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Anthology of Pharmacological activities from folklore medicine Artemisia

Shivani Dogra[a], Joginder Singh[a], Hem Raj Vashist[b]

[a]*Department of Microbiology, School of Bioengineering and Biosciences, Lovely Professional University, Phagwara, Punjab 144001*
[b]*CMJ University, Pharmacy Meghalaya, IN 793003*
Corresponding author: *Shivani Dogra, Research scholar, Department of Microbiology, School of Bioengineering and Biosciences, Lovely Professional University, Phagwara, Punjab 144001*
E.mail: *shvndogra241995@gmail.com*

Abstract

The name of Artemisia is derived from Artemis, the Greek mythological goddess of the moon and hunting. Artemisia is a genus comprising of over 20000 species belongs to the family of Asteraceae. Artemisia is a hardy herbaceous shrub known for valuable secondary metabolites in their plant. Common names for various species involve mugwort, southern worts, sagebrush, and wormwood. Presence of several bioactive ingredient participate in its broad spectrum bioactive activities through various mode of action. Because of its widespread pharmacological activity, it has been used in folklore medicine from ancient time as an antibacterial, antispasmodic, antiarthritic, anthelminthic agent and for the treatment of cancer, inflammation, malaria, menstrual related disorders and in hepatitis. This review includes the traditional uses and pharmacological activities of different Artemisia species.

KeyWords: Artemis**,** Artemisia, Secondary metabolites, Broad spectrum, Pharmacological activity, Folklore medicine.

Introduction

Artemisia is included in the tribe Anthemideae the wild Asteraceae family and comprises of over 500 species which are mainly found in the Asia, North America, Europe and Southern Africa [Bishop JF et al,1996, Abad MJ et al, 2013, Bora KS et al, 2011]. A large member of Asteraceae tribe members are important as flower, ornamental and used for essential oil extraction which exhibit several medicinal properties used in folk and modern remedy. The plants of this family are gaining good reputation in cosmetic and pharmaceutical industries [Teixeira da Silva J.A. et al, 2004]. Near 400 species of Artemisia have aromatic and bitter taste, main herb used in vermouth which is identified to give the characteristic bitter taste [Willcox M, 2009].
Globally, genus artemisia is widely used as traditional medicine with well known medicinal values. The therapeutic involves anti-malarial, antimicrobial, anti-inflammatory, antitumor, antioxidant, antispasmodic and many other [Maria, M. N., et al, 2019]. The volatile oil fraction of artemisia mainly involve 1,8-cineole, β-pinene, thujone, artemisia ketones, camphor, caryophyllene, camphene and germacrene D [Pande A.K.et al, 2017] which act by different mechanism. Solubility of these components had been described in different solvents like]i) 1,8-cineole is soluble in water miscible with ether, alcohol, glacial acetic acid, oil, soluble in ethanol, ethyl ether, slightly soluble in carbontetrachloride. ii) β- pinene is monoterpene colourless liquid soluble in alcohol but not in water. iii) Thujone is soluble in water. iv) Artemisia ketone is practically insoluble in water. v) Camphor is slightly soluble or insoluble in water and have anti-inflammatory and analgesic.vi) Caryophyllene is soluble in ethanol, oils and ether but insoluble in water. vii) Camphene is insoluble in water. viii) Germacrene D is sesquiterpene and soluble in chloroform, dichloromethane, DMSO, ethyl acetate.
The solubility of artemisinin had been studied in 12 different organic solvents ethanol, butanol, acetone, ethyl acetate, isopropyl acetate acetonitrile, hexane, heptane, 2-butanone, methyl tert- butyl-ether and toluene as well as in three binary solvent mixtures of ethyl acetate+ethanol, ethyl acetyate +acetone, and ethanol +acetone within the temperature range of 284.10 and 323.15 K [Gybaah, JN et al, 2010]. Similarly, the solubility of artemisinin been reported in seven different solvents including methanol, ethyl acetate, acetone, acetonitrile, cyclohexane, toluene and chloroform over the temperature range from (283.15 to 323.15) K at atmospheric pressure. The solubility of artemisinin was then reported to increase with the increase in

temperature in all the used solvents [Liu Y et al, 2009]. The best temperature with regard to thermal decomposition and high productivity was reported to be at 80 ^{o}C for artemisinin. Also, conventional percolation and soxhlation was found to be fit for the extraction of artemisinin [Sixt M et al, 2017].

