Pharmacological aspects of *Nerium indicum* Mill: A comprehensive review

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ABSTRACT

Phytomedicine is the oldest medical practice known to man. Since the dawn of mankind, various plant resources are used to cure different diseases and also for a long and healthy life. The ancient knowledge of plant based medicine has transferred from generations to generations and accumulated as ethnopharmacological knowledge among different ethnic groups. India is the spanning bed of traditional phytomedicinal system where Ayurveda was born out of the knowledge of traditional medicine. In various other countries of South-Eastern Asia, South America, and in Arabian countries, still today, a great number of people rely primarily on phytomedicines to cure diseases. In the complementary and alternative medicinal systems, *Nerium indicum* is one such plant which is famed for its therapeutic efficiency in different diseases globally. In the present time, when the pharmaceutical companies are concentrating more toward the plant based traditional medicines to avoid the side-effects and resistance against synthetic drugs, *N. indicum* has proved its efficiency in different disease models. Therefore, this review comprehensively covers the medicinal and pharmacological activities of different parts of the plant *N. indicum*.

Key words: Anvirzel, ethnopharmacology, herbal medicine, Nerium indicum, oleander, oleandrin

INTRODUCTION

Traditional medicine is a major part of the cultural heritage of a society and it has developed in accordance with the lifestyle and cultural practices of the society. Hands on practical experiences of the therapeutic efficiencies of the herbal remedies have enriched various traditional medicinal systems around the globe. Indian, Chinese, and Arabian traditional medicinal systems are highly developed and have gained importance in other countries too. Traditional Indian medicinal systems have reached to various other countries such as Malaysia and Latin America. Furthermore, 80% of the world's population primarily relies on traditional medicines, according to a report by WHO.[1]

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Ayurveda (the knowledge for long life), originated in India in the mid-second millennium BCE, known as the Vedic period.[2] *Susruta Samhita* and *Charaka Samhita* are the core of the Ayurvedic medicinal systems which have describe the therapeutic usage of thousands of plants. One such plant mentioned in Ayurveda[3] is *Nerium indicum* Mill. The review is therefore, based on the medicinal and therapeutic properties of *N. indicum*.

METHODS

University of North Bengal library web-portal[4] and Google search was performed using the keywords "Nerium and traditional medicine", "Nerium and therapeutic", "Nerium and anticancer", etc. Search for published research articles were also done in PubMed. In addition, reference and bibliographies of numerous published articles were searched for the keyword of "Nerium".

NERIUM INDICUM

Nerium indicum belongs to the family Apocynaceae. It is an evergreen shrub or small tree, which is cultivated all over the world, especially in south-west Asia. The ancient city of Volubilis in Morocco took its name from the old Latin name for the flower. It is naturalized in the vast area ranging from Mauritania, Morocco, and Portugal. It is used as an ornamental shrub in the Mediterranean region and in southern Asia. The white flower variety plant, *N. indicum*

is exclusively native to India, Bangladesh, Nepal, Myanmar, and China. It is most commonly known as oleander, from its superficial resemblance to the unrelated olive *Olea*.[5]

BOTANICAL DESCRIPTION

For proper botanical identification, *N. indicum* plant was collected from the garden of University of North Bengal and identified by taxonomist Prof. A. P. Das of the Department of Botany, University of North Bengal. The voucher specimen was stored at the herbarium of Department of Botany, University of North Bengal with an accession number of 9618. The plant *Nerium indicum* Mill. (syn. *N. oleander* L. and *N. odorum* Aiton.), commonly known as "Kaner" in Hindi and "Karabi" in Bengali, grows upto 2-6 m in height. The erect stems spread outward with maturation and possess greyish bark. The sap is viscous and gummy. Leaves are thick, leathery, hairless, and dark-green in color. Leaves grow 12 inches × 1.5 inches in dimension, positioned either opposite to each other or in whorls of three or four leaves together. Each leaf have a distinct midrib with parallel secondary veins extending toward the leaf margin. Flowers of white, pink or red color grow in the cluster at the end of each branch. They are tubular in shape comprising of five lobes. The fruits are of slender, long, capsular shape consisting of two follicles.

