IOSR Journal Of Pharmacy
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 10, Issue 9 Series. I (September 2020), PP. 19-32
www.iosrphr.org

Bioactive ingredients and pharmacological effects of *Nerium oleander*

Ali Esmail Al-Snafi
Department of Pharmacology, College of Medicine, Thi qar University, Iraq.
Received 17 September 2020; Accepted 02 October 2020

ABSTRACT:
The phytochemical screening showed that of Nerium oleander contained alkaloids, flavonoids, carbohydrates, tannins, phenolics, saponins, cardenolides, cardiac glycosides, pregnanes, triterpenoids, triterpenes and steroids. The previous pharmacological studies revealed that Nerium oleander possessed antioxidant, anticancer, antimicrobial, antiparasitic, antinflammatory, analgesic dermatological, hypolipidemic, antidiabetic, cardiovascular and central nervous effects. current review highlighted the bioactive ingredients and pharmacological effects of Nerium oleander.
KEYWORDS: Nerium oleander, ingredients, pharmacology, therapeutic

I. INTRODUCTION:

In the last few decades there has been an exponential growth in the field of herbal medicine. It is getting popularized in developing and developed countries owing to its natural origin and lesser side effects. Plants generally produce many secondary metabolites which are bio-synthetically derived from primary metabolites and constitute an important source of chemicals which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives[1-2]. Recent reviews revealed that the medicinal plants possessed central nervous[3-4], cardiovascular[5], antioxidant[6-7], reproductive[8-9], gastro-intestinal[10-12], respiratory[13], antidiabetic[14-15], galactagogu[16-17], antimicrobial[18-20], antiparasitic[21-22], dermatological [23], anticancer[24], anti-inflammatory, antipyretic and analgesic[25-26], immunological[27], hepato and reno-protective[28-30] and many other pharmacological effects. The phytochemical screening showed that of *Nerium oleander* contained alkaloids, flavonoids, carbohydrates, tannins, phenolics, saponins, cardenolides, cardiac glycosides, pregnanes, triterpenoids, triterpenes and steroids. The previous pharmacological studies revealed that *Nerium oleander* possessed antioxidant, anticancer, antimicrobial, antiparasitic, antinflammatory, analgesic dermatological, hypolipidemic, antidiabetic, cardiovascular and central nervous effects. current review highlighted the bioactive ingredients and pharmacological effects of *Nerium oleander*. The current review was designed to highlight the chemical ingredients and pharmacological effects of *Nerium oleander*

Synonyms:

Nerion oleandrum, Nerium carneum, Nerium flavescens, Nerium floridum, Nerium grandiflorum, Nerium indicum, Nerium indicum subsp. kotschyi, Nerium indicum var. leucanthum, Nerium indicum f. leucanthum, Nerium indicum var. lutescens, Nerium indicum f. lutescens, Nerium indicum var. plenum, Nerium japonicum, Nerium kotschyi, Nerium latifolium, Nerium lauriforme, Nerium luteum, Nerium mascatense, Nerium odoratissimum, Nerium odoratum, Nerium odorum, Nerium oleander var. indicum, Nerium oleander subsp. kurdicum, Nerium splendens, Nerium thyrsiflorum, Nerium verecundum, Oleander indica, and *Oleander vulgaris*[31].

Taxonomic classification:

Kingdom:Plantae, **Subkingdom**: Viridiplantae, **Infrakingdom**: Streptophyta, **Superdivision**: Embryophyta, **Division**: Tracheophyta, **Subdivision**: Spermatophytina, **Class**: Magnoliopsida, **Superorder**:Asteranae, **Order**: Gentianales, **Family**: Apocynaceae, **Genus**: *Nerium*, **Species**: *Nerium oleander*[32].

Common names:

Afrikaans: selonsroos; **Arabic**: Difla, Ward Al-Hemar, Sim Al-Hemar; **English**: oleander, rose bay, rose-laurel; **French**: oleander; **German**: Oleander; **Japanese**: kyōchiku-tō; **Portuguese**: espirradeira, oleandro; **Spanish**: Adelfa, balandre, laurel rosa, Pascua[33].

Distribution:

It was distributed in **Africa** (Algeria, Libya, Morocco, Tunisia, Niger), **Asia** (United Arab Emirates, Afghanistan, Cyprus, Iran, Iraq, Palestine, Jordan, Lebanon, Syria, Turkey, China, India,

Nepal, Pakistan), **Europe** (Albania, Croatia, Greece, Italy, Malta, France, Portugal, Spain) and cultivated in wide areas[33].

Description:

An erect evergreen shrub, branches glabrous. Leaves 10-15 X 1-2 cm, linear-lanceolate, tapering at both ends, acuminate, thick coriaceous, midrib prominent, petiole 5-7.5 mm long. Flowers white, pink or dark red, single or double, form, fragrant 3-4 cm across, peduncle and pedicel hairy, bracts small, 5-7.5 mm long. Calyx divided into 5 linear, acute lobes, hairy with gland at the base inside. Corolla tube 1.8 cm long, hairy within, throat narrow, ending in five twisted petals, tips rounded, corona of 5 scales near the throat of the corolla, cleft into 4-7 linear segments. Stigma two lobed. Fruit 12-20 cm x 7 mm long[34-35].

Traditional uses:

The leaves were used externally in chronic and obstinate skin diseases including leprosy and alopecia. The powder of leaves was used as a snuff for treating epilepsy. Root powdered with water was applied to alleviate venereal diseases and for the treatment of haemorrhoids[36].

Parts used:

All plant parts were used medicinally[36].

Chemical constituents:

The preliminary phytochemical screening showed that the plant contained alkaloids, flavonoids, carbohydrates, tannins, phenolics, saponins, cardenolides, cardiac glycosides, pregnanes, triterpenoids, triterpenes and steroids[37-39]

The plant contained cardenolides: [16-acetyl neogistonin; adynerin; 5alpha-adynerin; gentiobiosyladynerin; delta 16-dehydroadynerin; digitoxigenin; oleandroside; gentibioosyl-odoroside A; gentiobiosyl-oleandrin; glucosyl; leandrin; oleandrigenin glucoside; kaneroside; neriaside;nerigoside; jieriumoside; neridiginoside; nerizoside; neritaloside; odoroside-H; 12β-hydroxy-5β-carda-8,14,16,20(22)-tetraenolide; 3 beta-O-(D-2-O-methyldigitalosyl)-14 beta-hydroxy-5 beta-carda-16,20(22)-dienolide; 3 beta-hydroxy-8,14-epoxy-5 beta-carda-16,20(22)-dienolide; 3 beta-O-(D-digitalosyl)-14 beta-hydroxy-16 beta-acetoxy-5 beta-card-20(22)-enolide; 3 beta-O-(D-digitalosyl)-14 beta-hydroxy-5 beta-card-20(22)-enolide, cardenolides N-1, N-2, N-3, and N-4]; pregnanes and pregnane glycosides [12beta-hydroxy-16alpha-metfioxy-pregna-4,6-dien-3,20-dione, 21- hydroxypregna- 4, 6- diene- 3, 12, 20- trione, 20Rhydroxypregna-4,6-diene- 3, 12- dione, and 16beta, 17beta-epoxy- 12betahydroxypregna- 4, 6-diene- 3, 20- dione, 12beta- hydroxypregna- 4, 6, 16- triene3,20-dione (neridienone A) and 20S, 21- dihydroxypregna- 4, 6- diene-3, 12- dione (neridienone B)][40-49].

The maximum amount of oleandrin was in the roots, followed leaves, stems then flowers. Oleandrin concentrations in plant parts ranged from 0.18 to 0.31mg/g dry weight (10-18%) in leaves, and from 0.12-0.23mg/g dry weight (9-20%) in stem, and from 0.34 to 0.64mg/g dry weight (10-18%) in roots[50].

Triterpenoid: (alpha-neriursate, beta-neriursate, oleanderolic acid, kanerodione, neriucoumaric, isoneriucoumaric acids, 3β, 27- dihydroxy- urs- 18- en- 13, 28- olide and 3β, 22α, 28-trihydroxy-25-nor-lup-1 (10), 20 (29)-dien-2- one20, ciskarenin (3β-hydroxy-28-Z-pcoumaroyloxy-urs-12-en-27-oic acid) and trans-karenin (3-β-hydroxy-28-E-pcoumaroyloxy-urs-12-en-27-oic acid)were also isolated from the leaves of *Nerium oleander*[51-54].

Taraxasterane-type triterpenes (20beta,28-epoxy-28 alpha methoxy taraxasteran- 3beta-ol and 20 beta, 28-epoxytaraxaster-21-en-3beta-ol), and ursane-type triterpenes (28-nor- Urs-12-ENE-3beta,17beta-diol and 3beta-hydroxyurs-12-en-28-Aldehyde) were isolated from ethyl acetate extract of the leaves of *Nerium oleander*[55].

