REVIEW

Chemical Constituents of Plants from the Genus *Nerium*

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1. Introduction. – *Nerium* [1] is a genus with three species found in North Africa, eastern Mediterranean basin, and south-east Asia, and dry stream beds. It belongs to the family Apocynaceae [2]. *N. oleander* grows well in warm subtropical regions and is extensively used as an ornamental plant. It is planted in parks due to its beautiful and fragrant flowers. *N. odorum* and *N. indicum* are also well-known for their medicinal properties. *Nerium* is a fast growing plant and may reach up to twelve feet or more in height, with spreading to erect branches. Flowers are white, pink, or yellow, with a deeply five-lobed corolla. They are often, but not always, sweet scented. Over 400 varieties have been identified and named, with several additional flower colors including red, purple, pink, and orange; white and variety of pink are the most common colors. Young plants grow best in spaces where they do not have to compete with other

plants for nutrients. Isolation of a number of secondary metabolites has been reported from the genus *Nerium*. Though triterpenoids [3] are major constituents of this genus, other secondary metabolites, such as pregnanes, cardenolides [4–6], cardiac glycosides [7–12] *etc.* were also frequently isolated and characterized. The genus is reported to exhibit a wide range of biological activities, *i.e.*, cardiotonic [13–16], diuretic [17], cytotoxic [18], antibacterial, anticancer, antiplatelet aggregation [19–23], anti-inflammatory, hepatoprotective, antitumor, antihyperlipidemic [24–27], antiulcer, and depressant action on the central nervous system [25–33]. Oleander is one of the most poisonous [34–51] plants and contains numerous toxic compounds. The toxicity of oleander is extremely high due to the presence of toxic cardiac glycosides such as oleandrin [52][53] and neriine.

2. Chemical Constituents. – A considerable amount of work has been carried out on genus *Nerium*, mainly on chemical investigations and biological-activity evaluations. A number of triterpenoids [54–56], cardiac glycosides [57–67], cardenolides [30][68], and bioactive pregnanes [69][70] were isolated and characterized. Their structures are shown below, and their names and the corresponding plant sources are compiled in the *Table*.

2.1. *Cardenolides.* The leaves of *N. oleander* afforded five bioactive cardenolides, nerizoside, Δ^{16}-dehydroadynerigenin, neritaloside, odoroside-H [68], and neridigino-side (**1**–**5**, resp.) [30].

2.2. *Cardiac Glycosides.* The leaves of *N. oleander* and *N. odorum* yielded thirteen cardiac glycosides, **6**–**18**.

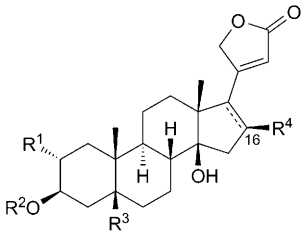
2.3. *Pregnanes.* The bark of *N. oleander* provided eight bioactive pregnanes, **19**–**26**.

2.4. *Triterpenoids.* Two triterpenoids, *cis*-karenin and *trans*-karenin (**27** and **28**, resp.) [54–56] were identified from the leaves of *N. oleander*.

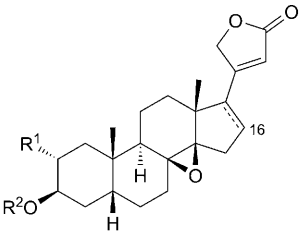
2.5. *Triterpenes.* Triterpenes are the major components of this genus [55][72–74][76–78]. Twenty-three triterpenes, **29**–**51**, were isolated from the genus *Nerium*. Some of them were reported to have biological activities, namely, oleanderolic acid, kanerodione, kaneric acid, uvaol, oleanderol, ursolic acid, and oleanolic acid.

2.6. *Steroids.* The roots of *N. oleander* yielded two steroids, **52** and **53** [79].