1. Antibacterial activity

i) The antibacterial activity of hexane, ethanolic and methanolic extracts of *Artemisia annua*, *Artemisia vulgaris* and *Artemisia absinthium* was assessed by Bauer-Kirby agar disk diffusion assay against five gram positive and two gram negative bacteria and one fungal strain. They reported ethanolic extract of *Artemisia annua* more effective against tested microorganism than ethanolic extract of other two species. They found that all extracts of all three species showed moderate effects against gram negative bacteria [Antonia P et al, 2009].
ii) Methanolic extracts and essential oil of the plants have been reported for antimicrobial activity using disk diffusion against 8 bacterial and 1 fungus. *Staphylococcus aureus* was reported to be most sensitive bacteria. *A scoporia* most effective plant against *Candida albicans* [Sura E et al,2012]
iii) Artemisinin and bioactive compounds derived from *in vitro* plantlets of *Artemesia annua* were reported to exhibit antimicrobial activity. These components have been found to be effective against gram positive and gram-negative bacteria but inactive for *Candida albicans.* Their antibacterial activity was reported similar to that of streptomycin [Appalasamy S. et al, 2014].
iv) Essential oil extracted by hydrodistillation from three species like *Artemisia absinthium*, *A. sieberi* and *A. scoparia* had tested against different fungal and bacterial strains. Four common compounds i.e., limonene, camphor, terpene-4-ol and ethyl 2- methylbutyrate were analyzed by combining gas chromatography-flame ionization detector with the gas chromatography-mas spectroscopy technique. The antimicrobial activity of essential oil from all species were evaluated by broth microdilution method. Researchers reported the growth inhibiting potential of essential oil extracted from all three species of Artemisia [Ati, HY et al,2020].
v) Stem, Root and Shoot extraction with petroleum ether, acetone, 90% ethanol on water were tested ethanol extract exhibit very moderate activity against *B. subtilis*, against *S aureus* and no activity against Methicillin staphylococcus aureus (MRSA). In their study it was concluded that acetone is a better solvent for the extraction of *A. annua* than ethanol [Mensah AA et al, 2015].
vi) Chloroform, butanol, and ethyl acetate extract of *Artemisia indica along* with *Medicago falcata* and *Tecoma stans* reported to show high inhibitory activities against *E. coli, P. aeruginosa, and S. aureus*. However, *Artemisia indica* reported to show inhibitory activity against *Salmonella typhi* [Javid T et al, 2015]
vii) Although the essential oil for all species shows common component but different in their composition. Because of different composition variability in antifungal activity was reported by the researchers. The found components were reported as davanone and its derivatives. The compounds with silphiperfolane skeleton, estragole, davanone oil, beta thujone, sabinyl acetate, herniarin, cis-chrysanthenyl acetate, 1,8- cineol and terpineol have been added as the main component of Artemisia essential oil [Obistioiu D et al, 2014].
viii) Effective results for antimicrobial activity of aqueous, alcoholic, petroleum ether, and benzene extract from the leaves of *Artemisia vulgaris* had tested against *Escherichia coli* and *Staphylococcus aureus* by using agar diffusion method in comparison with Gentamycin, Ampicillin, Tetracycline, Ciprofloxacin and Ofloxacin antibiotics as standard [Hiremath SK et al, 2011].
ix) The work as antimicrobial agent on different species of Artemisia was reported. *Artemisia lavendulaefolia* DC, *Artemisia scoparia* and *Artemisia capillarie*s showed antimicrobial activity against the *Streptococcus mutans* clinical isolates and reference strain [Seo JA et al, 2009].
x) Essential oil of *Aremisia vulgaris* had identified as sesquiterpenes, sesquiterpene hydrochlorides and oxygenated monoterpenes. Researchers reported the antibacterial and antifungal activity against *Staphylococcus aureus* and *Candida albicans*, respectively. Also, researchers found negative result for antihelmintic activity against *Haemonchus contortus* [Malik S et al, 2019].

2. Hepatoprotective activity

i) Researchers has showed *in vivo* hepatoprotective activity of the aqueous extract of *Artemisia absinthium L.* in mice. From histopathological study of mice liver they demonstrated that the aqueous extract of *A. absinthium* have significantly attenuated the extracellular necrosis. They reported that the extract reduced lipid peroxidation in the liver tissue and restore activities of defence antioxidant enzymes glutathion peroxidase and superoxide dismutase towards normal level [Amat N et al, 2010].

ii) The alcoholic extract of *Artemisia absinthium* was reported to lower the liver toxicity in rats trough reducing the serum level of alanin aminotransferase, aspartate aminotransferase and oxidative damage at the dose of 50mg/kg [Mohammadian A et al, 2016]. Similar in a study the preventive and curative effects of *Artemisia absinthium* on acetaminophen and CCL_4 - induced hepatotoxicity have been reported. In this study researchers concluded that the crude extract of A. *absinthium* exhibits hepatoprotective action partly through microsomal drug metabolizing enzymes inhibitory action [Gilani, A.U.H et al, 1995].
iii) Researchers has reported the antioxidant and hepatoprotective activity for the standardize blend of *Schisandra chinensis*, *Artemisia capillaris* and *Aloe barbadensis*. This compostion was shown to replenished depleted hepatic glutathion in association with an increase of hepatic superoxide dismutase and also an unexpected synergistic protection from liver damage was reported [Yimam M et al, 2016]
iv) .The nephroprotective and hepatoprotective activities of *A. absinthium* methanol and ethylacetate extract had reported against diclofenac induced toxicity. From the histopathological study researchers observed that *A. absithium* exhibits the potential to decrease hepatic and renal necrosis induced by diclofenac [Antonio SGW et al, 2020].
v) The aqueous extract of *C. dorserifolia* aerial parts and the polar fraction of *Artemisia annua* have been experimented for the characterization of hepatoprotective metabolites. Researchers reported that both the extract restored the level of liver enzymes compared to CCl_4 intoxicated group. They identified more than 50 phenolic compounds for both the extracts and reported that hydroxycinnamoyl quinic acid and flavonoids mainly responsible for their significant hepatoprotective activity [Askary HE et al, 2019]
vi) The water extract of *Artemisia annua* have been reported to exhibit effective treatment against non-alcoholic fatty liver disease. The inhibition of accumulation of lipids in HepG2 cells and protection of cells from oxidative stress mediated damage through the activation of antioxidant enzymes and its own scavenging activity [Choi EY et al, 2020].

