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PHYTOPHAMACOLOGICAL EFFECT OF *NERIUM OLEANDER* TO ANIMAL

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ABSTRACT

There are many natural crude drugs which have the potential to treat many disorders and illnesses; one of them is a Nerium oleander. Nerium oleander is an evergreen shrub of the Apocynaceae family which is a potentially lethal plant. It is highly poisonous to humans, pets, livestock and birds due to the presence of cardiac glycosides, mainly cardiac glycosides inactivate the Na^+/K^+ ATPase pump on the cytoplasmic membrane. These glycosides include neriin, oleandrin, cardenolides, gentiobiosyl and odoroside, mainly oleandrin is much more toxic. Apart from this plant species also produce secondary metabolites such as alkaloids, flavonoids and steroids which have pharmacological applications. The important pharmacological applications are antibacterial, anti-helminthes, anti-inflammatory, hepato-protective, immunopotential, anti-pyretic, anti-oxidant, anti-fungal and anti-HIV activity. The drugs derived from this plant, is used even for the treatment of cancer and the research is ongoing for its future implementation. The Nerium oleander is most prevalent, and its alluring flowers make it a particular hazard for accidental ingestion. The plant also has shown the toxicological importance for accidents when used in folk medicines, or suicides. Some insect such as Caterpillars of the polka-dot wasp moth (Syntomeida epilais) feed specifically on oleanders and survive by eating only the pulp surrounding the leaf-veins, avoiding the fibers. In the current article comprehensively covers the medicinal, toxicological and pharmacological, activities of the plant to animal.

***Keywords*:** Cardiac glycosides; Secondary metabolites; Seroids; Flavonoids

INTRODUCTION

Nerium oleander is an ornamental shrub or small, densely branched tree commonly known as "**Kaner**", belongs to the family Apocynaceae. It grows to heights between 6.5' and 19.5' tall and 6' to 10' wide. Leaves are 10 to 22 cm. long, narrow, acute in the apex, shortly petiolate, with a coriaceus dark green blade narrow, untoothed, short-stalked and dark or grey- green in color. All leaves have a prominent mid rib, are "leathery" in texture and usually arise in groups of three from the stem. The plant produces terminal flower heads, usually pink or white. Each flower is about 5 cm in diameter and five petalled although some cultivators have double flowers. Oleander has flexible branches with green, smooth bark eventually turning to dark grey on maturity. Cut or broken branches exude a thick, white sap. The fruit consists of a narrow follicle 7.5 to 17.5 cm long which opens to disperse fluffy seeds. Oleander can be propagated by seeds but, being allogamous and highly heterozygous, it shows great variability in seedling population.

Sticky latex is exuded if the stem is cut which is a poisonous substance or fluid of this plant. It is

poisonous substance or fluid of this plant. It is native to Indo-Pak subcontinent, widely distributed in Mediterranean region, subtropical Asia, southern United States. [1] But is now growing in many parts of the world such as Australia, USA, China and Middle East countries. All parts of oleander are toxic due to the presence of oleandrin, oleandrigenin and other cardiac glycosides. Toxic exposure of humans and different species of domestic animals to *N. oleander* cardenolides occurs commonly throughout the geographic regions where this plant grows. [2] The human mortality associated with ingestion of oleander is generally very low, but animals exposed to the plant are often found suddenly dead owing to cardiac dysfunction. *N. oleander* contains a mixture of very toxic cardiac glycosides of cardenolides, the most prominent of which are oleandrin and neriine. [3] Cardiac glycosides of *N. oleander* cause poisoning by inhibiting plasmalemmal Na+, K+-ATPase [4].The plant has also been used for suicidal or murderous intention [5]. On the contrary *N. oleander* has been also used in the Arabfolk-medicine as powder and decoction for treating solid tumors and for skin diseases. [6] All parts of the plant are reputed as therapeutic agents and have been used in folklore in a variety of ailments including skin complaints, ringworm infections, cancer, epilepsy, eczema, malaria and gastrointestinal disturbances. Leaves and bark are also used as heart tonic, antibacterial, diuretic and anti-emetics. [7, 8] A decoction of the leaves has been applied externally in the treatment of scabies and to reduce swellings. Plants have an extensive root system and are often used to stabilize soil in warmer areas. Oil prepared from the root bark is used in the treatment of leprosy and skin diseases of a scaly nature. Seeds are poisonous, abortifacient and alternative. They used as purgative in dropsy and rheumatism. The whole plant is said to have anticancer properties. [9]

