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Review Article

A Holistic Review on Vitex Negundo: “Traditional Uses, Active Constituents and Therapeutic Potential

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ABSTRACT

Nirgundi also called the plant known as Vitex negundo is commonly utilized in traditional medicine as well as acknowledged for its many therapeutic benefits. This plant is originally from the Philippines and India, thrives well in damp environments, and is commonly seen in open forests and wastelands. It parts of the Verbenaceae family and is a little tree or tall shrub, with bluish-purple blooms, little black drupes as fruits, and aromatic, composite leaves. Flavonoid, terpenoids, phenolic acids, and essential oils are some of the bioactive components of the plant; all the parts, including leaves, seeds, bark, roots, and fruits, possess medicinal properties. Only a few among its many pharmacological effects include anti-inflammatory, antioxidant, antibacterial, antipyretic, analgesic, anticancer, hepatoprotective, antifungal, and neuroprotective. Some of the properties of the herb also exhibit an anti-HIV effect, anti-histaminic, enzyme inhibition, and anti-amnesic effect. In conventional medical systems, Vitex negundo is used to treat ailments including bronchitis and rheumatism, arthritis, migraines, inflammation, skin ulcers, digestive problems, and respiratory illnesses. Although Unani medicine and Chinese pharmacopoeia emphasize its effectiveness in treating liver ailments, skin diseases, sinusitis, eye difficulties, and arthritic conditions, Ayurveda uses it to balance the kapha and vata doshas. This species, Vitex negundo, is highly relevant in both conventional and alternative medicine because of its high therapeutic potential. Its numerous bioactive compounds warrant further investigation into their pharmacological and therapeutic uses, especially in modern medicine.

INTRODUCTION

The nirgundi, or Vitex negundo, is a plant that exerts a wide range of medical benefits and has been highly valued due to its applications in

traditional medicine. Thus, through the healing properties of this plant, herbal medicine has played an important role in Asia and other cultures. (1) Nirgundi is considered to be a plant indigenous to

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India and the Philippines, belonging to the family Verbenaceae. It thrives in waterlogged habitats and is often encountered in wastelands as well as mixed open forests. (2) Nigundi has been used in Ayurveda and other traditional medical systems to cure ailments for thousands of years. This herb possesses features like hepatoprotective, analgesic, and anti-inflammatory properties. In summary, the long history and a number of applications in its practice can show the relevance that Nigundi holds in conventional and alternative medicine, which means further study is necessary to tap into its full potential. (3) Because of its well-known anti-inflammatory and analgesic qualities, the leaves and extracts can be used to treat rheumatism and arthritis. Significant antibacterial activity is shown by *Vitex negundo* against a large spectrum of pathogens, like *Staphylococcus aureus* and *E. coli*. Research suggests that antioxidant systems may help prevent cardiovascular illnesses. The cultural value of the plant is seen in its rituals and reverence used in Ayurvedic teachings. (4)

Botanical Description

Morphology: - A big shrub, or sometimes a tiny, narrow tree, with delicate tomentum and quadrangular, white branches and thin, grey bark. At 5-10 by 1.6-3.2 cm, the terminal leaflet's petiole is 1 to 1.3 cm long. The leaflets on the side are much shorter and smaller. petioles. Common petioles measure 2.5 to 3.8 cm in length, whereas leaflets are lanceolate, bases are pointed, and leaves are 3-5 foliate. A huge terminal, often compound pyramidal panicle has bracts that are 1.5–2.5 mm long, with a lanceolate caduceus, and arranged in pedunculate tomentose cymes with branches, which are opposed along the quadrangular tomentoserachis. The calyx is white tomentose, 3 mm long, and with triangular teeth measuring 0.8–1 mm. (5)

Habitat and cultivation:-

Up to five meters tall, *Vitex negundo* can develop into a highly branching shrub or, in certain situations, a little, narrow tree with thin, grayish bark. These leaves are composite palmate leaves, 3–5 foliated, the lanceolate entire or crenate and terminal 1–3 cm wide and 5–10 cm long while lateral much smaller. All of these are nearly glabrous on the top whitish tomentose on the bottom and fragrant when crushed. Small, bluish-purple flowers form huge, terminal, frequently compound, pyramidal panicles in peduncled cymes. In central India, fruiting takes place from September to February, and flowering takes place from June to December. The fruit is a juicy drupe that has a diameter of 5 to 6 mm and turns black when mature. Diameter of seeds 5–6 mm. The ripe seeds, They typically in two to three weeks, sprout after being sowed in nursery beds. (2)

