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ARGEMONE MEXICANA L. ROOT: A COMPREHENSIVE REVIEW OF ITS PHYTOCHEMISTRY, PHARMACOLOGICAL POTENTIAL AND TOXICOLOGICAL ASPECTS

Varsha Kaka Kedari[1*], Prof. Shital Uamakant Darekar[2]

[1*] Dattakala College of Pharmacy, Pune-Solapur Rd, Chincholi, Maharashtra 413130

[2] Assistant Professor, Dattakala College of Pharmacy, Pune-Solapur Rd, Chincholi, Maharashtra 413130

Abstract:

Argemone mexicana L. (Papaveraceae), the Mexican prickly poppy, is a pantropical weed whose root features in Ayurvedic, African and Latin American folk medicine for infections, pain, worm infestation, poisoning and gynaecological complaints. This review gathers the published information on the root's phytochemistry, pharmacology and toxicology, and, where the literature allows, separates evidence that truly concerns the root from evidence generated with leaves, aerial parts, seeds or the whole plant. The root is dominated by benzylisoquinoline-derived alkaloids: protoberberines (berberine, coptisine), protopines (protopine, allocryptopine) and benzophenanthridines (sanguinarine, chelerythrine and their dihydro derivatives), with a total alkaloid fraction of roughly a quarter of one percent in dried root and stem material. Root extracts have shown antibacterial action that is strongest against Gram-positive organisms, growth-inhibitory effects on a human colon cancer cell line, and anti-inflammatory activity of the alkaloid fraction in rodents. The most advanced clinical work on the species, a Malian antimalarial decoction, was built on leaf material rather than root. The same alkaloids that underlie these activities, above all sanguinarine, are responsible for the severe poisoning (epidemic dropsy) that follows ingestion of edible oil adulterated with argemone seed oil, and they justify caution about unsupervised internal use of root preparations. Root-specific pharmacokinetic, dose-finding and safety data are almost absent. Standardised root extracts, validated marker compounds and well-designed toxicity studies are needed before therapeutic claims can be supported.

Keywords: *Argemone mexicana; Papaveraceae; root; benzylisoquinoline alkaloids; sanguinarine; berberine; protopine; epidemic dropsy; ethnopharmacology*

Corresponding author:
Varsha Kaka Kedari,
Dattakala College of Pharmacy,
Pune - Solapur Rd, Chincholi, Maharashtra 413130
Mobile:
Email Id: *varshakedari359@gmail.com*

QR CODE

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INTRODUCTION:

Plants continue to supply many of the chemical scaffolds used in medicine, and interest in them has returned as antibiotic resistance spreads and the discovery of new antimicrobial and anticancer drugs has slowed.[1] Among the species being re-examined, *Argemone mexicana L.*, the Mexican prickly poppy, is unusually interesting. It is a spiny, yellow-flowered annual of the poppy family (Papaveraceae) that originated in Mexico and the West Indies and is now naturalised across the tropics, where it is mostly regarded as a weed of disturbed ground.[2] Its medicinal use is old. It is thought to go back to the Aztecs, and it later entered the folk pharmacopoeias of India, Africa and the Americas.[3]

Chemically, the species belongs to a genus of more than 25 members, all of which make benzylisoquinoline alkaloids (BIAs) from the amino acid tyrosine.[4] In *A. mexicana* the main products are the benzophenanthridines sanguinarine and dihydrosanguinarine and the protoberberine berberine. Their distribution in the plant is not uniform. In the mature plant, sanguinarine is confined to the roots and ripe seeds, whereas berberine is found in both aerial and underground organs but is absent from ripe seeds.[4] This organ-specific pattern is the main reason a root-focused review is worthwhile: what is learned about leaves cannot simply be carried over to roots, or the reverse.

The plant has already been reviewed as a whole. Brahmachari and co-workers compiled its chemistry and pharmacology up to 2012,[5] Rubio-Piña and Vázquez-Flota tied its pharmaceutical uses to the alkaloid classes and their biosynthesis,[6] and several overviews have appeared since.[7–10] Most of these treat the plant as a single pharmacological unit and seldom say which organ produced a given result. The best-known clinical programme, in Mali, tested a decoction against uncomplicated falciparum malaria and reported results comparable to a standard artemisinin combination in a randomised comparison,[3,11] yet that remedy is described as being prepared from leaves.[12] At the other end of the safety spectrum, the seed oil of the same species is the cause of epidemic dropsy, a poisoning that follows the consumption of edible oils adulterated with it.[13]

The purpose of this review is therefore threefold: (i) to describe the root and its traditional uses, (ii) to bring together what is known about the chemical constituents of the root and how they are analysed, and (iii) to weigh the pharmacological promise of root-derived material against its toxicological risks. Throughout, the review states whether a finding was obtained with roots, with other parts, or with isolated alkaloids, so that readers can judge how far each claim can be extended to the root.

Botanical profile, distribution and traditional use of the root

Plant description and taxonomy

Argemone mexicana grows as an erect, branched and extremely prickly annual that can reach about 150 cm, with a slightly branched taproot and a yellow juice that exudes when tissue is cut.[14] Other authors give roughly 1.2 m as the usual upper height and describe the flowers as bright yellow.[15] In the tropics the plant flowers and sets fruit throughout the year. The flowers open early in the morning and last two to three days, pollination is mostly by self-pollination, and a single plant may produce between 18,000 and 36,000 seeds that germinate best in moist soil at temperatures up to about 25 °C.[2] The seeds yield a non-edible oil known as argemone or katkar oil, a point of great toxicological importance that is taken up in Section 5.

