. During a study that compared the effect of *Peganum harmala* extract on pain reduction with drugs that were previously used for this purpose, such as morphine (narcotic) and aspirin, which is an anti-inflammatory drug and an inhibitor of acetic acid, the results showed that it can. By using this plant, we can reduce the sensitivity of pain receptors and ultimately reduce pain and inflammation [35].

5.8. *Peganum harmala* and Parkinson's Relationship

In many studies conducted on *Peganum harmala* alkaloids, it has been found that the compounds of Norharmine and 9-Methyl Inoharmine have a great effect on Parkinson's disease [7]. The mechanism of action is that *Peganum harmala* extract has an inhibitory effect on neurotoxins such as 1-methyl-1-4-phenyl-1-2-3-6-tetrahydropyridine and thus causes the anti-parkinsonian effect of this extract [5]. In addition to the presence of these compounds in *Peganum harmala*, it is also present in another plant called B. Cappi, and it confirms the anti-parkinsonian effects of these compounds in this plant [5].

5.9. *Peganum harmala* and Its Effects on Blood Pressure

Harmin, harmaline, and harmalol present in *Peganum harmala* can have many effects on pressure fluctuations, so that it can cause rapid or slow heart rate, decrease blood pressure in the main arteries and even in the peripheral veins of the body, and by contracting the walls of the vessels, it can cause decrease the pressure of the heart vessels [5].

6. Other Properties' of *Peganum harmala*

In addition to the medicinal effects mentioned, other effects of *Peganum harmala* include: regularization, reduction of menstrual pains, invigoration, reduction of heart attacks, anti-fever and cough, treatment of intestinal colic, etc. [7].

7. Disadvantages of *Peganum harmala*

Despite all the medicinal properties mentioned for *Peganum harmala*, excessive consumption of *Peganum harmala* seeds has many side effects. The maximum virtual amount that has been approved for *Peganum harmala* extract is 15 to 30 ml of

decoction (1:20 plant in water) or 2 to 4 ml of tincture (10:10 plant in hydroalcoholic solution) [7]. Otherwise, it will have the following complications.

7.1. *Peganum harmala* Toxicity

Peganum harmala extract is very toxic in high doses, which has a toxic effect on both humans and animals and causes side effects:

7.1.1. *Peganum harmala* Toxicity on Animals

The toxic effect of *Peganum harmala* has been proven on many animals. For example, in cows, the toxic effect has been seen in the form of colon spasms [38]. Many other domestic animals such as sheep and camels have been poisoned by consuming high doses of alkaloids. In addition to this, other reports of poisoning of animals such as monkeys, horses and deer have also been presented [11]. Symptoms of poisoning in these animals mostly include abortion, digestive disorders, blood homolysis, and in very high doses, even the death of the animal [11]. Another research has been done in this field, in which *Peganum harmala* extract was injected in doses higher than the permissible limit to a group of rabbits and the examination of symptoms showed that the most important toxic effect of this extract in rabbits was in the form of homolysis of their blood [36]. In another experiment conducted on mice, different treatments of toxic doses of *Peganum harmala* alkaloids were given to these mice, and then their red and white blood cells were examined as well as the Bonemarrow test in all treatments. On the other hand, in another study on the same mice, their liver enzymes (ALK¹², SGPT¹³, SGOT¹⁴) were checked, finally the results showed that the effective doses that were higher than the permissible limit (LD50)¹⁵ of *Peganum harmala* alkaloids caused a decrease in blood leukocytes and The homolysis of the blood of rats caused inflammation at the injection site and showed an extremely toxic effect on liver enzymes [3], [37]. And finally, in another study, the effect of *Peganum harmala* toxicity on ruminant livestock including cows, sheep and camels was investigated. The alkaloids in *Peganum harmala* extract were injected in high doses to these cattle and the red blood cells of their blood cells were examined. The results showed that in all three groups of these animals, *Peganum harmala* extract caused the homolysis of red blood cells and also disturbed the normal development. Blood cells cause abnormal growth or reduction of erythroids and other blood cells [4].

7.1.2. *Peganum harmala* Toxicity on Humans

Although *Peganum harmala* has many medicinal properties for humans, its toxic effect on humans has also been proven and reports have been published in this field, one case is related to a young lady who consumed 50 grams of *Peganum harmala* seeds and then Symptoms of poisoning have been observed in him for a few minutes. These

¹²- Anaplastic lymphoma kinase

¹³ -Serum glutamic pyruvic aminotransferase

¹⁴ -Serum glutamic-oxaloacetic transaminase

¹⁵ -Lethal dose

symptoms appeared in the form of convulsions, severe nausea and vomiting, severe double vision, increased levels of liver and heart enzymes, severe increase in blood pressure, and severe contractions of heart vessels, etc. [11]. Or in another report, a 35-year-old man who was addicted consumed *Peganum harmala* seeds and suffered severe poisoning. The third report was about a 25-year-old pregnant Moroccan woman who had a miscarriage due to the consumption of *Peganum harmala* [9]. The most important *Peganum harmala* alkaloid that causes abortion is quinazoline [5].

7.1.3. The Effect of *Peganum harmala* On the Nervous System

Peganum harmala extract affects the nervous system by affecting the monoamine oxidase enzyme. This enzyme is a type of flavoprotein that catalyzes the oxidative deamination of primary amines, and the substrates of this enzyme are serotonin, norepinephrine, epinephrine, dopamine, as well as some secondary and tertiary amines [33]. In fact, this enzyme is secreted from the central nervous system and nerve cells and controls blood pressure and releases serotonin (5-hydroxytryptamine) in the brain [12]. Studies show that high doses of *Peganum harmala* alkaloids cause the inhibitory effect of this plant on the activities of this enzyme and disrupt all the actions performed by this enzyme in the body [12, [9], [7]. The results of this mechanism appear in such a way that it disrupts the general activities of the body by inhibiting the secretion of stomach acid, stimulating the smooth muscles of the heart, contracting the walls of the vessels [7], [5]. On the other hand, studies have shown that these alkaloids have a significant effect on monoamine oxidases A, but have no effect on monoamine oxidases B [5]. In the end, it can be said that the highest toxic effects of *Peganum harmala* will occur when the amount of alkaloids in its extract is more than the permissible limit or its (LD50). Finally, other toxic effects of *Peganum harmala* include: vomiting, depression, hallucinations, narcotics. It is paralyzing, abortifacient, nauseating and psychoactive [7].

8. Findings

The findings of this research showed that *Peganum harmala* plant extract was much more effective in preventing the progression of cancer cells than its other pharmacological effects and a lot of research can be done on it seriously in the future investigations in the field of cancer treatment methods.

9. Conclusion

Peganum harmala plant is one of the most important medicinal plants that grow widely in Afghanistan. This plant grows wild and requires few agricultural requirements, therefore, due to the many pharmacological effects of this plant, it can be used for many medicinal purposes. This plant has many medicinal properties that, by having valuable alkaloids from the beta-carboline family, produce an effective substance against cancer cells that is effective in the treatment of cancer cells. On the other hand, other pharmacological effects of this plant have caused it to be used in the

treatment and control of many diseases such as high blood pressure, diabetes, bacterial and fungal infections, and even Parkinson's. At the same time, the field for further research of this plant is also provided.

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