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Argemone mexicana: chemical and pharmacological aspects[#]

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Abstract: The Papaveraceae, informally known as the poppy family, are an ethnopharmacologically important family of 44 genera and approximately 760 species of flowering plants. The present work offers a review addressing the detailed chemistry and pharmacology of *Argemone mexicana* L. regarded as one of the most significant plant species in traditional system of medicine. The plant is used in different parts of the world for the treatment of several ailments including tumors, warts, skin diseases, inflammations, rheumatism, jaundice, leprosy, microbial infections, and malaria. Interestingly, the plant is the source of a diverse kind of chemical constituents although alkaloids are mostly abundant. Beyond pharmaceutical efficacies, certain plant parts also show toxic effects as well. Hence, an up-to-date information on the chemical and pharmacological knowledge on this plant may be helpful to guide researchers anticipating to undertake further investigations in these directions. The present review covers literature up to 2012 and enlists 111 references.

Review

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Introduction

Argemone mexicana L., known as Ghamoya (class: Magnoliopsida Dicotyledons; subclass: Magnoliidae; order: Papaverales; family: Papaveraceae; Figure 1) is an exotic weed indigenous in South America but has widespread distribution in many tropical and sub-tropical countries including West Africa (Ibrahim & Ibrahim, 2009). This plant is common everywhere by roadsides and fields in India as well (Bhalke & Gosavi, 2009). The plant is an erect prickly annual herb of about 1 m high; leaves are usually 5 to 11 cm long, and more or less blotched with green and white, glaucous broad at the base, half-clasping the stem prominently sinuate-lobed, and spiny (Chopra et al., 1956). The flowers become 4 to 5 cm in diameter, and are terminal, yellow, and scentless. The capsule is spiny, obovate or elliptic-oblong, and about 3 cm in length. The seeds are spherical, shining, black and pitted.

A. mexicana is considered as an important medicinal plant in India; the yellow juice, which exudes when the plant is injured, has long been used in India as traditional medicine for dropsy, jaundice, ophthalmia, scabies and cutaneous affections (Chopra et al., 1956; Ambasta, 1986; Sharma et al., 2012). Different parts of this plant are used in chronic skin diseases, and also as emetic, expectorant, demulcent and diuretic; the seeds and seed oil are employed as a remedy for dysentery, ulcers, asthma and other intestinal affections (Chopra et al., 1956; Bose et al., 1963; Ambasta, 1986; Prajapati et al., 2003; Savithramma et al., 2007). Leaves and seeds are also reported to find application in maintaining normal blood circulation and cholesterol level in human body (Albuquerque et al., 2007); these plant parts possess anti-venom property as well (Makhija & Khamar, 2010; Minu et al., 2012). Flowers are found to be expectorant and have been used in the treatment of coughs (Brahmachari et al., 2010). In Brazil, the plant is commonly known as 'cardo-santo' and used traditionally in the treatment of a number of diseases (Agra et al., 2007; 2008; Bieski et al., 2012). Seeds of the plant are used as purgative, laxative and digestive while its latex is used against conjunctivitis (Agra et al., 2008). Besides, its infusion finds application against hypertension in Brazil (Bieski et al., 2012). The present review deals with the phytochemical and pharmacological aspects of *A. mexicana* covering the literature up to 2012.

Material and Methods

The chemical constituents isolated and identified from *Argemone mexicana*, pharmacological activities exhibited by the isolated compounds as well as by the crude plant extracts were searched across the Medline (National Library of Medicine) and ScienceDirect databases. The data were updated in January 2013, using the search-terms *Argemone mexicana*, chemical constituents, biological activities, pharmacological activities or properties of *Argemone mexicana* as keywords. In addition, the reference lists of all papers identified were reviewed.

[#] In memory of Santosh Kr. Brahmachari

Figure 1. *Argemone mexicana* L., Papaveraceae.

Chemical constituents

Chemical constituents isolated so far from this plant are presented in Table 1. Most of the isolated compounds belong to the class of alkaloids; besides, terpenoids, flavonoids, phenolics, long-chain aliphatic compounds, and few aromatic compounds are found to be other constituents of this plant.

Biological activities exhibited by the plant and plant constituents

Various biological activities exhibited by both the crude plant extracts and isolated chemical constituents are described categorically under the following sub-sections:

Antibacterial activity

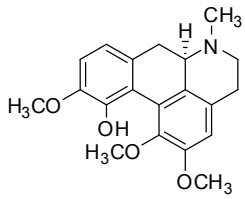
Crude plant extracts of *A. mexicana* L. as well as some of its chemical constituents were found to exhibit antimicrobial potential (Saranya et al., 2012). Rahman and his group (2009) studied *in vitro* antibacterial activity of the crude stems extracts (*n*-hexane, chloroform, ethyl acetate and ethanol) of the plant against a number of food-borne gram positive and gram negative bacteria such as *Bacillus subtilis, Staphylococcus aureus, Listeria monocytogenes, Clostridium botulinum, Clostridium perfringens, Escherichia coli, Pseudomonas aeruginosa* and *Salmonella typhimurium*. The organic crude extracts showed potent antibacterial activity against the bacterial strains at a concentration of 10 µL exhibiting zones of inhibition in the range of 10.1 to 21.4 mm with MIC values ranging from 62.5-500 µg/mL (Rahman et al., 2009). This study indicates the presence of some antibacterial chemical constituents in the plant, which might find useful applications. It was also reported that chloroform extract of *A. mexicana* seeds at a dose of 500 mg/mL show significant antimicrobial activity against both gram positive and gram negative microorganisms such as *E. coli, P. aeroginosa, Enterococcus* sp., *Salmonella typhi, S. aureus* with MIC values in the range of 2-5 mg/mL (Singh et al., 2009b); however, the methanol extract at the same dose showed a moderate activity only against *P. aeruginosa, S. typhi* and *S. aureus*. In addition, the 50% aqueous methanolic extract of *A. mexicana* fruits was tested for its antibacterial potential against some gram positive and gram negative bacteria such as *Klebsiella oxytoca, Vibrio damsella, Enterobactor aerogens* and *E. coli,* and it was revealed that the crude extract is more effective against gram negative bacteria as tested (Jain et al., 2012). Pandey & Karanwal (2011) also demonstrated that the ethanolic extract of the seeds possesses significant antibacterial activity against the pathogenic bacteria, *P. aeruginosa, E. coli* and *S. aureus* with MIC value 230 µg/L. Similar kind of studies on antibacterial efficacy of different organic and aqueous plant extracts were also investigated (Bhattacharjee et al., 2006; Abubacker & Ramanathan, 2012; Bhardwaj et al., 2012). Both ethanolic and aqueous extracts of *A. mexicana* were found to have antibacterial potential against *Streptococcus mutans* and *Porphyromonas gingivalis* responsible for oral cavity infection; the alcoholic extract showed greater potency against *S. mutans* with MIC value of 125 µg/mL, while the aqueous extract against *P. gingivalis* with MIC value of 78 µg/mL (Rosas-Pinon et al., 2012).