The accepted name is *Argemone mexicana L.* (Species Plantarum 1: 508, 1753), and a long list of synonyms and varietal names exists, among them A. mexicana var. ochroleuca, A. alba, A. spinosa and A. mucronata.[7] Older pharmacognostic sources place the genus in the order Papaverales, although modern phylogenetic classifications place the Papaveraceae in the Ranunculales. Table 1 summarises the taxonomic position and the main vernacular names used in India.

Table 1. Taxonomic position and vernacular names of *Argemone mexicana L.*

Category	Details
Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Magnoliidae
Order	Papaverales (older systems; Ranunculales in current phylogenetic systems)
Family	Papaveraceae
Genus / species	*Argemone mexicana L.*
English	Mexican poppy, prickly poppy
Hindi	Satyanashi; also Ghamoya in Hindi-speaking regions
Sanskrit	Kankkshiri
Marathi	Phirangi-dhotra

Telugu	Brahmadandi
Tamil	Kudiyotti
Kannada	Datturigidda
Malayalam	Ponnummattu
Bengali	Barashit-kantal



Figure 1. ***Argemone mexicana L. Plant***

Table 2. Traditional uses of *Argemone mexicana* root, by region

Region	Preparation	Reported use	Ref.
India (Ayurvedic and folk)	Root	Guinea-worm infestation, pruritus, menorrhagia, poisoning, constipation, flatulence, colic, malarial fever, vesicular calculus	7
India (local practice)	Root powder 1–2 g/day orally; root paste or ointment topically	Constipation and bloating; insect and scorpion bites; wounds	18
Southern Ethiopia (Sidama)	Root decoction	Malaria	19
Tropical Africa	Root and leaf decoctions (topical); root decoction as mouthwash and eye bath	Oedema, inflammation, muscle pain, ulcers, yaws, warts, wound healing; oral and eye infections	2
Vietnam / Philippines	Root	Rheumatism (Vietnam); abortifacient (Philippines)	16
Mexico	Root, leaf and seed (official pharmacopoeial drug)	General medicinal use	16

Phytochemistry of the root

Alkaloid classes

The chemistry of the root is, above all, the chemistry of benzylisoquinoline alkaloids. Three structural families dominate: the protoberberines (berberine and relatives), the protopines (protopine and allocryptopine) and the benzophenanthridines (sanguinarine, chelerythrine and their dihydro forms).[6] A compilation of constituents isolated from the whole plant lists berberine, protopine, sanguinarine, chelerythrine, pancorine, (+)-argenaxine, angoline, allocryptopine, coptisine, jatrorrhizine, columbamine, oxyberberine, dihydrocheilanthifoline and N-demethyloxysanguinarine, among others.[14] Much of this knowledge was built up in a series of isolation studies on whole plants. A Taiwanese group described two new protopines, argemexicaines A and B, together with the anti-HIV alkaloid 6-acetonyldihydrochelerythrine,[21] and reported cytotoxic benzophenanthridine and benzylisoquinoline alkaloids from the same material.[22] Four quaternary alkaloids, dehydrocorydalmine, jatrorrhizine, columbamine and oxyberberine, were reported for the first time in the genus by Singh and colleagues.[15] Earlier work had already described minor alkaloids,[23] and a further study isolated cheilanthifoline, protopine and nor-sanguinarine from the base fraction of the whole plant.[24] Alkaloids and flavonoids were characterised again in a later study.[25] Cell-suspension cultures confirm the same biosynthetic capacity: sanguinarine was the main alkaloid of an A. mexicana cell line, and dihydrosanguinarine, chelerythrine, dihydrochelerythrine and chelidoline

are among the benzophenanthridines found in tissues of the plant.[26]

What is specific to the root

Because most isolation work used whole plants, root-specific information has to be assembled from a smaller number of studies. Three observations stand out. First, the root is the sanguinarine organ. In the mature plant, sanguinarine is restricted to the roots and ripe seeds, while berberine is found in aerial and underground parts but not in ripe seeds.[4] Rootless in vitro shoots can synthesise sanguinarine, but once roots have formed they become its sole accumulation site.[4] Quantitative work on germinating seedlings shows how high the levels can be: sanguinarine in the radicles stayed between roughly 1,400 and 2,000 µg per g dry weight throughout seedling development, and berberine in the radicles stayed near 1,000 µg per g, while berberine in the aerial parts rose to about 3,000 µg per g once the first true leaves had formed.[4] Ripe seeds hold roughly 1,200 µg per g of sanguinarine, mostly in the seed coat.[4] These are seedling and seed values, not mature-root assays, but they indicate the order of magnitude and the strong organ bias.

Second, the root carries chelerythrine in addition to berberine. Methanol fractions of root and leaf, examined by ultra-performance liquid chromatography with mass spectrometry and by nuclear magnetic resonance, contained berberine and chelerythrine in the root, whereas the leaf lacked chelerythrine.[1] The same study separated the inner and outer root, and the outer root methanol extract was the more active against bacteria and cancer cells (Section 4).[1]

Third, a pharmacognostic summary puts the total alkaloid fraction of dried roots and stems at about 0.25 %, mainly protopine and berberine, with coptisine, allocryptopine, chelerythrine and dihydrochelerythrine as further root alkaloids.[16] Table 3 collects the principal alkaloids and what is known about where they occur.

