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Clematis Species: Phytochemicals and Pharmacological Effects- A Report

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ABSTRACT: The genus *Clematis* has been a source of various traditionally useful and pharmacologically active species. Many plants of this genus are prominently climbers and woody vines. The species are mosly wild however; few are grown as ornamental plants. The species *Clematis apifolia, Clematis ganpiniana, Clematis graveolens*, and *Clematis terniflora* were selected to study on their traditional use, chemical composition and pharmacological effects reported in literature. In folklore these species are used as antispasmodic, carminative, diuretic, anodyne, antidote, diuretic and sedative agents. The triterpenoid saponins are the dominant compounds of these species flavonoids, alkaloids, lignans, coumarins, steroids and volatile oils have also been reported. The pharmacological effects evaluated are antioxidant, cytotoxic, antimicrobial, antidiabetic, hepatoprotectve, and anti-inflammatory activities. As such these species has emerged as good source of traditional medicines. The chemical compounds isolated from these species have been reported for their pharmacological effects. Although, few experimental studies validated their traditional claim, but uncharacterized crude extracts were employed in most of the activities. Such species need to be explored properly for their bioactive principle and exploited as potential drug. The review will help the researchers to select medicinally potential species of *Clematis* for future research.

KEYWORDS: *Clematis apifolia, Clematis ganpiniana, Clematis graveolens, Clematis terniflora,* Triterpenoid Saponins.

INTRODUCTION

Genus *Clematis* L. (Ranunculaceae) consists of 295 species indigenous in north and south temperate, oceania and tropical African mountains [1]. In India, it is represented by thirty-two species including four sub species and five varieties [2]. The triterpenoids saponins, are the dominant components of this genus. The species are used traditionally for various ailments by the native and nomadic communities. The crude extract and isolated pure compounds possess extensive pharmacological effects such as anti-inflammatory, antitumor, analgesic, anti-inflammatory, arthiritis, antioxidant, antipypretic, antimicrobial, apoptosis, cardioprotective and cytotoxic agents as per their traditional claim. The extensive study revealed that monodesmodic saponins, flavonoids and alkaloids components present in these species were mainly responsible for most of the biological effects. As a source of herbal medicines for traditional use, chemical constituents diversity and various biological effects the species *Clematis apifolia, Clematis ganpiniana, Clematis graveolens*, and *Clematis terniflora* were selected for the study. In folklore, these species are used as antispasmodic, carminative, diuretic, anodyne, antidote, diuretic and sedative agents. The chemical compounds isolated were saponins, flavonoids, alkaloids, lignans, coumarins, steroids and volatile oils. The present study revealed that hederagenin aglycone based new saponins isolated were 1 from *C. apifolia*, 3 from *C. ganpiniana*, and 1 from *C. graveolens* and oleanane aglycone based were 1 from *C. apifolia and 5* from *C. terniflora*. The pharmacological activities have been antioxidant, cytotoxic, antimicrobial, antidiabetic, hepatoprotectve, and anti-inflammatory activities. The main objectives of the review are as under;

a) to evaluate the diversity of isolated chemical compounds on the basis of their structural and biological activities.
b) to evaluate whether the traditional use of *Clematis* species have validation in scientific methods in clinical studies.
c) to evaluate whether structure-activity relationship carried out from the isolated compounds.

The data has been compiled using various databases like Google Scholar, Scopus-Elsevier, PubMed, AGRICOLA and Shodhganga. The review will help the researchers to select the species for future investigations.

TRADITIONAL USES OF CLEMATIS SPECIES:

Clematis apiifolia- *The plant is native to central and southeast China, Korea, central and south Japan [3].* C. apiifolia *is a vigorous deciduous climbing plant with slender, woody stems, growing around 1 - 6 metres tall. The plant is harvested from the wild for local use as a food and medicine. It is an ingredient in commercial cosmetic products, and is sometimes grown as an*

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ornamental. Young shoots - cooked and used as a vegetable. The dried leaves are a tea substitute. The roasted leaves are also used as food. The plant is carminative and digestive. It is also used in the treatment of dysentery. An infusion of the stems is used in the treatment of colic, dysentery, dyspepsia and sweating [4].