DISTRIBUTION OF PLANT

Nerium oleander, belongs to the Apocynaceae family, is the only species currently classified in the genus Nerium. It is commonly known as oleander, from its superficial resemblance to the unrelated olive Olea. Nerium oleander is widely cultivated and though to be originated from Mediterranean region and Indo-Pakistan subcontinent and distributed in different geographical and ecological places. [10] Distributed in the Himalayas from Nepal westwards to Kashmir up to 1950m, extending to Baluchistan, Afghanistan and found throughout India in gardens.

BOTANICAL DESCRIPTION

Nerium oleander L. is an evergreen shrub reaching up to four meters in height and belongs to the family – Apocynaceae, is a shrub or occasionally tree distributed in tropical Asia Nerium oleander L. is cultivated worldwide as an ornamental plant. It is native to the Mediterranean region and is also found in Southern Europe and Southwest Asia, but is naturalized very easily and in many areas the plant is sub-spontaneous.

Leaves are 10 to 22 cm. long, narrow, acute in the apex, shortly petiolate, with a coriaceus dark green blade narrow, untoothed, short-stalked and dark or grey- green in color. Some cultivars have leaves variegated with white or yellow patches. All leaves have a prominent mid rib, are "leathery" in texture and usually arise in groups of three from the stem. The plant produces terminal flower heads, usually pink or white. Each flower is about 5 cm in diameter and five petalled although some cultivators have double flowers. Oleander has flexible branches with green, smooth bark eventually turning to dark grey on maturity. Cut or broken branches exude a thick, white sap. The fruit consists of a narrow follicle 7.5 to 17.5 cm long which opens to disperse fluffy seeds. Oleander can be propagated by seeds but, being allogamous and highly heterozygous, it shows great variability in seedling population. [11]

CHEMICAL CONSTITUENT

The plant contains a number of related cardiac glycosides similar in activity to digitalis. [12] The main glycosides oleandrin, neriine, cardenolides, gentiobiosyl, oleandrin and odoroside are also present. [13] In addition, a variety of other pharmacologically active compounds, including folinerin, rosagenin, rutin and oleandomycin have been identified in the plant.

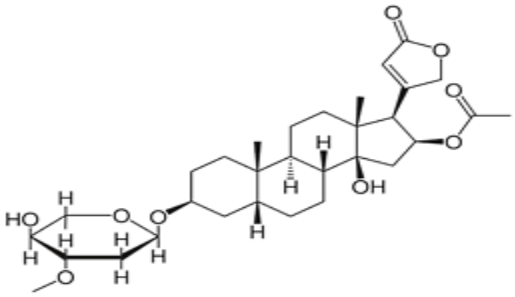
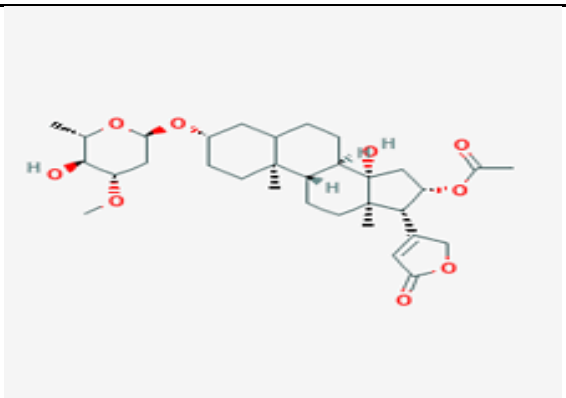
In leaves, two new cardenolides, 3 beta-O-(D-2-O-methyl-digitalosyl)-14 beta-hydroxy-5 beta-Carda-16,20 (22)-dienolide (1) and 3 beta-hydroxy-8,14-epoxy-5 beta-Carda-16,20 (22)-