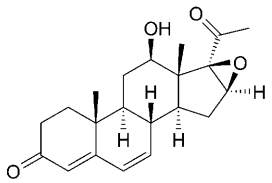
3. Biological Activities. – 3.1. *Antimicrobial Activity.* The *in vitro* antimicrobial activity [80] of *Nerium oleander* root and leaf extracts were studied against *Bacillus pumilus*, *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Aspergillus niger*. The $CHCl_3$, EtOH, and MeOH extracts of *N. oleander* showed high activity against all the tested bacteria. None of the crude extracts of the selected plant exhibited activity against *A. niger*. These results were compared with the zones of inhibition produced by commercially available standard antibiotics. The results obtained show that the EtOH extract of the roots of *N. oleander* exhibits moderate activity against *B. pumilus* and *S. aureus*; while the activity against *E. coli* was high, whereas, against *B. subtilis*, low activity was observed. The MeOH extracts of the leaves of *N. oleander* also showed high activity against *S. aureus* and *E. coli*, and showed moderate activity against *B. pumilus* and *B. subtilis.* The MeOH extracts of the roots of *N. oleander* revealed marked activity against all the bacteria tested. None of the crude extracts showed activity against *A. niger*. On the other hand, the $CHCl_3$ extracts of leaves and



		R^1	R^2	R^3	R^4
1		H	β-D-2-*O*-methyldigitalosyl	H	H
3		H	β-D-digitalosyl	H	AcO
4		H	β-D-digitalosyl	H	H
5		H	β-D-diginosyl	OH	H
7		OH	β-D-diginosyl	H	H
10		H	β-D-glucosyl-β-D-diginosyl	H	AcO
11	Δ^{16}	H	β-D-glucosyl	H	AcO
12		H	β-gentiobiosyl-α-L-oleandrosyl	H	AcO
13		H	β-gentiobiosyl-β-D-diginosyl	H	H
14		H	β-D-glucosyl-(1→4)-β-D-digitalosyl	H	AcO
16	Δ^{16}	H	β-gentiobiosyl-(1→4)-β-D-digitalosyl	H	H



		R^1	R^2
2	Δ^{16}	H	H
6	Δ^{16}	OH	β-D-diginosyl
8	Δ^{16}	H	β-D-diginosyl
9	Δ^{16}	H	β-D-digitalosyl
15	Δ^{16}	H	β-D-glucosyl-β-D-digitalosyl
17		H	β-gentiobiosyl-β-D-diginosyl
18	Δ^{16}	H	β-gentiobiosyl-β-D-diginosyl



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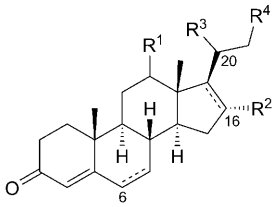
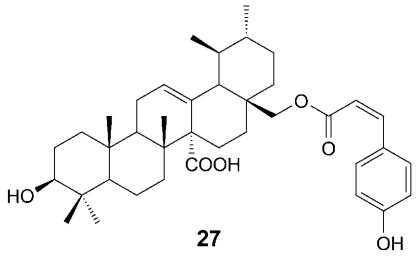


		R^1	R^2	R^3	R^4
19	Δ^6	=O	H	=O	OH
20	Δ^6	=O	H	OH (20*R*)	H
22	Δ^6,Δ^{16}	β-OH	H	=O	H
23	Δ^6	=O	H	OH (20*S*)	OH
24	Δ^6	β-OH	H	=O	H
25		β-OH	H	=O	H
26	Δ^6	β-OH	MeO	=O	H



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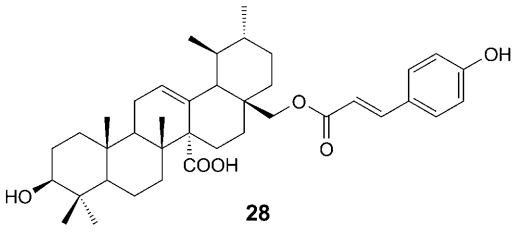

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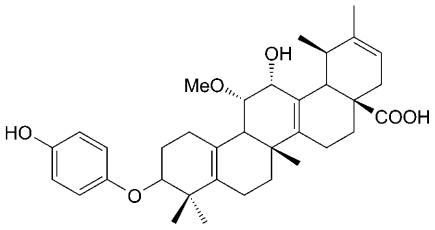

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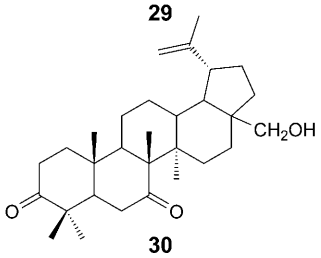

