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MAJOR GENERA OF PAPAVERACEAE (POPPY) PLANT FAMILY IN ISRAEL AND PALESTINE. PART II: *PAPAVER* (POPPY)

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ABSTRACT

Papaver is one of the genera included in the Papaveraceae plant family. All the species of this family have notable alkaloid content, and *Papaver* alkaloids that were isolated from the species of the reviewed region will be presented and discussed. These plants were used by humans since the dawn of humanity, and traditional uses are well documented. The greater part of this review article will be dedicated to *Papaver somniferum* because it is the most studied and most published among all *Papaver* species, including those that are not native to the reviewed region (RR). The chemical compositions of the plants will be extensively presented and discussed, including the factors that affect these compositions. Most of the information will be presented in tables, which enable readers to find it easily. Special attention will be drawn to dangers and toxicity of these plants. Finally, carefully selected, previously published review articles about the *Papaver* species will also be presented.

KEYWORDS: Papaveraceae, *Papaver*, Anticancer, Alkaloids, Ethnomedicine, Chemical composition, *Papaver somniferum*, Papaverine, Thebaine, Toxicity.

Abbreviations: ABTS 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), ahc and her/his colleagues, AChE acetylcholine esterase, BuChE butyrylcholine esterase, CUPRAC cupric reducing antioxidant capacity, DEE diethyl ether, DMSO dimethyl sulfoxide, DPPH 2,2-Diphenyl-1-picrylhydrazyl, EO essential oil, FRAP ferric reducing activity power, GCC general chemical composition, GC-MS gas chromatography mass spectrometry, GPx glutathione peroxidase, HPLC high performance liquid chromatography, LC-MS liquid chromatography mass spectrometry, MDA malondialdehyde, NI not indicated, NPs nanoparticles, PE petroleum ether, RR reviewed region, SOD superoxide dismutase, TAC total antioxidant capacity, TFC total flavonoid content, TOS total oxidative status, TPC total phenolic content

1. Taxonomy, Archeology and Presence of Wild *Papaver* Plants in the RR

The *Papaver* genus as part of the Papaveraceae (Poppy, خشخاشية, פרגיים, English, Arabic, Hebrew, respectively) plant family, has a common name of Poppy, خشخاش, פרג in these languages, and the common name of the family is derived from the name of the genus and not vice versa.

In the first article of this series, we briefly presented the taxonomy of the Papaveraceae plant family. As for the taxonomy of the *Papaver* genus, it includes 100 to 110 species.[1,2] In the RR, ten *Papaver* species grow wild, according to the “Flora of Israel and adjacent areas” website.[3] These are: *Papaver argemone*, *P. carmeli*, *P. decaisnei*, *P. humile*, *P. hybridum*, *P. libanoticum*, *P. polytrichum*, *P. somniferum*, *P. syriacum* and *P. umbonatum*.

Archaeological studies of *Papaver* uses by ancient humans are mostly focused on *Papaver somniferum* due to its high activity compared to other *Papaver* species, and consequently, its economic value. A. Salavert ahc used radiocarbon dating and found that this species has been used in Western Europe since 5900 years before present time.[4] A. D’Agostino ahc used the same dating method and found in a grave in Italy from the Neolithic period (around 6340 years before present) that this plant species was in use.[5] Another study of Italian group by G. Giordano ahc revealed use of this plant in seventeenth century hospital in Milan.[6] However, there are evidences that *Papaver somniferum* was utilized by human for medicinal purposes earlier than these findings, and some of these studies will be presented in the **Discussion** section.

2. Remarkable Published Review Articles about *Papaver* Genus and Species

A large number of review articles was previously published about this plant genus, where the vast majority of them focused on *Papaver somniferum* and its active constituents. For this reason, a very careful selection was applied. Most of these articles are presented in **Table 1**, and a few will be presented in the **Discussion** section.

Table 1: Selected published review articles about *Papaver* until 30/10/2025.

Author(s)	Pages	Ref's	Major topic(s), Ref.
J. Novák & V. Preininger	13	43	Chemotaxonomic review of the *Papaver* genus[7]
M. Butnariu ahc	23	181	*Papaver* genus. Very detailed and comprehensive: ethnomedicine, phytochemistry, medicinal activities, economics, safety[8]
F.S. Mohammed ahc	9	82	*Papaver* genus. Detailed, comprehensive, EOs and nutrition. Lacks ethnobotany.[9]
Z. Aghaali ahc	14	146	*Papaver* genus. Use of hairy roots to enhance alkaloids production. Outstanding figures.[10]
Y. Özgen & D. Burucu	9	37	*Papaver* genus. Focus on botany and farming in Turkey. Lacks important information.[11]
F. Labanca ahc	19	59	*P. somniferum*. Detailed taxonomy, uses, alkaloids in plant parts, biosynthesis[12]
M. Masihuddin ahc	5	43	*P. somniferum*. Traditional uses, phytochemistry, morphology[13]
A. Muhammad ahc	26	116	*P. somniferum*. Focus on nutritional and composition properties of seeds.[14]
M. Hedayati-Moghadama ahc	14	107	*P. somniferum*. Health benefits and adverse effects mainly on cardiovascular system[15]
Y. Jan & L.A. Peer	5	40	*P. somniferum*. Phytochemistry (no structures), detailed biological activities, toxicity[16]
A. Vadhel ahc	14	118	*P. somniferum*. Alkaloids (detailed), biosynthesis, health effects, link to cancer, mechanisms of action (detailed figures)[17]
H. Hamiksha	17	132	*P. somniferum*. Comprehensive. History, composition, legal aspects, health benefits and adverse effects, synthesis of active compounds[18]

3. Ethnobotanical Uses of *Papaver* Plants of Israel and Palestine

As mentioned earlier, *Papaver somniferum* is used by humanity for several millennia. These uses are nutritional, medicinal and rarely spiritual. However, some more uses will be presented in the **Discussion** section. So, unless special, the ethnobotanical uses of this species will not be presented in this section, unlike another wild *Papaver* plants of the RR. Summary of this data is presented in **Table 2**.

Table 2: Ethnobotanical Uses of *Papaver* Plants of Israel and Palestine.