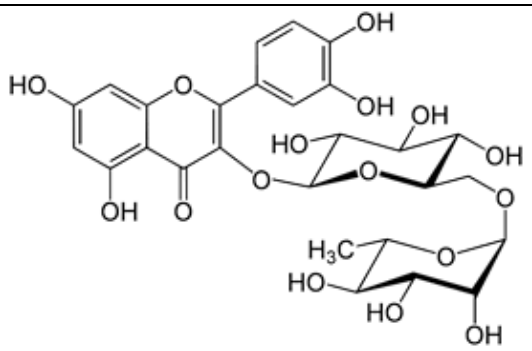
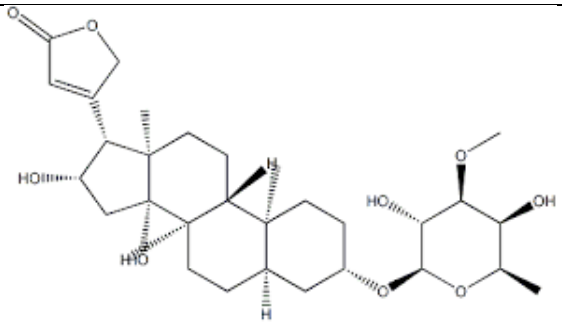
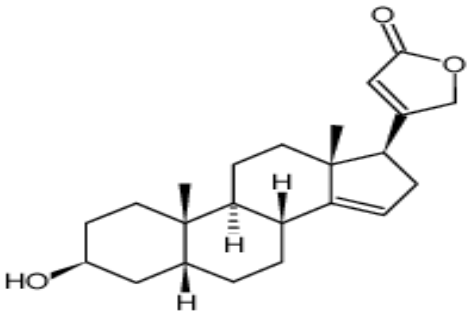
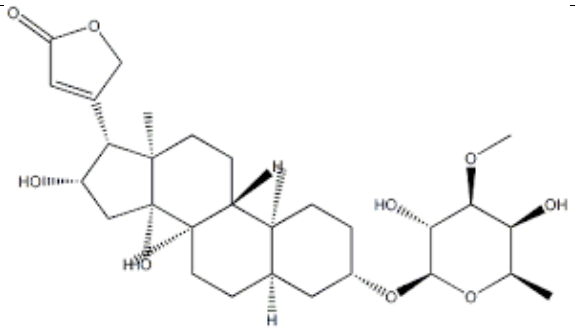
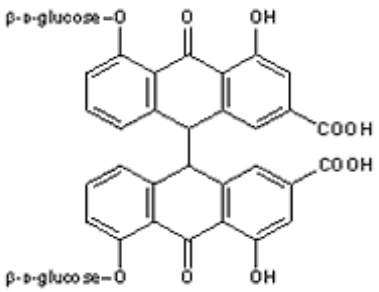
hydroxy-8,14-epoxy-5 beta-Carda-16,20 (22)-dienolide (2), and two known cardenolides, 3 beta-O-(D-digitalosyl)-14 beta-hydroxy-16 beta-acetoxy-5 beta-card-20 (22)-enolide (3) and 3 beta-O-(D-digitalosyl)-14 beta-hydroxy-5 beta-card-20 (22)-enolide (4), have been isolated. [14]