Taxonomical Classification (5)

Kingdom	Plantae
Subkingdom	Tracheobionta
Superdivision	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Asteridae
order	Lamiales
Family	Verbenaceae
Genus	<i>Vitex</i>
Species	<i>Negundo</i>

Phytoconstituents

Leaves: The monoterpenoids found in VN leaves include iridoids (2-p-hydroxybenzoyl mussaenoside, nishindaside, and negundoside), triterpenoids (ursolic acid, betulinic acid), flavonoids (corymbosin, vitexicarpin, gardenin A, gardenin B, 5 hydroxy-3,6,7,3,4-penta-methoxyflavone, 3,5-dihydroxy-6,7,3,4-tetramethoxyflavanol), and phenolic acid (p-hydroxybenzoic acid, 3,4-dihydroxybenzoic acid).

Seed: Benzoic and palmitic acid are examples of diterpenes, such as negundoin A, B, C, D, E, F, and G6. (6)



The stem and bark :- contain a number of chemical components, including 4-O-[4C-O- β -D-galactosyl], 3,6,7,3C,4'-Pentamethoxy-5-O-glucopyranosylrhamnoside, and vitexin cafeate. 3-O- This is β -D-galactopyranoside, or 4-O-methyl myricetin. Five-hydroxy-3- dihydroxy-7,8,4-trimethoxy flavanone, which includes 3-acetoxy-olean-12-en-27-oic acid, 3-hydroxy-olean-5, and 12-dien-28-oic acid. (7)

Roots:- Agnuside, R-dalbergiphenol, 6-hydroxy-4-(4-hydroxy-3-methoxy)- 3hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde, negundin A, negundin B, vitrofolal E, (+)-lyoniresinol, (+)-(-)-pinoresinol, and (+)diasyringaresinol, This novel furanoeremophilane includes 3-formyl-4,5dimethyl-8-oxo-5H-6,7- dihydronaphthofuran, vitexin and isovitexin, acetyl oleanolic acid, sitosterol, and 2 β ,3 α - diacetoxyoleana-5,12-dien-28-oic acid; 2 α ,3 α -dihydroxyoleana-5,12-dien-28-oic acid, and

2 α ,3 β diacetoxy-18-hydroxyoleana-5,12-dien-28-oic acid. (8).

Essential oil of fresh leaves, flowers and dried fruits :- δ -guaiene, guaia- 3,7dienecaryophyllene epoxide, ethyl-hexadecenoate, α -selinene, germacren-4-ol, caryophyllene epoxide, ϵ nerolidol, β -selinene, α -cedrene, germacrene D, hexadecanoic acid, p-cymene, and valencene [50], viridiflorol (19.55%), β -caryophyllene (16.59%),sabinene (12.07%), 4-terpineol (9.65%), γ -terpinene (2.21%), caryophyllene oxide (1.75%), 1-oceten-3-ol (1.59%), and globulol (1.05%) are among the different chemical constituents of essential oil derived from leaves, flowers, and dried fruits. (7). Fruits were subjected to the hydro distillation technique to extract their essential oils. The resulting yellowish oil was extracted from Hexane distillation is utilized for phytochemical investigation. (9)

Overview Of Bioactive Compounds (10)

Sr No.	Components	Cellular events	roles
1	Vitamins, caratene, and flavonoids	Resistance to oxidative stress	In charge of reducing the production of lipid peroxidation, which leads to oxidative potential in anity.
2	Flavone Vitexicarpin	Anticancer	Exihbit anticancer characteristics
3	vitexnegheteroins K-L ,Coumarin Glycosides vitexnegheteroins I-J iridoid glycosides.	Anti-oxidant	VN extract constituents are employed as potent antioxidants.
4	Vitexin-6 (VB6), Vitexin EVn-50, and 4- dihydro-2-Naphthdehyd 6-hydroxy-three-hydroxymethyl-7-methpxy-three,	Apoptosis	Extracts from VN Most cancer cells undergo apoptosis when vitaminxin-6 cleaves poly (ADP-ribose). both caspase-3 and polymerase.
5	Vitexin and Phytoestrogens	Menstrual cycle	Vitexin reduces the amount of increases the quantity of progesterone and pituitary estrogen.
6	Vitexi	Polycystic ovary Syndrome (PCOS)	Prolactin, luteinizing hormone, and testosterone production are all decreased by vitexin.
7	Flavone, 4-6-8-trimethoxy 5,7,3, trihydroxy.	Viability of sperms	Male mice's sperm motility and viability are increased when the extrinsic testosterone androgen movement in the male reproductive system is alienated.

