Chemoinformatic analysis of alkaloids isolated from *Peganum* genus

**Omer Bayazeid** - **Tohfa Nasibova**

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**Abstract**

*Peganum* genus is rich with its high phytochemical and botanical variability. *Peganum* species have been used as a sedative, antitumor, analgesic and antidepressant. This paper aims to study the molecular diversity of *Peganum* genus and to shed more light on the structure–activity relationship of the alkaloids isolated from *Peganum* genus. All *Peganum* alkaloids were grouped according to their structural properties. A chemoinformatic approach (SwissTargetPrediction) was used to determine the molecular targets of these alkaloids. To analyze and visualize the results, R software was used to generate hierarchical clustering heatmaps. The results of this study can help researchers to better understand the structure–activity relationship of *Peganum* alkaloids and how substitution can affect the biological activity of those alkaloids.

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**Author Information**

1. **Omer Bayazeid**
omerbayazid@gmail.com
   Department of Pharmacognosy, Faculty of Pharmacy, Hacettepe University, Sihhiye, 06100 Ankara, Turkey

2. **Tohfa Nasibova**
   Department of General and Toxicological Chemistry, Azerbaijan Medical University, A. Gasimzade 14, AZ1022 Baku, Azerbaijan
Introduction

*Peganum genus* belongs to *Nitrariaceae* family, and it contains six species: *Peganum harmala* L., *Peganum nigellastrum* Bunge, *Peganum multisectum* (Maxim.) Bobrov, *Peganum mexicanum* A. Gray, *Peganum rothschildianum* Buxb and *Peganum texanum* M.E.Jones [1]. *P. harmala* (also known as Harmala or Syrian rue) has a wider distribution area and is found in Asia, North Africa, America and Australia. Other species such as *P. nigellastrum* and *P. Multisectum* grow in specific regions, and they are found mainly in Asia; Mongolia and China. Moreover, *P. mexicanum* is found mainly in Mexico [2, 3]. *Peganum* species are categorized according to their morphological characteristics (seed shape, seed coat features, leaves, and petal color), as well as genetic and cytological differences. *Peganum genus* is widely used in traditional medicine, and it is used as carminative, emetic, analgesic, aphrodisiac and also to treat epilepsy and memory loss [4]. Traditional usages of *Peganum* species are available in Table 1.

The effect of *P. harmala* is well documented in Iran, Turkey, Mongolia and Xinjiang [13]. *P. harmala* is widely used in folk medicine, and for that reason, its biological activities have been well studied. All biological activities related to *Peganum* species can be found in Table 2. *Peganum* alkaloids in this study are grouped into four main groups:
β-carboline alkaloids (harmine, harmaline and harmol), indole alkaloids (6-methoxyindoline and Peganine A, B), quinazoline alkaloids (vasicine and vasicinone) and quinoline alkaloids (ipidacrine).

Tryptamine is a major precursor of a wide range of β-carboline alkaloids [31] (Fig. 1A). Tryptamine is formed from L-tryptophan by tryptophan decarboxylase which is produced through the shikimate pathway. On the other hand, quinazoline alkaloids can either be derived from L-asparagine or L-ornithine (Fig. 1B). Anthranilic acid forms the α part of quinazoline alkaloids, and anthranoylphenylalanine forms the β part of quinazoline alkaloid [32].

Chemoinformatics is an area that deals with indexing, collecting, and using the information to better understand chemical compounds. Here, we used chemoinformatics technique (SwissTargetPrediction) to predict the molecular targets of Peganum alkaloids. SwissTargetPrediction predicts the most possible molecular targets for small molecules based on shape similarity. The target estimation is based on 2D and 3D similarity of the small molecules using a library of 370,000 recognized molecules [33, 34]. We then used R software for data analysis and also to generate heatmaps to identify any pattern in the predicted data.