Different leaf extracts (acetone, methanol, ethanol and aqueous) of *A. mexicana* were found to exhibit antipseudomonal activity against multidrug resistant *P. aeruginosa* isolated from clinical samples (Sahu et al., 2012). Twenty-seven strains have been used for this antimicrobial study and applying agar well diffusion method, the MIC and minimum bactericidal concentration (MBC) values noted for acetone, methanol and ethanol are 10, 8, 8 mg/mL and 32, 28, 24 mg/mL, respectively, thereby demanding that leaf of *A . mexicana* as complementary medicine in treating diseases caused by multidrug resistant strains of *P. aeruginosa*. Following the same procedure, another research group (Alagesaboopathi & Kalaiselvi,

Table 1. Chemical constituents of *Argemone mexicana.*

Compound	Plant parts	Reference
		Alkaloids
isocorydine (**1**)	apigeal parts	Israilov et al., 1986
berberine (**2**)	apigeal parts, seeds	Israilov et al., 1986; Ito et al., 1990; Chang et al., 2003b; Haisova & Slavik, 1975; Fletcher et al., 1993
dehydrocheilanthifoline (**3**)	whole plants	Chang et al., 2003b
dehydrocorydalmine (**4**)	whole plants	Singh et al., 2010c; Singh et al., 2009a
jatrorrhizine (**5**)	whole plants	Singh et al., 2010c
columbamine (**6**)	whole plants	Singh et al., 2010c
coptisine (**7**)	whole plants	Chang et al., 2003b; Ito et al., 1990
(+)-reticuline (**8**)	apigeal parts, aerial parts	Israilov et al., 1986; Hussain et al., 1983; Chang et al., 2003a; Rahman, 1994
protopine (**9**)	apigeal parts, seeds	Israilov et al., 1986; Ito et al., 1990; Chang et al., 2003b; Haisova & Slavik, 1975; Tripathi et al., 1999
allocryptopine (**10**)	apigeal parts	Israilov et al., 1986; Chang et al., 2003b; Haisova & Slavik, 1975.
cryptopine (**11**)	whole plants	Haisova & Slavik, 1975; Shamma, 1972
muramine (**12**)	whole plants	Nakkady et al., 1988
argemexicaine A (**13**)	whole plants	Chang et al., 2003b
argemexicaine B (**14**)	whole plants	Chang et al., 2003b
protomexicine (**15**)	aerial parts	Singh et al., 2012
13-oxoprotopine (**16**)	aerial parts	Singh et al., 2012
(-)-cheilanthifoline (**17**)	apigeal parts	Israilov et al., 1986; Haisova & Slavik, 1975; Shamma, 1972
(-)-scoulerine (**18**)	apigeal parts	Israilov et al., 1986; Haisova & Slavik, 1975; Shamma,1972
(+)-cheilanthifoline (**19**)	whole plants	Tripathi et al., 1999
(-)-stylopine (**20**)	Whole plants	Haisova & Slavik, 1975; Shamma, 1972
nor-sanguinarine (**21**)	whole plants	Haisova & Slavik, 1975; Tripathi et al., 1999; Rahman, 1994
chelerythrine (**22**)	whole plants	Chang et al., 2003b
sanguinarine (**23**)	seeds	Chang et al., 2003b; Haisova & Slavik, 1975; Fletcher et al., 1993.
oxyhydrastinine (**24**)	whole plants	Hussain et al., 1983; Rahman, 1994; Nakkady et al., 1988
thalifoline (**25**)	whole plants	Nakkady et al., 1988
argemexirine (**26**)	whole plants	Singh et al., 2010b
(+)-argenaxine (**27**)	aerial parts	Chang et al., 2003a
(+)-higenamine (**28**)	aerial parts	Chang et al., 2003a
(±)-tetrahydrocoptisine (**29**)	whole plants	Singh et al., 2010b
(-)-tetrahydroberberine (**30**)	whole plants	Chang et al., 2003b
dihydrocoptisine (**31**)	whole plant	Singh et al., 2010b
oxyberberine (**32**)	whole plants	Singh et al., 2010c; Singh et al., 2009a
N-demethyloxysanguinarine (**33**)	aerial parts	Chang et al., 2003a
pancorine (**34**)	aerial parts	Chang et al., 2003a
O-methylzanthoxyline (**35**)	whole plants	Chang et al., 2003b
nor-chelerythrine (**36**)	whole plants	Haisova & Slavik, 1975
arnottianamide (**37**)	whole plants	Chang et al., 2003b
(±)-6-acetonyl dihydrochelerythrine (**38**)	whole plants	Chang et al., 2003b; Nakkady et al., 1988; Migahid, 1978
dihydrosanguiranine (**39**)	seeds	Fletcher et al., 1993; Chang et al., 2003a
dihydrochelerythrine (**40**)	tissues	Chang et al., 2003a
angoline (**41**)	whole plants	Chang et al., 2003b; Chang et al., 2003a

8-acetonyl dihydrosanguiranine (**42**)	whole plants	Nakkady et al., 1988
8-methoxy dihydrosanguiranine (**43**)	aerial parts	Singh et al., 2012
dihydropalmatine hydroxide (**44**)	seeds	Ito et al., 1990
(-)-argemonine (**45**)	plant resins	Rahman, 1994; Shamma, 1972



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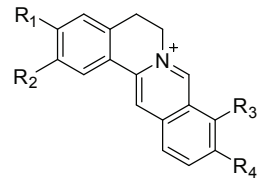

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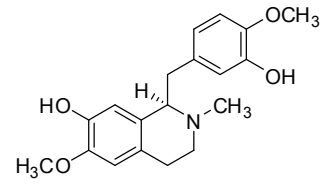
3 R_1=OCH_3; R_2=OH; R_3=R_4= -OCH_2O-
4 R_1=R_2=R_3=OCH_3; R_4=OH
5 R_1=OH; R_2=R_3=R_4=OCH_3
6 R_1=R_3=R_4=OCH_3; R_2=OH
7 R_1=R_2=R_3=R_4= -OCH_2O-



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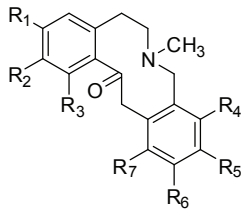
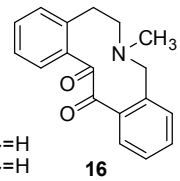