Papaver Species	Country; Plant part(s); method(s); use(s); reference
P. argemone	Iran; flowers and capsules; antidiabetic, hepatoprotective, analgesic, neuroprotective, anti-irritant, anti-ulcerogenic[19] Poland; NI; NI; NI[20] Turkey; flowers; added to drink (Sherbet)[21] Seeds; infusion; cardiovascular problems[22] Leaves; cooked; food[23]

	Flowers, aerial parts; cooked; food[24]
P. carmeli	Jordan; whole plant; eaten; CNS depressant, hypnotic[25]
P. decaisnei	Pakistan; whole plant; NI; NI[26]
P. humile	RR; flowers; ointment; wounds[27] Aerial parts; animal food, eaten (grazing)[28]
P. hybridum	Pakistan; flowers, fruits, stems; decoction; diaphoretic, sedative, demulcent, flu, cough, diarrhea[29] Flowers, fruits, decoction; ear and eye pain, cough, constipation[30] Flowers; NI; flu, cough[31] Fruits; decoction; insomnia[32] Seeds; decoction; weak eyesight, pain killer, narcotic, body strength enhancer[33] Spain; leaves, stems; human food; eaten[34]
P. libanoticum	Lebanon: flowers; infusion; catarrhs[35] Flowers; infusion; emollient, expectorant, sudorific sedative, cough, sleep enhancer[37] Turkey; flowers, leaves; tea; sedative, somniferous, analgesic, antitussive[36]
P. somniferum	China; fruits; NI; gastroenteritis, anti-inflammatory[38] India; seeds; NI; demulcent, spasmolytic[39] Iran; fruits, seeds; NI; laxative, tonic, hypnotic[40] Jordan; whole plant; eaten; CNS depressant, hypnotic[25] Pakistan; seeds, fruits; NI; cough[31] Fruits (unripe); decoction; insomnia[32] Seeds; decoction, tea; body strength enhancer, sedative, dental problems, cough, memory enhancer, cough[33] Fruits, seeds; tea; narcotic, cough, fever[41] Poland; flowers, fruits, seeds; pressed oil, decoction, infusion; food, varnish, feet pain, sleep enhancer, stomach disorders, cough[20] Turkey; fresh leaves; eaten; vasodilator[22] Flowers, leaves (fresh or dry), seeds, fruits (fresh or dry), bark; tea; analgesic, somniferous, vasodilator, children cry, sleep enhancer, massage (oil)[36]
P. umbonatum	Jordan; NI; NI; earache, toothache, neuralgia, cough, insomnia, poor digestion[42] Lebanon: fruits; decoction; measles in children[37]

4. Published Medicinal Properties-Activities of *Papaver* Plants of Israel and Palestine

Compared with other plant genera, the number of medicinal properties-activities is relatively limited. And again, like in previous sections, *Papaver somniferum* is with clear lead. A major part of these properties will focus on chemical compositions and selected reported natural ingredients will be presented in the figures after **Table 3**.

Table 3: Medicinal Properties-Activities of *Papaver* Plants of Israel and Palestine.

***Papaver* species**	**Property-Activity, Method, Results, Reference**
P. argemone	Aerial parts were separately extracted with PE, DEE, chloroform, acetone and ethanol. All five extracts were tested for **antimicrobial** activity (six bacterial and one fungal species), showing moderate activities. Three standard drugs were used as references.[43] Whole plant methanol-chloroform (25-75%)* extract was tested for **antibacterial** activity against six bacteria species, showing significant effect. The extract was analyzed by HPLC for alkaloids resulting the detection of four compounds: Morphine (major), Codeine, Papaverine and Thebaine (**Figure 1**).[44] Seeds were extracted (66-34% chloroform-methanol) and the extract was chromatographed for fatty acids composition. Results showed equal presence of saturated and unsaturated acids.[45] Fruits from various locations were harvested in several timings and were extracted (ethanol) for total alkaloid content. The extracts were analyzed with HPLC for major components: Morphine, Codeine, Papaverine Thebaine and Noscapine (**Figure 1**).[46]
P. carmeli	**No published articles about medicinal properties-activities and/or chemical composition**
P. decaisnei	Flowers, leaves and roots were extracted with methanol, and each extract was analyzed for GCC. They were tested for **antioxidant** (ABTS, CUPRAC, DPPH and FRAP methods) and **anticancer** (against Caco-2, MCF-7 and HeLa cancer cell lines) activities. The three extracts were chromatographed (HPLC) yielding previously known compounds, with very high content of Roemerine and lower content of Decarbomethoxytabersonine (**Figure 2**).[47]a Aerial parts were extracted with methanol and this extract was extracted again for total tertiary alkaloids content. Both extracts were tested for **antibacterial** activity against *E. faecalis* and *P. aeruginosa*. TLC analysis of the methanolic extract afforded: Mecambrine (**Figure 2**) and Roemerine.[49] Aerial parts methanolic extract had **antiulcer** activity in ethanol-induced rats. Effect was measured with oxidative-antioxidative and inflammatory-anti-inflammatory biomarkers. It was tested for **acute toxicity** in theses animals and found nontoxic.[50] a- Interestingly, the same results were published by the same research group in the same year (different title and very slight changes in the text) in another journal. See[48]
P. humile	**No published articles about medicinal properties-activities and/or chemical composition**
P. hybridum	Seeds were extracted (66-34% chloroform-methanol) and the extract was chromatographed for fatty acids composition. Results showed equal presence of saturated and unsaturated acids.[45] Aerial parts aqueous (alkaloid) extract was tested for **antimicrobial** activity against several bacterial and fungal stains, showing moderate effect. Several standard drugs were used as reference.[51] Aerial parts methanolic and methanolic-alkaloid extracts were evaluated for **antibacterial** activity (against 13 strains), with several standard

