Published online in http://ijam.co.in ISSN No: 0976-5921

International Journal of Ayurvedic Medicine, Vol 15 (1), 2024; 1-12

Traditional uses, phytochemistry, pharmacological significance and toxicology of *Argemone mexicana* L. – A review approach

Review Article

Srinivasan N[1*]

1. Department of Pharmacy, Faculty of Engineering and Technology, Annamalai University, Annamalai Nagar, Chidambaram 608002. India.

Abstract

Argemone Mexicana L. (AM, Papaveraceae) is found and native to tropical America. Many cultures have traditionally used this annual herb to treat a variety of ailments, including skin disorders, digestive problems, eye issues, and anti-dotes. *Argemone Mexicana* L. (AM), a plant with a long history of traditional use, has recently gained renewed attention from researchers due to its potential pharmacological benefits. The possibility that this plant could be used to develop new therapies has inspired further research. Information about AM was collected from scientific databases published between January 2000 and March 2022. These databases include Elsevier, PubMed, Web of Science, NOPR, Google Scholar, ResearchGate, Wiley, SpringerLink, and ACS publications. Numerous chemical constituents present in AM have been found to have medicinal properties, such as alkaloids, flavonoids, tannins, phenolic compounds, saponin, terpenoids, and cardiac glycosides. Various parts of the AM plant exhibit antimicrobial, wound healing, antioxidant, antimalarial, larvicidal, anthelmintic, antidiabetic, hepatoprotective, anticancer effects, and have been used to treat sexually transmitted diseases. However, the plant is also known to be toxic, and its use can lead to a number of adverse effects, including dermatitis, gastrointestinal disturbances, and neurological damage. This review critically evaluates recent developments in the traditional use, phytochemistry, pharmacology, and toxicology of AM in order to provide a scientific basis for reasonable utilization and further research.

Keywords: *Argemone mexicana,* Mexican prickly poppy, Alkaloids, Sanguinarine, Toxicity, Antimalarial activity.

Introduction

Throughout history, people have used plants to treat and cure various diseases, and this practice continues to the present day. Traditional Indian medicine has a long history of using plant-based therapies to promote health and well-being. Several traditional medicinal herbs have been incorporated into modern medicine, and some of these treatments are still employed. The fields of ethnobotany and ethnopharmacology have made significant contributions to the development of new compounds and sources of information. An expansive approach to uncovering new pharmaceuticals from medicinal plants has been implemented, encompassing botany, phytochemistry, biological testing, and molecular identification. Recent research regarding structure-activity relationships has yielded important advancements in the field of phytochemistry, a key component of pharmaceutical science. The potential of medicinal plant-based drugs to treat a variety of medical ailments such as cancer, HIV, diabetic complications, anti-inflammatory conditions, and both communicable and non-communicable diseases, has yielded promising results. The current global market value of pharmaceutical preparations derived from plants is $60 billion USD, according to a recent report. The market for plant-based medicines is expected to reach $5 trillion by 2050, indicating a rapid increase in demand. Out of an estimated total of 400,000 secondary plant metabolites, about 10,000 have been found and described using chemical techniques. This has sparked an increased focus on the discovery and research of these secondary plant metabolites, with the goal of finding potential treatments and cures for a variety of illnesses. It is estimated that 20-25% of all drugs in the pharmacopoeia come from natural sources. In developing countries, 70–80% of medicines rely on traditional plant-based remedies because modern drugs are more expensive, easier to obtain, and have fewer side effects. Therefore, natural sources play a crucial role in providing accessible and affordable remedies, especially in developing countries (1, 2). The annual herb AM, also known as the Mexican prickly poppy. The plant is grown in many different climates, from subtropical to temperate regions. The plant is spread out in a wide array of regions, including Nepal, Bangladesh, Fiji Islands, Mauritius, Mexico and the United States. In India, it can be found in temperate regions up to an altitude of 1,500 meters and is often observed colonising abandoned fields and crop land. The plant

*** Corresponding Author:**
Srinivasan N
Department of Pharmacy,
Faculty of Engineering and Technology,
Annamalai University,
Annamalai Nagar, Chidambaram 608002.
Email Id: seenu301@gmail.com

typically develops during the summer season (3, 4). The plant parts of AM, such as roots, leaves, and flowers, are believed to have healing properties. These properties can help with a variety of problems, from minor skin irritations to cancer and diabetes. The range of scientific studies investigating the biological functions of AM phytochemicals has revealed diverse therapeutic applications. The intention of this study is to gain a better understanding of the traditional uses, phytochemistry, recent pharmacological applications, and toxicology of the plant AM.

Methodology

In the literature review, a variety of search terms were utilized: "traditionally utilized," "traditional medicine," "phytochemistry or secondary metabolites or phytoconstituents," "pharmacological uses or pharmacological importance" and finally “toxicology”. Different pharmacological terms, such as "antioxidant," "antimicrobial," "anticancer," etc., are used to find an appropriate peer-reviewed article. These are prefixed with "*Argemone mexicana*" to facilitate searching electronic databases, books, and journals for relevant information about this plant. A number of databases, such as PubMed, Elsevier Scopus, Google Scholar, ResearchGate, NOPR, and MAPA, were used to find relevant articles. Our review included only English language studies published from January 2000 to March 2022. After screening 116 publications, we identified 86 papers that met our eligibility criteria. In the evaluation, only primary studies were considered. The process didn't take into account duplicate articles or contributions that didn't fit. Only peer-reviewed articles are used in this review process. Peer-reviewed literature is thought to be more reliable than other kinds of research because it is scientifically sound, and the data are accurate.

Taxonomy and botanical identification of AM

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida Dicotyledons
Subclass: Magnoliidae
Order: Papaverales
Family: Papaveraceae
Genus: *Argemone*
Species: *Argemone mexicana* Linn.

Figure 1: *Argemone mexicana* L.

Argemone mexicana Linn, a poisonous weed and prickly poppy that belongs to the papaveraceae family (Figure 1). It is originally from the United States-Mexico border but can be found in subtropical and tropical regions worldwide, including dry areas in Tamil Nadu, Maharashtra, Karnataka, and the Western Ghats in India. From January to June, this annual herb grows up to a meter tall with a prickly, sinuously lobed stem that produces yellow juice and brilliant yellow flowers. Its petiole less leaves have spiny margins and grey-white veins extending from the bluish-green upper leaf surface. The oblong stem cross-section contains a fruit with an oblong or ovoid capsule covered in shiny, dark, circular veins with a diameter of approximately 1 mm and a fine network of brownish-black veins. It has been used medicinally in Mexico, Nigeria, India, and the tropical US (5, 6). Traditionally various parts of AM, such as the entire plant, seeds, seed oil, flowers, latex, roots, and leaves, to treat different ailments.

Vernacular Names

Common name of AM is Mexican Prickly Poppy, Mexican poppy, Prickly Poppy, Satyanashi. The different regional vernacular names for AM are as follows: *Celangkringan, druju* (Javanese), *Chelang keringan, pokok popi* (Malaysia), *Deruju* (Indonesia), *Diluariu* (Tagalog of Philippines), *Fin naam* (Bangkok, Thailand), *Gai cua, Mufi cua, Caf gai hoa vafng* (Vietnam), *Kachumba, kasubang-aso* (Iloko of Philippines), *Chicalote, Cardosanto* (Mexico), *Khaya* (Myanmar), *Siyal-Kanta* (Bengal), *Darudi* (Gujarat), *Bharband, Shialkanta, Satyanashi* (Hindi), *Jungli post* (Jammu and Kashmir), *Datturigidda* (Kannada), *Kantankattiri, Ponnummattu* (Malayalam), *Daruri, Firangi dhotra* (Marathi), *Dhaturi* (Rajasthani), *Brahmadandi, Kshirini, Pitopushpa, Srigalkanta, Swarnakshiri* (Sanskrit), *Kudiyotti, Ponnummuttai, Perammathandu* (Tamil) and *Brahmadandi, Brahmadandicettu* (Telugu) (7-9).

