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Phytochemical and pharmacological properties on *Citrus limetta* (Mosambi)

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ABSTRACT

Sweet lime (Citrus limettarisso) is also known as 'Mosambi' in the Indian subcontinent region. It has multiple pharmacological effects and its constituents are extensively utilized for many clinical applications. Traditionally it has been widely used in the treatment of the scurvy, indigestion and constipation, diabetes, ulcers, urinary disorder and for improvement of immune system. Advancement in analytical techniques led to identification of multiple constituents among which d-limonene was found to be in abundant. Being chief component of Citrus limetta and having better pharmacokinetic and pharmacodynamics properties of d-limonene, it is worth full to explore it in detail. This study is focused on highlighting the phytochemical investigations, traditional uses and clinical applications of Citrus limetta as well as its chief constituent-limonene, which provides approval for further pharmacological and clinical investigations.

Keywords: Sweet lime, Mosambi, D-limonene, Vitamin C, Antioxidant, Scurvy treatment

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INTRODUCTION

Plants existed on the face of this earth since time immemorial and from ancient times human beings and animals are getting benefits from them in some or other way. In fact plants make earth worth living. The World Health Organization (WHO) estimates that about 80% of the population of the world still depends upon the herbal medicines for the treatment of various diseases due to easy availability, economic reasons and less side effects[1].Herbal medicines have made the basis of traditional systems of medicine for ages and have made a non-voidable place in modern pharmacology [1].

The sweet lime (*Citrus limettarisso*), is commonly known as "Mosambi" in Indian subcontinent. It is native to Asia and best cultivated in India, China, southern Japan, Vietnam, Malaysia, Indonesia and Thailand. This fruit is eaten fresh or squeezed to make juice, a rich source of vitamin C and replenish energy [2,3].

Citrus fruit juice finds its place as the major constituent product of the juice and food industry around the world. Along with the juice, fruit peel which is a waste to the juice industry is the main source of flavonoids, pectin and essential oils [4]. Peel oil have a strong aroma and refreshing effect and used as flavoring agent in different industries like food, beverages and pharmaceutical industries. Aromatic oils are considered to be safe due to their wide spectrum of biological activities such as antimicrobial, antioxidant, anti-inflammatory and as anxiolytic. Citrus fruits generally composed of 90% terpenes, 5% oxygenated compounds and less than 1% non-volatile compounds such as waxes and pigments [5]. D-limonene, the most abundant terpene has antimicrobial properties, primarily the

exhibition of antibacterial activity against gram positive bacteria and also increases the effectiveness of sodium benzoate as a preservative [6-8].

Table 1. Botanical classification of *Citrus limetta*

Kingdom	Plantae
Division	Magnoliophyta
Class	Dicotyledons
Sub class	Sapindales
Order	Rosidae
Family	Rutaceae
Sub family	Aurantoideae
Genera	Citrus
Sub genera	Papeda
Species	Limetta

2. Geographical distribution:

The Mosambi fruit which is also known as sweet lime is a native plant of Asia and it is best cultivated in India, China, south Japan, Vietnam, Malaysia, Indonesia and Thailand.

1. Synonyms

Citrus limetta is commonly known as sweet lime, sweet lemon and sweet limetta. It is called by different names in different parts of the world.

Table 2. Synonyms of *Citrus limetta* across the world

Iran	Limushirin
North India	Mausambi, mosambi or mosambi
South India	Moossambi (Kannada & Malayalam) Bathayakayalu (Telugu) SathuKudi (Tamil)
Nepal	Mausam
Sindh	Mosami
France	Bergamot

(a) **(b)**

Figure 1. *Citrus limetta* fruit and peel

4. Phytochemical analysis

Natural products are chemical compounds found in nature and they possess multiple pharmacological activities. These natural products are used in drug discovery and drug design. Separation of single molecular entity is very difficult from complex mixtures containing fats, oils, alkaloid, tannins and glycoside. In 1803 the first alkaloid nicotine was separated followed by morphine, strychnine, emetine and many others.