***Clematis graveolens*-** occurs as woody climber, generally present along the road banks and fences of agricultural fields. It is distributed from temperate (Asia), Western Asia (Afganistan), Xizang (China), to the tropical (Himachal Pradesh, Jammu Kashmir, Utter Pradesh, Nepal and Pakistan in the altitude range between 900-3000m [5]. The plant is harvested from the wild for local use as a medicine. It is sometimes grown as an ornamental. In traditional medicins the powdered stem, combined with powdered *Bistorta milletii*, is drunk with warm water as a treatment of coughs and colds [6]. The squeezed seeds are applied to the foreheads in order to relieve headaches [6]. The long, yellow-coloured root has an exceedingly bitter taste. It is considered to be antiseptic and cooling. It is prescribed as a gargle in the treatment of ulcerated throat, as an application in treating dog and serpent bites, and is also used in cases of haemorrhage from the stomach or throat [7]. The leaves of this plant possess distinct character of causing blister in the mouth [8]. The tincture prepared in the spirit is used for treatment of goiters and tumors of the neck [9].

Clematis terniflora (**sweet autumn clematis**, **sweet autumn virginsbower**) is a plant in the buttercup family, Ranunculaceae. It is native to northeastern Asia (China, Japan, Korea, Mongolia, Russia (Siberia), Taiwan) [10]. It was introduced into the United States in the late 1800s as an ornamental garden plant, and has naturalized in many of the eastern states. It is considered a Category II invasive plant in Florida (north and central) and some other eastern states, meaning invading native plant communities but not yet seen as displacing native species [11]. *C. terniflora* is a vine with opposite, pinnately compound leaves, on climbing stems. The flowers are white, borne in fall. The whole plant is used as antidote, antiscrofulatic and ophthalmic agent and in the treatment of corneal opacities [12]. In traditional Chinese medicine, it is used to treat tonsillitis, rheumatoid arthritis, and prostatitis [13]. Consistent with these uses, the medicinal properties of *C. terniflora* include anti-nociceptive and anti-inflammatory activities [14].

CHEMICAL CONSTITUENTS FROM *CLEMATIS* SPECIES:

The genus *Clematis* is distributed with wide range of chemical constituents such as triterpenic saponins, alkaloids, flavonoids, coumarins, volatile oils, organic acids, macromolecules, polyphenols etc. The triterpenoid saponins constitute the major class of constituents. The aglycone of *Clematis* species is five-ring triterpenoid oleanane structure (B), 23-OH hederagenin (A), 2, 23-OH Arjunolic acid (C) and quinatic acid (D) (Fig-1). These saponins are both monodesmodic and bidesmodic with glycosylation at Agl C←3 and Agl C←28 except in few cases at Agl C←23. The sugar moieties attached are D-Glucose (Glc), L-Rhamnose (Rha), L- Arabinose (Ara), D-xylose (Xyl), D-Ribose (Rib). The tabulation of saponins is attempted to present in order of increasing oligosaccharide chain on either side. In some cases oligosaccharide chains are also substituted with acetyl, caffeoyl (CA), isoferuloyl (IF), p-methoxy cinnamyl (MC), 3, 4-dimethoxy cinnamyl (DMC) moieties. Till date more than 120 new saponins are isolated from Clematis, including 70 oleanane, 50 hederagenin and 2 gypsogenin type [15].