Traditional uses

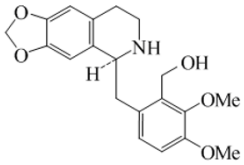
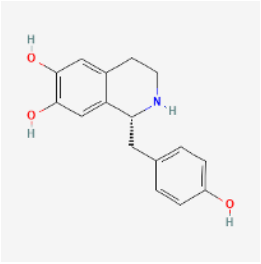
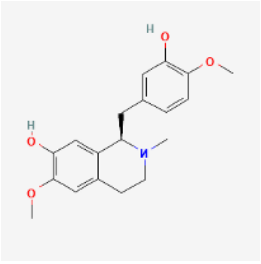
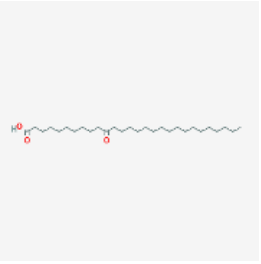
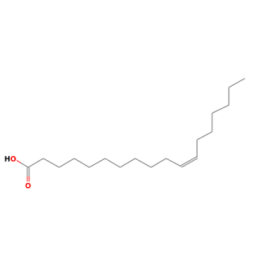
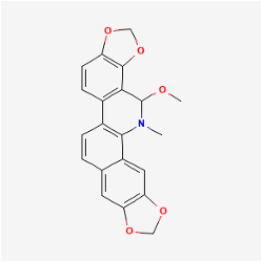
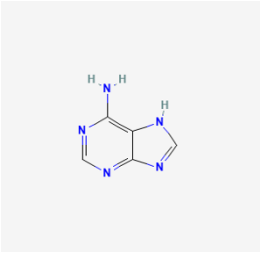
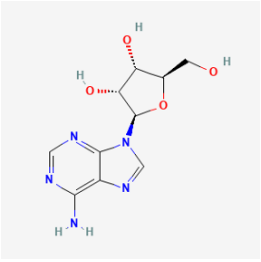
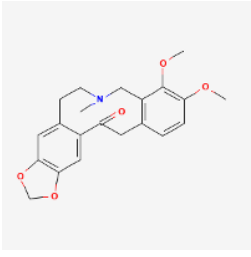
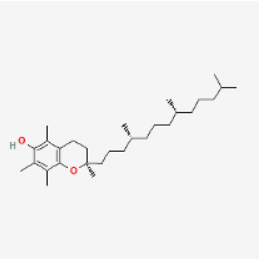
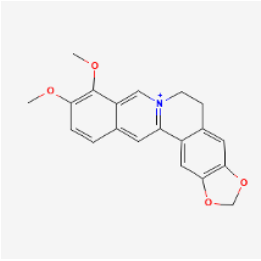
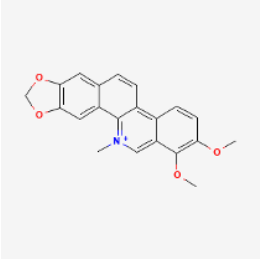
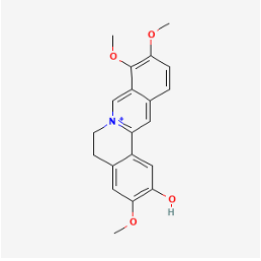
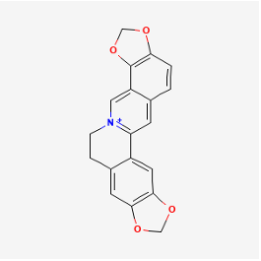
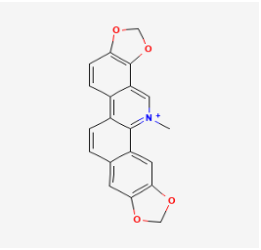
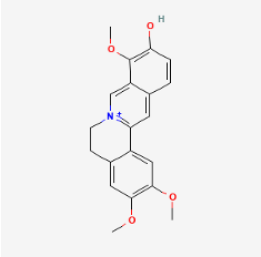
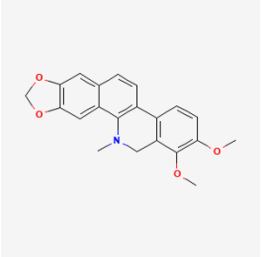
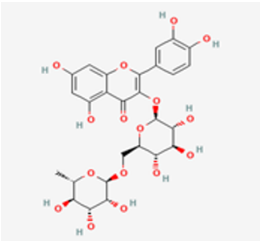
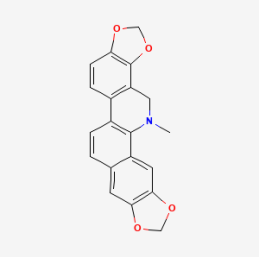
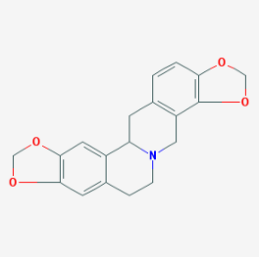
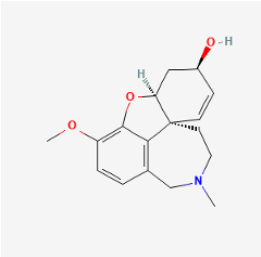
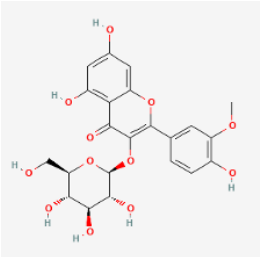
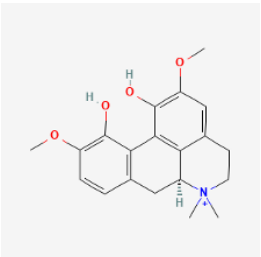
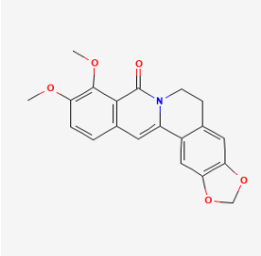
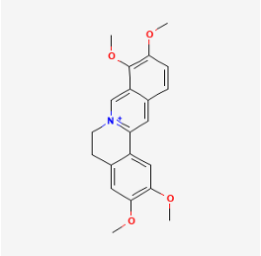
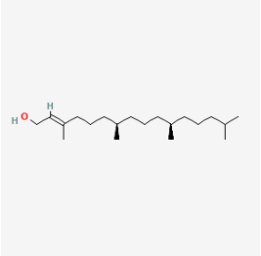
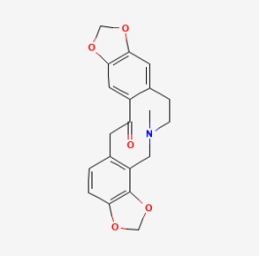
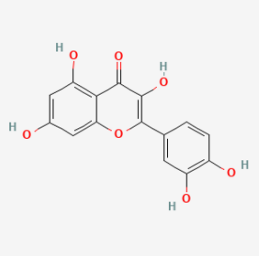
Knowledge of established medical practices is essential for the development of innovative medicines. According to a survey, the use of flora as therapeutic agents varies from 4% to 20% in various regions of the world. Approximately 2,500 species of plants are traded internationally, and many others have been used for millennia by local practitioners. The persistent use of numerous species for medicinal purposes to treat a diverse range of medical conditions has continued for decades. Also, it is more trusted and accepted because it is more closely tied to the culture and religion of the area. In diverse locales, the AM has been utilised as an efficacious medicinal plant. *Argemone* derives from the Greek word *argema*, meaning "cataract in one's eye," since past users have relied on its juice to offer relief for vision-related problems. Ophthalmia and opacity of the cornea can both be remedied with the juice of AM. Even though its seeds have properties that are both laxative and sedative, they are also used to treat constipation (10). Additionally, research is increasingly showing promise in its ability to fight various skin

conditions (e.g., eczema and ulcers), asthmatic problems, and even gastrointestinal troubles (11). The seeds of AM are frequently employed as antidotes to counteract the potency of snake venom in Mexico. Smoke from these seeds is commonly utilised in India for treating toothache. Fresh yellowish milky seed extracts (protein dissolving substances) can be utilised for treating wounds, skin problems, dropsy, mild pain-killer and decoction of leaves of AM is also used to treat liver ailments (5, 12). Benin, Mali, and Sudan are among the few African nations that utilise AM, an antimalarial medication, and employ the entire plant for the management of malarial infections (13). In Mali, a combination of three herbs known as "Malarial-5®" is managed to sell as an antimalarial agent (14). In India, particularly in the Himalayan region, the fresh juice of the entire plant of AM is combined with honey to treat malarial infections (9). In the realm of Ayurveda, the plant AM serves as an invaluable asset with its diverse range of applications, encompassing potent diuretic and purgative properties. The plant is used to treat leprosy-related afflictions; additionally, the yellow juice can be used for curative purposes in instances such as bilious fevers and also for externally applied on scorpion sting (15, 16). The mouthwash made from AM leaves can effectively treat gum infections (17). Rabies can be treated well with an aqueous root extract of AM, which is called *Yahya eshoh* in the Amhara Regional State of Ethiopia (18). In Mexican agriculture, the plant is used to produce organic insecticides (4, 19). Unani system utilises the seed of AM to treat skin diseases and leukoderma (20). Homeopathic medicine recommends AM for the treatment of tapeworms. It is known as *Svarnakshiri churna taila* in Ayurvedic formulations (21). In the Indian System of Medicine, practitioners commonly use it to treat skin infections, fever, and dysentery. (22). AM flowers have been used to treat coughs due to their expectorant properties (23). In America, it has been common for a long time to use tea made from different parts of plants to treat kidney pain, migraines, and labour and delivery pain (24).