9 R_1=R_2=R_4=R_5= -OCH_2O-; R_3=R_6=R_7=H
10 R_1=R_2= -OCH_2O-; R_4=R_5=OCH_3; R_3=R_6=R_7=H
11 R_1=R_2=OCH_3; R_4=R_5= -OCH_2O-; R_3=R_6=R_7=H
12 R_1=R_2=R_4=R_5=OCH_3; R_3=R_6=R_7=H
13 R_1=R_2= -OCH_2O-; R_3=R_4=R_5=H; R_6=R_7=OCH_3
14 R_1=R_4=R_7=H; R_2=R_3=OCH_3; R_5=R_6=-OCH_2O-
15 R_1=R_2= -OCH_2O-; R_3=R_4=R_5=H; R_6=OH; R_7=OCH_3



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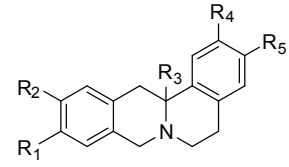
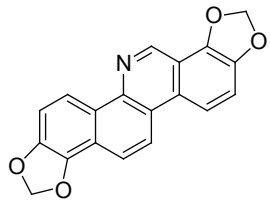


17 R_1=R_2= -OCH_2O-; R_3=H(β); R_4=OH; R_5=OCH_3
18 R_1=R_4=OH; R_2=R_5=OCH_3; R_3=H(β)
19 R_1=R_2= -OCH_2O-; R_3=H(α); R_4=OH; R_5=OCH_3
20 R_1=R_2=R_4=R_5= -OCH_2O-; R_3=H(α)



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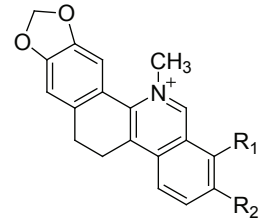
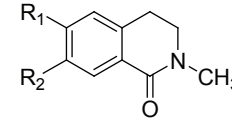
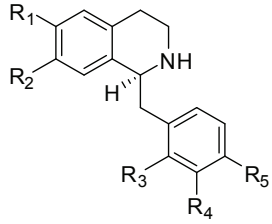


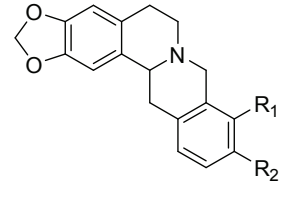
22 R_1=R_2=OCH_3
23 R_1=R_2= -OCH_2O-



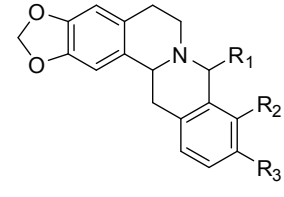
24 R_1=R_2= -OCH_2O-
25 R_1=OCH_3; R_2=OH



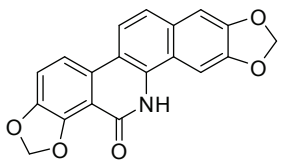
26 R_1=R_2=OH; R_3=R_4=R_5=H
27 R_1=R_2= -OCH_2O-; R_3=CH_2OH; R_4=R_5=OCH_3
28 R_1=R_2=R_5=OH; R_3=R_4=H



29 R_1=R_2= -OCH_2O-
30 R_1=R_2=OCH_3



31 R_1=H; R_2=R_3= -OCH_2O-
32 R_1= =O; R_2=R_3=OCH_3



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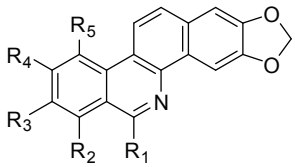
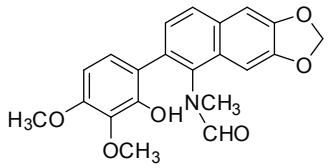


34 R_1=OCH_3; R_2=R_3= -OCH_2O-; R_4=R_5=H
35 R_1=R_2=R_3=H; R_4=R_5=OCH_3
36 R_1=R_4=R_5=H; R_2=R_3=OCH_3



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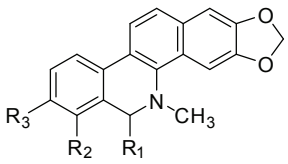
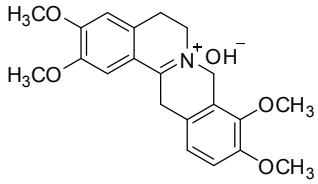


38 R_1=CH_2COCH_3; R_2=R_3=OCH_3
39 R_1=H; R_2=R_3= -OCH_2O-
40 R_1=H; R_2=R_3=OCH_3
41 R_1=R_2=R_3=OCH_3
42 R_1=CH_2COCH_3; R_2=R_3= -OCH_2O-
43 R_1=OCH_3; R_2=R_3= -OCH_2O-



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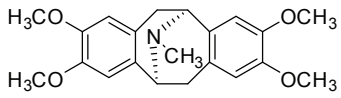

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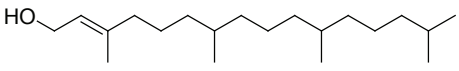
Terpenoids		
trans-phytol (**46**)	aerial parts	Chang et al., 2003a
β-amyrin (**47**)	leaves	Sukumar et al., 1984



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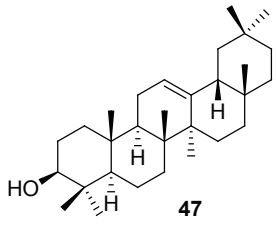
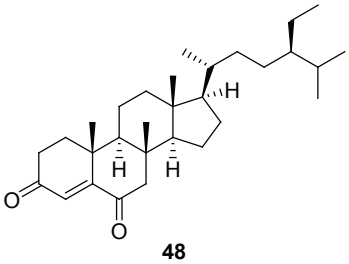


47

Steroids		
stigma-4-en-3,6-dione (**48**)	aerial parts	Chang et al., 2003a
β-sitosterol (**49**)	roots	Pathak et al., 1985



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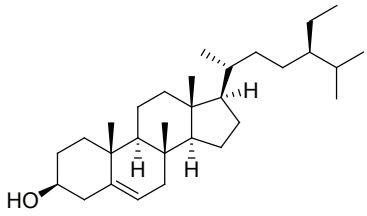
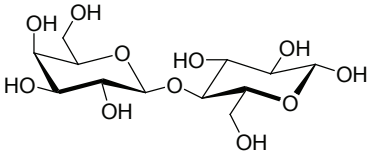


49

Carbohydrates		
lactose (**50**)	-	Sarraf et al., 1994
arabinose (**51**)	-	Sarraf et al., 1994



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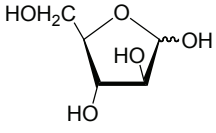