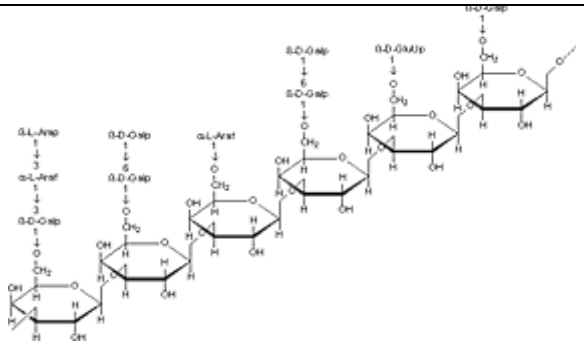
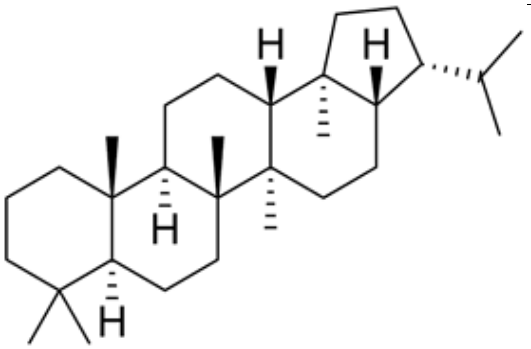
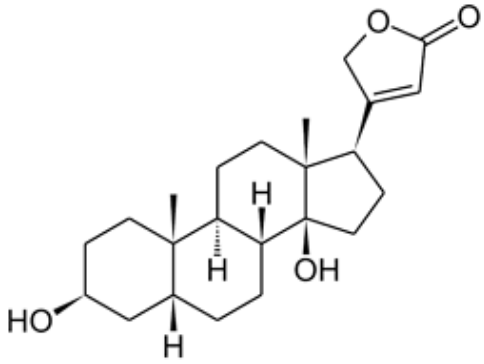
Four CNS depressant cardenolides including a new cardenolide, neridiginoside and three known constituents, nerizoside, neritaloside and odoroside-H, have been isolated which showed CNS antidepressant activity. The structure of neridiginoside was elucidated as 3 beta-O-(D-diginosyl)-5 beta, 14 beta-dihydroxy-card-20 (22)-enolide. [15] A polysaccharide fraction, NIB-2, was obtained from the 3% aqueous sodium carbonate extract which was composed of rhamnose, arabinose, galactose, in the ratios of 1.0:10.4:4.4, along with 4% of galacturonic acid. Further analysis showed that it mainly contained arabinogalactan having a backbone of 1,6-linked beta-Galp, with branches at O-3, consisting of a terminal, 1,5-, and 1,3,5-linked arabino furanosyl residues, and a small proportion of galactosyl residues at the termini. New ursane-type triterpene 1, oleanane-type triterpene 2, and dammarane-type triterpene 15 were isolated from the leaves of Nerium oleander together with 12 known triterpenes, 3beta-hydroxy-12-ursen-28-oic acid (ursolic acid,3beta,27-dihydroxy-12-ursen-28-oic acid, 3beta,13beta-dihydroxyurs-11-en-28-oic acid, 3beta-hydroxyurs-12-en-28-aldehyde, 28-norurs-12-en-3beta-ol, urs-12-en-3beta-ol, urs-12-ene-3beta,28-diol, 3beta-hydroxy-12-oleanen-28-oic acid (oleanolic acid), 3beta,27-dihydroxy-12-oleanen-28-oic acid, 3beta-hydroxy-20(29)-lupen-28-oic acid (betulinic acid, 20(29)-lupene-3beta,28-diol (betulin, and (20S,24R)-epoxydammarane-3beta,25-diol. [16]

Two new taraxasterane-type triterpenes, 20beta,28-epoxy-28 alpha-methoxytaraxasteran-3beta-ol and 20 beta, 28-epoxytaraxaster-21-en-3beta-ol, were isolated from an ethyl acetate extract of the leaves of Nerium oleander, together with ursane-type triterpenes, 28-nor-Urs-12-ENE-beta,17beta-diol and 3beta-hydroxyurs-12-en-28-aldehyde. [17] Hot-water extract of N. Indicum leaves yielded 3-O-caffeoylquinic acid (chlorogenic acid) and its structural isomer, 5-O-caffeoylquinic acid. Both compounds were shown to inhibit alpha-glucosidases in a non-competitive manner and thus were anti-hyperglycemias. [18]

Table 1: Major compounds available in *Nerium Oleander*

Sr. no.	Chemical name	Chemical Structure	Reference
1.	Oleandrin		NCBI PubChem, 2020.[6]
2.	Folinerin		NCBI PubChem, 2020[6]

3.	Rutin		Rachmat & Rainer. (2013) [33]
4.	3 beta -O-(D-2-O-methyl-digitalosyl)-14 beta -hydroxy-5 beta-Carda-16,20 (22)-dienolide		Hameed et al. (2015) [34]
5.	3 beta -hydroxy-8,14-epoxy-5 beta -Carda-16,20 (22)-dienolide		Gupta and Mittal (2010) [35]
6.	3 beta-O-(D-digitalosyl)-14 beta -hydroxy-16 beta -acetoxy-5 beta -card-20 (22)-enolide		Zibbu and Batra (2010) [11]
7.	Neridiginoside		Begum et al. (1999) [15]

8.	Arabinogalactan		Tolstikova et al . (2009) [18].
9.	Triterpene		NCBI PubChem (2020)[6]
10.	3 beta -O-(beta-D-diginosyl)-14, 15alpha-dihydroxy-5alpha-card-20(22)-enolide		Wang et al. (2009) [19]

Three nematocidal cardenolides were obtained from the AcOEt extract of Nerium indicum Mill. by bioassay-guided fractionation. They include a new compound, 3 beta-O-(beta-D-diginosyl)-14, 15alpha-dihydroxy-5alpha-card-20(22)-enolide, and two known compounds, uzarigenin and cardenolide N-1. [19] Two new cardenolide monoglycerides, cardenolides B-1 and B-2 were isolated from Nerium oleander, together with oleagenin which is the first isolated compound from natural sources.

