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Standardization study of aerial parts of Iceland Poppy (*Papaver Nudicaule L.*)

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Objective: This study aimed to establish quality standards for the aerial parts of the medicinal plant Iceland poppy (*Papaver nudicaule L*.). **Methods:** The anatomical structures of the aerial parts of plants were determined using microscopy. Bioactive compounds were identified and quantified using High-Performance Liquid Chromatography (HPLC). General quality parameters of the aerial parts of the Iceland poppy (*Papaver nudicaule L*.) were determined using the methods outlined in the European Pharmacopoeia. **Results:** The plant was collected from gravelly soil along the riverbank near the mouth of the Gorkhi-Terelj Valley in Erdene Soum, Tuv Province. The microstructure of the aerial parts of the Iceland poppy (*Papaver nudicaule L*.) was determined. The quality parameters of the aerial parts of Iceland poppy (*Papaver nudicaule L*.) were determined as follows: total ash content 5.54±0.2131%, moisture content 4.11±0.41%, and extractable substances with 70% ethanol were found to be highest at 27.61±0.43%. Additionally, the heavy metal and microbiological purity levels complied with the recommendations of the WHO and the requirements of the European Pharmacopoeia. **Conclusion:** The standardization criteria for the aerial parts of *Papaver nudicaule L*. were established. In addition, the pseudoprotopine alkaloid content in the aerial parts of *Papaver nudicaule* was found to be 0.0288 ± 0.0005%.

Keywords: Standardization, Medicinal plant, Iceland poppy, Pseudoprotopine alkaloid, *Papaver nudicaule L*.

Introduction

In recent years, significant attention has been paid to the use of natural medicinal substances, plant-based medicines, and preparations. According to the report from the International Union for Conservation of Nature and the World Wildlife Fund 50,000 to 80,000 species of flowering

plants are used for medicinal purposes worldwide.[1] Furthermore, according to the World Health Organization (WHO), the global market for medicinal plants and traditional plant-based medicines is expected to continue growing globally in the coming years.[2,3] In Mongolia, researchers have identified approximately 900 species from approximately 70 families that contain biologically active compounds with medicinal properties and are capable of treating various diseases. In traditional Mongolian medicine, many plants are used to treat various diseases, but most remain scientifically unstudied. One such plant is the Iceland poppy (*Papaver nudicaule L*.) of the Papaveraceae family, which includes about 44 genera and 760 species worldwide, with 32 species from 7 genera found in Mongolia.[4] The Iceland poppy (*Papaver nudicaule L*.) was first described by Carl Linnaeus in *Species Plantarum* (1753), with its type specimen preserved in London.[5] Iceland poppy contains isoquinoline alkaloids, among which protopine is a major bioactive compound. Protopine has been reported to possess pharmacological properties, including antispasmodic, anti-inflammatory, and hepatoprotective effects, making it an important marker for the standardization and quality control of *Papaver nudicaule L*. In Tibetan medical texts, the plant *Mé-tog-ser-chen* (identified as *Ixeris* sp.) is used in Traditional Tibetan medicine, where its bitter roots and aerial parts serve medicinal purposes. According to traditional Mongolian medicine, the Iceland poppy (*Papaver nudicaule L*.), orange poppy (*P. rubro-aurantiacum*), and false pale poppy (*P. pseudocanescent*) are used as substitutes.[6] The medicinal application in Mongolian traditional medicine of Iceland poppy (*Papaver nudicaule L*.) has been mentioned in multiple traditional Mongolian books.[6-10] According to the literature, the Iceland poppy (*Papaver nudicaule L*.) has a bitter, cold nature and is used to reduce fever, detoxify, and relieve lung congestion through its antibacterial effects. The Iceland poppy (*Papaver nudicaule L*.) is widely distributed across Mongolia, all parts of the plant, including the flowers and fruits are used as medicinal raw material.[4,11] However, research on Mongolia's medicinal plants remains limited. The absence of standard methods and quality criteria for the under-studied Iceland poppy (*Papaver nudicaule L*.) underscores the need for this study.