	drugs as references. Effect ranged from weak to moderate.[52] Flowers and leaves were combinedly extracted with 80% aqueous ethanol, and the extract was tested for **antimicrobial** activity against several bacteria and fungi strains. Results showed no effect.[53] Aerial parts (several locations and seasons) 80% aqueous methanolic extract was tested for **antioxidant** activity (DPPH method) and analyzed for GCC. The contents of Codeine and Papaverine were determined.[54] Follow up of previous cited study: same methods and same results.[55]
P. libanoticum	Aerial parts 86% aqueous ethanolic extract was analyzed for TPC and total alkaloid content. It was tested for **acute toxicity** in mice (nontoxic) and **analgesic** activity, using tail flick, hot plate and acetic acid-induced writhing tests. Significant effect was detected with proposed mechanism of action that includes involvement of opioids receptors.[56] Aerial parts 96% aqueous ethanolic (alkaloid) extract was analyzed affording Dehydroremerine, Berberine, Alborine, Remrefidine (**Figure 3**), Roemerine and Mecambrine. These compounds were tested for **anticancer** activity against MCF7 and HCT116 cancer cells showing significant effects. Doxorubicin was reference drug.[57]
P. polytrichum	Aerial parts aqueous (alkaloid) extract was tested for **antimicrobial** activity against several bacterial and fungal stains, showing moderate effect. Several standard drugs were used as reference.[51]
P. somniferum	Seeds were extracted (66-34% chloroform-methanol) and the extract was chromatographed for fatty acids composition. Results showed equal presence of saturated and unsaturated acids.[45] Fruits from various locations were harvested in several timings and were extracted (ethanol) for total alkaloid content. The extracts were analyzed with HPLC for major components: Morphine, Codeine, Papaverine Thebaine and Noscapine (**Figure 1**).[46] Oripavine (**Figure 4**) was isolated from fruits and straws by HPLC and tested for **analgesic** activity in mice using hot plate method. It was also tested for **toxicity** and found nontoxic. Commercial Morphine and Thebaine were reference compounds.[58] Fruits, leaves, roots and stems were separately extracted with *n*-hexane, ethyl acetate and methanol. All twelve extracts were tested for **anticancer** activity (against four cancer cell lines), with 5-fluorouracil as reference drug.[59] Flowers, fruits (without seeds), leaves, roots, seeds and stems were separately and combinedly extracted with methanol. All seven extracts were tested for **anticancer** (against five cancer cell lines) and **antioxidant** (ABTS, DPPH, FRAP methods). Extracts were analyzed for TFC, TPC and total alkaloid content. They were also partially analyzed for chemical composition of 3-Hydroxy-β-damascone, Meconine (**Figure 4**), Codeine, Morphine and Papaverine.[60] From ethanolic (alkaloid) fruits extract Noscapine was isolated.[61] Leaves methanolic (alkaloid) extract was analyzed with GC-MS affording 25 alkaloids. Molecular docking for **antiepileptic** activity was performed for: Salutaridinol, *R* and *S*-Scoulerine, Coclaurine (-)-Codeinone and 7-*O*-Acetylsalutaridinol, (**Figure 4**).[62] Theoretical work (molecular docking) of active components for

	antiepileptic activity resulted highest potency of: γ-Isomorphine (**Figure 4**) Morphine, Codeine, Codeinone and *S*-Scoulerine.[63] Seeds methanolic (alkaloid) extract had **antimicrobial** activity against *P. aeruginosa*, *L. monocytogenes*, *S. aureus*, *K. pneumoniae*, and *C. albicans*.[64] Leaves were separately extracted with ethyl acetate, ethanol, methanol, DMSO and water. The extracts were analyzed for TFC, TPC, total alkaloids content, glycosides, saponins and steroids. The extracts were tested for **antibacterial** (against six bacteria species) and **antioxidant** (DPPH method) activities. Effect ranged between non-existent to weak with clear dependence on solvent type.[65] Flowers EO was obtained by hydrodistillation and was tested for **antibacterial** activity against eight bacteria species. The EO was also analyzed for fatty acids (12 identified) composition using GC-MS.[66] Rats were orally administered with opium for a month until addiction was achieved. Th control group received Naloxone, a Morphine antagonist. Brain-related properties were tested such as **memory changes** (water maze method), **passive avoidance learning** (shuttle box method) and **oxidant-antioxidant** parameters (TAC, TOS, MDA, GPx and SOD).[67] Seeds were separately extracted with PE, chloroform and methanol, and the extracts were analyzed for GCC. They were also tested for **antioxidant** activity using DPPH method.[68] Seeds (several cultivars) were defatted with *n*-hexane and extracted with methanol. The extract was analyzed for TPC and tested for **antioxidant** activity using DPPH and FRAP methods.[69] Seeds (several genotypes) 50% aqueous ethanolic extract was analyzed for TFC and TPC, and tested for **antioxidant** (FRAP, TAC and reduction power methods) and **proteinase inhibition** activities.[70] Stalks were separately extracted with ethyl acetate, methanol and water. The extracts were tested for **antioxidant** (CUPRAC, FRAP and Fe^{+2} chelating methods) and **enzyme inhibition** (tyrosinase, AChE, BuChE, α-amylase and α-glucosidase) activities. The extracts were partially analyzed for chemical composition yielding 4-Hydroxybenzoic acid as major component in each extract.[71] Morphine content of cultivated plants is determined.[72] Seeds were extracted with PE and the resulting oil was analyzed for triglycerides, monoglycerides and free fatty acids.[73] Plants were cultivated in cold areas in Finland and their alkaloid (Morphine, Codeine, Thebaine, Noscapine and Papaverine) was determined by HPLC.[74] Fruits GCC and enzymes (Lipase, Phospholipase, Peroxidase and Protease) activities were determined.[75] Oil from different germplasms/varieties was extracted with PE and the yield and quality were determined.[76,78] Amine oxidase was isolated from seedlings.[77] Fruits from several varieties were extracted with 75% aqueous methanol and the extracts were analyzed with HPLC to determine total alkaloid content and Morphine, Thebaine, Noscapine and Papaverine.[79] Literature summary of metal (Cd, Pb, Fe) contents in seeds from