TOXICITY

Nerium oleander has historically been considered a poisonous plant based on a number of its compounds that may exhibit toxicity, especially to animals, when consumed in high amounts. The entire oleander plant contains toxic cardiac glycosides. The highest levels are found in the roots and seeds. Plants with red flowers produce more cardiac glycosides than plants with white flowers, especially in the flowering stage. [20] Even smoke from the plant and water in which the plant has been immersed can be toxic. Among these compounds are oleandrin and oleandrigenin, known as"cardiac glycosides" which are known to have a narrow therapeutic index and are toxic when ingested. [21] Cardiac glycosides of N. oleander cause poisoning by inhibiting Na+, K+-ATPase pump on the cytoplasmic membrane of cardiac cells. [22] Ingestion of this plant can affect the gastrointestinal system, the heart, and the central nervous system. The gastrointestinal effects can consist of nausea and vomiting, excess salivation, abdominal pain, diarrhea that may contain blood. Cardiac reactions consist of

irregular heart rate, sometimes characterized by a racing heart at first that then slows to below normal further along in the reaction. Extremities may become pale and cold due to poor or irregular circulation. The effect on the central nervous system may show itself in symptoms such as drowsiness, tremors or shaking of the muscles, seizures, collapse, and even coma that can lead to death.

MECHANISM OF ACTION OF CARDIAC GLYCOSIDES

Normally, Na+-K+ pumps in the cardiac myocytes pump the potassium ions inside and sodium ions out. Cardiac glycosides inhibit this pump using by stabilizing it in the E2-P transition state; so that sodium cannot be extruded and intracellular sodium concentration therefore increases. A 2nd membrane ion exchanger, i.e., Na+/Ca2+ exchanger, is responsible for "pumping" calcium ions out of the cell and sodium ions in (3Na/Ca); raises intracellular sodium levels, which inhibit this pump; thus, calcium ions are not extruded and begins to build up inside the cell.[23] Increased cytoplasmic calcium concentrations cause increased calcium uptake into the sarcoplasmic reticulum (SR) through the sarco/endoplasmic reticulum Ca2+-ATPase transporter.

Raised calcium stores in the SR allow for greater calcium release on stimulation so that myocytes could achieve faster and more powerful contraction by cross-bridge cycling [Figure 3]. The refractory period of the atrioventricular node is increased and finally cardiac glycosides function to regulate heart rate. Binding of cardiac glycoside to Na-K-ATPase is slow, but after binding, intracellular calcium increases gradually.[24] Thus, the action of cardiac glycosides is delayed. Raised extracellular K+ decreases binding of cardiac glycoside to Na-K-ATPase. Consequently, increased toxicity of these drugs is observed in the presence of hypokalemia. If calcium of SR stores becomes too high, some ions are released spontaneously through SR receptors. After depolarization, this effect leads initially to bigeminy (regular ectopic beats following each ventricular contraction). If higher glycoside doses are given, rhythm is lost and ventricular tachycardia originates, followed by fibrillation.

BIOLOGICALACTIVITIES

Antioxidant activity

The total level of antioxidant activity was higher in Crude Nerium oleander leaves extract (72.8%), as compared to flower (68%) and superoxide radical whereas scavenging activity was higher in Crude flower extract (66%) as compared to leaves 25%. Nerium oleander possesses an effective antioxidant activity, which includes free radical scavenging and reducing power and the antioxidant activity was correlated with the amount of the total phenolic content present in the respective extracts in each assay. [25] The leaf, stem and root extracts of N. Oleander is an effective free radical scavenger and might be used as a natural source of potent antioxidant.