Phytochemistry of AM

Since ancient times, the plant kingdom has been essential to human health and progress. Phytochemicals are extremely valuable to medicinal plants and constitute a substantial portion of their pharmaceutical significance. Despite their diverse chemical compositions and pharmacological properties, medicinal plant-derived chemicals remain a topic of keen interest among researchers. Figure 2 shows the chemical structures of the active components found in the medicinal plant AM. The aerial parts of AM contain alkaloids, flavonoids, phenolic compounds, tannins, glycosides, and gums in their ethanolic extract. The flower concentrate of AM also includes saponins, alkaloids, amino acids, phenols, tannins, terpenoids, flavonoids, and cardiac glycosides (25, 26). The aqueous extracts of flowers in AM had a phenolic content of 14 mg/g, followed by leaves with 7.5 mg/g, fruit with 4.62 mg/g, and stems with 2.5 mg/g (27). The methanol extract of the leaf, stem, and flower of AM contained various phytochemicals, including saponins, phenols, flavonoids, terpenoids, steroids, aldehydes, and ketones. The highest total phenolic content (28.5 ± 1.15 mg GAE/g plant extract) was found in the methanol extract of AM stems, compared to the flower and leaf. Meanwhile, the methanol extract of AM flowers had the highest flavonoid content (41.76 ± 0.74 mg QE/g of plant extract) compared to the stems and leaves. Additionally, GC-MS analysis revealed the presence of fatty acids and heterocyclic compounds in the leaf, stem, and flower of AM (28). A variety of alkaloids have been found in different parts of AM extracts, including protoberberine, benzophenanthridine, benzylisoquinoline, and protopine, among others. The total alkaloids in the AM whole plant account for 0.125% of the ethanol extract, with berberine (0.041%) and protopine (0.084%) being the two most alkaloids. Other alkaloids have been found in the whole plant of AM besides allocryptopine, sanguinarine, chelerythrine, coptisine, and traces of dihydrosanguinarine and dihydrochelerythrine. The seed of AM contains isoquinoline alkaloids, namely dihydrosanguinarine, the predominant alkaloid, with minor amounts of sanguinarines and berberine. Its seed oil primarily contains the keto fatty acids 11-oxo-octacosanoic acid and 11-oxotricontanoic acid. The chloroform extract of the AM's aerial part contains a bounty of alkaloid compounds. N-demethyloxysanguinarine and pancorine, benzophenanthridine-like compounds, are among its repertoire, as are (+)-argenaxine, (+)-higenamine, and (+)-reticulin, benzylisoquinoline-type alkaloids. A number of compounds have been identified by researchers, including alpha-tocopherol, phytol, stigma-4-en-3,6-diene, adenine, adenosine, and isorhamnetin-3-O-d-glucopyranoside (29). In another study, using a methanol extract of the whole plant AM, the same author found two new compounds known as argemexicaine A and B (30). Four quaternary isoquinoline alkaloids have been found in the methanolic extract of the whole AM plant. These are dehydrocorydalmine, jatrorrhizine, columbamine, and oxyberberine (3). A methanolic extract of the whole plant of AM yielded two protoberberine alkaloids, dl-tetrahydrocoptisine and dihydrocoptisine, as well as the benzylisoquinoline alkaloid argemexirine (31). The n-hexane extract of the leaves of AM yields a total of seventeen constituent compounds. The most abundant is nonacosane (n-C_{29}; 10.6814 mol%), followed by octadecane (n-C_{18}; 1.2080 mol%) (32). The aerial portion of AM's methanol extract was used to isolate the alkaloids protomexicine and isoflavone mexitin. In addition, it contains 8-methoxydihydrosanguinarine, 13-oxoprotopine, rutin, and quercetin (33). AM seed oils (22–36%) are known for having potentially harmful alkaloids like sanguinarine and dihydrosanguinarine, known as argemone oil or katkar oil, which are a pale yellow in colour (34). The roots of AM contained galanthamine, berberine, palmatine, magnoflorine, and coptisine in the dichloromethane extract. For the first time, galanthamine, palmatine, and magnoflorine have been identified in AM (35).

Figure 2: Chemical structures of the active constituents isolated from *Argemone mexicana* L.

(+)-Argenaxine	(+)-Higenamine	(+)-Reticulin	11-Oxo-octacosanoic acid	11-oxotricontanoic acid
				
8 Methoxy dihydro-sanguinarine	Adenine	Adenosine	Allocryptopine	Alpha-tocopherol
				
Berberine	Chelerythrine	Columbamine	Coptisine	Sanguinarine
				
Dehydrocorydalmine	Dihydrochelerythrine	Rutin	Dihydrosanguinarine	DL-tetrahydrocoptisine
				
Galanthamine	Isorhamnetin-3-o-d-glucopyranoside	Jatorrhizine Magnoflorine	Nonacosane	Octadecane
				
Oxyberberine	Palmatine	Phytol	Protopine	Quercetin
				

Pharmacological significance of AM

Antimicrobial activity of AM

The World Health Organization reports that infectious diseases cause a significant number of deaths and pose challenges for people all over the world. Around 50% of all fatalities in tropical regions are due to tropical diseases. As a result, prevention and treatment of these illnesses are paramount to improving health outcomes in these areas. The WHO also says that more than a million deaths occur each year from malaria and that HIV/AIDS and tuberculosis behead hundreds of thousands of people each year (36). People around the world have relied on traditional medicines as first-line treatments for thousands of years. It is especially pertinent in places that don't have access to modern health care and facilities. Today, people are paying more attention to how medicinal plants can help fight off microbial infections. The spread of drug-resistant and new microbes poses an unprecedented health risk. Without proper treatment and prevention, antibiotic resistance is likely to get worse, making it even harder for public health organizations to keep people healthy. It is evident from this statement that a novel antimicrobial agent is urgently required. The discovery of antibiotic drugs relies heavily on medicinal plants. AM is utilized in different traditional medical practices to manage microbial infections. The inhibitory effect of the methanol extract of AM seeds against *Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli,* and *Bacillus subtilis* is better than that of the AM leaf extracts, as shown by the agar-well diffusion method. The inhibition zones measured 22, 18, 21, and 20 mm, respectively. Methanol extracts inhibited the microorganisms more effectively than both hot and cold aqueous extracts of AM leaves and seeds. In addition, AM seed extract may also contain most of the active compounds that give it its antibacterial properties (12). Another study revealed that varying levels of antibacterial activity in chloroform extracts from AM seeds. The extract demonstrated a minimum inhibitory concentration of 2.0-5.0 mg/ml against Gram (+) and Gram (-) bacterial strains. Additionally, alkaloids and flavonoids, known for their antibacterial properties, were present in the chloroform extracts (37). The AM stem extracts exhibit antibacterial activity against various food-borne bacteria, including *Bacillus subtilis, Staphylococcus aureus, Listeria monocytogenes, Clostridium botulinum, Clostridium perfringens, Escherichia coli* 0157, *Pseudomonas aeruginosa,* and *Salmonella typhimurium,* at a concentration of 10 µl. The extracts produce inhibition zones between 10.1 to 21.4 mm and MIC values ranging from 62.5 to 500 g/ml against these bacteria. Significant antimicrobial activity is observed in the polar solvent extract of AM (38). The aqueous AM leaf extracts used to synthesize silver nanoparticles (AM-Ag NPs) with diameters ranging from 25 to 50 nm and featuring cubic and hexagonal shapes. These silver nanoparticles exhibited antifungal activity against *Aspergillus flavus* (food poisoning method) and antibacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa* using the disc diffusion method (39). The chloroform fraction of AM seed extracts effectively combated *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa,* exhibiting a minimum inhibitory concentration between 1.5625 and 3.125 mg/mL. A chloroform fraction of AM seed extract has been found to contain an alkaloid called N-demethyloxysanguinarine, which is responsible for AM's antibacterial activity. Active constituents of AM may leak cytoplasmic constituents by forming pores in the cell wall (40). The ethanol extract of AM exhibits robust antimicrobial activity against *E. coli* (DH5-α), *S. aureus* (MTCC-96), *P. vulgaris* (MTCC-1751), and *C. albicans* (MTCC-3017). The MIC values are 16, 18, 6 and 18 mg/ml, respectively (41). In another study, it was found that different leaf extracts from AM could stop multidrug-resistant *Pseudomonas aeruginosa* from growing in clinical samples. The effect was found to be dose-dependent (42). The synthesized iron oxide magnetic nanoparticles and treated with ethanol extracts of AM leaves were very effective against bacterial infections. Nanoparticles with a spherical shape range in size from 10 to 30 nm. They effectively combat *Proteus mirabilis* MTCC 425 and *Escherichia coli* MTCC 443, according to the Kirby-Bauer disc diffusion method, with mean zone values of 13 mm and 18 mm, respectively. The antibacterial efficacy of IO-NPs might result from the synergistic effects of phytochemicals and reactive oxygen species generation by the nanoparticles (15). Compared to amphotericin-B, the aqueous and methanol extracts of AM stems and leaves demonstrated antifungal activity against *Mucor indicus, Aspergillus flavus, Aspergillus niger,* and *Penicillium notatum* (43). A bloom-concentrated extract of AM-arbitrated Ag-NPs using a simple bio-reduction method. The nanoparticles, with an average size of 29.34 nm, have a spherical shape. They exhibit significant antibacterial activity against *Klebsiella aerogenes*, followed by *Pseudomonas aeruginosa, Escherichia coli,* and *Staphylococcus aureus,* with average zone of inhibition (ZOI) values between 20 and 24 mm (26). The isoquinoline alkaloid berberine from AM leaves, which demonstrated potent antibacterial activity against clinical isolates of *Staphylococcus aureus, Bacillus cereus, Escherichia coli,* and *Pseudomonas aeruginosa* (44). A polyherbal formulation combining methanolic extracts of *Plumbago zeylanica* Linn, *Datura stramonium* Linn, and AM exhibited promising antimicrobial activity against both Gram (+) and Gram (-) bacteria. The synergistic effects of the active ingredients in the polyherbal formulation contribute to its effective antimicrobial activity (45). AM leaves extracted using three different organic solvents: chloroform, ethanol, and methanol. The ethanol extracts proved most effective in inhibiting bacterial and fungal growth (46). The ethanol extract from the entire AM plant demonstrated maximum growth inhibition against *E. coli* and *S. aureus* at a concentration of 2 mg/mL. The high phenolic content of ethanol extracts may contribute to their effectiveness in inhibiting microbial growth (47). The particle size distribution is closely related to temperature during nanoparticle synthesis.