	Slovakia and Czech Republic in the 1990s.[80] Seeds EO was obtained by *n*-hexane extraction, and it was tested for **antibacterial** activity against *E. coli* (inactive) *S. aureus* (active). The residue left after extraction was active against both bacteria. The EO was analyzed for GCC.[81] Seeds of twelve varieties harvested in different several seasons and several locations were analyzed for protein contents and fatty acids compositions. GCCs were also determined and physical properties (mainly seeds and flowers colour) were compared.[82] Seeds of several varieties grown in Estonia were extracted with 50% aqueous ethanol and the extracts were analyzed (HPLC) for Morphine, Codeine, Papaverine, and Apomorphine (**Figure 4**) contents.[83] Seeds were analyzed with LC-MS before and after thermal treatment to compare the contents of Morphine, Codeine, Thebaine, Noscapine and Papaverine. In this study, *P. setigerum* was also analyzed.[84] Seeds were sequentially extracted with *n*-pentane, ethyl acetate and 70% aqueous methanol and the extract was analyzed for bitter-tasting components and their derivatives. Five compounds were found: Palmitic, Oleic, Linoleic (and ethyl ester) and α-Linolenic acids.[85] Seeds EOs were prepared using *n*-hexane, supercritical CO_2 and CO_2 with 10% of acetone, ethanol, or ethyl acetate as co-solvents. The yields and compositions of the EOs were clearly different: fatty acids, phytosterols, squalene, tocopherols and phenolic acids.[86] Seeds with low Morphine contents from several varieties were cold pressed to obtain their EOs, which were analyzed for lipids (fatty acids, tocopherols and some volatile components). Higher concentrations were recorded compared with higher Morphine containing seeds.[87] Total alkaloid, Morphine, Codeine, Thebaine contents were determined in several Slovakian varieties.[88] Feeding pigs with seeds had positive effects growth and health.[89] Commercial seeds oil had **insecticidal** against Cowpea weevil (*Callosobruchus maculatus*) in stored Cowpea (*Vigna unguiculata*).[90] Seeds were harvested from several locations (Hungary) and their flour sensory and oil composition (volatiles and fatty acids) are reported.[91] Four out of 28 workers in morphine production in Spain were diagnosed with occupational asthma. Authors link this **toxicity** to their work.[92]
P. syriacum	Aerial parts aqueous (alkaloid) extract was tested for **antimicrobial** activity against several bacterial and fungal stains, showing moderate effect. Several standard drugs were used as reference.[51] Roemerine was isolated from aerial parts methanolic (alkaloid) extract and used as reference compound for the antimicrobial activity of alkaloids with very close structure, isolated from another plants.[93]
P. umbonatum	Flowers were separately extracted with acetone, ethanol, methanol and water. The four extracts were tested for **antibacterial** activity (against three bacterial strains). Activities ranged from none to moderate, where ethanolic extract was most active and acetone extract was weakest.[42] Aerial parts aqueous (alkaloid) extract was tested for **antimicrobial** activity against several bacterial and fungal stains, showing moderate effect. Several standard drugs were used as reference.[51]

* Unless stated otherwise, percentages of solvent mixtures are V/V.