3. Antihelmintic activity

i). Anthelmintic activity of *Artemisia vestita* wall ex DC and *Artemisia martima* L. extract against *Haemonchus controtus* has been reported by using sheep as experimental animal.The result obtained were compared with ivermectin to check the plant extract on survival of infective L3 and adults under *in vitro* condition. Researchers infected sheep with L3 stage of 5000 larvae/sheep then plant extract was given to it orally. They reported the significant decrease infaecal egg count of *H. controtus* after post treatment period for both plant extracts [Irum S et al, 2015]
ii). The antihelmintic activity of Artemisia *indica* and *Artemisia roxburghiana* methanolic extract assessed against mixed infection of gastrointestinal nematodes in small ruminants using albendazole 10 % as standard drug. Baermann technique was used first time in larval mortality assay and was proved to be effective. The maximum antihelmintic activity of methanolic extract for both the plants reported at the concentration of 50mg/ml but as compared to albendazole their statistically insignificant results were reported at the same dose [Khan S et al,2015] .
iii). Antihelmintic activity of aqueous extract from *Artemisia absinthium* L and *Malva sylvestris* L was reported against *Haemonchus contortus* in sheep. In the result researchers added insufficient intensity in the reduction of parasitic infection because of the low varieties and lack in the synergy of plant polyphenols and combination of bioactive compounds from both the plants. From the results they concluded that the study add new knowledge on the antihelmintic effects of dry medicinal plant as dietary supplement [Mravcakova D et al 2020]
iv). Antihelmintic activity of artemisinin from *Artemisia annua* had been evaluated for anthelmintic activity in ruminants. The aqueous, 0.1 % sodium bicarbonate, dichloromethane and ethanol extract evaluated *in vitro* by egg hatch test and bicarbonate extract which was evaluated *in vitro* by the egg hatch test. The result showed that the artemisinin and *Artemisia annua* treated sheep maintained the blood haematocrit throughout the experiment but in untreated sheep significant decrease in haematocrit was reported [Cala AC et al, 2014].
v). The antihelminthic activity of crude aqueous extract of *Artemisia absinthium* to find out the alternative of praziquantel was experimented against *Hymenolepis nana.* The plant extract was reported to induce worm paralysis, death and ultrastructural alterations, such as tegumental damage, lipid accumulation, and destruction of the nephridial canal and the intrauterine eggs, in a dose dependant manner. The significant

reduction in the egg count per gram of faeces were also reported in the rat treated with *A. absinthium* extract [Beshay EVN et al, 2018].

vi). Chloroform, methanol and aqueous extract of *Artemisia indica* reported for antihelmintic activity against *Pheretima posthuma*. chloroform and methanol extract at the concentration of 6.25mg/ml reported to show efficient antihelmintic activity and only chloroform extract at concentration of 2.5mg/kg was reported significant in the comparison of standard drug Piperazine citrate [Sarnim G et al, 2013]

vii). The *in vitro* antihelmintic activity of ethanolic and aqueous extract of aerial part of Artemisia campestris had investigated on eggs and adults of *Haemonchus contortus.* Hatching of the eggs were reported at the concentration of 2mg/ml for both the extracts and complete inhibition reported at concentration of 0.83 and 1.00 mg/ml respectively for both ethanolic and aqueous extracts respectively. Researchers after chemical analysis also reported that both the extracts dominated by flavonoids and among them quercetin and apigenin were found to be main flavonoids. The results from their research indicates that *Artemisia campestris* is a effective alternate treatment as an antihelminthic drug and also the flavonoids quercetin and apigenin can be used to formulate effective drug against *H. contortus* [Akkari H et al, 2014].

4. Neuroprotective activity

i) The neuroprotective effect of *Artemisia judaica* extract have been reported in a murine diabetic mode. Researchers tested the neuroprotective effect of *A. judaica* extract against neuronal deficits in diabetes model induced by high fat dose and streptozotocine. In the result of this work researchers added that the extract of *A. judaica* elevated significantly the neuronal impairment associated with diabetes and sugggested extract may be use to elleviate neurological impairments in diabetic patients [Albasher G et al, 2020]. Neuroprotective effect of methanolicextract of *Artemisia absinthium* L. reported on focal ischemia and reperfusion induced cerebral injury. Researchers found the significant attenuation of the brain oxidative stress, damage and behavioural deficits by pre treatment with methanolic extract of *Artemisia absinthium* [Bora K et al, 2010].

ii) Anti-inflammatory and immunomodulatory activity of *Artemisia annua* L. has been examined in mouse model of contact hypersensitivity. From their result data they reported that topical administration of artemisinin could effectively suppress contact hypersensitivity response and induced T cell proliferation, they reported that artemisinin gave inhibitory effect on the production of IL-17 and diminish IL-6.these results indicated the potential of artemisinin as effective in the treatment of immune related diseases [LiTan et al,2012].