Table 3. Principal alkaloids reported from *Argemone mexicana*, with emphasis on the root

Alkaloid	Structural class	Part(s) reported	Remarks	Ref.
Berberine	Protoberberine	Root, aerial parts; absent from ripe seed	Antibacterial marker; present in root methanol fractions	1, 4
Coptisine	Protoberberine	Root	Minor root alkaloid	16
Jatrorrhizine, columbamine, dehydrocorydalmine, oxyberberine	Quaternary protoberberines	Whole plant	First reported in the genus	15
Protopine	Protopine	Root, whole plant	One of the two main alkaloids of the root and stem fraction; antiplasmodial in vitro	14, 16
Allocryptopine	Protopine	Root, whole plant	Antiplasmodial in vitro	14, 16
Argemexicaines A and B	Protopine (new)	Whole plant	New protopines from Formosan material	21
Sanguinarine	Benzophenanthridine	Root and ripe seed (mature plant)	Toxic principle of argemone seed oil; accumulates only in root once roots form	4, 14
Dihydrosanguinarine	Benzophenanthridine	Root and seed	Co-occurs with sanguinarine	4, 26
Chelerythrine, dihydrochelerythrine	Benzophenanthridine	Root	Chelerythrine absent from leaf	1, 16
6-Acetonyldihydrochelerythrine	Benzophenanthridine	Whole plant	Anti-HIV activity reported	21
N-Demethyloxysanguinarine	Oxy-benzophenanthridine	Whole plant	Listed among whole-plant alkaloids	14
Cheilanthifoline, nor-sanguinarine	Tetrahydroprotoberberine; benzophenanthridine	Whole plant	Isolated with protopine from base fraction	24

Non-alkaloid constituents

Beyond alkaloids, the plant has been reported to contain flavonoids, terpenoids, long-chain aliphatic alcohols, amino acids, carboxylic acids, steroids, carbohydrates and phenols.[9] Phytochemical screens that report phenolics, flavonoids, tannins and saponins have, however, mostly been run on leaves, stems or the whole plant, and the non-alkaloid chemistry of the root remains thinly documented. Given that traditional root preparations are usually water decoctions or powders, the contribution of phenolics and other polar constituents to the activity of such preparations is an open question.

Biosynthesis and tissue-level regulation

All the principal alkaloids originate from tyrosine. A condensed view of the pathway in A. mexicana places norcoclaurine synthase (NCS) at the start, followed by the berberine bridge enzyme (BBE) that forms the protoberberine skeleton. From there the route splits: scoulerine O-methyltransferase (SOMT) and tetrahydroprotoberberine oxidase (STOX) commit intermediates to berberine, while S-cheilanthifoline synthase (ChESYN, a cytochrome P450 of the CYP719 family) commits them to the sanguinarine branch.[4] Protopine-type alkaloids lie on the route to the benzophenanthridines, which explains why protopine, allocryptopine and sanguinarine occur together.[6] Figure 2 shows the pathway in simplified form.

