A Systematic Review on Main Chemical Constituents of *Papaver bracteatum*

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Abstract

Papaver bracteatum **Lindly (Papaveraceae) is an endemic species of Iran which has economic importance in drug industries. The main alkaloid of the plant is thebaine which is used as a precursor of the semi-synthetic and synthetic compounds including codeine and naloxone, respectively. This systematic review focuses on main component of *Papaver bracteatum* and methods used to determine thebaine.**

All studies which assessed the potential effect of the whole plant or its extract on clinical or preclinical studies were reviewed. In addition, methods for determination of the main components, especially thebaine, which have been published from 1948 to March 2013, were included. Exclusion criteria were agricultural studies that did not assess.

This study has listed alkaloids identified in *P. bracteatum* which reported since 1948 to 2013. Also, the biological activities of main compounds of *Papaver bracteatum* including thebaine, isothebaine, (-)-nuciferine have been reviewed. As thebaine has many medicinal and industrial values, determination methods of thebaine in *P. bracteatum* were summarized. The methods have being used for determination of thebaine include chromatographic (HPLC, GC and TLC) and non chromatographic methods.

HPLC methods seem to be the best method from the angle of time consuming, cost and data accuracy and precision.

Keywords: ***Papaver bracteatum*****, Chemical constituents, Systematic review, Thebaine**

Introduction

Since time immemorial, medicinal plants have drawn human's attention. Past decades have seen a rapid development in phytomedicine and as a result over 500 different plant species has exploded and many of them are still being collected from the wild [1]. The major products of *Papaver somniferum*, opium, morphine and codeine are the first choice analgesic and hypnotic drugs which play an important role in medicine.

Some alkaloids have been identified in dried latex of *Papaver* spp. [2, 3]; at least 25 alkaloids occur in the latex [4]. However, benzylisoquinolines, papaverine and noscapine, and the phenanthrenenes, codeine and morphine are clinically the most important ones.

Papaver bracteatum Lindley was first recognized by J. Lindley in 1821. This plant is endemic to a region between the Black Sea and the Caspian (the mountains of Iran, eastern Turkey and northern Caucasian), but can be grown in many climates, even as far north as Finland [5]. It is a medicinal plant with economic importance and contains a high concentration of thebaine which is readily converted to codeine. Moreover, thebaine is also used as a precursor of the synthetic compound naloxone and other derivatives which used as morphine antagonists, and for other therapeutic purposes [6]. Since much of the worldwide legal production of opium is justified by the need for it in codeine manufacturing [7], any plant capable of producing codeine or its precursors without concomitant production of other opiates, such as morphine, is seen as having great potential. *P. bracteatum* contains the toxic alkaloid thebaine which can be converted to codeine. Thebaine cannot be readily changed to illegal drugs [8]. It has been known for many years that thebaine occurs in many species of the Papaveraceae [9]. *P. bracteatum* has become more widely appreciated as a source of thebaine. As a result, many of researches have become interested in the species as an alternative source for codeine. Another reason for cultivating *P. bracteatum* is the production of poppy seed and poppy seed oil which can be used by the food industry [10]. In most previous researches reported on this species, seed yield and the potential of the plant as an oil crop have not been emphasized.

Because of historical uses and economic importance that mentioned for alkaloid content of *P. bracteatum*, many studies have been done on the alkaloid content and seed oil of this plant. However, in this article we reviewed the phytochemical and biological studies which were done on *P. bracteatum*.

Methods

We have searched MEDLINE, PROCUEST, ACS, RSC, Springer, Thieme, Science direct, Taylor & Francis Sciences & Technology and Wiley Blackwell. Library Database from 1948 to March 2013 using a combination of the terms: *Papaver bracteatum,* thebaine, thebaine and determination, identification. We did not include supplements made from chemically synthetized reactions and agricultural process. We limited studies to those published in the English language.

Results

Fatty-acid composition of the seed oil of *Papaver bracteatum*

Denisenko and Stepanenko collected *P. bracteatum* cultivated in the Botanical Garden of the Pyatigorsk Pharmaceutical Institute, and also the seeds of a wild-growing

plant collected in the environs of Pyatigorsk, Russia.

The oil content of the seeds as extracted by petroleum ether, referred to the absolutely dry weight, was 20.7% for the wild-growing and 26.0% for the cultivated plant of *P. braeteatum*. The fatty-acid compositions of the oils which were determined by the GC method were presented in Table 1 [11].