iii) Anti-inflammatory and immunosuppressive effect of flavones isolated from ethanolic extract of *Artemisia vestita* has been reported. The extract was found to possess significant inhibitory activity against the picryl chloride induced contact hypersensitivity in mice. Researchers isolated nine flavones from the extract by column chromatography as pectolinarigenin, Jaceosidin, crsilineol, crisimaritin, hispidulin, qurecetin, methoxytricin, acacetin and apigenin. These compounds were reported for their inhibitory activity on the proliferation and activation of T cells *in vitro*. In result they suggested that crisilineol, 6-methoxyttricine and apigenin played a significant role to inhibit T cell proliferation and activation in the bioassay [Yin Ye et al, 2008].

iv) Evaluation of *in vitro* immunomodulatory effect of methanolic extract of Artemisia indica wild has been assessed in chicken lymphocyte culture system through lymphocyte proliferation assay. In their result they reported significant upregulation of 11.76 % and 12.018 % in B and T cell proliferation in the presence of B and T mitogen as compared to control [Ruwali P et al, 2018].

v). The in vitro immunomodulatory and anti-inflammatory activity of *Artemisia khorassanica* was evaluated. In the result researchers reported that the ingredients present in the plant can be utilize to regulate the immune responses and to improve several ailments related to immune disturbances [Rabe ZTS et al, 2015].

vi) Anti-inflammatory and immunomodulatory potential of methanolic extract of *Artemisia amygdalina* D was evaluated using carrageenan paw oedema model using Wistar rats for inflammation and sheep red blood cells pacific haemogglutination titre and delayed type hypersensitivity assay in Balb/C mice for observing the effect of extract on immune system. In result, plant methanolic extract was reported to possess anti-inflammatory and immunosuppressant activity [Mubashir K et al,2013].

vii). Ethanolic extract of *Artemisia abrotanum* evaluated in a study for its immunomodulatory activity by testing humor and cellular immune response to the antigen challenging in healthy albino mice RBCs at the dose of 100 and 200 mg/kg/day. Researchers found significant decrease in delayed type hypersensitivity

response as well as the humoral response to sheep RBCs was reported in their result. They added ethanolic extract of *A. abrotanum* shows non singnificant decrease in primary antibody titer and significant decrease in secondary antibody titre at the dose of 200mg/kg/day [Joghee S et al, 2013].

5.Antimalarial activity

i) A suppressive anti-paracytic activity of ethanolic extract from the leaves of *Artemisia vulgaris* had reported upto 87.3% and 79% for 1000 and 500mg/kg against *Plasmodium berghei* murine model [Bamunuarachchi G et al, 2013].Similarly the screening of antimalarial activity on *Plasmodium berghei* in mice had been reported for *Artemisia absinthium* extract [Zafab M et al,1990].

ii) Antimalarial activity of green silver nanoparticals prepared from two artemisia species *A. Arbotanum* and *A. arborescens* had been reported for antimalarial activity against *Plasmodium falciparum.* Both the silver nanoparticle for *A. arbotanum* and *A. arborescens* had were dsignated as A. AgNPs (1) and A. AgNPs (2) in their work. Researchers reported A. AgNMPs effective to stop the growth of parasite in ring stage [Avitabile, E et al, 2020].

iii) The six organic extracts of *Artemisia nilagirica* had been evaluated for antimalarial activity against *Plasmodium falciparum.* All n-hexane, chloroform, petroleum ether, ethanol, methanol and aqueous extracts were noticed to possess promising antiplasmodial activity [Panda S, 2018].

iv) Exiguaflavone A and B extracted from *Artemisia indica* wild had been reported to possess *in vitro* antimalarial activities against *Plasmodium falciparum* at the dose of $4.60*10^{-6}$ and $7.05*10^{-6}$. , methylenedioxybenzofuran were also added in the study [Chanphen R et al, 1996].

v). The comparative study between flavonoids and artemisinin have been reported to show which one is mainly responsible for antimalarial activity in *Artemisia annua.* Before it was assumed that either flavonoid alone responsible for antimalarial activity or act with artemisinin or give synergism with artemisinin. In this study it was cleared that only artemisinin is responsible for the antimalarial activity in *A. annua* [Czechowski T et al, 2019].

vi). Ten different polarity extracts from *Artemisia aucheri* Bioiss and *Artemisia armeniaca* Lam. had screened for their antimalarial properties by *in vitro* beta hematin formation assay. The dichloromethane extracts of both plants were reported to show significant antimalarial activity. Researchers isolated seven fractions from dichloromethane extracts of both plants by vacuum liquid chromatography using silica gel and different polarity solvents mixture. Seven fractions were isolated from dichloromethane extracts of both plants. Two fractions from extract from *A. armeniaca* and four fraction from *A. aucheri* were reported to show significant antimalarial activity [Mojarrab M et al, 2014]

vii).Similarly, ten extracts by cold meceration method from two species of Artemisia namely *A. kopetdaghensis* and *A. turcomanica* had been evaluated for their antiplasmodial activity.researchers assessed antimalarial activity for all extracts beta haematin formation method.in result the dichloromethane extract of *A. Koptaghensis* and petroleum ether extract of *A.turcomanica* found to show remarkable antimalarial activity. Ether extract of *A. turcomanica* possessed greatest antimalarial activity and can be used to formulate novel antimalarial formulation [Mojarrab, M et al, 2016].