ETHNOMEDICINAL USE

Nerium indicum is used as traditional medicine in different parts of the world, especially in India and China.[6] Its ethnomedicinal uses include in the treatment of diverse ailments such as cardiac illnesses, asthma, corns, cancer, and epilepsy.[7] A green dye from the flower is used in the treatment of skin diseases and also possess wound healing and antiinflammatory property. The plant is used in Trinidad and Tobago for reproductive problems.[8] Hot water extract of the leaves and seeds are used for upper respiratory tract and gastrointestinal infections in Kenya.[9] In Calabria, southern Italy, the plant is used for the treatment of malaria in local folklore medicinal systems.[10] The juice prepared from the stem bark of *N. indicum* is used to cure ear pain in the traditional therapeutic systems in the Kancheepuram district of Tamil Nadu, India.[11] It is also used as antidiabetic in Morocco.[12] In Iloilo, Philippines, the plant is used as ethnomedicine to treat fever, headache, and dermatological problems.[13] In the Errachidia province of Morocco, *N. indicum* is used in the treatment of hypertension and diabetes.[14]

In the past few decades, extensive research on the pharmaceutical properties of *N. indicum* has demonstrated its medicinal properties which are discussed below.

ANTINOCICEPTIVE ACTIVITY

The process in which noxious external stimuli is encoded and processed by the body is termed as "nociception".[15] Some external stimuli generate afferent activity in the central nervous system as well as in the peripheral one due to tissue damage. Thus, this afferent activity triggers a series of autonomic responses, which results in the sensation of pain.[16] Zia *et al*.,[17] isolated and purified two fractions namely B1 and B3 from the methanolic leaf extract of *N. indicum*. Both fractions were investigated for their action on the central nervous system and behavior pattern using p-benzoquinone-induced abdominal contractions in mice. Both the fractions affected the locomotor activity, rotarod performance and potentiation of hexobarbital sleeping time in the experimental animals. The number of writhings was lowest for ethanol extracts of fresh (15.0 ± 0.6) and dried flowers (15.0 ± 0.7) with an inhibitory ratio of 66.6% ($^{***}P < 0.001$) in both cases out of the extracts of fresh flower, dried flowers, and leaves prepared in methanol and water.

ANTIMITOTIC ACTIVITY

Antimitotic agents inhibit the cell division or halts cell-cycle. Proliferation of the cancer cells and their metastasis are chiefly mediated by the proliferation of cells by mitotic divisions, and thus, mitotic inhibitors are used for anticancer treatment. Currently, various mitotic inhibitors have been found successful to halt the uncontrolled growth of cancer cells such as paclitaxel, docetaxel, vinblastine, vincristine, vinorelbine, etc. Tarkowska[18] studied the antimitotic activity of a complex mixture of glycosides derived from *N. oleander* root tips of *Allium cepa* and endosperm of *Haemanthus katherinae*. The root tips were submerged in the solution of oleander glycosides for 6-48 h and the results were observed by microscopic technique. Chromosomes of *A. cepa* under aceto-orcein staining resulted in shortening in length and were scattered throughout the cell. However, the kinetochore remained integrated. In case of *H. katherinae*, the continuous microtubules were disoriented and are irregularly arranged. Restitution nuclei of varying sizes developed due to partitioning of chromosome and chromatids into uneven groups. Hindrance in the phragmoplast development was also noticed leading to multi-terminal phragmoplasts and abnormal cell plates.