51

Long-chain alcohols		
triacotan-11-ol (**52**)	aerial parts	Sangwan & Malik, 1998
triacotan-6, 11-diol (**53**) (mexicanol)	aerial parts	Sangwan & Malik, 1998; Dinda & Banerjee, 1987
hentriacontane-3,20-diol (**54**)	flowers	Brahmachari et al., 2010
11-oxo octacosanoic acid (**55**)	seeds	Rahman & Ilyas, 1962; Gunstone et al., 1977
11-oxo triacontanoic acid (**56**)	seeds	Fletcher et al., 1993; Gunstone et al., 1977
9-oxo octacosanoic acid (**57**)	seeds	Gunstone et al., 1977
(+)-6-hydroxy-6-methyl-9-oxo-octacosanoic acid (argemonic acid) (**58**)	oil	Rukmini, 1975
myristic acid (tetradecanoic acid) (**59**)	oil	Badami & Gunstone, 1962
palmitic acid (**60**)	oil	Badami & Gunstone, 1962
stearic acid (**61**)	oil	Badami & Gunstone, 1962
arachidic acid (**62**)	oil	Badami & Gunstone, 1962
oleic acid (**63**)	oil	Badami & Gunstone, 1962
linoleic acid (**64**)	oil	Badami & Gunstone, 1962
mexicanic acid (**65**)	aerial parts	Dinda & Banerjee, 1987

$CH_3(CH_2)_nCH_3$

52 n=28 (11-ol)
53 n=30 (6,11-diol)
54 n=29 (3,20-diol)

$CH_3(CH_2)_nCO_2H$

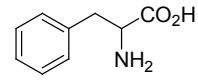
55 n=26 (11-one)
56 n=28 (11-one)
57 n=26 (9-one)
58 n=26 (6-CH_3; 6-OH; 9-one)
59 n=12
60 n=14

61 n=16
62 n=18
63 n=16 (9-ene)
64 n=16 (9,12-diene)
65 n=15 [4-ene(*Z*); 10-OH)

Amino acids		
cysteine (**66**)	leaves	Sukumar et al., 1984
phenylalanine (**67**)	leaves	Sukumar et al., 1984

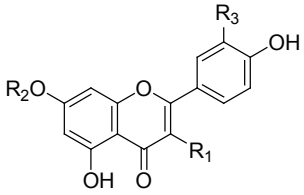
$HSCH_2(CH(NH_2)CO_2H$

66

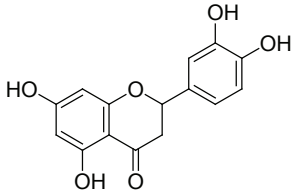


67

Flavonoids		
luteolin (**68**)	seeds	Harborne & Williams, 1983
eriodictyol (**69**)	seeds	Harborne & Williams, 1983
isorhamnetin-3-*O*-β-D-glucopyanoside (**70**)	leaves, flowers	Chang et al., 2003a; Sukumar et al., 1984; Rahman & Ilyas, 1962; Krishnamurthi et al., 1965; Anthal et al., 2012
isorhamnetin (**71**)	flowers	Pathak et al., 1985; Rahman & Ilyas, 1962
isorhamnetin-7-*O*-β-D-diglucopyanoside (**72**)	flowers	Rahman & Ilyas, 1962
isorhamnetin-3,7- *O*-β-D-diglucopyanoside (**73**)	flowers	Krishnamurthi et al., 1965
quercetin (**74**)	whole plants	Singh et al., 2011
quercetrin (**75**)	aerial parts	Singh et al., 2012
rutin (**76**)	whole plants, aerial parts	Singh et al., 2011; Singh et al., 2012
mexitin (**77**)	aerial parts	Singh et al., 2012



68 R_1=R_2=H; R_3=OH
70 R_1=OGlc; R_2=R_3=H
71 R_1=OCH_3; R_2=H; R_3=OH
72 R_1=OH; R_2=di-Glc; R_3=H
73 R_1=OGlc; R_2=Glc; R_3=H
74 R_1=R_3=OH; R_2=H
75 R_1=ORha; R_2=H; R_3=OH
76 R_1=ORut; R_2=R_3=H



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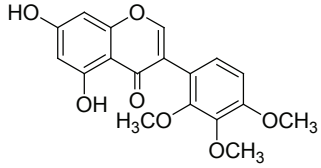
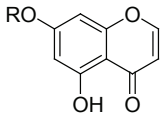
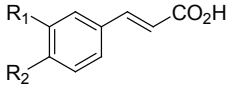


77

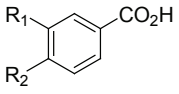
Phenolics and aromatic acids		
5,7-dihydroxy chromone -7-neohesperidoside (**78**)	seeds	Bhardwaj et al., 1982
tannic acid (**79**)	-	Singh et al., 2010a
caffeic acid (**80**)	-	Singh et al., 2010a
ferulic acid (**81**)	-	Singh et al., 2010a
benzoic acid (**82**)	-	Dwivedi et al., 2008
cinnamic Acid (**83**)	-	Dwivedi et al., 2008
vanillic acid (**84**)	Flowers	Pathak et al., 1985



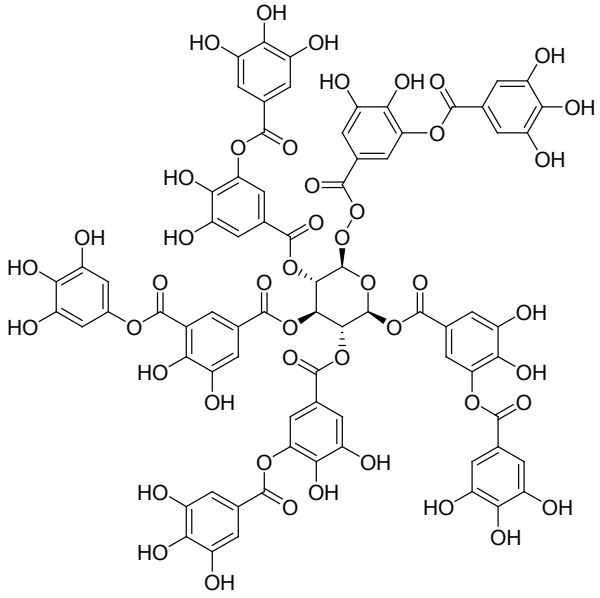
78 R=neohesperidosyl



80 R_1=R_2=OH
81 R_1=OCH_3; R_2=OH
83 R_1=R_2=H

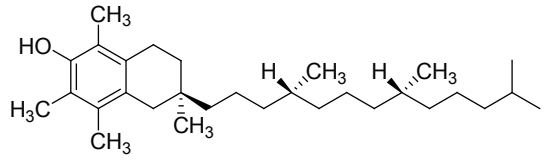


82 R_1=R_2=H
84 R_1=OCH_3; R_2=OH



79

Miscellaneous		
α-tocopherol (**85**)	aerial parts	Chang et al., 2003a
adenosine (**86**)	aerial parts	Chang et al., 2003a
adenine (**87**)	aerial parts	Chang et al., 2003a
benzphetamine *N*-demethylase	seeds	Dalvi, 1985
Sn-glycerol-1-eicosa-9,12-dienoate-2-palmitoleate-3-linoleate (**88**)	seeds	Saleh et al., 1987



