IJPSR (2012), Vol. 3, Issue 08 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 24 April, 2012; received in revised form 14 May, 2012; accepted 21 July, 2012

A REVIEW ON *ARGEMONE MEXICANA* LINN. - AN INDIAN MEDICINAL PLANT

Saurabh Rajvaidhya*[1], B.P. Nagori, G.K. singh, B.K. Dubey, Prashant Desai and Sanjay Jain

T.I.T. College of Pharmacy, Bhopal, Madhya Pradesh, India
Lachoo Memorial College of Science and Technology, Pharmacy Wing, Jodhpur, Rajasthan, India

Keywords:
Argemone mexicana,
Papaveracea,
Plant description,
Biological activities,
Phytoconstituents

Correspondence to Author:

Saurabh Rajvaidhya

T.I.T. College of Pharmacy, Bhopal, Madhya Pradesh, India

Email: srajvaidhya@gmail.com

ABSTRACT

Argemone mexicana Linn has been reported to posses anti microbial, cytotoxic, anti malarial and other pharmacological activity. Alkaloids, amino acids, phenolics and fatty acids are the main constituents isolated from the plant. The present article reviews the pharmacological and phytochemical work done on the plant and determines a scientific base for novel study for future research to establish toxin free response of plant or its phytoconstituents.

INTRODUCTION [1-14]**:** *Argemone mexicana* Linn (Papaveracea) is a common plant found everywhere by road-sides and fields in India. The plant, *Argemone mexicana* Linn. belonging to the family papaveraceae, is a widely distributed plant throughout the subtropical and tropical regions of the world.

It is commonly known as 'Mexican prickly poppy' and 'Satyanashi' is a common name, it is a well known weed in the agricultural and waste lands. It is an erect, prickly annual herb, up to 1.2 meter in height, naturalized throughout India up an altitude of 1,500 meter.

Leaves are sessile, semi-amplexicaul, sinuately pinnatifid, and spiny on margins, mid-rib and veins beneath; flowers yellow; capsules elliptic or oblong, prickly, rarely unarmed; seeds small, round, blackish brown, deeply reticulate-scrobiculate. The various part of the plant reported to posses potent emetic, narcotic activities ant traditionally been used to treat, syphilis and skin-diseases [1].

Seeds are useful in cough and asthma. Seeds are laxative, nauseant, emetic, expectorant and demulcent. The root is an antihelmintic [2]. Chemical investigations of this plant have revealed the presence of alkaloids, amino acids [3], phenolicsand fatty acids [4].

The plant contains alkaloids as berberine, protopine, sarguinarine, optisine, chelerytherine etc. The seed oil contains myristic, palmitic, oleic, linoleic acids etc. The yellow juice containing small quantities of berberine, potassium nitrate was identified among the salts naturally existing in the plant.

Two aliphatic compounds; mexicanol & mexicanic acid have been isolated from leaves. Three isoquinoline alkaloids have been isolated as dihydropalmitine hydroxide; berberine & protopine, from the seeds. Oil contain up to 40% free glycerides of fatty acids [5]. The plant Argemone mexicana traditionally used as a potent diuretic agent. Along with the plant shows anti antihelmintic, anti inflammatory, wound healing, anti bacterial, antifungal [6].

The plant is bitter, acrid, cooling, vulnerary, purgative, inflammatory, expectorant, aphrodisiac, emetic, depurative, anodyne, anthelmintic, antipyretic, ophthalmic, stomachic and sedative. It cures leprosy, skin – diseases, inflammation and bilious fevers. Roots are useful in guinea-worm infestation, skin diseases, leprosy, pruritus, blennorrhagia, inflammations, all type of poisoning, constipation, flatulence, colic, malarial fever and vestibular calculus. The leaves are useful in cough, wounds, ulcers and in skin diseases. Juice is used to cure opthalmia and opacity of cornea. Seeds are purgative and sedative. Seeds resemble mustard seeds and in India it is used to adulterate mustard seed.

Seeds are also useful in vitiated conditions of cough, asthma, pertussis, skin diseases, leprosy, wounds, odontalgia, dentalcaries, constipation, rheumatalgia, colic and flatulence. The latex is useful in dropsy, jaundice, skin diseases, leprosy, blisters, conjunctivitis, inflammation, burning sensation and malarial fever. The oil is useful in indolent ulcers, wounds, leprosy and skin diseases, constipation, flatulences, colic and rheumatalgia. In Homeopathic system of medicine the drug prepared from this herb is used to treat the problem caused by tape worm.

