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CLEOME PLANTS OF ISRAEL AND PALESTINE: SMELLY, BEAUTIFUL AND MEDICINALLY ACTIVE. A REVIEW

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ABSTRACT

The Cleomaceae plant family, consists of two genera, *Cleomella* and *Cleome*, and only the second is present in Israel and Palestine, where five species grow wild, and they will be discussed in this review article. These five *Cleome* plants are stinky, and this might be the reason of their very limited use in traditional medicine. On the contrary, modern research studied these plants and the number of publications is relatively sufficient. Published activities are quite diverse, so several review articles were also published. Some discuss the *Cleome* genus while others focus on single species. By far, our review is the most comprehensive. In addition to taxonomy, archeology and ethnomedicinal uses of these plants, published results of modern research will be presented and discussed. Important natural product contained in these plants will be presented. In the final part of this article, conclusions and future research possibilities will be highlighted.

KEYWORDS: Cleomaceae, *Cleome*, smelly, ethnomedicine, chemical composition, antidiabetic, hepatoprotective, anti-inflammatory, antioxidant, antihyperlipidemic.

Abbreviations: ABTS 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), ahc and her/his colleagues, AChE acetylcholine esterase, BHA butylated hydroxyanisole, BHT butylhydroxytoluene, BuChE butyrylcholine esterase, COX cyclooxygenase, CUPRAC cupric reducing antioxidant capacity, DPPH 2,2-Diphenyl-1-picrylhydrazyl, DCM dichloromethane, EDTA ethylenediaminetetraacetic acid, EO essential oil, FRAP ferric reducing activity power, FSH follicle stimulating hormone, G6PD glucose-6-phosphate dehydrogenase, G6Pase glucose-6-phosphatase, GCC general chemical composition, GC-MS gas chromatography mass spectrometry, GSH glutathione, HDL high density lipoprotein,

HPLC high performance liquid chromatography, LDL low density lipoprotein, LH luteinizing hormone, LPS lipopolysaccharide, LOX lipoxygenase, MDA malondialdehyde, NBT (test) nitroblue tetrazolium, NPs nanoparticles, ORAC oxygen radical absorbance capacity, PBD phosphomolybdenum (assay), PE petroleum ether, SOD superoxide dismutase, STZ streptozotocin, TAC total antioxidant capacity, TBARS thiobarbituric acid reactive substances, TFC total flavonoid content, TPC total phenolic content, TTC total tannins content

1) INTRODUCTION: Taxonomy and Archeology

Cleomaceae or spider-flowers by common name is a medium size plant family that includes around 27 genera and approximately 270 species.[1] In the reviewed region of Israel and Palestine, and more precisely between the Mediterranean sea and the Jordan river, this plant family is represented by a single genus, *Cleome*.[2] Among more than 200 species that this genus includes,[3] only five taxa grow wild in the reviewed region: *C. amblyocarpa*, *C. arabica*, *C. chrysantha*, *C. droserifolia*, and *C. gynandra*.

Interestingly, very few publications have mentioned use of these plants in ancient times as archaeological research revealed. In ancient Chile, *Cleome* plants (species are not specified) remains were found in archaeological sites dating 15680-15259 years before present Time.[4] And in ancient Egypt, several *Cleome* plants including *C. chrysantha*, and *C. gynandra*, had very special use during Ptolemaic period (around 2200 year before present time): they were part of a royal jelly that had psychotropic activities.[5] This study is notably comprehensive and includes identification of some active ingredients.

2) Ethnobotany and Ethnomedicine of *Cleome* Plants of Israel and Palestine

Traditional medicine and ethnobotany that people of the reviewed region practiced made very limited use of the *Cleome* plants. This can be easily concluded from the small number of documented and published uses, which we summarized in **Table 1**.

Table 1: Ethnobotany and Ethnomedicine of the *Cleome* Plants of Israel and Palestine.

Country	Species	Uses, Reference
Egypt	*C. amblyocarpa*	Aerial parts; antibacterial[6]
	C. chrysantha	Leaves, flowers, seeds; antimicrobial
	C. droserifolia	Leaves; urinary tract pains, diabetes, wounds, dermatitis and antimicrobial
Qatar	*C. amblyocarpa*	Plant part not specified; abdominal and rheumatic pains[7]

Saudi Arabia	*C. amblyocarpa*	Whole plant; mostly as a decoction, insecticidal, scabies, rheumatism, kidney problems, sexual stimulator, rheumatism, rheum, scabies, rheumatic fever, anti-inflammatory
	C. gynandra	Leaves, roots, seeds; infusion mostly taken orally, appetizer, carminative, ear pain, splenomegaly, muscles problems, scorpion stings, muscle weakness, diabetes, anti-inflammatory, anticancer[8]
Tunisia	*C. amblyocarpa*	Leaves; decoction or infusion, cough relief, sedative, women fertility enhancer, toxic for animals[9]

3) Selected Published Review articles about *Cleome* Plants of Israel and Palestine

Most of the review articles that present the *Cleome* plants genus, were inclusive and discussed the entire genus, where some other articles presented specific species, like our article. Among the five species of the reviewed region, *Cleome amblyocarpa* and mainly *Cleome gynandra* were published in separate articles. A summary of the most important, selected articles is shown in **Table 2.**

Table 2: Selected review articles about the *cleome* plants of Israel and Palestine.

Species	Pages/ References	Major Subject, Reference
C. amblyocarpa	7/11	Extensive phytochemistry including structures, biological activities and traditional uses[10]
Cleome	11/38	Extensive phytochemistry including structures and a few biological activities[11]
Cleome	12/71	Very extensive phytochemistry including structures and biological activities. Photo of some species are shown.[12]
Cleome	22/73	Very extensive phytochemistry including structures, focusing on anti-inflammatory and antinociceptive activities.[13]
Cleome	11/34	Biological activities[14] The article is in Portuguese and in the English title, the word "gênero" was translated to "gender" instead of "genus"
Cleome	18/133	Very extensive phytochemistry including structures, mechanisms of action and biological activities. Photo of some species are shown.[15]
Cleome	10/41	Geographical distribution, extensive traditional uses, partial phytochemistry including structures and biological activities.[16]
C. gynandra	8/14	Extensive botanical and geographical descriptions, limited phytochemistry with no structures, partial listing of biological activities and traditional uses[17]
C. gynandra	9/37	Extensive botanical and geographical descriptions, limited

		phytochemistry including structures, partial listing of biological activities and traditional uses[18]
C. gynandra	14/99	Extensive botanical and geographical descriptions, limited phytochemistry not including structures, partial listing of biological activities and detailed traditional uses[19]
C. gynandra	16/97	Extensive botanical and geographical descriptions, genetics, morphology and taxonomy[20]
C. gynandra	18/110	Comprehensive: botany, geography, plant photos, detailed traditional uses, biological activities and limited phytochemistry with no structures[21]
C. gynandra	3/11	Very small review that includes very partial information of all aspects, including plant photos[22]

4) Published Activities-Properties of *Cleome* Plants of Israel and Palestine

The Published biological, medicinal and other properties-activities of the five *Cleome* species of Israel and Palestine include most typical properties-activities of other plants, and they are notably diverse. Some species are relatively active, while others have much fewer activities. A summary of these activities-properties is presented in **Table 3**.

Table 3: Published Activities-Properties of *Cleome* Plants of Israel and Palestine.