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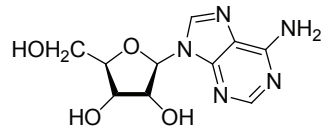

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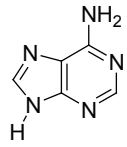

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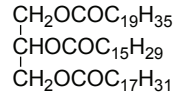

88

Glc: β-D-glucopyranosyl; Rha: α-L-rhamnopyranosyl; Rut: rutinosyl; neohesperidosyl: 2-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]

2012) evaluated the antibacterial activity of the aqueous, acetone, ethanol and chloroform extracts of the leaves, stems and roots of the plant against four strains of bacterial species, namely, *E. coli, Klebsiella pneumoniae, Bacillus cereus* and *S. aureus*, and found that stems extract possesses greater inhibitory activity compared to the roots and leaves extracts. They reported that ethanol stem extract showed greatest antibacterial activity against *K. pneumoniae* (22.86 mm) followed by acetone extract (17.35 mm) whereas the highest inhibition zone observed for ethanol extract of root against *B. cereus* was 20.05 mm and the maximum activity of ethanol leaf extract against *S. aureus* was 19.12 mm. Doss et al. (2012) evaluated the leaf extracts (aqueous and alcoholic) of *A. mexicana* to show significant antibacterial activity against a number of bacterial strains such as *Streptococcus agalactiae, Escherichia coli, Staphylococcus aureus* and *Klebsiella pneumonia* exhibiting zone of inhibition ranging from 9.0 to 15.0 mm and MIC values between 0.225 to 2.00 mg/mL (Doss et al., 2012). Osho & Afetunji (2010) investigated *in vitro* antimicrobial study with essential oil of the plant against some common bacterial and fungal pathogenic microbes and found promising results (Osho & Afetunji, 2010). The alkaloid, *N*-demethyloxysanguinarine (**33**), isolated from chloroform extract of *A. mexicana* has been found to show antibacterial activity against *K. pneumonia, S. aureus, E. coli* and *P. aeroginosa* with MIC value ranges from 1.5625 to 3.1250 mg/mL (Bhattacharjee et al., 2010). Rahman et al. (2011) reported that acetone, ethyl acetate and petroleum ether extracts of leaf and stem of *A. mexicana* exhibit efficiency to inhibit water borne pathogens such as *E. coli, Shigella* sp., *Staphylococcus* sp. and *Salmonella* sp. Petroleum ether extract of both leaf and stem shows maximum activity whereas ethyl acetate shows moderate activity but acetone extract remains inactive.

The alkaloids, dehydrocorydalmine (**4**) and oxyberberine (**32**), isolated from *A. mexicana*, were found to exhibit antifungal activities against some fungal strains such as *Helminthosporium* sp., *Curvularia* sp., *Alternaria cajani, Bipolaris* sp. and *Fusarium udum* (Singh et al., 2009a). Dehydrocorydalmine (**4**) was found to inhibit spore germination of all the fungal species studied. The spores of *Helminthosporium* sp. and *Curvularia* sp. did not germinate at all at 5000 ppm, while *Curvularia* sp. was found to be highly sensitive at 4000 ppm. *Alternaria cajani, Bipolaris* sp. and *Fusarium udum* were slightly resistant to this compound as they showed 11.74%, 10.15% and 5.74% germination, respectively, even at 5000 ppm. The other alkaloid, oxyberberine (32) inhibited 100% spore germination of *Bipolaris* sp. and *Curvularia* sp. at 5000 ppm. The germination of all the tested fungi was greatly inhibited at 1000 to 4000 ppm. *A. cajani, Helminthosporium* sp. and *F. udum* were slightly resistant at 5000 ppm (Singh et al., 2009a). A similar study was also carried out by the same group (Singh et al., 2010c) with a mixture of quaternary alkaloids and some phenolic acids (tannic acid **79**, caffeic acid **80** and ferulic acid **81**) of the plant. The experimental results also supported significant antifungal potentials of the test compounds.

Anti-HIV activity

The benzo[*c*]phenanthridine alkaloid, (±)-6-acetonyl dihydrochelerythrine (**38**) isolated from the methanolic extract of air-dried whole plants of *A. mexicana* was found to exhibit potent anti-HIV activity in H9 lymphocyte assay with EC50 value of 1.77 µg/mL (Therapeutic Index: 14.6) (Chang et al., 2003b).

Anti-inflammatory activity

The ethanolic extract of leaves of *A. mexicana* is reported to have significant anti-inflammatory and analgesic activity at a dose of 200 mg/kg in mice (Sharma et al., 2010). It is also reported that leaf extract of *A. mexicana* is able to show significant anti-inflammatory activity in rats; the investigators (Sukumar et al., 1984) are in opinion that the chemical constituents of the leaf extract such as isorhamnetin-3-*O*-β-D-glucopyanoside (**70**), β-amyrin (**47**), cysteine (**66**) and phenylalanine (**67**) might be responsible for such activity.

Wound healing activity

Ghosh and his group (2005) studied *in vivo* wound healing activity of the extract and the latex of *A. mexicana* on excision wound healing model — the results demonstrated significant wound healing activity of the test extracts that is comparable with the established drug, nitrofurazone; the tensile strength of the extract treated group was found to be higher than the latex treated group of animals on 12th post wounding day (Ghosh et al., 2005). Significant wound healing activity of petroleum ether and butanol fractions of ethanol extract of *A. mexicana*, containing some sterols, alkaloids, proteins and carbohydrates, was also reported in albino rat model by Patil and his group (2001). Dash & Murthy (2011) investigated wound healing activity using excision, incision and dead space wound models in Wistar albino rats with different extracts of *A. mexicana* leaves. The results revealed that the treatment with methanol extract of leaves of *A. mexicana* accelerated wound healing agent in rats.

Anti-stress and antiallergic activity

Both the polar extracts (*i.e.* aqueous and methanolic) of *A. mexicana* stems were evaluated to exert antiallergic as well as antistress efficacy in asthma developed by milk-induced leucocytosis and milk-induced eosinophilia at a dose of 50 mg/kg *i.p.* in albino mice model; both of the test extracts showed significant (p<0.05) decrease in leucocytes and eosinophils in vivo (Bhalke & Gosavi, 2009).

