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Medicinal Property and Ethnopharmacological Activities of *Argemone mexicana: An* Overview

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ABSTRACT

Argemone mexicana (Mexican poppy), commonly known as "Satyanasi orBhatkatiya" in India, is a valuable medicinal plant and considered to have miraculous therapeutic potential.It is used to cure several diseases in the Indian traditional medicine system of Ayurveda for over 5000 years. Its leaves, stem, latex, roots and seeds have several pharmacological activities.Many of the bioactive compounds obtained from the *Argemone* seeds are especially effective in the treatment of chronic diarrhea, dysentery, peptic ulcers, as well as respiratory infections. Scientific studies have validated numerous medicinal applications of *Argemone mexicana*, which include analgesic, antispasmodic, depurative, emetic, antipyretic, emmenagogue, sedative, vulnerary, healing dermatological problems *etc*. However, its medicinal property is not much highlighted due to a popular misconception that this plant is poisonous andcauses epidemic dropsy, with symptoms including extreme swelling, particularly of the legs, but this is what after the adulteration process of edible oils. The present overview deals with the general and ethnopharmacological profile of *Argemone mexicana*, emphasizing its medicinal property against various human ailments along with other current uses, which has been reviewed from literature up to January, 2020 and enlists 109 references.

Keywords: Traditional medicine, Mexican poppy, Ethnopharmacology, Antimicrobial, Antiulcer activity.

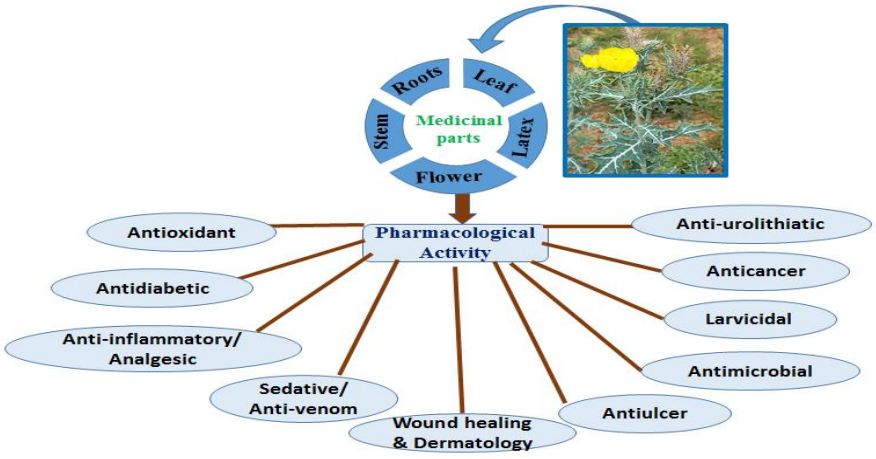

Fig. Graphical Abstract

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1. Introduction

Traditional medicines obtained from plant source are always recognized as God's gift to human beings. The use of herbal medicine has been in practice for preventing or treating various ailments since time immemorial. [1, 2] Moreover, the traditional system of medicine, which has been followed by our ancestors, is well-thought-out as the main source of knowledge behind the evolution of modern allopathic or synthetic medicine. Herbal plants are a vast reservoir of many chemical compounds, which are responsible for medicinal property in that plant. [3] An exhaustive screening of these natural chemical compounds and their both *in vitro* and *in vivo* testing in the treatment of a particular disease has led to the discovery of a new drug. [4-6]

A. mexicana is a plant originally from Mexico, North America, has been now naturalized all over the world. [7] The wide diversity of climatic condition available in India, ranging from deserts to swap lands, is best suited for its harvesting. In India, it grows as a weed in the wastelands, roadside, dried river area or as a crop weed in fields. It is a herb has showy yellow flowers of six petals and yellow juice, brings us to its Sanskrit name, Swarnakshiri. [8] When the plant is injured the yellow colour juice exudes bitter in taste, has long been used in India as traditional medicine for dropsy, jaundice, ophthalmia, scabies and cutaneous affections. [9,10]

The literature on medicinal properties of the oil extracted from the seeds of the *A. mexicana* dates back to 1866 or earlier, wherein its great usefulness in the cure of skin diseases have been reported. [11] Over the past 50 years, researchers have shown great interest on evaluation of remedial properties of this medicinal plant by employing different experimental approaches towards complete characterization and examination of phytochemistry of its natural and derived bioactive compounds using advanced techniques and protocols. *A. mexicana* is the source of a variety of chemical constituents although alkaloids are mostly abundant. [12] Others are terpenoids, flavonoids, phenolics, long chain aliphatic compound and few aromatic compounds.[13-15] These chemical of this plant exhibits various biological activities like antibacterial, anti-HIV, anti-inflammatory, wound healing, anti-stress, anti-allergic, vasoconstrictor and vasorelaxtant effect, anti-fertility, cytotoxic, nematicidal, anti-feedant effect on ileum organ fungitoxic, antioxidant, anticancer, antidiabetic, antihepatotoxic activities and many more miscellaneous activities.[16-18] People in Mali boil the plant whole and drink the decoction to cure malaria.[19] Bio-diesel can also be produced from it by mixing it with manganese carbonate.[20]

A. mexicana has been used in traditional medicine system from several hundreds of years by natural healers and annotation about its pharmacological potential was disseminated from generation to generation. These traditional medicines in the form of powder, paste, latex, oil or extract find their popularity through their perceived effectiveness without or less side effect.[21,22] Available literature contains several review articles revealing novel medicinal property of *A. mexicana* and its importance in human ailments as well as pharmacopoeias.[23-28] However, on careful examination of available research reports leaves a number of grey areas of advance research to be conducted in establishing full potential for disease management. The present

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review provides detailed information on the medicinal uses of *A. mexicana* based on the results of various *in vitro* and *in vivo* experimental studies carried out in last ten years. Additionally, this review also brings out novel non medicinal applications of *A. mexicana* such as biodiesel, bio-adsorbent and effective corrosion inhibitor of mild steel.

Scientific Classification and local names:
Kingdum: Plantae
Phylum: Angiosperm
Class: Eudicots
Order: Ranunculales
Family: Papaveraceae
Genus: *Argemone*
Species: *mexicana*
Vernacular names: English: Mexican prickly poppy, flowering thistle, cardo or cardosanto; **French:** Argemone; **German:** Doppelklappen; **Sanskrit:** Swarna ksheeri, Kanchani, Karshani, Hemadugdha, Tikta Dugdha; **Hindi:** Satyanasi, Kataila; **Urdu:** Baramdaandi; **Bengali:** Siyal-Kanta; Bharband; **Kannada:** Datturigidda; **Konkani:** Phirangi dhutro; **Malayalam:** Ponnummattu; **Manipuri:** Khomthongpee; **Marathi:** Firangi dhotra; **Punjabi**: Bhataiktheya; **Tamil:** Kudiyotti; **Telugu:** pichi kusuma.