There are various classes of phytoconstituents like Alkaloids, Glycosides, Flavonoids, Phenolic, Tannins, Terpenes, Saponins, Anthraquinones, Essential oils and Steroids. On a complete basis the phytochemical investigation of a plant involves the selection, collection, identification and authentication, extraction of the plant material (first fractionation), fractionation/separation (second fractionation) and isolation (third fractionation) of the constituents,

characterization of the isolated compounds and investigation of the biosynthetic pathways of particular compound, quantitative evaluations and pharmacological activities. After selection, collection, identification and authentication of the plant drug there comes extraction and isolation of the phytoconstituents [9]. Out of many techniques available for isolation of a compound many researchers have taken Gas chromatography along with Mass spectrophotometry of the phytochemicals present in *Citrus limetta* peel essential oil. Various compounds have been identified by the process of Mass spectrophotometry. Till now about 30 compounds have been identified in various studies. Limonene is the main component of the citrus peel oils and it ranges from 40-95% in concentration in citrus fruits.

Table 3. Chemical composition of the *Citrus limetta* peel as analyzed by GCMS[2]

S. No	Retention time	Active constituents	Quantity (%)
1	11.32	d-limonene	78.3
2	14.59	Bergamol	6.21
3	9.14	β-pinene	5.6
4	14.51	Linalool	5.15
5	7.54	α-pinene	1.58
6	11.51	1,8 cineole	0.76
7	14.60	α-terpineol	0.51
8	21.50	Neral	0.28
9	22.31	Geranial	0.21
10	31.72	β-Bisabolol	0.10
11	30.03	β-Bisabolene	0.10
12	9.78	β-Myrcene	0.08
13	10.30	Sabinene	0.08
14	16.95	Citronellal	0.07
15	15.06	α-Terpineol acetate	0.06
16	8.07	Camphene	0.06
17	31.72	α-Bisabolol	0.05
18	31.80	Bicyclogermacerene	0.03
19	20.97	Farnesol	0.03
20	51.07	Terpinen-4-ol	0.03
21	14.59	Trans-nerodilol	0.03
22	53.01	β Farnesene	0.03
23	10.29	Nonanal	0.01
24	44.30	Phytol	0.01
25	34.07	Hinesol	0.01
26	10.11	α-phellandrene	0.01
27	17.57	Borneol	0.01
28	42.10	Myrcenil acetate	0.01
29	27.09	β-Santalene	0.01

2. Introduction and pharmacokinetic of d-limonene

It is one of the most common terpenes in nature. It has the molecular formula (1-methyl-4-(1-methylethynyl) cyclohexane. It is a monocyclic monoterpene with a lemon like odor and is major constituent in several citrus oils like orange, lemon, mandarin, and grape fruit. Because of its pleasant citrus fragrance additive in perfumes, soaps, foods, chewing gum and beverages. d-limonene is listed in the code of federal regulations as generally recognized as safe (GRAS) for a flavoring agent [10].

Oral administration of d-limonene is rapidly and almost completely absorbed in the gastrointestinal tract in humans as well as animals [11-14].It is rapidly distributed to different tissues in the body and is readily metabolized. d-limonene or its metabolite are detectable in serum, liver, lung, kidney, and many other tissues [11], with higher concentration in adipose tissues and mammary glands than in less fatty tissues [13]. Half-life ofd-limonene is metabolized to oxygenated metabolites in rats and humans. In humans, the predominant circulating metabolites and perillic acid, dihydroperillic acid and limonene-1,2-diol. Other metabolites in plasma include limonene 3-9-diol and perillic acid isomer [14-16].

5. Safety and Toxicity issues of d-limonene

d-limonene is considered to have fairly low toxicity when tested for carcinogenicity in mice and rats. Although initial results showed d-limonene increased the incidence of renal tubular tumors. Subsequent studies have determined the pathogenesis and further suggested that d-limonene does not pose a mutagenic, carcinogenic or nephrotoxic risk to humans. In humans, d-limonene has demonstrated low toxicity after single and repeated dosing

for up to one year. The oral dose LD_{50} for d-limonene in male and female mice is reported to be 5.6 to 6.6 g/kg body weight, respectively while LD_{50} in male and female rats is reported to be 404 and 5.1 g/kg body weight respectively.

The toxicity of d-limonene at doses ranging from 413-6600 mg/kg daily administered to rats and mice five days/week for 3 weeks. No sign of compound related toxicity were noted at doses <1650 mg/kg daily [17, 18].