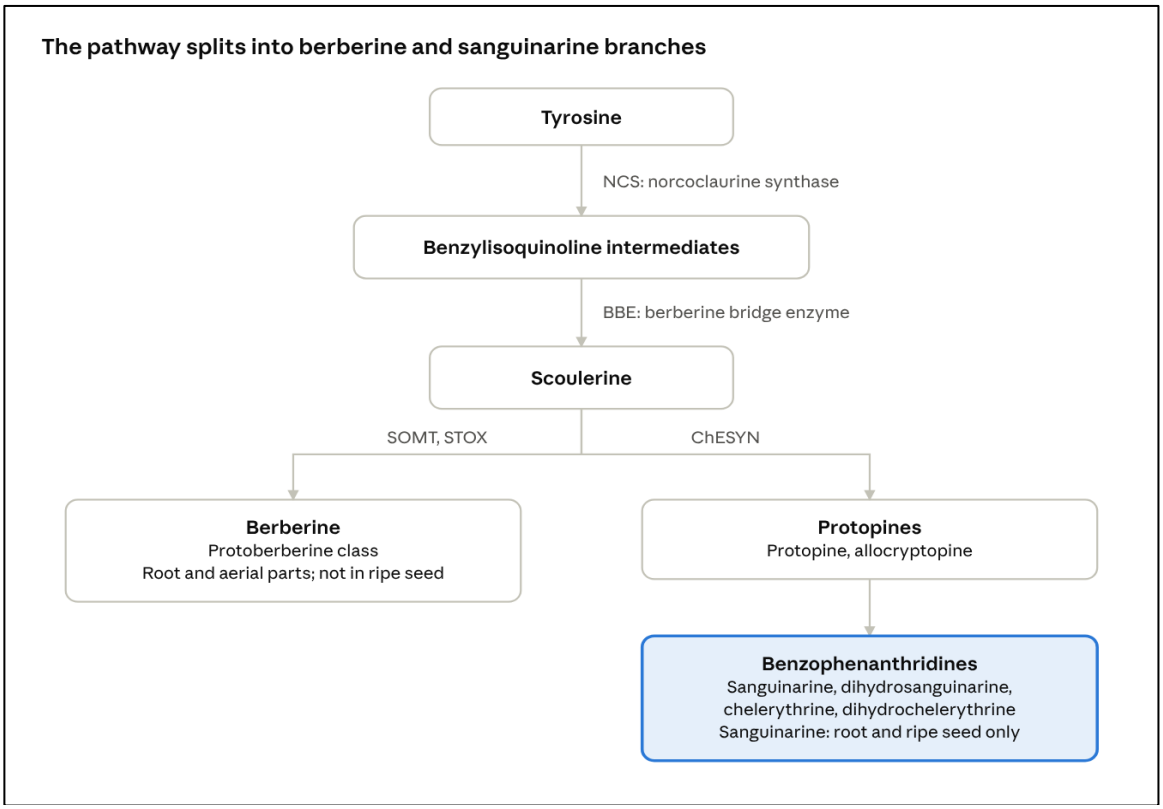


Figure 2. Simplified biosynthetic pathway of the principal alkaloids of *Argemone mexicana*. NCS, norcoclaurine synthase; BBE, berberine bridge enzyme; SOMT, scoulerine O-methyltransferase; STOX, tetrahydroprotoberberine oxidase; ChESYN, S-cheilanthifoline synthase.

Two features of its regulation matter for the root. During germination, the radicle starts to make both berberine and sanguinarine once it emerges from the seed, and in the mature plant the presence of a gene transcript does not always match the presence of its alkaloid product, which points to long-distance movement of alkaloids between shoot and root.[4] Consequently, alkaloid content in harvested root is expected to depend on developmental stage and growth conditions, as well as on genotype.

Extraction and analysis

Alkaloids from A. mexicana tissue have been extracted with methanol containing 0.5 % hydrochloric acid, shaken for two hours at room temperature, and then quantified by thin-layer chromatography with in situ fluorescence scanning, using n-butanol:water:ammonia (8:1:1) for berberine and benzene:ethanol (9:1) for sanguinarine.[4] Methanol extraction followed by liquid chromatography–mass spectrometry and

NMR was used to identify berberine and chelerythrine in root material.[1] For the Malian decoction, a quantitative NMR method that uses the methylenedioxy proton signal of each alkaloid with anthracene as internal standard allowed protopine, allocryptopine and berberine to be measured together; allocryptopine was the most concentrated of the three.[27] Taken together, these methods show that analytical tools exist, but a validated chromatographic method with defined limits for sanguinarine and chelerythrine in root drug, which would be the logical safety markers, was not found in the literature reviewed.

Pharmacological activities

Pharmacological reports on A. mexicana fall into three groups, and the distinction matters for a review of the root. The first group tests root extracts directly. The second tests isolated alkaloids that are known to occur in the root, such as berberine, protopine, allocryptopine and sanguinarine. The third, by far the largest, uses leaves, stems, flowers, fruits, seeds, aerial parts or whole plants. Each subsection below states which group a finding belongs to, and Table 5 at the end of this section summarises how strong the root-specific evidence is for each activity.

Antimalarial and antiplasmodial activity

The strongest human data come from Mali, where ethnobotanical work identified the plant as the most effective local remedy for malaria. In a prospective, dose-escalating, quasi-experimental trial with a traditional healer, 80 patients with falciparum parasitaemia above 2,000 per µL and no signs of severe malaria received a decoction in one of three regimens: once daily for 3 days (n = 23), twice daily for 7 days (n = 40), or four times daily for 4 days followed by twice daily for 3 days (n = 17). About 80 % of the patients were under five years old and a quarter were under one year.[3] The proportion with adequate clinical response at day 14 was 35 %, 73 % and 65 % in the three groups respectively (P = 0.011) and was lower in infants under one year (45 %) than in patients over five years (81 %).[3] Complete parasite clearance was uncommon, but 67 % of the patients with an adequate response had parasitaemia below 2,000 per µL at day 14. No patient needed referral for severe disease, and only minor side effects were seen.[3]

A second trial randomised 301 patients with presumed uncomplicated malaria (median age 5 years) to the decoction or to artesunate–amodiaquine. Second-line treatment was not needed over 28 days in 89 % of the decoction group and 95 % of the artemisinin-combination group; deterioration to severe malaria occurred in 1.9 % of children aged five or under in both arms, and none developed coma or convulsions.[11,19] The decoction has since received government approval in Mali.[19] A follow-up of 294 of these patients to 84 days asked whether residual parasitaemia at day 28 predicted later malaria episodes or anaemia.[28] The overall development of the remedy has been described as a model of reverse pharmacology.[29]

Bioguided fractionation of the clinical decoction led to three alkaloids: allocryptopine, protopine and berberine. All three were active against Plasmodium falciparum in vitro, and allocryptopine and protopine were selective for the parasite.[27] Reported half-maximal inhibitory concentrations are 0.32 µg/mL for protopine, 1.46 µg/mL for allocryptopine and 7.02 µg/mL for sanguinarine.[14] These alkaloids are precisely those found in the root (Table 3), which makes the root pharmacologically plausible as an antimalarial drug. Two cautions apply, however. The Malian remedy is described as a leaf preparation,[12] so the trials do not test the root. And in Ethiopia, where roots are used, malaria transmission involves both P. vivax and P. falciparum, and the effectiveness of the plant in that setting has not been established.[19] Table 4 summarises the human studies.