2. Habitat and Distribution

Argemone mexicana tends to grow along roadsides, in fallow and cultivated lands, riverbanks, disturbed areas, and on floodplains. It competes with and replaces native species in some cases and is also a significant crop weed. [29, 30] It is widely spread throughout the region, especially on Tanzania, Kenya, Uganda and south-eastern USA (Florida), Mexico, Central America, the Caribbean and tropical south America. [31] In India, it grows in the temperate region as a weed in waste lands, cultivating fields and road sides. It prefers light sandy well-drained soil and also grows in nutritionally poor acidic, neutral and basic (alkaline) soil. [32]

2.1 Botanical Description and Identification features

Argemone mexicana is an erect annual herb, growing up to 100 to 150 cm with a slightly branched tap root. Its stem is branched and extremely prickly and oblong in cross-section. It exudes a yellow juice when cut. Leaves are 5 to 11 cm long, alternate, without leaf stalks (petioles), toothed (serrate) and the margins are spiny. [33] They are more or less blotched with green and white veins, stand out against the bluish-green upper leaf surface. Flowering/Fruiting time of *Argemone* species starts from January-May. Flowers are complete, bisexual, *i.e.*, with functional male (androecium) and female (gynoecium), including stamens, carpels and ovary. Pollination is entomophilous *i.e.*, by insects. [34] They are at the tips of the branches (are terminal), solitary, and scentless and of 2.5-5 cm diameter with six petals bright yellow or rarely pale lemon yellow; stamens 30-50, filaments yellow, pistil 4-6-carpellate. Fruit is a prickly

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oblong or egg-shaped (ovoid) capsule. Seeds are brownish black coloured, very numerous, nearly spherical, covered in a fine network of veins and about 1 mm in diameter. [35]

2.2 Useful parts of plant

Every part of *A. mexicana* possesses so many medicinal properties, either in small of large proportion. However, different parts of the plant contain same or different active ingredients.[36-38] Most of the bioactive compounds are quite harmless whereas toxicity has been evaluated in Argemone oil. [39] All the parts of the plants are highly useful. They are stem, leaves, flowers, fruits and seeds. The various parts of the plant are depicted in Fig. 1 and their part vise medicinal uses are mentioned in Table-1. It is clearly evident that all parts of *A. mexicana* plant having target specific medicinal value. Some of the commercially available Ayurvedic medicines with *A. mexicana* ingredient are mentioned in Table-2.

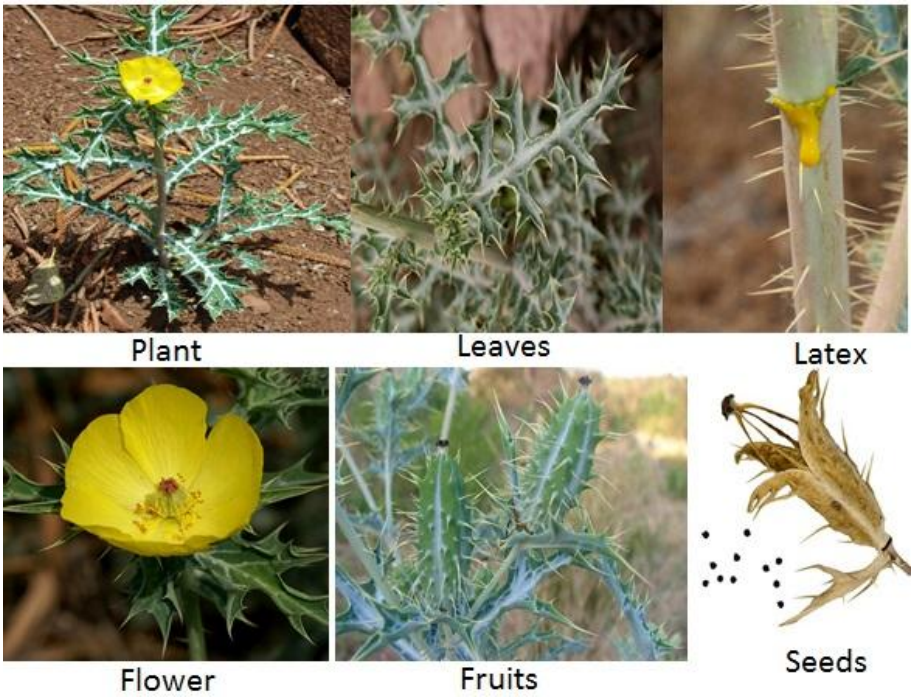

Fig1:Some useful partsof*A. mexicana*

Table 1:Parts viseuse of*A. mexicana*

Parts of Plant	Medicinal Properties
Stem	Leprosy, malaria, jaundice, rheumatism, pain, inflammation, skin diseases, fever, piles, warts, dysentery, tumors and worm infestations. [7, 10, 34, 40, 42, 43, 70, 81, 82]
Latex	Treat boils, scorpion sting, dermatitis, disinfectant, dropsy, jaundice, skin diseases, leprosy, blisters, indolent ulcers, conjunctivitis, inflammations, burning sensation and malarial fever, rheumatic pain. [22, 26, 28, 29, 38, 41, 47, 56, 63, 82]
Leaf	Diabetes, fever, ulcers, maintains blood circulation and cholesterol level, anti-venom, anti-inflammatory stomach aches, muscular pain, cough, wounds,

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	ulcer, warts, cold sores, cutaneous infections, skin diseases, itches *etc.* [42, 52, 64, 70, 73, 74, 84]
Flower	Expectorant, Antioxidant [57, 60]
Seed	Purgative, laxative, antidote to snake poisoning, [41, 46] toothache. diuretic, anti-inflammatory, malarial fever, leprosy, scorpion sting, warts, cold sores, wound healing, skin diseases, itches, jaundice, [42,45,49] demulcent, emetic, expectorant, sedative for children, dysentery, ulcers, asthma and other intestinal affections, [55]conjunctivitis, [51] hypertension, pertussis, ulcers, wounds, odantalgia, dental caries, constipation, rheumatalgia, colic, hallucinogenic, antibacterial, antifungal and antiprotozoal. [44,73]
Root	Chronic skin diseases, leprosy, inflammations, anthelmintic, [47] antibacterial, cytotoxicity, wound healing, antioxidant, antifungalagent, [50, 53, 54, 58] expectorant, antidote to snake poison, constipation, flatulence, colic, malarial fever, and vesicular calculus. [48] Vaginal discharge and hepato-biliary problems.

Table -2 Ayurvedic medicines with *A. mexicana* ingredient: [59]

Medicine	Use
Kasisadi Tailam	It is only meant for external application over the piles.
Liverson Syrup	used in the treatment of jaundice, splenomegaly *etc.*
Mishraka Sneha	For the treatment of abdominal distention, abscess, neurological conditions, and abdominal colic.
Sishutone syrup	It is a proprietary ayurvedic medicine useful to treat respiratory diseases and improve the immunity of the child.
Brahamdine tablet	It is a proprietary ayurvedic medicine useful to treat menstrual disorders.