Vasoconstrictor and vasorelaxant effects

Paez-Sanchez and his group (2006) evaluated the vascular effects of methanolic extract of the aerial parts *A. mexicana* in rat aortic rings; the test extract was found to produce relaxation from contraction induced by noprepinephrine in a concentration-dependent manner. The overall experimental results demonstrated that the plant extract is able to induce a direct and dual specific effect upon the vascular smooth muscle, mediated, at least in part, by adrenergic receptors.

Anti-fertility activity

Three isoquinoline alkaloids, dihydropalmatine hydroxide (**44**), berberine (**2**) and protopine (**9**), isolated from the seeds of *Argemone mexicana* were evaluated to have inhibitory activity against spermatogenesis in dogs at the stage XII of late spermatids on administration at a dose of 30 mg/kg for 70 days; the numbers of spermatids were found to decrease by 46.5, 58.0 and 97.7% with compounds **44**, **2** and **9**, respectively (Gupta et al., 1990). In addition, the total numbers of mature Leydig cells were also decreased by compounds **2** and **9**. The relative antispermatogenic activity was reported to be: **9** > **2** > **44**.

Cytotoxic activity

Methanolic extract of *A. mexicana* leaves was found to exhibit cytotoxic activity against healthy mouse fibroblasts (NIH3T3) and three human cancer-cell lines (AGS, HT-29 and MDA-MB-435S) using the MTT [3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide] assay as reported by Uddin and his group (2011). The result showed that the extract is much active against MDA-MB-435S cancer cell line (IC50 1.82 mg/mL). Chang and his group (2003a) isolated a number of alkaloids from *A. mexicana* and evaluated cytotoxic activity of some of the isolated alkaloids *viz. N*-demethyloxysanguinarine (**33**), pancorine (**34**), (+)-argenaxine (**27**), (+)-higenamine (**28**), (+)-reticuline (**8**), angoline (**41**) and chelerythrine (**22**) to human nasopharyngeal carcinoma (HONE-1) and human gastric cancer (NUGC) cell lines. Chelerythrine (**22**) was found to be the most active among the series against NUGC cell lines, whereas (+)-argenaxine (**27**) showed only a moderate activity. On the other hand, angoline (**41**) inhibited both HONE-1 and NUGC cancer cell lines (Chang et al., 2003a).

Nematicidal activity

It was reported that the seed oil of *A. mexicana* is found to kill *Meloidogyne incognita* larvae in 17 min (Das & Sukul, 1998). The investigators found reduction of nematode infection in terms of root galling, root protein content and nematode population in soil and roots after application of aqueous mixture (0.2%) to soil and leaves of *Hibiscus esculentus* inoculated with *M. incognita.* Nath et al. (1982) investigated nematicidal properties of plant extracts of different parts of *A. mexicana* against *M. juvanica* in experimental test tubes of microplots. They reported that plant extracts are capable of lowering nematode population in the field while larvae were found

to be immobile in 24 h. Another research group (Shaukat et al., 2002) reported that juvenile mortality of *M. juvanica* is caused by different extracts of *A. mexicana* leaf material, out of which polar solvent extract found to be more effective. Again, seed soaking in aqueous extract of *A. mexicana* is found to reduce penetration of the nematodes juvenile in chick pea, thereby supporting nematicidal efficacy of the plant (Mojumder & Mishara, 1991).

Antifeedant activity

It is reported that petroleum ether and aqueous leaf extracts of *A. mexicana* were found to exhibit significant antifeedant activity against second stage larvae of *Henosephilachna vigintiocto puncata* Fabricius (Rao et al., 1990).

Lousicidal activity

Kumar and his group (2002) investigated lousicidal efficacy of aqueous leaf extract of *A. mexicana* by conducting mortality and repellency tests on tropicalis peters and found lousicidal activity with 73% mortality.

Mollucicidal activity

Two alkaloids, protopine (**9**) and sanguinarine (**23**), isolated from the plant are found to exhibit mollucicidal activity by decreasing significantly in the levels of protein, free amino acid, DNA and RNA in the nervous tissue of *Lymnaea acuminata* and also to cause a significant reduction in phospholipids levels and a simultaneous increase in the rate of lipid peroxidation in the nervous tissue of treated snails (Singh & Singh, 1999).

Effect on ileum organ

Capasso and his group (1997) studied the effect of the methanolic extract, its partially purified fraction, and the isolated pure compounds such as protopine (**9**) and allocryptopine (**10**) from *A. mexicana* on the morphine withdrawal effect in guinea pig isolated ileum; all the tested materials were observed to reduce the effect significantly and in a concentration-dependent manner, thereby suggesting the possible application of isoquinoline alkaloids as potential agents in the treatment of drug abuse. Further investigation in this direction also indicated that that $CHCl_3$/MeOH and MeOH extracts reduced the contractions of isolated guinea-pig ileum in a dose-dependent manner (Piacente et al., 1998); the effects were attributed to the active compounds identified as protopine (**9**), allocryptopine (**10**) and berberine (**2**).

Fungitoxic activity

A. mexicana seed extract is found to be fungitoxic against a number of fungal strains (Shah et al., 1992). The latex of the plant was found to exhibit toxicity against *Trichophytan mentagrophytes* (Asthana et al., 1989). The leaf extract of *A. mexicana* is found to exhibit significant fungitoxic activity against few fruit pathogens like *Alternaria alternata, Dreschlera halodes*, and *Helminthosporium speciferum* (Srivastava & Srivastava, 1998), and also against *Curvularia tuberculata* (Upadhyay & Rai, 1990), responsible for die-back diseases.

Antihelmintic activity

The aqueous plant extracts of *A. mexicana* find useful as significant antihelmintic against Indian earthworm *Pheritima posthuma* (Jaliwala et al., 2011). Majeed et al. (2011) also investigated antihelmintic activity of alcohol and aqueous extracts of leaves against *P. posthuma* and *Ascardia galli* in a dose dependent manner (6.25, 12.5, 25, 50, 100 mg/mL) and found that both the extracts show significant antihelmintic activity at a concentration of 100 mg/mL.