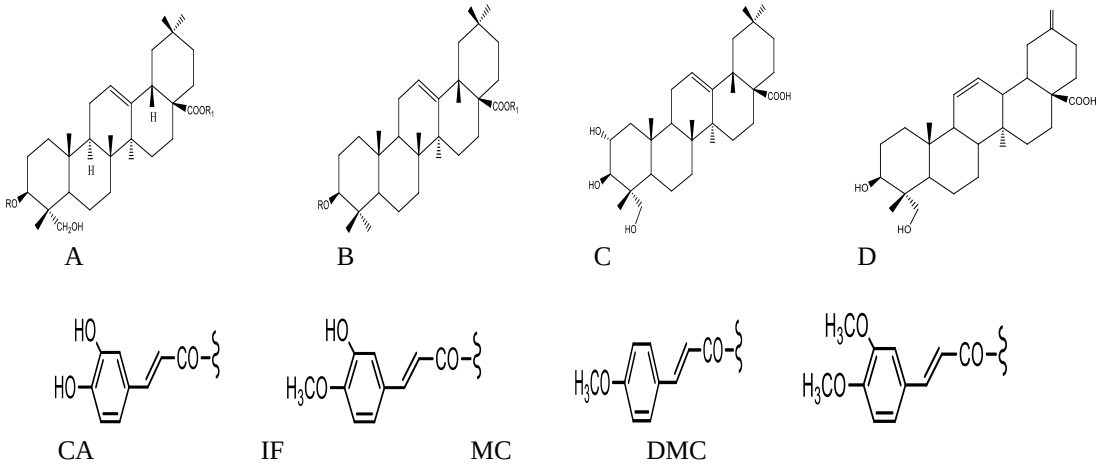

Fig-1 The aglycones from *Clematis*: A-hederagenin, B-oleanane, C-arjunolic acid, D- quinatic acid; moieties- caffeoyl (CA), isoferuloyl (IF), p-methoxy cinnamyl (MC), 3,4-dimethoxy cinnamyl(DMC).

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Table-1 Saponins from Clematis species.

Compound	Structure	Source	Ref.
	Hederagenin Type-A		
Hederagenic acid	R =H R^1 = H	*C. apiifolia*	[16]
Clematiganoside A	R= Rib(1→3)Rha(1→2)Ara R^1 = Rha(1→4)Glc(1→6)Glc	*C. ganpiniana*	[17]
Hederacholichiside F	R= Glc(1→4)Rha(1→2)Ara R^1 = Rha(1→4)Glc(1→6)Glc	*C. ganpiniana*	[17]
Prosapogenin CP11	R= Glc(1→4)Glc(1→4)Rib(1→3)Rha(1→2)Ara R^1 = Rha(1→4)Glc(1→6)Glc	*C. ganpiniana*	[17]
Clematograveo-lenoside A	R= Rib(1→3)Rha(1→2)[Glc1→4)Glc(1→4)]Ara R^1= Rha(1→4)Glc(1→6)Glc	*C. graveolens*	[18]
	Hederagenin 11,13- dien-28-oic acid		
5.*	R= Rib(1→3)Rha(1→2)Ara R^1 = H	*C. argentilucida*	[19]
	Oleanane Type-B		
Oleanolic Acid	R = H R^1= H	*C. apiifolia*	[20]
Clematernoside E	R=Glc[(2←1)IF][(3←1)Glc(6←1)Rha][(4←1)Glc](1→4)Glc(1→4)Rib(1→3)Rha(1→2)Ara R^1 = Rha(1→4)Glc(1→6)Glc	*C. terniflora*	[21]
Clematernoside I	R=Glc[(4←1)Glc][(6←1)Rha(2←1)Glc](1→3)Glc(1→4)Glc(1→4)Rib(1→4)Rha[(2←1)IF](1→2)Ara R^1 = Rha(1→4)Glc(1→6)Glc	*C. terniflora*	[21]
Clematernoside J	R=Glc[(4←1)Glc(2←1)Glc][(6←1)Rha](1→3)Glc(1→4)Glc(1→4)Rib(1→4)Rha[(2←1)IF](1→2)Ara R^1 = Rha(1→4)Glc(1→6)Glc	*C. terniflora*	[21]
Clematernoside K	R=Glc[(2←1)IF][(3←1)Glc][(6←1)Rha(2←1)Glc](1→4)Rib(1→3)Rha(1→2)Ara R^1 = Rha(1→4)Glc(1→6)Glc	*C. terniflora*	[21]