3. Reported phytochemicals

Scientific studies have shown that *A. mexicana* contains numerous phytochemicals in high levels, such as carotenoids, phenolic, alkaloids, pectins, tannins, coumarins, flavonoids and terpenoids. [13,14] Similarly, various bioactive compounds from those groups have been isolated and identified.The following substances are among the products isolated from the *A. mexicana*: α & β allocryptopines, codeine, paveramine, narcotine, papaverine etc. Important bitter principles derived are papaverosin, chelidoxanthin, glaucopicrin *etc.* [25, 46]The fresh flowers of *A. mexicana* contain isorhamnetion etc. and seed contain essential oil which is known as Argemone oil while resin contains berberine and protopine. [57] The chemical structures of some active constituents of *A. mexicana*are shown in Fig. 2.

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4. Pharmacological profile

A. mexicana has great pharmacological potency and it is being used from the tradition. Traditionally, the whole plant is analgesic, antispasmodic, depurative, emetic, emmenagogue, hallucinogenic, sedative and vulnerary. The roots, seeds and leaves are registered officially in the Mexican pharmacopoeia [Plant Resourses of South-East Asia; Book]. It contains alkaloids and so can be used as a mild pain-killer. Flavonoids equally present in the aqueous extract have been reported as antioxidants and scavengers of free radicals can also exert anti-inflammatory effects. [60] To cure ailments of the spleen, liver, and for jaundice or whooping cough a decoction of the leaves is given. An infusion of the young leaves or flowers is taken to relieve fever, cough and asthma. [55] A summary of various pharmacological activities of *A. mexicana* extracts and some isolated compounds are shown in Tables 3. The following section highlights important pharmacological activity of *A. mexicana* in detail.

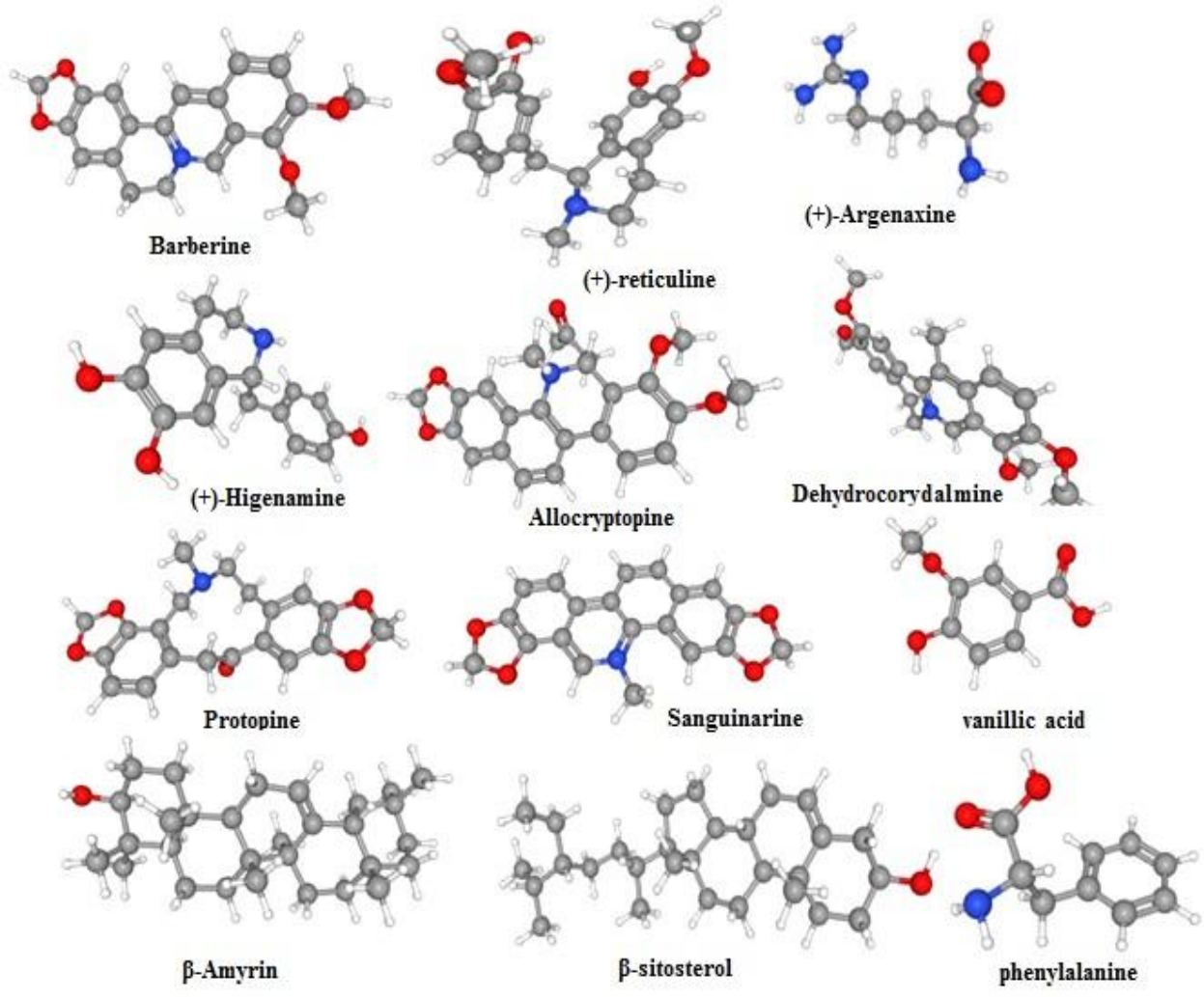

Fig.3.The 3D chemical structure of some important bioactive constituents obtained from *Argemone mexicana*. = N, = O, = C, = H, = sigle bond, = double bond.

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Table 3. Pharmacological activities of *A. mexicana* extracts and isolated compounds.

Antioxidant activity			
Extract/active compound	**Model**	**Result**	**Ref.**
Alchoholic, aquous acidic and alkaline extract	*In vitro*	Scavenging activity against DPPH and Hydroxyl radical	[40]
Methanolic extracts of leaves, stems, roots, flowers and fruits	*In vitro*	Possess significant antioxidant activity	[60]
Methanolic extract of plant	*In vitro*	Protection against free radicals damage	[61]
Ethanolic and aqueous extract	DPPH and Hydrogen peroxide-scavenging model	Ethanol extract of aerial parts showed high scavenging activity	[62]
Methanolic extract of stem and leaves	*In vitro*	Free radical-scavenging activity comparable to standard antioxidant	[63]
Methanol extract of leaves	*In vitro*	Free radical-scavenging activity	[64]
Anti-diabetic activity			
Ethanolic and aqueous extract	Alloxan induced hyperglycemic rats	Progressive fall of blood sugar level in a significant extent	[65]
Hydroalcoholic extract	Streptozotocin induced Wistar albino rats	Reduces the fasting blood glucose level significantly	[66]
Chloroform and aqueous extract	Alloxan induced diabetic rats	Anti-diabetic and lipid-lowering activity	[67]
Hydroalcoholic and alkaloidal extracts	*In vitro*	Alkaloidal extracts shown highest aldose reductase inhibitory activity	[68]
Anti-inflammatory/ analgesic activity			
Lyophilized leaf extract	young male and female white mice	Exhibit effective anti-inflammatory and analgesic activity	[69]
Polyherbal methanolic extract	Healthy Wistar albino rats	Significant anti-inflammatory Effect	[70]
Sedative /anti venom activity			
Methanolic and ethyl acetate extracts	Wistar albino mice of either sex	Whole plant possesses analgesic, sedative and anxiolytic activity	[71]

