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Nerium indicum (Linn.): A potential phytomedicine against various health problems

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ABSTRACT

Nerium indicum (Linn Apocyanaceae family) is wild plant and commonly known as "Kaner". It is used against various health problems in India and China as ethno medicine. India and China is among the oldest civilizations on earth. Ethno medicines are developed in ancient time by experiences sharing with nature. Aim of the present study is to explore the ancient knowledge of phytomedicine in context of modern science. Vedic period is the oldest cultural representation of human civilization. Ayurvedic system of medicine was developed in 'Susruta Samhita' and 'Charak Samhita'. *Nerium indicum* (Linn.) is one of the thousands of plants mentioned in Ayurvedic system of India as important medicine for the treatment of various ailments. The flowers and leaves of *N. indicum* have been used to stimulate cardiac muscle, relieve pain and eliminate blood stasis. Present review mainly deals with the phytomedicinal properties such as analgesic, anti-diabetic, anti-oxidant, anti-bacterial, anti-viral, insecticidal/molluscicidal, hepatoprotective, neuroprotective, anticancer, anti-hyperlipidemic, anti-feedent activity of *N. indicum.* Its role as bioindicator in predicting the environmental condition is also discussed. *N. indicum* contains glycoside, oleandrin, tannin, volatile oil 0.25%. Glucoside, neriin and oleandrin are found in leaves of this plant. *Nerium indicum* is one of the wild plants, which is commonly used in various cultures as ethnic medicine. Although recent researches on its medicinal properties had established its therapeutic value in treatment of ailments, yet lot of studies are still required to explain its potentials as safe phytomedicine.

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INTRODUCTION

Nerium indicum Linn., usually known as 'Kaner' and belongs to the family Apocyanaceae. *N. indicum* is ornamental plant having leathery leaves and flowers of different colours. It is native of Indian sub continent and widely distributed in Mediterranean region, subtropical Asia (Chetwani *et al.*, 2017). In the traditional systems of aurvedic medicine, *N. indicum* is used to cure variety of human ailments. In ancient Indian Ayurvedic book 'Charak Samhita', karvir (*N. indicum*) was recommended for the management of *Twark Roga*. Its stem bark juice is used in cure of ear pain in traditional eth-

nic treatment in Tamil Nadu India (Muthu *et al.*, 2006). Traditionally it is used in cure of epilepsy, skin diseases, wound healing reproductive problem, gastro-intestinal infection, malaria, hypertension, diabetes (Tagarelli *et al.*, 2010; Tantiado, 2012). Various constituents isolated from different part of *N. indicum* showed wide spectral biological activities such as its cardiotonic, diuretic properties (Zia *et al.*, 1995). Its leaves are also used against snake bites. The cardiotonic and diuretic properties is mainly due to the active component oleandrin. Roots have been used externally for the cure of different types of cancers, leprosy, headache, ringworm and other skin complains (Nagargoje and Phad, 2013). *N. oleander* caused severe cardiac arrhythmia and severe diarrhea, sometimes with blood (Tokarnia *et al.*, 1996). Its 11-dihydroxyhexadecanoic acid and its glycoside have been reported as anti-cancer and anti-microbial agents (Siddiqui *et al.*, 1987). Root, bark and seed of *N. indicum* contain cardiac glycosides, which have paralyzing action on the spinal cord. Oil of *N. indicum* root is very effective in treatment of leprosy and skin disease (Saini, 2010). The leaves and bark are used as heart tonic, diuretic, expectorant, diaphoretic and emetic (Patel, 2010b; Jawarkar *et al.*, 2012). Root boiled in water is helpful, in treatment of skin complaints, herpes and ringworms infections (Nagargoje and Phad, 2013). A very little dose of leaf juice is used against snake or other venomous bites (Nagargoje and Phad, 2013). Root part is used in hemorrhoids, various type of cancer, ulceration and leprosy treatment (Vinayagam and Sudha, 2011; Chauhan *et al.*, 2013). *N. indicum* plant consists of cardiac glycosides in its leaves, stem and flowers. The barks consist of toxic glycoside: rosaginin and nerlin, volatile oil (Chetwani *et al.*, 2017). Flowers also have alkaloid, glucoside, carbohydrate, flavonoid and tannins' and phenolic compound (Patel, 2010a). *N. indicum* leaves decoctions are used in the treatment of scabies, and to reduced swelling. Shah and Chakraborthy (2010) have been reported antibacterial and anti-inflammation activities of *N. indicum*. Different part of the *N. indicum* used as a molluscicides, insecticide and rat poison (Singh and Singh, 1998; Shah and Chakraborthy, 2010; Nagargoje and Phad, 2013).