Activity-Property, Testing Method(s), Result(s), Reference
Cleome amblyocarpa
Aerial parts EO (hydrodistillation) was analyzed with GC-MS resulting the presence of 48 compounds, where the highest concentrations were of (%): caryophyllene oxide 36.01, hexahydrofarnesyl acetone 7.92, alloaromadendrene epoxide 6.17, myrtenyl acetate 5.73, isoshyobunone 4.52, shyobunol 4.19 and *trans*-caryophyllene 3.45 (**Figure 1A**). EO had allelopathic effect against *Dactyloctenium aegyptium*, antioxidant (DPPH method) and anti-inflammatory (LOX, COX1, COX2 inhibition) activities.[23]
Leaves and stems were separately extracted with 80% (v/v) aqueous ethanol and extracts were analyzed for chemical compositions by GC-MS. The major compounds in leaves extract were (%): ethyl 3-methylpentanoate 16.2, 7-epi-silphiperfol-5-ene 11 and α-copaene 7 (**Figure 1A**); and in the stems extract were: *trans*-caryophyllene 46.9, eugenol 25.6. TFC, TPC and TTC were determined for both extracts resulting higher values for leaves. Extracts were tested for antioxidant (DPPH, Fe^{+2} chelating, TBRAS methods), antimicrobial (against 8 bacterial and 4 fungal strains), cytotoxic (against A549 and H1299 human lung cancer cells), analgesic (acetic acid-induced ear writing test) and acute toxicity (in mice, not toxic up to 3000 mg/kg) activities.[24]
Whole plant was extracted with methanol and extract was partitioned with 50, 75 and 95% ethyl acetate in hexane and with 95% ethyl acetate in methanol. Extract and fractions were chromatographed affording 10 active compounds that were tested for biological tests and molecular docking, where two of them were highly active: 15-α-acetoxycleomblynol A and 11-α-acetylbrachy-carpone-22(23)-ene (**Figure 1A**). Analgesic activity was tested with hot plate method in rats and anti-inflammatory activity was tested with carrageenan-induced paw edema in mice.[25]
Whole plant was defatted with PE and extracted with 70% aqueous methanol. The extract was fractionized with water, chloroform, ethyl acetate and *n*-butanol. Fractions were chromatographed yielding several previously well-known phenolics. Extracts were tested

for antidiabetic and anti-inflammatory activities in STZ-induced diabetic rats. Hepatoprotective activity was tested against CCl_4 – induced hepatotoxicity in the same animals.[26]

Aerial parts were extracted with 80% aqueous ethanol and the extract was partitioned with chloroform. This fraction was tested for antioxidant activity (ABTS, DPPH, CUPRAC, phenanthroline assay, β-carotene bleaching methods, with five known antioxidants as references, including BHA and BHT), and it was analyzed for TFC and TPC. GC-MS analysis of this fraction resulted in identification of 133 compounds where the major ones were (%): tetracosane 35.6, linolic acid 4.14, palmitic acid 8 and 2-aminothiazole (**Figure 1A**) 4.21. Enzymatic inhibition was tested against AChE, BuChE (galantamine was reference); α-amylase and α-glucosidase (antidiabetic activity, acarbose was reference). The anti-inflammatory activity was tested with bovine serum albumin inhibition method and the antimicrobial activity was tested against five bacterial species and *C. albicans*.[27]

Aerial parts 80% aqueous methanolic extract was analyzed for TPC, nutritional and chemical compositions, with special focus on abscisic acid (**Figure 1A**) content. Extract was tested for antioxidant (DPPH method with ascorbic acid as reference) and antimicrobial (against 4 bacterial and 2 fungal species, with two standard antibiotics as references) activities.[28]

Arial parts were defatted with PE and extracted with methanol. The methanolic extract was fractionized with several solvents and solvent mixture. Fractions were analyzed for GCC, TFC and TPC. The antioxidant activity was determined with ABTS, DPPH, hydroxyl radical scavenging (α-tocopherol and ascorbic acid were references) and Fe^{+2} chelating (EDTA was reference) methods.[29]*

Whole plant and seeds EO's were separately prepared (hydrodistillation) from plants that were grown under three different irrigation conditions (Symbolized with T1, T2, T3). The mineral composition of soil was tested and reported. EO's had different antioxidant activity (ABTS, DPPH, FRAP methods), and notable differences in their chemical compositions (GC-MS). The major components (**Figure 1A**) of these EOs were (%): T1 isobornyl formate 43.9, T2 *trans*-chrysanthenyl acetate 38.6, T3 (e)-ocimenone 39.66.[31]

EOs of three *Cleome* species were obtained by hydrodistillation, among these species, only *C. amblyocarpa* is in our interest. The antioxidant activity (ABTS, DPPH, Fe^{+2} chelating methods) of the EO was determined and it was analyzed for chemical composition. The major two components were (%): 2-methoxy-4-vinyl phenol 20.06 and *cis*-dihydrocarvone 13.09 (**Figure 1A**).[32]

Aerial parts were extracted with methanol and the extract was partitioned with several solvents and solvent mixtures, then analyzed for phenolics affording ten previously well-known compounds. Extract and isolated compounds inhibited SRAS-CoV-2 proteases, and molecular docking of active compounds is presented for this inhibition activity.[33]

Leaves 80% aqueous methanolic extract was prepared and qualitatively analyzed for chemical composition affording 26 previously known compounds. It was also tested for acute toxicity in mice and found nontoxic. Extract was tested for anti-inflammatory activity against carrageenan-induced paw edema in rats, and for analgesic activity in acetic acid-induced writhing in rats.[34]

Fresh aerial parts 95% aqueous ethanolic extract was chromatographed yielding three new dammarane triterpenes and another new tetra decacyclic compound (**Figure 1A**).[35]

Several new dammarane triterpenes with very close structures to the three previously reported and shown in (**Figure 1A**).[36]

Aerial parts 95% aqueous ethanolic extract was analyzeded affording six previously known phenolics and a new one: kaempferol 7-methyl ether 3-α-D-rhamnoside. (**Figure 1B**).[37]

The structure of cleoamblynol A that was reported by F.M. Harraz ahc[36] was revised by A.A. Ahmed ahc (**Figure 1B**).[38]

Whole plant ethanolic extract was analyzed yielding 18 dammarane triterpenes, where 12 of them were new, with very close structures to those shown in **Figure 1A** and **Figure 1B**. Some of these compounds were active against mouse P388 leukemia cells.[39]

Aerial parts were extracted with methanol-DCM (1:1), and the extract was chromatographed yielding a new derivative of cleoamblynol A that was reported by A.A. Ahmed ahc (**Figure 1B**): An acetoxy group is attached to C15 and enantiomer of C20 due to C21.[40]

Whole plant methanolic extract had no genotoxicity but was highly toxic in neutral red test, especially in high uptakes.[41]

Whole plant aqueous decoction proved nontoxic to rats up to 10 mL/kg.[42]

Whole plant PE extract was fractionized with acetone yielding acetone-soluble and acetone-insoluble fractions. The defatted material was extracted with 70% aqueous methanol and this extract was partitioned with water, chloroform, ethyl acetate and *n*-butanol. Extracts and fractions were tested for antidiabetic activity (STZ-induced diabetic rats, mainly blood glucose levels), hepatoprotective activity (CCl_4 – induced liver toxicity in rats, four biomarkers) and anti-inflammatory activity in the diabetic rats by measuring four biomarkers.[83]

* The same findings were published by the same group a year later.[30]

Cleome arabica

Leaves 80% aqueous methanolic extract was prepared and qualitatively analyzed for chemical composition affording 57 previously known compounds. It was also tested for acute toxicity in mice and found nontoxic. Extract was tested for anti-inflammatory activity against carrageenan-induced paw edema in rats, and for analgesic activity in acetic acid-induced writhing in rats.[34]

Different parts of the plant were separately extracted with water, *n*-hexane, chloroform and methanol (total of 16 extracts). All extracts were tested for allelopathic activity against four plant species showing significant activities. Analysis of extracts for bioactive compounds revealed dammarane triterpenes with close structures to those shown in **Figure 1A** and **Figure 1B**, in addition to calycopterin (**Figure 2**).[43]

Pods methanolic extract had notable allelopathic activity against lettuce (*Lactuca sativa*). Analysis of the extract for bioactive compounds yielded mainly calycopterin (**Figure 2**) and some of its derivatives, in addition to a new compound, cleomside A (**Figure 2**).[44]

Fruits 80% aqueous methanolic was analyzed for TPC and single phenolic compounds revealing previously well-known compounds. For some of these compounds, molecular docking of anti-apoptotic activity was performed. The extract was tested for anti-apoptotic (against HEK293 cells) and antioxidant (DPPH, FRAP methods) activities.[45]

Leaves 70% aqueous ethanolic was tested in seven different concentrations against five different cancer cell lines showing significant activities.[46]

Forty-eight fractions were prepared from this plant: leaves, pods, roots, seeds and stems were collected in two different seasons. Each one of the ten samples was extracted with two solvents, 70% aqueous methanol and 80% aqueous acetone, using two methods of maceration and ultrasonication. Each extract was fractionized with three solvents. Fractions were analyzed for TFC and TPC, tested for antioxidant (DPPH method) and for α-amylase inhibition activities.[47]