Seed yield non edible toxic oil and causes lethal dropsy when used with mustard oil for cooking and show lots of toxic effect [7].

Hepatotoxicities of varied etiology are widely encountered among the people of entire world irrespective of the age, ethnic, racial, environmental and geographical variability. The reasons are broad ranging from drugs or substance induced to various metabolic and physiological disturbances, becoming one of the ten leading causes of death across the world hence, there is a way or great hope to do toxicity study and determine the dose for claimed pharmacological activity and if some constituents are responsible for toxicity, so its not meant that whole plant is responsible for different toxicity because plant and its part are responsible for other pharmacological activity. So there is a hope to identify and isolate various phytoconstituents in this plant for above mentions or related pharmacological activity and scope to check lots of pharmacological activity in various or low dose or calculated dose according to toxicity study.

Currently researches are going on *Argemone mexicana* have focused on its hepatoprotective activity, anti microbial [8], cytotoxic [9] and anti HIV activity [10].

Pharmacological Investigation:

1. **Anti malarial activity:** A prospective, dose-escalating, quasi-experimental clinical trial was conducted with a traditional healer using a decoction of *Argemone mexicana* for the treatment of malaria. The remedy was prescribed in three regimens: once daily for 3 days to group A; twice daily for 7 days to group B; and four times daily for the first 4 days followed by twice daily for 3 days to group C. Thus, 80 patients were included, of whom 80% were aged <5 years and 25% were aged <1 year.

   All presented to the traditional healer with symptoms of malaria and had a *Plasmodium falciparum* parasitaemia >2000/µl but no signs of severe malaria. The proportions of adequate clinical response (ACR) at Day 14 were 35%, 73% and 65% in Groups A, B and C, respectively (P = 0.011). At Day 14, overall proportions of ACR were lower in children aged <1 year (45%) and higher in patients aged >5 years (81%) (P = 0.027). Very few patients had complete parasite clearance, but at Day 14, 67% of patients with ACR had a parasitaemia <2000/µl [15].

2. **Antiplasmodial activity:** By the research 20 species, with low IC50 values of 9–43 mg dry extract / ml have been shown to possess antiplasmodial activity in all of them, Argemone mexicana L. (Papavaraceae) also shown the same activity which is vary by varying extract dose per kg/ body wt. concentration: *In vitro* inhibition (%) of plant extracts against chloroquine susceptible strain of P. falciparum. The result shows: Mg dry extract / 80 mg part dry plant material 2.50, % Inhibition (mg:ml) according to dose i.e. 100 µg/ml (87); 50 µg/ml (76); 25 µg /ml (60); 12.5 µg /ml (51); and IC50 µg /ml [16].

3. **Larvicidal activity:** The acetone fraction of the petroleum ether extract of seeds from *Argemone mexicana* exhibited larvicidal and growth inhibiting activity against the second instar larvae of *Aedes aegypti* (Linn). This activity occurred at higher

concentrations (200, 100, 50 and 25 ppm). Chemosterilant activity, including reduction in blood meal utilization (27.70%), reduction in fecundity (19.00%), formation of larval–pupal intermediates, formation of pupal–adult intermediates, adult mortality and sterility of first generation eggs (100%), occurred at low concentration (10 ppm) [17].

4. **Antibacterial activity:** The sensitivity of two Gram positive (*Staphylococcus aureus* and *Bacillus subtilis*) and two Gram negative (*Escherichia coli* and *Pseudomonas aeruginosa*) pathogenic multi-drug resistant bacteria was tested against the crude extracts (cold aqueous, hot aqueous, and methanol extracts) of leaves and seeds of *Argemone mexicana* L. (Papaveraceae) by agar well diffusion method.

   Though all the extracts were found effective, yet the methanol extract showed maximum inhibition against the test microorganisms followed by hot aqueous extract and cold aqueous extract [18]. The petroleum ether and alcoholic extracts of aerial parts of *Argemone mexicana* were evaluated for antimicrobial activity against 2 bacterial strains (gram positive and negative), *Bacillus subtilis* and *Escherichia coli*. Both extracts showed high antimicrobial activity on the 2 pathogens, but the alcohol extract showed higher activity when compared to petroleum ether extract [19].