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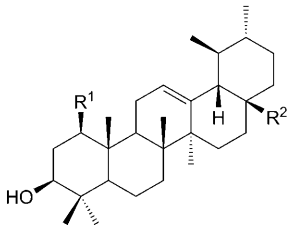
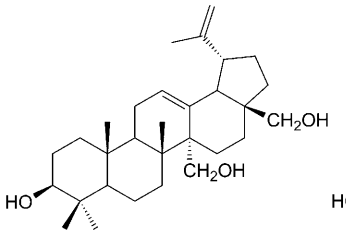


	R^1	R^2
31	OH	COOH
32	H	$HOCH_2$



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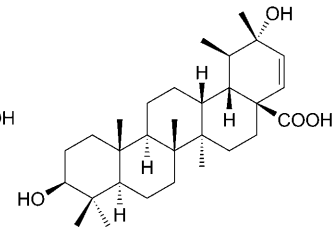

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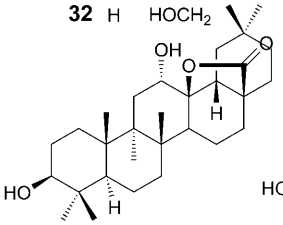

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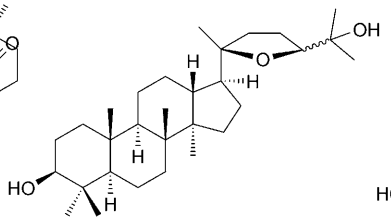
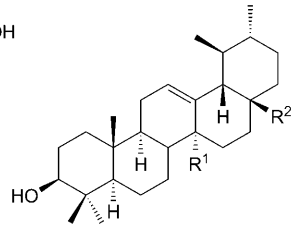
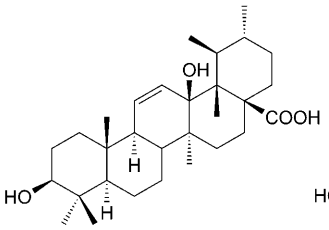


36 (20*S*,24*S*)
48 (20*S*,24*R*)



	R^1	R^2
37	Me	COOH
38	CH_2OH	COOH
40	Me	CHO
41	Me	H
42	Me	Me
43	Me	$HOCH_2$



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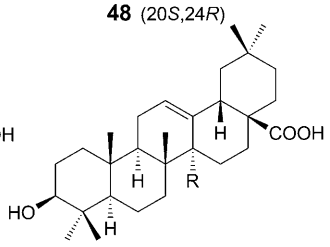
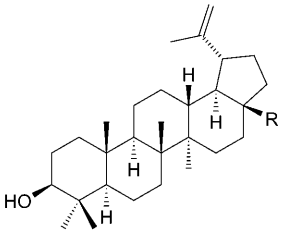
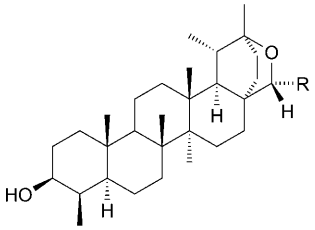


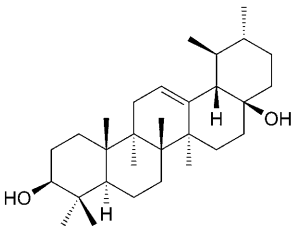
44 R = Me
45 R = $HOCH_2$



46 R = COOH
47 R = $HOCH_2$



49 R = MeO
50 R = H



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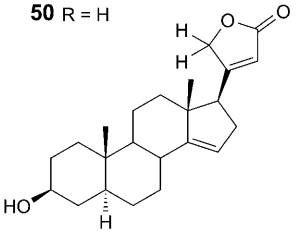

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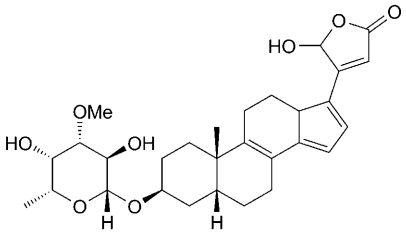

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roots of *N. oleander* did not show any appreciable activity against any of the above microbes.