The isoproponolic extract of AM is rich in flavonoids and phenolic compounds. Synthesis of AgNPs at 25°C using an AM isopropanolic extract synergistically inhibits the growth of resistant bacteria as well as fungal strains of *Candida albicans* (8).

Wound healing activity of AM

The skin serves as a crucial organ, protecting the body from disease, regulating temperature, and excreting toxins. Wound healing, a complex process occurring after any injury to the skin or delicate tissues, consists of three phases: inflammation, cell proliferation, and tissue remodelling. Using medicinal plants to treat wounds is gaining recognition as an important part of healthcare (48). Researchers investigated the wound healing properties of AM leaves using excision, incision, and dead space wound models in Wistar albino rats. In comparison to other organic extracts of AM leaves, methanol extracts promoted faster wound healing in rats (20). Another study found that an ointment made from an alcoholic extract of AM's root accelerated wound healing. It has been demonstrated that both the rate at which the wound seals and the time it takes for the protective epithelium to form have been significantly accelerated (49). Three medicinal plants, including an aerial portion of AM, were included in the polyherbal formulation that showed wound healing activity in adult Wistar rats. Polyherbal preparations are endowed with impressive wound healing capabilities throughout the various stages of recovery. It is conceivable that the synergistic effects of polyherbal mixtures may have influenced collagen synthesis, wound closure, and revascularization, as well as diminishing microbial presence, which could potentially contribute to enhanced wound healing (45). The wound-healing ointment prepared from the ethyl acetate fraction of AM fruit (400 mg/kg) exhibits promising wound-healing properties in rats. The application of the ointment resulted in a remarkable decrease in wound size, faster epithelialization, and elevated levels of fibrosis, neovascularization, and collagen tissue formation. There was an increased degree of tensile strength, oedema inhibition, and granuloma mass development (50).

Antioxidant activity of AM

Oxidative stress is closely associated with conditions such as cancer, diabetes, heart disease, neurological disorders, and Alzheimer's disease. Additionally, it has been linked to premature aging and a higher risk of stroke. An imbalance between stress and protective elements in the body results in oxidative stress. Antioxidants shield cells and tissues from damage caused by free radicals, which are unstable molecules. As antioxidants are capable of providing a variety of health benefits, they are a vital part of health and wellness. Additionally, exercise has been linked to increased production of antioxidants, which can help protect cells from further damage. This facilitates the body's elimination of toxins. Natural antioxidant supplements can offer additional defence against diseases brought on by oxidative stress. Natural antioxidants derived from plants, fruits, vegetables, and herbs can be effective in reducing inflammation, protecting cells from free radical damage, boosting immunity, and supporting a healthy aging process. Natural antioxidants have the potential to revolutionize the medical and food industries, and further research is needed to fully realize this potential. A number of studies have revealed that AM is an effective antioxidant. A comparison of antioxidant activity in three different organic extracts of AM fruit revealed that the acetone extract inhibited free radicals more effectively than the standard antioxidant, ascorbic acid. The quenching of DPPH and NBT primarily relies on dose-dependent mechanisms. The IC_{50} value for the acetone extract was 52.0 µg/ml in the NBT assay and 69 µg/ml in the DPPH assay (51). AM bloom extract-synthesized Ag-NPs exhibit strong DPPH scavenging activity, reaching up to 87.06% at 500 µg/ml concentrations, and possess high reducing power compared to the standard ascorbic acid, which has a DPPH-scavenging efficiency of 96.83% (26). According to another study, the high concentration of total phenolics and flavonoids in the ethanol extract of AM flowers may contribute to its antioxidant properties (52). The ethyl acetate fraction of the ethanol extract of AM flowers showed excellent anti-radical efficacy in scavenging DPPH radicals and the FRC assay at a concentration of 250 µg/ml, achieving peak inhibition of 83.25 ± 0.55% and 83.95 ± 0.47%, respectively (53). Upon comparing ethanol, methanol, and aqueous extracts of the whole AM plant, it was found that the ethanol extract was the most effective at eliminating ABTS and DPPH radicals, and that the effect was dose-dependent. The IC_{50} values for obstructing DPPH and superoxide radicals were 34.39 ± 3.32 µg/mL and 61.90 ± 1.09 µg/mL, respectively (47). Quantitative phytochemical analysis of the AM leaves revealed a significant level of antioxidant potential, primarily attributed to the presence of an array of phytoconstituents. As evidence for this, FT-IR analysis showed that there was a broad peak associated with hydroxyl groups in the alcoholic extracts of those AM leaves (54).

Antimalarial activity of AM

Globally, malaria affects millions of people, making it one of the most prevalent health problems. Malaria remains a global challenge despite being preventable and curable. To address this challenge effectively, implementing strategies to limit disease transmission and reduce case numbers is crucial. Focusing on the prevention and treatment of malaria is essential. The antimalarial drug chloroquine, derived from the *Cinchona* species, has some drawbacks, including low tolerability and low compliance with its complex dosing regimens. More than that, plasmodium-drug-resistant strains diminish antimalarial effectiveness. *Artemisia annua* L. was recently found to have artemisinin, which is used to treat malaria. Finding new treatments for this deadly disease has become a priority. Researchers have recently identified

antimalarial agents from medicinal plants, offering a new source of treatment options. AM is one of the natural sources utilized in several traditional approaches to treating malaria. A key component of AM, berberine has an IC_{50} value of 0.141-0.148 µg/ml against *P. falciparum*, which is very encouraging in the treatment of malarial infection. Clinical trials have shown that berberine and pyrimethamine can be used together safely to treat malaria. This has led to fewer side effects in 1 out of every 84 patients (55-57). In Africa, Benin, Mali, and Sudan use AM to treat malaria. A Mali ethnobotanical and retrospective clinical study in the Sikasso and Bandiagara regions revealed AM's application for malaria treatment. *In vitro* studies demonstrated the anti-plasmodial activity of AM crude extract against chloroquine-resistant *P. falciparum* cultures (5µl/ml) (58). The AM decoction relieves uncomplicated malaria if taken twice daily for seven days. On day 14 of this regimen, 73% of all cases and 89% of those over 5 years old had an adequate clinical response, likely due to an enhanced immune defence system (59). In another investigation, during a 28-day post-treatment follow-up in Mali, decoction of AM was enough to eliminate symptoms in 89% of patients, while artemisinin combination therapies resulted in a 95% success rate among those treated. AM can be used as a first-line treatment for malaria when other antimalarial drugs are not available in places where severe malaria is rare and well-tolerated (60). The alkaloid-enriched dichloromethane fraction extracted from the leaves of AM was found to be the most potent *in vitro* inhibitor against *P. falciparum* with an IC_{50} value of 1.71 µg/mL possibly due to its content of allocryptopine, protopine, and berberine compounds (61).