Fruits aqueous extract was not toxic to rats (up to 2000 mg/kg) and had positive effect in STZ-induced diabetic animals.[48]

Leaves aqueous extract had positive effect in high cholesterol-fed rats and had antioxidant activity measured in animals organs functioning and with TBRAS method.[49]

Fruits aqueous extract oral administration (100 mg/kg) to STZ-induced diabetic rats had positive hypolipidemic, antihyperglycemic and antiatherogenic effects, each tested with several biomarkers.[50]

Leaves ethyl acetate extract was active against inflammatory cells in rats. Effect was measured by several biomarkers with diclofenac as reference.[51]

Leaves 70% aqueous methanolic extract had *in vivo* (carrageenan-induced paw edema in rats) and *in vitro* (human neutrophils) anti-inflammatory activities. Authors refer this activity to high phenolics content (15%).[52]

A follow-up of the previous two studies using leaves 70% aqueous methanolic extract. The extract as well as two of its phenolic components, rutin and quercetin, inhibited soy LOX and the generation of inflammatory eicosanoids by human neutrophils.[53]

Aerial parts aqueous extract was analyzed for TFC, TPC, TTC and chromatographed for single phenolics resulting five previously very well-known compounds. The extract was tested for antioxidant activity with DPPH, FRAP and NO radical-inhibition methods. Extract and compounds were tested for anti-inflammatory activity (formalin-induced in rats), and effect was measured with several biomarkers, especially oxidative stress. Molecular docking was performed for the binding of indomethacin and catechin to COX-2.[54]

Aerial parts defatted with PE and were extracted with methanol and the extract was fractionized with several solvents. EO was also prepared from aerial parts by hydrodistillation. Methanolic extract was analyzed for TFC and TPC and was tested for antioxidant activity with ABTS, DPPH, Fe^{+2} chelating and hydroxyl-radical inhibition methods. The extract and its fraction had notable activity against four bacterial strains. Extract and EO were analyzed for chemical compositions and the major compounds were isoorientin and 2-methyl butyl isothiocyanate, respectively (**Figure 2**).[55]

Leaves ethyl acetate extract was tested for antioxidant activity with HOC*l*.[56]

Leaves, roots and seeds were separately extracted with 70% aqueous ethanol, and the three extracts were analyzed for GCC, TFC and TPC. They were also tested for antioxidant activity with DPPH, FRAP and PBD methods.[57]

Leaves 80% aqueous methanolic extract was analyzed for TFC, TPC, TTC, and its antioxidant activity was tested with ABTS, CUPRAC, DPPH, FRAP and PBD methods.[58]

Leaves 70% aqueous methanolic extract was analyzed for TFC, TPC and tested for antioxidant activity with DPPH, Fe^{+2} chelating and TAC methods. The extract had also hematoprotective effect against AraC (Cytarabine) toxicity in mice, including clear antipyretic effect.[59]

Leaves aqueous extract was administered to rats in three stress tests: plus maze, open field and forced swimming. Results showed positive effects on animals' behaviour and in the activity of several biomarkers: ACTH hormone (Adrenocorticotropic hormone), cholesterol, creatinine, glycemia, triglycerides and urea.[60]

Seeds methanolic extract analysis afforded a new dammarane triterpene (**Figure 2**).[61]

Aerial parts ethanolic extract inhibited carbon steel corrosion. Authors link this activity to relatively high concentrations of phenolic compounds in this extract.[62]

Whole plant ethanolic extract increased sexual activity and orientation of rats.[63]

Another research by the same group of reference 63: leaves aqueous extract had an inconsistent decrease in the sexual activity and orientation.[64]

Fruits aqueous extract was tested for antioxidant activity measured with TAC and NBT tests. It was administered to female rats poisoned with bisphenol A resulting clear positive effect on four inflammatory biomarkers, four blood biomarkers and ovarian dysfunction. Molecular docking was performed for five known phenolics that the extract contained.[65]

Leaves, seeds and stem were separately and sequentially extracted with *n*-hexane, chloroform and methanol. All nine extracts in several concentrations were tested against *Spodoptera littoralis* (cotton leafworm) showing clear activity, where methanolic extract was most active.[66]
Leaves aqueous extract had negative effect on the sexual activity of vinegar fly (*Drosophila melanogaster*).[67]

Cleome chrysantha
Seeds EO (hydrodistillation) was analyzed by GC-MS leading to the identification of 23 compounds, where the three major components were (%): 1-isocyano-4-methyl benzene 21.72, γ-Muurolene16.10, nerolidole 13.67 (**Figure 3**). The EO and some of the components were active against seven microbial species.[68]
Aerial parts 95% aqueous ethanolic extract was chromatographed affording a new dammarane triterpene (**Figure 3**).[69]

Cleome droserifolia
Aerial parts EO (hydrodistillation) had allelopathic activity against four weed species and its antioxidant activity was determined using DPPH method. It was analyzed with GC-MS where the major components were (%): *α*-cadinol 9.29, *δ*-cadinene 7.65 (**Figure 4A**), *cis*-nerolidol 37.56, *γ*-muurolene 4.10.[70]
Aerial parts methanolic extract was fractionized with *n*-hexane, DCM, ethyl acetate and *n*-butanol. Extract and fractions were tested against human cancer cells (MCF-10A, MCF-7, MDA-MB-231, HeLa) revealing caspase-dependent activity.[71]
Aerial parts 70% aqueous ethanolic extract had antimicrobial (against 4 bacterial and 2 fungal species), antiviral (against hepatitis A virus) and anticancer (against MCF-7, HepG2, WI-38 cell lines) activities. It was analyzed (GC-MS) for chemical composition resulting 69 compounds, where the highest concentrations were (%): benzene-1-pentyloctyl 5.77, benzene-1-butylheptyl 5.06, benzene-1-methyldecyl 4.93, benzene-1-methyldecyl 4.77, benzene-1-methylundecyl 4.66 and benzene-1-pentylheptyl 4.38.[72]
Aerial parts aqueous extract was partitioned with several solvents, and along with its chloroform, 95% aqueous ethanolic fractions and several pure compounds isolated from these fractions, were tested against two human cancer cell lines: (HCT116, MCF7). Chloroform and aqueous ethanolic fractions were chromatographed for chemical composition yielding six and three compounds, respectively (**Figure 4A**). New compounds are indicated.[73]
Aerial parts 95% aqueous ethanolic extract was administered to rats with glucose intolerance caused by tetracycline, resulting notable lowering of blood glucose and LDL-cholesterol. A mechanism of action is proposed.[74]
Leaves and small branches 95% aqueous ethanolic extract was supplemented to alloxan-induced diabetic mice. Results showed reduction of blood glucose levels, increase of glycogen content, decrease alpha-globulin and beta-globulin concentrations, hepatic glutathione levels were significantly elevated and insulin the treated was significantly decreased in treated diabetic mice.[75]
Leaves 95% aqueous ethanolic extract was supplemented to alloxan-induced diabetic rats. Results showed reduction of blood glucose levels, increase of glycogen content and insulin the treated was significantly decreased in treated diabetic mice. GCC of the extract is presented.[76]
Aerial parts were separately extracted with water, 50% and 70% aqueous ethanol. The aqueous extract was partitioned with *n*-hexane, chloroform, ethyl acetate and *n*-butanol. The three extracts and four fractions were tested for hypoglycemic activity in alloxan-induced diabetic rats, resulting highest activity for the aqueous extracts. This extract also had the highest content of phenolics (previously known compounds) followed by the ethyl