Pharmacological Activities

Anti- amnesic Activity :- Vitex negundo Linn extract's anti-amnesic properties were investigated in rats with scopolamine-induced amnesia. Since the scopolamine was administered according to the phases of memory acquisition, consolidation, and retention, the standard donepezil and Vitex negundo Linn's anti-amnesic qualities were contrasted. According to the study, the groups that received the extract from Vitex negundo Linn revealed an improvement in memory by reducing the occurrence of amnesia due to the antioxidant's effect. Vitex negundo Linn. Leaves (HEVN) hydroalcoholic extract demonstrated improvements in memory and learning. HEVN's effects were evaluated utilizing the EPM (Elevated Plus Maze) and ORT (Object Recognition Test) in both normal and scopolamine-induced cognitive impairment mouse scenarios. The study demonstrated how well HEVN works to enhance memory and learning in both paradigms. The impact may result from an increase in cholinergic transmission, an antioxidant action, or suppression of Ach E.(11)

Anti-Inflammatory properties :- The anti-inflammatory qualities of an ethanolic root Vitex negundo extract was examined utilising the Plethysmometer technique. In the rat paw oedema method caused by carrageenan, it has been revealed that the ethanolic root extract of Vitex negundo exhibited a higher level of anti-inflammatory effect. It assessed the inflammatory reducing properties of a root extract made with ethanol from Vitex negundo. assessing acute inflammation by inducing rat paw oedema with carrageenan. The unique drug's action has been paralleled by the ethanolic extract of Vitex negundo. This study indicates that, in comparison to the common medication indomethacin, the ethanolic extract has demonstrated exceptional anti-inflammatory effect. (8).

Anti-Oxidants activity :- The initial research indicated that V. negundo leaves were rich in natural antioxidants and exhibited antioxidant properties. It was the aim of this research is to assess a number of in vitro antioxidant assays to evaluate the antioxidant properties of V. negundo leaf extracts in methanol, hexane, and essential oil. In addition, HPLC was used

to quantify the total phenolic content, carotenoids, flavonoids, and tocopherol in V. negundo leaves. (12).

Anti-pyretic Activity :- The antipyretic action of the leaf extract caused a rise in body temperature in yeast. Due to the methanolic extract, there was a reduction in body temperature. The antipyretic effect may be due to the presence of flavonoids, which the study found reduced lipid peroxidation. (9)

Antinociceptive Activity :- Vitex negundo leaf extract in ethanol was examined for its antinociceptive properties in mice utilizing the writhing test produced by acetic acid and in rats with tail flick at dosages of 100, 250 and 500 milligrammes per kilogramme. The test of writhing with aspirin administered 50 milligrammes per kilogramme of body weight, and the tail flick method using 40 mg/kg of meperidine served as the standard controls for the aforementioned effect. Interaction of this tail flick method with an interaction of its mechanism of central analgesic effect in relation to an interaction with naloxone hydrochloride in both experimental models. These demonstrated a good dose dependent analgesic effect of the drug and indicated its analgesic activity, throughout the central nervous system as well as the neurological systems in the periphery. Opioid receptors seemed not to be involved with the central analgesic activity. This central activity may be acting through the opioid receptor as a mediator. It might work well as an adjuvant treatment in addition to a typical analgesic medication. (13).

Enzyme inhibitory activity :- α -chymotrypsin, xanthine-oxidase, tyrosinase, butyrylcholinesterase, and lipoxygenase were all inhibited by the VN root extracts. According to reports, the aqueous extract of VN's aerial portions exhibits reverse transcriptase inhibitory activity against HIV type 1. (14).