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Ethanolic extract	Female Wistar rats	Potential anxiolytic agent	[72]
Decoction of leaf and seeds	Unknown	Oral intake for 7 days neutralize venom toxins	[73]
Wound healing/dermatological activity			
Petroleum ether, chloroform, methanol and aqueous extracts of the leaves	Wistar albino rats	Methanol and aqueous extracts showed faster rate of wound healing	[74]
Ethanolic extracts of stem and root	Swiss albino rat of either sex	Ethanolic extract found to be effective in the functional recovery of the wound	[70] [75]
Anticancer activity			
Methanol extract of aerial part	Human colon cancer cells	Strongly inhibit the cell proliferation	[76]
Cold aqueous and methanolic extracts	The human non-small cell lung carcinoma, -A549, human cervical cell, -SiHa, and oral cancer cell, -KB	Exhibit significant cytotoxicity on A549, SiHa and KB immortalized cell lines	[77]
Ethyl acetate fraction from the flower extract	HepG2 cell lines (liver cancer)	Cytotoxic effect against HepG2 cell line	[78]
Root and leaf methanol extracts	*In vitro*	Inhibitory effects against T84 human colon cancer cells	[79] [80]
Antiulcer/anti-urolithiatic activity			
Aqueous and methanolic extract	Cysteamine induced male albino wistar rats	Prevention of duodenal ulceration and increased healing of gastric ulceration in rats	[82]
Ethanolic extract of aerial part	Indomethacin induced albino wistar rats	Significant inhibition of gastric lesions	[83]
70% Hydro-Ethanolic Leaf Extract	Aspirin induced mucosal damage and water immersion stress induced gastric ulcer models in albino wistar rats	The ulcer protective effects	[84]

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Methanol extract of leaves	In vitro	Potential anti-urolithiatic activity against calcium oxalate crystal	[85]
Larvicidal / anti-parasitic / antimalarial activity			
Petroleum ether leaf extracts of plants	*Culex quinquefasciatus*, vector of lymphatic filariasis	Synergistic action of *A. mexicana* against 3rd - 4th instar larvae of *Cx. quinquefasciatus.*	[86]
Petroleum ether and hexane extracts of leaf, stem, and roots	dengue vector, *Aedes aegypti*	Effective larvicides leading to 100 % larval mortality	[87]
Hexane, chloroform, methanol and water extracts	*Cx. Pipiens* and *Ae. Aegypti* colonies	Promising as naturally occurring insecticides	[88]
Silver Nanoparticle from *Argemone mexicana*	*Aedes Albopictus*	Suitable for bio-formulation against mosquitoes and microbes	[89]
Ethanol extracts of flowers	*Culex quinquefasciatus* an arboviral and filarial vector	Flower extract exhibited the strongest larvicidal activity	[90]
Petroleum ether, Chloroform and Methanol extracts of seeds, aerial part, and roots	grain pests *S. oryzae*, and *C. chinensis*	Lethal effect on *C. chinensis* and *S. oryzae* adults, and also have potentials to repel the test insects	[91]
Antimicrobial (Antifungal/ Antibacterial/ Antiviral) activity			
Various extracts from stems	In vitro study against a range of food-borne bacteria	Potent antibacterial effect against *B. subtilis, S. aureus, L. monocytogenes, C. Botulinum, C. perfringens, E. coli, P. aeruginosa* and *S. typhimurium*	[92]
Various extracts of the poppy	Fungal stains viz. *Aspergillus niger, Aspergillus terreus, Aspergillus stolonifer, Candida albicans*	A good antifungal activity was observed	[93]
Leaf extracts using 3 organic solvent and water	*P. aeruginosa* NCTC strain no. 10662	The methanol extract has shown highest antipseudomonad activity.	[94]

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Ethanol and methanol extracts of seeds and leaves	Gram positive bacteria *S. aureus* and *B. subtilis* and Gram negative bacteria *E. coli* and *P.aeruginosa*	Great antibacterial against gram-positive as well as gram-negative bacteria	[95]
Cold aqueous and methanolic extracts of stem and leaves	*Mucor indicus, Aspergilus flavus,Aspergilus niger* and *Penicillium notatum* fungi	Strong antifungal activity	[96]
Cold aqueous and methanolic extracts of leaves	Gram positive bacteria *Staphylococcus aureus&Bacillus cereus* and Gram negative bacteria *Escherichia coli* & *Pseudomonas aeruginosa*	Exhibited comparable broad spectrum antibacterial activity	[97]
Methanolic extract of leaves	In vitro Antiamoebic Activity against *Entamoeba Histolytica*	Showed growth inhibition activity against trophozoites of the *E.histolytica* strain	[98]
Methanol, ethanol and chloroform extracts of flowers, berries and leaves	Agar disc diffusion and agar tube dilution Methods	Good antimicrobial activities against all the tested micro-organisms.	[99]
Ethyl acetate extracts of stem and root	Antiviral and immunostimulant screening against WSSV and *Vibrio harveyi*	Effectively suppressed the WSSV and also boosted the hematological and immunological parameters	[100]
Other non-medicinal importance of *Argemone Mexicana*			
Oil of *A. mexicana*	Low cost production of ester	Methyl ester produced by transesterification technique can become a suitable alternative fuel	[104]
Leaf extract	Corrosion inhibition of mild steel	Effective corrosion inhibitor	[105]
Seed of *A. mexicana*	Adsorption of textile dye Rhodamine B.	Efficient adsorbent for removal of textile dye from waste water	[106]
Seed of *A. mexicana*	Removal of a di azo sulphonated dye, Direct Red 81	Good adsorption leading with 98% saturation of dye	[107]
Methyl ester of *A. mexicana*	Biodiesel-Diesel Blends	Improved performance and reduced emissions	[108]

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Argemone oil and mahua oil	Biodiesel blends	Showed slight increase in brake power and reduced carbon monoxide (CO) and hydrocarbon (HC)emissions	[109]