5. **Cytotoxic activity:** The alkaloid isolated by fractionation of the chloroform extract from the aerial part of *Argemone mexicana* were evaluated for their cytotoxicity to human nasopharyngeal carcinoma (HONE-1) and human gastric cancer (NUGC) cell lines. Chelerythrine was found to exhibit significant activity against NUGC cell line, while angoline inhibited both types. (+)-Argenaxine showed moderate activity against the NUGC cell line [20].

6. **Wound healing activity:** The wound healing effects of the leaf extract (50% ethanol) and latex of *Argemone mexicana* were investigated on albino rats using both excision and incision wound models. Topical application of the extract and latex, respectively, gave 67.08 and 57.86% healing after 12 days in the excision model and increased tensile strength to 188.50 and 154.61 gm in the incision model. However, both the extract and latex of *A. mexicana* were not as effective as the standard nitrofurazone in both excision and incision models [21].

7. **Vasorelaxant activity:** The vascular effects of a methanolic extract of the aerial part *Argemone mexicana* was investigated in rat aortic rings. The extract produced relaxation from contraction induced by norepinephrine (NE: 1X10-7 M) in a concentration-dependent manner (0.1 at 1000 µg/ml). At higher concentrations (310 and 1000 µg/ml), the extract induced significant additional tension. When applied to relaxed aortic tissue, addition of the extract produced concentration dependent contraction.

   Vasoconstrictor and vasorelaxant effects produced by the extract, were not altered significantly in endothelium-denuded rings, however, phenoxi-benzamine (1 mg/ml) produced a rightward shift in the concentration–contractile response curve to the extract. On the other hand, the extract relaxed significantly the contraction induced by KCl (40 mM). The results indicate that the extract induces a direct dual specific effect upon the vascular smooth muscle, mediated, at least in part, by adrenergic receptors [22].

   The petroleum ether, CHCl3, CHCl3/MeOH (9:1), MeOH extract and partially purified fractions and pure compounds from *Argemone mexicana* examined on the electrically induced contractions of the isolated guinea-pig ileum (E.C.I.). The results of the experiments indicate that CHCl3/MeOH (9:1) and MeOH extracts, tested at a concentration of 400, 200 and 100 mg/mL, dose-dependently reduced the guinea-pig ileum contractions, whereas the petroleum ether and $CHCl_3$ extracts did not affect it.

   Furthermore, the partially purified fractions II-V from the MeOH extract, each tested at concentrations of 200, 100 and 50 mg/mL also inhibited E.C.I. Finally the pure compounds 1-2 (5×10-6-1×10-5-5×10-5 M) isolated and purified from the above fractions significantly reduced, in a

dose dependent manner, the electrical contractions of the ileum, whereas compound 3 (5×10-6-1×10-5×10-5 M) increased them. Since the active compounds 1-3 were respectively identified as protopine, allocryptopine and berberine by NMR, the observed effects could be related mainly to these compounds [23].

8. **Antiasthmatic activity:** The research title i.e. Medicinal plants used to treat asthma in Andhra Pradesh, India proved that *Argemone mexicana* L. (Papaveraceae) (common or local name: Brahmadand) Seed powder, 100–200 mg taken twice a day, for 2 weeks shows significant effect on asthama as antiasthamatic activity [24]. Anti-Stress and Antiallergic Effect of *Argemone mexicana* Stems in Asthma shows: Petroleum ether, acetone and methanol and aqueous extracts of *Argemone mexicana* stem (50 mg/kg, i.p.) was screened for its antiallergic and antistress potential in asthma by milk-induced leucocytosis and milk-induced eosinophilia.

   Aqueous extracts showed significant (P<0.05) decrease in leucocytes and eosinophils, methanol extract also showed comparable results with aqueous extract while petroleum ether and acetone extracts were inactive. This shows polar constituents of *A. mexicana* stem are responsible for antistress and antiallergic activity.

9. **Milk-induced leucocytosis**: Amongst mice pretreated with various extracts of *A. mexicana* stem, aqueous and methanol extracts showed significant reduction in leucocytes, induced by milk.