Antimalarial market formulations (Table 1) Artemisinin is mainly known for antimalarial activity which is commercial with following products in market.

6. Cardioprotective activity

i). Cardiovascular effect of aqueous extract of *Artemsia afra* and long chain fatty acid mixture and scopolatin isolated from the plant had been tested in rabbits. Long chain fatty acids were found to induce hypotensive effect and in that the diastolic pressure had noted more than the systolic. Scopoletin was observed to induced dose dependent decrease in inotropic activity eith appreciable chronotropic effect. Also researchers added that the aqueous extract of *A. afra* exhibit hypotensive activity *in vivo* and biphasic effect on heart *in vitro.* From their result they concluded that *A.afra* and its constituents can be utilize to manage hypertensive conditions [Gauntai AN et al, 2008]. The cardioactive activity had been given for *A. sieberi* along with nephroprotective, hepatoprotective and antidiabetic potential in rat [Ishaid FI et al,2012].

ii) The hypotensive activity of aqueous extract of *Artemisia herba* alba was reported in spontaneously hypersensitive rat. Lyophilized dose of 150mg/kg for 20 days daily were administered to rats. After eight days of administration significant decrease in systolic blood pressure was recorded and at the end of treatment

sustained decrease was found. Researchers also corded no change in heart rate during 20 days of drug administration they observed urinary sodium and potassium excretion from fourth day of experiment and also increase in chloride excretion from day eight, it was reported that the extract have no effect on plasma angiotensin-converting enzyme activities [Zeggwagh NA et al, 2008].

7. Antiepileptic activity

i). Anticonvulsant activity of diethylether, chloroform and ethanol extracts of *Artemisia nilagirica* was reported by using phenylenetetrazole induced convulsion in swiss albino mice. From the result they added that among the extract ethanol extract showed better result than chloroform result but were less potent than diazepam treatment. They observed no anticonvulsant activity for diethyether extract [Santilna KS et al, 2014].
ii). The antiepileptic activity and essential oil composition from the aerial parts of *Artemisia dracunculus* L. had been assessed. Dose and time dependent antiseizer activity of essential oil was reported in both maximal electroshock and pentylenetetrazole model of experimental seizure. Monoterpenoids presence in the essential oil was supposed to be responsible for anticovulsant and sedative effects they added [Sayyah M et al, 2004].
iii) The effect of hydroalcoholic extract of *Artemisia persica* was investigated on pentylenetetrazole-induced seizure and memory impairment in mice. Significant increase the serum and brain level of malondialdehyde. The extract was reported for significant improvement in pentylenetetrazole-induced memory impairment. Also, the extract of *A. persica* was reported to have protective effect against phenyltetrazole-induced seizure [Daneshkhah M et al, 2019].
iv) Anticonvulsant activity of essential oil from the fresh leaves and flowering tops of the *Artemisia abrotanum* collected from the Nilgiri Hills reported in pentylenetetrazole injected swiss albino mice. Sigificant delay in one set of myoclonic seizures was reported at the dose of 100mg/kg. No significant changes in the convulsive parameters was recorded at the dose of 400 and 800mg/kg in comparision with control vehicle group [Dhanabal SP et al,2007]

8. Antiasthmatic and bronchodilator activity

i) The folkloric use of *Artemisia vulgaris* in hyperactive gut and airway disorders have been proved by confirming anticholinergic and Ca^{2+} antagonist mechanism. Also, it was reported that the antisplasmodic and bronchodilator activities of artemisia vulgaris acted through muscarinic receptor and calcium reflux blockage. Researchers study these activities in the crude extract of the plant in isolated tissue preparation of guinea pig trachea and rabbit jejunum as well as in the *in vivo* castor oil induced diarrhoea and bronchodilator techniques. The reported presence of secondary metabolites like saponin coumarin alkaloids, flavonoids, sterols tannins and terpenes were found to cause dose dependent relaxation of jejunum spontaneous contraction. The extract was reported to inhibit the carbachol induced concentration in a pattern similar to that of dicyclomine. Also the protective effect for castor oil induced diarrhoea in rodent was reported in similar manner [Khan AU et al, 2009].
ii) Bronchodilatory activity of butanolic extract *Artemisia caerulescens* subsp. gallica on anaesthetized gunea pigs and in vitro preparation of guinea pig trachea was reported. In this study researchers found the antagonistic action of the extract on acetylcholine and histamine induced bronchoconstriction [Moran A et al, 1989]
iii) Chloroform extract of the *Artemisia annua* L. has found to relax the mouse airway smooth muscle. Researchers prove chloroform extract of *Artemisia annua* L. by using patch-clamp technique and ion channel blockers to explore the mechanism to find the mechanism for the relaxant effect of chloroform extract. The extract was reported to eliminate acetylcholine and K^+ elicited contractions of mouse tracheal rings. In the result of this work researchers reported that the chloroform extract almost fully abolished voltage dependent ca^{2+} channel current and markedly enhanced large conductance ca^{2+} activated K^+ channel on airway smooth muscle cells [Huang J et al, 2017].
iv) *Artemisia absinthium* have been reported to show a higher antitussive effect on cough induced by ammonia compared with the other studied medicinal plants [Saadat S et al, 2018].
v) Expectorant, Antitussive and Antiasthmatic activity of *Artemisia annua* was reported for its essential oil. Significant expectorant action of its volatile oil was reported using phenol red method in mice. Mice were fumigated with strong ammonia to check the antitussive action of volatile oils from *A. annua* whereas its