Nearly, 30 species have been characterized through isolation and structure determination of saponins from *Clematis.* In the present study the hederagenin aglycone based (-OH group at C-23 position) new saponins identified from species are 3 from *C. ganpiniana*, 1 from *C. apiifolia* and 1 from C. graveolens. The oleanane aglycone based (-H at C-23 position) (Fig.-1) 5 from *C. ternoflora* and 1 from *C. apiifolia* new saponins have been identified (Table-1). The sugars and their point of attachment with the sugar chain saponins have large structural diversity. Out of 56 reported saponins, 45 are bidesmodic and 11 are from monodesmodic class. In monodesmodic saponins glycosylation of sugars at (C-3-O←1)Ara(2←1)Rha(3←1)Rib in mostly present however, substitution and further enlargement of chain with glucose, rhamnose and xylose, galactose sugars have also been encountered. Among bidesmodic saponins glycosylation at (C-3-O←1)Ara(2←1)Rha(3←1)Rib and (C-28-O←1)Glc (6←1)Glc(4←1)Rha are commonly observed (Table-1). However, the sugar chains on either side are further enlarged with glucose, rhamnose, galactose and xylose moities.

Steroids, Lignans, Coumarins, Macrocyclic, Volite oils from Clematis species

The clematis species has been subjected to isolate various biologically active compounds other than saponins. The alkaloids identified are - phenanthrene, indolecarbonate, clemaine from *C.erecta, C. mandshurica, C. parviloba*. The flavonoids from Clematis species are mainly flavonols, flavones, isoflavones, flavanones, xanthones and their glucosides, the aglycones of which are mainly apigenin, kaempferol, luteolin and quercetin. The lignans from *Clematis* are mainly eupomatene lignans, cyclolignans, monoepoxylignans, bisepoxylignans and lignanolides from *C. viornae L., C. vitalba, C. purpurea, C. armandii, C. hexepetala, C. intricate, C. stans, C. terniflora*. Steroids - stigmasterol, β-sitosterol, α, β-amyrin and their glycosides. Macrocyclic compounds- clemoarmanosides, bercholine, clemahexapetoside Clemochinenoside, Ibotanolide from *C.*

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armandii, *C. hexapetala*. The volatile oils- palmitic acid, myristic acid, caffeic acid, ferulic acid, inositol, coniferaldehyde, vanillin, pluchoic acid, protocatechualdehyde, caffeic acid mainly from *C. armandii*, *C. delavayi*, *C. crassifolia*, *C. hexepetala* and *C. montana* (Table-2).

Table-2 Steroids, Lignans, Coumarins, Macrocyclic, Volite oils from Clematis species.

Compound	Source	Ref.
Alkaloids		
Corytuberine, b-magnoflorine, a-magnoflorine, Me-7-methoxy-3-indolecarbonate, Clemaine	C. erecta, C. mandshurica, C. purpurea	22, 23,24
Flavonoids		
Apigenin, Vitaboside, Kaempferol, Clematine, Hesperetin, Daidzein, Genistein, Luteolin, Quercetin, Rutin, Tangeritin, Isovitexin-6-O-e-p-coumarate, 3,5,7,3' tetrahydroxy flavone	C. viornae L., C. vitalba, C. purpurea , C. armandii, C. hexepetala, C. intricate, C. stans, C. terniflora	25,25,27,28, 29, 30,31
Lignans		
Armandiside, Clemastanin B, (þ)-lariciresino-4-O-β-D-glucopyranoside, Salvadoraside, episyringaresinol, Clemaphenol A, (þ)-pinoresinol , Clemastanin A, Isolariciresinol	C. armandii, C. stans, C. parviloba, C. chinensis C. hexapetala	32,30,34,33, 28
Steroids		
Stigmasterol, Daucosterol, β-sitosterol, β-amyrin, α-amyrin and their glycosides	C. apiifolia, C. hexapetala, C. montana, C. purpurea	35,36,37,24
Coumarins		
4,7-dimethoxy-5-methyl-coumarin, Siderin, Scopoletin	C. delavayi, C. ligusticifolia, C. intricate	38,39,40
Macrocyclic compounds		
Clemoarmanosides A, B, Bercholine, Clemahexapetoside A, B, Clemochinenoside A, B, Ibotanolide B	C. armandii, C. hexapetala, C. chinensis, C. crassifolia	27,36,33,23
Phenolic compounds		
Ibotanolide B, Calceolarioside B, Clemomandshuricoside A, B, C, Tricosanol, Heptacosanoic acid	C. crassifolia, C. mandshurica, C. terniflora	41,23,31
Anemonin, Protoanemonin, Ranunculin	C. angustifolia, C. apiifolia, C. flammula	43,35,42
Volatile oils		
Palmitic acid, Myristic acid, Decasanoic acid, Para-coumatic acid, Caffeic acid, Ferulic acid, 3-hydroxy-4-methoxy benzaldehyde, Inositol, Coniferaldehyde, Vanillin, Pluchoic acid, Protocatechualdehyde, Caffeic acid	C. angustifolia, C. armandii, C. delavayi, C. crassifolia, C. hexepetala, C. montana	43,31,38,41, 36,44