Larvicidal activity

Acetone fraction of the petroleum ether extract of seeds from *A. mexicana* exhibited larvicidal and growth inhibiting activity against the 2nd instar larvae of *Aedes aegypti* at concentrations from 25 to 200 ppm having IC50 values of 13.58 ppm and 17.43 ppm at field condition and laboratory condition, respectively (Sakthivadivel & Thilagavathy, 2003). Willcox et al. (2007) also reported significant larvicidal activity of acetone fraction of petroleum ether extract of *A. mexicana* seeds against 2nd instar larvae of *A. aegypti*. The leaf extract (in petroleum ether) of the plant also exhibits high larvicidal potential with LC50 value of 48.89 ppm against 3rd -4th instar larvae of *Culex quinquefasciatus* (Sakthivadivel et al., 2012). A synergistic action of this plant was also reported in their findings; larvicidal potential of leaf extract of *A. mexicana* increases (LC50 value of 28.60 ppm) when mixed (1:1) with that of *Clausena dentate.*

Antioxidant activity

Perumal et al. (2010) reported that ethanol extract of *A. mexicana* roots possesses antioxidant activity; at a dose of 100 µg/mL concentration, the extract showed high scavenging activity against DPPH (85.17%), ABTS (75.27%) and H_2O_2 (84.25%) radicals. Different extracts of *A. mexicana* leaves were also reported to exhibit superoxide anion scavenging

activity by Nitro blue tetrazolium assay with maximum percentage of free radical scavenging at a dosage of 200 µg/mL; acetone extract being the most active showing IC50 value double to that of L-ascorbic acid (Bhardwaj et al., 2011).

Anticancer activity

The ethanol extract of *A. mexicana* was reported to exhibit inhibitory activity against human cancer cell lines such as HeLa-B75 (48%), HL-60 (20.15%) and PN-15 (58.11%) (Gacche et al., 2011). Gali et al. (2011) also reported anticancer activity of methanolic extract of *A. mexicana* leaves against HeLa and MCF-7 cancer cell lines with IC50 values ranging from 1.35 to 1.2 µg/µL based on MTT assay results. The investigators also proved that the nature of this cytotoxic activity is apoptotic rather than necrosis and this activity may be due to the presence of flavonoid constituents in leaf.

Antidiabetic activity

Aqueous extract of aerial parts of *A. mexicana* at a dose of 200 and 400 mg/kg body weight was reported to have hypoglycemic efficacy in alloxan-induced diabetic rats; significant reduction in blood glucose levels, plasma urea, creatinine, triacylglyceride, cholesterol values and recovery in body weight compared to diabetic control rats and the standard drug treated rats are found when treated with the aqueous extract at a dose of 400 mg/kg body weight (Nayak et al., 2011). Rout et al. (2011) also found that the hydro-alcoholic extract of aerial parts of *A. mexicana* reduces fasting blood glucose levels in Streptozotocin-induced hyperglycemic Wistar albino rats at a dose of 200 and 400 mg/kg body weight; experimental results also showed that the extract dosage of 400 mg/kg body weight has effective hypoglycemic activity in comparison with the standard drug metformin at a dose of 300 mg/kg body wt. (Rout et al., 2011).

Antihepatotoxic activity

Das et al. (2009) showed promising antihepatotoxic activity of aqueous extract of *A. mexicana* stem in carbon tetrachloride-induced hepatotoxic male Albino Wistar rats; oral administration of 150 and 250 mg/kg body weight of the extract decreased serum asparate transaminase, alanine aminotransferase and alkaline phosphatase levels. Another research group (Sourabie et al., 2012) also investigated the anti-icterus activity of crude leaf powder of the plant against CCl4-induced hepatotoxicity in Wistar rats; the investigators observed significant increase in the levels of ASAT/GOT (aspartate aminotransferase), ALAT/GPT (alanine aminotransferase) and ALP (alkaline phosphate) while decrease in total bilirubin (TBIL) and direct bilirubin (DBIL) level tested at different doses of 125, 250 and 500 mg/kg b.w.

Miscellaneous activities

The Department of Traditional Medicine in Mali has recognized *A. mexicana* as a standardized phytomedicine for home-based management of malaria (Willcox, 2011; Schrader et al., 2012). Aqueous extract of the aerial parts of the plant was found to exhibit anti-parasite activity against the chloroquine-resistant K1 strain of *Plasmodium falciparum* with an IC50 value 5.89 µg/mL; in a randomized, controlled clinical trial, 89% of patients recovered clinically (95% with artemisinin based combination therapy), although parasite clearance was only achieved in 9% of patients (Schrader et al., 2012). No deterioration of severe malaria in patients >5 years and 1.9% deterioration in children ≤5 years were observed in the clinical trials (Willcox et al., 2011). As far as phytochemical constituents are concerned, *A. mexicana* contains the alkaloids berberine (**2**), protopine (**9**) and allocryptopine (**10**); although these compounds showed in vitro antimalarial activity (IC50 of protopine against the W2-strain 0.91 µM) (Avello Simoes Pires, 2009), berberine is purely absorbed, and the aqueous decoction of the plant was not active against *Plasmodium berghei* in the mouse model (Willcox et al., 2011; Schrader et al., 2012).

Recently, Amartha & Chaudhari (2011) reported on neuropharmacological applications of *A. mexicana*; the ethyl acetate and methanol extract of the whole plant of *A. mexicana* exhibited analgesic, locomotor and muscle relaxant activity in Wistar albino mice at an oral dosage of 100, 200 and 400 mg/kg b.w. Both extracts showed significant activities but methanol extract at a dosage of 200 mg/kg body weight was found to be more potent for central nervous system activities such as analgesic, anxiolytic and sedative effects (Amartha & Chaudhari, 2011). In addition, acetone leaf extract of the plant showed significant anti-termitic activity against the Formosan subterranean termite pest, *Coptotermes formosanus* Shiraki, in a dose-dependent manner; after 48 h of exposure, the plant extract exhibited LD50 and LD90 values of 253 and 1511 ppm, respectively (Elango et al., 2012). Table 2 offers a closer look at the bioactive chemical constituents of *A. mexicana*.

Toxicity and safety evaluation of *A. mexicana*

Few works on the toxicity and safety evaluation of *A. mexicana* are reported. Ibrahim & Ibrahim (2009) showed that the plant extract exhibits acute toxicity