Phytoconstituents

Polysaccharides purified from leaf and flower of *N. indicum* have higher soluble sugar. The sugar has large number of stereo-isomerism, because they contain many asymmetrical carbon atoms. Neriin and oleandrin, glucosides found in leaves of *N. indicum* have same properties as digitalin. The oleandrin is highly toxic (Chopra *et al.*, 1986). The plant having digtoxin properties like steroid glycoside. The stems and flower have higher levels of phenol, lipids, respectively (Vijayvergia and Kumar, 2007). Phytochemical glycoside, neriodorin, neoriodorein and kreabin are the main constituents of *N. indicum* root. The bark contains scopoletin, scopolin (Sharma *et al.*, 2013). It also contains tannins, aromatic oil, wax and flobefin and yellow coloured stable oil. Neriodin, nerium D, rutin and anhydro-oleandrin are also reported in root of *N. indicum*. The root consists of bitter glycosides fenolinic acid and aromatic oil (Nagargoje and Phad, 2013). Presence of a-amyrin, b-sitosterol were noted in alcoholic extract of root, bark, whereas odoroside betulinic acid, oleonolic acid Sharma *et al.* (2013) were found in the ether extract.

Phytomedicinal properties

N. indicum is very poisonous plant as it contains powerful cardiac toxin. Therefore, it is used with extreme caution. The root is powerful resolvent and used in the form of plasters and is applied to tumors. It is only used externally. It is prepared in form of powder and mixed with water to form paste and then applied to lesion and ulcer on the penis (Nagargoje and Phad, 2013). Bark is better used as cathartic, febrifuge in intermittent fever. Oil prepared from the root, bark is applied in treatment of leprosy and skin diseases of the scaly nature (Nagargoje and Phad, 2013). Seeds of *N. indicum* are poisonous, abortifacient. They are used as purgative in dropsy and rheumatism. The part of entire plants is used as anti-cancerous agent. The flower, leaves, latex, bark and roots are used against corns, warts, cancerous ulcer, carcinoma, ulceration and hard tumors (Zibbu and Batra, 2010).

Anti-diabetic properties

Ingestion of leaves of *N. indicum* before a meal reduced the postprandial level in type II diabetic patients (Ishikawa *et al.*, 2007). According to them active principal compound 3- O-caffeoylquinic acid and 5-O-caffeoylquinic acid inhibit α-glucosidase in non-competitive manner. The effect of different extract on glucose tolerance test in normal rats was evaluated. After 30 minutes of glucose administration the peak of blood glucose level increased rapidly from the fasting value and then subsequently decreased. Mwafy and Yassin (2011) reported the antidiabetic activity of aqueous extract of the leaves on streptozotocin-induced diabetics' models in rats. Significant 128% and 18.5% changes in serum glucose level and insulin level at the 4th day of observation was noted respectively. Sikarwar *et al.* (2009) have been reported the effect of chloroform/ethanolic extract of *N. indicum* leaves

on alloxaninduced diabetic rat model were reported by Sikarwar *et al.* (2009). Treatment with dose of ethanolic extracts (300mg/kg b.w.) of *N. indicum* significantly (P<0.01) reduced the blood glucose level as compared to diabetic control on the 7^{th} day of the study. Different extract of *N. indicum* has different effects on glucose level. Chloroform and ethanolic extracts (500 mg/kg b.w.) has shown significant reduction of blood glucose after one hour, three hours of is taken, respectively. Whereas aqueous extract of the same plant has no significant, effect in reducing the glucose level (Sikarwar *et al.*, 2009).

Analgesic properties

Flower extracts of *N. indicum* caused significant inhibition 89.14% and 93.20% of control writhing responses at oral doses of 250 mg/kg body weight of mice, respectively, whereas the root extract showed analgesic activity with 59.18% and 95.92% writhing inhibition at 125mg/kg and 250mg/kg body weight of mice, respectively. The results were found to be dose dependent and highly effective in comparison to the control. The stem extracts showed only 6.78% and 27.89% inhibition of writhing response at oral doses of 125mg/kg 250mg/kg body weight of mice, respectively. The analgesic activity of stem extract was lower in comparison to the crude flower and root extract, whereas crude leaf extract of *N. indicum* showed 100% inhibition of writhing reflex. Ahamed *et al.* (2006) noted that administration of the crude leaf extract reduced the pain sensation produced by acetic acid as mice did not show writhing reflex.