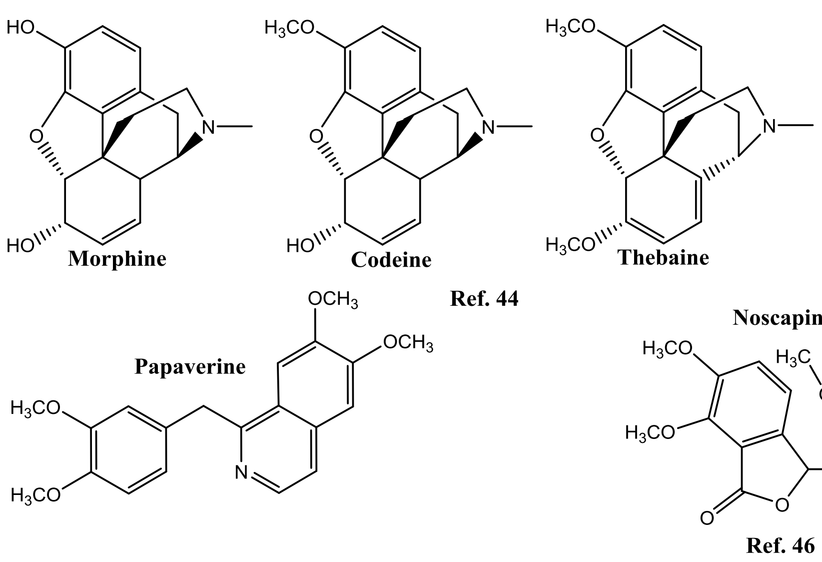


Figure 1: Natural products isolated from *Papaver argemone.*

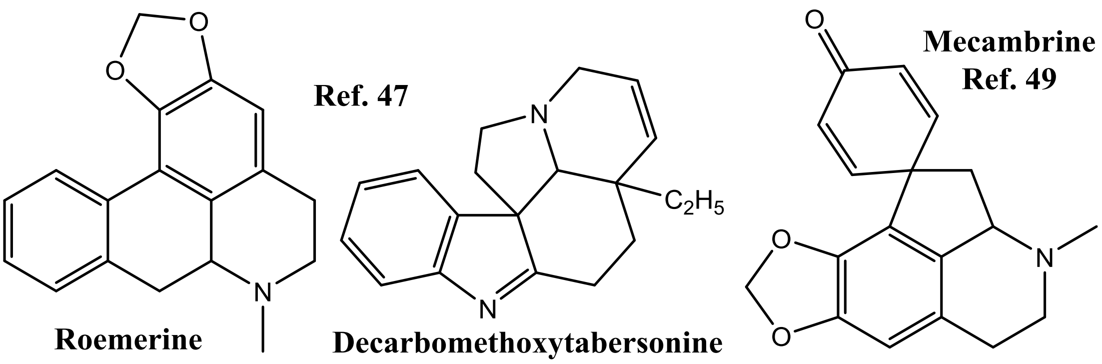


Figure 2: Natural products isolated from *Papaver decaisnei.*

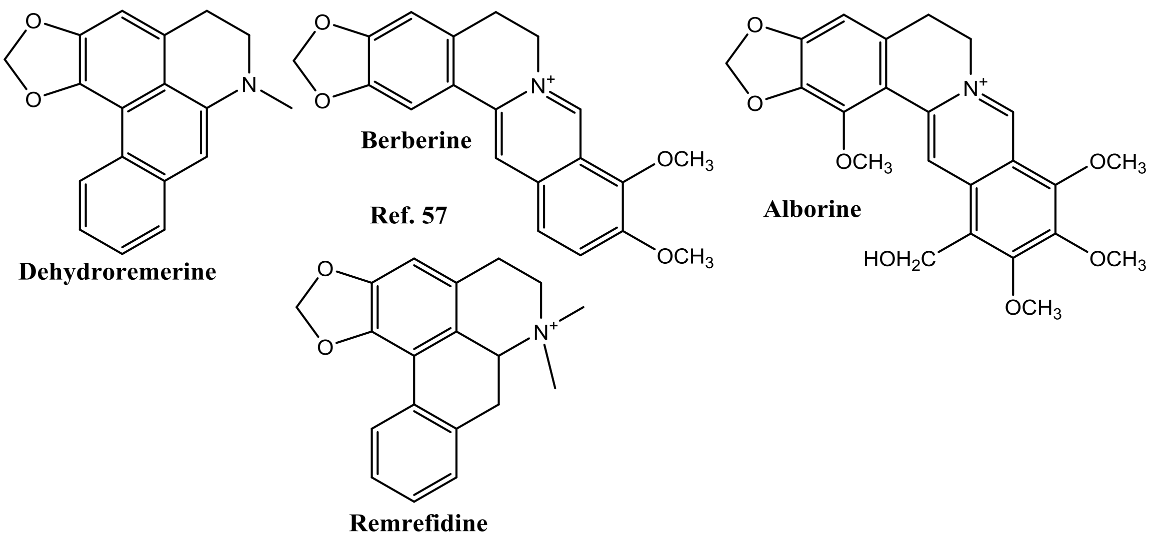


Figure 3: Natural products isolated from *Papaver libanoticum.*

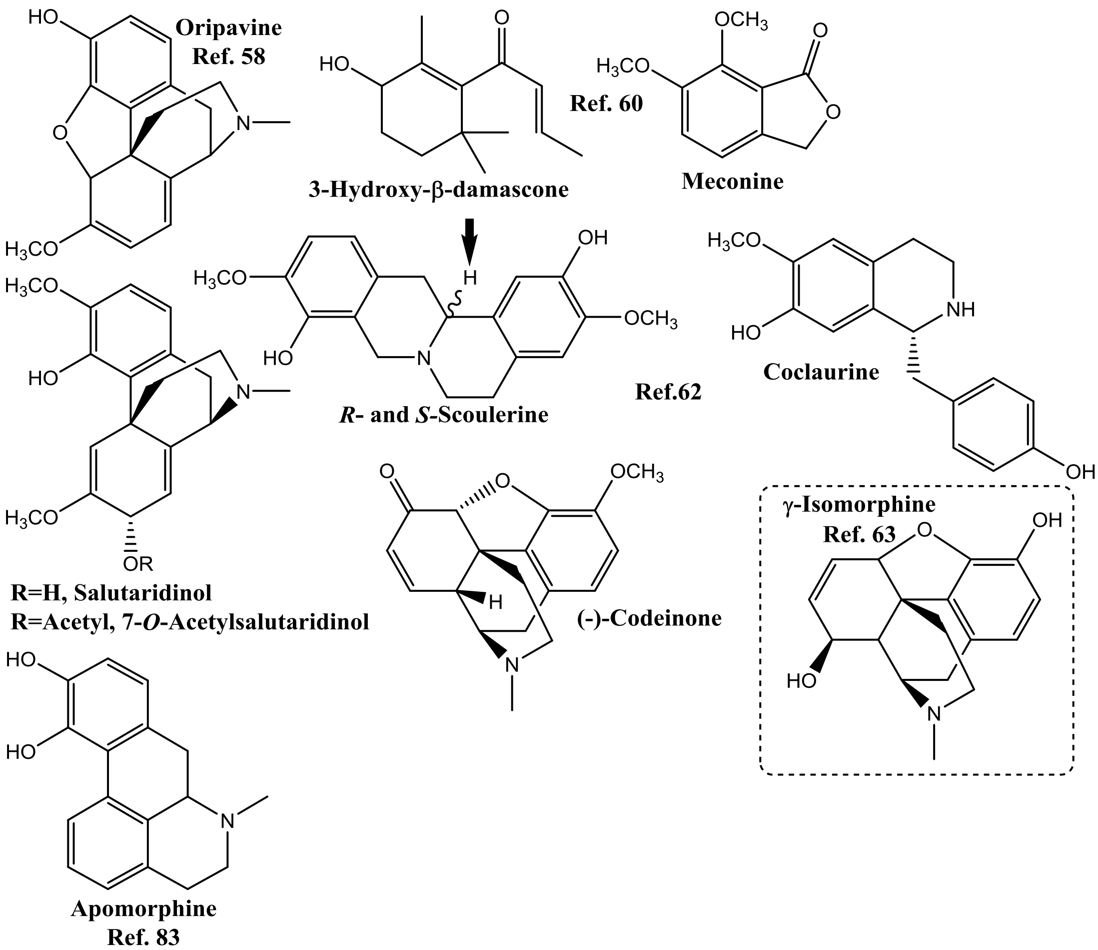


Figure 4: Natural products isolated from *Papaver somniferum*.

5. DISCUSSION

Reviewing the publications about *Papaver* plants of Israel and Palestine is a task of very high interest, yet it is also challenging since a clear majority of these publications focus on a single species: *Papaver somniferum*. But some published works had comprehensiveness like the work of O. Bayazeid and F.N. Yalçin.[94] They carried out *in silico* predictions of possible activities of all 92 known alkaloids of *Papaver* genus. In addition, they classified and arranged these alkaloids according to their structural groups and linked these groups according to their biosynthesis. These groups are (with an example of each, **Figure 5**): Benzylisoquinoline (Armepavine), Promorphinane (8,14-Dihydropromorphinane), Morphinane (O-Methilflavinantine), Aporphine (N-Acetylanonaine), Proaporphine (Amuronine), Protoberberine (Canadine), Secoberbine (Macrantaline), Phthalideisoquinoline (Corlumine), Protopine (Hunnemanine), Rhoeadine (Oreogenine), and Isoquinoline (Cotarnoline) alkaloids.