3.2. *Anti-Inflammatory Activity.* The anti-inflammatory activity [76] of the oleander compounds was evaluated *in vitro* by an assay on inhibitory activity of induction of intercellular adhesion molecule-1 (ICAM-1) [81–84]. Expression of an excess amount of ICAM-1 on the surface of endothelial cells of a blood vessel plays an important role in the progress of the inflammatory reaction. These observations suggest that the anti-inflammatory activities of traditional medicinal plants on induction of ICAM-1 are due to their inhibitory potential. Four compounds, *viz.* 20β,28-epoxy-28α-methoxytaraxasteran-3β-ol (**49**), 20β,28-epoxytetraxaster-21-ene-3β-ol (**50**), 28-norurs-12-ene-3β,17β-diol (**51**), and 3β-hydroxyurs-12-en-28-aldehyde (**40**) were screened for inhibition of induction of ICAM-1, using human cultured A549 cells (lung carcinoma) and an *in vitro* model of human endothelial cells. Cell viability was measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium hydrobromide (MTT) assay and reported as IC_{50} values. Compound **49** showed weak inhibitory activity on induction of ICAM-1. The results of the MTT assay indicated that the above mentioned compounds showed weak cell-growth inhibitory activity on A549 cells.

3.3. *Anticancer Activity.* It has been reported that tumor initiation and promotion are inhibited by ursolic acid and oleanolic acid [73][75]. Cytotoxic [76][85][86] and antileukemic activities of lupine derivatives were also reported recently. The cell-growth inhibitory activity of compounds, *viz.* 20β,28-epoxy-28α-methoxytaraxasteran-3β-ol (**49**), 20β,28-epoxytetraxaster-21-en-3β-ol (**50**), 28-norurs-12-ene-3β,17β-diol (**51**), and 3β-hydroxyurs-12-en-28-aldehyde (**40**) was examined. The cell-growth inhibitory activity was evaluated on WI-38 cells (normal human fibroblast cells induced by lung cells), VA-13 cells (malignant lung tumor cells induced by WI-38), and HepG2 cells (human liver cancer cells). Compounds **49** and **51** showed significant and moderate cell-growth inhibitory activity, respectively, and compounds **50** and **40** showed weak cell-growth inhibitory activity against WI-38 cells. Compound **49** showed significant cell-growth inhibitory activity against VA-13 cells. Compounds **49** and **51** showed significant and moderate cell growth inhibitory activity, respectively, and compound **40** showed weak cell-growth inhibitory activities against HepG2 cells.

3.4. *Central Nervous System* (CNS)-*Depressant Activity.* Nerizoside (**1**), Δ^{16}-dehydroadynerigenin (**2**), neritaloside (**3**), and odoroside H (**4**), isolated by *Siddiqui et al.*, showed CNS-depressant activity [68] in mice. Compound **1** produced a decrease in locomotor activity at a dosage of 25 mg/kg, but no other signs of depression were observed. At a dosage of 50 mg/kg, the animals showed other signs in addition to decreased motor activity, such as a decrease in touch response and a staggering gait, which lasted for 40 min. The animals regained normal activity in 1.5 h. Compound **3** also showed a decrease in motor activity of the animals at a dosage of 25 mg/kg ip; again, there was no decrease in touch response; however, staggering was observed after 30 min. At the dosage of 50 mg/kg, the animals exhibited signs of fast respiration and abduction of limbs; slight tremor on movement and passivity was observed in 1 h in the experimental animals at a 50-mg/kg dose. The treated animals showed a normal behavior after 4 h.

3.5. *Neuroprotective Effects.* Degeneration of neurons is a key problem in *Alzheimer*'s disease (AD), and neuroprotection is a possible way to safeguard neurons