ANTIBACTERIAL ACTIVITY

Bacteria are the source of a wide range of diseases such as cholera, tetanus, diphtheria, tuberculosis, typhoid fever, etc. Numerous antibiotics derived from plant sources have displayed potent antimicrobial activity against a vast spectrum of pathogenic bacteria. Cold chloroformic, ethanolic, and methanolic extracts of and root bark and leaves were tested against *Bacillus pumilus*, *Bacilllus subtilis*, *Staphyloccus aureus*, and *Escherichia coli*.[19] The results display that the extracts possessed potent antibacterial activity. The zone of inhibition of the chloroformic leaf extract resulted in a zone of inhibition of 19 mm throughout the experiment (48-46 h). At 96 h, the activity of ethanolic leaf extract was highest against *B. pumilus* and *S. aureus*, resulting in the zone of inhibition of 24 mm each. The methanolic root extract

demonstrate comparatively better antibacterial activity among all extracts.

ANTIFUNGAL ACTIVITY

A vast array of diseases occurs due to the fungal infections such as athlete's foot, pneumocystis pneumonia, candidiasis, chronic pulmonary aspergillosis, etc. Various plants are tested for their antifungal efficiency under complementary and alternative medicinal approaches. Hadizadeh *et al*.,[20] studied the antifungal activity of the ethanolic flower extracts of this plant against different fungal pathogens. The flower extract at the highest concentration (0.9%) resulted for 46.3 ± 0.02%, 70.3 ± 0.05%, 90.3 ± 0.01%, and 89.2 ± 0.13% growth reduction for *Alternaria alternate, Fusarium oxysporum, Fusarium solani*, and *Rizoctonia solani*, respectively. Furthermore, Kalita and Salkla[21] demonstrated the antifungal activity of 50% of the ethanol fraction of *N. indicum* leaves against *Aspergillus niger* and *Candida albican*. Zone of inhibition of 10 mm and 13 mm were found in case of *A. niger* and *C. albican*, respectively.

ANTIVIRAL ACTIVITY

Ethnopharmacology provides an alternative path in the present antiviral therapy to fight against various virus borne diseases. Various polyherbal formulations and bioactive compounds isolated from the plants have demonstrated potent antiviral activity. Singh *et al*.,[22] studied the effect of an aqueous extract (Anvirzel™) of the plant on HIV infectivity in human peripheral blood mononuclear cells. They have demonstrated that without any alteration in the total number of virus particles, Anvirzel™ reduced the potentiality of HIV to infect new cells. Oleanderin, which is a cardiac glycoside isolated from the leaves, down-regulated HIV coat protein g120 expression, which is the primary mediator of HIV infection. As low as 10 μg/ml concentration of Anvirzel™ was potent enough to inhibit the HIV infectivity. Rajbhandari *et al*.,[23] demonstrated that the methanolic extract of *N. indicum* possess potentiality against influenza virus and herpes simplex virus. The extract showed inhibitory concentration 50 (IC_{50}) value of 10 μg/ml against the influenza virus.

CARDIOTONIC ACTIVITY

Efficiency of the heart muscle gets accelerated under the influence of cardiotonic agents. The contractions of the myocardium is chiefly regulated by Na^+/K^+-pump and Ca^{2+}-pump which gets affected by these agents. Certain agents alter the electrolyte balance across the myocardial lipid membrane, resulting in increased efflux of potassium and decreased influx of sodium and calcium into the cell. Two major cardiac glycoside digitoxin and digoxin were isolated from the plant *Digitalis purpurea* (Foxglove) which displayed the capacity to stimulate the myocardial contractions. In Uganda, this plant is used as a first aid to treat various cardiovascular diseases. Adome *et al*.,[24] have demonstrated the cardiostimulatory effect of the crude ethanolic extract of *N. oleander* leaves on pig cardiac model. Three parameters namely, force of myocardial contraction, heart-beat rate, and flow of cardiac blood were measured under the influence of the extract. The results displayed that under the influence of 100 mg/ml extract, the heart beat rate was increased from 28 beats/min to 41 beats/min, blood flow volume increased from 0.4 ml/min to 1.9 ml/min and amplitude of myocardial contraction increased from 22-49 mm. The results of the leaf extract were much higher than that of the positive control acetylcholine and adrenalin.