Insecticidal and pesticidal activities :- Numerous reports claim that V. negundo of plant product has insecticidal effectiveness against product pests in storage, houseflies, larvae of mosquito, and larvae that devour tobacco leaves. Leaf oil from the plant has been shown to have a propellant effect on pests that affect stored products. (15).

Anti-cancer Activity: - The tissues were not affected. In the study, dependent on dosage alterations were found in the liver, lungs, and heart tissues. COLO-320 tumor cells were used to Verify the cytotoxic effects of

the extracts from leaves of *Vitex negundo*. It was established that a panel of human cancer cell lines was cytotoxically affected by the chloroform extract of *Vitex negundo* leaves, but not mice genitourinary or mammary cells. (16).

Anti-microbial Activity :- selected bacteria starting with a 20 mg/ml of concentration. All the concentrations showed antibacterial impact on the gram-negative *E. coli*, with a maximum ZOI of 12 mm at 100 mg/ml. Against *S. aureus*, in a concentration of 80 and 100 mg/ml, maximum area of inhibition of 15 mm was recorded. The maximum ZOI against *Klebsiella pneumonia* was 11 mm at 100 mg/ml concentration. (17)

Analgesic Activity :- it is using different solvents found that several leaf and root extracts administered interperitoneally had analgesic efficacy.

it used the tail flick, hot plant and formalin tests in order to assess the analgesic activities of an aqueous extract from female Wistar rats' fresh *Vitex negundo* leaves. Aspirin 100 mg/kg was the typical drug for tail flick and hot plate. (18)

Hepatoprotective Activity:- In addition to the properties mentioned above, extracts from the herb *Vitex negundo* has been used to studied for a variety of additional systemic uses. Studies have been conducted on the hepatoprotective properties of *Vitex negundo*'s negundoside and agundoside. According to reports, serum bilirubin, aspartate, aminotransferase, and alanine are lowered by *Vitex negundo* extract. Total Protein (TP), Alkaline Phosphates, and Aminotransferase levels in cases of liver injury. It was shown that *Vitex negundo* leaf extracts has hepatoprotective qualities against d-galactosamine, carbon tetrachloride, and commonly used tubercular drugs that can cause liver injury. (19).

Impact on the capacity for reproduction :- The results of *Vitex negundo*'s reproductive efficacy were conflicting. Many studies revealed the inhibitory effect of *Vitex negundo* extract to Male rats' spermatogenesis and reproduction. Hu et al., however, found the same extract to have estrogenic-like activity and suggested hormone replacement treatment uses it. It has been explored whether *Vitex negundo* seeds can treat polycystic ovarian syndrome. (20)

Neuroprotective Activity :- Male wistar rats were administered oral paracetamol to induce kidney injury, and the methanolic bark extracts were evaluated for nephroprotective efficacy against this injury. The biochemical markers used in the evaluation included serum glutamate pyruvate transaminase (SGPT), kidney injury was investigated using SGOT, In addition to non- enzymatic antioxidants (GSH), total protein, CAT, bilirubin, ALT, enzymatic antioxidant SOD, GPx, and Px. The biochemical parameters were found significantly decreased in the *Vitex negundo* Linn bark methanolic extract, and it also possesses nephroprotective activity. (7)

Anti-fungal Activity :- Antifungal activities against phytopathogenic fungi were also exhibited by *V. negundo*, and the maximum MIC was elicited by bark extracts in chloroform and methanol against *C. albicans*. Similarly, *Aspergillus niger* was efficiently inhibited by the stems of *V. negundo*. and *Candida albicans* the extract of ethanol from seeds of *V. negundo* revealed actions taken against behaviour that goes against *Microsporum canis* (60%) and *Fusarium solani* (90%), while it was nontoxic to *Candida albicans*. The methanolic leaf extract showed action against *Candida albicans* as well as *Penicillium sp.*, whereas chloroform activity against *Candida albicans* and *Candida tropicalis* was demonstrated by leaf extract. The ethanolic leaf extract showed significant antifungal properties against *Candida albicans* and *Sclerotinia sclerotiorum*. (21)