Table. *Chemical Constituents of Plants from the Genus* Nerium

No.	Compound class and name	Ref.
	Cardenolides	
1	14β-Hydroxy-3β-*O*-(D-2-*O*-methyldigitalosyl)-5β-carda-16,20(22)-dienolide (Nerizoside)	[68]
2	3β-Hydroxy-8,14-epoxy-5β-carda-16,20(22)-dienolide (Δ^{16}-Dehydroadynerigenin)	[68]
3	16β-Acetoxy-3β-*O*-(D-digitalosyl)-14β-hydroxy-5β-card-20(22)-enolide (Neritaloside)	[68]
4	3β-*O*-(D-Digitalosyl)-14β-hydroxy-5β-card-20(22)-enolide (Odoroside-H)	[68]
5	3β-*O*-(D-Diginosyl)-5β,14β-dihydroxycard-20(22)-enolide (Neridiginoside)	[30]
	Cardiac Glycosides	
6	3β-*O*-(D-Diginosyl)-2α-hydroxy-8,14β-epoxy-5β-carda-16 : 17,20 : 22-dienolide	[57]
7	3β-*O*-(D-Diginosyl)-2α,14β-dihydroxy-5β-carda-16 : 17,20 : 22-dienolide	[57]
8	β-D-Diginoside	[58]
9	β-D-Digitaloside of Δ^{16}-dehydroadynerigenin	[58]
10	Oleandrigenin-β-D-glucosyl-β-D-diginoside	[71]
11	Oleandrigenin-β-D-glucoside	[71]
12	Oleandrigenin-β-gentiobiosyl-α-L-oleandroside	[71]
13	Digitoxigenin-β-gentiobiosyl-β-D-diginoside	[71]
14	16-*O*-Acetyldigitalinum verum	[71]
15	Δ^{16}-Dehydroadynerigenin-D-glucosyl-β-D-digitaloside	[71]
16	Odoroside G	[71]
17	Adynerin	[71]
18	Δ^{16}-Dehydroadynerin	[71]
	Pregnanes	
19	21-Hydroxypregna-4,6-diene-3,12,20-trione	[69]
20	(20*R*)-20-Hydroxypregna-4,6-diene-3,12-dione	[69]
21	16β,17β-Epoxy-12β-hydroxypregna-4,6-diene-3,20-dione	[69]
22	12β-Hydroxypregna-4,6,16-triene-3,20-dione	[69][70]
23	(20*S*)-20,21-Dihydroxypregna-4,6-diene-3,12-dione	[69][70]
24	12β-Hydroxypregna-4,6-diene-3,20-dione	[70]
25	12β-Hydroxypregn-4-ene-3,20-dione	[70]
26	12β-Hydroxy-16α-methoxypregna-4,6-diene-3,20-dione	[70]
	Triterpenoids	
27	28-[(*Z*)-*p*-Coumaroyloxy]-3β-hydroxyurs-12-en-27-oic acid	[54]
28	28-[(*E*)-*p*-Coumaroyloxy]-3β-hydroxyurs-12-en-27-oic acid	[54]
	Triterpenes	
29	Oleanderolic acid	[72]
30	28-Hydroxylup-20(29)-ene-3,7-dione	[72]
31	1β,3β-Dihydroxyurs-12-en-28-oic acid	[55]
32	3β,28-Dihydroxyurs-12-ene	[55]
33	Lupa-12,20(29)-diene-3β,27,28-triol	[73]
34	3β,20α-Dihydroxyurs-21-en-28-oic acid	[74]
35	3β,12α-Dihydroxyoleanan-28,13β-olide	[74]
36	(20*S*,24*S*)-Epoxydammarane-3β,25-diol	[74]
37	3β-Hydroxyurs-12-en-28-oic acid	[73–75]
38	3β,27-Dihydroxyurs-12-en-28-oic acid	[74]
39	3β,13β-Dihydroxyurs-11-en-28-oic acid	[74]
40	3β-Hydroxyurs-12-en-28-aldehyde	[74]
41	28-Norurs-12-en-3β-ol	[74]

Table (cont.)

No.	Compound class and name	Ref.
42	Urs-12-en-3β-ol	[74]
43	Urs-12-ene-3β,28-diol	[74]
44	3β-Hydroxyolean-12-en-28-oic acid	[73–75]
45	3β,27-Dihydroxyolean-12-en-28-oic acid	[74]
46	3β-Hydroxylup-20(29)-en-28-oic acid	[73][74]
47	Lup-20(29)-ene-3β,28-diol	[73][74]
48	(20*S*,24*R*)-Epoxydammarane-3β,25-diol	[74]
49	20β,28-Epoxy-28α-methoxytaraxasteran-3β-ol	[76]
50	20β,28-Epoxytaraxaster-21-en-3β-ol	[76]
51	28-Norurs-12-ene-3β,17β-diol	[76]
	Steroids	
52	3β-Hydroxy-5α-carda-14(15),20(22)-dienolide	[76]
53	3β-*O*-(D-Digitalosyl)-21-hydroxy-5β-carda-8,14,16,20(22)-tetraenolide	[76]

from neurodegeneration. Recently, *Yu et al.* isolated two pure polysaccharides [87][88] from the flowers of *N. indicum*, which were shown to stimulate proliferation and differentiation of PC12 pheochromocytoma cells [89]. Pretreatment with *Nerium* polysaccharides significantly reduced the number of apoptotic neurons revealed by DAPI staining, when neurons were exposed to serum-free medium. Besides, the polysaccharides could also decrease the activity of caspase-3 triggered by AB peptides. These results suggest that the polysaccharides extracted from the flowers of *N. indicum* are potential neuroprotective agents against neurodegeneration.