Materials and methods

Plant Material: The medicinal plant Iceland poppy (*Papaver nudicaule L*.) was collected from gravelly soil along the riverbank near the mouth of the Gorkhi-Terelj valley in Erdene Soum, Tuv Province, at 48°01'49.6" N, 107°43'08.2" E). The plants were identified by T. Munkh-Erdene, Curator of the Plant Collection and Phylogenetics Laboratory, Department of Plant Taxonomy, Institute of Botany, Mongolian Academy of Sciences. Plant samples were dried and prepared in a well-ventilated area with shelves at the Department of Medicinal Plants, School of Pharmacy, Mongolian National University of Medical Sciences.[12]

Standards and Chemicals: Pseudoprotopine alkaloid with a purity of 99.9% (series number 1701010323), produced by Sichuan Xieli Pharmaceutical Co., Ltd., China, was used. The solvents used in the High-Performance Liquid Chromatography (HPLC) analysis were of high purity, specifically designed for HPLC, and all other reagents and solvents used were of suitable purity for the analysis.

Leaf Microscopy: The aerial parts of the Iceland poppy (*Papaver nudicaule L*.) were soaked, and thin sections were cut from the soaked samples using a sharp scalpel. A chloral hydrate solution was used for clarification. The clarified sections were placed on a glass slide, stained with safranin solution for 1 min, and then rinsed twice with distilled water. The sections were then covered with distilled water and sealed with cover glass to prepare the slides. The prepared microscopic samples were observed under a light microscope at magnifications of 10×10 and 10×40, and images were captured using a 13-megapixel digital camera for analysis.

Determination of Quality Parameters: The total ash content, moisture content, extractable substance content, heavy metal levels, and microbiological purity were determined in accordance with the WHO guidelines and methods outlined in the European Pharmacopoeia.[13]

Chemical Analysis: HPLC determination of pseudoprotopine alkaloid as a biologically active compound

Preparation of the Standard Solution for Alkaloid Quantification.[13,14,15]

Preparation of Extract: A 3.0 g sample of finely ground plant material was extracted three times with ethanol (30 mL each, 30 min each, with 10-min intervals) using ultrasonic-assisted extraction. The residue was then evaporated and dissolved in methanol.

The cooled extract was filtered, adjusted, passed through a 0.45 µm membrane, and injected for analysis

Preparation of the Standard Solution: 25 ng of pseudoprotopine alkaloid was weighed, diluted three times, filtered through a 0.45 µm membrane, and injected for chromatographic analysis.

Chromatographic Procedures: Analysis used a C18 column (250 × 4.6 mm, 5 µm) with water (A) and acetonitrile (B) in a gradient (6-30 min), flow rate 1.0 mL/min, column temperature 40 °C, injection volume 20 µg/mL, and UV detection at 290 nm.

Validation of the developed HPLC method for the quantitative determination of pseudoprotopine ICH guidelines was performed to validate the developed methods with specificity, linearity, accuracy, precision, repeatability, LOD, and LOQ.[16,17]

Selectivity and Specificity: The selectivity and specificity of the developed method for measuring pseudoprotopine alkaloid in the aerial parts of *Papaver nudicaule L*. were defined.

Linearity: Linearity was assessed by injection of pseudoprotopine standard solution in a range consisting of 5, 15, 25, 35 and 45ng/ml. The slope, the correlation coefficient (R2) and the intercept were calculated.

Precision: Three different drug concentrations were analyzed in triplicate, three times on the same day, to determine the intraday precision of the chosen method. The same sample analysis used for the intraday precision assay was also used to evaluate the intraday precision, and this process was done three days in a row. The precision of the analytical process was assessed and presented as %RSD for a statistical analysis.

Accuracy: For the accuracy of the proposed method, recovery studies were performed by the standard addition method. A known amount of the reference pseudoprotopine alkaloid was added to the pre-analyzed plant powder, and the sample was then analyzed using the proposed method.

Limit of Detection and Limit of Quantification: The limit of detection (LOD) and the limit of quantification (LOQ) for pseudoprotopine were determined.