### Materials and methods

#### Database search

We used Web of Science to search for the alkaloids isolated from Peganum genus with keywords, “Peganum,” “β-carboline alkaloid,” “indole alkaloid,” “quinazoline alkaloid” and “quinoline alkaloid”. We collected: 27 β-carboline alkaloids, 12 indole alkaloids, 15 quinazoline alkaloids and 6 quinoline alkaloids.

#### Chemical structure drawing

Marvin was used for drawing, displaying and characterizing chemical structures, Marvin 19.17, 2019, ChemAxon (http://www.chemaxon.com).

#### Canonical SMILES

PubChem database was searched to retrieve the structure of each compound, and canonical SMILES of the alkaloids was obtained from PubChem [35]. For the alkaloids that are not registered in PubChem, Marvin sketch was used for drawing the structure and SMILE generation.

### Table 1 Traditional usage of *Peganum* species

| Species         | Part used       | Traditional usage                                                                 |
|-----------------|-----------------|------------------------------------------------------------------------------------|
| *Peganum harmala* | Seeds           | Hypertension, thrombosis, constipation, meteorism, diarrhea, pain (intestinal, rheumatic, headache, toothache, back pain), memory loss, depression, abortion, stimulation of menstruation, subcutaneous tumors, bacterial, fungal, viral infections, diabetes mellitus, healing wound, fever, dermatosis, ulcer, malaria, asthma, bronchitis, expectoration, cough, kidney stone, eye complaints, syphilis [3, 5–11] |
| *Peganum nigellastrum* | Whole plants or seeds | Rheumatism, irregular menstruation, cough, asthma, abscesses, inflammatory diseases [12] |

### Table 2 Biological activities of *Peganum* species

| Species         | Part used       | Biological activity                                                                 |
|-----------------|-----------------|------------------------------------------------------------------------------------|
| *Peganum harmala* | Seeds           | Acetyl- and butyrylcholinesterase inhibitor [14], adrenergic receptor inhibitor [15], analgesic [8] |
| *Peganum harmala* | Seeds, roots    | MAO-A inhibitor [16], COMT inhibitor [17], human DNA topoisomerase I inhibitor [18] |
|                 | Seeds, leaves   | Antimicrobial [19], antitumor [20], antiproliferative [21], antioxidant [22], anti-inflammatory [23], RNA- and DNA-binding [24] |
| *Peganum nigellastrum* | Seeds       | Anti-Alzheimer [25], acetylcholinesterase inhibitor, antitumor activity, antiviral [12], butyrylcholinesterase inhibitor [26], cytotoxic activity, inhibitory activity against topoisomerase I and II [27, 28] |
| *Peganum multisectum* | Seeds       | Antitumor activity [29], acetylcholinesterase inhibitor [12, 30], butyrylcholinesterase inhibitor [26] |
Swiss target prediction

Structure similarity search is based on the idea if two molecules possess similar 2D/3D structure similarity, they may have similar molecular targets/biological activities. The 2D similarity is quantified by the Tanimoto coefficient between the fingerprints vectors of both the query and the screened molecules; the 3D similarity is quantified by the Manhattan distance between the ElectroShape vectors of 20 conformers for both the query and the screened molecules. A query molecule (alkaloid) was submitted to SwissTargetPrediction server as SMILES, and then, Homo sapiens library was selected as a specie. Swiss then compared each query molecule with the ChEMBL library of 370,000 known active molecules and assigned a Swiss score. The score is based on similarity value with the most similar ligands where zero denotes lowest score, no similarity and 1 denotes maximum score, high similarity [33, 34].