4.1 Anti-oxidant activity

The antioxidants are the free radical scavengers.It is well established that reactive oxygen species (ROS) such as superoxide (O_2^-), hydrogen peroxide (H_2O_2), and the hydroxyl radical (OH) as well as reactive nitrogen species (RNS) such as nitrous oxide (N_2O), nitrosyl cation (NO^+), peroxynitrite ($OONO^-$), nitrogen dioxide ($NO_2^\bullet$), nitroxyl anion (NO^-) and nitrous acid (HNO_2) are involved in the progression of various diseases, including cardiovascular disease and cancer.[60, 63] Antioxidant or polyphenol compounds present in plants can effectively neutralize these ROS and RNS species ensuing slow progression of disease.[74, 75] In addition, naturally occurring antioxidants are healthier substitute of currently available synthetic antioxidant like butylated hydroxyl anisole (BHA), butylatedhydroxytoluene (BHT) and gallic acid esters since these have been suspected to cause or prompt negative health effects. In a study carried out by Esha Sharma and Arti Prasad, the extract of *A. mexicana* showed its potent antioxidant activity and effectively scavenged free radicals at all different concentrations. [40] Another similar study reports the antioxidant efficacy of methanolic extracts of different plant parts (leaves, stems, roots, flowers and fruits) of *A. mexicana*. In DPPH (1,1-diphenyl-2-picrylhydrazyl) scavenging assay it was observed that flower methanol extract has high potential of radical scavenging activity with IC_{50} = 23.75µg/ml. [60] Similarly, Monica *et al* examined the free radical scavenging activity of different parts of *A. mexicana* using peroxidase assay, ABTS (2,2'-azinobis-(3-ethylbenzothioline-6-sulfonic acid) diammonium), Ferric Reducing Ability of Plasma (FRAP) and Lipid Peroxidation assay (LOP). The fruits exhibited remarkable ability to scavenge the species LPO (39.193±1.256MDA/gDW), ABTS (68.23±3.02mML^{-1}g^{-1}) while flowers showed maximum peroxidase activity (0.513mM/min^{-1} g^{-1} DW) and FRAP (287±9.64) [61]. The hydrogen-peroxide scavenging activity of ethanolic extract of *A. mexicana* was investigated in another study and found to be 87.1% which is comparable to the standard Ascorbic acid (90.5 %). [62]

The antioxidant activity of *A. mexicana* Linn available in Yemen was evaluated by Wafa Al-Madhagi *et al*. [63]The methanol extracts obtained from stem and leaves were tested for their antioxidant activity using 2% of (DPPH) radical on TLC. The plant showed the presence of alkaloids, flavonoids, terpenoids, saponins, tanninswhich could be responsible for the obtained antioxidant activities. The phytochemical screening and antioxidant activity of methanol leaves extracts of *A. mexicana* is well documented in a recent review article. [64] Owning to these results, it can be understood that *A. mexicana* has the potential to be used as a medicine against the diseases caused by free radicals.

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4.2 Anti-diabetic activity

Diabetes mellitus is a chronic metabolic disorder which is characterized by the symptom of hyperglycemia. The plant of *A. mexicana* is known to have anti-diabetic effects in traditional medicine system. Several *in vitro* and *in vivo* studies have been carried out to determine the role of various extracts of different parts of *A. mexicana* for potential anti-diabetic activity. The anti-diabetic effect of *A. mexicana* aqueous extract was evaluated in a study involving alloxan induced diabetic rats. [65] The results confirmed the anti-diabetic property of *A. mexicana*, as the test extracts showed a persistent decrease in blood glucose level till the end of 10 hr., with maximal decrease noted in aqueous extract at 400 mg/kg dose, reaching 70.25% while the standard drug glibenclamide showed 66.65% decrease. In continuation of this work, the researcher further investigated a mechanistic approach towards hypoglycaemic potential *of A. mexicana*. They concluded that the test fractions significantly increase the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) in liver, kidney and pancreas, suggesting that the anti-hyperglycaemic activity of *A. mexicana* is accompanied by the phytochemicals augmenting the endogenous antioxidant mechanisms. [67]

The hypoglycemic activity of hydro-alcoholic extract of aerial parts of *A. mexicana* were evaluated in another study involving normal, glucose loaded, and streptozotocin (STZ) induced hyperglycaemic rats, at dose levels of 200 and 400 mg/kg by taking Metformin (300 mg/kg) as standard drug. [66] It has been reported that at higher dose and repeated administration the efficacy of the extract is comparable with that of the standard drug. After two weeks of treatment, the blood glucose level returned to level comparable with metformin treated group with 400 mg/kg dose indicating that the plant extract possesses great anti-diabetic potential. Sakshi Gupta and co-workers evaluated the aldose reductase inhibitory potential of alkaloidal fractions of *Piper nigrum, Murraya koenigii, Argemone mexicana, and Nelumbo nucifera* toexamine their anti-diabetic effect by measuring biochemical parameters. [68] Aldose reductase is primarily involved in development of long-term diabetic complications due to increased polyol pathway activity. Therefore, the pharmacological inhibition of aldose reductase has been recognized as an important strategy in the prevention and attenuation of long-term diabetic complications. Among the alkaloidal extracts, highest inhibitory activity was shown by *A. mexicana* (IC50 value 25.67 ± 1.25 μg/mL), followed by *N. nucifera* (IC50 value 28.82 ± 1.85 μg/mL), *P. nigrum* (IC50 value 30.21 ± 1.63 μg/mL), and *M. koenigii* (IC50 value 35.66 ± 1.64 μg/mL). Based on these, it can be concluded that *A. mexicana* possess great anti-diabetic activity and may be exploited therapeutically in diabetes-related complications.

4.3 Anti-inflammatory/ Analgesic Activity

Inflammation is a biological process that occurs at the beginning of many pathological situations which releases some anti-inflammatory agents like histamine, kinins, serotonins, and prostaglandin. Inflammation is considered as a primary physiologic defense mechanism that helps the body to protect itself against infection, burn, toxic chemicals, allergens or other noxious stimuli. The term analgesic refers to “relief from pain” and some of the phytocompounds obtained from *A. mexicana* have been proved to be very effective analgesic. To

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evaluate the anti-inflammatory and analgesic property of *A. mexicana*, various scientific studies have been carried out using different modalities. [69] The study on anti-inflammatory activity of *A. mexicana* is reported by using carrageenan-induced paw edema method, whereas hot plate test method and acetic acid writhing method has been usedfor its analgesic property. The lyophilized leaves extract was used and found very effective in acute inflammatory disorders. The plant extract was lyophilized and tested to exhibit significant analgesic activity. The experiment for both the activity was performed in-vivo on young male and female mice. The observed anti-inflammatory activity can be explained due to presence of phytochemicals tannins, flavonoids etc. and the analgesic activity exhibited by the lyophilized extract of plant can be attributed to phytochemical such as tannins, flavonoids, isoquinoline and alkaloids, *etc*.). In an interdisciplinary study concerned with antimicrobial, anti-inflammatory and wound healing activity of polyherbal formulation of *Plumbago zeylanica Linn, Datura stramonium Linn* and *Argemone mexicana Linn* revealed the synergistic effect on wound healing process. [70] The anti-inflammatory and antimicrobial activities of polyherbal composition might be the contributing factors that accelerated the wound healing activity. These works have provided clear justification for the traditional medical use of *A. mexicana* particularly as anti-inflammatory agents and also supporting analgesic activity.