Larvicidal activity of AM

The *Aedes aegypti* L. mosquito primarily spreads dengue in India. To prevent mosquito populations from growing uncontrollably, insecticides may be necessary in addition to other methods. The petroleum ether extracts of acetone fraction from AM seeds demonstrated a lethal effect on *Aedes aegypti* mosquito larvae at concentrations ranging from 25 to 200 ppm. The LC_{50} values in the field and laboratory were 13.58 ppm and 17.43 ppm, respectively. Due to their inability to develop into adult mosquitoes, these compounds may have an adverse effect on insect fertility (62). The mosquito that transmits lymphatic filariasis in India is *Culex quinquefasciatus*. A petroleum ether extract of AM leaves exhibited the highest larvicidal activity with a LC_{50} value of 48.89 ppm; when combined with leaves of *Clausena dentata* extract at a ratio of 1:1, the toxicity level synergistically improved to a LC_{50} value of 28.60 ppm (63). Another investigation revealed that the acetone extract of AM leaves had LC_{50} and LC_{90} values of 87.9, 149.8, 105.8, and 780 ppm against second- and fourth-instar *Culex quinquefasciatus* larvae (64). The hexane root extract of AM was the most effective larvicide against 3rd instar larvae of *Culex pipiens*, exhibiting an LC_{50} value of 91.331 ppm after 24 hours of exposure. It caused 1.8 and 2.4 times more toxicity compared to the hexane leaf and stem extracts, respectively (65). Exposure to flower extract resulted in more potent larvicidal activity for second instar *Culex quinquefasciatus* mosquito larvae compared to stem and seed extracts. After 24 hours, the LC_{50} and LC_{90} values were 18.61 ppm and 39.86 ppm, respectively. After 48 hours, the values were 9.47 ppm and 21.76 ppm, respectively (19).

Anthelmintic of AM

Intestinal parasites are a widespread global health problem, affecting one in every three people worldwide. According to the WHO report, the prevalence of parasitic infections exceeds 1.5 billion people globally, indicating a significant cause for concern (66). Recent studies have shown that medicinal plants are effective against intestinal parasites in lab animals, suggesting possible applications for human parasitosis treatment. AM is one of the most studied plants for treating and preventing parasites in people. Berberine and jatrorrhizine are identified in the active fractions of the leaves of AM and are responsible for the growth-inhibiting activity observed *in vitro* against *Entamoeba histolytica* at a concentration of 78.39 µg/ml (67). The methanolic subfraction of AM, along with the AM extracts and berberine, were found to inhibit third-stage *Strongyloides venezuelensis* larvae (L3) without haemolytic activity against human erythrocytes. The 96-hour LC_{50} values for these compounds were 1.6, 19.5, and 92.1 µg/ml, respectively (68). According to *in vitro* studies, the aerial portion of AM and its major components, berberine, significantly diminish the viability of the adult stage of *Schistosoma mansoni*. After 48 hours, a concentration of 50 µg/ml of AM is lethal to *S. mansoni*, while a concentration of 10 µM of berberine is lethal after 24 hours. The inhibitory activity is dose-dependent. AM possesses this activity for a variety of reasons, including its antioxidant capacity (69).

Antidiabetic activity of AM

Diabetes mellitus is responsible for the most deaths worldwide and Indian systems of medicine have suggested numerous plants for diabetes treatment, which are being tested experimentally. Several of these plants have been found to control blood sugar levels and manage diabetes. The aerial part of the AM aqueous extract demonstrated a hypoglycemic effect in alloxan-induced diabetic rats at doses of 200 and 400 mg/kg body weight, p.o. Glibenclamide (5 mg/kg) served as the standard drug. Compared with diabetic control rats, treatment with AM led to a significant reduction in blood glucose levels, plasma urea, serum creatinine, triglycerides, and cholesterol values, as well as an increase in animal body weight (70). Using a streptozotocin-induced hyperglycaemia model in Wistar albino rats, a hydroalcoholic extract of the aerial portion of AM at a dose level of 400 mg/kg body weight was found to normalise the fasting blood sugar levels. The hypoglycaemic activity is compared with metformin (300 mg/kg body weight) (71). In 21 days of AM extract treatment in alloxan-induced diabetic rats (150 mg/kg body weight i.p.), chloroform and aqueous

fractions of the hydroalcoholic extract (150 mg/kg body weight daily, p.o.) demonstrated a prominent reduction in blood sugar level and normalisation of the serum biochemical profile, including lipid contents, as compared with alloxan-control rats. Also, there is a significant modulation of endogenous nonenzymatic (GSH) and enzymatic (CAT) antioxidant and detoxification status (72).

Hepatoprotective activity of AM

The liver is the primary organ responsible for metabolic activity and excretion. The CCl_4 induced hepatotoxicity in Swiss albino rats, 500 mg/kg body weight of methanol extracts from the leaves and flowers of the AM plant had no effect on blood serum levels rather than being toxic (73). Aqueous extracts of AM leaves demonstrated hepatoprotective effects against CCl_4 induced liver toxicity in Wistar rats. An acute toxicity study found that 2500 g/kg of AM was safe. When orally administering 250 mg/kg of either AM leaf extract or AM leaf powder suspension, the elevated levels of serum glutamic oxaloacetic transaminase, serum glutamate-pyruvate transaminase, alkaline phosphatase activity, and serum bilirubin in CCl_4 exposed rats significantly decreased (74). The aerial part of AM, in two different extracts and three varying doses, displayed hepatoprotection against CCl_4 induced liver damage in Wistar rats. The protective function of the liver is compared with silymarin (70 mg/kg, p.o.). Treatment with a 100 mg/kg p.o. dose of methanol extract of the AM aerial part provided significant hepatoprotective activity by lowering SGOT, SGPT, and ALP. At higher doses of AM aqueous (400 mg/kg, p.o.) extract, it exhibits similar protective effects as methanol extract. Histopathological examination of the liver section also suggests that the liver parenchyma is healing, and that liver cells are regenerating (75).

AM against sexually transmitted diseases

The benzo[c]phenanthridine alkaloid (±)-6-acetonyl dihydrochelerythrine, isolated from the methanol extract of the whole AM plant and tested in the H9 lymphocyte assay, strongly inhibited human immune virus activity with an EC_{50} value of 1.77 µg/mL and a therapeutic index of 14.6 (76). The parasitic protozoan *Trichomonas vaginalis* is implicated in the transmission of trichomoniasis. A high concentration of phytocompounds is observed in methanol and chloroform extracts from AM whole plant, which yield a more potent inhibition against *T. vaginalis* than metronidazole. At 1000 µg/ml concentrations, the chloroform and methanol extracts demonstrated 100% inhibition after 216 hours and 192 hours, respectively. (77). In another study conducted on AM stems and leaves, extracts exhibited cytotoxic effects on *T. vaginalis* with IC_{50} values of 70.6 and 67.2 µg/mL, respectively (78).

Anticancer activity of AM

Anti-cancer agents derived from plants have led to the development of countless innovative therapeutic options in recent times. The extracts and secondary metabolites of medicinal plants are thought to be responsible for their anti-cancer effects. These compounds counteract the deleterious effects of tumour cells in a synergistic manner, thereby enhancing their efficacy. The future discovery and advancement of plant-derived drugs may usher in a new era of medicine. Mutations are alterations to nucleotide sequences within the DNA molecule. Most of the time, oxidative stress causes DNA changes that lead to the first mutations in diseases like cancer. Antioxidants can be used to minimize the mutagenic effects. Among the multitude of compounds present in AM fruit, methanol extract has been shown to exhibit more pronounced antimutagenic activity compared with acetone and chloroform extracts. AM fruit extracts possess powerful antioxidant and antimutagenic properties. There is a remarkable correlation between these two properties, demonstrating their importance in the treatment of cancer (51). The ethanol extract of AM showed inhibitory activity against human cancer cell lines, including PN-15, HeLa-B75, and HL-60. In contrast, it did not have any observable benefit against the HEP-3B cell line. Overall anticancer efficacy when compared with suramin (41). Six alkaloids were isolated from an ethanol extract of the AM aerial part and exhibited varying inhibitory potential against SW480 human colon cancer cells *in vitro*. Jatrorrhizine and 8-oxyberberine inhibited cell viability the most effectively, with up to 100% inhibition levels. 8-Oxyberberine, an oxo derivative of berberine, displayed varying cytotoxicity based on concentration and exposure duration. Jatrorrhizine reduced cell viability by 44% and 76% at 25 mg/mL after 24 and 48 hours, respectively, and by 90% after 24 and 48 hours at 100 mg/mL concentration. Alkaloids, including jatrorrhizines, have hydroxyl and methoxy groups in positions 3 and 10, respectively, with their anticancer efficacy determined by their relative positioning (22). The cold aqueous and methanol extracts of AM leaf and stem were potent in inducing cytotoxic effects on A549, SiHa, and KB immortalized cell lines, similar to berberine inhibition. The A549 cell line showed higher susceptibility to the AM extracts compared to KB and SiHa cell lines (43). AM-silver nanoparticles (AM-Ag NPs) were cytotoxic to various cancer cell lines, such as HeLa, MCF-7, and HCT-15, by preventing cell division and inhibiting the p53-mediated apoptotic pathway (79). The most potent inhibition of HeLa, MCF-7, and HCT-15 cancer cell lines is demonstrated by ethanol extracts of AM, the most efficacious among aqueous, methanol-derived extracts from the whole plant. The DNA fragmentation assay demonstrated that dissimilar concentrations of plant extracts in aqueous, methanol, and ethanol induced cytotoxicity in cancer cell lines. HeLa, MCF-7, and HCT-15 cells exposed to plant extracts displayed extensive DNA double-strand breaks, demonstrating AM's genotoxic potential (47). The AM-AuNPs inhibited cell proliferation in the HCT-15 cell line, with an IC_{50} of 20.53 µg/mL after 24 hours and 12.03 µg/mL after 48 hours of exposure. The AM-AuNPs caused noticeable changes in the morphology of HCT-15 cells, which led to increased apoptosis and heightened