Another study observed decreased weight gain and even death in male rats starting at a dose of 600 mg/kg daily and at dose reached 1200-2400 mg/kg/day rats developed rough hair coats, lethargy and excessive lacrimation. Nephropathy was noted in all male rats at the end of the study. In the case of mice decreased body weight, lethargy and rough hair coats were observed at (1000 and 2000 mg/kg/day [17-19]. Whereas in a chronic study of two years, female rat given 600 mg/kg daily experienced significantly lower survival compared to controls [18].

5.1. Human Safety Studies

In a study for the human safety study performed on five healthy subjects by giving a single dose of 20 g d-limonene it was observed that subjects complained about increased bowel movements (2-3 times daily) and tenesmus, blood tests showed no abnormalities in liver (total protein, bilirubin, cholesterol, AST,ALT, and alkaline phosphatase), kidney (BUN), or pancreatic (amylase) functions [20].d-limonene has also been found to be safe, without gradable toxicity, when 100 mg/kg (equivalent to about 7 g for an average adult male) was ingested. Only mild eructation for 1-4 hours post-ingestion, mild satiety for 10 hours post-ingestion, and slight fatigue for four hours post-ingestion were reported [15].

In a dose escalation study of 32 subjects with refractory solid tumors, d-limonene was given orally at0.5-12 g/m2/day (1-24 g/day, considering an average area per person is 1.9 m^2). Patients initially received d-limonene for 21 days. The maximum tolerated oral dose was 8 g/m^2/day (15 g/day). Nausea, vomiting, and diarrhea were the only side effects observed and were dose dependent. One breast cancer patient was on the dose of 8 g/m^2/day (15 g/day) for 11 months. The authors concluded that d-limonene had low toxicity after single and repeated dosing for up to one year [14].

Nephropathy seen in rats on high-dose of d- limonene does not appear to be possible in humans, since neither the quantity nor type of protein that binds d-limonene or d-limonene-1,2-oxide is present. The protein content of human urine is very different from rat urine, as humans excrete very little protein if any (1percent or less of the concentration found in urine of male rats). There is also no protein in human plasma or urine identical to α_{2u}-globulin and no α_{2u}-g-like protein has been detected in human kidney tissue. AlthoughD-limonene-1,2-oxide binds to α_{2u}-g, no other proteins, particularly those synthesized by humans, bindd-limonene-1,2-oxide. Finally, there is no evidence that any human protein can contribute to a renal syndrome similar to α_{2u}-globulin nephropathy [18, 19].

6. Clinical applications

Because it is a solvent of cholesterol, d-limonene (in-vitro)has been clinically used to dissolve cholesterol-containing gallstones. It has also been used to relieve heartburn, because of its potential for gastric acid neutralization and its support for healthy peristalsis. d-limonene has potent anticancer activity which were established through different cancer model studies as well as through clinical trials like evidence from a phase I clinical trial shows a partial response in a patient with breast cancer and stable disease for more than six months in three patients with colorectal cancer [10].

6.1. Gallstone dissolution

In an in vitro study performed on d-limonene, it was observed that it could dissolve human gallstones within two hours [21]. In animals, infusion of d-limonene into the gallbladder dissolved and disintegrated gallstones, which were excreted through the common bile duct [21]. In patients post gallstone surgery, infusion of20 mL d-limonene every other day dissolved gallstones overlooked during surgery. In some patients gallstone dissolution occurred after only three infusions [21].

6.2. Anticancer activity

Animal studies have set the stage for further investigation into the chemoprotective activity of d-limonene for several types of cancer. Several studies suggested that inhibition of chemically-induced mammary cancer in rodents administered either orange peel oil or pure d-limonene [22-25] caused inhibition in either the initiation or promotion

phases, depending on the chemically-induced medium used [26-28]. Other experimental studies demonstrated that d-limonene inhibited development of liver cancer, pulmonary adenoma, and for stomach tumors [29-31].