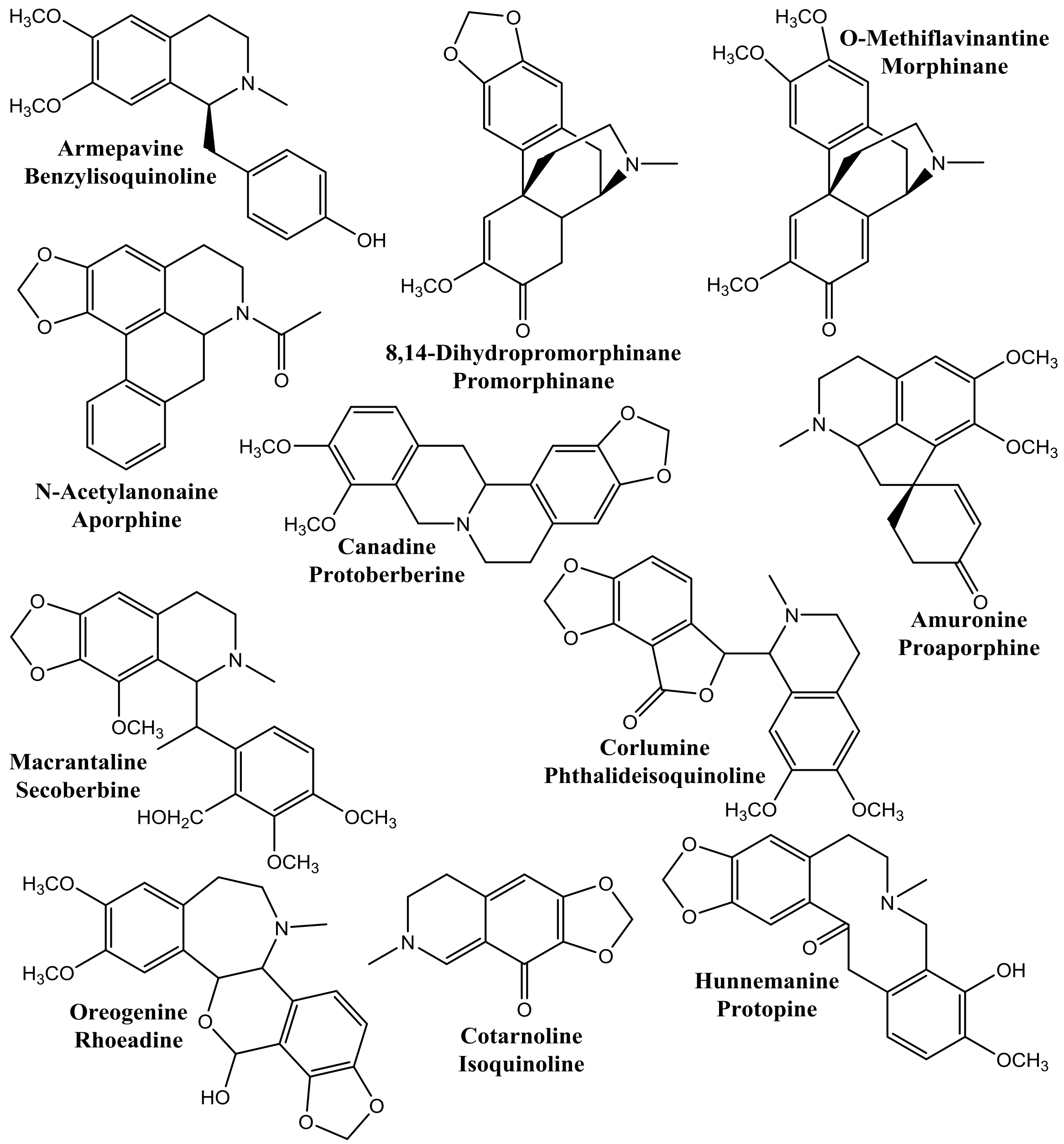
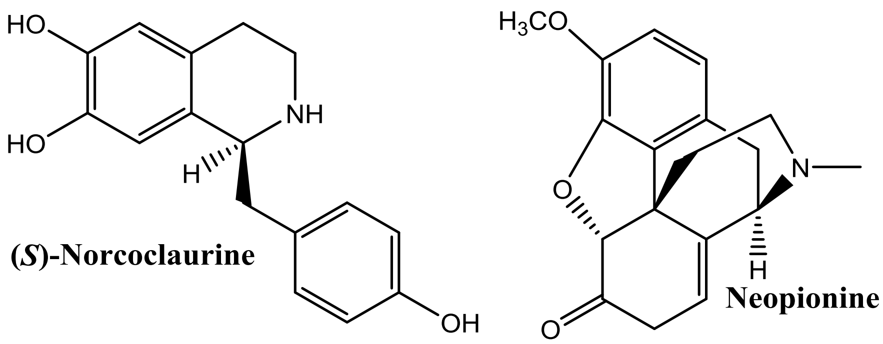


Figure 5: Alkaloid Groups of *Papaver* Genus and Examples.[94]

Because of its high economic and medical importance, this alkaloid “paradise” was thoroughly studied, especially in *P. somniferum*. As mentioned above, the biosynthesis of these alkaloids was briefly presented in the previous cited article, and it is notably presented by J. Ziegler ahc.[95] In a detailed scheme, the biosynthesis is presented, step by step, from L-Tyrosine to (*S*)-Norcoclaurine (**Figure 6**) to (*S*)-Reticuline, and then the biosynthesis branches to several pathways. The major interest of this publication is the biosynthesis of Morphine, and all alkaloids in this path were presented in **Figures 1-4** except Neopionine (**Figure 6**). It is important to mention that this publication presents the enzymes that catalyse the reactions.



(*S*)-Norcoclaurine Neopionine

Figure 6: Two of the Alkaloids Involved in the Biosynthesis of Morphine.[95]

For this review article, we summarized (**Table 4**) selected publication that presented the influence of various factors on the chemical composition and components isolation and identification of *Papaver somniferum*.

Table 4: Influencing Factors on the Chemical Composition of *Papaver somniferum*.