Statistical Analysis

The data are reported as the mean±standard deviation. Quality parameter experiments were repeated three times, and the quantitative determination of the content of pseudoprotopine alkaloids and rutin flavonoids in a sample was repeated six times using linear regression analysis. Analyses were performed using SPSS Statistics software (version 26.0).

Results

Microstructural Study

The leaves of the Iceland poppy (*Papaver nudicaule L*.) have a dorsiventral structure, with chlorenchyma in two columnar layers and 4-5 layers of spongy tissue. Collateral vascular bundles lie between these tissues. The leaf comprises epidermis, columnar tissue, spongy tissue, and vascular bundles. Epidermal cells are large, thin-walled, and rectangular, with numerous anomocytic stomata, especially on the lower surface. (Figure 1)

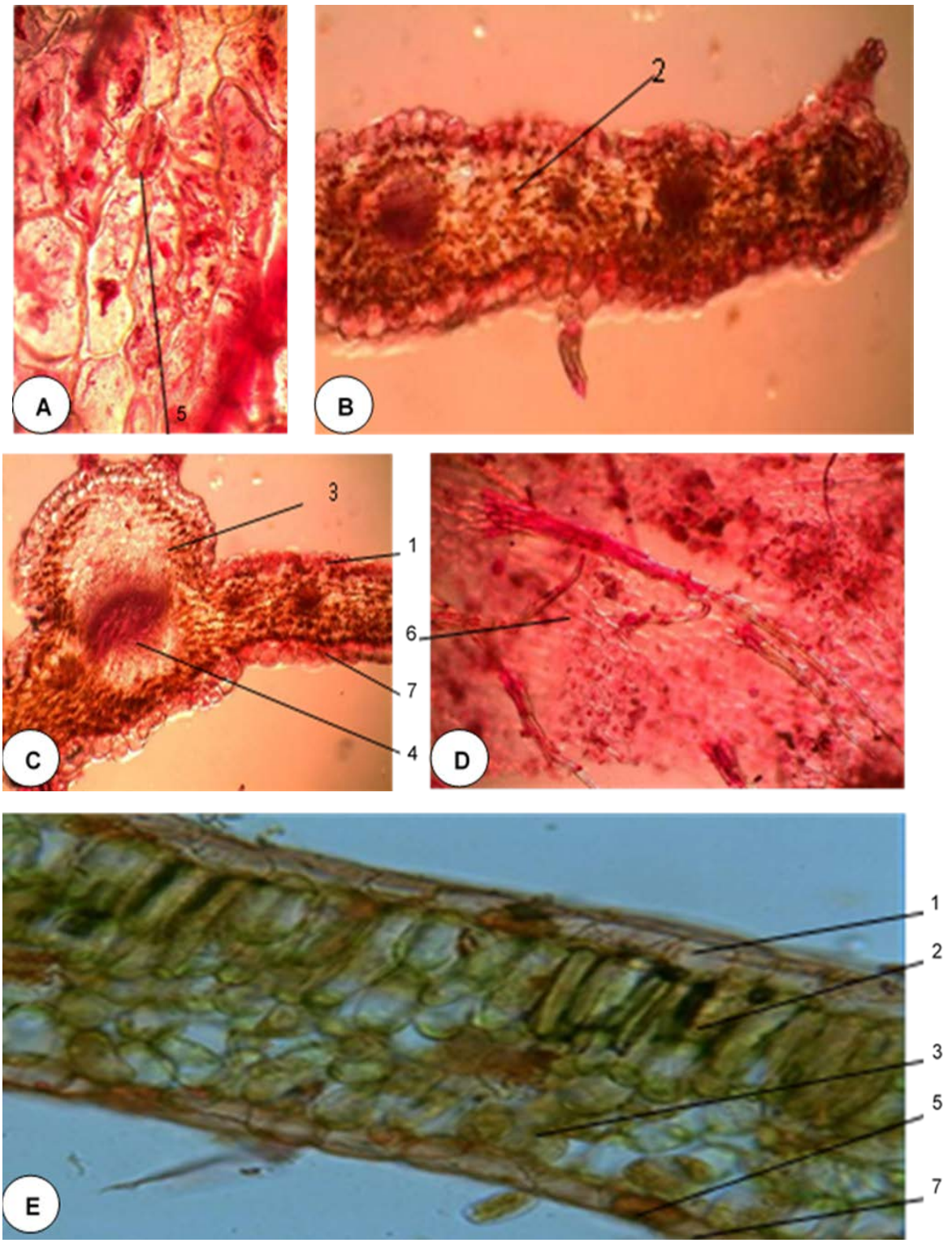

Figure 1. The Figure 1. The anatomy of the leaves of the Iceland poppy (Papaver nudicaule L.) A. Upper epidermis. B, E. Leaf anatomy. C. Anatomical components of the leaves. D. Lower epidermis. Abbreviations: 1 = Upper epidermis, 2 = Palisade parenchyma, 3 = Spongy collenchyma, 4 = Vascular bundle, 5 = Stoma, 6 = Unicellular trichomes, 7 = Lower epidermis. Bars: A,D,E = 400x; B,C = 100x

Quality Parameters

The quality parameters of the medicinal plant Iceland Poppy (Papaver nudicaule L.) were determined in accordance with the European Pharmacopoeia (Figure 2)