10. **Milk-induced eosinophilia**: Amongst mice pretreated with various extracts of *A. mexicana* stem, aqueous and methanol extracts showed significant reduction in eosinophil count [25].

11. **Anti-HIV activity:** The alkaloids isolated from methanolic extract of the *Argemone mexicana* were evaluated for anti-HIV activity. In which benzo[c]phenanthridine (+/-)-6-acetonyldihydro chelerythrine exhibited significant anti-HIV activity in H9 lymphocytes with EC50 and TI (Therapeutic Index) values of 1.77 µ /ml and 14.6, respectively [26].

12. **Hepatoprotective activity:** The root bark of *Argemone mexicana* was investigated on CCl4 (Carbon tetra Chloride) induced liver damaged in rats. Acute toxicity study, efficacy study, blood and tissue biochemical assays like ALT, AST, bilirubin, total protein, glucose, LM and EM etc have been studied for evaluation of Hepatoprotective action. From above observations of biochemical parameters it was demonstrated that *Argemone mexicana* indeed has a high potential in healing liver parenchyma and regeneration of liver cells hence it may act as a potent liver tonic [27].

    The protective effects of the aqueous extract of *Argemone mexicana* (Linn.) whole plant; against CCl4 induced hepatic failure in male albino rats (Wistar strain) was investigated. For acute and massive invasion of hepatopathy, CCl4 (i.p injection of CCl4+Olive Oil in 1:1 ratio; 2ml/kg) was used and various biochemical parameters followed by significant (p<0.001) weight loss in toxic control group (-12.83±1.13). The administration of aqueous extracts (250mg/kg and 150mg/kg of body weight) for 7 days, elicited protective action since the elevated levels of marker enzymes (AST, ALT, ALP) of liver functions were found to be decreasing progressively in a dose dependent manner with net weight gain.

    In the aqueous extract, 250mg/kg treated rat group all the marker enzymes were analysed to be decreasing significantly (p<0.001), (AST, 272.77±24.08; ALT, 189.15±7.16; ALP, 97.15±6.54) and the final body weight was also significantly (p<0.001) increased (6.16±1.01) when compared with the toxic control group. The serum total protein and the serum albumin were also approaching normal values. The results found in aqueous extract 250mg/kg treated rat were quite promising and were comparable with a standard polyherbal drug Liv-52.

    The statistically processed results support the conclusion, that the aqueous extract of *Argemone mexicana* (Linn.) whole plant (250mg/kg and 150mg/kg) possesses dose dependent, significant protective activity against CCl4 induced hepatotoxicity [28].

13. **Molluscicidal activity:** Molluscicidal property of seeds of *Argemone mexicana* against snail *Lymnaea acuminata* was studied. It was observed that molluscicidal activity of seed powder of *A. mexicana*, was both time and dose dependent. Protopine and sanguinarine in seed of *A. mexicana* was identified as the active moiety causing snail death by co-migration of active agent with seed powder [29].

14. **Opoid withdrawal:** The MeOH extract, partially purified fraction (IV), and pure compounds from *Argemone mexicana* examined for its effect on the morphine withdrawal in guinea pig isolated ileum. The MeOH extract, the partially purified fraction (IV), and the pure compounds isolated from *A. mexicana* significantly and in a concentration-dependent manner reduced the morphine withdrawal. Since the pure compounds were identified as protopine and allocryptopine, the observed effects could be related to these compounds. The results of the present study suggest that isoquinoline alkaloids may be potential agents in the treatment of drug abuse [30].

Toxicity and safety evaluation: The alkaloid sanguinarine isolated from seeds of *Argemone mexicana* was examined for its hepatotoxic potential in rats. The studies showed that a single i.p. dose (10 mg/kg) of sanguinarine not only increased the activity of SGPT and SGOT substantially but also caused a significant loss of microsomal cytochrome P-450 and benzphetamine N-methylase activity. Furthermore, the treated rats exhibited considerable loss of body and liver weight, peritoneal edema and slightly enlarged livers with fibrinous material. Microscopic examination of the liver tissue showed progressive cellular degeneration and necrosis further substantiating that sanguinarine is a potential hepatotoxic alkaloid [31].