Author(s), Reference	**Influencing Factor**	**Affected Factor**
J.C. Laughlin[96]	Time of harvest	Yield of Morphine
J.C. Laughlin, D. Munro[97]	Fungal colonization	Yield of Morphine
P.J. Hofman, R.C. Menary[98]	Kiln drying	Alkaloid concentration (loss)
R. Luthra, N. Singh[99]	Triacylglycerols deposition	Fatty acid composition
K. Subrahmanyam ahc[100]	Sulfur fertilizers	Seed oil, alkaloid content
J.C. Laughlin, B. Chung[101]	N-fertilizers, irrigation	Yield and composition of alkaloids
R. Chizzola[102]	Low Cadmium stress	Micronutrient composition
T. Grothe ahc[103]	Salutaridinol 7-*O*-Acetyltransferase	Morphine biosynthesis
É. Németh ahc[104]	Successful breedings	Low alkaloid content
A. Balažová ahc[105]	Fungal elicitor	Sanguinarine content, Polyphenoloxidase activity
U. Fisinger ahc[106]	Thebaine synthase	Morphine biosynthesis
R. Khan ahc[107]	Gibberellic acid and Triacontanol	Morphine production
A. Mahdavi-Damghani ahc[108]	Water shortage	Alkaloids yield
I. Holkova ahc[109,111]	Purification method	Isolated Lipoxygenase
N. Kara[110]	Sowing season	Oil and Morphine yields
R.K. Verma ahc[112]	Forensic methods	Compounds identification (review article)
M. Satranský ahc[113]	Cultivar type	Oil content, fatty acid profile
L. Yazici[114]	Sowing season, genotype	Oil and alkaloid contents
R.W. Neugschwandtner ahc[115]	Sowing season and rate	Yield and composition of components
Z. Aghaali ahc[116]	Various methods	Yield and composition of components (review article)
S.C. Carr ahc[117]	Aldo-Keto reductases	Morphine production

I. Varga ahc[118]	Selenium compounds	Seed and oil yields, fatty acid composition
D. Apaydin[119]	γ-Irradiation	Yields and compositions of phytosterols and fatty acids

One of the articles that demonstrate the extensive interest in *Papaver somniferum* was published by A. Diaz-B´arcena and P. Giraldo.[120] It is a review article that presents analysis and statistics of published articles about this plant species (and *Cannabis sativa*). Along with very readable text, this article includes very useful figures and graphs, which makes it very informative. In a similar fashion, yet less extensive but highly illustrative and informative, T. Beycioğlu recently published a bibliometric analysis of *Papaver* alkaloids and Morphine biosynthesis.[121] The earliest recorded use of *Papaver somniferum* by humans started around 8000 years ago, stated R.M. Kunwar and R.W. Bussmann in their review article of the ethnobotany in the Nepal Himalaya.[122] Another very early and very interesting article about this plant species was published by F.R. Stermitz and H. Rapoport in 1961.[123] By supplying $^{14}CO_{2\,(g)}$ to the growing plantlets, they investigated the biosynthesis and the interconversions of alkaloids. Interestingly, they reported that *Papaver somniferum* does not contain Oripavine (**Figure 4**). This report is inaccurate according to later publication (1998) by M.P. Gómez-Serranillos that isolated this compound from this species and even reported its analgesic activity.[58]

V. Lopez asks, "are traditional medicinal plants and ethnobotany still valuable approaches in pharmaceutical research?".[124] He positively answers his question and gives *Papaver somniferum* as an example with its components and medicinal activities, and that it was described by the Greek physician-researcher Dioscorides (70 AD). The relevance and importance of *Papaver somniferum* can be found in other modern fields of research and medicine like preparation of nanoparticles (NPs). A summary of published *Papaver somniferum* extract assisted preparations of NPs and their activities, is presented in **Table 5**.

Table 5: NPs prepared with *Papaver somniferum* plants and their medicinal activities.

Nanoparticle(s)	Property-Activity, Reference
Ag	None[125]
Ag-Polyvinyl alcohol	Skin repair[126]
Au	None[127]
Co_3O_4-NiO	$NaBH_4$ hydrolysis[128]
Fe_2O_3 , PbO	Antimicrobial, antioxidant, antidiabetic, anticancer[129]
ZnO	Antidiabetic, haemolytic activity, antibacterial[130]
ZnO	Anticancer[131]

But *Papaver somniferum* is TOXIC and its toxicity reached fatality in some cases and was published many times. Here, four of these toxicity cases will be cited. H. Küçüker and F. Aydıner reported the death of 65-year-old woman in Turkey after boiling 10-15 capsules and drinking the solution.[132] G. Bozan ahc reported another fatality of 4-years-old female, also from Turkey, that ingested raw plants.[133] Y.P. Tan ahc reported saving a 21-years-old male that had acute cardiotoxicity after drinking self prepared seeds tea, and in the hospital (United Kingdom) was intensively treated with Naloxone.[134] The fourth case, H. Hoummani ahc reported saving the life of a two-month-old infant (Morocco) who developed respiratory distress and hypotonia after his mother administered an oral preparation of opium poppy to calm him and help him sleep at a family party.[135] This plant must be used legally and with extreme caution.

To conclude this discussion, we will elaborate on three out of six major alkaloids, Morphine, Papaverine and Thebaine (**Figure 1**), where the other three are Codeine, Oripavine and Noscapine.[136]

In an outstanding review article, K. Brook ahc present the chemical history of Morphine.[137] The presentation advances step by step along 8000 years of use, historically and chemically, with very useful timeline at the end of the article. Morphine was tested and found potent in many medicinal activities, and consequently, many review articles were published about it. For example, and one of the most recent, the review article of A.J. Teunissen ahc which focuses on its use in non-abdominal surgery.[138] On the top of the properties of Morphine and the first that humans used is the analgesic activity. Modern science approved this ancient use and pain killing is the major use of this compound. Here are two examples from two different centuries: the work of A.A. Megens ahc and the work of X. Song ahc.[139,140] But morphine is addictive.[141,142] Morphine has adverse side effects: dry mouth, sedation, constipation, nausea, myoclonus, dysphoria and other minor health disorders.[143] And Morphine is toxic with some fatal cases.[144-148] This compound must be used legally and with extreme caution.