Table 4. Human studies of *Argemone mexicana* decoction in malaria

Study	Design and setting	Participants	Main findings	Ref.
Willcox et al., 2007	Prospective, dose-escalating, quasi-experimental; Mali	80 patients with P. falciparum parasitaemia > 2,000/µL	Adequate clinical response at day 14: 35 %, 73 %, 65 % across three regimens (P = 0.011); minor side effects only	3
Graz et al., 2010	Randomised comparison with artesunate–amodiaquine; Mali	301 patients, median age 5 years	No second-line treatment to day 28: 89 % vs 95 %; severe malaria 1.9 % in both arms (children ≤ 5 y)	11, 19
Willcox et al., 2011	Follow-up to 84 days of the randomised trial	294 of 301 patients	Tested whether residual parasitaemia at day 28 predicted later episodes or anaemia	28
Tekassa et al., 2022	Community-based cross-sectional survey; Jimma Zone, Ethiopia	Community members and traditional healers	Use of the plant for malaria documented; efficacy where P. vivax and P. falciparum co-exist not yet assessed	19

Antimicrobial activity

The most informative root study compared methanol and hexane extracts of seeds, leaves, and inner and outer root against four bacteria, two fungi and a human colon cancer cell line, using 1 mg of extract per disc.[1] The methanol extracts of the outer root and of the leaf had the strongest antimicrobial effect, with the greatest activity against Gram-positive bacteria and less against Gram-negative bacteria and fungi.[1] Berberine and chelerythrine were identified as two main antibacterial compounds; the roots contained both, while the leaf lacked chelerythrine.[1] This suggests that the antibacterial activity of the root may be concentrated in its outer layers rather than evenly distributed, although the study did not define the tissues involved. A comparison of aqueous, acetone, ethanol and chloroform extracts of leaves, stems and roots against Escherichia coli, Klebsiella pneumoniae, Bacillus cereus and Staphylococcus aureus found the stem extract more inhibitory than those of root or leaf,[5] which illustrates how strongly results depend on part and solvent.

Solvent extracts of the plant have also inhibited a range of pathogenic bacteria in older work,[30] and ethanol, methanol and chloroform extracts of flowers, berries and leaves gave roughly 80 % inhibition against most bacterial strains tested and more than 50 % inhibition of fungi.[31] A mixture of quaternary alkaloids isolated from the plant was active against several phytopathogenic fungi,[32] and berberine has been reported as a nematocidal alkaloid against Strongyloides venezuelensis.[33] Extracts of stem, leaf, flower and fruit were active against Salmonella typhi, Staphylococcus epidermidis, Citrobacter, Neisseria gonorrhoeae and Shigella flexneri and also inhibited HIV-1 reverse transcriptase.[18] A specific anti-HIV alkaloid, 6-acetonyldihydrochelerythrine, was described earlier.[21] None of these antiviral findings is root-specific.

Taken together, the data support the idea that berberine and chelerythrine contribute to a modest, mainly Gram-positive antibacterial effect of root extracts. They do not yet allow a root preparation to be positioned against standard antibiotics, because minimum inhibitory concentrations, time-kill data and cytotoxicity-to-host-cell comparisons for root extracts are lacking.

Antioxidant activity

Root material has been included in in vitro antioxidant screening,[34] but most quantitative antioxidant work concerns other parts. Leaf extracts, particularly the ethyl acetate extract, showed marked radical-scavenging activity in DPPH and nitric oxide assays and were rich in phenolics,[35] and extracts of several parts showed strong antioxidant activity in a separate study.[18] Such assays are useful for screening but are not proof of in vivo benefit: they measure chemical reactivity in a test tube, and they are easily influenced by solvent and by non-specific phenolic content. For the root, whose alkaloid-rich extracts may owe much of their biological effect to quaternary alkaloids rather than phenolics, antioxidant data should be interpreted cautiously.

Anti-inflammatory, analgesic and neuro-cardiovascular effects

For the root, the best-documented pharmacology outside infection is anti-inflammatory and cardiovascular. The alkaloid fraction isolated from the roots showed anti-inflammatory activity in rabbits and rats, and the same fraction lowered blood pressure in anaesthetised dogs, an effect that was not altered by atropine, antihistamines or adrenergic blockers.[16] Protopine and allocryptopine each significantly reduced morphine withdrawal in experimental models.[16] Analgesic and anti-inflammatory studies on root extracts have also been reported.[36] Whole-plant extracts add to the picture: methanolic and ethyl acetate extracts given orally to Swiss albino mice at 100, 200 and 400 mg/kg showed analgesic, anxiolytic and sedative effects in hot-plate, writhing, locomotor and muscle-relaxant tests, and both extracts were reported safe up to 2,500 mg/kg in the acute toxicity test.[37] The review literature also credits the plant with neurological properties linked to its alkaloids.[6] Because many of the root findings are decades old and were obtained with alkaloid fractions of unspecified composition, they should be repeated with characterised extracts and modern dose–response designs.