d-limonene induces phase I and phase II carcinogen-metabolizing enzymes (cytochrome p450), which metabolize carcinogens to less toxic forms and prevent the interaction of chemical carcinogens with DNA. d-limonene has been shown to enhance gastrointestinal UDP-glucuronosyltransferase (UGT) activity in rats [32]. It also inhibits tumor cell proliferation, acceleration of the rate of tumor cell death and/or induction of tumor cell differentiation. Furthermore, d-limonene inhibits protein isoprenylation. Many prenylated proteins regulate cell growth and/or transformation. Impairment of prenylation of one or more of these proteins might account for the antitumor activity of d-limonene [26]. It was found that d-limonene attenuates gastric cancer through increasing apoptosis, while decreasing DNA synthesis and ornithine decarboxylase activity of cancer cells [27-28]. d-limonene inhibits hepatocarcinogenesis via inhibition of cell proliferation, enhancement of apoptosis, and blockage of oncogene expression [33-34]. d-limonene may also exhibit immune-modulating properties. One experimental study suggested that increased survival in lymphoma-bearing mice placed on a high d-limonene diet. These mice also demonstrated increased phagocytosis, microbicidal activity, and nitric oxide production [35].

6.3. Gastroesophageal reflux

d-limonene has been shown to be effective in relieving occasional heartburn and gastroesophageal reflux disorder (GERD). In a clinical setting, 19 adults suffering from chronic heartburn or GERD were invited to use d-limonene to relieve their symptoms. All participants had a history of chronic heartburn or GERD, with symptoms ranging from mild/moderate to severe for at least five years. Before taking d-limonene, each participant was asked to rate the frequency and severity of symptoms on a scale of 1-10, with 1 corresponding to complete relief and 10 corresponding to severe and/ or painful symptoms that occur every day. Most participants had an initial severity and frequency rating of 5 or greater. Participants were asked to discontinue current treatments (OTC and/or prescription medications), take one capsule containing 1,000 mg d-limonene every day or every other day, and rate symptoms daily using the frequency/severity index described above. On the second day of taking d-limonene, 32 percent of participants experienced a significant relief of symptoms (severity rating=1-2); this relief rate improved gradually during the regimen. By day 14, 89 percent of participants achieved complete relief of symptoms [36].

7. Pharmacological properties

Citrus flavonoids have a large spectrum of biological activity including antibacterial, antifungal, antidiabetic, anticancer and antiviral activities [37, 38]. Flavonoids can function as direct antioxidants and free radical scavengers, and have the capacity to modulate enzymatic activities and inhibit cell proliferation [39]. In plants, they appear to play a defensive role against invading pathogens, including bacteria, viruses and fungi [40].

7.1. Antibacterial and antifungal effects:

Even though pharmacological industries have produced a number of new antibiotics in the last three decades, resistance to these drugs by microorganisms has increased. In general, bacteria have the genetic ability to transmit and acquire resistance to drugs, which are utilized as therapeutic agents [41]. Above stated activities were shown by the peel oil extract when applied against different food borne pathogens including bacteria (*Staphylococcus aureus* ATCC 25923, *Bacillus subtilis* ATCC 6633, *Bacillus cereus* ATCC 14579, *Lactobacillus acidophilus* ATCC 4356, E. coli ATCC 25922, *Salmonella typhymurium* ATCC 14028 and fungi (*Aspergillus niger* ATCC 16404, *Aspergillus flavus* ATCC 204304, *Aspergillus fumigatus* KM 8001, *Aspergillus ficuum* ATCC 66876, *Aspergillus oryzae* ATCC 10124, *Fusarium oxysporum* ATCC 48122, *Penicillum digitatum* ATCC 201167, *Fusarium miniformes* MAY 3629, *Fusarium saloni* MAY 3636, *Candida utilis* ATCC 9950). It was found that peel oil exhibited maximum zone of inhibition against *B. cereus* ATCC 6633 (26 mm) followed by *S. aureus* ATCC25923 (21 mm) after 48 hours of incubation at 37^0 C, whereas the minimum zone of inhibition was shown by *F. oxysporum* ATCC 48122 (11 mm) after 48 hours of incubation at 25^0 C in comparison with streptomycin/fluconazole at 20 µl per disc. However, A. niger ATCC 16404, *A. flavis* ATCC 204304, *A fumigates* KM 8001, *A. ficuum* ATCC 66876, *C. utilus* ATCC 9950, *P digitatum* ATCC201167, *E. coli* ATCC 25922, *L. acidophilus* ATCC 4356, *S. typhimurium* 14028 and *E. aerogenes* ATCC 13048 gave 22,19,14,12,13, 18, 13, 18, 17 mm of zone of inhibition [42].