acetate fraction.[77]
Aerial parts 80% aqueous methanolic extract had notable blood glucose lowering in alloxan-induced diabetic rats. The amelioration effect of oxidative stress was measured by levels of MDA, GSH, SOD, catalase and glutathione peroxidase (GPx).[78]
A follow-up of the previous study where antihyperlipidemic was also studied.[79] ∗
Whole plant aqueous decoction was tested for antidiabetic activity in STZ-induced diabetic rats, where effect was measured by levels of blood glucose, insulin, glycogen, G6PD and G6Pase. Antioxidant activity was measured by activities of GSH, MDA and SOD, while antihyperlipidemic activity was measured with levels of cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol.[81]
Aerial parts 80% aqueous ethanolic extract was tested for antidiabetic activity in alloxan-induced diabetic rats (blood glucose, insulin), effect on liver functioning (liver enzymes) and oxidant-antioxidant biomarkers. Anti-inflammatory activity was measured with NO (nitric oxide) concentration.[82]
Whole plant PE extract was fractionized with acetone yielding acetone-soluble and acetone-insoluble fractions. The defatted material was extracted with 70% aqueous methanol and this extract was partitioned with water, chloroform, ethyl acetate and *n*-butanol. Extracts and fractions were chromatographed and detailed chemical compositions are provided. 3-Ethylsulfonyl-2,3-dimethoxypropyl glucosinolate (**Figure 4A**) was isolated as lead compound and its molecular docking with α-amylase was performed. It was tested for antidiabetic activity (STZ-induced diabetic rats, mainly blood glucose levels), hepatoprotective activity (CCl_4 – induced liver toxicity in rats, four biomarkers) and anti-inflammatory activity in the diabetic rats by measuring four biomarkers.[83]
Aerial parts 95% aqueous ethanolic extract was separately administered to alloxan-induced diabetic rats or combination with melatonin. The combination had stronger positive effect, measured by several parameters, especially blood glucose concentrations and oxidant-antioxidant biomarkers.[84]
Aerial parts methanolic extract ameliorated oxidative stress in alloxan-induced diabetic rats. Effect was measured with blood glucose and MDA levels.[85]
Aerial parts were defatted with PE then extracted with 80% aqueous methanol. The extract had activity against β-cells in alloxan-induced diabetic rats. Effect was measured by body weight, blood glucose and insulin levels, triglycerides and cholesterol, and oxidant-antioxidant biomarkers.[86]
Aerial parts aqueous extract had positive effect in alloxan-induced diabetic rats that was measured by blood glucose level, triglycerides and cholesterol, and oxidant-antioxidant biomarkers.[87]
Aerial parts were separately extracted with water and 95% aqueous ethanol. The aqueous extract was partitioned successively using *n*-hexane, chloroform, ethyl acetate and *n*-butanol. The chloroform and ethyl acetate fractions were chromatographed affording 9 compounds which their structures were published by this group a year later (see Ref. 73 and **Figure 4A**). The extracts, fractions and the isolated compounds were tested for antidiabetic activity using C2C12 skeletal muscle cells and 3T3-L1 adipocytes.[88]
Aerial parts methanolic extract suppressed NO (nitric oxide) production in LPS-induced inflammation in microphages. Chromatography of the extract afforded two active phenolics (**Figure 4A**).[89]
Shoots 70% aqueous methanolic extract was analyzed for TPC and phenolics composition, and 16 known compounds are reported. It was tested *in vitro* for antioxidant activity (ABTS, DPPH methods, ascorbic acid reference) and antimicrobial activity (five species). It was fed to rabbits resulting improvement of their blood parameters, especially

redox biomarkers and notable immunomodulatory activity (12 biomarkers).[90]
Fresh aerial parts EO (hydrodistillation) was analyzed for chemical composition and the major components were (%): (E)-3,7,11-trimethyl-1,6,10-dodecatrien 11.8, carotol 10.1, δ-cadinene 8.9 and β-eudesmol 7.0 (**Figure 4A**). EO antibacterial activity was tested against 11 bacterial species.[91]
Aerial parts methanolic extract was active against *S. aureus* both *in vitro* and *in vivo*. The extract was qualitatively analyzed for chemical composition yielding 44 previously known compounds.[92]
Aerial parts 95% aqueous ethanolic extract had activity against *Schistosoma mansoni*-infected mice. Based on several biochemical tests, a mechanism of action is proposed.[93]
Whole plant was extracted with methanol and the extract was partitioned with water, PE, DCM, ethyl acetate and *n*-butanol. All fractions were tested against three viruses where the DCM and ethyl acetate fractions were most active. The DCM fraction was analyzed for chemical composition resulting 13 previously known compounds that were also tested for antiviral activity. The structures of two compounds are shown in **Figure 4B**.[94]
Aerial parts methanolic extract ameliorates epinephrine-induced cardiac injury. The effect was measured with several parameters, especially redox and inflammatory.[95]
Aerial parts 70% aqueous ethanolic extract was fractionized with several solvents. Fractions were chromatographed and from the *n*-hexane fraction three compounds were isolated: stigmasterol glucoside, buchariol (**Figure 4A**, Ref. 73) and a novel natural product, drosericarpone (**Figure 4B**).[96]
Aerial parts were defatted with PE and extracted with methanol. Both defatted material and methanolic extract were separately fractionized in several steps and several solvents. The analysis of the fractions afforded three new dolabellane diterpenes (**Figure 4B**).[97]
A follow-up of the previous study obtained five new natural products (**Figure 4B**) along with other previously known compounds.[98]
Leaves were extracted with 1 M NaOH solution, and this extract had weaker corrosion effect on aluminum compared with base solution with no plant extract.[99]
Whole plant aqueous extract had protective effect against λ-cyhalothrin-induced testicular toxicity in male rats. Effect was measured with oxidant-antioxidant and inflammatory biomarkers, as well as concentrations of FSH and LH.[100]
Very similar research (published two years before by the same research group) to the previous study that compared between the published method and stem cell therapy.[101]
A follow-up study published by the same research group with very similar findings.[102]
Aerial parts 90% aqueous ethanolic extract was fractionized with several solvents. Analysis of the methanolic fraction afforded two compounds (**Figure 4B**) where the glycoside is new and had protective effect against CCl_4 hepatotoxicity in rats. Chromatography of the chloroform fraction yielded seven compounds that six of them had the same activity. Effect was measured with four biomarkers and silymarin was reference.[103]
Aerial parts aqueous extract had protective effect against CCl_4 -induced toxicity in HepG-2 cells. Effect was measured by cell viability and three biomarkers. Extract was analyzed for phenolics resulting 20 known compounds.[104]
Whole plant 70% aqueous methanolic extract was administered to rats causing damages in the liver and kidney tissues.[105]
Aerial parts methanolic extract ameliorated adrenaline-induced damages (injection) of liver and kidney in male rats. The positive effect was measured by organs weight (minor changes) and eight biomarkers.[106]
Leaves aqueous extract was mixed with *Allium sativum* bulbs aqueous extract and honey to produce chitosan nanofibers. These were active against four drug-resistant bacterial

species. The nanofibers had also notable wound (biopsy puncher) healing activity in mice.[107]
* Interestingly, this article was published again in the same journal. See reference[80]

Cleome gynandra

Aerial parts were successively extracted with chloroform and methanol. The methanolic extract had activity against tumor induced by Ehrlich Ascites Carcinoma cells planted in mice. Positive effect was measured by cancer cells viability, tumor size and several biomarkers. Acute toxicity test showed that the methanolic extract is not toxic to mice.[108]

Leaves were converted to ash by strong heating and ash was extracted for inorganic salts with water. Water was evaporated to obtain white solid mixture. The GCC of the solid was determined and it was tested against MCF-7 cancer cells showing notable activity.[109]

Follow-up research to the study cited in reference 108, published by the same group. In this case, the extract was fractionized using column chromatography and the fractions were tested with the same method. Results showed higher activity. Authors relate this effect to antioxidant activity indicated by levels of several oxidant-antioxidant biomarkers.[110]

Follow-up research of the study cited in reference 109, published by the same group. Leaves methanolic extract was tested for antioxidant activity (DPPH method) and for anticancer activity (three cell lines). In both tests significant results were detected, and researchers link these two activities.[111]

Leaves methanolic extract was tested for anticancer (against A549 cell lines), antioxidant (DPPH method) and antimicrobial (against *E. coli, S. paratyphi, P. aeruginosa* and *K. Pneumoniae*) activities. GCC of the extract is reported.[112]

Leaves were sequentially with *n*-hexane, DCM, ethyl acetate and methanol. All extracts were analyzed for chemical composition yielding three active anticancer compounds (against A549, MDA-MB-4368, HCT-116 and HCT-15 cell lines). These compounds are shown in **Figure 5** where compounds A and B are new, while compound C is previously known.[113]

Shoots ethanolic extract had positive effect in STZ-induced diabetic rats. Effect was measured by blood glucose, cholesterol and triglycerides concentrations. Treatments had also positive effect on body weight. Glibenclamide was standard drug.[114]