Cytotoxic and anticancer activity

The outer root methanol extract and a seed hexane extract showed pronounced inhibitory effects on human colon cancer cells in an MTT assay, and the authors went on to quantify messenger RNA for the oncogene c-MYC and the tumour suppressor APC to explore how the root extract might act.[1] Cytotoxic benzophenanthridine and benzylisoquinoline alkaloids from the plant had been described earlier.[22] At the level of the single compound, sanguinarine has been widely studied. Reviews describe antiproliferative, pro-apoptotic, antiangiogenic and anti-invasive effects in many tumour models,[38] but they also stress that the compound has been labelled a toxicant and even a carcinogen in some toxicological work, and that its development potential has to be weighed against that risk.[39] Methanolic stem extract, tested on human hepatoma (HepG2) and glioblastoma (U87MG) cells, reduced cell viability significantly,[40] although this is not a root result.

Two points follow for a pharmacy reader. First, cytotoxicity in a cancer cell line is not selective anticancer activity; the same alkaloids that kill tumour cells in a dish injure normal tissue in poisoning episodes (Section 5). Second, no study found here compared the root extract's effect on cancer and non-cancer cells, so a therapeutic index cannot yet be calculated.

Other reported activities

Wound healing is the best-known traditional topical use of the root, which is applied as a paste or ointment,[18] but this review found no controlled study of a root preparation in a wound model. Hepatoprotective activity has been reported for an aqueous extract of the whole plant against carbon tetrachloride-induced liver injury in rats, with 150 and 250 mg/kg lowering serum aspartate transaminase, alanine transaminase and alkaline phosphatase, and an aqueous extract of aerial parts at 200 and 400 mg/kg lowered blood glucose in alloxan-induced diabetic rats.[14] These results derive from non-root material and cannot be assigned to the root.

Table 5. Strength of root-specific evidence for reported pharmacological activities

Activity	Evidence from root	Evidence from other parts or isolated alkaloids	Root-specific evidence
Antimalarial	Root decoction used traditionally in Sidama, Ethiopia (no efficacy trial)[19]	Decoction trials in Mali (leaf remedy);[3,11] in vitro IC50: protopine 0.32, allocryptopine 1.46, sanguinarine 7.02 µg/mL[14]	Low
Antibacterial	Outer root methanol extract active, mainly Gram-positive[1]	Leaf, flower, berry, stem extracts[5,31]	Low to moderate (in vitro only)
Antifungal, antiviral	Not shown for root	Quaternary alkaloid mixture;[32] extracts inhibit HIV-1 reverse transcriptase[18]	Insufficient
Antioxidant	Root included in in vitro screening[34]	Leaf, stem and whole-plant extracts[18,35]	Low
Anti-inflammatory, analgesic	Root alkaloid fraction active in rabbits and rats;[16] root extract studies[36]	Whole-plant extracts in mice[37]	Low to moderate (animal)
Cardiovascular, CNS	Root alkaloid fraction lowered blood pressure in dogs; protopine and allocryptopine reduced morphine withdrawal[16]	Whole-plant analgesic, anxiolytic, sedative effects[37]	Low (animal, dated)
Anticancer	Outer root methanol extract inhibited colon cancer cells[1]	Sanguinarine reviews;[38,39] stem extract on HepG2 and U87MG[40]	Low (in vitro only)
Hepatoprotective, antidiabetic, wound healing	Traditional root paste for wounds[18]	Whole-plant and aerial-part extracts in rats[14]	Insufficient

Toxicological aspects

The toxicology of A. mexicana is dominated by one clinical syndrome, epidemic dropsy, which is caused by the seed oil and not by the root. That distinction should not be allowed to produce false reassurance. The alkaloids responsible for dropsy are also present in the root, and the root is in fact their main storage organ in the mature plant. For a pharmacy reader, the lessons of epidemic dropsy are therefore directly relevant to any proposal to use root preparations internally.

Sources of toxicity

The seeds of the plant yield a pale, non-edible oil whose toxic alkaloids are sanguinarine and dihydrosanguinarine.[13] This oil is sometimes added to mustard oil in India to increase pungency, which is the route by which people are exposed.[2] In the root, sanguinarine is the characteristic alkaloid, since in the mature plant it accumulates only in roots and ripe seeds,[4] and chelerythrine, another cytotoxic benzophenanthridine, is also present.[1] The root should therefore be treated as a toxic-alkaloid drug in the same way as other isoquinoline-alkaloid plants, whatever its therapeutic promise.

Epidemic dropsy: clinical picture

Epidemic dropsy is the clinical state that follows ingestion of edible oil adulterated with argemone oil.[13] Large outbreaks have occurred repeatedly in India.[41] Patients typically present with bilateral pitting oedema of the legs, reddened and sometimes pigmented skin, a fast heart rate without fever, and loss of albumin in the urine; in one paediatric series, hypoalbuminaemia was present in 55–60 % of cases in earlier studies and mortality was about 3 % against a published range of 3–7 %.[41] Ocular involvement, notably glaucoma, has

been documented,[42] and cardiovascular manifestations, from tachycardia to cardiac failure, were described in classic clinical work.[43] A review of the condition characterises it as a distinct but frequently missed entity, with symptoms ranging from leg oedema, diarrhoea and breathlessness to heart failure, and with exposure possible through food or body massage.[44]

The dermal route deserves emphasis. Exposure is usually inadvertent, arising from adulterated cooking oil, but cases have followed topical use of argemone-containing massage oil. The severity of illness has been reported to correlate with plasma sanguinarine concentration, and black salve, a topical skin-cancer remedy that also contains sanguinarine, can carry far more of the alkaloid than contaminated massage oil, so a theoretical risk of epidemic dropsy exists from that product.[45] The point for root preparations is that application to the skin, which traditional medicine regards as the safer route, does not remove the hazard when the preparation is rich in sanguinarine.