7.2. Antioxidant activity

Antiradical activity was evaluated by measuring the scavenging activity of the examined C. limetta oil on the 2, 2-diphenyl-1-picrylhydrazil (DPPH) radical. The DPPH assay was performed as described by [43]. The samples (100 µl each) were mixed by 3 ml of DPPH solution. The absorbance of the resulting solution and the blank (with only

DPPH and no sample) were recorded after an incubation time of 30 min at room temperature against ascorbic acid as a positive control. For each sample, three replicates were recorded. The disappearance of DPPH was measured spectrophotometrically at 517 nm. The percentage of radical scavenging activity was calculated. It is the ability of essential oils to act as a donor for hydrogen atoms or electrons in the transformation of DPPH-H (which is measured spectrophotometrically) gives them antioxidant activity characteristic. The results of DPPH scavenging activity of C. limetta oil compared with ascorbic acid as a reference standard indicating that it has slightly lower antioxidant activity comparative to reference standard, ascorbic acid, being a strong antioxidant reagent [44].

7.3. Antihyperglycaemic activity

Citrus limetta fruit peel contain the flavonoids hesperidin and naringin. Hesperidin and naringin both are proven to be potent hypoglycaemic agents and their hypoglycaemic activity is postulated to be partly mediated by hepatic glucose regulations enzymes in C57BL/KsJ-db/db mice. Dietary hesperidin also exerts hypoglycemic and hypolipidemic effects in streptozotocin-induced diabetic rats [45]. Naringin provided a significant amelioration of hypoglycaemic and antioxidant activity in STZ-induced diabetic rats [46]. Therefore, it can be postulated that the presence of flavonoids in the extract might be the reason of the antihyperglycemic action.

7.4. Antitumor potential of Citrus limetta peel

Methanolic extract of *Citrus limetta* peel at the dose level of 200 and 400 mg/kg body weight increased the life span, non-viable tumor cell count and decreased the cell count compared to the Ehrlich ascites carcinoma (EAC) control mice [47].

7.5. Antagonizing the hypertensive effect of angiotensin II

In a study reported acute response of blood pressure to angiotensin II administration was measured in mice. Also, the acute oral toxicity profiles were determined. Investigations showed that different concentrations of the aqueous extract prevented the raise of systolic blood pressure, diastolic blood pressure and mean blood pressure with a dose dependent effect for diastolic pressures at 125-500 mg/kg dosages. The 500 and 1000mg/kg doses inhibited the action of Ang II in similar extent to telmisartan. Toxic signs or deaths were not observed in mice treated at 2000mg/kg of *Citruslimetta* extract. All doses of *C. limetta* aqueous extract, used in this assay, were safe and effective [48].

7.6. Larvicidal activity

Citrus limetta peel extracts were prepared using hexane and petroleum ether as the solvents and it was assessed against dengue fever vector, *Aedesaegypti* and malarial vector, *Anopheles stephensi*. Toxicity effects were evaluated on early fourth instars. Both the extracts were found effective against both the species. Evaluation results revealed that the hexane extracts possessed 1.9 fold more larvicidal potential against *A. stephensi* as compared to the extracts obtained using petroleum ether as solvent [49].

8. Traditional uses of *Citrus limetta*

***In the treatment of scurvy*:** This disease is caused by vitamin C deficiency characterized by swollen gums, frequent bouts of flu, clod and cracked lip corners. Being rich in vitamin C, mosambi is effective in curing scurvy.

***As digestive aid*:** Due to its sweet fragrance, mosambi juice facilitates the release of saliva from the salivary glands which assists in quick digestion. The flavonoids present in lime juice enhance the digestive process by stimulating the secretion of bile, digestive juices and acids. Thus, drinking mosambi juice frequently throughout the day can ward off stomach problems, indigestion, nausea and dizziness. The acids present in mosambi juice help in the removal of toxins from the bowel tracts, thus easing constipation. Sweet mosambi juice with a pinch of salt can provide immediate relief. Additionally, it is effective in case of stomach upsets, dysentery, diarrhea and loose motions as it is rich in potassium. Due to its tasty flavor, it helps in avoiding vomiting and nausea. It also helps in curing bloody amoebic dysentery.