antiasthmatic action was performed by contrast-pressure histamine-acetylcholine spraying method in whole guinea pigs. Single 0.24 mL/kg dose of volatile oil after intragastric administration significantly reduce in grade IV responses to histamine given by number of animals used in the study [YuYu, Tu et al,2017].

9. Antiulcer activity

i) Dihydro-epidexyarteanniuin B, deoxyartemisinin and artemisinin from the sesquiterpene lactone-enriched fraction had extracted from ethanolic extract of *Artemisia annua* L. These compounds were tested on ethanol and indomethacin induced ulcer models. Only first and second compounds were reported to decrease the ulcerative lesion index. Artemisinin did not show any cytoprotection in the experimental model used here [Foglio MA et al, 2002].

ii) Significant decrease in the volume of gastric juice in rats had been reported for the extract from *Artemisia absinthium* L. with this acid output and peptic activity but no effect was reported on mucin activity in acetylsalicylic ulcerated rats. Also, the significant decrease in ulcer index was reported [Shafi N et al 2004].

iii) The protective effect of aqueous extract of *Artemisia campestris* had given against aspirin induced gastric lesion and oxidative stress in rat. Researchers suggested potent antiulcer and anti-oxidant activity of *A. campestris*. They found that up to an extent the ability of its aqueous extract to counteract the gastric mucosal damage might be related to the safety of sulfohydryl group in addition to its opposite effect on some intracellular mediators like free ion, calcium and hydrogen peroxide [Sebai H et al, 2014].

iv) The antiulcer activity of ethanolic extract of *Artemisia absinthium* checked on lesions due to *Leishmania* major parasites in BALB/C mice. In this study researchers selected 40 mice and in each mouse 3 to 5×10^3 amastigotes of standard *Leishmania major b* strain were inoculated intravenously in their tail base region. From the result researchers concluded that the oral administration of extract showed an effect similar to standard drug Glucantime® and led to repair of ulcer. They also reported that *A. absithium* extract by oral administration caused ulcer size reduction and tissue repair [Azizi K et al, 2016]

10. In Renal disease

i) The effect of ethanolic extract of *Artemisia deserti* was reported on pathology and function of wistar rat kidney.no significant change in urine and uric acid was observed in this study but significant change in creatinine was observed some rats. Histological changes were also observed in the kidney. Congestion of inflammatory cells, glomerular atrophy, and degeneration of the renal tubules were reported [Noori A et al, 2014].

ii) Study on *Artemisia absinthium* performed for poorly responsive early- stage IgA nephropathy had done by using pilot-controlled trial as study design. Monthly assessment of urine protein- creatinine ratio and blood pressure measurement were also performed. The significant decrease in urine protein creatinine ratio and also significant mean arterial blood pressure [Krebs S et al 2010].

iii) A study to check the proficiencies of *Artemisia scoparia* against CCl_4 induced DNA damage and renal toxicity in rat was had performed. Significant reduction in the DNA damage in rats after co-administration of methanolic extract of *Artemisia scoparia* intraperitoneally had been reported. From the result researchers reported about the therapeutic role of the extract in oxidated stress related disorder in kidneys [Sajid M et al 2016].

iv) The effect of Wormwood extract had been investigated for reduction of renal toxicity in Azathioprine treated rat. From the result researchers reported that wormwood extract reduces the pathological effects of azathioprine in rats due to its antioxidant properties [Farzaneh F et al, 2015].

v) Protective effect of *Artemisia asiatica* extract and its active compound Eupatilin have been studied for their renal protective action against Cisplatin. The results of the study suggested that both extract of *Artemisia asiatica* and eupatilin bearing the ability to cure the Cisplatin induced renal damage [Park JY et al, 2015].

vi) Nephroprotective activity for hydroalcoholic extract of *Artemisia arborescens* against oestroprogestative induced kidney damage in wistar rats had evaluated. From the result researchers reported the *A. arborescens* showed protection against the oestroprogestative induced neptrotoxicity by restoring the activity of kidney. This protective effect had been mainly attributed to antioxidant properties as well as the presence of phenolic acids and flavonoids after HPLC detection [Dhibi S et al, 2016].