4.4 Sedative /anti venom activity

A study evaluating the anxiolytic and sedative effects of *A. mexicana* shed light on significant central and peripheral nociceptive activity on Swiss albino mice. Methanolic and ethyl acetate extract have also showed significant decrease in motor activity and fall off time of animals on rotating rod. This study demonstrated that phytochemicals such as flavonoids, steroids, alkaloids and tannins present in plant extracts may be responsible for the CNS depressant activity. [71] In a similar study, the anxiolytic-like effect of ethanolic extract of *A. mexicana* was investigated in Wistar rats. Phytochemical screening confirmed the presence of alkaloids, terpenoids, sterols, steroids, flavonoids and quinones in the extracts which are intrinsically related to some action on the central nervous system. In order to examine the anxiolytic-like effect on Elevated Plus Maze (EPM) test, the alkaloid-enriched extract was administered to independent groups of animals at a dose of 200 μg/kg and results were analysed in terms of reduced anxiety index. It has been observed that ethanolic extract of *A. mexicana* (100 and 200 mg/Kg, respectively) and alkaloids mixtures (200 μg/ml) significantly reduces anxiety index similar to standard diazepam (2 mg/kg); indicating that this plant exerts anxiolytic effects due to its alkaloids and this action is probably mediated through gamma-aminobutyric acid ($GABA_A$) receptor chloride channels. [72] In addition, *A. mexicana* plants possess anti-venom property. Leaf and seed decoction is given orally for 7 days; root paste is also used. It is used for all types of poisonings including scorpion sting. [73] Its anti-venom activity is reported in a review on anti-snake venom properties of medicinal plants, suggesting that decoction of seeds and leaves of *A. mexicana* found beneficial for the treatment of snakebite and may find alternative to antivenom serum. [41]

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4.5 Wound healing/dermatological activity

Das & Murthy investigated wound healing activity using excision, incision anddead space wound models in Wistar albino rats with different extracts of A. *mexicana* leaves. [74] The petroleum ether, chloroform, and aqueous extracts of the leaves of *A. mexicana* have shown significant wound healing activity. It has been reported in another study that wound healing activity in rats was much faster when treated with methanol extract of *A. mexicana*leaves. [70] The effect of *A. mexicana* roots and its stem is verified in a study on experimentally induced excision wound in Swiss albino rats. The ethanolic extracts of stem, root and other parts of the plant *A. mexicana* were examined for wound healing activity and compared with gentamycin (0.3% w/w), a standard wound healing agent. The results of this study revealed that the ethanolic extract ointment of root of *A. mexicana* possesses better wound healing potency, which was evidenced by the increased rate of wound contraction, reduction in the period of epithelisation justify its use as potential wound healing herbal medicine as claimed in folk literature. [75]

4.6 Anti-cancer activity

Large numbers of plants and their isolated constituents have been found to possess potential anticancer activity. Among the ethnomedicinal plants *A. mexicana* has been extensively studied to inhibit proliferation of tumor cells since it contains a diverse kind of chemical constituents, alkaloids being most abundant. In one of the study, six alkaloids, 13-oxoprotopine, protomexicine, 8-ethoxydihydrosanguinarine, dehydrocorydalmine, jatrorrhizine, and 8-xyberberine were isolated from aerial part of *A. mexicana* and their cytotoxicity were evaluated on SW480 human colon cancer cell line. [76] The cytotoxic activities of isolated alkaloids were evaluated at different concentrations in terms of cell viability. At 200 mg/mL, protomexicine and 13-oxoprotopine showed mild cytotoxicity (~24–28%) whereas dehydrocorydalmine exhibited moderate cytotoxicity (~48%). 8-Oxyberberine was mildly cytotoxic (~27%) at 24h but was more potent (~76%) at 48h. Jatrorrhizine and 8-methoxydihydrosanguinarine were most potent (~95–100%) in inhibiting the human colon cancer cell proliferation showing complete reduction in cell viability. In another study conducted on A549 (The human non-small cell lung carcinoma), SiHa (human cervical cell) and KB (oral cancer cell) immortalized cell lines. Anticancer activity against immortalized cell lines was assessed by trypan blue assay. The vinblastine at 20 µg per well was used as a control in this assay while berberine, at parallel concentration of *A. mexicana* extracts, served as an example of alkaloid known to have anticancer potential. [77] Data reported in this study indicate that *A. mexicana* leaves and stem extracts exhibit significant cytotoxicity on A549, SiHa and KB immortalized cell lines. After 72h incubation the cytotoxicity of A549 cell was found to be 67% with leaf extracts and 70% with stem extracts which was comparable with berberine 71%, at same concentration level. However, SiHa and KB immortalized cell lines have shown less effective cytotoxicity at similar experimental condition. Similarly, the anticancer activity of the flowers of *A. mexicana* explored against the human hepatoma cell line (HepG2). The outcomes of this study revealed that ethyl acetate fraction of *A. mexicana* flowers have strong cytotoxic effect against HepG2 cell line.[78] In a recent study, Najdeska *et al* reported that, when using the MTT colorimetric assay, the outer

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root and leaf methanol extracts and the seed hexane extract have pronounced inhibitory effects against T84 human colon cancer cells.[79] The bioactive phytoconstituents present in *A. mexicana* such as sanguinarine, a slightly toxic polycyclic ammonium ion and berberine, an alkaloid, were found to have antitumour and antiviral properties. Sanguinarine is antiangiogenic, blocks the formation of blood vessels, and has even greater potential as an anticancer agent. Hussain *et al* reviewed various ethnomedicinal plants against proliferation on different cancer cell lines and concluded that *A. mexicana* shows maximum anticancer activity on various cancer cell lines in comparison to other medicinal plants. [80]

4.7 Antiulcer/anti-urolithiatic activity

The plant *A. mexicana* is traditionally used to treat ulcers and associated diseases. Das *et al* investigated the effect of oral administration of methanolic and aqueous extract of *A. mexicana* against cysteamine hydrochloride-induced duodenal ulcerationin rats. [82] The study revealed that both the extracts of the plant produced a significant activity to prevent the development of experimentally induced duodenal ulceration in rats. The aqueous extract at the dose-dependent manner showed the potent activity than methanolic extract. However, the exact constituents and mechanism by which the plant *A. mexicana* reduced duodenal ulcer formation has not been explained in this study. Similar results were also found by Raveendra Singh *et al* when they induced gastric lesions in albino wistar rats by administering 90% ethanol (5ml/kg) in one model for seven days and indomethacin (IND; 5mg/kg) in another model for five days, then investigated the protective effect of the ethanolic extract of aerial part of *A. mexicana* at the dose of 300mg/kg and 600 mg/kg rat body weight.[83] In both models the ulcer index (UI) was common and results of this study showed significant dose dependent reduction in the animal pretreated with ethanolic extract of *A. mexicana.* The UI was found to be 4.38 ± 0.66 at dose of 300 mg/kg and 4.12 ± 0.69 at dose of 600 mg/kg which corresponds to 68.51% and 70.38% gastro protection respectively as compared with reference drug (ranitidine and misoprostol). The antiulcer activity is probably due to the presence of bioactive compounds like phenolics compounds, glycoside, alkaloids, flavonoids, saponins and tannins. Fatima *et al* investigated anti-ulcer activity of 70% Hydro-Ethanolic leaf extract of *A. mexicana* L. at a dose of (100, 200 & 400 mg/kg b.w p.o) in Pylorus ligation, Aspirin induced mucosal damage and water immersion stress induced gastric ulcer models in Albino wistar rats.[84] The maximum ulcer protection in all the three models was found to be 39.9%, 43.6% and 54.7% respectively at highest studied extract dose of 400mg/kg b.w.p.o. The presence of flavonoids in the extract which have astringent property could be responsible for the anti-ulcer activity. Results of their study also suggest that the ulcer protective effects of the extract were comparable with those of standard drugs Ranitidine and Misoprostol.