expression of p53 and caspase-3 (80). The principal alkaloids present in the AM root methanol extract are chelerythrine and berberine. The root extract diminished the upregulation of c-MYC, an oncogene that can cause cancer in RKO colon cells and recruit a tumour suppressor gene such as APC (24). The p53-mediated apoptosis pathway is involved in the antiproliferative activity of the chloroform fraction of the AM aerial portion against the squamous cell carcinoma cell line A431. The chloroform fraction of AM induces apoptosis through the regulation of apoptosis-related genes such as p53, Fas, PUMA, and APAF1. The presence of polyphenolic compounds contributes to its potency as an anti-proliferative agent (81).

Toxicology of AM

Many people consider traditional medicinal herbs safe to use for treating various diseases, with no or minimal side effects. However, prolonged or excessive use of these herbs can be hazardous, even low-toxicity extracts may damage various organs. Several scientific studies have demonstrated that using AM can cause toxicity. Alkaloids like dihydrosanguinarine and sanguinarine, which are benzophenanthridine derivatives of glycosides and are toxic, are found in argemone oil. The alkaloids found in organs such as the heart, liver, eyes, gastrointestinal tract, and kidneys increase blood vessel permeability. While the exact mechanism of toxicity causing epidemic dropsy is unknown, sanguinarine and dihydrosanguinarine bind strongly to plasma proteins and accumulate in gastrointestinal tract, serum, and tissues. These toxic alkaloids can harm the liver by binding to Na-K-ATPase, inactivating cytochrome P-450 enzymes, depleting glutathione, and disrupting carbohydrate metabolism. It is worth noting that Argemone oil comprises toxic alkaloids that can endure high temperatures of up to 240°C. For safe consumption in endemic areas, it is highly recommended to heat mustard oils to at least 240°C for a minimum of 15 minutes (82, 83). Epidemic dropsy is characterized by diluted lymph in the tissues and cavities of the body, which is caused by poisoning from the AM plant. Adverse Symptoms will occur if the percentage of argemone oil (Katkar oil) in edible oil exceeds 1% and AM's most toxic alkaloid is sanguinarine. The adulteration of AM oil with sesame oil has resulted in two reported casualties. Given the high incidence of anaemia associated with this type of poisoning, there is speculation that the toxins present in the bone marrow may play a direct role in the development of anaemia and extramedullary haematopoiesis (84). In another study conducted on female Swiss albino mice showed that there was no significant increase in tumour development when mice were treated with 1,3-dimethylbutylamine (DMBA) followed by a single application of sanguinarine at a concentration of 4.5 µM, compared to those mice treated only with DMBA. However, when mice initiated with DMBA were treated with topical 1.5 µM sanguinarine twice weekly for 25 weeks, they developed tumours earlier and the number of tumours per mouse increased from 5 to 7.07, compared to the mice initiated with DMBA/TPA. Sanguinarine may promote tumour growth (85). Several studies have revealed that genotoxicity is linked to argemone oil. Even a small concentration of argemone oil can cause genotoxic effects in Swiss albino mice after just one exposure. Sanguinarine, which inhibits epidermal histidase activity, can lead to increased keratin formation and tumour growth (86).

Conclusion

The discovery of new drugs and drug candidates is greatly facilitated by the study of medicinal plants. Medicinal plants have been used for centuries in various cultures for their therapeutic properties, which are derived from bioactive compounds. AM is one such plant. This paper provides a detailed review of the traditional importance, phytochemistry, pharmacological activities, and toxicology of AM, a plant with many active ingredients including dihydrosanguinarine, sanguinarine, (+)-argenaxine, and berberine. While it has been used in traditional medicine for thousands of years, caution should be exercised when consuming AM due to the toxicity of its oil, primarily caused by dihydrosanguinarine and sanguinarine, even at low concentrations. To mitigate this, it is recommended that AM oil containing mustard oil be heated to at least 240°C for at least 15 minutes before use. *In vitro* and *in vivo* models have demonstrated the pharmacological activities of AM, supporting its various ethnomedicinal uses and indicating its potential usefulness in treating different diseases. Despite the potential toxicity, AM has many beneficial effects, including antimicrobial, wound healing, antioxidant, antimalarial, larvicidal, anthelmintic, antidiabetic, hepatoprotective, and anticancer activities, and is used for treating sexually transmitted diseases. While many studies have shown its potential as a medicine, the exact mechanism of action of various active constituents remains unclear, highlighting the need for further research.

References

1. Aslam MS, Ahmad MS. Worldwide importance of medicinal plants: Current and historical perspectives. Recent Adv Biol Med. 2016;2(2016):909.
2. Balunas MJ, Kinghorn AD. Drug discovery from medicinal plants. Life Sci. 2005;78(5):431-41.
3. Singh S, Singh TD, Singh VP, Pandey VB. Quaternary alkaloids of *Argemone mexicana*. Pharm Biol. 2010;48(2):158-60.
4. Sharanappa R, Vidyasagar G. Plant profile, phytochemistry and pharmacology of *Argemone Mexicana* Linn. A review. Int J Pharm PharmSci. 2014;6(7):45-53.
5. Chopra RN. Glossary of Indian medicinal plants. New Delhi: NISCOM, CSIR; 1956. 23 p.
6. Nancy A, Praveena A. *Argemone mexicana*: A boon to medicinal and pharmacological approaches in current scenario. Cardiovasc Hematol Agents Med Chem. 2017;15(2):78-90.