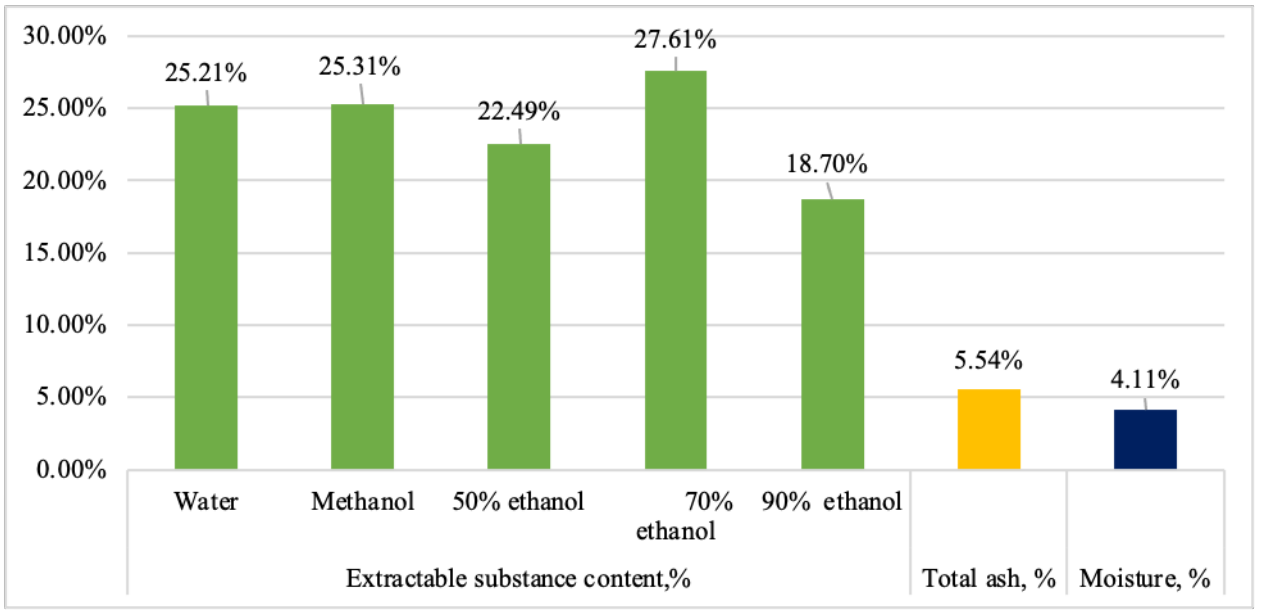

Figure 2. The extractable substance content from the aerial parts of *Papaver nudicaule L*. was highest with 70% ethanol (27.61 ± 0.41%), followed by water (25.21 ± 0.39%), methanol (25.31 ± 0.32%), and 50% ethanol (22.49 ± 0.46%), with the lowest yield using 90% ethanol (18.70 ± 0.063%). The total ash content of the aerial parts of *Papaver nudicaule L*. averaged 5.54%, with values ranging from 5.29% to 5.78% and a maximum deviation of ±0.30%. Deviations from the mean (D) and their squares (D^2) were calculated, showing consistent ash content and a stable level of inorganic matter, important for assessing the quality and purity of the herbal material. The moisture content of the aerial parts of *Papaver nudicaule L*. was determined from six replicates, averaging 4.11% (min 3.95%, max 4.38%). Deviations from the mean (D) and their squares (D^2) were calculated, yielding a standard deviation of 0.155 and a confidence error of 0.074, indicating low variability and stable moisture content.

HPLC analysis:

HPLC analysis of 5 µL injections of standard and sample solutions showed pseudoprotopine alkaloid eluting at 2.852 min, with six replicates in Iceland poppy (*Papaver nudicaule L*.) yielding 0.0288 ± 0.0005%. (Figure 3)

The alkaloid pseudoprotopine in the aerial parts of Papaver nudicaule L. was quantified by HPLC (n = 6). Retention time averaged 2.852 ± 0.003 min (RSD 0.1%), with a mean peak area of 679.824 ± 13.416 mV (RSD 1.97%). The mean pseudoprotopine content was 0.0288 ± 0.0005% (RSD 1.74%), demonstrating accurate, reproducible, and precise quantification.

Method Validation

The HPLC method for pseudoprotopin alkaloid was developed and validated following ICH Q2 (R1) guidelines. Specificity was confirmed by analyzing chromatograms of the blank (mobile phase), the pseudoprotopine standard, and the sample solution. Linearity was demonstrated, showing that test results were directly proportional to analyte concentration within the tested range.

Precision

The intermediate precision of pseudoprotopin was evaluated by analyzing three replicates of a standard solution on three different days by an analyst. The results are presented in Table 1.