3.6. *Piscicidal Activity.* The Et_2O, $CHCl_3$, acetone, and MeOH extracts of *Nerium indicum* leaves were evaluated for their piscicidal activity [90] against common freshwater air-breathing predatory fish *Channa punctatus*. The rank order of toxicity (LC_{50}) of the leaf extracts was Et_2O (17.34 mg/l) > acetone (40.01 mg/l) > $CHCl_3$ (40.61 mg/l) > MeOH (106.37 mg/l). There was a significant negative correlation between LC_{50} values and exposure periods. Thus, increase in exposure period led to a decrease of LC_{50} from 17.34 mg/l (24 h) to 13.58 mg/l (96 h) in the Et_2O extract. Similar trends were also observed for acetone, $CHCl_3$, and MeOH extracts. Exposure of sub-lethal doses (40 and 80% of LC_{50}) of the Et_2O extract of *N. indicum* leaf (which has maximum piscicidal activity) for 24 or 96 h caused significant alterations in the levels of total protein, total free amino acid, nucleic acid, glycogen, pyruvate, lactate, and in the activities of enzymes protease, phosphatases, alanine aminotransferase, aspartate aminotransferase, and acetylcholinesterase in liver and muscle tissue. The alterations in all of the above biochemical parameters were significant ($P < 0.05$) and were found to be dose-dependent. There was a significant recovery in all of the above biochemical parameters, in both liver and muscle tissues of fish, after the 7th day of the withdrawal of treatment. Thus, the leaf extracts of *N. indicum* have potent piscicidal activity against the fish *C. punctatus*, and also significantly affect both aerobic and anaerobic respiration pathways in fish.

3.7. *Effect of Sap on Male Fertility and Spermatogenesis in Tobacco Budworm. Jeong et al.* investigated the effects of sap [91] of the common oleander *Nerium indicum* (Apocynaceae) on male fertility and spermatogenesis in the oriental tobacco budworm

Helicoverpa assulta. It was found that continuous feeding of oleander sap during the larval period significantly affects fertility in males, but not in females. This effect was induced by direct injection of oleander sap into the hemocoel of 2-day-old pupae. Histological analyses of developing testes following oleander injection revealed a developmental delay and progressively more severe morphological abnormalities in the later stages of development. The effect of oleander sap on spermatogenesis in *H. assulta* was associated with greatly reduced levels of the two major polyamines, spermidine and spermine, in testes compared with saline-injected controls.

3.8. *Effect on Proliferation and Differentiation of PC12 Pheochromocytoma Cells.* Two polysaccharides, a rhamnogalacturonan and a xyloglucan, were isolated and purified from the whole flowers of *Nerium indicum*, and characterized by *Ding et al.* including their bioactivities against PC12 cells [89]. The rat pheochromocytoma PC12 cell line is a nerve growth factor (NGF)-responsive model system that has been useful for studying the underlying mechanisms of NGF actions. PC12 Cells were exposed to different concentrations of rhamnogalacturonan and xyloglucan in order to examine the potential effects on neurite outgrowth (NGF served as a positive control). The NGF-treated cells showed significantly enhanced neuritogenic potential. The potency was better for rhamnogalacturonan. The results obtained showed that these polysaccharides can significantly promote the proliferation and differentiation of PC12 cells.

4. Concluding Remarks. – The genus *Nerium* includes three species, and all of them have been used as traditional herbal medicines in the indigenous systems of medicine. Triterpenoids isolated from *N. oleander* were shown to inhibit tumor formation besides their anti-inflammatory and antimicrobial activities. The biological studies on these *Nerium* species have revealed that they possess significant medicinal potential. In the future, much more phytochemical and biological studies should be carried out on this genus in order to disclose their active principles and mechanisms of their activity.

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