A. mexicana is also reported to possess diuretic and anti-urolithiasis activity. Urolithiasis is the calcifications that form in the urinary system, initially in the ureter (ureterolithiasis) or kidney (nephrolithiasis) and may also form in or migrate into the lower urinary system like bladder or urethra. Common signs of urolithiasis include reduced urinary volume caused by obstruction of the bladder or urethra by a stone and often described as one of the strongest pain sensations.

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There are several modern methods available for the treatment of urolithiasis that includes allopathic medicines, shock wave lithotripsy and surgical treatment. These treatment options often caused side effects such as, chance of urinary tract infections, internal bleeding, weakness, itching, weight loss and peripheral vasodilation. To overcome these side effects through natural remedy the anti-urolithiatic activity of *A. mexicana* leaves extracts has been evaluated in detail. Chilivery *et al* reported the anti-urolithiasis activity by *in vitro* experiments (nucleation, aggregation and microscopic assay's) using petroleum ether, chloroform, methanol, and aqueous extract of *A. mexicana* leaves. The extracts were tested for the inhibition percentage against calcium oxalate crystal. It has been reported that methanol extract of *A. mexicana* leaves showed significant inhibition (77.24%) compared to standard cystone drug (69.33%) at 100 mg/ml concentration. [85]

4.8 Larvicidal / anti-parasitic / antimalarial activity

The plant extracts or phytochemicals are popularly gaining interest as ecofriendly, environmentally safe, biodegradable, and low-cost natural sources of pest management, to prevent the inevitable toxicity and resistance issues caused by synthetic chemical insecticides. *A. mexicana* plant parts have been reported to show mortal effect on various parasitic organisms such as mosquitoes, pests, worms and insects. Several studies have confirmed that *A. mexicana* contains alkaloids such as berberine, palmatine, sanguinarine, protoberberine, benzophenanthridine, benzylisoquinoline, and protopine that show target specificity to certain vectors causing infectious diseases. M Sakthivadivel *et al* evaluated the larvicidal activity of plants leaf extracts against *Culex. quinquefasciatus* larvae, the vector of lymphatic filariasis. The toxic effects of petroleum ether leaf extracts of some potential larvicidal plants viz., *Argemone mexicana, Clausena dentata, Cipadessa baccifera, Dodonaea angustifolia* and *Melia dubia* were evaluated under laboratory conditions in individual and in combination against 3rd-4th stage larvae of *Cx. Quinquefasciatus*. [86] It has been reported that among the selected plants, *A. mexicana* showed maximum larvicidal activity. Its toxicity was enhanced when the extract was mixed (1:1) with that of *C. dentata* indicating synergistic action of *A. mexicana.*

Warikoo *et al* studied the potential of leaf, stem, and root extracts of *A. mexicana* in five different solvents (petroleum ether, hexane, benzene, acetone, and ethanol) against *Aedes aegypti* larvae. The petroleum ether and hexane extracts, at a dose of 1000 ppm, have shown effective larvicidal activity with 100% mortality after 24 h against dengue vector *A. aegypti*. [87] The results of their study revealed that the root extracts are most effective with 1.6 to 2.4 fold higher efficacies as compared to the leaf and stem extracts. They have also demonstrated morphological and behavioral response of treated larvae. Excitation, violent vertical and horizontal movements with aggressive anal biting behavior of treated larvae, suggesting the effect of extracts on their neuromuscular system. Whereas, morphological studies of the treated larvae revealed the demelanization of cuticle and shrinkage of internal cuticle of anal papillae indicating the anal papillae as the probable action sites of the *A. mexicana* extracts. In a similar study, strong larvicidal activity of *A. mexicana* was recorded against the medically important vectors *Culex pipiens* and *Aedes aegypti*. The chloroform and methanol extracts of *A. mexicana* seeds showed

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significant larvicidal activity against 3rd instar larvae of *Cx. pipiens* with LC_{50} values 9.63 and 23.29 mg/l respectively. *Ae.aegypti*showed a slightly insignificant difference with LC_{50} values 12.59 and 25.21 mg/l, respectively after 24 hour of treatment suggesting that the chloroform and methanol extracts of *A. mexicana* seeds are promising in controlling the most important mosquito-borne diseases. [88] Kamalakannan *et al* studied that *A. mexicana* synthesized silver nanoparticles (AgNPs) give rapid control on mosquito larvae of dengue vector, *Aedes albopictus* and also inhibit the growth of microbes. [89]The efficacy of AgNPs, spherical size ranging (5-50 nm) was tested at concentration of 2 to10 ppm against L1 to L4 larval instar of *A. albopictus* and results obtained confirm the concentration dependent mortality. These AgNPs were also tested for antimicrobial activity and was found to show significant toxicity against the gram positive bacteria but mild toxicity against *P. aeroginosa*, a gram negative bacterium. The effect of continuous exposure to crude extracts of *A. mexicana*, on the development and growth stages of second-instar larvae of the mosquito was studied by Carlos*et al* along with qualitative chemical analysis of the different plant parts.[90] The ethanol extract from flowers exhibited the strongest larvicidal activity against *Culex quinquefasciatus* with LC_{50} and LC_{90} values after 24 h of exposure as 18.61 and 39.86 ppm, respectively, and 9.47 and 21.76 ppm after 48 h. The flower extract showed greatest larvicidal potential in the first 5 days and 100% mortality was recorded at the end of the experiment (26 d). Phytochemical screening and TLC analysis showed the presence of alkaloids, flavonoids, tannins present in all crude extract, anthraquinones in stem extract, and terpenoids in flower extract. In a recent study, Hasan Ali and coworkers screened various extracts of seeds, aerial part, and roots of *A. mexicana* thoroughly for their insecticidal and repellent activity against the stored grain pests *Sitophilus oryzae* L. and *Callosobruchus chinensis* L. under laboratory conditions.[91] The study revealed that petroleum ether, chloroform and methanol extracts of seeds of *A. mexicana* have lethal effect on C. chinensis and S. oryzae adults, and also have potentials to repel the test insects at 1% (moderate) to 5% (mild) level of significance.