Table 2. A quick look at the bioactive compounds from *A. mexicana.*

Compound	Biological activity	Reference
berberine (**2**)	Anti-fertility activity Effect on ileum contraction in guinea pig Antimalarial activity	Gupta et al., 1990 Piacente et al., 1998 Avello Simoes Pires, 2009
dehydrocorydalmine (**4**)	Antifungal activity	Singh et al., 2009a
(+)-reticuline (**8**)	Cytotoxic activity	Chang et al., 2003a
protopine (**9**)	Anti-fertility activity Effect on ileum in guinea pig Mollucicidal activity Antimalarial activity	Gupta et al., 1990 Capasso et al., 1997; Piacente et al., 1998 Singh & Singh, 1999 Avello Simoes Pires, 2009
allocryptopine (**10**)	Effect on ileum in guinea pig Antimalarial activity	Capasso et al., 1997; Piacente et al., 1998 Avello Simoes Pires, 2009
chelerythrine (**22**)	Cytotoxic activity	Chang et al., 2003a
sanguinarine (**23**)	Mollucicidal activity	Singh & Singh, 1999
(+)-argenaxine (**27**)	Cytotoxic activity	Chang et al., 2003a
(+)-higenamine (**28**)	Cytotoxic activity	Chang et al., 2003a
oxyberberine (**32**)	Antifungal activity	Singh et al., 2009a
N-demethyloxysanguinarine (**33**)	Cytotoxic activity	Chang et al., 2003a
pancorine (**34**)	Cytotoxic activity	Chang et al., 2003a
(±)-6-acetonyl dihydrochelerythrine (**38**)	Anti-HIV activity	Chang et al., 2003b
angoline (**41**)	Cytotoxic activity	Chang et al., 2003a
dihydropalmatine hydroxide (**44**)	Anti-fertility activity	Gupta et al., 1990
β-amyrin (**47**)	Anti-inflammatory & analgesic activity	Sukumar et al., 1984
cysteine (**66**)	Anti-inflammatory & analgesic activity	Sukumar et al., 1984
phenylalanine (**67**)	Anti-inflammatory & analgesic activity	Sukumar et al., 1984
isorhamnetin-3-*O*-β-D-glucopyanoside (**70**)	Anti-inflammatory & analgesic activity	Sukumar et al., 1984

in mice with LD50 value of 400 mg/kg body weight when administered intraperitoneally in the subjects having weight of 18-25 g and averagely aged between 4-6 weeks. Seed oil of the plant is also reported to show toxic effects in experimental animals, and such toxicity is supposed primarily due to sanguinarine (**23**). The alkaloid **23** is reported to be 2.5 times more toxic than its reduced product, dihydrosanguinarine (**39**), and both of them are interconvertable by simple oxidation and reduction process (Verma et al., 2001). It is also reported that alkaloid **23** is the causative component of glaucoma and epidemic dropsy, a disease resulting in neuroparalysis and death of several people (Verma et al., 2001). The mechanism of toxicity of *Argemone* oil is still not cleared but four different postulations have been described so far to explain the toxicity of sanguinarine — inhibition of Na^+/K^+ATPase, cell membrane damage by reactive oxygen species and lipid peroxidation, inhibition of DNA polymerase activity, and accumulation of pyruvate due to increased glycogenolysis (Verma et al., 2001). It is believed that sanguinarine present in *Argemone* oil is toxic and interferes with the oxidation of pyruvic acid which will accumulate causing dilation of capillaries and small arterioles (Husain et al., 1999). Sanguinarine (**23**) is reported to have hepatotoxic potential in rats (Dalvi, 1985), because a single *i.p*. dose (10 mg/kg) of the compound not only increased the activity of SGPT and SGOT substantially but also caused a significant loss of microsomal cytochrome P-450 and benzphetamine *N*-demethylase 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, thereby, establishing that the test compound **23** is a potential hepatotoxic alkaloid (Dalvi, 1985). A detailed study on the metabolism of sanguinarine characterizing the oxidative metabolites produced by human CYP1A1 and CYP1A2 and rat liver microsomes was recently reported by Deroussenta et al. (2010).

Since consumption of mustard oil adulterated with *Argemone* oil leads to a clinical condition, commonly referred to as "*Epidemic dropsy*" (Sood et al., 1985; Deroussenta et al., 2010), the *in vivo* clastogenic and DNA damaging potential of *Argemone oil* was investigated by Ansari and his group (2004) in mice. In their investigation, Swiss albino mice were

intraperitoneally administered 0.5, 1.0, 2.0 and 4.0 mL/kg body weight of the oil to analyze chromosome aberrations and micronucleus test, while 0.25, 0.5, 1.0 and 2.0 mL/kg body weight were given for alkaline comet assay. The frequencies of chromosomal aberrations and micronucleated erythrocytes formation in mouse bone marrow cells increased in a dose-dependent manner following the oil treatment. However, significant induction in chromosomal aberrations (83%) and micronucleated erythrocytes formation (261%) were observed at a minimum dose of 1.0 mL/kg. The results of comet assay revealed DNA damage in blood, bone marrow and liver cells following *Argemone* oil treatment. These results clearly suggest that single exposure of test oil even at low doses can produce genotoxic effects in mice (Ansari et al., 2004). The same research group (Ansari et al., 2005) also studied the *in vivo* DNA damaging potential of sanguinarine **23** 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 body weight, 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 24 h treatment of sanguinarine alkaloid **23**. 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 body weight. These results indicate that single exposure of the test compound causes DNA damage in blood and bone marrow cells of mice, which could be responsible for the genotoxicity of *Argemone* oil (Ansari et al., 2005). Upreti et al. (1989) showed that membrane destruction may be a possible mode of action for damaging liver, lungs, heart and kidneys of rats due to *Argemone* oil toxicity in rats. This oil, one of the adulterants encountered in edible oil, is also reported to be responsible for gall bladder cancer in Swiss albino rat-model (Mishra et. al, 2012).

Discussions and critical comments

The present article deals with an up-to-date review on the chemistry and pharmacology of *Argemone mexicana*, a useful medicinal plant finding applications in indigenous systems of medicine. The plant species belongs to the family Papaveraceae, informally known as the poppy family; plants under this family are an ethnopharmacologically important family of 44 genera and approximately 760 species of flowering plants. *Argemone mexicana* L. is used in different parts of the world for the treatment of several diseases including tumors, warts, skin diseases, inflammations, rheumatism, jaundice, leprosy, microbial infections, and malaria. Beyond alkaloids, the plant species is the source of a diverse kind of other chemical constituents that include terpenoids, steroids, carbohydrates, long-chain aliphatic alcohols and carboxylic acids, amino acids, flavonoids and other phenolics. Besides pharmaceutical efficacies, certain parts of the plant also show toxic effects as well; toxicity and safety evaluation of using this plant and its chemical constituents are also dealt in this review. Hence, an up-to-date information on the chemical and pharmacological knowledge on this plant may be helpful to guide researchers anticipating to undertake further investigations on this plant. Pharmacological and clinical studies of different chemical constituents of *A. mexicana* are found to be very promising, which calls for more-systematic research of this medicinal plant and its active principles; more in-depth and extensive studies in all relevant aspects are still warranted. We do anticipate that the present overview would boost the on-going development in this direction.

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Authors' contributions

The concept, design, and arrangement of the present review article were contributed by GB; he also analyzed all the data, supervised the process of drafting and contributed in finalizing the article through critical reading of the draft manuscript. DG and RR both contributed equally in collecting exhaustive searching on the databases, summarizing the data and preparing a draft. All the authors have read the final manuscript and approved the submission

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