PHARMACOLOGICAL EFFECTS OF CLEMATIS SPECIES:

Clematis apiifolia:

Antimicrobial activity- The fresh fruits of *C. apifolia* blended with water were used for measurement of antimicrobial activity against microbial strains- *Staphylococcus aureus*, *Escherichia coli*, *Enterobacter plantanum*, *Saccharomyces cerevisiae*, *Candida utilis*, *Candida albicans* and *Zygosaccharomyces rouxii*. Immature fruits with light green appearance exhibited strongest antimicrobial activity showing MIC against *C. utilis* broth of 0.06-0.07%.

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Once fruit start to mature and attain brownish appearance the activity decreased abruptly, showing MIS of larger than 0.3% or more to the same indicator [45].

Clematis ganpiniana*:*

Apoptosis activity- The methanol extract of saponins of C. ganpiniana was uesd in the concentration of 0.08, 0.4, 2 and 10µg/ml. Cells treated with only DMSO were used as the control. MCF-7 and MDA-MB-231 breast cancer cell lines were tested using cytotoxic effect assay (MTT assay). Compared to the negative control group, CHS showed cytotoxic effect on both types of breast cancer cells after 12, 24 and 48 h of treatment, in a time- and dose-dependent manner ($P<0.05$). After 6, 12, and 24 h of treatment with 2.0 µg/ml CHS, MCF-7 and MDA-MB-231 cells were evaluated using flow cytometry to determine the apoptosis rate. The results showed that CHS induced apoptosis in breast cancer cells and the apoptosis rate increased over time. MCF-7 and MDA-MB-231 cells treated with 2.0 µg/ml CHS for 24 h showed an early apoptosis rate of 29.3 and 19.8%, respectively. CHS regulated the mitochondrial Apaf-1 and Cyto c level.MCF-7 and MDA-MB-231 cells were treated for 2, 6, 12 or 24 h with CHS (2 µg/ml) and both mitochondrial Apaf-1 and Cyto C level were detected by western blotting. CHS significantly reduced mitochondrial Apaf-1 and Cyto C proteins in breast cancer cells, indicating the enhanced release of Apaf-1 and Cyto C from mitochondria in breast cancer cells. After the cells were treated with the compound for 2 to 24 h, there was gradual reduction of mitochondria Apaf-1 and Cyto C proteins [46].

Cytotoxic and antibacterial activity-The dried plant of *Clematis ganpiniana* was extracted with 70% EtOH. The estrogen independent human breast cancer cell line MDA-MB-231 and the estrogen dependent human breast cancer cell line MCF-7 adriamycin (2 g/ml) was used as positive control. The MTT assay was used to measure the cytotoxicity of compounds. Antibacterial activities of compounds were determined against *Micrococcus luteus, Escherichia coli, Bacillus subtilis, Salmonella paratyphi B, Candida albicans, Staphylococcus aureus*, and *Bacillus pumilus* by the paper diffusion method. Rifampicin was used as a positive control against pathogenic bacteria with ten concentrations of 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, and 2.0 g/disk [47].

Cytotoxic activity- The IC_{50} value and apoptosis rates of four compounds were evaluated and showed in the range of MCF-7 (0.7 to 2.3) and MDA-MB-23 (0.9- 3.7) as in comparison to the adriamycin 2.4 and 7.2 respectively. The apoptosis % of MCF-7 (25.5 to 38.9) and MDA-MB-23 (17.3- 28.9) as in comparison to the adriamycin 27.3 and 16.3%. The compound 1, 2, 4 showed lower IC_{50} comparing with adriamycin, compounds 1 and 4 showed higher apoptosis rates than that of adriamycin, and the apoptosis rate of compound 2 was similar with positive control, so all of these three compounds are potential anti-tumor agents. Especially, compound 4 showed the strongest activity against cancer cells and highest apoptosis rates among these four com-pounds.