NEUROPROTECTIVE ACTIVITY

PB-05204 is a CO_2 extract of the leaves of oleander. PB-05204 and oleanderin were tested for their neuroprotective activity in the ischemic injury model under oxidative damage and glucose deprivation.[25] Results suggested that yellow fluorescent protein tagged coronal brain slices had more protection from oxygen and glucose deprivation when treated with 23 μg/ml PBI-05204 (approximately containing 1 μM oleandrin). At 69 μg/ml PBI-05204, the extent of protection was same as 23 μg/ml PBI-05204, whereas 10 fold increase in PBI-05204 concentration (230 μg/ml) decreased the extent of neuroprotection. PBI-05204 also increased levels of α1 and α2 subunits of Na^+/K^+-ATPase in the rat brain slices. Therefore, these findings suggested the neuroprotective potentiality of the plant extract in ischemic stroke model.

ANTIOXIDANT ACTIVITY

Reactive oxygen species (ROS) are the causative agents behind a wide range of disorders and several plant based products possess tremendous ROS scavenging capacity. Hydro-methanolic extract of the leaf, stem, and root of *N. indicum* was studied for their antioxidant capacity[26,27] by investigating various free radical scavenging assays. Leaf displayed excellent hydroxyl radical, peroxynitrite, hypochlorous acid scavenging, iron chelation activity with IC_{50} value of 29.65 ± 0.21 μg/ml, 1672.80 ± 56.68 μg/ml, 124.74 ± 1.91 μg/ml, and 216.70 ± 9.82 μg/ml, respectively. Nitric oxide and DPPH radical scavenging capacity were highest in the stem (IC_{50}: 29.65 ± 0.21 μg/ml and 63.56 ± 1.63 μg/ml, respectively), whereas the root displayed lipid peroxidation, superoxide anion, hydrogen peroxide, and singlet oxygen scavenging activity with IC_{50} value of 110.03 ± 12.75 μg/ml, 170.69 ± 2.41 μg/ml, 37.05 ± 2.99 μg/ml, and 275.08 ± 7.5 μg/ml, respectively.

ANTIMALARIAL ACTIVITY

Sharma *et al*., have studied the larvicidal activity of ethanol and acetone extracts of the plant by investigating efficiency of these extracts on the 3rd instar larvae of two malaria causing vectors

Anopheles stephensi and *Culex quinquefasciatus*.[28] The ethanolic extract was proved to be more potent than the acetone extract against *A. stephensi* and vice versa against *C. quinquefasciatus* after 24 and 48 h. Lethal concentration 50 value of the methanolic extract on *A. stephensi* was 185.99 ppm (24 h) and 184.05 ppm (48 h), whereas on *C. quinquefasciatus* was 494.07 ppm (24 h) and 194.49 ppm (48 h). In case of acetone extract, the lethal dose 50 (LD_{50}) value was 229.28 (24 h) and 149.43 (48 h) for *A. stephensi* and 209.00 ppm (24 h) and 155.97 ppm (48 h) for *C. quinquefasciatus*.

HEPATOPROTECTIVE ACTIVITY

Drug-induced hepatotoxicity is one of the most burning problem in the pharmaceutical industry and haloalkane-induced hepatotoxic model provides an efficient way to test the hepatoprotective potential of a drug. Therefore, the methanolic flower extract of *N. indicum* was tested for its efficiency in CCl_4 mediated hepatotoxic model.[3] The results demonstrated that the flower extract ameliorated the damaged liver of rats by decreasing the levels of glutamic oxaloacetic transaminase, glutamic-pyruvic transaminase, alkaline phosphatase, bilirubin, and malondialdehyde levels in the serum of the experimental animals. The level of superoxide dismutase, which gives protection against free radical mediated damage to the liver, was also elevated. Histopathological studies demonstrated that the extract treated livers possessed less signs of inflammation and necrotic tissue as well as the normal liver architecture was restored with increased dose of the flower extract.