Papaverine was first isolated from *Papaver somniferum* by George Merck Fraz in 1848.[149] One of its earliest and most common use was as spasmolytic drug[150], where this study compared between Papaverine and two of its synthetic analogues, Octaverine and Perparine (**Figure 7**). Both synthetic compounds were more active than Papaverine.

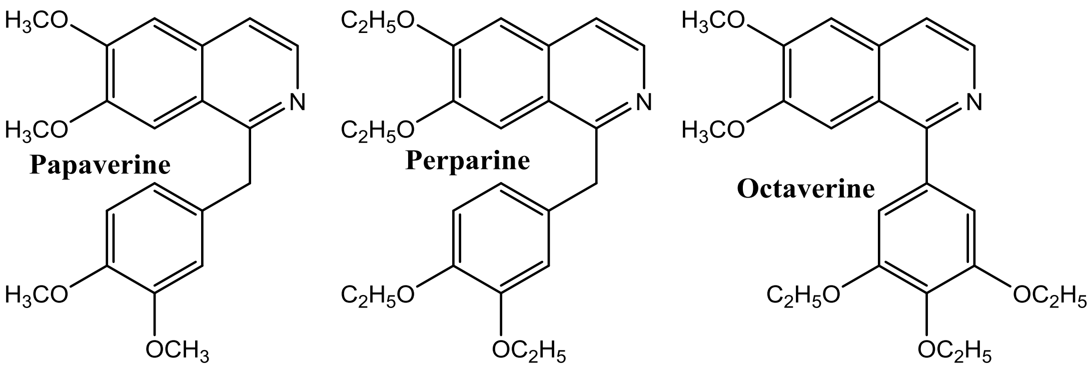


Figure 7: Papaverine, Perparine and Octaverine - Spasmolytic Drugs.[150]

Modern pharmacological research discovered many more medicinal activities of this natural product, and here are some selected examples. Antiviral[151,152], cardioprotective[152,153] and anti-Parkinson.[154] As a result, several review articles were published about this compound and the article of S. Ashrafi ahc is a very good example.[155] It is comprehensive and detailed, and even though they name this compound "miraculous alkaloid", they also indicate some of its negative side effects and complications. But Papaverine has adverse side effects.[156,157] And Papaverine can be toxic.[158-160 (review article)] This compound must be used legally and with high caution.

Thebaine is an important alkaloid that has no direct use as a drug, but it can be easily transformed to other useful compounds like Morphine and Codeine (see below). For this reason, many attempts were carried out to find cheaper methods than chemical synthesis to produce Thebaine. Among these, the works of P.G. Vincent ahc and D. Palevitch and A. Levy, where both research groups increased the concentration of this natural product in *Papaver bracteatum.*[161,162]

Since Thebaine is an intermediate in the biosynthesis of Morphine[163], many studies were published about Thebaine transformations that can occur or be induced because of the effects of many active factors. H. Kodaira and S. Spector transformed Thebaine to Oripavine, Codeine, and Morphine using rat liver, kidney, and brain microsomes.[164] X. Li ahc used engineered *Escherichia coli* strains that increased the major enzymes (especially neopinone isomerase), that catalyse production codeine from thebaine.[165] And an interesting finding was made by M.G. Carlin ahc that interconversion between the epimers of Thebaine in the presence of 80% water or more (**Figure 8**).[166]

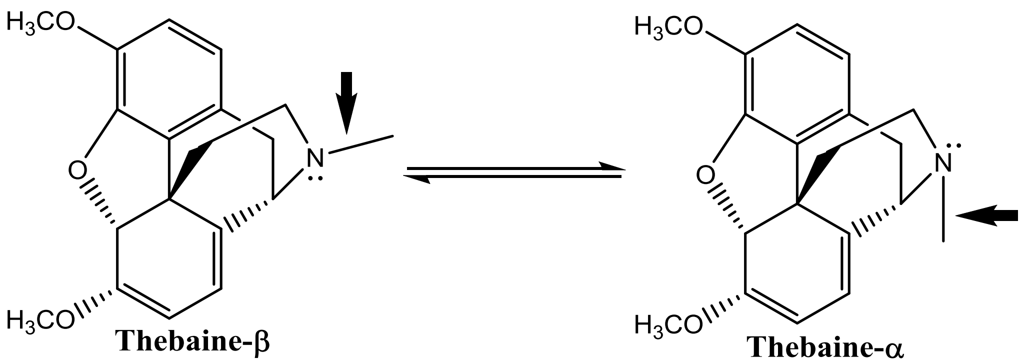


Figure 8: Interconversion Between Thebaine Epimers.[166]

Several methods were developed to detect Thebaine. G. Cassella ahc published a new method for detection of Thebaine in urine using GC-MS.[167] This method aimed to detect this compound as an indication of Poppy seed consumption. S. Lee ahc also used GC-MS to detect Thebaine in hair of rats that were administered with Poppy seeds.[168] This method aimed to detect this compound as an indication of illegal opium substances chronic use.

But Thebaine has adverse side effects. Seeds of some cultivars of *Papaver somniferum* are used for food. The German Federal Institute for Risk Assessment (BfR) has published a clear warning that "the content of opium alkaloid thebaine should be reduced as much as possible".[169] J.W. Sloan ahc reported that Thebaine caused convulsions in rats after administration of a single dose of 20 mg/kg.[170] In a short review article, A. Eisenreich ahc stated that "thebaine exhibits a higher acute toxic potential than morphine. Therefore, exposure to thebaine by consumption of poppy seed-containing food could pose a health risk".[171] G. Navarro and H.W. Elliot reported that high doses of Thebaine caused adverse effects in rabbits and cats, tested by electroencephalogram (EEG).[172] Finally, R. Penafiel ahc reported after examining the cases of toxicity, stated that Thebaine can be toxic to "those consuming non-food grade poppy seeds as a tea".[173] This compound must be used legally and with high caution.

6. CONCLUSIONS

1. *Papaver* species of Israel and Palestine have extraordinary medical importance.
2. Some of these species were extensively studied and published while others were hardly published or not at all. So, research efforts are needed.
3. It is also important to test these plants and their materials for additional medicinal properties-activities.

4. Natural products isolated from these plants can be toxic. They must be legally used with high caution.
5. Because of their potential toxicity, these plants must be used legally and with high caution.

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