R programming language

The obtained results were processed via R software to combine each alkaloids type in one table by using tidyverse package; lapply() and reduce().

```
fl <- list.files(pattern = "\.csv$").
mf <- lapply(fl, function(x) { DT <- fread(x). new_colname <- x %>% basename %>% str_replace_all(c("^output_" = "", "\.csv$" = "")) %>% ! str_c("", .) setnames(DT, old = "prediction_score", new = new_colname). return(DT). })

final_table <- merged_data %>% reduce(mf, merge, by = "molecular_target", all = TRUE).
```

Obtained similarity scores were used to generate hierarchical clustering heatmap using R software by using pheatmap package [36].

```
pegaum_alkaloids <- as.matrix(pegaum_alkaloids).
install.packages("pheatmap").
library("pheatmap").
pheatmap(pegaum_alkaloids).
```

Result and discussion

We have labeled unnamed alkaloids to improve the readability of the data analysis in the heatmaps. Table 3 lists the new labels assigned to each alkaloid.

Table 3 Compounds associated labels

| Compound name                                      | Associated label |
|---------------------------------------------------|------------------|
| 2-aldehyde-tetrahydroharmine                      | Compound I       |
| 3,4-dihydro-β-carboline                           | Compound II      |
| 6-methoxytetrahydro-1-norharmanone                | Compound III     |
| 1-ethyl-7-methoxy-9H-pyrido[3,4-b]indole          | Compound IV      |
| 2-(indol-3-yl)ethyl-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside | Compound V       |
| 2-(indol-3-yl)ethyl-β-D-glucopyranoside           | Compound VI      |
| 10-methyl-11-acetylvasicine                       | Compound VII     |
| 2-carboxy-3,4-dihydroquinazoline                  | Compound VIII    |
| 2-deoxypeganylacetic acid                         | Compound IX      |
| Vasicine-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside | Compound X      |
| 3-(4-Hydroxyphenyl)quinoline                      | Compound XI      |
| 3-(1H-indol-3-yl)quinoline                        | Compound XII     |
| 3-phenylquinoline                                 | Compound XIII    |
| 4-amino-2-ethyl-3 methylquinoline                 | Compound XIV     |
β-carboline alkaloids

β-carboline alkaloids are a wide group of natural and synthetic alkaloids with a tricyclic pyrido[3,4-b]indole ring structure. They are characterized as a combination of indole structure and a pyridine ring. β-carboline alkaloids possess strong neuroactivity by targeting 5-hydroxytryptamine receptors, monoamine oxidase (MAO), N-methyl-D-aspartic acid receptors, and dopaminergic signaling pathways [37]. β-carboline alkaloids have been reported as inhibitors of DYRK1A kinase activity [38]. Some β-carboline derivatives have also been reported to act as serine/threonine-protein kinase PLK1 [39] and CDK inhibitors [40]. Swiss predicted that the carbonyl substitution (R–C = O–R) at position 1 of β-carboline alkaloids (compound III; 6-methoxytetrahydro-1-norharmanone and harmalacidine) could increase the inhibitory effect of MAP kinase activated protein kinases. β-carboline alkaloids are potent dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A) inhibitors, e.g., harmol has a half maximal inhibitory concentration (IC₅₀) of 90 nM [41]. Nevertheless, substitution could play a major role in increasing or diminishing the DYRK1A inhibitory effect of β-carboline alkaloid. Position 1 should always be substituted with only one group (it can be methyl or carbonyl). Adding hydroxyl or methoxy group to either position 6 or 7 could increase the activity dramatically especially in the methoxy group (Figs. 2 and 3). Inhibiting DYRK1A leads to a reduction in the phosphorylation of microtubule-associated protein tau [42]. Swiss predicted that β-carboline alkaloids that can inhibit DYRK1A (with high Swiss score) are able to target microtubule-associated protein tau, e.g., tetrahydroharmine (Fig. 2).