4.9 Antimicrobial (Antifungal/ Antibacterial/ Antiviral) activity

A. mexicana plant inhibits the growth of numerous microbes such as viruses, bacteria and pathogenic fungi. Bacteria are the most versatile unicellular pathogens, normally transmitted through soil, water, air and food causes many infectious diseases in humans as well as in animals. Such types of diseases can be treated by many natural products obtained from medicinal plants. The role of *A. mexicana* in the prevention of microbial growth is described in a number of research papers. Rahman et al studied various extracts (hexane, chloroform, ethyl acetate and ethanol) of *A. mexicana* stems *in vitro* and determined the antibacterial activity, using agar diffusion and minimum inhibitory concentration (MIC) determination method against ten (five Gram positive and five Gram negative) food-borne pathogenic bacteria.[92] The chloroform, ethyl acetate and ethanol extracts exhibited strong antibacterial effects against all five Gram positive bacteria (*Bacillus subtilis,Staphylococcus aureus, Listeria monocytogenes,Clostridium botulinum* and *Clostridium perfringens*) and three Gram negative bacteria (*Escherichia coli,Pseudomonas aeruginosa* and *Salmonella typhimurium*) with their MIC values ranging from 62.5 to 500 μg/ml.

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However, no antibacterial activity was observed against two Gram negative bacteria: *Campylobacter jejuni* and *Vibrio cholerae* at the studied concentration of 300 µg/disc of plant extracts. In one of the study, the protein and alkaloids was extracted from *A. mexicana* leaves and tested against four different fungal strains viz. *Aspergillus niger, Aspergillus terreus, Aspergillus flavus and Rhizopus stolonifera*. [93] A good antifungal activity was observed at temperature 20^{o}C-25^{o}C. Among the various extracts, methanol extracts have been reported to show maximum potency. Sahu and co-workers studied antipseudomonad activity of *A. mexicana* on 27 clinically isolated strains of multidrug resistant (MDR) *Psudomonas aeruginosa* bacteria along with a standard strain, which was sensitive to all antibiotics. [94] The MIC values of leaf extracts of *A. mexicana* using acetone, methanol and ethanol as solvent were found to be 10, 8 and 8 mg/ml respectively. The study concluded that the methanol extract of leaf had the highest level of antipsudomonad activity both with cold and hot extracts. Many other researchers have also confirmed great antimicrobial activity of *A. mexicana* seeds and leaves against gram-positive as well as gram-negative bacteria, fungi and other pathogenic micro-organisms. [95-99]Several studies have proved that the *A. mexicana* had potent antiviral activities against various viruses. The active principles of *A. mexicana* effectively inhibited viral multiplication and stimulating immune system in Pacific white leg shrimp *Litopenaeus vannamei* against white spot syndrome virus; [100] Ridge gourd mosaic virus (RGMV); [101] demonstrated a promising anti-HIV potential in human through CD4+ T-cell line, CEM-GFP cells infected with HIV-1NL4.3 [102] and the aqueous extract of leaves had the antiviral effects against Newcastle disease virus (NDV) and Infectious bursal disease Virus (IBDV) through chicken embryo fibroblast (CEF) cell culture.[103] These studies clearly indicates that various extract of *A. mexicana* suppressed the propagation of micro-organism and also boosted the hematological and immunological parameters against virus challenge.

4.10 Other non-medicinal importance of *A. mexicana*

A. mexicana seed oil has been explored for low cost production of methyl ester. In this study, researchers examined the *A. mexicana* crop pattern and potential of seed production in field conditions, oil extraction process from the seeds and the transesterification process for ester production. They have also determined economic feasibility in terms of oil production and its methyl ester yield and compared to that of commercial diesel fuel. [104] The results of study revealed that cultivation of *A. mexicana* as a commercial waste land crop may become an idea of profitability with 35% average oil yield and subsequent conversion into useful products, such as methyl ester, glycerine and residual cake of seeds. *A. mexicana* leaf extract has been investigated for corrosion inhibition of mild steel in 0.5 M H_2SO_4. Maximum inhibition efficiency of 87% has been reported at 600 mg/L concentration of extract. [105]*A. mexicana* seeds have also been explored as cost effective natural bio-adsorbent. Khampariaa and Jaspal carried out in-depth study to explore the potential of *A. mexicana* towards decolorization of toxic textile dye, Rhodamine B (RHB) from textile effluent. [106]The adsorbent showed about 80% removal of RHB at optimum pH 3 with 0.06 g of adsorbent. In another study, same author reported the adsorption of a di azo sulphonated dye, Direct Red 81 onto *A. Mexicana* seeds. [107] Adsorption

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studies were carried out in both batch and column mode operations depicting good adsorption leading with 98% saturation of dye. Breakthrough studies also indicated the quantitative recovery of the dye using NaOH. Thus, the affinity of *A. mexicana* seeds for the dye ions present in waste water, introducing a novel adsorbent that have a potential of replacing the use of costly activated carbon in the field of waste water treatment.

Recently, biodiesel has been receiving much attention due to its less polluting nature. Moreover, biodiesel is a renewable energy resource as against the conventional diesel, which is a fossil fuel leading to a potential exhaustion. The feasibility of biodiesel production from *A. mexicana* seed oil was investigated by Rao *et al* using manganese carbonate as a heterogeneous catalyst. [20] The author stated that optimum process conditions for the conversion of *A. mexicana* oil to its methyl ester by transesterification required 1% manganese carbonate as catalyst with alcohol to oil ratio 5:1 at 60 ^{o}C to yield biodiesel of 99.99% purity. M.K. Parida *et al* evaluated multiple response of a VCR engine using *A. mexicana* biodiesel-diesel blends to improve performance and reduce emissions. [108]The biodiesels obtained from *A. mexicana* pass standard tests by fulfilling the parameters that made them competitive and substitute options to diesel fuel. Similarly, Rakesh Kumar *et al* conducted experiments to determine the performance and emission characteristics of a single cylinder direct injection diesel engine operated on diesel/biodiesel blends.[109]The performance, emissions and combustion parameters of 20% Argemone oil and 80% diesel fuel (volume basis) were found very close to neat diesel with improved brake thermal efficiency (BTE), brake specific fuel consumption (BSFC) and significantly decreased level of carbon monoxide (CO), hydrocarbon (HC) emission and smoke.

5. Conclusion:

A weed can also be a good medicine if one is aware of its action. Also it is very essential to know its qualities and actions through unremitting research and development studies. In this respect, the researchers have to come forward along with the natural healers for looking upon wide ranging prospects and potential of traditional medicinesfor various purposes. Present review has attempted to highlight the medicinal activity and presence of potentially active drug components in *A. mexicana*, which could be developed as novel drugs for treatment, prevention or relief of diabetes, cancer and various pathogenic infections. The use of natural substances, obtained from medicinal plants, to inhibit proliferation of various ailments is a rapidly evolving aspect of pharmacological research. Moreover, plants have been recognized for their beneficial effect by naturally increasing the immunity of the body, inducing antioxidant action, endorsing making of shielding enzymes, hindering cancer triggering enzymes and hormones, and exciting DNA restoration mechanism. However, more extensive and critical *in vivo* studies are necessary to assess the biological activity of the active components for drug discovery. Based on several pharmacological activities of *Argemone mexicana*, a number of well-established Ayurvedic medicines are commercially available, yet several other remedial and therapeutic effects have to be explored. Thus, it is worthwhile to cultivate this plant on large scale from medicinal point of view especially on unproductive and wasteland.

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Ethical issues
NA

Conflict of interests
Authors declare that there is no conflict of interest.

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