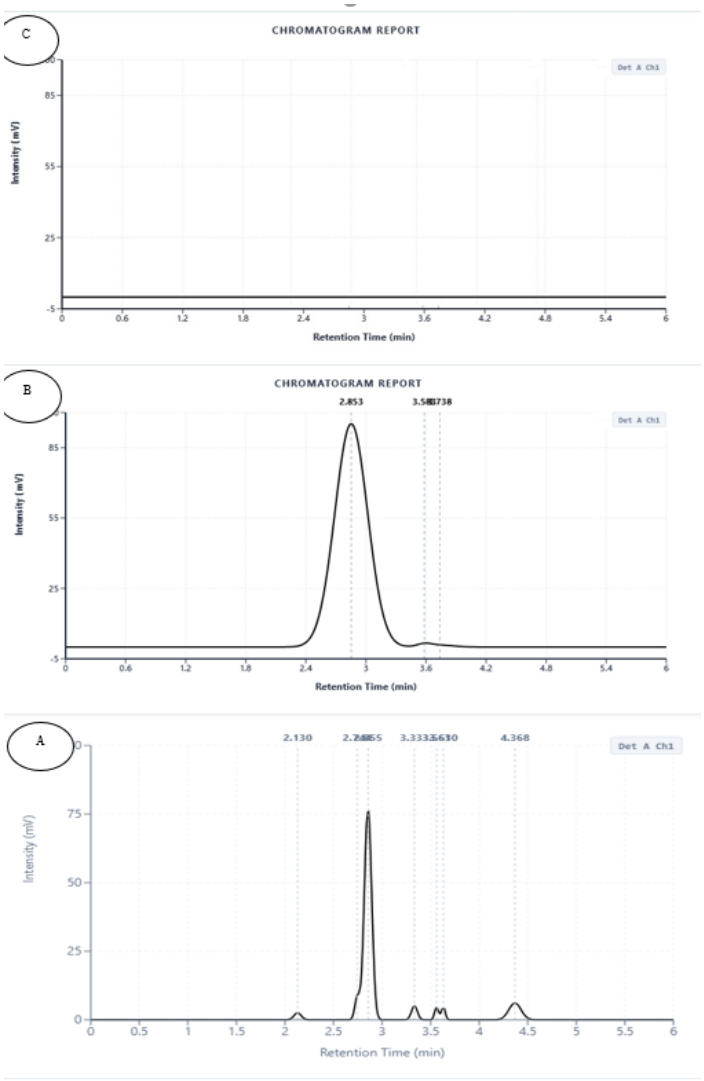

Figure 3. Chromatogram showing the detection and quantitative determination of the pseudoprotopine alkaloid in the aerial parts of the medicinal plant Iceland poppy (*Papaver nudicaule L.*). A. HPLC Chromatogram of the sample of Papaver nudicaule L., B. Standard solution of pseudoprotopine, C. Methanol

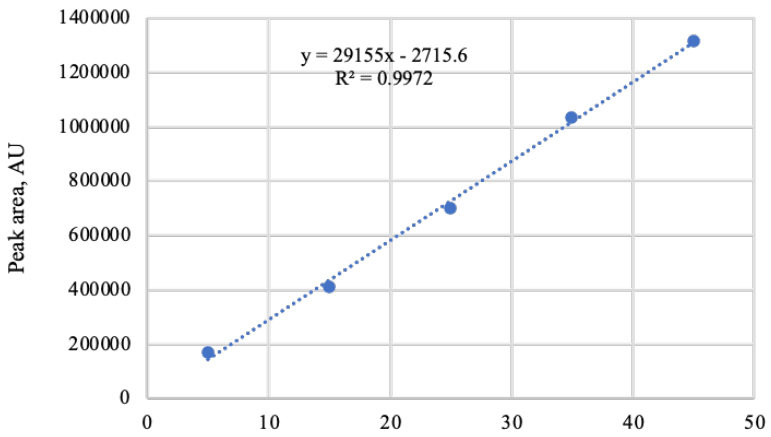

Figure 4. Calibration curve showing the linearity of the method

Table 1. Precision of pseudoprotopine alkaloid

Peak area	Samples	Inj 1	Inj 2	Inj 3	Intra assay		Inter assay	
					Prep-to-prep n=9		Day-to-day n=27	
					Mean	%RSD	Mean	%RSD
Day 1	Prep-1,2,3	683943.67	685455	685189	684862.556	0.4805		
Day 2	Prep-1,2,3	688212.67	686600.33	685925.33	686912.778	0.5516	677392.67	677392.67
Day 3	Prep-1,2,3	677392.67	677579.67	679442.67	678138.333	0.9522		

The precision of the method for quantifying pseudoprotopine was confirmed through intra- and inter-assay evaluations. Intra-assay %RSD values ranged from 0.48% to 0.95%, and inter-assay %RSD was 0.87%, all within acceptable limits (<2%). These results indicate that the method is highly repeatable, reproducible, and reliable for the consistent quantification of pseudoprotopine in Papaver nudicaule L.

Accuracy

The mean percent recovery of pseudoprotopine at each level should not be less than (NLT) 95.0% and not more than (NMT) 105.0% Table 2.

Table 2. Result of Accuracy

%, Level	Amount spiked (ug/ml)	Amount recovery (ug/ml)	%, Recovery	Main %, Recovery
50	50	49.61	99.22	99.51
100	100	99.6533	99.6533	
150	150	149.3	99.6666	

The results of the accuracy study for the quantification of pseudoprotopine. Accuracy was evaluated using a standard addition (spiking) method at three concentration levels: 50%, 100%, and 150% of the target concentration.

Limit of detection and limit of quantification

LOD and LOQ values were determined by the formulae LOD=3.3 σ/S and LOD=10σ/S (where σ is the standard deviation of the responses and S is the slope of the calibration curves) Table 3. The LOD and LOQ for pseudoprotopine were found to be 0.034 ng/ml and 1.028 ng/ml, respectively.