ANTIDIABETIC ACTIVITY

Mwafy and Yassin studied the antidiabetic activity of the aqueous extract of the leaves on streptozotocin-induced diabetes model in rats.[29] The results displayed that at the peak of 4th week, the serum glucose level in extract treated group was 238.5 ± 10.3 mg/dl and serum insulin level was 1.10 ± 0.07 mg/dl corresponding to 128% and −18.5% change, respectively. On the contrary, linear correlation analysis between the serum glucose and insulin levels did not resulted in close correlation and they yielded a weak correlation coefficient (r) of −0.3. In the extract treated group, the levels of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase in the serum were 96.3 ± 4.7 U/l, 44.4 ± 1.7 U/l, and 63.4 ± 2.9 U/l, respectively representing 93.2%, 13.3%, and 63.4% change, respectively, for the three liver enzymes.

ANALGESIC ACTIVITY

Ahmed and his team studied the analgesic activity of methanolic extracts of flower, root, stem, and leaves of *N. indium* by acetic acid-induced writhing model in rats.[30] At the highest dose of flower, root, stem and leaf extract the percentage of writhing was 6.80%, 72.11%, 4.08%, and 0.0%, respectively, when writhing in the control was considered as 100%. The percentage of inhibition in writhing was 93.20%, 27.89%, 95.92%, and 100%, respectively. Positive control, aminopyrine resulted in 63.27% inhibition in writhing at 50 mg/kg dose.

ANTIULCER ACTIVITY

Methanolic extract of *N. indicum* leaves were investigated by Patel *et al.*,[31] for possible antiulcer activity by studying pylorus ligation and indomethacin-induced ulcer *in vivo*. They have shown that the leaf extract at 250 and 500 mg/kg dose in indomethacin-induced ulcer resulted in 65.97% and 69.63% protection respectively, with an ulcer index of 5.416 ± 0.200 and 4.833 ± 0.494, respectively based on six parallel experiments. Furthermore, in pylorus ligation-induced ulcer in rats, 250 and 500 mg/kg dose resulted in ulcer index of 5.666 ± 0.527 and 4.583 ± 0.860, respectively, which was much lower than that of the control (14.083 ± 0.676). Besides, the gastric acidity was much lower (63.15 ± 0.295 meq/1/100 g) in the 500 mg/kg dose compared to the control (102.43 ± 0.224 meq/1/100 g) with reduced gastric volume.

ANTI-INFLAMMATORY ACTIVITY

Inflammation is a biological response against invading bacterial and viral pathogens, autoimmune reactions, and persistent foreign bodies which results in tissue damage. Inflammatory responses are primarily mediated by various cytokines, inflammatory proteins and nitric oxide.[32] Erdemoglu *et al.*, studied the anti-inflammatory activity of 500 mg/kg dose of ethanolic and aqueous extracts of the plant on carrageenan-induced paw edema model[33] and measurement of paw thickness was done in an interval of 90, 180, 270, and 360 min. Among all the fractions, ethanolic extract of the dried leaves resulted in the least amount of inflammatory reaction (37.2 ± 4.9 × 10^{-2} mm thickness at 90 min).

ANTICANCER ACTIVITY

Like various other herbal medicines, different extracts and compounds isolated from *N. indicum* were tested for their efficiency as anticancer agents. Newman *et al.*, tested the efficiency of a major glycoside oleandrin on human pancreatic tumor cells PANC-1.[34] Oleandrin not only paused the cell proliferation of PANC-1 cells but also arrests cells at G (2)/M stage of cell cycle. The results indicate that oleandrin stimulated death of PANC-1 cells were not mediated by autophagy processes; rather it was governed by apoptotic pathway. Mamdooh *et al.*,[35] studied the effect of an extract of the leaves, *N. oleander* leaf extract (NOE-4), on the susceptibility of Raji cells (human Burkitt's lymphoma) to the natural killer cell mediated cytotoxicity. After 24 h of incubation, the control Raji cells were found to be unaffected by human mononuclear cell (MNCs) mediated cytoxicity, whereas NOE-4 treated Raji cells were heavily affected in a dose dependent manner. In addition to the increased conjugate formation between Raji cells and MNC or NK-cells, the