The flowers yielded 1.76% total oil, 34 compounds were identified in the oil, the major components were nériine (22.56%), digitoxigénine (11.25%), amorphane (8.11%), 1.8-cineole (6.58%), α-pinene (5.54%), calarene (5.12%), limonene (5.01%), β-phellandrene (4.84%), terpinene-4-ol (3.98%), sabinene (3.22%), isoledene (2.94%), 3-carene (2.56%), humulene (2.29%), β-pinene (2.01 %) and cymen-8-ol (1.67%)[56].

A water extract of crushed leaves of *Nerium oleander* yielded 2.3% crude polysaccharide. The main fraction (67%) was a pectic polysaccharide, which mainly mainly composed of galacturonic acid besides rhamnose, arabinose and galactose[57-58].

The total phenolics of *Nerium oleander* flower was 136.54±3.32mg gallic acid equivalent/ g essential oil[59]. The total phenolic content of water, methanol, water: methanol and acetone extracts of *Nerium oleander* leaves were 4.54 ± 0.23, 4.25 ± 0.23, 2.08 ± 0.38 and 4.21 ± 0.29 and of flowers were 7.52 ± 0.93, 7.15 ± 0.43, 6.24 ± 0.57 and 7.13 ± 0.49µg gallic acid equivalent per 100 µg extract respectively[60]. Kaempferol, kaempferol 3-O-β-glucopyranoside and chlorogenic acid were isolated from the ethyl acetate sub-extract of the *Nerium oleander* flower ethanolic extract[61].

Pharmacological effects:

Antioxidant effect:

The antioxidant activity of the essential oil was studied by three methods (DPPH assay; β-Carotene/linoleic acid a bleaching assay and ferric reducing power assay). *Nerium oleander* essential oil possessed significantly antioxidant activity compared to synthetic antioxidants (trolox and BHT)[59].

The antioxidant effects of the leaves and flowers extracts (0.5, 0.25, 0.125, 0.0625, 0.0312, 0.0156, 0.0078, 0.0039 and 0.0019 mg/ml) were evaluated by DPPH. The methanol extracts of the leaves and flowers possessed high antioxidant activity with RC_{50} value of 0.27, 0.2mg/ml, respectively[62].

The antioxidant activity of water, methanol, water: methanol, and acetone extracts of *Nerium oleander* grown in the north of Iran was studied by employing various *in-vitro* assay (DPPH free radical scavenging, reducing power and total antioxidant capacity). The methanolic and aqueous methanolic extracts were the most potent antioxidant extracts. The total antioxidant activity of four extracts (water, methanol, water: methanol and acetone) of *Nerium oleander* leaves were 1.280 ± 0.02, 1.246 ± 0.01, 0.982 ± 0.01, 0.912 ± 0.004 and *Nerium oleander* flowers were 2.330 ± 0.04, 1.386 ± 0.02, 1.596 ± 0.04, 2.930 ± 0.01 mg ascorbic acid equivalents/mg extract[30]

The antioxidant activity of the flower extract of *Nerium oleander* was determined using DPPH free radical scavenging assay and reducing power assay. The DPPH antioxidant assay indicated that the ethanolic extract had a considerable scavenging capacity and reducing power activity[63].

In vitro antioxidant activity of methanolic extract of flowers of *Nerium oleander* was evaluated by different *in vitro* models. The extract showed potent activities on reducing power, lipid peroxide, DPPH, ABTS, superoxide anion, hydroxyl radical and metal chelation[64].

The free radical scavenging potential of the hydroethanolic extract of *Nerium oleander* flower and its fractions (glycosidic and nonglycosidic) were studied using DPPH and ABTS models. The extract exhibited better radical scavenging activities than its fractions[65].

Anticancer effect:

Antitumor activity of the essential oil was tested on Ehrlich ascites carcinoma cells line. The result revealed gradually increase of antitumor activity with increasing of oil concentration[59].

The cytotoxic effects of dichloromethane extracts of the leaves and flowers were studied against T47D: human breast cancer (Pasteur, C203), HepG-2: human hepatocellular carcinoma (Pasteur, C124) and K562: human chronic myeloid Leukemia (Pasteur, C122) cell lines. The dichloromethane extracts of the leaves possessed high cytotoxic effects against T47D, HepG-2 and K562 cell lines with IC_{50} value of 57.77, 55.90 and 70.03µg/ml, while the same extract of the follower showed IC_{50} value of 233.42, 108.31 and 102.31 µg/ml, against the same cell lines, respectively[62].

The cytotoxic effect of the alcohol extract of *Nerium oleander* was studied against liver cancer cell line (HEPG2) using 10 concentrations. The results showed that the inhibition of tumor cell line was increased gradually with the increase of the extract concentration, with a maximum inhibitory effect (39%) at a concentration of 75µg/mt. However, the inhibitory effect was decreased to (23%) at a concentration of 150 µg/ml of *Nerium oleander* extract[66].

The cytotoxic activity of five compounds [21-hydroxypregna-4,6-diene-3,12,20-trione; 20R-hydroxypregna-4,6-diene-3,12-dione; 16β,17β-epoxy-12β-hydroxypregna -4,6-diene-3,20-dione; 12β-hydroxypregna-4,6,16-triene-3,20-dione (neridienone A) and 20S,21-dihydroxypregna-4,6-diene-3,12-dione (neridienone B)] isolated from *Nerium oleander*, was evaluated against four human cell lines, normal human fibroblast cells (WI-38), malignant tumor cells induced from WI-38 (VA-13), human liver tumor cells (HepG2), and human lung carcinoma cells (A-549). Neridienone A, showed significant cell growth inhibition of VA-13 and HepG2 cells. The MDR-reversal activity of the isolated compounds was evaluated on the basis of the amount of calcein accumulated in MDR human ovarian cancer 2780AD cells in the presence of each compound. Three compounds [21-hydroxypregna-4,6-diene-3,12,20-trione; 20R-hydroxypregna-4,6-diene-3,12-dione; and 20S,21-dihydroxypregna-4,6-diene-3,12-dione (neridienone B)] showed significant effects on calcein accumulation[42].

The hydroalcoholic extract from the leaves of *Nerium oleander* (containing 4.75 ± 0.32 % of cardenolides) was tested for its cytotoxic activity in A549 lung cancer cells vs. MRC5 nonmalignant lung fibroblasts. The cytotoxicity of the *Nerium oleander* extract against the cancer cell line was significantly higher than that against the nonmalignant cell line, with a potency and selectivity similar to those of cisplatin[67].

Seven compounds isolated from the dried aerial parts of *Nerium oleander* exhibited significant cytotoxicity against four colon cancer cell lines (HCT116, HT29, SW620, RKO), one gastric cancer cell line (GT) and one cervical cancer cell line (HeLa) *in vitro*[68].

The *in vitro* cytotoxic effect of *Nerium oleander* leaves, stems and roots extracts was investigated against HL60 and K562 leukemia cell lines. The cells were incubated with six different concentrations of each

of the three extracts. It appeared that 1000, 500 and 50 microg/ml from each extract possessed marked antileukemic effects. *Nerium oleander* leaf and root extracts were more cytotoxic than the stem extract according to LC_{50}. It also appeared that their cytotoxic effects were mediated by inhibiting of the P-gp pump in leukemia cells[69].

The cardenolide containing fractions from the cold aqueous extract of *Nerium oleander* leaves possessed anticancer effects (IC_{50} 0.85 µg/ml) against 36 human tumor cell lines[70].

The mechanisms and differential cell-killing effects of Anvirzel, an extract of *Nerium oleander* (1.0 ng/ml to 500 microg/ml), and its derivative compound oleandrin (0.01 ng/ml to 50 microg/ml) on human, canine and murine tumor cells were studied *in vitro*. Both Anvirzel and oleandrin were able to induce cell killing in human cancer cells, but not in murine cancer cells; the cell-killing potency of oleandrin was greater than that of Anvirzel. Canine oral cancer cells treated with Anvirzel showed intermediate response (abnormal metaphases and cell death)[71].

The antitumor efficacy of PBI-05204, a supercritical CO_2 extract of *Nerium oleander* containing oleandrin was studied in a human pancreatic cancer Panc-1 orthotopic model. All the control mice exhibited tumors by the end of treatment, while, only 2 of 8 mice (25%) treated for 6 weeks with PBI-05204 (40 mg/kg) showed dissectible tumor at the end of the treatment period. The average tumor weight in mice treated with PBI-05204 (20 mg/kg) was significantly reduced (222.9 ± 116.9 mg) from that in controls (920.0 ± 430.0 mg) ($P < 0.05$). Histopathologic examination of serial sections from each pancreas with no dissectible tumor in the PBI-05204 (40 mg/kg) treated group showed that the pancreatic tissues of 5/6 mice were normal. PBI-05204 markedly enhanced the antitumor efficacy of gemcitabine. Ki-67 staining was reduced in pancreatic tumors from mice treated with PBI-05204 (20 mg/kg) compared to that of control, suggesting that PBI-05204 inhibited the proliferation of the Panc-1 tumor cells. PBI-05204 also suppressed expression of pAkt, pS6, and p4EPB1 in a concentration-dependent manner in both Panc-1 tumor tissues and human pancreatic cancer cell lines[72-73].