Fermented leaves aqueous extract decreased blood glucose levels in STZ-induced diabetic rats. Metformin was positive control.[115]

Leaves ethanolic extract had alleviating effect in alloxan-induced diabetic rats. Effect was measured with blood glucose level, cholesterol, triglycerides, HDL and LDL. Metformin was reference in this research.[116]

Aerial part 70% aqueous methanolic extract had antidiarrheal activity that was separately induced by magnesium sulfate and castor oil, in rats.[117]

Leaves 70% aqueous ethanolic extract had ameliorating effect in dexamethasone-induced hyperlipidemic rats. Effect was measured with levels of cholesterol, triglycerides, HDL and LDL. Atorvastatin was reference in this research.[118]

Fresh leaves 90% aqueous methanolic extract had activity against Freund's complete adjuvant-induced arthritis in rat paws. Effect was mainly measured by paw volume along with several biomarkers.[119]

Aerial parts 70% aqueous ethanolic extract had activity against three fungal strains that cause the fungan infection of the scalp, *Tinea capitis* (*Microporum canis, Trichophyton rubrum Trichophyton mentagrophytes*).[120]

Seeds were separately extracted with chloroform and methanol, and the extracts were analyzed (GC-MS) for chemical compositions, yielding mainly fatty acids and their esters. Extracts were tested against ten bacterial species showing no to moderate

activities.[121]
Leaves aqueous extract was analyzed for GCC and tested against three bacteria species: *S. aureus*, *P. aeruginosa* and *K. pneumoniae*. The thrombolytic effect was measured in healthy blood sample as clot lysis percentage after serum removal and incubation.[122]
Follow up of the research cited in reference 119 and published by the same group. In the present study, the fresh leaves ethanolic extract was used and its effect was measured with the following parameters: rat paw volume, SOD and catalase activities, plasmaTBARS, vitamin C, vitamin E, ceruloplasmin and reduced glutathione.[123]
Whole plant 80% aqueous acetone extract was prepared and after the acetone removal, the remaining aqueous extract was fractionized with *n*-hexane, DCM, acetonitrile, ethyl acetate, methanol and *n*-butanol. Each fraction was analyzed for TFC and TPC, and tested for antioxidant activity using ABTS, DPPH and FRAP methods: *n*-butanol fraction was most active.[124]
Leaves were sequentially extracted with *n*-hexane, benzene, chloroform, acetone and 90% aqueous ethanol. These extracts were analyzed for GCC and mineral composition. The antioxidant activity (ABTS method) of the leaves was determined using four extracts that were prepared by separate extraction: aqueous, 70 and 95% aqueous ethanolic and acetone. The 70% aqueous ethanolic extract was most active and vitamin C was reference.[125]
Fruits, leaves and stems were separately extracted with acetone, and TFC, TPC, TTC and GCC of each extract was determined. Leaves antioxidant activity was tested with DPPH method.[126]
Whole plant 96% aqueous ethanolic extract was analyzed for TFC and GCC and tested for antioxidant activity using DPPH method. The toxicity of the extract was determined using *Artemia salina* larvae and found practically nontoxic.[127]
Fresh whole plant pieces were active against nematodes (*Meloidogyne spp*).[128,129]
Whole plant was defatted with PE and chromatographed affording cleogynol, a new dammarane triterpenoid, along with five previously known others. In **Figure 5**, the structure of cleogynol and three other compounds are shown.[130]
Leaves methanolic extract was analyzed for GCC and its antioxidant activity was tested using DPPH method.[131]
Leaves were separately extracted with PE, chloroform, acetone, ethanol and methanol, and GCCs of these extracts were determined.[132]
Leaves ethanolic extract had activity against acetylcholine-induced spasms in chicken ileum. Atropine was reference in this research.[133]
Shoots wee separately extracted with water and 95% aqueous ethanol and both extracts were analyzed for GCC. Their antioxidant activity was tested with DPPH method and ascorbic acid was reference.[134]
Aerial parts were defatted with PE and extracted with methanol. The extract was analyzed for GCC focusing on alkaloids content, with atropine as a standard.[135]
Leaves were analyzed for mineral composition and extracted with methanol where this extract was analyzed for GCC.[136]
Whole plant was analyzed for minerals content, TFC, TPC, ascorbic acid, β-carotene and three phenolic acids. It was extracted with 80% methanol and the antioxidant activity of the extract was determined with DPPH and ORAC methods.[137]
Aerial parts ethyl acetate analysis with GC-MS yielded several known compounds.[138]
Aerial parts were separately extracted with *n*-hexane, chloroform, ethyl acetate, and methanol, and these extracts were analyzed (HPLC) for GCCs.[139]
Mineral composition including trace elements, was determined.[140]
Calcium concentrations in fresh and fermented leaves were 313.23 mg/g and 197.63

mg/g, respectively.[141]
Whole plant was separately extracted with methanol and water and both extracts were analyzed for GCCs. They were tested for toxicity in *Artemia salina* proving nontoxic.[142]
Leaves aqueous extract was administered to female rats resulting harmful effect (500 mg/kg). The damage occurred in estrous cycle and histomorphology of the ovary and uterus.[143]
Whole plant methanolic extract had weak haemolytic activity in red cell suspension.[144]
Leaves ethanolic extract reversed scopolamine-induced amnesia in mice. Effect was measured with behavioural and biochemical parameters.[145]

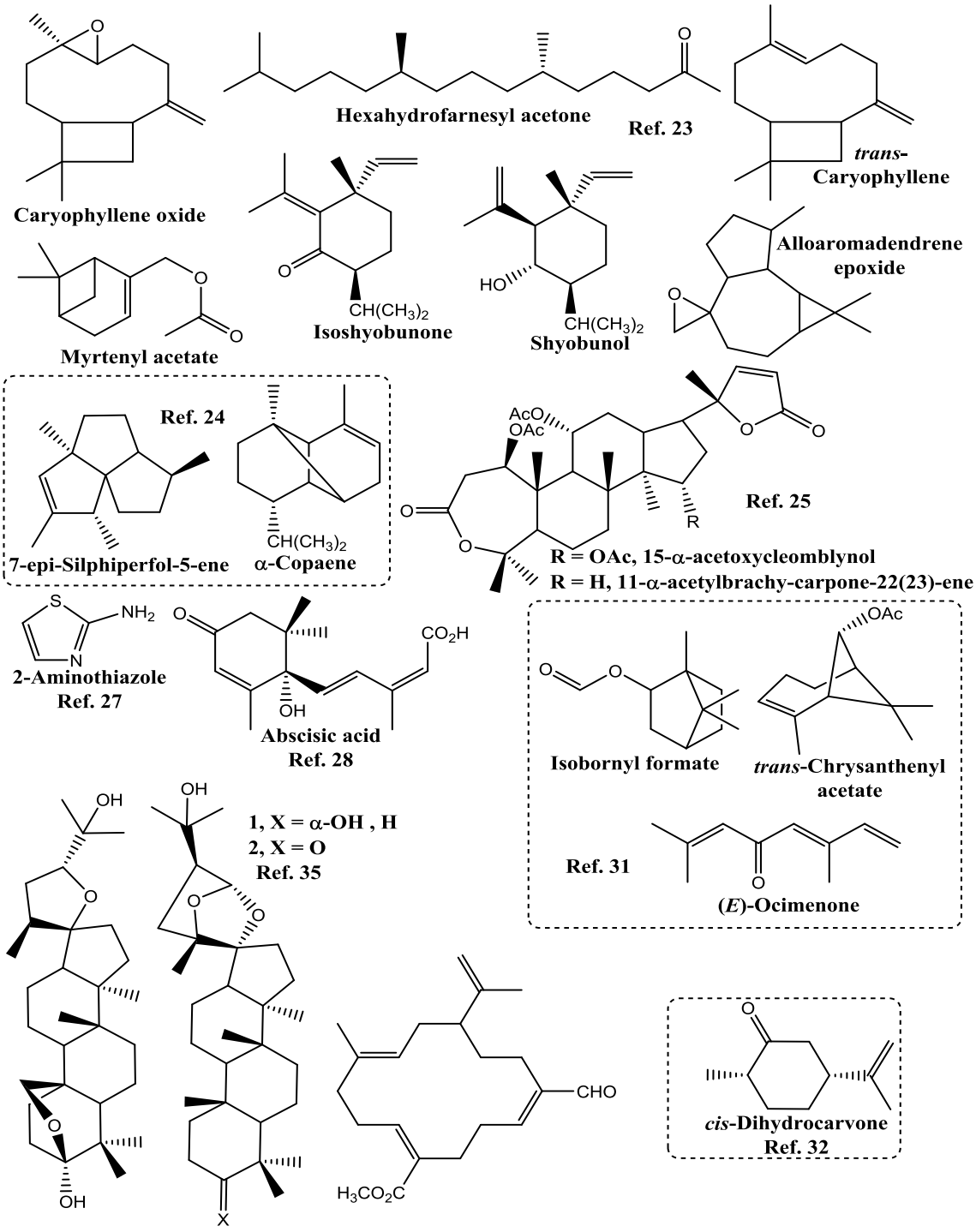


Figure 1A: Natural products isolated from *Cleome amblyocarpa*.