Anti-ulcer properties

On the basis of experiments it was noted that treatment with leaf extract of *N. indicum* at 250 and 500 mg/kg body weight in indomethacin-induced ulcer resulted 65.97% and 69.63% protection in rats, with an ulcer index of 5.416 and 4.833, respectively. Furthermore, in pylorus ligation-induced ulcer in rats, 250 and 500 mg/kg body weight dose resulted an ulcer index of 5.666 and 4.583, respectively, which was lower than that of the control (14.083) (Patel *et al.*, 2011).

Anti-oxidant properties

Reactive oxygen species (ROS) are the causative agents to many disorders in physiology of body. The methanolic extract of leaves/flower of *N. indicum* was analyzed for anti-oxidant activity (AOA) in terms of DPPH (diphenylpicrylhydrazyl) free radicals. Enzymatic anti-oxidant activity such as superoxide dismutase, glutathione peroxidase and catalase of *N. indicum* flowers were 10% to 30% more pronounced than leaves. Methanol extract of *N. indicum* flowers are more potent anti-oxidant than leaves (Vinayagam and Sudha, 2011). Mohale *et al.* (2016) reported the antioxidant activity of ethyl acetate extract of *N. indicum* flowers. According to them treatment with this extract caused significant increase in the endogenous antioxidants, superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH) in blood and brain of rats (Mohale *et al.*, 2016). Several plant based products contain tremendous ROS scavenging capacity (Dey and Chaudhari, 2014). Several free radical scavenging elements were recognized in hydromethanolic extract of the leaf, stem and root of *N. indicum* (Dey *et al.*, 2012; Dey and Chaudhuri, 2013).Leaf displayed excellent hydroxyl radical, peroxynitrite, hypochlorous acid. Whereas stem, indicate the presence of nitric oxide and DPPH (diphenylpicrylhydrazyl) radical scavenging capacity. *N. indicum* root displayed lipid peroxidation, superoxide anion, hydrogen peroxide and singlet oxygen scavenging activity (Dunn *et al.*, 2011).

Anti-viral properties

N. indicum exhibited considerable anti-viral activity against herpes simplex virus and showed no cytotoxic effects (Rajbhandari *et al.*, 2001). Anti-influenza viral activity with 50% inhibition was noted at dose of 10 μg/ml *N. indicum* methanolic extract. Singh *et al.* (2013) demonstrated that an aqueous extract of plant (AnvirzelTM) containing oleandrin compound of *Nerium* is effective against HIV in human. This product AnvirzelTM reduced the potentiality of HIV to infect new cells. Oleandrin extract from leaves of *Nerium*, down regulated HIV coat protein 120g expression at 10 mg/ml concentration (Chauhan *et al.*, 2013).

Anti-bacterial properties

The anti-microbial activity of methanolic extracts of *N. indicum,* exhibited growth inhibition on selected bacterial strains viz. *Bacillus species*, *Escherichia coli, Klebsiella species, Yersinia species, Enterococcus* species (Ramya *et al.*, 2010). Reddy (2010) reported *in vitro* anti-bacterial activity of *N. indicum* leaf extract at 2 mg, 4 mg, 6 mg, 8 mg/well. Recently, Chetwani *et al.* (2017) reported that *N. indicum* extracts viz. acetone, ethanol and aqueous have anti-bacterial activity against *Pseudomonas aeruginosa*. Among all these extracts acetone was most effective. Hussain and Gorsi (2004) noted the anti-bacterial activity of chloroformic/ethanolic/methanolic extract of root, bark and leaves against *Bacillus pumilus, Bacillus subtilis, Staphyloccus aureus* and *Escherichia coli*. Methanolic root extract demonstrate comparatively better anti-bacterial activity than bark and

leaves. Organic solvent extract of different parts of the *N. indicum* displayed broad spectrum antibacterial effect against gram positive bacteria. It blocks the microbial growth, having micro biostatic effects. Methanolic, chloroform, hexane extracts have shown considerable antimicrobial activity of the plant (Chauhan *et al.*, 2013).