Anvirzel, (an extract of *Nerium oleander* which contained two active glycosides oleandrin and oleandrigenin) produced a 51.9 and 30.8% inhibition of FGF-2 release from two human prostate cancer cell lines, DU145 and PC3, respectively at non toxic concentrations (100 ng/ml), which could be contributed to the antitumor activity of Anvirzel [74].

Antimicrobial effect:

Antimicrobial activity of th**e** essential oil was examined against different strains of Gram-positive and Gram-negative bacteria, yeast and mold. The essential oil showed a variable degree of antimicrobial activity against the tested strains, the MIC values were ranged from 125 to 500 and 250 to 2000 ug/µl for bacteria and fungi respectively[59].

The extracts of the leaves and flowers were studied for antibacterial activity against *Escherichia coli*, *Staphylococcus epidermis*, *Staphylococcus aureus*, *Bacillus cereus*, *Erwinia carotovora* and *Bacillus pumillus*. Dichloromethane and methanol extracts of both leaves and flowers, showed strong antibacterial activity against both Gram negative and Gram positive bacteria (except *Staphylococcus epidermis*)[62].

The antibacterial activity of essential oils of *Nerium oleander* was examined against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The tested bacterial strains were sensitive to essential oils, the MIC against *Escherichia coli* was 1.45, *Pseudomonas aeruginosa* 2.87 and *Staphylococcus aureus* 5.10mg/ml[56].

The antimicrobial activity of the roots bark and leaf extracts of of *Nerium oleander* was studied against *Bacillus pumilus*, *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Aspergillus niger*. The chloroform, ethanol and methanol extracts of *Nerium oleander* showed high activity against all the tested bacteria (zone of growth inhibition 20-23 mm after 24 hrs incubation). All the crude extracts showed no antifungal activity against *Aspergillus niger*[75].

The aqueous and ethanol extracts of *Nerium oleander* were tested for their antibacterial activity against *Shigella dysenteriae, Aeromonas hydrophila, Escherichia coli, Enterobacter spp, Klebsiella spp, Pseudomonas aeruginosa* and *Staphylococcus aureus*. The ethanol extracts showed higher antibacterial activity compared with the aqueous extract. The MICs of the aqueous extracts were 25- 100 mg/ml, while that of the ethanol extract was 25 -50 mg/ml, the minimum MBCs were 25-100 mg/ml for ethanol extract, and 25-200 mg/ml for the aqueous extracts[76].

The antibacterial activity of aqueous leaf extract of *Nerium oleander* was studied against Gram positive (*Bacillus subtilis*, *Staphylococcus aureus*), and Gram negative bacteria (*Pseudomonas aeruginosa*, *Escherichia coli* and *Proteus mirabilis*). The aqueous leaf extract of *Nerium oleander* significantly inhibited the growth of all the tested bacteria, at concentration of 100%, 80% and 60%[77].

The antimicrobial effect of the flower extract of *Nerium oleander* was evaluated against two Gram-positive (*Bacillus subtilis*, *Staphylococcus aureus*) and three Gram-negative bacteria (*Escherichia coli*, *Salmonella typhi* and *Pseudomonas aeruginosa*). The antifungal activity was tested against *Aspergillus niger*,

Aspergillus flavus, Aspergillus fumigates and *Rhizopus* species. The ethanolic flower extract was the most active against the selected microorganisms (zone of inhibition 17-25mm). Aqueous extract also possessed significant antibacterial activity (zone of inhibition 10-25mm), while, chloroform extract was the least effective one (zone of inhibition 9-18mm). All extracts possessed antifungal activities against all the tested fungi (zone of inhibition 10-18mm)[63].

The antimicrobial activity of aqueous ethanolic extract of *Nerium oleander* was investigated against *Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa*. The ethanolic extract of *Nerium oleander* leaves showed high concentration dependent antibacterial action against all the tested microorganisms (*Staphylococcus aureus* 22 mm, *Escherichia coli:* 24 mm and *Pseudomonas aeruginosa* 28 mm at 900mg/ml)[78].

The antimicrobial effects of the crude and pure extracts of *Nerium oleander* were investigated against three Gram negative (*Escherichia coli, Pseudomonas aeruginosa and Salmonella enteritidis*), and three Gram positive bacteria (*Bacillus subtilis, Listeria monocytogenes and Staphylococcus aureus*) and six fungal species (*Aspergillus flaws, A. fumigatus, A. niger, Fusarium moniliforme, Penicillium expansum* and *Rhizopus oryzae*). The crude extract of *Nerium oleander* possessed significant antimicrobial activity against all the tested Gram positive and negative bacterial species (diameter of growth inhibition ranged from 2-15 mm). The maximum antibacterial activity (15 mm) was exhibited against *B. subtilis.* The MIC of the crude extract of *Nerium oleander* were: *E. coli* 50, *P. aeruginosa* 75, *S. enteritidis* >l00, *B. subtilis* 50, *L. ntonocytogenes* >l00 and *S. aureus* >l00μg/ml. The maximum antifungal activities (15 and 20 mm inhibition zone) was exhibited by the crude extract against *A. flavus*. The MIC of the crude extract was *A. flavus* 25, *A. fumigates* >l00, *F. moniliform* >l00, *P. chrysogenium* 50 and *R. oryzae* >l00μg/ml[79].

The therapeutic effectiveness of Anvirzel™, an aqueous extract of *Nerium oleander*, was studied against HIV infection of human peripheral blood mononuclear cells. Virus in cultures treated with oleandrin (the main constituents of Anvirzel™) significantly reduced expression of the envelope protein gp120, the sole determinant of virus infectivity, suggesting a novel mechanism underlying the impaired infectivity[80].

The antiviral activity of hot and cold extract of *Nerium oleander* was studied against six different viruses [herpes simplex virus type 1 (HSV-1), polio virus type 1 (Sb-1), vesicular stomatitis virus (VSV), reovirus type-1 (Reo-1), human immunodeficiency virus type-1 (HIV-1), and yellow fever virus (YFV)]. The results of plaque reduction assay demonstrated that both, hot and cold extracts inhibited Sb-1 viral infection. they exerted their effect after infection period, particularly during the first two hours post infection[81].

The antifungal activities of *Nerium oleander* (leaves, stem and root aqueous, methanol, ethanol, choloroform and acetone extracts) were examined against three fungi (*Macrophomina phaseolina, Sclerotium rolfsii* and *Fusarium oxysporum*). All the parts of the plant displayed variable results against the three fungi. Chloroform root extract was the most effective one in reducing the growth of *M. phaseolina*, followed by acetone root extract. Leaves chloroform extract displayed the best antifungal activity against *S. rolfsii* followed by methanol, acetone, and ethanol leaves extracts. Shoot extracts induced the maximum effect against *F. oxysporum*, followed by chloroform and ethanol shoot extracts respectively[82].

Antiparasitic effect:

The aqueous leaf extract of *Nerium oleander* possessed ovicidal and larvicidal properties when tested against *Culex tritaeniorhynchus* and *Culex gelidus*[83].

The crude hexane and aqueous extract of *Nerium oleander* flowers were investigated for larvicidal activity against the filarial vector, *Culex quinquefasciatus*. Mortality was observed for 24 and 48 hours. Hexane flower extract exhibited highest larvicidal activity with a LC_{50} value of 102.54 ppm and 61.11ppm after 24 and 48 hours respectively[84].

The insecticidal activity of the extract of *Nerium oleander*, was studied against the larval stages 3 and 4 of *Culex pipiens*. The LC_{50} and LC_{90} of the ethanolic extract of *Nerium oleander* were 57.57 mg/ml and 166.35 mg/ml, respectively[85].

The larvicidal activity of water, chloroform, acetone and diethyl ether extracts of *Nerium oleander* leaves, was tested against *Culex pipiens*. The toxicity of the four extracts, using the LC_{50}, at 10 °C was higher than that at 35 °C. Diethyl ether extract of *Nerium oleander* leaves was the most potent extract, with LC_{50} of 10500 mg/l. The diethyl ether extract significantly decreased the larval duration, pupal duration, percentage of pupation, percentage of adult emergence, longevity of females, fecundity, and oviposition activity index, whereas the growth index and the percentage of development per day of larvae and pupae were significantly increased compared to non-treated insects[86].