7. Devanathan K. *Argemone mexicana* L. Papaveraceae. Switzerland: Springer Nature; 2020.
8. Téllez-de-Jesús DG, Flores-Lopez N, Cervantes-Chávez J, Hernández-Martínez A. Antibacterial and antifungal activities of encapsulated Au and Ag nanoparticles synthesized using *Argemone mexicana* L extract, against antibiotic-resistant bacteria and *Candida albicans*. Surf Interfaces. 2021;27:101456.
9. Shah GM, Abbasi AM, Khan N, Guo X, Khan MA, Hussain M, et al. Traditional uses of medicinal plants against malarial disease by the tribal communities of Lesser Himalayas–Pakistan. J Ethnopharmacol. 2014;155(1):450-62.
10. Moore M. Los remedios: traditional herbal remedies of the Southwest: Museum of New Mexico Press, Santa Fe; 1990.
11. Sharma B, Malhotra S, Bhatia V, Rathee M. Epidemic dropsy in India. Postgrad Med J. 1999;75(889):657-61.
12. Bhattacharjee I, Chatterjee SK, Chatterjee S, Chandra G. Antibacterial potentiality of *Argemone mexicana* solvent extracts against some pathogenic bacteria. Mem Inst Oswaldo Cruz. 2006;101(6):645-8.
13. Willcox ML, Graz B, Falquet J, Diakite C, Giani S, Diallo D. A "reverse pharmacology" approach for developing an anti-malarial phytomedicine. Malar J. 2011;10(1):1-10.
14. Diallo D, Maiga A, Diakité C, Willcox M. Malarial-5: Development of an antimalarial phytomedicine in Mali. Boca Raton: CRC Press; 2004. 464 p.
15. Arokiyaraj S, Saravanan M, Prakash NU, Arasu MV, Vijayakumar B, Vincent S. Enhanced antibacterial activity of iron oxide magnetic nanoparticles treated with *Argemone mexicana* L. leaf extract: an *in vitro* study. Mater Res Bull. 2013;48(9):3323-7.
16. Alagesaboopathi C. Ethnomedicinal plants and their utilization by villagers in Kumaragiri hills of Salem district of Tamilnadu, India. Afr J Tradit Complement Altern Med 2009;6(3):222–7.
17. Rosas-Piñón Y, Mejía A, Díaz-Ruiz G, Aguilar MI, Sánchez-Nieto S, Rivero-Cruz JF. Ethnobotanical survey and antibacterial activity of plants used in the Altiplane region of Mexico for the treatment of oral cavity infections. J Ethnopharmacol. 2012;141(3):860-5.
18. Chekole G, Asfaw Z, Kelbessa E. Ethnobotanical study of medicinal plants in the environs of Tara-gedam and Amba remnant forests of Libo Kemkem District, northwest Ethiopia. J Ethnobiol Ethnomed. 2015;11(1):1-38.
19. Granados-Echegoyen CA, Chan-Bacab MJ, Ortega-Morales BO, Vásquez-López A, Lagunez-Rivera L, Diego-Nava F, et al. *Argemone mexicana* (Papaverales: Papavaraceae) as an alternative for mosquito control: First report of larvicidal activity of flower extract. J Med Entomol. 2019;56(1):261-7.
20. Dash G, Murthy P. Evaluation of *Argemone mexicana* Linn. Leaves for wound healing activity. J Nat Prod Plant Resour. 2011;1(1):46-56.
21. Bhatt M, Shah U. On poisonous plant but medicinally active *Argemone mexicana*. J Med Pharm Allied Sci. 2014;3(6):20-8.
22. Singh S, Verma M, Malhotra M, Prakash S, Singh TD. Cytotoxicity of alkaloids isolated from *Argemone mexicana* on SW480 human colon cancer cell line. Pharm Biol. 2016;54(4):740-5.
23. Magos-Guerrero GA, Santiago-Mejía J, Carrasco OF. Exploratory studies of some Mexican medicinal plants: cardiovascular effects in rats with and without hypertension. J Intercult Ethnopharmacol. 2017;6(3):274-9.
24. Orozco-Nunnelly DA, Pruet J, Rios-Ibarra CP, Bocangel Gamarra EL, Lefeber T, Najdeska T. Characterizing the cytotoxic effects and several antimicrobial phytocompounds of *Argemone mexicana*. PLoS One. 2021;16(4):e0249704.
25. Sarkar KK, Mitra T, Acharyya RN, Sadhu SK. Phytochemical screening and evaluation of the pharmacological activities of ethanolic extract of *Argemone mexicana* Linn. aerial parts. Orient Pharm Exp Med. 2019;19(1):91-106.
26. Chandrasekhar N, Vinay S. Yellow colored blooms of *Argemone mexicana* and *Turnera ulmifolia* mediated synthesis of silver nanoparticles and study of their antibacterial and antioxidant activity. Appl Nanosci. 2017;7(8):851-61.
27. Srivastava N, Chauhan AS, Sharma B. Isolation and characterization of some phytochemicals from Indian traditional plants. Biotechnol Res Int. 2012;2012:1-8.
28. Khan AM, Bhadauria S. Analysis of medicinally important phytocompounds from *Argemone mexicana*. J King Saud Univ Sci. 2019;31(4):1020-6.
29. Chang Y-C, Chang F-R, Khalil AT, Hsieh P-W, Wu Y-C. Cytotoxic benzophenanthridine and benzylisoquinoline alkaloids from *Argemone mexicana*. Z Naturforsch C. 2003a;58(7-8):521-6.
30. Chang Y-C, Hsieh P-W, Chang F-R, Wu R-R, Liaw C-C, Lee K-H, et al. Two new protopines argemexicaines A and B and the anti-HIV alkaloid 6-acetonyldihydrochelerythrine from formosan *Argemone mexicana*. Planta Med. 2003b;69(02):148-52.
31. Singh S, Singh T, Singh V, Pandey V. A new benzylisoquinoline alkaloid from *Argemone mexicana*. Nat Prod Res. 2010;24(1):63-7.
32. Bhattacharjee I, Ghosh A, Chowdhury N, Chatterjee SK, Chandra G, Laskar S. n-Alkane profile of *Argemone mexicana* leaves. Z Naturforsch C. 2010;65(9-10):533-6.
33. Singh S, Pandey VB, Singh TD. Alkaloids and flavonoids of *Argemone mexicana*. Nat Prod Res. 2012;26(1):16-21.
34. Samal PK. HPTLC analysis of berberine in *Argemone mexicana*, L. J Glob Trends Pharm Sci. 2013;4(2):1073-6.
35. Kukula-Koch W, Mroczek T. Application of hydrostatic CCC–TLC–HPLC–ESI-TOF-MS for the bioguided fractionation of anticholinesterase alkaloids from *Argemone mexicana* L. roots. Anal Bioanal Chem 2015;407(9):2581-9.

36. WHO WHR. World Health Organization Geneva, Switzerland: WHO Publications Office; 2003.
37. Singh SK, Pandey VD, Singh A, Singh C. Antibacterial activity of seed extracts of *Argemone mexicana* L. on some pathogenic bacterial strains. Afr J Biotechnol. 2009;8(24):7077-81.
38. Rahman MM, Alam MJ, Sharmin SA, Rahman MM, Rahman A, Alam M. In vitro antibacterial activity of *Argemone mexicana* L (Papaveraceae). CMU J Nat Sci. 2009;8(1):77-84.
39. Singh A, Jain D, Upadhyay M, Khandelwal N, Verma H. Green synthesis of silver nanoparticles using *Argemone mexicana* leaf extract and evaluation of their antimicrobial activities. Dig J Nanomater Bios. 2010;5(2):483-9.
40. Bhattacharjee I, Chatterjee SK, Chandra G. Isolation and identification of antibacterial components in seed extracts of *Argemone mexicana* L.(Papaveraceae). Asian Pac J Trop Med. 2010;3(7):547-51.
41. Gacche RN, Shaikh RU, Pund MM. In vitro evaluation of anticancer and antimicrobial activity of selected medicinal plants from Ayurveda. Asian J Trad Med. 2011;6(3):1-7.
42. Sahu MC, Debata NK, Padhy RN. Antibacterial activity of *Argemone mexicana* L. against multidrug resistant *Pseudomonas aeruginosa*, isolated from clinical samples. Asian Pac J Trop Biomed. 2012;2(2):S800-S7.
43. More NV, Kharat AS. Antifungal and Anticancer Potential of *Argemone mexicana* L. Medicines. 2016;3(4):28.
44. More N, Kharat K, Kharat A. Berberine from *Argemone mexicana* L exhibits a broadspectrum antibacterial activity. Acta Biochim Pol. 2017;64(4):653-60.
45. Dev SK, Choudhury P, Srivastava R, Sharma M. Antimicrobial, anti-inflammatory and wound healing activity of polyherbal formulation. Biomed Pharmacother. 2019;111:555-67.
46. Andleeb S, Alsalme A, Al-Zaqri N, Warad I, Alkahtani J, Bukhari SM. *In-vitro* antibacterial and antifungal properties of the organic solvent extract of *Argemone mexicana* L. J King Saud Univ Sci. 2020;32(3):2053-8.
47. Datkhile KD, Patil SR, Patil MN, Durgawale PP, Jagdale NJ, Deshmukh VN. Studies on phytoconstituents, *in vitro* antioxidant, antibacterial and cytotoxicity potential of *Argemone mexicana* Linn.(family: Papaveraceae). J Nat Sci Biol Med. 2020;11(2):198-205.
48. Garg VK, Paliwal SK. Wound-healing activity of ethanolic and aqueous extracts of *Ficus benghalensis*. J Adv Pharm Technol Res. 2011;2(2):110-4.
49. Saravanan R, Senthilkumar K, Dhachinamoorthi D, Mahesh PU, Krishna GV, Pavani KV. Evaluation of wound healing and anti microbial activity of the *Argemone mexicana* linn (Papavraceae). Res J Pharm Technol. 2017;10(6):852-7.
50. Mengie Ayele T, Chekol Abebe E, Tilahun Muche Z, Mekonnen Agidew M, Shumet Yimer Y, Tesfaw Addis G, et al. Evaluation of *In Vivo* Wound-Healing and Anti-Inflammatory Activities of Solvent Fractions of Fruits of *Argemone mexicana* L. (Papaveraceae). Evid-based Complement Altern Med. 2022;2022:1-17.
51. Duhan JS, Bhardwaj M, Surekha S. Free radical-scavenging and antimutagenic potential of acetone, chloroform and methanol extracts of fruits of *Argemone mexicana*. Afr J Biotechnol. 2011;10(43):8654-61.
52. Marimuthu M, Manikandan R, Varma MS. Studies on phytoconstituents and antioxidant properties of *Argemone mexicana* flower extract. Infokara Res. 2019;8(11):1325-36.
53. Prabhakaran D, Rajeshkanna A, Senthamilselvi M. Antioxidant and Anti-inflammatory activities of the flower extracts of *Argemone mexicana* L. Int J Res Pharm Sci. 2020;11(1):323-30.
54. Sharath J, Taj RAS, Bhagya M. Phytochemical Characterisation of *Argemone mexicana* Leaf Extracts: An Evidence for its Antiandrogenic and Antioxidant Activities. Indian J Pharm Educ Res. 2022;56(2s):S294-S302.
55. Vennerstrom JL, Klayman DL. Protoberberine alkaloids as antimalarials. J Med Chem. 1988;31(6):1084-7.
56. Sheng WD, Jiddawi M, Hong X, Abdulla S. Treatment of chloroquine-resistant malaria using pyrimethamine in combination with berberine, tetracycline or cotrimoxazole. East Afr Med J. 1997;74(5):283-4.
57. Simonsen HT, Nordskjold JB, Smitt UW, Nyman U, Palpu P, Joshi P, et al. *In vitro* screening of Indian medicinal plants for antiplasmodial activity. J Ethnopharmacol. 2001;74(2):195-204.
58. Diallo D, Graz B, Falquet J, Traoré AK, Giani S, Mounkoro PP, et al. Malaria treatment in remote areas of Mali: use of modern and traditional medicines, patient outcome. Trans R Soc Trop Med Hyg. 2006;100(6):515-20.
59. Willcox ML, Graz B, Falquet J, Sidibé O, Forster M, Diallo D. *Argemone mexicana* decoction for the treatment of uncomplicated falciparum malaria. Trans R Soc Trop Med Hyg. 2007;101(12):1190-8.
60. Graz B, Willcox ML, Diakite C, Falquet J, Dackuo F, Sidibe O, et al. *Argemone mexicana* decoction versus artesunate-amodiaquine for the management of malaria in Mali: policy and public-health implications. Trans R Soc Trop Med Hyg. 2010;104(1):33-41.
61. Simoes-Pires C, Hostettmann K, Haouala A, Cuendet M, Falquet J, Graz B, et al. Reverse pharmacology for developing an anti-malarial phytomedicine. The example of *Argemone mexicana*. Int J Parasitol: Drugs Drug Resist. 2014;4(3):338-46.
62. Sakthivadivel M, Thilagavathy D. Larvicidal and chemosterilant activity of the acetone fraction of petroleum ether extract from *Argemone mexicana* L. seed. Bioresour Technol. 2003;89(2):213-6.
63. Sakthivadivel M, Eapen A, Dash A. Evaluation of toxicity of plant extracts against vector of lymphatic filariasis, *Culex quinquefasciatus*. Indian J Med Res. 2012;135(3):397.