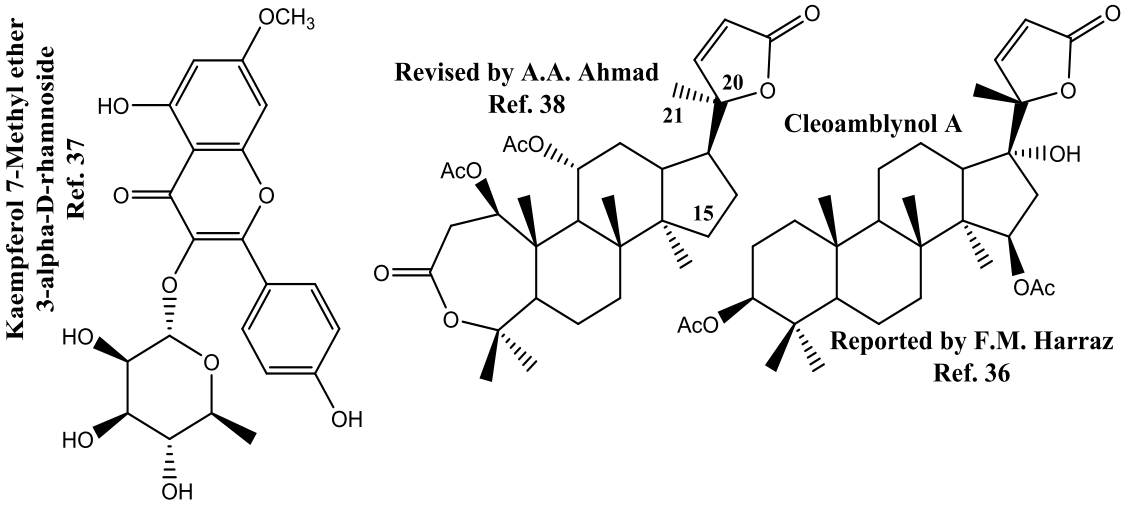


Figure 1B: Natural products isolated from *Cleome amblyocarpa.*

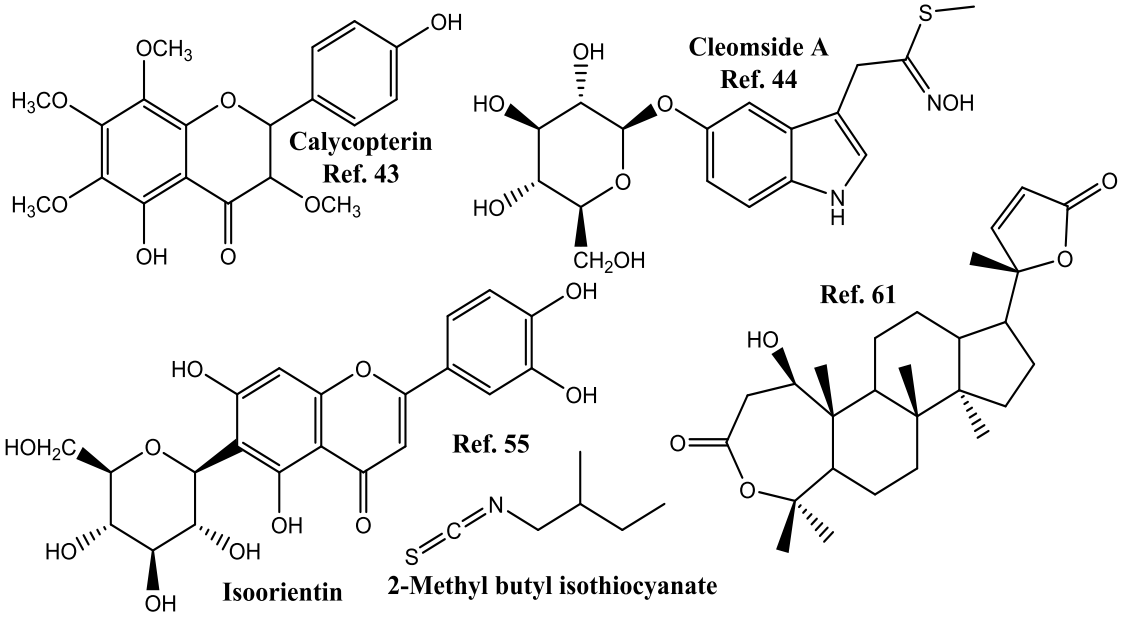


Figure 2: Natural products isolated from *Cleome Arabica.*

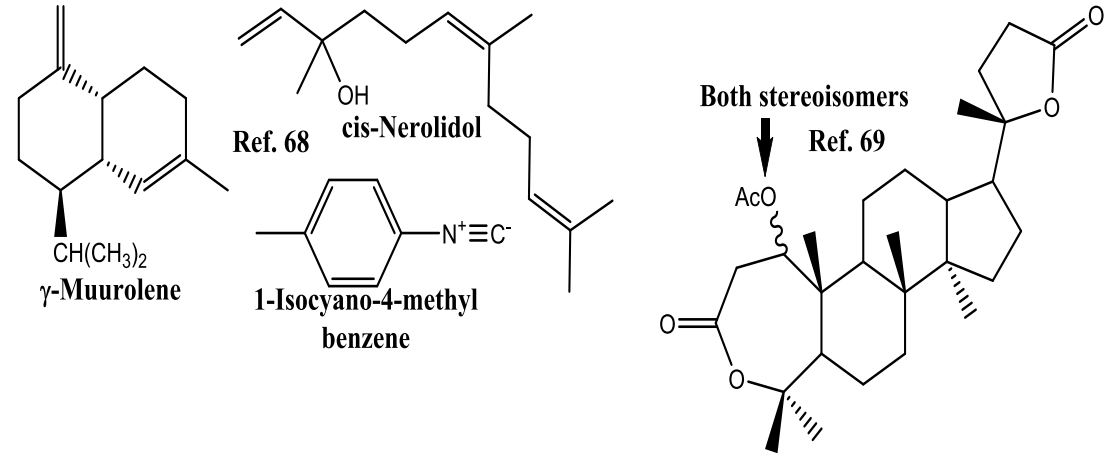


Figure 3: Natural products isolated from *Cleome chrysantha.*

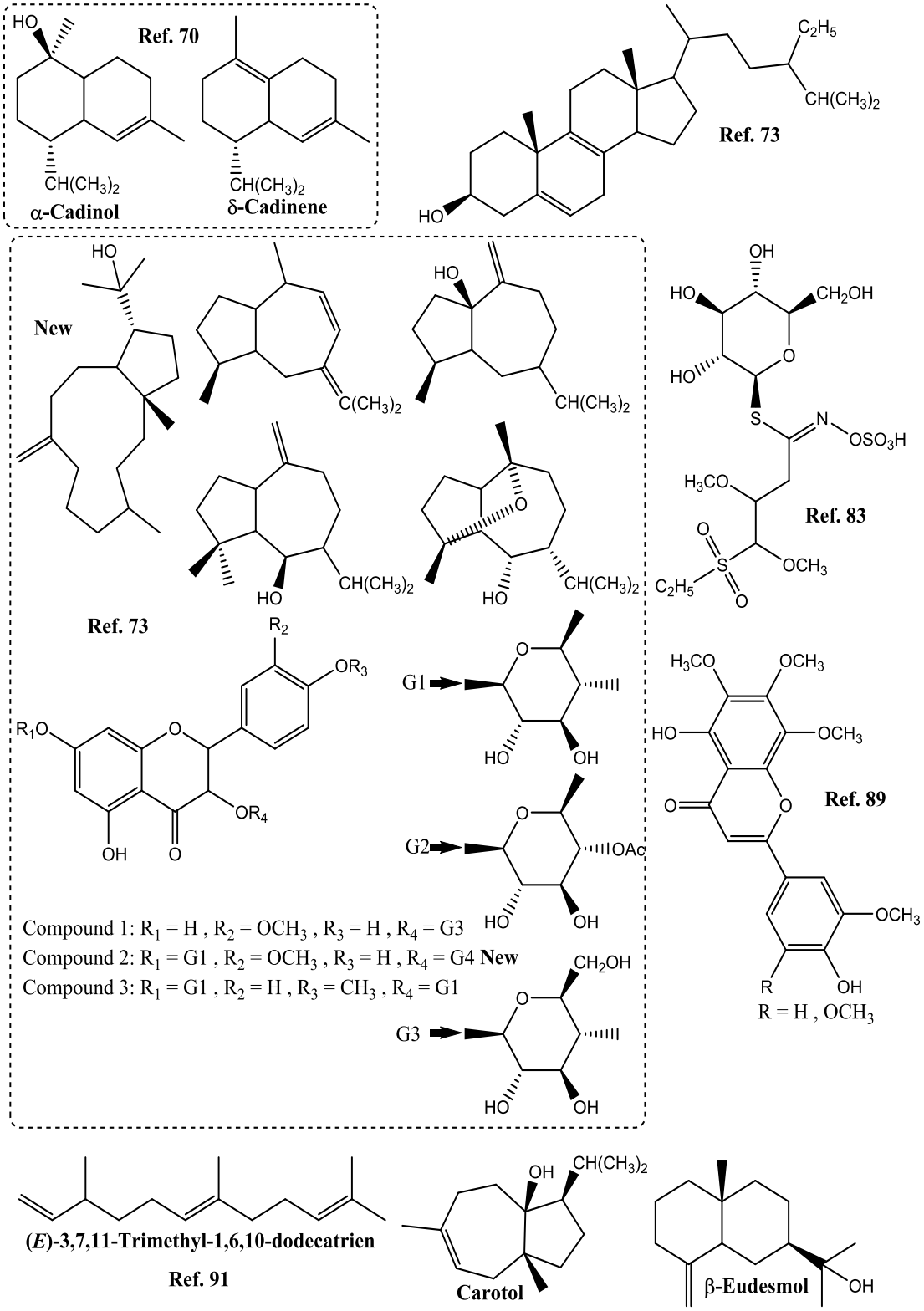


Figure 4A: Natural products isolated from *Cleome droserifolia.*

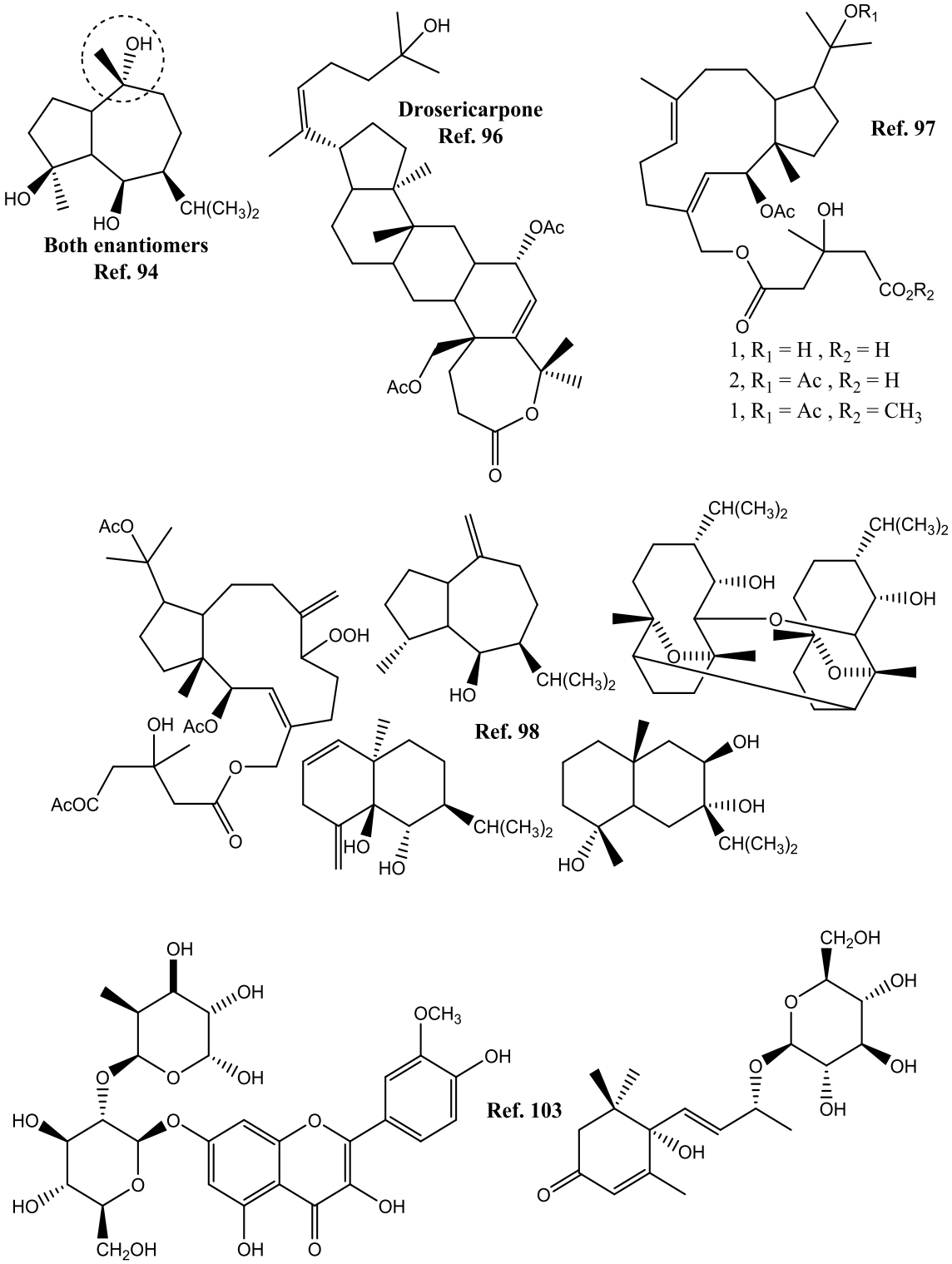


Figure 4B: Natural products isolated from *Cleome droserifolia.*

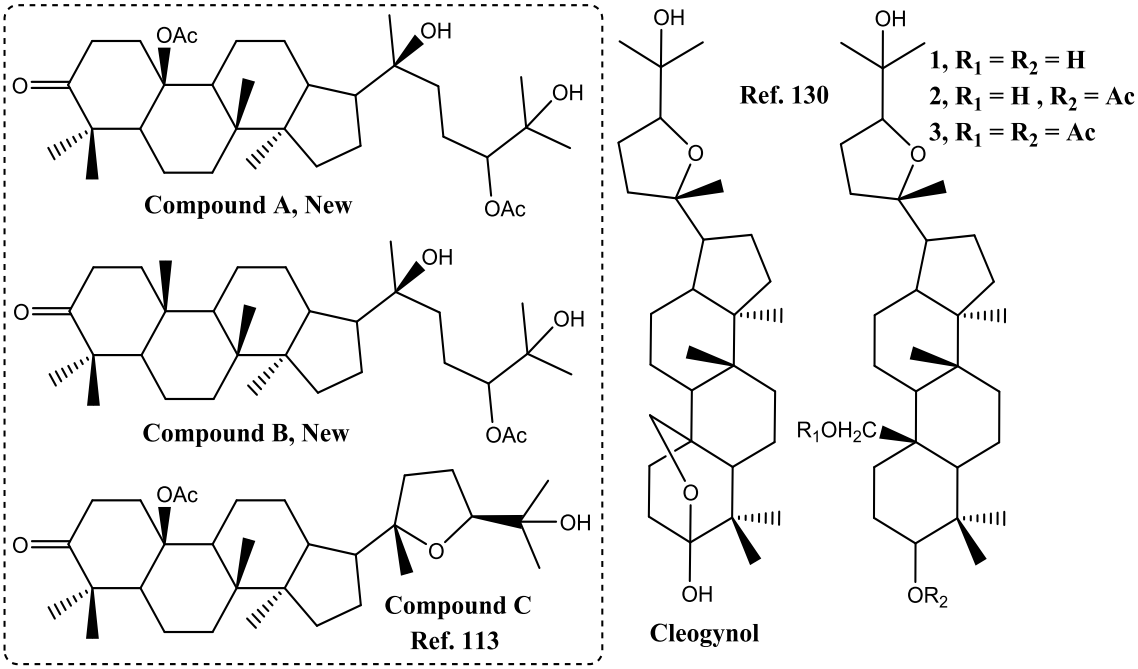
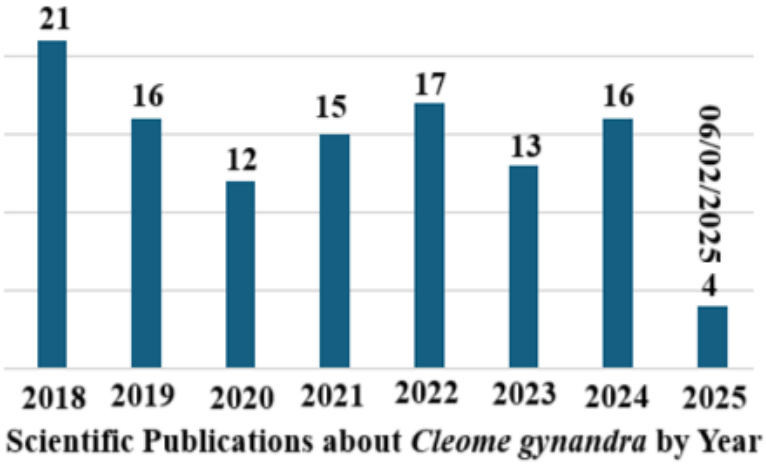


Figure 5: Natural products isolated from *Cleome gynandra.*

5) DISCUSSION

Scanning literature for articles about the *Cleome* genus is notably interesting task. One of the best examples of this statement is the number of articles that were published every year about this and/or its species, including those that do not grow wild in Israel and Palestine. But since our focus is on the five species of the reviewed region, we will consider *Cleome gynandra* as representing example. According to AI-based search website, R Discovery[146], the number of scientific publications in the years 2018-2025 about this species are as shown in the following chart, keeping in mind that tis review article is submitted for publication in the first half of February 2025.



One of the most recent articles which are within the scope of this review article was published by M.N. Mohamad Rosdi ahc.[147] It is a review article that focuses on anti-inflammatory activity of *Cleome gynandra*, but it also presents some traditional uses and pharmacological activities. Moreover, due to its nutritional values, *Cleome gynandra* is considered a vegetable with economic importance for some cultures.[148]

As for other *Cleome* species of the reviewed region such as *Cleome amblyocarpa*, its cultivation was tested under various growth conditions. S. Shahin ahc cultivated this species in sandy soils under various conditions of irrigation and water stress.[149] They found out significant variations in physical-morphological properties as well as differences in carotenes and proline contents. S. Soliman ahc published a closely related research where they expanded their study to drought conditions.[150] In addition to anatomical changes, they reported that notable variations in the contents of lipophilic compounds: hydrocarbons (cyclic and non-cyclic) and long hydrocarbon chains with other functional groups such as amine, alcohol and ester. A. Bennaoum ahc cultivated this species in uranium-contaminated soil and found out that the plant was tolerant to this pollution, and so, they conclude that it can be used as uranium phytoremediator.[151]