The larvicidal activity of *Trigonella foenum* and *Nerium oleander* leaf extracts was studied against different mosquito larvae, the larvicidal effect of the combination of both plant extracts was also studied. The results showed that the leaf extract of *Trigonella foenum* and *Nerium oleander* possessed larvicidal activity (3% concentration showed 50 and 20% mortality after 72 hrs exposure, respectively), and the combination of the

extracts, showed higher larvicidal activity (3% concentration of the combination showed 100% mortality after 48 hrs exposure)[87].

The insecticidal effect of ethanolic extract of the leaves of *Nerium oleander* was studied against 2nd instar larvae of the medically important false stable fly *Muscina stabulans*. LC_{50} of the extract was 113.66 ppm. It delayed larval and pupal duration, suppressed oviposition and decreased adult longevity of the survivors[88].

Antinflammatory and analgesic effects:

The anti-inflammatory activity of compounds neridienone A isolated from *Nerium oleander*, was evaluated on the basis of inhibitory activity against the induction of intercellular adhesion molecule-1 (ICAM-1). The compound neridienone A, possessed significant inhibitory activity against the induction of ICAM-1[42].

The *in vitro* anti-inflammatory activities of the *Nerium oleander* flower ethanolic extract and its subextracts (n-hexane, dichloromethane, ethyl acetate and water) were evaluated on LPS induced Raw 264.7 macrophages. The effects of the crude ethanolic extract and its subextracts were also studied on nitric oxide (NO) production and cell viability. The most active anti-inflammatory subextract was the ethyl acetate, without exerting any toxicity towards Raw 264.7 macrophages. This subextract significantly inhibited NO production of Raw 264.7 macrophages after LPS induction (62.56±1.91% at 200 µg/ml concentration). It reduced the levels of iNOS up to 67.50%. It also slightly reduced the phosphorylation levels of MAP kinases (p-ERK, p-JNK, p-38). The highest inhibition was observed for ERK phosphorylation, which was inhibited by 20.53% at 200 µg/ml concentration[89].

The anti-inflammatory potential of the ethonolic extract of the flowers of *Nerium oleander* was investigated against denaturation of egg albumin. The extract caused concentration dependent inhibition of protein (albumin) denaturation at concentration ranged from 100 to 500 µg/ml. IC_{50} value of the ethanolic extract of *Nerium oleander* was 236.03 µg/ml whereas that of diclofenac sodium was 231.76 µg/ml[90].

Ethanolic and aqueous extracts were evaluated for *in vivo* anti-inflammatory and antinociceptive activities. *Nerium oleander* possessed significant antinociceptive activity against p-benzoquinone-induced abdominal contractions in mice. It also exhibited potent anti-inflammatory activity against carrageenan-induced hind paw edema model in mice without inducing any gastric damage[91].

Dermatological effects:

The effect of aqueous leaf extract of *Nerium oleander* (80% and 100 % applied twice daily) on healing of wound was investigated in incision wounds in rabbits. Wound showed complete healing at 6-7 days compared with local antibiotic fucine ointment without complication[77].

The wound healing effects of Aloev era- based extract of the *Nerium oleander* leaf (NAE-8®) (topical application twice a day for 14 consecutive days) were studied in thermal injury in comparison with silver sulfadiazine treatment in rats. Thermal injury- induced alterations in malondialdehyde, glutathione, myeloperoxidase, TNF-α, interleukin-1β, and % DNA in the tail, these alterations were significantly reversed by NAE-8® treatment. The ameliorative effects of NAE-8® were also supported by histological findings[92].

The NAE-8® (an Aloe vera-based *Nerium oleander* extract, a novel component of a commercial cosmetic product), provided significantly better antioxidant protection in the cellular antioxidant protection of erythrocytes (CAP-e) bioassay than aqueous extract of *Nerium oleander*. NAE-8® and aqueous extract of *Nerium oleander* both protected cellular viability and intracellular reduced glutathione, and reduced the ROS formation significantly when compared to control cells, both under inflamed and neutral culture conditions. The treatment of dermal fibroblasts with NAE-8® resulted in selective secretion of cytokines involved in collagen and hyaluronan production as well as re-epithelialization during wound healing. The authors concluded that NAE-8®, showed beneficial antioxidant protection in several cellular models, without the induction of leukocyte activation and secretion of inflammatory cytokines[93].

Antihyperlipidemic activity:

The antihyperlipidemic activity of the 50% hydroethanolic extracts of *Nerium oleander* flowers was studied using Triton WR-1339-induced hyperlipemic rats compared with atorvastatin. Plasma lipids and lipoproteins were significantly elevated by the intraperitoneal infection of Triton WR 1339 in rats at 6th and 24th hour. Extract pretreatment showed a significant ameliorative action on elevated lipids and lipoproteins in a dose dependent manner compared to standard[94]

The effect of *Nerium oleander* on the regulation of cholesterol metabolism in response to a high-fat diet was studied in rats. The high-fat diet group exhibited alterations in the expression levels of about 1945 genes compared to the normal diet group. The results showed that expression levels of 47 genes were altered related to cholesterol metabolism in high-fat diet and *Nerium oleander* leaf distillate-supplemented diet groups. The expression levels of seven genes in the *Nerium oleander* leaf distillate-supplemented diet group were significantly closer to those in the normal diet group than those of the high-fat diet group. The *Nerium oleander*

leaf distillate-supplemented food exerted considerable beneficial effects on cholesterol metabolism-related gene expression levels[95].

Nervous effects:

The central nervous activity of 50 % hydroalcoholic flower extract (100 and 200 mg/kg orally) of *Nerium oleander* was studied in mice. The locomotor activity was measured with an actophotometer, muscle relaxant activity by rotarod apparatus, the anticonvulsant activity by electroshock and pentyleneterazol- induced convulsion and sedative activity by potentiation of pentobarbital-induced sleep. The extract (at doses of 100 and 200 mg/kg) significantly reduced ($P< 0.01$) spontaneous locomotor activity and potentiated pentobarbital-induced sleep. At the higher dose (200 mg/kg) the extract showed 66 % protection against electroshock-induced convulsions, while the lower dose (100mg/kg) produced a significant reduction ($P< 0.01$) in pentylenetetrazol-induced convulsions[96].

Two fractions B-1 and B-3 purified from the methanolic extract of fresh, undried and uncrushed leaves of *Nerium oleander*, were studied to determine their actions on the central nervous system and behavior pattern in mice. Both fractions produced reduction in locomotor activity, rotarod performance and potentiation of hexobarbital sleeping time. These fractions also showed analgesic activity. Fraction B-1 showed 40% protection against picrotoxin induced convulsions, while fraction B-3 exhibited 60% protection against bicuculline induced convulsions[97].

The anti-anxiety effects of petroleum ether, chloroform, ethyl acetate, and methanol extracts of *Nerium oleander* flowers were evaluated using the elevated plus maze model. Chloroform and ethyl acetate extract showed significant increases in open arm entries and mean time spent in open arms at the dosages of (25 and 50 mg/kg) and (100 and 200mg/kg) respectively[98].

The anxiolytic activity of the aqueous extract (200 and 400 mg/kg) of *Nerium oleander* flowers, was studied in rats using elevated plus maze and digital actophotometer models. In elevated plus maze model, the aqueous extract at 200, 400 mg/kg showed that the number of entries and time spent in the open arms were increased significantly compared to the control animals. ($P<0.001$). In actophotometer model, two different doses of the extract (200 and 400mg/kg) showed a dose- dependent decrease in the locomotor activity, compared to the control animals ($P<0.001$)[99].

Cardenolides (3 beta-O-(D-2-O-methyldigitalosyl)-14 beta-hydroxy-5 beta-carda-16,20(22)-dienolide; 3 beta-O-(D-digitalosyl)-14 beta-hydroxy-16 beta-acetoxy-5 beta-card-20(22)-enolide and 3 beta-O-(D-digitalosyl)-14 beta-hydroxy-5 beta-card-20(22)-enolide) isolated from the leaves of *Nerium oleander*, were found to exhibit sedation in mice at a dosage of 25 mg/kg[43].

The skeletal muscle relaxant activity of the aqueous extract of *Nerium oleander* flowers was investigated in rats in comparison with diazepam. The result of the actophotometer test and rotarod test showed that the extract significantly ($P< 0.05$) reduced the motor coordination of the rats[100].

PBI-05204, a supercritical CO_2 extract of *Nerium oleander*, exerted significant neuroprotection to neural tissues damaged by oxygen and glucose deprivation occured in ischemic stroke. The neuroprotective activity of PBI-05204 was maintained for several hours after oxygen and glucose deprivation treatment. The neuroprotective activity of PBI-05204 was mediated through oleandrin and/or other glycoside constituents. Accordingly, the authors suggested a clinical potential for PBI-05204 in the treatment of ischemic stroke and prevention of associated neuronal death[101].