64. Elawad L, Eweis E, Abou-Bakr H. Larvicidal activity of Argel (*Solenostemma argel* Del Hyne) and Prickly Poppy (*Argemone mexicana* L.) Acetone Extracts against Mosquito Larvae of *Culex quinquefasciatus* (Say.) and Anopheles arabiensis (Diptera: Culicidae). Egypt J Biol Pest Control. 2014;24(1):259-64.
65. Abou-Elnaga ZS. Strong larvicidal properties of *Argemone mexicana* L. against medically important vectors *Culex pipiens* and *Aedes aegypti*. Int J Mosq Res. 2015;2(1):9-12.
66. Mokdad AH, Forouzanfar MH, Daoud F, El Bcheraoui C, Moradi-Lakeh M, Khalil I, et al. Health in times of uncertainty in the eastern Mediterranean region, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Glob. 2016;4(10):e704-e13.
67. Elizondo-Luévano JH, Castro-Ríos R, Sánchez-García E, Hernández-García ME, Vargas-Villarreal J, Rodríguez-Luis OE, et al. *In vitro* study of antiamoebic activity of methanol extracts of *Argemone mexicana* on trophozoites of *Entamoeba histolytica* HM1-IMSS. Can J Infect Dis Med Microbiol. 2018;2018:1-8.
68. Elizondo-Luévano JH, Castro-Ríos R, López-Abán J, Gorgojo-Galindo O, Fernández-Soto P, Vicente B, et al. Berberine: A nematocidal alkaloid from *Argemone mexicana* against *Strongyloides venezuelensis*. Exp Parasitol. 2021;220:108043.
69. Elizondo-Luévano JH, Castro-Ríos R, Vicente B, Fernandez-Soto P, López-Aban J, Antonio M, et al. *In vitro* antischistosomal activity of the *Argemone mexicana* methanolic extract and its main component berberine. Iran J Parasitol. 2021;16(1):91-100.
70. Nayak P, Kar DM, Maharana L. Antidiabetic activity of aerial parts of *Argemone mexicana* Linn. in alloxan induced hyperglycaemic rats. Pharmacologyonline. 2011;1:889-903.
71. Rout S, Kar D, Mandal P. Hypoglycaemic activity of aerial parts of *Argemone mexicana* L. in experimental rat models. Int J Pharm Pharmaceut Sci. 2011;3(5s):533-40.
72. Nayak PS, Kar DM, Nayak SP. Antidiabetic activity and modulation of antioxidant status by fractions of *Argemone mexicana* in alloxan induced diabetic rats. Int J Green Pharm. 2012;6(4):321-9.
73. Ahsan R, Islam KM, Musaddik A, Haque E. Hepatoprotective activity of methanol extract of some medicinal plants against carbon tetrachloride induced hepatotoxicity in albino rats. Glob J Pharmacol. 2009;3(3):116-22.
74. Sourabié T, Kone H, Nikiéma J, Nacoulma O, Guissou I. Evaluation of the antihepatotoxic effect of *Argemone mexicana* leaf extracts against CCl_4-induced hepatic injury in rats. Int j biol chem sci. 2009;3(6):1499-503.
75. Adam S, Idris I, Abdelgadir E, Ahmed R, Kamal E. Evaluation of hepatoprotective activity of *Argemone mexicana* aerial Part Extracts on CCl_4 induced liver damage in wistar rats. Br J Pharmacol. 2011;2(5):251-6.
76. Chang Y-C, Hsieh P-W, Chang F-R, Wu R-R, Liaw C-C, Lee K-H, et al. Two new protopines argemexicaines A and B and the anti-HIV alkaloid 6-acetonyldihydrochelerythrine from formosan *Argemone mexicana*. Planta Med. 2003;69(02):148-52.
77. Dahab M, Koko W, Osman E. *In Vitro* Antitrichomonal Activity of'*Xanthium brasilicum*'Vell and'*Argemone mexicana*'L Different Extracts. J Med Plant Res. 2011;5(2):151-5.
78. Elizondo-Luevano JH, Verde-Star J, González-Horta A, Castro-Ríos R, Hernández-García ME, Chávez-Montes A. *In vitro* effect of methanolic extract of *Argemone mexicana* against *Trichomonas vaginalis*. Korean J Parasitol. 2020;58(2):135-45.
79. Datkhile KD, Patil SR, Durgawale PP, Patil MN, Jagdale NJ, Deshmukh VN, et al. Biogenic silver nanoparticles synthesized using Mexican poppy plant inhibits cell growth in cancer cells through activation of intrinsic apoptosis pathway. Nano Biomed Eng. 2020;12(3):241-52.
80. Datkhile KD, Patil SR, Durgawale PP, Patil MN, Hinge DD, Jagdale NJ, et al. Biogenic synthesis of gold nanoparticles using *Argemone mexicana* L. and their cytotoxic and genotoxic effects on human colon cancer cell line (HCT-15). J Genet Eng Biotechnol. 2021;19(1):1-11.
81. Attri S, Kaur P, Singh D, Kaur H, Rashid F, Kumar A, et al. Induction of apoptosis in A431 cells via ROS generation and p53-mediated pathway by chloroform fraction of *Argemone mexicana* (Pepaveraceae). Environ Sci Pollut Res. 2022;29(12):17189-208.
82. Rangan C. Food contamination. Barceloux DG, editor: Wiley; 2009.
83. Das M, Khanna SK. Clinicoepidemiological, toxicological, and safety evaluation studies on argemone oil. Crit Rev Toxicol. 1997;27(3):273-97.
84. Verma S, Dev G, Tyagi A, Goomber S, Jain G. *Argemone mexicana* poisoning: autopsy findings of two cases. Forensic Sci Int. 2001;115(1-2):135-41.
85. Ansari KM, Das M. Potentiation of tumour promotion by topical application of argemone oil/ isolated sanguinarine alkaloid in a model of mouse skin carcinogenesis. Chem-Biol Interact. 2010;188(3):591-7.
86. Ghosh I, Mukherjee A. Argemone oil induces genotoxicity in mice. Drug Chem Toxicol. 2016; 39(4):407-11.

*****