11. Diuretic activity

i) High therapeutic efficacy of *Artemisia annua* and *Artemisia afra* reported for the treatment of diabetes by collecting data from five case reports. This result had been reported first time for these Artemisia species teas in humans. They reported that blood sugar could be lowered to standard level and added it as polytherapy where various constituents from plants participated for synergistic work with no toxicity and side effect [Munyangi J et al, 2020].

ii) Ethanol extract of Artemisia absinthium have been evaluated for its antidiabetic activity in alloxon induced diabetic rats taking glibenclamide for treatment. Significant decrease in the blood glucose level was determined in *Artemisia absinthium* ethanolic extract treated rats and also in the glibenclamide treated group. In the conclusion of this study researchers added that *A. absinthium* acts in similar manner as glibenclamide [Daradaka, HM et al, 2014].

iii). Petroleum ether, ethyl acetate, methanol and hydroethanolic extract of *Artemisia amygdalina* had been tested for their antidiabetic activity in streptozotocin induced diabetic rats. After biochemical, physiological and histopathological study of diabetic rats significant hyperglycaemic activity have been reported. From the histopathological study of the treated rats it get cleared that extract exerted the regenerative protective effect on β-cells of pancreas in diabetic rats [Ghazanfar K et al 2014].

12. Antidepressant activity

i) Polyphenol and flavonoid fraction from the aerial part of *Artemisia absinthium* at its flowering stage had been checked for its antidepressant activity by forced swimming and tail suspension method on swiss albino mice. Better antidepressant activity was observed in combination of all components present in the extract except polyphenol fraction [Ahangar N et al, 2011]. In a similar study, antidepressant and antioxidant activity of *Artemisia absinthium* L. at its flowering stage had been determined by forced swimming and tail suspension method. *A. absinthin* extract showed significant reduction in immobility period in both the model. Extract dose at 500 mg/kg was reported to show similar action as that of 10 mg/kg dose of imipramine which was used as standard drug in this study [Mahmoudi M et al, 2009].

ii) Comparison between *Artemisia dracunculus* and *Stachys lavandulifolia* antidepressant activity, their phenolic and flavonoid contents. In this study the antidepressant activity of extracts was compared by using forced swimming and tail suspension method. Because of the major role of phenolic and flavonoid contents their quantity had also been checked. No significant difference of phenolic components were observed but *S. lavandulifolia found* to have more flavonoid contents. Both the plant extracts were reported to have antidepressant activity but it was reported less for *A. dracunculus* [Jahni R et al,2019]

iii) The chlorogenic acid isolated from *Artemisia capillaris* thumb had evaluated for its antidepressant effect. The expression of the pituitary gland and hypothalamic POMC mRNA or plasma β-endorphin levels were found to be increased by *Artemisia capillaries* thumb extract or its flavonoids administered orally. Antidepressant activity was studied using forced swimming and tail suspension method and rotarod test in a chronically restrained immobilization stress group in mice. Significant reduction in immobility time was recorded and in rotarod test, the riding time remained similar to that of the control group at 15rpm. From these results researchers concluded that the flavonoid isolated from *A. capris* thumb shows a potent antidepressant activity [Park S.H et al, 2010]

13. Larvicidal activity

i). The larvicidal activity of ethanolic leaf extracts of *Artemisia campestris* var. *glutinosa* and *Artemisia molinieri* on mosquito *Culex pipiens* Linnaeus. *Artemisia molinieri* was reported to show more larvicidal activity than *Artemisia campestris* var. *glutinosa* after 48 hours of exposure but calculated lethal concentration after 48 hours were found less for both plant extracts. Researchers also added that the cultivation of *Artemisia molinieri* having a value as environmental friendly biocide and its culture development may be of interest for both pesticide activity and conservation purposes [Masotti V et al, 2012].

ii). Methanolic extract of root, stem and leaf of *Artemisia vulgaris* had evaluated for its larvicidal activity against *Culex quinquefasciatus.* By exposing larvae of *Culex quinquefasciatus.* for 24 hours to different concentration of (in ppm) methanolic extract of leaf roots and stem researchers noted that the leaves extract resulted significantly higher mortality than that of leaves and stem. In the conclusion they indicated that the methanolic extract of *Artemisia vulgaris* may be a good source of preparation for pest control especially for mosquito control [Llahi, Ikram et al, 2013].