Toxicolethal effects of seeds of *Argemone mexicana* were investigated in to roof rat, (*Rattus rattus* L). The argemone seeds were fed at 100% of the diet up to the death or for a maximum of 10 days. Observed signs of poisoning were sedation, passiveness, sluggishness, feeble or no muscular jerks, abdominal contractions and increased defecation. Also black secretions from the eyes, corneal opacity, erection of hairs, and edema of the hind legs and submandibular space in were noted. Fourteen of 16 rats died. Significant reduction in the weights of the rats was observed. There were significant increases in blood glucose, BUN and SGOT. Major histopathological lesions were: hepatocytolysis, nuclear degeneration, pyknosis, cloudy swelling and dilatated sinusoids disturbing the lobulalar architecture of the liver; proliferated endothelium of glomeruli, hemorrhage in glomeruli and interstitium, and cloudy swelling of convoluted tubular epithelium in the kidney cortical region; erosion and atrophy of the upper stomach mucosa and calcification in the cardiac stomach, and; erosion and congestion of the upper mucosa of the duodenum. No change was noticed in the ileum [32].

Safety evaluation studies on argemone oil through dietary exposure for 90 days in rats: Epidemic dropsy is a disease caused by the consumption of mustard oil contaminated with argemone oil (AO). During 1998 dropsy in New Delhi, which is so far the largest with more than 3000 victims and over 60 deaths, it was enquired at various scientific and regulatory meetings about the maximum tolerated dose of AO. Animals were given AO in diet at a dose of 0.001%, 0.01%, 0.1%, 0.5% and 1% daily for 90 days and the two control groups received the standard diet with and without 1% mustard oil.

A decrease in body weight gain (28–31%) was observed in 0.5% and 1% AO groups; while significant increases in relative lungs and liver weight was noticed in respective doses of 0.01% and 0.1% AO groups as well as in higher dosage animals. Reduction in RBC count and haemoglobin content ($p < 0.05$) was noticed in 0.01% and 0.1% AO exposed animals. This effect was more pronounced in higher AO doses. Serum marker enzymes including alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) were found to be significantly elevated in 0.01–1% AO groups.

Further, a decrease in albumin/globulin ratio (42–78%) was observed in the serum of 0.01% to higher AO dose groups. The levels of serum triglycerides and VLDL cholesterol were found to be enhanced ($p < 0.05$) in AO treated (0.01–1.0%) animals. Histopathological changes in lung were observed at 0.01% dose of AO while liver, kidney and heart produced changes at 0.1% AO and above doses.

None of the parameters were found to be affected in 0.001% AO treated animals. These results suggest that the no observed adverse effect level (NOAEL) dose of AO is 0.001% in rats and considering a factor of 100 for humans for highly toxic compound, the safe limit of 0.00001% (100 ppb or 100 ng AO/g oil) AO can be implicated which shall contain only 0.55% of sanguinarine equivalent to 0.6 ng sanguinarine per gram oil. However, the minimum detectable limit of AO is 5 ppm (equivalent to 5 ng sanguinarine per gram oil) with the present existing HPLC method, thereby suggesting that mustard oil should be absolutely free from AO contamination [33].

In vivo DNA damaging potential of sanguinarine alkaloid, isolated from argemone oil, using alkaline Comet assay in mice: Consumption of mustard oil contaminated with argemone oil is well known to cause clinical manifestation referred to as ''Epidemic Dropsy''. Our prior studies have shown that argemone oil produces genotoxic effects in mice[30]Since, sanguinarine alkaloid is the major component of argemone oil, the in vivo DNA damaging potential of the isolated alkaloid was investigated in blood and bone marrow cells of mice using alkaline Comet assay. Swiss albino male mice were given single intraperitoneal administration of 1.35, 2.70, 5.40, 10.80 and 21.60 mg sanguinarine alkaloid/kg bwt., while controls were treated with saline in the same manner.

The results revealed a dose dependent increase in DNA damage in blood and bone marrow cells following 24h treatment of sanguinarine alkaloid. All the three parameters of Comet assay including olive tail moment (OTM), tail length and tail DNA showed significant ($p < 0.05$) increases in blood and bone marrow cells at respective doses of 10.80 and 5.40 mg alkaloid/kg bwt. However, some of the parameters were significantly increased even at lower doses of sanguinarine alkaloid (2.70 mg/kg bwt.).