Antidiabetic effect:

The anti-diabetic capacity of a standardized hydromethanolic leaf extract (50 and 200mg/kg bw, for 20 days) of *Nerium oleander* was studied in alloxan induced diabetes in mice. The extract possessed antihyperglycaemic activity, it reduced blood glucose level by 73.79% after 20 days of treatment. Oral glucose tolerance test revealed increase in glucose tolerance as evident by 65.72% decrease in blood glucose in 3h post treatment. Percentage decrease in different liver marker enzymes were significant along with decrease in triglyceride and cholesterol levels, displaying potent antihyperlipidemic activity. Peroxidase and catalase activity in liver, kidney and skeletal muscle were significantly restored besides marked reduction in lipid peroxidation and normalization of hepatic glycogen level in the extract treated alloxanized mice[102].

The effect of *Nerium oleander* extract (250 mg/ kg bw/day for 4 weeks) on insulin, glucose levels and some liver enzymes activities, in comparison with sulfonylurea drug (glimepiride) was studied in streptozotocin- induced diabetic rats. Diabetic rats showed hypoinsulinemia and hyperglycemia compared to controls. The results revealed that glimepiride and the plant extract improved insulin and glucose levels. Treatment of diabetic rats with glimepiride or *Nerium oleander* extract also improved liver enzymes activities[103].

Cardiovascular effect:

The methanolic leaf extract exhibited potent action on the isolated right atrial preparation of rat, it inhibited the rate of spontaneously beating atria in a concentration dependent manner. The negative chronotropic effect was not antagonized either by antimuscarinic drug and adrenergic agonist. The extract also potentiated both spontaneous and electrically evoked contractions of vas deferens of rats and ileum of Guinea pig, this effect was not antagonized by the adrenergic blocker (tolazoline). The extract also inhibited electrically stimulated neurogenic twitch responses of rat phrenic nerve diaphragm preparation. This effect could not be reversed by the neostigmine[104].

The cardiac effects of the crude ethanolic extracts of the dried leaves on the force of contraction, heart rate and cardiac flow were studied in isolated Guinea pig hearts. The extracts possessed dose-dependent increases in all these parameters. The extract showed the same effects possessed by digoxin, since their dose-contraction-response curves were parallel[105].

The therapeutic and the protective effect of distillated *Nerium oleander* in diabetic cardiomyopathy was studied in rats. Type 2 diabetes was induced by combination of single dose streptozotocin injection and high fat diet for four weeks. Type 2 diabetes induced intracellular action potentials prolongation, which was prevented by therapeutic and preventive distillated *Nerium oleander* treatments. Treatments produced nearly complete restorations of diabetes-induced depressed amplitude and altered kinetics of contractile activities. Furthermore, both histopathological and biochemical results indicated that the distillated *Nerium oleander* induced beneficial effects on the diabetes induced excitation-contraction coupling alterations[106].

The cardioprotective role of the hydroethanolic extract of *Nerium oleander* flower (10, 30, 100 mg/kg, per oral) was tested in isoproterenol-induced myocardial toxicity in rats compared to propranolol. Pretreatment with the extract (10, 30, and 100 mg/kg) and propranolol for 2 weeks followed by isoproterenol challenge in rats prevented the elevation of marker enzymes such as lactate dehydrogenase, γ-glutamyl transferase, creatine kinase (CK-MB and creatine phosphokinase), aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase in plasma. Furthermore, pretreatment with the extract and propranolol significantly attenuated the lipid peroxidation by maintaining the levels of enzymatic (superoxide dismutase and glutathione peroxidase) and nonenzymatic antioxidants (reduced glutathione and nitrite). The protective effects were also confirmed histologically[65].

Hepatoprotective effect:

The hepatoprotective and antioxidant and activities of *Nerium oleander* methanolic flower extract (100, 200 and 400 mg/kg, orally once daily for seven days) was investigated against CCl_4- induced hepatotoxicity in rats. The elevated serum enzymatic levels of AST, ALT, ALP and total bilirubin were restored towards normalization significantly by the extract in a dose dependent manner with maximum hepatoprotection at 400 mg/kg dose level. The histopathological observations supported the biochemical evidences of hepatoprotection. Elevated level of SOD and decreased level of MDA also confirmed the hepatoprotective observations[64].

Toxicity:

There were numerous reports of poisoning and death from ingestion of *Nerium oleander*, oleander leaf tea, and its extract in human adults, children, dogs, cats, horses, cattle, sheep, goats, llamas, birds and insects. All parts of this plant, either fresh, dried or boiled, were toxic. Even a small amount of oleander can cause death due to its effects on the heart. Inhaling the smoke from burning oleander or eating honey made from its nectar can produce poisonous effects. The main poisonous principles are cardiac glycosides[69,107].

Nerium oleander ingestion caused both cardiac and gastrointestinal signs and symptoms. The clinical picture usually starts with gastrointestinal signs: nausea, vomiting, abdominal pain and diarrhoea. Later, cardiovascular and neurological symptoms were occur. Sinus bradycardia or different degrees of atrioventricular (AV) block are the most frequent cardiac features. In severe cases, ectopic beats occur which may be followed by ventricular tachycardia and fibrillation. The main neurological symptoms are: tremor, drowsiness and ataxia. Hypotension and unconsciousness may also occur. Seizures have been described. The cardiac effects of the glycosides are due to direct cardiotoxicity and an indirect effect via the vagal nerve. The direct effect is due to the inhibition of the Na-K ATP-ase pump. This specific action increases intracellular sodium ion and serum potassium concentrations. The sodium influx lowers the membrane potential threshold, increasing excitability. The chronotropic effect is primarily central, mediated by an increase of vagal tone which decreases the rate of sinoatrial node depolarization[108-112].

The toxic effects of *Nerium oleander* were evaluated in monkeys. Dried and ground oleander leaves were given at intervals of 48 h in doses of 30, 7.5, and 3 mg/kg bw. The cumulative lethal dose ranged from 30 to 60 mg/kg bw in monkeys. Monkeys that received doses of 3 mg/kg bw (total cumulative dose: 60 mg/kg) were survived. Clinical signs were vomiting, salivation, polyuria , bradycardia, vaginal hemorrhage, abortion,

anorexia, constipation, loss of body weight, narcosis, restlessness, weakness, and shallow and rapid respirations. Changes in blood values were leukocytosis; neutrophilia; reticulecytopenia; increased potassium, glutamic-oxalacetic transaminase, glutamic-pyruvic transaminase, blood urea nitrogen and globulins; and decreased calcium, glucose, total serum protein, albumin, ϒ-globulin levels and albumin-globulin ratios. Hemorrhages, degeneration, or necrosis were observed in the heart , gastrointestinal tract , skeletal muscles, ovaries, adrenal glands, liver, kidneys, and pancreas. The organ weights of the pancreas were significantly reduced. Adrenal weights were significantly increased in monkeys that received the highest dose level[(113)].

Horses that consume a lethal dose of oleander leaves are often found dead 8 to 10 hours later, and symptoms of poisoning rarely last more than 24 hours before death. Clinical symptoms include colic, diarrhea, labored breathing, muscle tremors, ataxia, inability to stand, irregular and weak pulse, cold extremities due to the decreased cardiac output, and convulsions prior to death[(114)].

The pathological and biochemical changes of oleander poisoning was evaluated in sheep. Sheep were administrated the lethal dose of 110 mg/kg bw of dried oleander leaves. Animal died of ventricular arrhythmias within 41 to 56 hours after dosing of the plant. The main lesions recorded in the dead animals were hepatonephropathy and varying degrees of coagulative necrosis of cardiac muscle cells and necrosis of hepatocytes and necrosis of tubular epithelium in kidneys, accompanied by significant increases in concentration of glucose, BUN and bilirubin[(115)].

Clinical signs of toxicosis in goats appeared about 1 hr after intake of oleander and included abdominal pain, ruminal atony and tympany, frequent urination, bradycardia, tachycardia, tachyarrhythmia, depression, weakness and convulsive movement and death at the end stage. Electrocardiography revealed sinus bradycardia, sinus tachycardia, A-V dissociation, ventricular premature beats, depression of S-T segment, ventricular tachycardia and ventricular fibrillation. Haemorrhages in varying degrees were observed in internal organs at necropsy. Histopathological investigation revealed extensive tubular necrosis in kidneys with haemosiderin pigment in the cytoplasm of convoluted tubular cells, varying degrees of coagulative necrosis of cardiac muscle cells associated with haemorrhage and infiltration of mononuclear inflammatory cells, scattered necrosis of hepatocytes, perivascular and perineural oedema, haemorrhagic foci and ischemic cell changes in brain, congestion and oedema in lungs. Severe hyperaemia and infiltration of inflammatory cells were also observed in tissue sections of forestomachs, abomasum and different parts of the intestines[(116)].