Mechanisms of toxicity

Sanguinarine and dihydrosanguinarine are considered to cause widespread capillary dilatation, proliferation and increased vascular permeability, which explains the oedema and the cardiac and pulmonary complications.[13] Experimental work in rats and guinea pigs on the elimination and organ retention of sanguinarine showed that the alkaloid persists in tissues,[46] and retention in the gastrointestinal tract, liver, lung, kidney, heart and serum at 96 hours after exposure has been taken to identify these organs as likely targets.[13] In an everted gut sac model, sanguinarine impaired the transport of essential nutrients, with a role proposed for the sodium–potassium ATPase.[47] Biochemical toxicology studies of argemone oil in rats showed effects on hepatic cytochrome P450 and xenobiotic-metabolising enzymes,[48] and antioxidants and radical scavengers modified toxicity in the same animals,[49] in line with oxidative damage of plasma proteins and lipids and altered antioxidant status in patients.[50] Sanguinarine also interacts with hepatic cytochrome P450 in rats,[51] which raises the possibility of herb–drug interactions when sanguinarine-rich preparations are taken together with other medicines.

Beyond acute poisoning, genotoxic and carcinogenic concerns have been raised. Argemone oil, and sanguinarine, caused genotoxic effects in the bone marrow of mice,[52] and sanguinarine was proposed decades ago to be a carcinogenic contaminant of edible oils in India.[53] A recent review of sanguinarine as a potential anticancer agent notes that it has been classed as a toxicant and even a carcinogen in some studies and that clinical observations have linked sanguinarine-containing products to precancerous change in the mouth or skin.[39] These data come from oil or from isolated sanguinarine, not from root extracts, but they set the safety question that root studies must answer.

Toxicity in animals

Whole-seed feeding studies confirm the toxic potential of the plant. Roof rats fed argemone seed as the entire diet for up to 10 days showed sedation, passiveness, sluggishness, feeble or absent muscular jerks, abdominal contractions and increased defecation.[54] In pigs, freshly milled seed of the related *Argemone ochroleuca* at 1 % of the diet was toxic within three to four weeks, with reduced feed intake, lethargy, reddening of the skin and mild diarrhoea, whereas sunlight-exposed seed was non-toxic at 4 %; the difference could not be explained by the content of sanguinarine, chelerythrine, protopine or berberine alone, but may reflect total isoquinoline alkaloid content, and similar concentrations of A. mexicana seed were expected to be tolerated on the basis of alkaloid content.[55] Animal toxicity of argemone oil itself was studied in experimental animals more than four decades ago.[56] In contrast to this material, acute oral toxicity data for the plant are reassuring: methanolic and ethyl acetate extracts of the whole plant were reported to be safe up to 2,500 mg/kg in mice in an acute test.[37] A single-dose test with a whole-plant extract does not, however, address repeated exposure, organ-specific damage or the root, so it cannot be used to declare root preparations safe.

Detection, management and prevention

Prevention rests on keeping argemone oil out of edible oil: selective cultivation of mustard types that cannot be confused with argemone seed, strict enforcement of food adulteration law and deterrent punishment of offenders are the main measures proposed in a review of the disease in India.[57] Chemical and chromatographic tests for argemone oil in edible oils are available for surveillance.[57] Management is largely supportive; a limited trial of antioxidants was reported during an outbreak in Barabanki district of Uttar Pradesh, motivated by the evidence of oxidative damage.[58] These measures concern oil, but a pharmacist can apply the same logic to herbal products: a sanguinarine-rich preparation should be identified, quantified and kept out of products meant for internal or extensive topical use unless a safety margin has been shown.

Table 6. Summary of toxicological evidence relevant to *Argemone mexicana* root

Material	Model or setting	Principal findings	Ref.
Argemone seed oil in edible oil	Human outbreaks	Oedema, hypoalbuminaemia, cardiac failure, glaucoma; mortality about 3–7 %	13, 41–43
Argemone oil by skin (massage oil)	Human cases	Epidemic dropsy after transcutaneous exposure; severity linked to plasma sanguinarine	45
Sanguinarine	Rats, guinea pigs	Persistence in gut, liver, lung, kidney, heart and serum	13, 46
Sanguinarine	Rat gut sac	Impaired nutrient transport; Na^+/K^+-ATPase implicated	47
Argemone oil	Rat liver	Changes in cytochrome P450 and xenobiotic enzymes; antioxidants modify toxicity	48, 49
Sanguinarine	Rats	Interaction with hepatic cytochrome P450	51
Argemone oil, sanguinarine	Mouse bone marrow	Genotoxic effects	52
Argemone seed	Roof rats	Sedation, sluggishness, abdominal contractions	54
Argemone ochroleuca seed	Pigs	Reduced feed intake, lethargy, skin reddening	55
Whole-plant extracts (methanol, ethyl acetate)	Mice, acute oral	Safe up to 2,500 mg/kg	37
Root extract or root alkaloid fraction	No study located	Root-specific toxicity data absent	—

Implications for the use of root preparations

Three conclusions follow from the evidence. First, because the root is the only organ in which sanguinarine accumulates in the mature plant and also contains chelerythrine, the root cannot be assumed to be safer than the seed oil on a chemical basis; what protects patients is dose, route and extraction, and none of these has been defined for root drugs. Second, uses recorded in tradition, such as abortifacient use in the Philippines and internal use against poisoning or jaundice, are exactly the contexts in which hepatic and reproductive toxicity would be most damaging.[2,16] Third, the capacity of sanguinarine to interact with cytochrome P450 enzymes means that concurrent medicines are a real concern.[51] Taken together, these considerations justify treating root products as unproven and potentially hazardous until root-specific toxicology, including repeated-dose studies, reproductive toxicity and interaction testing, has been done.