Alkaloid contents and their classification

Investigation on the alkaloids of *P. bracteatum* started about 1963, when Neubauer and Mothes [5] found the thebaine as the main alkaloid. 15 years earlier Kiselev and Konovalova [12] had already isolated four alkaloids from the same species; namely isothebaine as the main alkaloid, oripavine, and two alkaloids whose structure they could not elucidate, bracteine and bractamine. Apparently they used plant material in which thebaine was not presented yet. In 1972 the United Nations Division of Narcotic Drugs began a project entitled "Scientific research on *Papaver bracteatum*", which chemical compositions determined as well as botanical features.

The other alkaloids including norsanguiranine, sanguinarine, oxysanguinarine, dihydrosanguinarine, chelirubine and magnoflorine have been identified in the whole plant or cell cultures (Table 2) [22].

Table 1- The fatty-acid compositions (%) of the seed oil of *Papaver bracteatum*

Fatty Acid	Cultivated Poppy (%)	Wild Poppy (%)
Palmitic acid	12.3	12.5
Stearic acid	1.4	1.7
Oleic acid	10.2	7.9
Linoleic acid	76.1	77.9
Palmitoleic acid	Trace	Trace

Table 2- Alkaloids identified in *Papaver bracteatum* Lindl

Classification	Alkaloids
Morphinans	(-)-Thebaine [5]; (-)-Oripavine [12]; 6,7,8,9,10,14-hexadehydro-4,5-epoxy-3,6-dimethoxy-l7-methylthebinan [13]; (+)-Salutaridine = Floripavine [14]; Codeine; Neopine [15]; *α*-Thebaine-*N*-oxide; *β*-Thebaine-*N*-oxide [16]; 14*β*-Hydroxycodeine; 14*β*-Hydroxycodeinone [17]; *O*-methylflavinantine [18]; Salutaridine-*N*-oxide [19]; Thebainemethochloride [20]; Northebaine [21]
Aporphines	(+)-Corytuberine [12]; (+)-Isothebaine; (-)-Orientalinone [14]; (+)-Magnoflorine [22]; Bracteine = (+)-Orientalinone; (-)-Nuciferine [23]; (+)-Bracteoline; Floripavidine [24]; Corydine; Isoboldine [25]
Protopines	Protopine [26]; Muramine [27]
Rhoeadines/ papaverrubines	Papaverrubine G; Rhoeadine [25]; Alpinine [27]; Alpinigenine = Alkaloid E [28]; Papaverrubine B; Papaverrubine C = Epiporphyroxine; Papaverrubine D = Porphoxine; Papaverrubine E; PapaverrubineF [28,29]; Epialpinine [30]
Isoquinolines	*N*-Methylcorydaldine [17]; Corypalline; *O*-methylcorylpalline [26]
Benzophenanthridines	Sanguinarine; Norsaguinarine; Oxysanguinarine; Dihydrosanguinarine; chelirubine [22]
Dibenz[*d,f*]azoines	Neodihydrothebaine; Bractazonine [31]
Protoberberines	(-)-Orientalidine = Bractavine [10]; Oreophiline = (-)-Mecambridine [15]; Stylopine [22]; Coptisine [23]; Scoulerine [25]; Tetrahydropalmatine; Tetrahydropalmatinemetho salt [27]

Methods for thebaine determination

In order to exploit the variation for genetical and breeding purposes, the need for a rapid and reliable method of thebaine determination emerged quite early in all studies.

Chromatographic methods

Gas-liquid chromatography (GC) has been used routinely to determinethebaine from *P. bracteatum* extract. Resulting fractions from GC were collected separately and fractions were applied to a silica gel TLC plate [32-38]. One of the disadvantages of GC procedure is the uncertainty in identifying peak as the trusted pure peak. That may belong to a mixture of phytoconstituents and/or their decomposition products. In order to overcoming this problem several studies have been done.

Wu and Dobberstein (1977) have developed a high-pressure liquid chromatographic (HPLC) isocratic procedure, employed milder conditions than previous reports [39]. These methods require pre-treatment of the extract to remove polar impurities (e.g., ion-exchange chromatography), gradient elution equipment, and/or they do not produce separation of thebaine from other constituents. The operating conditions for HPLC were: flow-rate of eluting solvent, methanol-water containing 0.3 ammonium carbonate (4:1), 1 ml/ min; RP-18 column as stationary phase; wavelength of UV detector, 285 nm; ambient temperature.