Insecticidal/ Molluscicidal properties

Siddiqui *et al.* (1990) showed insecticidal property of the *Nerium* leaves against sugarcane mites and citrus leaf minor. Guzman and Ambros (1992) noted the insecticidal activity of *N. indicum* against pest *Blatta orientalis*. Sap of *N. indicum* bark extracted in the proportion of 30, 20 and 10g per 200 ml of water, were as effective as the commercial household insecticide. The addition of 25 ml of kerosene with 100 ml of extracts resulted into higher activity. Root extracts of the plant are toxic to black carpet beetle larvae. Singh *et al.* (1993) observed that the latex of *N. indicum* is potent molluscicide. Its toxic effect is both time and dose dependent. Very low concentration (24 h LC_{50}, 0.565 mg/l) of the *N. indicum* latex was effective against *L. acuminata*. Singh and Singh (1997) reported that different preparations of *N. indicum* leaf were toxic against *Lymnaea acuminata*. Purified fraction of leaf extract was 14 times more toxic to *L. acuminata* than standard molluscicide niclosamide. According to them molluscicidal activity was due to glycoside oleandrin present in the leaf extract of *N. indicum* (Singh and Singh, 1997). They studied the molluscicidal activity of bark of *N. indicum* against *Lymnaea acuminata.* According to them toxic components of *N. indicum* bark are soluble in water and ethanol. The toxicity of different bark preparations was both dose and time dependent. The 24h LC_{50} of lyophilized aqueous extract of bark against *L. acuminata* was 34.5 mg/l. Low concentration of vacuum-dried ethanolic extract (24h LC_{50}: 4.9mg/l) and purified bark (24h LC_{50}: 0.87mg/l) was more effective to treat the vector snail *L. acuminata* (Singh and Singh, 1997, 1998).

Hepatoprotective properties

Carbon tetrachloride induced a significant rise in serum glutamate pyruvate transminase (SGPT), serum glutamate oxaloacetate transminase (SGOT) and alkaline phosphatase (ALP) activity in liver cells. Treatments of rats with different dose of *N. indicum* extract significantly altered serum marker enzymes levels in carbon tetrachloride treated rats. The activity of the extract at dose was comparable to the standard drug silymarin. Hepatopancreatic activity of *N. indicum* was noted by various workers. Methanolic flower extract of *N. indicum* was evaluated for hepatoprotective activity in rats. Dose of 500 and 1000 mg/kg body weight prevented carbon tetrachloride induced damage in liver cells of rats (Patel, 2010b). Singhal and Gupta (2012) reported that *N. indicum* methanolic extract of flower is potent hepatoprotective agent as evident by less inflammation and necrosis resulted from carbon tetrachloride induced liver damage. Normal liver architecture was restored at higher dose of the flower extract (Singhal and Gupta, 2012).

Anti-cancer properties

Nerium oleander leaf extract (NOE-4) used against human Burkitt's lymphoma (Raji cell) was significantly effective in a dose dependent manner. In study control Raji cells were not affected with human mononuclear cell (MNCs) mediated cytotoxicity (Dey and Chaudhari, 2014). Turan *et al.* (2006) studied the anti-leukemic effects of various extracts of the *Nerium* on HL 60 and K 562 cell lines. They noted that cytotoxic index on K562 cells were 66.2%, 57, 8%, 58.1% and HL 60 cells were 69.3, 66.5 and 62.8% for leaf, stem root extracts, respectively. ATP binding cassette transporter P-glycoprotein was affected by these extracts, which ultimately kill the K562 cells. Different extracts and compounds isolated from *N. indicum* were tested for their efficiency as anti-cancer agents (Turan *et al.*, 2006). Newman *et al.* (2007) noted the efficiency of a major glycoside oleandrin on human pancreatic tumor cell, PANC-1. Oleandrin not only checked cell proliferation of PANC-1 cell but also arrests cell at G (2)/M stage of cell cycle. Oleandrin stimulated death of PANC-1 cells were governed by apoptotic pathway (Newman *et al.*, 2007).