Anti-HIV Activity :- Assessed the impact of 85% ethanolic *V. negundo* leaf extract on HIV- 1 RT activity utilizing a colorimetric HIV-RT nonradioactive ELISA kit reverse transcriptase activity. Substantially inhibited the effects of At 200 µg/ml, it enhanced the 92.8% of HIV-1 RT activity. The plant possesses high levels of myricetin, quercetin, and kaempferol contents that may be responsible for its anti-HIV properties. (22)

Anti-histaminic Activity :- *Vitex negundo* leaf methanolic extract possesses antihistaminic activity. The a for mentioned extract was found to be potent in inhibiting mast cell histamine release. *Vitex negundo*'s stabilizing action on mast cells. The activity of compound 48/80 and albumin from eggs were studied in terms of their degranulating effect on employing a leaf ethanolic extract on male Wistar rat peritoneal

mast cells the extract was discovered to exert a stronger inhibitory action when the mast cells were degranulated immunologically.(23)

Traditional and medicinal uses :-

Folk remedies and indigenous uses :-Most South East Asian, Bangladeshi, and Indian states use *Vitex negundo* as a traditional medicine. The leaves are most effective due to their medicinal properties .Among the many conditions it has been used to treat are bronchitis, inflammation, eye disease, toothache, ulcers, fever, asthma, and headaches, digestive issues, sinusitis, analgesia, insecticidal, antibacterial, antipyretic, antihistaminic, and snakebite antidote. It has been proven that the leaves of these plants have anti-mosquito and anti-ant properties. It was also established that the plant has hepatoprotective, anticancer, and rheumatoid arthritis-healing properties.⁵ Skin ulcers, pneumonia, gonorrhea, and inflammation are treated using the leaves. They are also vermifuges and tonics for the treatment of catarrhal fever. When used orally, the leaves are said to include antihyperglycemic, antibacterial, antipyretic, antihistaminic, and anti-implantation properties.(24)

Uses in traditional medicines system: -

1.Ayurvedic applications: - Since *Vitex negundo*, known by most as Nirgundi, it is a member of the Verbanaceae family and offers protection against a wide array of diseases. It grows as small trees or large shrubs on the banks of the streams or wet places with quadrangular branches, emitting fragrance. The other names for these Sinduvara, Shephali, Sugandhika, and Bhutakeshi are considered classics. it points out that one with leaf-smelling qualities annihilates evils like evil creatures, and that one which arrests the progress of water in the body, an insects preferred species.

It is said that nigundi possesses the properties of laghu (light), Katu (alkaline), and ushna veerya (hot potency), tikta (bitter), and kashaya (astringent). vipaka (metabolism and digestion). The main pharmacodynamic action is kaphavata shaamaka, reducing vata and kapha. nirgundi is used to treat gridhrasi (sciatica) condition which is associated with vitiation of vata (25)

2.Unani applications: - Nisinda, sometimes referred to as vitex in Unani medicine, Folk medicine uses it to treat conditions like urticaria, jaundice, and asthma.

Assamese liver diseases, eczema, carbuncles, and abscesses; Himachal Pradesh's wounds and physical aches; The Lodhas use the dried leaves as a tonic; they are occasionally smoked to relieve headaches and Simali is used in Nepal for the treatment of sinusitis and whooping cough. It is used as an anti-allergenic and to treat skin and gum conditions in Pakistan. It is used as a tonic, carminative, vermifuge, and to cure rheumatism, toothaches, and eye conditions in Sri Lanka.(2)

3.Chinese medicinal application:- According to Chinese pharmacopoeia, the fruit of the *vitex negundo* plant is used to treat arthritic joints, headaches, and red, painful, and swollen eyes.(26)