Cattle intoxicated with *Nerium oleander*, showed polydipsia, bloody diarrhea, muscle tremors and ataxia, fever (39.5 ° C), moderate dehydration, bloody secretion through the nostrils, tachypnea, tachycardia, strong pulse, hypomotile digestive tract. Blood test revealed normochromic normocytic anemia, hypoproteinemia and hyperfibrinogemia, in addition to neutrophilia, leukocytosis, and basophilia. Serum globulins, gamma glutamyl transferase, creatine kinase, glucose, insulin and cardiospecific enzymes CK-MB (myocardial band) and troponin, were elevated. These changes participated in the death of the animals after two days, post mortem examination showed hemorrhages in the intestinal loops, mesenteric, lungs, and with greater severity in the heart (in the pericardium, epicardium and endocardium). In histology, multifocal to accentuated coalescent areas of necrosis of muscle fibers associated with hemorrhage surrounded by a discrete infiltrate neutrophilic, mainly in the epicardial region, as well as diffuse edema. There was degeneration of muscle fibers and moderate multifocal inflammatory infiltrate of lymphocytes, plasmocytes and occasionally neutrophils[(117)].

II. CONCLUSION:

This review discusses the traditional uses, bioactive ingredients, pharmacological and therapeutic effects of *Nerium oleander* as promising herbal drug because of effectiveness.

REFERENCES:

[1]. Al-Snafi AE. Oils and fats contents of medicinal plants, as natural ingredients for many therapeutic purposes- A review. IOSR Journal of Pharmacy 2020; 10(7): 1-41.
[2]. Al-Snafi AE. Phenolics and flavonoids contents of medicinal plants, as natural ingredients for many therapeutic purposes- A review. IOSR Journal of Pharmacy 2020; 10(7): 42-81.
[3]. Al-Snafi AE. Medicinal plants with central nervous effects (part 2): plant based review. IOSR Journal of Pharmacy 2016; 6(8): 52-75.
[4]. Al-Snafi AE, Talab TA and Majid WJ. Medicinal plants with central nervous activity - An overview (part 1). IOSR Journal of pharmacy 2019, 9(3): 52-102.
[5]. Al-Snafi AE. Medicinal plants for prevention and treatment of cardiovascular diseases - A review. IOSR Journal of Pharmacy 2017; 7(4): 103-163.
[6]. Al-Snafi AE. Medicinal plants with antioxidant and free radical scavenging effects (part 2): plant based review. IOSR Journal Of Pharmacy 2016; 6(7): 62-82.
[7]. Al-Snafi AE. Medicinal plants possessed antioxidant and free radical scavenging effects (part 3)- A review. IOSR Journal of Pharmacy 2017; 7(4): 48-62.

[8]. Al-Snafi AE. Medicinal plants affected reproductive systems (part 2) - plant based review. Sch Acad J Pharm 2016; 5(5): 159-174.
[9]. Al-Snafi AE. Arabian medicinal plants affected female fertility- plant based review (part 1). IOSR Journal of Pharmacy 2018; 8(7): 46-62.
[10]. Al-Snafi AE. Beneficial medicinal plants in digestive system disorders (part 2): plant based review. IOSR Journal of Pharmacy 2016; 6(7): 85-92.
[11]. Al-Snafi AE. Arabian medicinal plants possessed gastroprotective effects- plant based review (part 1). IOSR Journal of Pharmacy 2018; 8(7): 77-95.
[12]. Al-Snafi AE. Arabian medicinal plants for the treatment of intestinal disorders- plant based review (part 1). IOSR Journal of Pharmacy 2018; 8(6): 53-66.
[13]. Al-Snafi AE. A review of medicinal plants with broncho-dilatory effect- Part 1. Scholars Academic Journal of Pharmacy, 2015; 5(7): 297-304.
[14]. Al-Snafi AE, Majid WJ and Talab TA. Medicinal plants with antidiabetic effects- An overview (Part 1). IOSR Journal of pharmacy 2019, 9(3): 9-46.
[15]. Al-Snafi AE. Traditional uses of Iraqi medicinal plants. IOSR Journal of Pharmacy 2018; 8 (8): 32-96.
[16]. Al-Snafi AE. Galactagogue action of the crude phenolic extracts of grape seeds (Vitis vinifera). International Journal of Biological & Pharmaceutical Research 2015; 6(8): 577-580.
[17]. Al-Snafi AE. Mammary gland stimulating effects of the crude phenolic extracts of green tea (Camellia sinensis). International Journal of Biological & Pharmaceutical Research 2015; 6(7): 573-576.
[18]. Al-Snai AE. Iraqi medicinal plants with antifungal effect- A review. IOSR Journal of Pharmacy 2019; 9(7): 16-56.
[19]. Al-Snai AE. Iraqi medicinal plants with antiviral effect- A review. IOSR Journal of Pharmacy 2019; 9(7): 57-75.
[20]. Al-Snai AE. Iraqi medicinal plants with antibacterial effect- A review. IOSR Journal of Pharmacy 2019; 9(8): 22-103.
[21]. Al-Snafi AE. Antiparasitic effects of medicinal plants (part 1)- A review. IOSR Journal of Pharmacy 2016; 6(10): 51-66.
[22]. Al-Snafi AE. Antiparasitic, antiprotozoal, molluscicidal and insecticidal activity of medicinal plants (part 2) – plant based review. Sch Acad J Pharm 2016; 5(6): 194-207.
[23]. Al-Snafi AE. Arabian medicinal plants with dermatological effects- plant based review (part 1) . IOSR Journal of Pharmacy 2018; 8(10): 44-73.
[24]. Al-Snafi AE. Anticancer effects of Arabian medicinal plants (part 1) - A review. IOSR Journal of Pharmacy 2017; 7(4): 63-102.
[25]. Al-Snafi AE. Arabian medicinal plants with antiinflammatory effects- plant based review (part 1). Journal of Pharmacy 2018; 8 (7): 55-100.
[26]. Al-Snafi AE. Arabian medicinal plants with analgesic and antipyretic effects- plant based review (Part 1). IOSR Journal of Pharmacy 2018; 8(6): 81-102.
[27]. Al-Snafi AE. Immunological effects of medicinal plants: A review (part 2). Immun Endoc & Metab Agents in Med Chem 2016; 16(2): 100-121.
[28]. Al-Snafi AE and Thwaini MM. Nephro- protective effects of Arabian medicinal plants (part 1). Research Journal of Pharmaceutical, Biological and Chemical Sciences 2018; 9(5): 1504-1511.
[29]. Al-Snai AE, Talab TA. A review of medicinal plants with nephroprotective effects. GSC Biological and Pharmaceutical Sciences 2019; 8(1): 114-122.
[30]. Al-Snai AE, Mousa HM, Majid WJ. Medicinal plants possessed hepatoprotective activity. IOSR Journal of Pharmacy 2019; 9(8): 26-56.
[31]. The plant list, Nerium oleander, http://www.theplantlist.org/tpl/record/kew-135196
[32]. ITIS, Nerium oleander, https://www.itis.gov/servlet/SingleRpt/SingleRpt? search_ topic=TSN&search_value=30184#null
[33]. U.S. National Plant Germplasm System, Nerium oleander, https://npgsweb.ars-grin.gov/gringlobal/taxonomydetail.aspx?id=25229
[34]. Flora of Pakistan, Nerium oleander, http://www.efloras.org/florataxon.aspx? flora_ id=2&taxon_id=200018424
[35]. Flora of China, Nerium oleander, http://www.efloras.org/florataxon.aspx? flora_ id=2&taxon_id=200018424
[36]. Khare CP. Encyclopedia of Indian medicinal plants, Springer-Verlag-Heidelberg, 2004: 328-330.
[37]. Chaudhary K, Prasad DN and Sandhu BS. Preliminary pharmacognostic and phytochemical studies on Nerium oleander Linn. (White cultivar). Journal of Pharmacognosy and Phytochemistry 2015; 4(1): 185-188.