Antibacterial Activity- The antibacterial activities of compounds 1-4 were tested against *Micrococcus luteus, Escherichia coli, Bacillus subtilis, Salmonella paratyphi B, Candida albicans, Staphylococcus aureus*, and *Bacillus pumilus*, compound 4 showed weak active against almost all tested bacterium besides *Salmonella paratyphi* B. [47].

Clematis graveolens:

Antioxidant activity - Different assays were used to analyse antioxidant potential of the essential and fixed oils of *C. graveolens.* The linoleic acid system was used to determine the antioxidant activity of essential oil and fixed oil of the plant in terms of percentage inhibition per oxidation in the linoleic acid system. DPPH radical scavenging activity of essential oil and that of fixed oil sample. The percentage inhibition in linoleic acid system of essential oil ranges from 69.69-71.61% and that of fixed oil from 59.59-79.92. The fixed oil of stem showed lower free radical scavenging activity and highest IC_{50} values (47.82 µg/ml) and fixed oil of leaves showed lower IC_{50} values (14.06 µg/ml) and highest free radical scavenging activity. On comparing the fixed and essential oil of stem and leaves maximum IC_{50} values were shown by fixed oil of stem (47.82µg/ml) [48].

Antibacterial activity- The antimicrobial activity of *C. graveolens* was evaluated against selected bacterial strains *Escherichia coli, Staphylococcus aureus, S. epidermidis, Nitrosapira* and fungal strains *Aspergillus niger, C. albicans* and *Aspergillus flavus* by disc diffusion and minimum inhibitory concentration method. Results showed that essential oil of leaves showed good inhibitory activity against *E. coli* (15.66 mm) and minimum activity against *B. cereus* (9.44 mm) and for fungal strains good activity was shown against *C. albicans* (11.44 mm) and minimum activity was shown against *A. niger* (9.86 mm). The fixed oil of stem was maximum

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against *B. cereus* (13.87 mm) and minimum activity was shown against *E. coli* (8.91 mm) Fungone and Novidate standards were used. [48].

Antifungal Activity: The crude ethanolic extract of flowers of *C. graveolens* showed antifungal activity. Food poisoned technique was used to determine the growth inhibition of fungi by the plant extracts. Terbinafine, was used as positive control. Antifungal assay of *C. graveolens* was carried out in five solvents. The flowers extract in methanol: The extract was tested at three different doses 500, 1000 and 2000 ppm. At 500 ppm, the percent inhibition in the growth of *A. fumigatus* was 41.10%±9.21, followed by *A. flavus* 39.52%±5.51 and *A. niger* 32.82%±1.85. Ethanol: The inhibition in at 2000 ppm, the percent inhibition in the linear growth of *F. oxysporum* (92.22%±1.33) was maximum, followed by *A. fumigatus* (86.13%±1.20), *A. flavus* (85.83%±1.15), *A. niger* (83.46%±1.76), *S. cerevisiae* (80.69%±2.60) and *P. notatum* (73.59%±1.67). Chloroform: At 2000 ppm, the percent inhibition in the growth of *F. oxysporum* (95.37%±1.53) was maximum, followed by *S. cerevisiae* (93.22%±1.76), *A. niger* (90.46%±2.03), *A. fumigatus* (86.99%±0.67), *A. flavus* (83.95%±5.69) and *P. notatum* (59.04%±3.51). DW: 2000 ppm the inhibition was up to 97.92%±0.58 in *A. niger*, followed by 90.94%±1.45 in *F. oxysporum*, 80.28%±1.53 in *A. fumigatus*, 69.02%±4.81 in *S. cerevisiae*, 77.50%±6.08 in *A. flavus* and 65.92%±0.67 in *P. notatum*. Acetone: In lower dose (500 ppm), inhibition in the fungal growth was found maximum in case of *A. niger* 69.33%±1.76, followed by *S. cerevisiae* 58.45%±0.88, *F. oxysporum* 55.74%±1.45, *A. fumigatus* 50.50%±0.88 and minimum in case of *P. notatum* 19.67%±1.67 and *A. flavus* 8.55%±1.45 [49].