Table 3. The summary report of validation data

Parameters	Limit	Value
Retention Time, min		2.852 ± 0.003
Linearity range (ng/ml)		5-45
Regression coefficient		0.9972
Slope (m)	R<0.99	29155
Intercept (c)		2715.6
Regression equation (Y=mx+c)		Y=29155x-2715.6
Assay (% mean assay)		0.0288 ± 0.0005
Specificity	No interfrence of any peak	Specific
Precision (% RSD)		
a) Intraday	Not More than 2.0%	0.48
b) Inter Day	Not More than 2.0%	0.86
Accuracy % recovery	95-105%	99.51
LOD	NMT 3	7.75
LOQ	NMT 10	23.49

Table 3 method validation for pseudoprotopine quantification showed stable retention time (2.852 ± 0.003 min), excellent linerity (545ng/ml, R - 0.9972), acceptable precision (intra-day %RSD 0.48%, inter-day %RSD 0.86%), high accuracy (recovery 99.51%), no interfering peaks, and high sensitivity (LOD 7.75 ng/ml, LOQ 23.49 ng/ml), confirming the method as accurate, precise, specific, linear, and sensitive for routine use.

Discussion

We conducted a study on the standardization of the medicinal plant Iceland poppy (*Papaver nudicaule L*.) by comparing the results with those of researchers from other countries.

Chemical Composition

According to Selenge Dangaa, et al. 320 alkaloids were isolated from 30 Mongolian medicinal plants. In Iceland poppy (*Papaver nudicaule L*.), identified compounds include isoquinoline derivatives such as (-)-8,14-dihydropalmatine, amurensine, (-)-amurensinine, (-)-dihydroamuramine, (-)-O-methylthalizopavine, (-)-palmatine, (+)-amuramine, 8,14-dihydroamuramine, allocryptopine, amurensinine-α-N-oxide, amurensinine-β-N-oxide, and pseudoprotopine.[18] Gerelt-Od Yadamsuren, et al. identified a new promorphinane alkaloid, (-)-8,14-dihydroflavinantine, from the aerial parts of *Papaver nudicaule L*. Six known isoquinoline alkaloids-(+)-amuronine, pseudoprotopine, allocryptopine, (-)-dihydroamuronine, (-)-amurensinine N-oxide A, and (-)-amurensinine N-oxide B-were also isolated. Pseudoprotopine was reported for the first time in Papaveraceae, while (-)-dihydroamuronine and the two N-oxides are new to the genus *Papaver*. Structures were confirmed using spectral and physical data.[19] Brian G, et al. (1984) studied alkaloids from cell suspensions of four Papaveraceae species and the effects of temperature stress. Protopine was identified by TLC using two solvent systems, with Rf values of 0.87 and 0.10.[20] Dudek, et al. investigated flavonoids in the basal and apical areas of petals, stamens, and capsules of four *P. nudicaule* cultivars using chromatographic and spectroscopic methods. Gossypetin glycosides were found in the basal petal spots, while kaempferol glycosides were the main metabolites in capsules. Contrary to earlier reports, yellow stamens contained carotenoids, not nudicaulins. Nudicaulins, pelargonidin, and kaempferol glycosides were confirmed in the apical petal area.[21] Schliemann, et al. isolated seven kaempferol derivatives and gossypitrin from the yellow petals of Iceland poppy. Known compounds included kaempferol 3-O-beta-sophoroside and kaempferol 3-O-beta-sophoroside-7-O-beta-glucoside, along with their mono- and dimalonyl conjugates identified by MS and NMR. Analysis of co-occurring nudicaulins showed identical acylated glycoside moieties attached to a pentacyclic indole alkaloid skeleton, with the structure of 19-(4-hydroxyphenyl)-10H-1,10-ethenochromeno[2,3-b] indole-6,8,18-triol determined using MS, NMR, and chemical and chiroptical methods.[22] Tatsis, et al. examined petals from eight Papaveraceae species, where flower color was influenced by nudicaulins. Nudicaulins I–VIII were found in yellow and orange *P. nudicaule* flowers and in yellow and orange Papaver alpinum flowers. *Meconopsis cambrica* petals showed a distinct nudicaulin profile with a 3-hydroxy-3-methyl-glutaryl (HMG) group instead of malonyl on one glucose unit. Accompanying flavonols and anthocyanins were also identified.[23] Dudek, et al. reported that nudicaulins are derived from pelargonidin glycoside and indole, products of the flavonoid and indole/tryptophan pathways. To study nudicaulin biosynthesis, they integrated transcriptome, DIGE-based proteome, and UPLC-HRMS metabolome data from *P. nudicaule* petals with chemical analyses, identifying candidate genes, proteins, and key metabolites across five petal development stages.[24]