researchers also found a decrease in the expression of Bcl-2 molecules, which gave a clue that NOE-4 perhaps, may be used to treat immune resistant cancers. Antileukemic effects of various extracts of the plant was studied on HL60 and K562 cell lines by Turan *et al.*,[36] which showed that the cytotoxic index on K562 cells were 66.22%, 57.82%, 58.10%, and on HL60 cells were 69.33%, 66.50%, and 62.81% for leaf, stem, and root extracts, respectively. The levels of P-glycoprotein (ATP-binding cassette transporter) were also found to be affected by the extracts, resulting in toxicity to the K562 cells.

CHEMOTHERAPY SUPPLEMENTATION

Platinum derived cisplatin is a chemotherapeutic drug. Apostolou *et al.*, have recently shown[37] that cisplatin supplemented with Anvirzel™ holds enhanced potentiality against breast (MDA-MB 231, T47D, and MCF-7), colon (HCT-116, HT55, and HCT-15), lung (CALU-1, COLO699N, and COR-L 105), prostate (PC3, LNCaP, and 22Rv1), melanoma (A375), and pancreatic (PANC-1) cancer models. Cancer cells were incubated with 0.1-100 μg/ml for cisplatin supplemented with 0.01-10 ng/ml for Anvirzel™ for up to 3 days. Combination of 0.1 μg/ml cisplatin with 0.01 ng/ml Anvirzel™ displayed most potent toxicity for most of the cell lines, whereas 1 μg/ml cisplatin with 0.01 ng/ml Anvirzel™ displayed high efficiency against PC3 and MDA-MB231 cells.

RADIOTHERAPY SUPPLEMENTATION

Oleandrin is an active constituent of Anvirzel™, an aqueous extract of *N. indicum* leaves. Nasu *et al.*, studied the effect of oleandrin as a supplement to radiotherapy on PC3 (human prostate cancer) cell line.[38] PC3 prostate carcinoma cells were cultured with 0.05 μg/ml of oleandrin and after 24 h, the cells were irradiated with gradual increasing dose of γ-rays and then studied for colony forming capacity. The test group (oleandrin treated) reduced the colony forming efficiency from 95% to 21% of the PC3 cells. Furthermore, the extent of radiosensitivity depended on time for which cells were incubated with oleandrin. Survival rate of cells with 0.05 μg/ml oleandrin exposure prior to radiation was 30%, which was lower than the control group (50%). PC3 cells were found to be more prone to apoptosis when treated with oleandrin prior to radiation compared to individual treatment with oleandrin and radiation.

MUTAGENICITY

Shaziyl *et al.*, investigated ethanolic extracts of the leaves for possible mutagenic activity through hypoxanthine phosphoribosyl transferase method.[39] Antichrysen-1, 2401-3, 4-oxide (ACDO) was used as positive mutagenic control. The mutation frequency was $2.42/10^6$ cells and $3.07/10^6$ cells for 50 ppm and 25 ppm, respectively, which were much lower than ACDO, resulting in very high frequency of mutation ($1111.83/10^6$ cells).

ANTIANGIOGENESIS ACTIVITY

Hu *et al.*, isolated three galacto-oligosaccharides (OJ1-OJ3) from the *N. indicum* leaves by acid hydrolysis method and tested their effect on the human microvascular endothelial cells (HMEC-1)[40] in the tube formation assay. After 16 h incubation, control HMEC-1 cells formed distinct tube-like structures, but tube formation was disrupted for OJ2 and OJ3 at 100 μM concentration, whereas OJ1 displayed no antiangiogenesis activity. The authors hypothesized that though all the three polysaccharides possessed backbone of a (1 → 4)-linked linear galactan chain, but their activity differed due to the difference in their sizes.