Thebaine was decomposed by the high temperature used in GC procedure, and on TLC chromatograms no spot corresponding to thebaine could be observed. In this method, thebaine was well separated from all other compounds present in the total alkaloid extract of *P. bracteatum*.

Vincent and Engelke (1979) have developed a HPLC isocratic procedure for determination and quantitation of the five major alkaloids narcotine, papaverine, thebaine, codeine and morphine [40]. In contrast to previously reported procedures, the advantage of this method is that no precolumn or other purification other than solvent extraction of the capsular tissue is necessary. Isocratic chromatography alone on a single column resolved the 5 major alkaloids.

The existing methods for thebaine analysis were laborious and slow, therefore there were limitation a large scale screening of populations of this species.

Lavie et al. (1979) have developed a rapid and reliable method based on standardization of TLC involving the comparison of spot sizes and intensities of the tested samples appearing on fluorescent chromatoplates with calibrated standard spots of known concentrations [41]. For the chromatoplates, fluorescent TLC alumininm sheets, Si gel 60 F254, were used. The developing solvent was toluene: Me_2CO: EtOH: NH_4OH (6N) (80:80:15:4).

Milo et al. (1988) have designed a reversed-phase high-performance liquid chromatographic method for the simultaneous quantitation of the alkaloids of *Papaver* species in section *Oxytona*: salutaridine, thebaine, oripavine, alpinigenine, isothebaine and orientalidine [42]. The reversed-phase HPLC was carried out on a RP-18 column. Separation of the alkaloids was accomplished at 25°C by the mobile phase 5% 2-propanol, 40% acetonitrile, 55% water with 1% ammonium carbonate.

Huo X (1999) has developed a method based on GC for determination of thebaine in various tissues of *P. bracteatum* [43]. In this method, powdered materials were extracted with methanol under ultrasonic condition.The procedure of extraction is simple, rapid and

reliable. The assay method gave satisfactory reproducibility for a wide range of plant materials (coefficient of variation 2.9% to 5.4%). The operating time of the assay is about 20 min.

Non chromatographic methods

Seidi et al. (2011) have studied a method based on electromembrane extraction for determination thebaine in water sample, biological fluids, poppy capsule and narcotic drugs followed by high-performance liquid chromatography analysis [44].

Biological activity

P. bracteatum has several classes of alkaloids as well as wide variation of the biological activities of individual compounds. Among these alkaloids, biological activities of thebaine, isothebaine and (-)-nuciferineare are well-recognized. Codeine has been established as drug and used as common pain killer. There are numerous reports on its pharmacological effects. As a consequence, discussion of these publications will be omitted here.

Thebaine

Toxic Effects

After 1835 when thebaine (Fig. 1) was isolated from opium for the first time, several studies were done to investigate its pharmacology [45]. Subcutaneous LD_{50} of thebaine in mice was found 31 mg/kg and its intraperitoneal LD_{50} was 20 mg/kg. It should be emphasized that other authors have reported a LD_{50} value of 42 mg/kg in mice [46].

Pharmacological Effects

The toxic effects of thebaine are much more than morphine and as a narcotic it is more effective than morphine, but analgesic effects of morphine are stronger [45]. Thebaine decreases the heart and brain catecholamine levels slightly. It has been previously demonstrated that it has an inhibitory effect on human, guinea-pig and horse cholinesterase, as well as on human procainesterase, however it has no inhibitory effects on neither lactic and citric acid, nor glucose dehydrogenases. Rat central vagal stimulation of pancreatic secretion induced by 2-deoxy-D-glucose was not affected by thebaine [46]. In rabbits, 2 mg/kg of thebaine can antagonize the respiratory inhibition related to 5 mg/kg morphine. 1 mg/kg IV of thebaine strongly stimulates respiration when it is injected with narcotine (15 mg/kg IV). Electrophysiologically, the spasmolytic effect of thebaine was similar to that of strychnine, but it was different from morphine and codeine [46]. Naloxone, an opioid receptor antagonist, antagonized the convulsions induced by thebaine in mice (convulsive dose 7.4 mg/kg IV), however, it was not potent as much as against heroin. In mice, treated with thebaine 30 mg/kg SC, neither sotalol nor propanolol changed the survival rate; propanolol (25 mg/kg SC) prevented the tonic phase of the convulsions, but did not prevent death [47]. In rabbits, thebaine antagonized phenobarbital. It potentiated the effect of caffeine [45]. It have been reported that thebaine induced pseudo-hyperfeminization in chicken embryo. Several studied have been done to investigate the physical dependency related to thebaine, most of which have indicated that thebaine does not induce serious physical dependence compare with morphine [47]. Moreover, it shows limited signs of withdrawal syndrome compare with that of morphine. The limited dependence capacity has been attributed to the rapid metabolism of thebaine in the brain. The teratogenicity of thebaine has been investigated in hamsters and

the results have shown that at the dose of 140 and 190 mg/kg (one SC injection) it causes congenital malformations in 2 % and 4.2 % of the offspring, respectively. Cranioschisis was the most common malformation found [48].