Toxicology Studies: -

Acute toxicology studies :- There were six groups of 18 Wistar albino rats, with three rats in each. Starting dosage level was selected as the limit test (2 g/kg) dose and then multiples of first dose as 4 and 8g/kg. To the overnight starved rats, calculated amounts of aqueous and alcoholic extracts were administered to the respective groups through gavaging as single dose. Rats, which received 8g/kg of aqueous and alcoholic extracts were administered extracts in two divided doses at 12 h interval. The animals' overall behavior, toxicity markers, and death were regularly observed for one hour following treatment, then sporadically for four hours, and finally for a total of twenty-four hours. For as long as 14 days after treatment, the rats were monitored for alterations in behavior, signs of toxicity or death, and the time until death. There had unlimited access to food and water during the study time. **Sub-acute toxicology studies :-** Both sexes of Seven batches of wister albino rats weighing 150–200 g were created of six rats each for the sub-acute study. After their body weight was noted, three males and three females were housed in separate cages. The first group was kept as the control, and over the course of 28 days, Groups II, III, and IV were given 2, 4, and 8 g/kg of aqueous extract, while Groups V, VI, and VII were given 2, 4, and 8 g/kg of alcohol extract. It was split into two gavagings wherever the dose was high. The experimental animals' mortality, toxic symptom manifestation, behavioral changes, food and water intake, excreta type, and weight increase or loss were all monitored. Every day, the weight of each individual



animal was determined using an electronic weighing equipment. Blood from the retro-orbital plexus of all experimental animals was drawn using a capillary tube on day 29^a. The blood was collected in different collection tubes (for biochemical and haematological data, respectively) with and without EDTA. Hematological factors such hemoglobin, platelet count, leucocytes (DC), total erythrocytes, and leucocytes (TC) were all taken into account for the study. The biochemical indicators including blood urea nitrogen, serum creatinine, total proteins, serum glucose, AST, ALT, total bilirubin, and direct bilirubin were estimated. Following blood collection from experimental animals, each animal was killed, and samples of the brain, liver, kidney, heart, lungs, spleen, and intestines were among the essential organs removed and put in labelled containers with 10% NBF (Neutral Buffered Formalin) solution for histological examination.

RESULT: - In the above experiments none of the animal died during study period. None of the experimental animals showed any signs of losing body weight. Form and consistency of faecal matter became semisolid and sticky in group 7 animals, whereas in other groups, it was more or less normal. The bedding material, that is, paddy husk had to be changed repeatedly from the cages of group 4 and 7, which meant repeated urination by experimental animals. Drowsiness was noticed in all groups in dose dependent manner during study period. Nothing had changed in haematological Leucocyte characteristics such as total and differential numbers, but slight decrease in total erythrocyte count and haemoglobin was needed. Marked fall in thrombolytic count was noticed among the dosage groups in more or less similar way serum biochemical characteristics such as serum glucose, total proteins and bilirubin direct were not affected by the drug. However, there was a dose dependent slight elevation of serum creatinine and blood urea nitrogen (BUN) in each dosage group. Histologically, congestion of blood vessels, haemorrhagic spots and mild degenerative changes were noticed in Brain (ILLUSTRATION 1 & 2), heart, liver, spleen and kidney sections. Reduced glomerular space and fatty degeneration were well appreciated in kidney sections (ILLUSTRATION 3 & 4). Deposition of protein

material and karyorrhexis were the characteristic changes in liver only (ILLUSTRATION 5 & 6). Marked inflammatory signs and protein matter was found to be deposited in the lungs (ILLUSTRATION 7). Higher dosage groups showed heart sections with findings of hemorrhagic spots and mild degenerative changes in myocardium (ILLUSTRATION 8). Histopathological changes were not noted in intestinal sections. (27)

CONCLUSION: -This review tries to encapsulated the body of research on Vitex negundo that covers its chemical components, traditional use, and an overview of its many pharmacological activities. Therefore, the pharmaceutical industry has a strong chance of developing this plant as a medication.. Vitex negundo is an excellent resource that holds promise in contemporary pharmacological breakthroughs, paying tribute to the vast knowledge ingrained within old medical systems. This plant can make an enormous contribution towards solving global health issues while maintaining ecological and cultural value by filling research gaps and upgrading its therapeutic application. For both the prevention and treatment of illnesses, vitex negundo may be the ideal medication. Being a rich source of phytochemicals, it is responsible for many diverse pharmacological activities. Beyond its medicinal value, Vitex negundo holds importance in agriculture and pest management due to its insecticidal and pesticidal properties. This positions the plant as an environmentally sustainable resource with multiple applications beyond healthcare resource. Continued exploration of its phytochemical composition and mechanism of action could be responsible for the creation of novel therapeutic compounds. Furthermore its integration into modern healthcare system could bridge traditional and contemporary medicine, benefitting global healthcare.

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