To achieve higher activities of *Cleome arabica* methanolic extracts, C. Atef ahc prepared them using two methods: traditional maceration and ultrasound-assisted.[152] They report clear and notable advantages of the second method in extract yield, TPC, TFC, antioxidant activity (DPPH method) and antibacterial activity (against *E. coli* and *S. aureus*). For similar objective of enhancing the biological activities of *Cleome arabica* leaves extract described in reference 52, H. Bouriche and J. Arnhold treated this extract with naringinase in order to deglycosylate the active flavonoids.[153] Compared with the untreated extract, the treated one had notable higher activity of chemotaxis reduction in human neutrophils.

Cleome droserifolia is considered an endangered species in most of its natural habitat, especially in the Middle East. For this reason, attempts to conserve this plant are being done for almost four decades. Among these attempts, A.K. Hegazy examined the ecology of *Cleome droserifolia* in Egypt.[154] Based of his findings, he recommends several steps of conservation. And in a more recent publication also from Egypt, A.A. Moustafa and M.K. Mahmoud, published a review article about this species.[155] The article presents the medicinal properties of this plant, its traditional uses, but focuses on its ecology, endangered status and propose some conclusions for future conservation efforts.

P.B. Ambre ahc published an article in 2020 titled: Isolation and phytochemical characterization of alkaloids from *Cleome gynandra*".[135] Reading this publication very carefully reveals that not a single alkaloid was isolated and more important, characterized. So, this title is misleading in best case. Contrary to that, M. Srief ahc isolated 2-aminothiazole (**Figure 1A**) from *Cleome amblyocarpa*.[27] And even though numerous publications reported the presence of alkaloids in *Cleome* species of Israel and Palestine, these reports were almost exclusively as part of general chemical compositions. So, in addition to the report of Srief ahc, J. Hussain ahc reported a new alkaloid isolate from *Cleome droserifolia* (**Figure 6**).[156] This alkaloid was tested for inhibition of urease (moderate) and α-glucosidase (high).