The frequency of cells exhibiting greater DNA damage was found to be increased by sanguinarine alkaloid in a concentration dependent manner. These results indicate that single exposure of sanguinarine alkaloid causes DNA damage in blood and bone marrow cells of mice, which could be responsible for the genotoxicity of argemone oil.

The present study clearly indicates that sanguinarine alkaloid, an active ingredient of argemone oil possesses DNA damaging potential in blood and bone marrow cells using alkaline Comet assay. These results fully support the earlier observation that in vivo argemone oil caused genotoxicity by enhancing the frequencies of chromosomal aberrations, micronuclei formation and development of Comets resulting in DNA damage [30]. In this regard studies have shown that sanguinarine forms DNA adducts following metabolism by cytochrome P-450 system under in vitro conditions [34].

It has been suggested that sanguinarine may undergo N-demethylation by cytochrome P-450.[32] Since, sanguinarine has been shown to cause inactivation of cytochrome P-450, it can be argued that the N-demethylated product of sanguinarine or any other electrophilic metabolite, could be responsible for this effect.

The decrease in cytochrome P-450 thereby impairs the elimination of a metabolite of sanguinarine, identified as benzacridine, in urine and feces. Although, minimum group of sanguinarine has been shown to have affinity with b-form duplex DNA by intercalation with a high preference to G–C base pairs nonetheless, it could not reveal genotoxicity in SOS chromtest using *E. coli* PQ37 in the absence and presence of metabolic activation system. However, it raised the possibility of usage of Sanguinaria extract in toothpaste in the development of oral leukoplakia [35].

Phytochemical evaluation: A large number of chemical constituents have been isolated and identified from various parts of *Argemone mexicana* including alkaloids, amino acids, phenolics and fatty acids, the constituents of pharmacological importance are presented in **table 1** [16, 36, 37, 38].

Quaternary alkaloids of *Argemone mexicana*: Four quaternary isoquinoline alkaloids, dehydrocory-dalmine, jatrorrhizine, columbamine, and oxyber-berine,have been isolated from the whole plant of Argemone mexicana Linn. (Papaveraceae) and their structures established by spectral evidence. This is the first report of these alkaloids (dehydrocorydalmine, jatrorrhizine, columbamine, and oxyberberine) from *Argemone mexicana* and the Argemone genus [37 & 38].

TABLE 1: PHYTOCHEMICAL EVALUATION

S. No.	Constituents isolated	Parts
	Alkaloids	
01	*N*-Demethyloxysanguinarine	Whole plant
02	Pancorine	Whole plant
03	(+)-Argenaxine	Whole plant
04	(+)-Higenamine	Whole plant
05	(+)-Reticuline	Whole plant
06	Chelerythrine	Whole plant
07	Angoline	Whole plant
08	*O*-Methylzanthoxyline	Whole plant
09	Norchelerythrine	Whole plant
10	Sanguinarine	Whole plant
11	6-Acetonyldihydrosanguinarine	Whole plant
12	6-Acetonyldihydrochelerythrine	Whole plant
13	Aronttianamide	Whole plant
14	Berberine	Whole plant
15	Dihydrocheilantifoline	Whole plant
16	Protopine	Whole plant
17	Allocryptopine	Whole plant
18	Coptisine	Whole plant
19	Dehydrocorydalmine	Whole plant
20	Jatrorrhizine	Whole plant
21	Columbamine	Whole plant
22	Oxyberberine	Whole plant

CONCLUSION: The extensive survey literature reviewed that *Argemone mexicana Linn*, has some important medicinal activity but also cause considerable toxicity. Few novel chemical constituent isolated from the *Argemone mexicana* showed anti-HIV properties too. Further evaluation need to be carried out on *Argemone mexicana* in order to explore concealed areas and their practical clinical application, which can be used for the welfare of the mankind. There is a scope to identify new compound and check claimed pharmacological activity by eliminating toxic effect. And identify new mean for elimination of toxic effect to get toxic free as well as significant response on claimed pharmacological activity.

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How to cite this article:
Rajvaidhya R, Nagori BP, Singh GGK, Dubey BK, Desai P and Jain S: A Review on *Argemone mexicana* Linn. - An Indian Medicinal Plant. *Int J Pharm Sci Res*, 2012; Vol. 3(8): 2494-2501.