PHYTOCHEMICAL ANALYSIS

Dey *et al.*, performed the phytochemical analysis of various parts of *N. indicum*[6] and identified the presence of a wide range of phytochemicals such as phenolics, glycosides, alkaloids, tannin, flavonoid, etc., in the plant. Quantification of these phytochemicals revealed the presence of 67.86 ± 1.54 g/100 g alkaloid, 82.53 ± 2.41 mg/g phenolics, 1.01 ± 0.06 mg/100 g ascorbic acid in the root; 12.56 ± 0.67 g/100 g saponin, 8.05 ± 0.19 mg/g flavonoid, 0.42 ± 0.04 mg/g riboflavin, and 0.48 ± 0.05 mg/g thiamine in the leaves.

THE HISTORY OF ANVIRZEL™

Turkish surgeon Dr. H. Ziya Ozel invented a special extract Anvirzel™ out of the leaves of this plant, which have demonstrated miraculous anticancer effects against cancer cell lines.[41] In 1973, he successfully treated some critically ill cancer patients with the extract without any side-effects like hair loss or decrease in blood leucocyte count.[42] In the following years, further working with the extract, Ozel discovered anticancer efficiency of the plant.[43] In 1987, the extract was tested by Sandoz pharmaceutical company (now Novartis) and confirmed that the extracts possess immunomodulatory activity.[44] In 1988, a research team from Munich University Pharmacology Institute collaborating with Dr. Ozel isolated some bioactive polysaccharides which were responsible for the tremendous immunomodulatory activity.[45,46] In 1992, the European patent office granted US patent to Dr. Ozel and in 1995, a US Pharmaceutical Company (formerly known as Pharmaceutical Ventures Trust) registered the extract under the trademark Anvirzel™ and conducted phase I trials at the Cleveland Clinic, Ohio.[47] Today all over the world, various medicinal and pharmaceutical tests are being performed with this extract, which are revealing more of its therapeutic potential.

CONCLUSION

Phytomedicine is the oldest therapeutic known to mankind and *N. indicum* is one such plant which is used extensively in

ethnomedicinal practices all over the world for the treatment of dermatitis, eczema, psoriasis, herpes, sores, abscesses, warts, corns, skin cancer, ringworm, scabies, epilepsy, asthma, malaria, and heart disease.[48] Medicinal usage of the plant dates back to 1500 years BC.[49] In Dan Brown's historical mystery-fiction "The Davinci Code", rose is symbolized as feminine half of God, highlighting powerful healing power according to pagan and early Christianity.[50] Furthermore, in the holy Bible the oleander plant is mentioned as the "the desert rose", symbolizing its medicinal value. However on the contrary, the plant has been labeled to be poisonous due to the presence of glycosides such as oleandrin, adynerin, digitoxigenin, and folineriin.[51] The amount of cardiac glycosides present in red flowered plants are higher than that of the white flowered plants[52] and thereby making the white flowered oleander less toxic. Some cases were also reported which highlighted the lethal nature of the plant.[53,54] However, according to the 2002 report of Toxic Exposure Surveillance System, out of 874 cases of high level exposure to the plant, only three cases turned to be lethal.[52]

Following the words of Paracelsus, the father of natural toxicology that, "dose makes the poison," caution must be taken before conducting *in vivo* experiments with the plant extracts of *N. indicum* (oleander). LD_{50} experiment must be conducted to assess the toxicity and the optimum and sub-lethal dose of the extracts. Today, even snake venom has gained importance as a therapeutic agent in different fields of medicine.[55,56] Therefore, utmost importance must be given to explore the medicinal and pharmacological properties of *N. indicum*, which holds immense potential as a therapeutic agent. It is hoped that *N. indicum* will prove itself as a nature's miracle herb in the long run with the ancient knowledge of traditional medicine blending with modern science.

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