iii) The larvicidal efficacy of volatile oils from *Artemisia absinthium* and its three major chemical constituents against six mosquito vectors.
Percentage of toxicity with lethal concentration of toxicity for methanolic extract leaves, stem and roots was studied (Table 2) and after hydrodistillation of leaves, stem and roots, researchers analysed the volatile oil by GC-MS spectrometry (Table 3). After this study researchers concluded that the essential oil from the *A. absinthium* could be effective in mosquito larvicides and can be employed in malaria and arbovirus control programs [Govindarajan M et al, 2016].
iv) Larvicidal activity of *Artemisia vulgaris* L., stem essential oil was evaluated against the dengu vector *Aedesaegypti.* The compositionofthe volatile oil was reported as camphor, camphene, α-thujone, 1,8- cineole, γ-muurolene and β-caryophyllene. The 100 % larval mortality was reported from 500 ppm oil solution with an exposure time of 8 hours. In conclusion researchers concluded that such natural insecticide could be used in the place of synthetic insecticides [Govindaraj S et al, 2013].
v) larvicidal and repellent activity of leaf essential oil from *Artemisia vulgaris* against vector of dengue fever *Aedes aegypti*. Highest mortality rate was reported after 24 hours exposure period of third and fourth stage (Table 4). From the histopathological study of larvae researchers found cleared that 50% concentration of the essential oil showed the highest repellent activity at 60 min. protection time against *A. aegypti* female mosquitoes. To clarify the results molecular docking calculation was performed with the active components from volatile oil as ligand and NS3 protease domain as receptor [Balasubramani S et al, 2018]. (E)-β-caryophyllene was reported to bind strongly with NS3 protease domain than other components and was found to be responsible insecticidal activity.
vi). Larvicidal activity of four solvents leaf extracts from *Artemisia annua* taking four different concentrations had been assessed against *Aedes aegypti* under laboratory condition. Aqueous, ethyl acetate, chloroform and ethanol were selected as four solvents for extraction. Among all, ethanol and aqueous extracts were reported to show higher mortality of *A. aegypti*. Both the extracts were reported to show concentration dependent toxicity against *A. aegypti*. From the result of the study it become clear that both these extract from the leaves of artemisia annua can be utilized for management of dengue fever mosquitoes [Alanazi NA et al, 2018].
vii) Ethanolic leaf extract and flower extract and leaf essential oil from *Artemisia vulgaris* had been evaluated for larvicidal effect against *Aedes aegypti* larvae of Myanmar strain. The leaf and flower extract were reported to exhibit strong larvicidal activity against third and fourth stage of Aedes larvae whereas the leaf essential oil were reported to protect from the bites of Aedes mosquitoes [Mya MM et al, 2016].
Viii) Chemical composition and larvicidal activities of essential oils of medicinal plants, *Artemisia sieberi* and *Tanacetum balsamita* against malaria vector, *Anopheles stephensi* have been reported (Table 5) [Kazempour S et al, 2020].

14. Wound healing activity

i) Wound healing activity of five and ten percent *Artemisia absinthium* essential oil have been reported. After GC-FID and GC-MS analysis essential oil was reported as camphor and chamazulene. Significant effect had been reported for ointment prepared with ten percent essential oil. This ointment enhances skin wound epithelialization and speeded up the healing process [Benkhaled A et al, 2020]
ii) *Artemisia sieberi* petroleum ether extract have been evaluated for second degree burn on mice in comparison with one percent ointment silver sulfadiazine and negative control which was kept untreated. *A. sieberi* extract was found to heal via significantly decreased inflammation, increased granulation tissue, hydroxyproline content and healing percentage in comparison to negative control [Katadj JK et al 2016].
iii) The wound healing activity of ethyl acetate fraction of *Artemisia vulgaris* linn., had been evaluated. Along with ethyl acetate the methanolic and chloroform extracts were fractionated to check the chemical component of the plant. The ethyl acetate fraction yielded the highest phenol and flavonoids than other two. Researchers selected ethyl acetate fraction to evaluate the wound healing activity after dissolving in tween 80 to make 25% and 50 % suspension of it. The wound healing activity was tested in the excision wound model and incision wound mode against 2% Mupirocin ointment as standard drug. The wound healing capacity of this was reported to be similar as compare to standard [Tolentino MS et al, 2016].
iv) Aqueous extract of *Artemisia campestris* have been reported to exhibit major important wound healing activity due to the antioxidant, anti-inflammatory activities of its constituents [GhlissiZ et al,2016].

v) Essential oil from *Artemisia Montana* evaluated for skin regeneration using normal human keratinocytes. Essential oil at the dose 50,8.5 µg/ml increased cell proliferation in HACats. From this result it was reported that the essential oil is efficient to induce proliferation and might increase the synthesis of collagen in human skin keratinocytes and can be utilize for wound healing [YoonMS et al, 2014].

vi) Wound healing potential of *Artemisia dracunculus* had assessed in combination with chitosan nanoparticle biofilm on MRSA infected excisional wound. From the result of this study *Artemisia dracunculus* with chitosan nanoparticlebiofilm resulted in significant improvement in full thickness wound healing. Also, the utilization of *Artemisia dracunculus* with chitosan nanoparticle biofilm was justified [RanjbarR e al, 2018].

vii) The antimicrobial and wound healing efficacy of reaction mixture of hot methanolic extract of leaves of *Artemisia absinthium* prepared in milli-Q water and assed for its antimicrobial activity in Gram-positive and Gram- negative activity. Also, the wound healing activity of reaction mixture had been screened in male rats by comparing with standard povidone iodine [SultanMH et al, 2020].

The study time frequency for various pharmacological activities from different Artemisia species represents in Table 6 and Fig. 1

In Ayurveda whole plant (Panchanga) of *Artemisia vulgaris* (Table 7) has been mentioned for its ability to reduce all ailments in the body as 'Tridoshahara' (all dosha in body) .

Conclusion

Genus Artemisia is a versatile plant having several inherent biological activities. The present review is a compilation of different pharmacological activities for different species of Artemisia. The plant is having remarkable antimalarial, antibacterial, anthelmintic, neuroprotective larvicidal and wound healing effect. Though several antimalarial market formulations were found to be reported, the plant need novel product formulation for market. From the study it is concluded that the plant needs more study for the renaissance of its medicinal properties in pharmaceutical sciences, cosmetics and for the formulation of new drugs from its active constituents.

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Declaration of interest.

The authors are declaring no conflict of interest

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