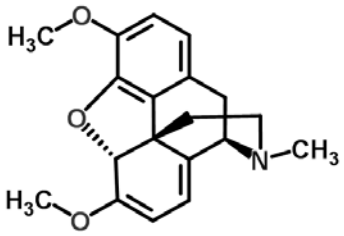

Fig. 1- Thebaine structure

Isothebaine

Isothebaine (Fig. 2) was first isolated in 1911 from *P. orientale* [49]. In mice its LD_{50} is 26 mg/kg and animals died from respiratory arrest after clonic-tonic convulsions. One SC injection at the dose of 2.5 or 5 mg/kg for 40 days was determined as a chronic model of isothebaine toxicity and as a consequence of this, significant decrease in body and kidney weight gain was observed [50]. Several studies have shown that isothebaine can alter the muscle tonus of intestine. Konson and Saksonov showed that isothebaine at the concentration of 4×10^{-2} mg/ml or less caused an increase in muscle tonus of intestine, however at the concentration of 8×10^{-2} mg/ml caused muscle relaxation [50, 51]. Respiration frequency and pulse rate were decreased. In rabbits, 5 mg/kg IV caused an initial fall in blood pressure followed by an increase above the initial value with concomitant increase in the tonus of the small intestines. It can decrease forced and spontaneous motor activity in mice. Moreover, it is well established that isothebaine has some anti-inflammatory effects, mainly in the exudative phase of the inflammation [51].

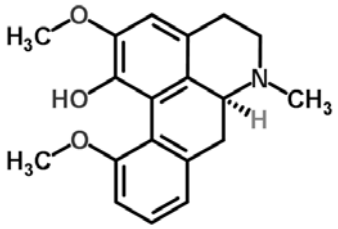

Fig. 2- Isothebaine structure

Nuciferine

Oral LD_{50} of nuciferine (Fig. 3) in mice and rat is 240 mg/kg and 280 mg/kg (PO), respectively. Since ancient time it has been used as a remedy for many diseases. Literatures show that it acts as a CNS depressant by blocking the receptors for neurotransmitters. It decreased motor activity, ptosis, hind-leg spread and hypotonia in rodents [52]. However, it did not stimulate locomotor activity in rats with 6-hydroxydopamine lesions of the nucleus accumbens [53]. In rat and cat thalamus, it can antagonize the action of L-glutamate, L-aspartate and DL-homocysteate, and at higher concentrations also of acetylcholine [54, 55]. Nuciferine can also block the kainic acid functions, but not of N-methyl-D-aspartate. It must be emphasized that it had no significant effect on the action of quipazine, strychnine, or bicuculline [56]. Macko et al. have determined that it has some anti-inflammatory; analgesic, and anti-tussive properties (ED_{50} in dogs 15 mg/kg PO) [49]. It exhibited adrenergic blocking, and probably peripheral dilating activity. It did not act as an antihistaminic agent [52].

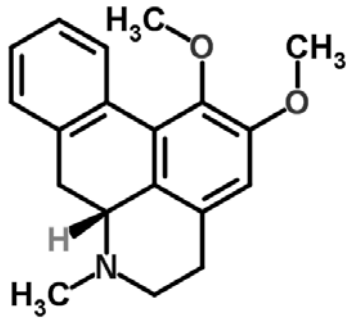

Fig. 3- Nuciferine structure

Conclusion

P. bracteatum contains several alkaloids among them thebaine has the highest concentration and also economical and medicinal value. Thebaine is the starting material for the preparation of codeine, oxycodone and hydrocodone, and thebaine derivatives such as the potent "Bentley compounds". *P. bracteatum* commercially can be cultivated for thebaine production, but in this context phytochemical content especially thebaine and determination of thebaine plays an essential role. For determination of thebaine many different methods were done such as chromatographic methods (GC, TLC and HPLC) and none chromatographic methods that in this context were reported.

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