Insecticidal activity- Insecticidal activity of compounds clematograveolenoside A, tomentoside A, huzhangoside D, clematoside S was evaluated against aphid, Aphis craccivora and termite, Coptotermis homii: Toxicity of pure compounds was tested following Potters spray tower method against A. craccivora and force-feeding method against C. homii. For control, leaf disks were sprayed with distilled water containing 0.05 percent Tritone. Mortality was determined after 72 and 96h of treatment. The synthetic insecticide dimethoate at recommended dose (1-25 ppm) was used as a positive control for comparison. For C. homii: The test solutions of compounds and the imidacloprid (chemical insecticide) were prepared at different concentrations (50, 100, 500, 1000 ppm/mL). A. craccivora: Among the compounds tested, tomentoside A was more effective against A. craccivora with an LC_{50} of 1.2 and 0.5 mg/mL after treatment for 72 and 96 h, respectively and was followed by compound clematoside S (LC_{50} = 2.3 and 1.9 mg/mL) and clematograveolenoside A (LC_{50} = 3.2 and 2.6 mg/mL). The huzhangoside D was not effective and its mortality was < 50%. C. homii: The insecticidal activity of compounds has been investigated against the C. homi showed encouraging results. Among the compounds tested, compound clematograveolenoside A was more effective against C. homi with an LC_{50} of 0.1 mg/mL after 24 h of treatment and was followed by compounds tomentoside A, huzhangoside D, and clematoside S (LC_{50} = 0.1, 0.2 and 0.2 mg/mL respectively). All these compounds are comparable with positive control, imidacloprid (LC_{50} = 0.1 mg/mL) and can be used as effective biotermiticide and an efficient alternative to synthetic insecticides [50].

Clematis terniflora

Apoptosis activity- The aqueous extract of *Clematis terniflora* at the concentration of 300 and 500 µg/ml was used to evaluate the neuroprotective effects against corticosterone-induced apoptosis in rat pheochromocytoma (PC 12) cells. The extract at respective concentration decreased apoptotic cell death and mitochondrial damage induced by 200 µM corticosterone. The extract decreased expression of andoplasmic reticulum (ER) stress proteins GRP78, GADD153 and mitochondrial damage- related protein BAD. These protective effects were mediated by upregulation of p-AKT and p-ERK1/2, which are involved in cell survival signaling [51].

Antinociceptive activity and anti-inflammatory activity- these activities were evaluated from water, 70% ethanolic extratc and fractions using mice writhing test with different doses. The anti-inflammatory activity was tested on rat models of carrageenan-induced chronic non-bacterial prostatis (CNP). Significant writhing inhibitory effect was found with EE at small (7.5 g/kg body wt.), moderate (15 g/kg body wt.) and large (30 g/kg body wt.) doses as well as EEPMR at moderate and large doses by oral administration (OA) ($p \leq 0.01$). Data from prostatic index, lecithin microsome density and white blood cell level showed that moderate dose of EE and EEPMR both had significant ($p \leq 0.05$ or $p \leq 0.01$) inhibition effect on carrageenan-induced inflammation in rat prostate[52].

Antibacterial activity and antifungal activity- these activities were recorded in methanolic leaf extract of *C. terniflora*. Agar well diffusion method for antibacterial and well diffusion assay to analyse the anti-fungal activity of the plant extract. The extract (40 and 80 µL) from 100 mg/mL stock was added to the wells. One well with cotrimazole was taken as the positive control and

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solvent without the compound as negative control. Eight important strains of micro organisms were selected for the present study which included bacteria (*Bacillus substilis, Pseudomonas fluorescence, Staphylococcus aureus, Escherichia coli*) and fungi (*Candida albicans, spergillus niger, Fusarium solani, Pencillium notatum*). At the concentrations (40µl & 80µl) of methanolic extracts of leaf and stem used for the analysis. Anti bacterial activity is less compared to the standard antibiotic available in the market. Methanolic leaf extraction (80 µl) showed greater inhibitory zone against *E. coli* compared to other organism[53].