Neuroprotective properties

Polysaccharide J6 isolate from flowers of *N. indicum* can be used against Alzheimer's disease (Yu *et al.*, 2007). Cortical Neurons stressed by beta-amyloid (Aβ) peptides or deprivations of nutrition from serum were potentially protected by *N. indicum* extract. A new polysaccharide from the flowers of *N. indicum* (named as J6) was investigated to study its neuroprotective effects against Aβ-induced apoptosis. Apoptosis caused by caspase-3 as well as the Aβ peptide was reduced significantly by pretreatments of the polysaccharide J6. Pretreatment activate survival signals Akt found in J2, J3, and J4 fractions. Dunn *et al.* (2011) demonstrated that oleandrin from leaves of *N. indicum* has potential to act as neuroprotective against in ischemic injuring oxidative damage and glucose deprivation. They formed that yellow fluorescent protein tagged coronal brain slices had more protection from oxygen and glucose deprivation, when exposed to 1 μm oleandrin. This

treatment also increased the $\alpha 1$ and $\alpha 2$ subunits of Na+/K+ ATPase in rat brain (Dunn *et al.*, 2011).

Anti-hyperlipidemic properties

The anti-hyperlipidemic effect of petroleum ether chloroform, ethanol and aqueous extracts of *N. indicum* leaves was studied against in triton induced and atherogenic diet induced hyperlipidemic rats. Chloroform extract of *N. indicum* leaves caused a significant reduction in serum lipid profile *i.e.* like total cholesterol, triglycerides, low density lipoprotein (LDL) very low density lipoprotein (VLDL) and enhance the high density lipoprotein (HDL) in hyperlipidemic rats and their control (Patel, 2010a).

Bio-indicator

Dried flower can be used as bio-indicator as they show remarkable colour change. Dried flower are pink in colour. When treated with alkali it becomes green and reappears when acid is added. Portillo *et al.* (1994) reported that leaves of *Nerium* plant can be used as a bio-indicator, a tool used for measurement of lead produced by the effluent of motor vehicle. Use of plant products in old Indian Aurvedic system against various diseases is well known.

Anti-feedant properties

Anti-feeding compounds can cause death impairment development or reproduction and may involve chronic as well as acute toxic effects. *Spodoptera litura* consumed minimum castor leaf sprayed with *N. indicum* leaf extract than fresh castor leaf. In addition to the leaf protection, enzymatic inhibition in insects is more, when it is consumed with castor leaf sprayed by *Nerium* leaf extract. It indicates that *N. indicum* leaf is an effective anti-feeding agent Dhanapakiam and Shanazbegum (1995).

CONCLUSION

Present review, deals with the information on the activities of different phytoconstituents of *N. indicum* against various diseases. *N. indicum* is source of mainly therapeutically important phytoconstituents such as glycoside, oleandrin, tannin, neriin, phytosterin, and I-strophnathin, rosaginin and nerlin, volatile oil, fixed oil, neriodori and neriodorein. In recent years, ethnomedicines are become a topic of global awareness. Plants have their own phytochemicals. Some of these chemicals have therapeutic importance in solving human health problems. *N. indicum* is a popular remedy used among the various ethnic groups. It is used in Ayurvedic and traditional practitioners of various ethnic groups in treatment of ailments. Researchers has explored the therapeutic potential of this plant as analgesic, antidiabetic, antiulcer, antioxidant, antibacterial, antiviral, hepatoprotective, neuroprotective, anticancer, antihyperlipidemic, and anti-feedant activity. Instead of its use as insecticidal/molluscicidal and bio-indicators is also recommended by various workers. Although medicinal properties of different phytoconstituents of *N. indicum* are noted by various workers, yet lot of investigations are still required to explore its full potential in medical science of 21^{st} century.

Abbreviations

ROS - Reactive oxygen species; AOA- Anti-oxidant activity; DPPH- Diphenylpicrylhydrazyl; SOD- Superoxide dismutase; CAT- Catalase; GSH- Glutathione; DPPH- Diphenylpicrylhydrazyl; SGPT- Serum glutamate pyruvate transminase; SGOT- Serum glutamate oxaloacetate transminase; ALP- Alkaline phosphatase; MNCs- Mononuclear cell; NOE- *Nerium oleander* leaf extract; MNCs- Human mononuclear cell; Aβ- Beta-amyloid; LDL- low density lipoprotein; VLDL- very low density lipoprotein; HDL- high density lipoprotein; PANC - human pancreatic cancer cell line

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Conflict of Interest

The authors have no conflict of interest.

Author contribution

All author contributed equally.

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