[38]. Begum S, Siddiqui BS, Sultana R, Zia A and Suria A. Bio-active cardenolides from the leaves of Nerium oleander. Phytochemistry 1999; 50(3): 435-438.
[39]. Sharma P, Choudhary AS, Parashar P, Sharma MC and Dobhal MP. Chemical constituents of plants from the genus Nerium. Chem Biodivers 2010; 7(5): 1198-1207.
[40]. PDR for herbal medicines. Medical Economics Company, Inc. at Montvale, NJ, 2000: 555.
[41]. Zhao M, Bai L, Wang L, et al. Bioactive cardenolides from the stems and twigs of Nerium oleander. Journal of Natural Product 2007; 70(7):1098-1103.
[42]. Bai L, Wang L, Zhao M, et al. Bioactive pregnanes from Nerium oleander. Journal of Natural Product 2007; 70 (1):14- 18.
[43]. Siddiqui BS, Sultana R, Begum S and Zia A, Suria A. Cardenolides from the methanolic extract of Nerium oleander leaves possessing central nervous system depressant activity in mice. J Nat Prod 1997; 60(6): 540-544.
[44]. Trease GE and Evans WC. Pharmacognosy 15 th ed. WB. Saunders, Edinburg, London, NY, Toronto, 2002: 311.
[45]. Tiwari S and Singh. A. Toxic and sub-lethal effects of oleandrin on biochemical parameters of freshwater air breathing murrel, Channa punctatus (Bloch.). Indian J Exp Biol 2004; 42: 413-418.
[46]. Abe F and Yamauchi T. Cardenolide triosides of oleander leaves. Phytochemistry 1992; 31: 2459-2463.
[47]. Siddiqui BS, Khatoon N, Begum S, et al. Flavonoid and cardenolide glycosides and a pentacyclic triterpene from the leaves of Nerium oleander and evaluation of cytotoxicity. Phytochemistry 2012; 77: 238-244.
[48]. Mostaqul HM, Jabbar A, Rashid MA et al. A novel antibacterial and cardiac steroid from the roots of Nerium oleander. Fitoterapia 1999; 70: 5-9.
[49]. Wang X, Plomley JB, Newman RA and Cisneros A. LC/MS/MS analyses of an oleander extract for cancer treatment. Anal Chem 2000;72(15):3547-3552.
[50]. Tayoub G, Sulaiman H and Alorfi M. Analysis of oleandrin in oleander extract (Nerium oleander) by HPLC. Journal of Natural Products 2014; 7: 73-78.
[51]. Siddiqui BS, Khatoon N, Begum S and Durrani SA. Two new triterpenoid isomers from Nerium oleander leaves. Nat Prod Res 2009; 23(17):1603-1608.
[52]. Begum S, Sultana R and Siddiqui BS. Triterpenoids from the leaves of Nerium oleander Phytochemistry 1997;44(2):329-332.
[53]. Siddiqui BS, Begum S, Siddiqui S and Lichter W. Two cytotoxic pentacyclic triterpenoids from Nerium oleander. Phytochemistry 1995; 39 (1): 171-174.
[54]. Siddiqui S, Siddiqui BS, Hafeez F and Begum S. Isolation and structure of neriucoumaric and isoneriucoumaric acids from the leaves of Nerium oleander. Planta Med 1987; 53(5):424-427.
[55]. Zhao M, Zhang S, Fu L, Li N, Bai J, Sakai J, et al. Taraxasterane and ursane-type triterpenes from Nerium oleander and their biological activities. Nat Prod 2006; 69:1164-1167.
[56]. Derwic E, Benziane Z and Boukir A. Antibacterial activity and chemical composition of the essential oil from flowers of Nerium oleander. Journal of Environmental, Agricultural and Food Chemistry 2010; 9(6):1074-1084.
[57]. Müller BM, Rosskopf F, Paper DH, Kraus J and Franz G. Polysaccharides from Nerium oleander: structure and biological activity. Pharmazie 1991; 46(9): 657-663.
[58]. Siddiqui A, Begum S, Hafeez F and Siddiqui BS. Two triterpenes from the leaves of Nerium oleander. Phytochemistry 1989; 28(4): 1187-1191
[59]. Ali HFM, El-Ella FMA and Nasr NF. Screening of chemical analysis, antioxidant, antimicrobial and antitumor activity of essential oil of oleander (Nerium oleander) flower. Intern J of Biolog Chem 2010; 4(4):190-202.
[60]. Mohadjerani M. Antioxidant activity and total phenolic content of Nerium oleander L grown in north of Iran. Iranian J of Pharmac Res 2012; 11(4): 1121-1126.
[61]. Mary SJ, Chithra B and Sivajiganesan S. Evaluation of the in vitro anti-inflammatory activity of Nerium oleander L. flower extracts and activity-guided isolation of the active constituents. Records of Natural Products 2018; 12(2):128-141.
[62]. Namian P, Talebi T, Germi KG et al. Screening of biological activities (antioxidant, antibacterial and antitumor) of Nerium oleander leaf and flower extracts. American J of Phytomed and Clinical Therap 2013; 1(4): 378-384.
[63]. Saranya S, Archana D and Santhy KS. Antimicrobial and antioxidant effects of Nerium oleander flower extracts. International Journal of Current Microbiology and Applied Sciences 2017; 6):1630-1637.
[64]. Singhal KG and Gupta GD. Hepatoprotective and antioxidant activity of methanolic extract of flowers of Nerium oleander against CCl_4-induced liver injury in rats. Asian Pac J Trop Med 2012; 5(9):677-685.

[65]. Gayathri V, Ananthi S, Chandronitha C, et al. Cardioprotective effect of Nerium oleander flower against isoproterenol-induced myocardial oxidative stress in experimental rats. J Cardiovasc Pharmacol Ther 2011;16(1):96-104.
[66]. Al-Hakak ZM, Khaleel ZI and Fadel MA. Study the effect of the toxic alcoholic extract of Nerium oleander on the liver cancer cell line in vivo and the effects on the liver histology in Mus Musculus. J Pharm Sci & Res 2019; 11(1): 201-205.
[67]. Calderón-Montaño JM, Burgos-Morón E, Orta ML, Mateos S and López-Lázaro M. A hydroalcoholic extract from the leaves of Nerium oleander inhibits glycolysis and induces selective killing of lung cancer cells. Planta Med 2013;79(12):1017-1023.
[68]. Cao YL, Zhang MH, Lu YF, Li CY, Tang JS and Jiang MM. Cardenolides from the leaves of Nerium oleander. Fitoterapia 2018;127:293-300.
[69]. Turan N, Akgün-Dar K, Kuruca SE, Kiliçaslan-Ayna T, Seyhan VG, Atasever B, Meriçli F and Carin M. Cytotoxic effects of leaf, stem and root extracts of Nerium oleander on leukemia cell lines and role of the p-glycoprotein in this effect. J Exp Ther Oncol 2006; 6(1):31-38.
[70]. Rashan LJ, Franke K, Khine MM, Kelter G, Fiebig HH, Neumann J and Wessjohann LA. Characterization of the anticancer properties of monoglycosidic cardenolides isolated from Nerium oleander and Streptocaulon tomentosum. J Ethnopharmacol 2011; 134(3):781-788.
[71]. Pathak S, Multani AS, Narayan S, Kumar V and Newman RA. Anvirzel, an extract of Nerium oleander, induces cell death in human but not murine cancer cells.Anticancer Drugs 2000;11(6):455-463.
[72]. Pan Y, Rhea P, Tan L, Cartwright C, Lee HJ, Ravoori MK, Addington C, Gagea M, Kundra V, Kim SJ, Newman RA and Yang P. PBI-05204, a supercritical CO_2 extract of Nerium oleander, inhibits growth of human pancreatic cancer via targeting the PI3K/mTOR pathway. Invest New Drugs 2015;33(2):271-279.
[73]. Newman RA and Yang P. Response to: Does the Nerium oleander extract PBI-05204 have potential for pancreatic cancer? Invest New Drugs 2015; 33(3): 788-789.
[74]. Smith JA, Madden T, Vijjeswarapu M and Newman RA. Inhibition of export of fibroblast growth factor-2 (FGF-2) from the prostate cancer cell lines PC3 and DU145 by Anvirzel and its cardiac glycoside component, oleandrin. Biochem Pharmacol 2001; 62: 469-472.
[75]. Hussain MA and Gorsi MS. Antimicrobial activity of Nerium oleander Linn. Asian Journal of Plant Sciences 2004; 3(2):177-180.
[76]. Aboud AS. Antimicrobial activities of aqueous and ethanolic extracts from Nerium oleander used in the treatment of burns infections isolates. Journal of Pharmaceutical, Chemical and Biological Sciences 2015; 2(4):248-258.
[77]. Minnat TR. In vivo and in vitro antibacterial assessment of Nerium oleander aqueous leaf extract against bacterial pathogens and its effect in treatment of wounds. AL-Qadisiyah Journal of Vet Med Sci 2016; 15(2):31-39.
[78]. Malik R, Bokhari TZ, Siddiqui MF, Younis U, Hussain MI and Khan IA. Antimicrobial activity of Nerium oleander L. and Nicotiana tabacum L: A comparative study. Pakistan Journal of Botany 2015; 47(4):1587-1592.
[79]. El Sawi NM , Geweely NS, Qusti S, Mohamed M and Kamel A. Cytotoxicity and antimicrobial activity of Nerium oleander extracts. Journal of Applied Animal Research 2011; 37(1): 25-31.
[80]. Singh S, Shenoy S, Nehete PN, Yang P, Nehete B, Fontenot D, Yang G, Newman RA and Sastry KJ. Nerium oleander derived cardiac glycoside oleandrin is a novel inhibitor of HIV infectivity. Fitoterapia 2013; 84:32-39.
[81]. Sanna G, Madeddu S, Serra A, Collu D, Efferth T, Hakkim FL and Rashan L. Anti-poliovirus activity of Nerium oleander aqueous extract. Nat Prod Res 2019; 25: 1-4.
[82]. Siddiqui I, Bokhari NA and Perveen K. Antifungal ability of Nerium oleander against Fusarium oxysporum, Sclerotium rolfsii and Macrophomina phaseolina. The Journal of Animal & Plant Sciences 2016; 26(1): 269-274.
[83]. Kumar G, Karthik L, Rao KVB, Kirthi AV and Rahuman AA. Phytochemical composition and mosquito controlling property of Nerium oleander leaves (Apocynaceae) against Culex tritaeniorhynchus and Culex gelidus (Diptera: Culicidae). Asian Pacific Journal of Tropical Biomedicine 2012; 2: 1-6.
[84]. Raveen R, Kamakshi KT, Deepa M, Arivoli S and Tennyson S. Larvicidal activity of Nerium oleander L. (Apocynaceae) flower extracts against Culex quinquefasciatus Say (Diptera: Culicidae). International Journal of Mosquito Research 2014; 1 (1): 38-42.
[85]. El-Akhal F, Guemmouh R, Ez Zoubi Y, et al. Larvicidal activity of Nerium oleander against larvae west Nile vector mosquito Culex pipiens (Diptera: Culicidae). J Parasitol Res. 2015;943060. doi:10.1155/2015/943060.