Anti-inflammatory and Antinociceptive effects activities [54]–The anti-inflammatory properties of the 70% ethanol extract of *C. terniflora* DC. (EECTD) were evaluated using the xylene-induced ear swelling test, the carrageenan-induced edema model and the cotton pellet granuloma method. Its antinociceptive activities were determined using both the acetic acid-induced writhing test and the hot plate assay. In parallel, in vitro assay in LPS-induced RAW264.7 cells to examine the anti-inflammatory effects of EECTD and its purified form, aurantiamide acetate (AA) on inhibition of nitric oxide (NO) and prostaglandin E_2 (PGE_2) release.

Anti-inflammatory activities- The mice retreated with either extract or the positive drug control aspirin had significantly reduced swelling. In acute xylene-induced inflammation the dose of 300mg/kg had swelling rate 49.08% and aspirin 39.92%. In the carrageenan-induced model, the paws of vehicle-treated rats began to exhibit swelling one hour after carrageenan injection and had a maximum edema of 48.99% at 6 h. Rats pre-treated with the EE (300 mg/kg) showed significantly reduced paw edema from 2 h until 6 h. This reduced in edema resembled that of the positive control, reference drug aspirin. Six hours after carrageenan injection, vehicle-treated animals showed obvious symptoms of acute inflammation upon histopathological examination, including a large number of neutrophils, lymphocytes,and other inflammatory cells. However, the infiltration of inflammatory cells in rats pre-treated with EE was significantly reduced, and the tissue damage was markedly improved.

Antinociceptive effects-The result of the acetic acid-induced writhing test showed that EE derived from C. terniflora DC. decreased the number of writhing. Compared to the vehicle group, a high dose of EE (300 mg/kg) had a significant inhibitory effect (81.78%) that was comparable to the positive, drug control (aspirin, 88.48%). The writhing test was used to investigate peripheral analgesic activity. However, the hot-plate assay was used to evaluate the central antinociceptive effects of the extract in mice, The results indicated that the extract extended the latency to reaction against hyperthermic stimulation. Moreover, those two doses of EECTD (300 mg/kg body and 150 mg/kg) caused a significant extension to the time of paw licking when compared to the vehicle group[54].

CONCLUSION

Out of 355 species of genus *Clematis (Ranunculaceae)* 30 species have been systematically characterized for their chemical constituents. The constituents identified from *Clematis* species are flavonoids, triterpenoid saponins, lignans, steroids, polyphenols, and coumarins. Few compounds, especially flavonoids and alkaloids also possess strong evidence of biological importance but no systematic work has been carried out to validate pharmacological activities responsible for bioactive principles. The triterpenoid saponins are mainly of interest of this genus as these are most potent compounds responsible of most of activities. In literature, 26 species are reported in traditional use for the treatment of various ailments like gout, dysentery, rheumatism, analgesic, antitumor, antibacterial, diuretic, anticancer, antimicrobial, anti-inflammatory, arithritis, hepatoprotective, osteoarthritis and HIV-1 protease inhibitors activities. The chemical constituents isolated were hederagenin and oleanane aglycone based saponuns, flavonoids, alkaloids, lignans, coumarins, steroids and volatile oils. The present study revealed that hederagenin aglycone based new saponins isolated were 1 from *C. apifolia*, 3 from *C. ganpiniana*, and 1 from *C. graveolens* and oleanane aglycone based were 1 from *C. apifolia and 5* from *C. terniflora*. The pharmacological effects reported have been antioxidant, cytotoxic, antimicrobial, antidiabetic, hepatoprotectve, and anti-inflammatory. In most of activities crude extract was used to evaluate these activities. Being a potential folklore medicine and pharmacologically active species clinical studies are needed to establish biological alternatives to synthetic drugs. In lieu of these observations, it is suggested that the research is needed:

(i) to validate more *Clematis* species of traditional uses with pharmacological effects.

(ii) to characterize and isolate bioactive constituents as per market need.

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(iii) to investigate more *Clematis* species for isolation of compounds and their mode of actions.
(iv) more clinical studies to establish structure -biological activity relationship.

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