β-carboline alkaloids can be grouped into three main groups according to the saturation of the nitrogen-containing ring: fully aromatic β-carbolines, dihydro-β-carbolines (partially saturated ring) and tetrahydro-β-carbolines (completely saturated ring) [37]. Swiss predicted that only fully aromatic β-carbolines has the ability to inhibit MAO-A and B. The methoxy substitution at position 7 is important for the activity as this part of the β-carboline alkaloid is expected to interact with the hydrophobic pocket of MAO [43]. Serotonin (5-HT) receptors consist of seven families and more the 15 subfamilies. Selectivity is a major problem when targeting 5-HT receptor. 5-HT (indolealkylamine) binds to all 5-HT receptors at a nanomolar level. The term “semiselective agent” concept was created to distinguish molecules that have more selectivity (selective for two or three 5-HT subfamilies) than those who can bind to all 5-HT receptors. 5-HT subfamily specificity does not depend on

Fig. 2 Consensus molecular targets of β-carboline alkaloids isolated from Peganum genus (Part I)
Fig. 3 Consensus molecular targets of β-carboline alkaloids isolated from *Peganum* genus (Part II)

Fig. 4 Consensus molecular targets of indole alkaloids isolated from *Peganum* genus
specific chemical class, it mainly depends on the substituent type in the same chemical class. This means that any small structural changes can lead to a great change in the selectivity [44]. Results show that tetrahydro-β-carbolines is the class of β-carbolines alkaloids with the least selectivity toward 5-HT receptor subfamilies. The selectivity of tetrahydro-β-carbolines could be enhanced if position 1 is substituted with carbonyl group (compound III) or the nitrogen at position 2 is substituted with an aldehyde -CHO (compound I; 2-aldehyde-tetrahydroharmine). Dihydro-β-carbolines could be also less selective if they do not have any substitution (compound II; 3,4-dihydro-β-carboline) (Fig. 2). All fully aromatic β-carbolines such as harmine have higher Swiss score (better activity) and better selectivity (Fig. 3).

Indole alkaloids

Indole alkaloids are bicyclic alkaloids that have benzene ring connected to a five-membered pyrrole ring. The nitrogen atom in the pyrrole ring is behind the pharmacologically properties of indole alkaloids [40]. Indole alkaloids have been reported to have antinociceptive, antioxidant, anti-inflammatory, antitumor and antimicrobial properties as well as anti-butyrylcholinesterase and anti-acetylcholinesterase properties. They are frequently linked to G-protein receptor function, especially neuronal signal transmission through 5-HT/hydroxytryptamine receptors [45]. Compound VII (2-acetyl-3-(2-acetamidoethyl)-7-methoxyindole) and pegaharmaline F are very similar to melatonin structure (Fig. 4). Melatonin is a cytoprotective agent, and it stimulates the immune system to regulate the sleep/wake cycle. The pyrrole-ring in the melatonin is cleaved by the liver to produce N1-acetyl-N2-formyl-5-methoxykynuramine. This secondary metabolite supports mitochondrial function and acts as neuroprotection [46]. Compound VII and pegaharmaline F are the only indole alkaloids that Swiss predicted to interact with melatonin receptor 1A and 1B. In addition, they are the only indole alkaloids that can inhibit DYRK1A. Peganum indole alkaloids possess opioid receptor activity by target mu, delta and kappa-type opioid receptor. Swiss also predicted that peganumaline A (dimeric form of peganumaline B) has the strongest mu, delta and kappa-type opioid receptor activity among other Peganum indole alkaloids (Fig. 4). This is due to high 2D similarity between peganumaline A and 3-spirocyclic indolin-2-ones (CHEMBL381429). CHEMBL381429 binds with kappa-type opioid receptor with IC₅₀ of 1.2 µM [47]. Swiss predicted that Peganum indole alkaloids have a weak MAO and acetylcholinesterase activity.