Anti-inflammatory activity

The ethanolic extracts of Nerium oleander dried leaves and fresh flowers exhibited potent anti-inflammatory activity against carrageenan-induced hind paw edema model in mice without inducing any gastric damage. [26]

Antimicrobial activity

The plant has provided a source of inspiration for novel drug compounds, as plants derived medicines have made significant contributions towards human health. The effect of ethanolic leaf extract was significant on bacterial strains such as B. Subtilis and Nyctanthes arbortristis. The antibacterial activity of oleander extracts on gram-negative bacteria was found and the results concluded that antibacterial activity was found due to phenolic compounds that decrease the concentration of radicals. [27]

Anticancer activity

The aqueous extract of Nerium oleander L. has been undergoing clinical investigations as an anticancer agent. Oleandrin and its aglycone oleandrigenin are the active compounds that are isolated from this plant which showed to have anticancer properties. Anvirzel has also revealed cytotoxicity in human tumor cell lines with evidence of apoptosis as a principal mode of cell death. [28]

Diuretic effect

The chief active principle oleandrin was found to stimulate the heart function and also had a diuretic effect. The effect of odorin on the heart of rabbits and dogs is identical with that of digitalis group

whereas neriodin is twice as active as digitoxin in digitalis like action similar to that of oleandrin. [29]

Immunomodulating activity

CNS depressant activity: After the isolation of oleandrin a number of new chemical constituents have been isolated from this plant and their pharmacological properties have also been evaluated. [30] Experiments have been demonstrated that the crude alcoholic extract from the leaves has CNS depressant activity. Nerium oleander contains at least 2% cardiac glycosides. Rosagenin may be extracted from the bark and has a strychnine-like action. Several flavones (0.5%) and volatile oils (unimportant amount), as well as rubber, fats, sugars and hydrocyanic acid, can be isolated from its leaves. [31]

Table 2: Phyto-pharmacological effect of *Nerium Oleander*

Sr. no.	Biological Activities	Constituents responsible	References
1.	Antioxidant activity	Superoxide radical	Iran (2012) [25]
2.	Anti-inflammatory activity	Neriin and oleander	Nagourney et al. (2001). [26]
3.	Antimicrobial activity	cardenolide, 12β - hydroxy-5β- carda-8, 14, 16, 20 (22) - tetraenolide	Dunk and Klaus, (1980). [27]
4.	Anticancer activity	Anvirzel and Oleandrin	Judith and Smith, (2001). [28]
5.	Diuretic effect	Oleandrin	Sen. (2000) [29]
6.	Immunomodulating activity	Galacturonic acid , rhamnose, arabinose and galactose	Sharma et al. (2008)[31]

FUTURE APPLICATION OF *NERIUM OLEANDER*

Utilizing biotechnology research and new breakthrough extraction technology, Nerium is continuing to develop a complete line of products that harnesses Nerium oleander's unique and effective properties. Anti-aging skin creams are abundant in today's cosmetic marketplace. Future product development includes Nerium AD Eye Cream Spot Cream, Skin Repair Cream, Blemish Cream and lots of such products. According to the American Cancer Society, "even a small amount of oleander can cause death", and "the effectiveness of oleander has not been proven". Nerium is also effective in increasing the CD4 counts of HIV-positive individuals with initial CD4 counts of less than 400 in a meaningful way over a 60-day period. Nerium oleander aqueous extract as a novel anti-HIV therapeutic. This oleander is useful in future cancer and AIDS treatment. [32] Nerium is environmentally safer and greener approach for mosquito control and other pest control measure in the future.

CONCLUSION

From the review of the existing work it was concluded that N. oleander has been used in the treatment of various diseases and shows anticancer and antitumor properties as well as acts as a novel anti-HIV therapeutic. In recent years, ethnobotanical and traditional uses of natural compounds, especially of plant origin received much attention as they are well tested for their

efficacy and generally believed to be safe for human use. It is the best classical approach in the search of new molecules for management of various diseases. Various bioactive compounds have been isolated from different parts of this plants. So, it is an utmost of importance to explore its potential in the field of medicinal and pharmaceutical sciences for novel application. As N. oleander is a popular remedy among the various ethnic groups, this plant is used in Ayurvedic and traditional medicine. So further or more work is needed to investigate the therapeutic potential of this plant.

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