[86]. El-Sayed SH and El-Bassiony GM. Larvicidal, biological and genotoxic effects, and temperature-toxicity relationship of some leaf extracts of Nerium oleander (Apocynaceae) on Culex pipiens (Diptera: Culicidae). J Arthropod Borne Dis 2015; 10(1):1-11.
[87]. Lokesh R E, Leonard Barnaba P, Saurav MK and Sundar K. Larvicidal activity of Trigonella foenum and Nerium oleander leaves against mosquito larvae found in Vellore city. India, Curr Res J Biol Sci 2010; 3: 154-160.
[88]. El-Shazly MM, Nassar MI and El-Sherief HA. Toxic effect of ethanolic extract of Nerium oleander (Apocynaceae) leaves against different developmental stages of Muscina stabulans (Diptera-Muscidae).J Egypt Soc Parasitol 1996; 26(2):461-473.
[89]. Balkan IA, Gören AC, Kırmızıbekmez H and Yeşilada E. Evaluation of the in vitro anti-inflammatory activity of Nerium oleander L. flower extracts and activity-guided isolation of the active constituents. Rec Nat Prod 2018; 12(2): 128-141.
[90]. Mary SJ, Chithra B and Sivajiganesan S. In vitro anti-inflammatory activity of the flowers of Nerium oleander (white). Intern J of Res- Granthaalayah 2017; 5(6): 123-128.
[91]. Erdemoglu N, Esra K and Erdem Y. Anti-inflammatory and antinociceptive activity assessment of plants used as remedy in Turkish folk medicine. Journal of Ethnopharmacology 2003; 89:123-129.
[92]. Akgun SG, Aydemir S, Ozkan N, Yuksel M and Sardas S. Evaluation of the wound healing potential of Aloe vera-based extract of Nerium oleander. North Clin Istanb 2017; 4(3):205-212.
[93]. Benson KF, Newman RA and Jensen GS. Antioxidant, anti-inflammatory, anti-apoptotic, and skin regenerative properties of an Aloe vera-based extract of Nerium oleander leaves (Nae-8®). Clin Cosmet Investig Dermatol 2015;8:239-248.
[94]. Gayathri V, Ananthi S and Vasanthi HR. Antihyperlipidemic potential of polyphenol and glycoside rich Nerium oleander flower against triton WR-1339-induced hyperlipidemia in experimental Sprague Dawley rats. Journal of Chemistry 2013; http://dx.doi.org/10.1155/2013/825290
[95]. Demirel Kars M, Odabaşı BA, Kars G, Üney K, Bağcı Y and Baş AL. Implications from a pharmacogenomic analysis: Nerium oleander leaf distillate supplemented diet regulates cholesterol metabolism in rats. Pharm Biol 2014;52(8):988-993.
[96]. Singhal KG and Gupta GD. Some central nervous system activities of Nerium oleander linn (Kaner) flower extract. Trop J Pharm Res 2011; 10 (4): 455-461.
[97]. Zia A , Slddlqul BS , Begum S , Slddlqul S and Suria A. Studies on the constituents of the leaves of Nerium oleander on behavior pattern in mice. Journal of Ethnopharmacology 1995; 4: 33-39.
[98]. Singhal KG and Gupta GD. Anti-anxiety activity studies of various extracts of Nerium oleander Linn flowers. International Journal of Pharmacy and Pharmaceutical Sciences 2011; 3:323-326.
[99]. Shashikala GH, Shilpa BN and Shah MJ. Evaluation of anxiolytic activity of aqueous extract of Nerium oleander flowers in albino rats. Int J of Basic & Clinical Pharmacology 2018; 7(9):1797-1802.
[100]. Tirumalasetti J, Patel M, Shaikh U, Harini K and Shankar J. Evaluation of skeletal muscle relaxant activity of aqueous extract of Nerium oleander flowers in albino rats. Indian J Pharmacol 2015;47(4):409-413.
[101]. Dunn DE, He DN, Yang P, Johansen M, Newman RA and Lo DC. In vitro and in vivo neuroprotective activity of the cardiac glycoside oleandrin from Nerium oleander in brain slice-based stroke models. J Neurochem 2011; 119(4): 805-814.
[102]. Dey P, Saha MR, Chowdhuri SR, et al. Assessment of anti-diabetic activity of an ethnopharmacological plant Nerium oleander through alloxan induced diabetes in mice. J Ethnopharmacol 2015;161:128-137.
[103]. Mwafy SN and Yassin MM. Antidiabetic activity evaluation of glimepiride and Nerium oleander extract on insulin, glucose levels and some liver enzymes activities in experimental diabetic rat model.Pak J Biol Sci 2011; 14(21): 984-990.
[104]. Mazumder PK, Lakshmana Rao PV, Kumar D, Dube NS and Das Gupta S. Toxicological evaluation of Nerium oleander on isolated preparations. Phytotherapy Research 1994; 8(5):297–300.
[105]. Adome RO, Gachihi JW, Onegi B, Tamale J and Apio SO. The cardiotonic effect of the crude ethanolic extract of Nerium oleander in the isolated Guinea pig hearts. Afr Health Sci 2003; 3(2):77-82.
[106]. Ayaz M, Baba F, Akgun N, Bas AL, Uney K and Dik B. Protective effect of distillated Nerium oleander on heart of type 2 diabetic rats. Bratisl Lek Listy 2015; 116(7):451-456.
[107]. Aslani MR, Movassaghi AR, Mohri M, Abbasian A and Zarehpou M. Clinical and pathological aspects of experimental oleander (Nerium oleander) toxicosis in sheep. Vet Res Commun 2004; 28: 609–616.
[108]. Gopalakrishnan SK, Kandasamy S, Isaac B, Jayasankar C and Chandru. Oleander toxicity- the clinical spectrum and mortality predictors: an observational study. Internet Journal of Medical Update 2017; 12(1): 4-8.
[109]. Osterloh J, Herold S and Pond S. Oleander interference in the digoxin radio-immunoassay in a fatal ingestion. JAMA 1982; 247(11):1596-1597.

[110]. Spevak L and Soc M. Two cases of poisoning by tea from Oleander leaves. Arch Hig Rada Toksicol 1975; 26: 147-50.
[111]. Shaw D and Pearn J. Oleander poisoning. Med J Aust 1979; 2: 267-269.
[112]. Langford SD and Boor PJ. Oleander toxicity: an examination of the human and animal toxic exposures. Toxicology, 1996; 109: 1–13.
[113]. Schwartz WL, Bay WW, Dallal-lite WD, Storts RW and Russell LH. Toxicity of Nerium oleander in the Monkey (Cebus apella). Vet Path 1974;1:259-277.
[114]. Turner LL and Torres P. Oleander poisoning of horses, https://aces.nmsu. edu/pubs/ _b/B712/welcome.html
[115]. Ozmaie S , Akbari G , Asghari A , Sakha M and Mortazavi P. Experimental oleander (Nerium oleander) poisoning in sheep: Serum biochemical changes and pathological study. Annals of Biological Research 2013; 4 (1):194-198. 194.
[116]. Aslani MR, Movassaghi AR, Janati-Pirouz H and Karazma M. Experimental oleander (Nerium oleander) poisoning in goats: a clinical and pathological study. Iranian J of Vet Res, University of Shiraz 2007; 8(1): 58-63.
[117]. de Souza LM, de Andrade Neto AQ, et al. Acute poisoning in cattle by Nerium oleander (Apocynaceae). Medicina Veterinária (UFRPE) 2018; 12(1): 129.

Ali Esmail Al-Snafi. "Bioactive ingredients and pharmacological effects of Nerium oleander." *IOSR Journal of Pharmacy (IOSRPHR),* 10(9), 2020, pp. 19-32.