Pharmacological Effects

According to Aalinezhad, et al. the genus *Papaver L.* includes 159 species across 11 sections. Studies on some species show antimicrobial, anti-inflammatory, anti-cancer, and anti-depressant activities, as well as analgesic and sedative effects for pain, cough, and neurological disorders. These effects are mainly linked to their alkaloid content, which includes aporphines, morphinanes, protoberberines, protopines, and simple benzylisoquinolines. Structure–activity studies of these alkaloids have revealed additional effects on metabolic syndrome, neurodegenerative, and psychiatric disorders.[25] The number of studies on poppies is vast. Among the pharmacological effects some of the targets were also reported for *Papaver nudicaule*. Kim H, et al. (2021) and colleagues investigated the anti-inflammatory and antioxidant activities of *Papaver nudicaule* L. and *Papaver rhoeas* L. extracts in LPS-induced RAW264.7 cells. The extracts showed both anti-inflammatory and strong antioxidant effects, reflecting the presence of alkaloids in these medicinal plants.[26] Additionally, Kim S, et al (1999) and others demonstrated that the methanol extract of plants from the Papaveraceae family had a strong inhibitory effect on acetylcholinesterase.[27] Acetylcholinesterase (AChE) is a cholinergic enzyme located mainly at postsynaptic neuromuscular junctions in muscles and nerves. It hydrolyzes acetylcholine (ACh) into acetic acid and choline, terminating neuronal transmission and preventing activation of nearby receptors. Organophosphates inhibit AChE and are key components of pesticides and nerve agents.[28] Next to the aforementioned activity of protopine

alkaloids, their immunomodulatory action, regulation of the cytokines IL-6, IL-12, IL-1α, TNF-α, IL-1β, and IL-10 was also described. Moreover, flavonoids presented a similar portfolio of biological effects, including the antioxidant, anti-inflammatory, and immunomodulatory activities.[29] Ellis G, et al. studied the cardiovascular effects of cryptopine and protopine, similar to allocryptine. Intravenous cryptopine (4×10^{-6} to 2×10^{-5} mol/kg) initially stimulated, then depressed the cardiovascular system at higher doses. On the heart, cryptopine dilated coronary vessels like papaverine and protopine. The alkaloids reduced stroke volume and heart rate dose-dependently, alone or combined, with protopine showing the lowest toxicity.[30] The research by Gerelt-Od Yadamsuren, et al. and colleagues showed that the alkaloids 8,14-dihydroamuramine, 8,14-dihydrofavinanthine, and palmatine from the promorphinane group had a promising activity against anti-human rhinovirus-14 of the Picornaviridae family.[31] Falah Saleh Mohammed, et al. studied *Papaver* species, focusing on usage, essential oils, nutrients, elements, and biological activities. The study found that Papaver spp. are rich in essential nutrients and minerals and may serve as natural sources of antioxidant, antimicrobial, and anticancer compounds, highlighting their potential as valuable natural resources.[32]

Study Limitation

The limited availability of high-purity pseudoprotopine standards for accurate identification and quantification of pseudoprotopine alkaloids constitutes a notable limitation of this study.

Future Directions

Comprehensive standardization of raw Iceland poppy (*Papaver nudicaule L*.) material is warranted to facilitate the development of reliable and safe pharmaceutical formulations.

Conflicts of interest

The authors declare no conflicts of interest.

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