Challenges, research gaps and future perspectives

The root-specific evidence gap

The most striking finding of this review is how little of the pharmacology credited to A. mexicana was actually obtained with roots. The clinical programme in Mali used a leaf-based remedy;[3,12,19] the best-quantified antioxidant, hepatoprotective, antidiabetic and cytotoxic data come from leaves, stems or whole-plant extracts;[9,14,35,40] and the root has a small set of in vitro antibacterial and cytotoxic observations[1] plus older animal data on an alkaloid fraction.[16] No controlled study of a root preparation in humans was found. There are also no published pharmacokinetic data for root alkaloids in the form in which they are consumed, although a quantitative NMR method has shown that the Malian decoction contains measurable amounts of allocryptopine, protopine and berberine.[27] Without exposure data, neither efficacy nor safety margins can be estimated.

Standardisation and quality control

The alkaloid content of the root depends on the stage of development and on growth conditions, because organ-specific patterns of berberine and sanguinarine are set from the earliest germination stages and appear to involve transport between shoot and root.[4] Material is collected from wild stands rather than cultivated,[2] and varies between sites and seasons. A rational quality system would therefore define two kinds of marker. Efficacy markers could include berberine, protopine and allocryptopine, which are the alkaloids linked to antimicrobial and antiplasmodial activity.[1,27] Safety markers would include sanguinarine and chelerythrine, with upper limits. Validated chromatographic assays, such as HPLC with photodiode-array or mass-spectrometric detection, would be needed for both groups, together with macroscopic and microscopic identity criteria such as those already described for the root.[17] Cell-suspension cultures that accumulate sanguinarine and dihydrosanguinarine,[26] and biotechnological approaches generally, might in future supply reference alkaloids and defined extracts without reliance on wild harvest.

Safety-first study design

Given the known toxicology, root studies should begin with safety rather than efficacy. A sensible sequence would be: characterisation of the extract;

acute and repeated-dose oral toxicity under guideline conditions, including liver, kidney, heart and eye endpoints; genotoxicity testing, since argemone oil and sanguinarine produced genotoxic effects in mice;[52] reproductive toxicity, given the abortifacient use recorded in tradition;[16] and interaction testing on cytochrome P450 enzymes, because sanguinarine interacts with hepatic P450 in rats.[48],[51] For anticancer claims, selectivity must be quantified by comparing cancer and non-cancer cells, which none of the root studies located here has done.[1],[38],[39] Topical products, such as the root pastes and ointments of tradition,[18] should be tested for dermal absorption, since skin exposure to sanguinarine-rich preparations has caused systemic poisoning.[45]

Lessons from the Malian experience

The development of the Malian decoction shows how a traditional remedy can be moved towards approval. The path began with an ethnobotanical and retrospective treatment-outcome study, continued through a dose-escalating clinical study and a randomised comparison with a standard artemisinin combination, and was supported by bioguided fractionation, quantification of the active alkaloids and a follow-up of patients for three months.[3],[11],[27–29] The result was government approval of the remedy in Mali.[19] The same logic could be applied to the root, but it starts from a weaker position: the root has not been studied in a defined traditional preparation in an endemic population, and its higher sanguinarine content makes the margin of safety a first-order question.

Public-health and regulatory perspectives

The public-health importance of this plant lies as much in the harm of adulteration as in therapeutic promise. Control of argemone seed in mustard fields and of oil in the market remains the main preventive measure,[57] and the same vigilance is needed for herbal products that might contain argemone alkaloids. For pharmacists, practical points follow: counselling that internal use of argemone root products is not supported by safety data, particular warnings for pregnancy, liver disease, heart disease and concurrent drug therapy, and reporting of any suspected adverse reaction through pharmacovigilance systems.

CONCLUSION:

The root of *Argemone mexicana* is a chemically rich and pharmacologically suggestive drug. It accumulates protoberberine, protopine and benzophenanthridine alkaloids, among which sanguinarine is characteristic of the root and the ripe seed, and its extracts have shown antibacterial, cytotoxic, anti-inflammatory and cardiovascular effects in laboratory systems. The best clinical evidence for the species, in malaria, rests on a leaf-based decoction and therefore cannot be transferred to the root. At the same time, the alkaloids that make the root interesting are those that cause epidemic dropsy, genotoxic effects and interactions with drug-metabolising enzymes, and no root-specific toxicity study has been published. The balance of evidence therefore favours continued research but not therapeutic use of unstandardised root preparations. Priority should be given to validated analytical methods, repeated-dose and reproductive toxicology, quantified selectivity in cytotoxicity assays, and exposure studies. If these studies show an acceptable margin of safety, standardised root extracts or specific alkaloid fractions could then be taken forward in carefully designed clinical studies, following the pathway established for the Malian antimalarial decoction.

CONFLICT OF INTEREST:

The Author declares that there is no conflict of interest.

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