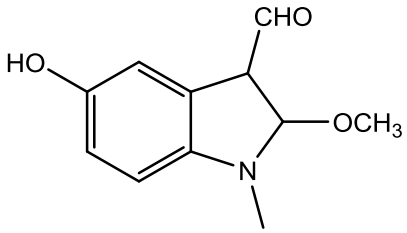


Figure 6: Indole alkaloid isolated from *Cleome droserifolia*.[156]

Cleome gynandra is the most investigated species among the five *Cleome* plants of the reviewed region, and several publications reported successful trials to cultivate it. One of these trials was published by B. Maniaji, where he applied various phosphorous levels and spacing between the cultivated plants.[157] T.M. Mwarozva ahc cultivated *Cleome gynandra* using animal manure as fertilizer and they reported high yields and other positive outcomes.[158] And because of the importance of this plant for large number of populations, and due its high adaptation to climate changes, C.V. Mashamaite ahc consider it vital for nutritional security of these populations.[159] In addition to cultivation and environmental condition, the drying method of its parts and harvest time, have also clear effect on the nutritional (and general) content of this plant, C. Abugre ahc reported.[160]

The importance of nanotechnologies in general and nanoparticles (NPs) is acknowledged by almost the entire scientific community.[161] Many of these NPs are prepared with "green" methods (Especially metal NPs), using plants extracts, mainly aqueous. These NPs have proved highly active, with or without additional pharmacological load. In **Table 4** a summary of the NPs that were prepared using *Cleome* species of Israel and Palestine or using these NPs for drug delivery.

Table 4: NPs of *Cleome* Plants of Israel and Palestine.

Cleome species	NPs and their use	Reference
C. amblyocarpa	Ag, antifungal	[162,163] *
C. droserifolia	Se-Plant-Extract, antidiabetic	[164]
C. gynandra	Ag_2O, antimicrobial	[165]
	Ag, antimicrobial	[166,167]
	Ag, anticancer	[168]
	Solid lipid-Extract, antidiabetic	[169]
	ZnO, anticancer	[170]

* These two publications of the same research group reported the same results.

6) CONCLUSIONS

1) Species of *Cleome* genus in Israel and Palestine possess important medicinal activities.
2) Yet, additional research is needed to study many other properties that were not published.
3) Special attention should be drawn to safety contradicting reports.
4) *Cleome* are good candidates for arid zones agriculture in climate change conditions.
5) It is highly important to investigate the medicinal properties of *Cleome chrysantha*.

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