Antidiabetic benefits: Mosambi juice is beneficial for diabetes patients. To treat diabetes, you can mix 2 teaspoons mosambi juice, 4 teaspoons amla juice and 1 teaspoon honey and take this on an empty stomach every morning for best results.

Antiulcer effects: Peptic ulcers are open sores that occur on the inner lining of your esophagus, stomach or upper intestine and cause a lot of abdominal pain. The acids in lime juice provide relief against peptic ulcers by causing an

alkaline reaction in the system, thus reducing gastric acidity. For best results, you can drink a mixture of mosambi and lemon Juices. Drinking mosambi juice in warm water treats mouth ulcers and bad breath.

Immunity booster: Regular consumption of mosambi juice ensures proper blood circulation by improving the function of the heart. This results in a much healthier immune system.

Weight reduction: Being low in fat and calories, mosambi juice helps in reducing weight. You can drink a mixture of mosambi juice and honey to burn extra calories.

Beneficial in pregnancy: Pregnant women are often advised to drink mosambi juice as it provides a lot of calcium that benefits both the growing fetus and the mother to be.

Treatment of urinary disorders: Being rich in potassium, mosambi juice helps in treating urinary disorders such as cystitis. Cystitis is an inflammation of urinary bladder, also known as urinary tract infection (UTI). Mosambi juice boiled in water should be taken within a couple of hours after cooling for immediate relief in cystitis. Potassium facilitates the detoxification process of kidneys and bladder, preventing various types of urinary tract infections.

Ophthalmic benefits: Due to its antioxidant and anti-bacterial properties, this juice protects your eyes from infections and muscular degeneration. Washing your eyes with a few drops of mosambi juice mixed in plain or salt water can help in treating infections like conjunctivitis.

Remedy for Common Cold: Being rich in vitamin C, mosambi juice helps in clearing common cold and improves the body's resistance towards cold.

Antihyperlipidemic effects: Drinking mosambi juice reduces cholesterol and lowers blood pressure.

9. Benefits of Mosambi Juice in various skin diseases:
Mosambi juice has an important role to play in skincare. Being rich in vitamin C, it improves the skin color naturally and is used in several beauty products and alternative medicine supplements and vitamins. Some of its skin benefits are**:**

Treatment of Pigmentation, Spots and Blemishes: Mosambi juice treats various pigmentation issues such as spots, pimples and blemishes. For this purpose, apply fresh mosambi juice on the affected area at bedtime and wash with warm water the next day.

Prevention of Skin Problems: Mosambi juice is great for skin health due to the presence of vitamins and minerals. Its antioxidant, antibiotic and disinfectant properties rejuvenate the skin by protecting it from infections. Mosambi juice cleanses your blood, thus providing relief against skin problems.

Treatment of Body Odor and Sweat: Taking a bath with mosambi juice mixed water helps in tackling body odor and sweat.

Treatment of Cracked Lips: Rubbing mosambi juice on lips 2-3 times a day can reduce the darkness of lips and also treats chapped lips.

Reduction of Swelling and Pain: Applying a mixture of mosambi juice and castor oil on the affected area can lessen swelling and pain**.**

CONCLUSION

Mosambi is well cultivated in central and south Asia. It is the place from where most of the production of the fruit comes from. Citrus species is known for its medicinal and nutritional properties. It is commonly known as the rich source of vitamin C. Nearly all parts of the plant as peel, flower, and fruit juice are used as the traditional medicine. Literature available does not give the sufficient information about the toxicity and adverse effects of any part of the plant. Some pharmacological activities are reported such as antibacterial and antifungal activity, antioxidant activity, anti-hyperglycemic activity, antitumor potential, Larvicidal property and property to antagonize the hypertensive effect of angiotensin II. d-limonene, one of the most abundant terpene found in the plant is reported to be very low

toxic. Studies have determined that this isolated chemical does not pose a mutagenic, carcinogenic or nephrotoxic risk to humans. d-limonene helps in gallstone dissolution, shows anticancer activity and shown potential in Gastroesophageal reflux disorder. This study concluded with findings of many pharmacological/clinical values of Mosambi as well as d-limonene and with a view to explore and established the d-limonene in various disorders as a good alternative for modern medicine.

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