Quinazoline alkaloids

Quinazoline alkaloids have a bicyclic structure that consists of two fused six-membered aromatic rings, a benzene ring,
and a pyrimidine ring. These alkaloids are especially distinguished for their antimalarial and anticancer properties [48]. In addition, they also act as bronchodilator, antitussive, cytotoxic, antimycobacterial, antileishmanial and antiulcer effects [49]. Swiss predicted that *Peganum* quinazoline alkaloids possess weak serotonergic activity and some quinazoline alkaloids could have potent cholinesterase activity. Substitution of quinazoline alkaloids has a big impact on its biological activities. Swiss predicted that quinazoline alkaloid with huge structure, e.g., dimers (dipegine and dipегинол), and glucosides (vasicinol-Glu and vasicine-Glu) do not have cholinesterase activity as well as quinazoline alkaloid that lacks the five-member ring (compound VIII; 2-carboxyl-3,4-dihydroquinazoline) (Fig. 5). Swiss predicted that both desoxypeganine and its derivative vasicine (hydroxy group at position 3) have very high cholinesterase activity. It has been reported that desoxypeganine inhibits acetylcholinesterase with \( IC_{50} \) of 3.72 \( \mu \)M [50] and vasicine inhibits butyrylcholinesterase with a \( IC_{50} \) of 3.13 \( \mu \)M [51]. Changing the position of the hydroxy group (peganol) or adding a second hydroxyl group to desoxypeganine (vasicinol and 4-vasicinol) could decrease the cholinesterase activity of quinazoline alkaloids.

**Quinoline alkaloids**

Quinoline alkaloids are derived from either anthranilic acid or tryptophan. Most of quinoline alkaloids are substituted at position 2 of the heterocycle [50]. Swiss predicted that some of *Peganum* quinoline alkaloids have kinase activity and some have cholinesterase activity. Ipidacrine has the strongest cholinesterase activity, and it is probably due to the additional five-member ring and the amine substitution; ipidacrine inhibits cholinesterase with \( IC_{50} \) of 70 nM [52]. Swiss also predicted that compound XII (3-(1H-indol-3-yl)quinoline) could target platelet-derived growth factor receptor tyrosine kinase (PDGF) (high score) and epidermal growth factor receptor (EGFR) (low score) (Fig. 6). It has been reported that compound XII inhibits PDGF with \( IC_{50} \) of 8 \( \mu \)M and EGFR with \( IC_{50} \) of 20 \( \mu \)M [53]. In addition,
quinoine alkaloids with phenol ring such as compound XI (3-(4-hydroxyphenyl)quinoline) could have mild mitogen-activated protein kinases activity and this is due to its high similarity with CHEMBL248643 which can inhibit mitogen-activated protein kinase p38 with IC$_{50}$ of 20 μM and c-Jun N-terminal kinase 3 with IC$_{50}$ of 0.59 μM [54, 55].

**Conclusion**

In conclusion, these research-based findings include an overview of *Peganum* genus phytochemical and bioactivity data. The molecular targets of alkaloids were predicted using chemoinformatic approach, which shed light on the structure–activity relationship of alkaloids isolated from *Peganum* species. Regarding the anticancer effect of β-carbolines alkaloids, Swiss predicted that the carbonyl substitution (R–C=O-R) at position 1 of β-carboline alkaloids could increase the inhibitory effect of MAP kinases. In addition, β-carboline alkaloids are neuroactive molecules, and Swiss predicted that only fully aromatic β-carboline alkaloids have the ability to inhibit MAO A and B. β-carboline alkaloids also have serotonergic effect, and the selectivity of tetrahydro-β-carboline can be enhanced if position 1 is substituted by carbonyl group or the nitrogen at position 2 is substituted with an aldehyde -CHO. Swiss predicted that the indole alkaloids such as compound VII and pegaharmaline F are the only indole alkaloids to interact with several neurotransmitters and opioid receptors including the μ, δ, and κ opioid receptors, and Swiss predicted that the indole alkaloids such as compound VII and pegaharmaline F are the only indole alkaloids to interact with melanin receptor 2. Swiss also predicted that peganumaline A has the strongest mu, delta and kappa-type opioid receptor activity among other *Peganum* indole alkaloids. Swiss predicted that substitution of quinazoline alkaloids has a big impact on its biological activities of quinazoline alkaloid; huge structure differences and seed coat morphology. Plant Biol 13:940–947.

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