

REVIEW ARTICLE

A REVIEW ON PHARMACOLOGICAL PROFILE OF *CITRUS PARADISI*Yogendra Singh^{*1}, S. Ramasamy² and Mohd Ruman Khan³¹BIU College of Pharmacy, Bareilly International University, Bareilly-243006 (Uttar Pradesh), India²Department of Pharmacy, M.J.P. Rohilkhand University, Bareilly-243006 (Uttar Pradesh), India.³Rakshpal Bahadur College of Pharmacy, Bareilly-243004 (Uttar Pradesh), India

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ABSTRACT

Grapefruit (*Citrus paradisi*) is an important member of Citrus genus from family Rutaceae. It has been used as a folk medicine in many countries as anti-inflammatory, antipyretic, anti-arthritic, antioxidant, analgesic activity, antibacterial activity, antitumor activity, anti-amnesic activity, anxiolytic activity, nephroprotective activity, anti-HIV activity, antitubercular activity, antieosinophilic activity, anti-snake venom activity. Now days an herbal and traditional medicines mostly used in all over the world according to WHO, about 60 to 65% world population practicing herbal and traditional medicines. Plant have many chemical constituents as flavonoids, volatile oil, triterpenes, diterpenes, sesquiterpenes, lignan, flavones, glycosides, iridoid glycosides and stilbene derivative. These chemical constituents are present in each part of the plant. The traditional use of Citrus paradise as internal fruit peel is used to treat for malaria, gastro-protective and antiulcer. Citrus fruit peel is 1000 times sweeter than sucrose. This review article provides a depth information related to plant morphology, cultivation, chemical constitutes, pharmacological activities and their medicinal uses.

KEYWORDS: Grapefruit, Antioxidant, Flavonoids, Antidepressant, Antibacterial activity, Terpenes

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INTRODUCTION

Citrus is considered one of the world's most valuable fruits, and in the human diet, *Citrus paradisi* has greater importance. From the large family of citrus examples, sweet orange, lemon etc., there are several choices available^[1]. *Citrus paradisi* is the one of the most important members of the genus citrus from family Rutaceae. It is commonly known as grapefruit.

The island of Barbados is native to it. In Spain, Morocco, Israel, Jordan, South Africa, Brazil, Mexico, Jamaica, and Asia, it is also cultivated commercially. Other grapefruit varieties were grown mostly in Florida and Texas, in the United States of America^[2]. Today, in the U.S. states of Texas, Arizona, California, and Florida, it is the

second most significant citrus worldwide and a primary commercial crop. More than 2.5 million tonnes of grapefruit are harvested annually in Florida alone^[3].

The yield of grapefruit and orange juice is around half of the weight of the fruit, creating a very large amount of annual waste. Florida produces 1.2 million of the 36 metric tonnes of citrus waste produced annually, which is sold as feed stock for cattle. With the ability to produce more annually, Nigeria produces around 0.3 million tonnes. This is one of the main agricultural waste that poses a threat to health and the environment in many streets and markets in Nigeria^[4]. Various plants are used for anxiety in complementary and alternative drugs.

In the treatment of anxiety, volatile lemon-isolated oils (*Citrus limon*), bergamot (*Citrus bergamia*), lime (*Citrus aurantifolia*), mandarin (*Citrus nobilis*) and orange (*Citrus aurantium*) are also used. As an antibacterial, antifungal, anti-inflammatory, antimicrobial, antioxidant, antiviral, astringent, and preservative, *Citrus paradisi* is used as a traditional medicine in several nations. It has also been used to prevent cancer, cell regeneration, cholesterol reduction, washing, detoxification, maintenance of heart health, lupus nephritis, rheumatoid arthritis, and weight loss [5].

Due to its broad range of biological activities, such as antimicrobial, antioxidant, anti-inflammatory and anxiolytic, citrus essential oil has been recognised as safe [6]. Many essential oils, which are of consumer and economic importance, are the most important product of this massive processing industry. It is also used in cosmetics, perfumes, soaps and detergents as an ingredient. Citrus paradisi 's estimated essential oil yield is 3.9%, which includes open chain hydrocarbons, alcohols, aldehydes, ketones, esters, and alpha-terpenoids.

Grapefruit peel is candied and is an important source of pectin for other fruits to be preserved. Peel oil, expressed or distilled, is widely used in the flavouring of soft drinks after the removal of 50% of monoterpenesis. In "tonic" foods, bitter chocolate, ice cream and ice cream, Naringin, extracted from the inner peel, is used as bitter. It is important to explore the medicinal significance of this plant, taking into account its various uses [7].

Taxonomical Description

Botanical Name:	<i>Citrus paradisi</i>
Kingdom:	Plantae
Division:	Magnoliophytes
Class:	Magnoliopsida
Order:	Sapindales
Family:	Rutaceae
Genus:	Citrus
Species:	<i>Citrus paradisi</i>

Description

Citrus paradisi is a subtropical and tropical citrus tree that is a bitter fruit cultivated because of it. With spreading leaves, the tree reaches 4.5-6.0 m tall. Evergreen, ovate (7.5-15.0 cm long and 4.5-7.5 cm wide) and dark green are the leaves. The white, four-petal flowers are 4.5-5.0 cm wide and are borne in the leaf axils

individually or in clusters. In soft drink flavourings, the peel is widely used, while the seed can be used after extracting the oil for soil conditioning.

To overcome insomnia, an essence prepared from the flower of the grapefruit tree is taken and the pulp is considered to be an effective aid in the treatment of urinary disorders. The fruit is a hesperidium, a specialised berry, globose to elongated, 4-30 cm (1.6-11.8 in) long and 4-20 cm (1.6-7.9 in) in diameter, a "exocarp" called the flavedo, usually referred to as the zest, with a lethargic rind or "peel" called a pericarp. The mesocarp, which consists of the white spongy "albedo" or "pith" in citrus fruit, is the middle layer of the pericarp. The pericarp's innermost layer is the endocarp. The segments are often called "lith" and a locule filled with juice vesicles, or "pulp", is the space inside each lith [8].

Cultivation of *Citrus paradisi*

Due to limiting growing conditions, limiting water supplies and a high incidence of pests and diseases, *Citrus* cultivation in India is plagued by numerous problems that require great care from planting until the plants come to bear in order to maintain a productive life of at least 15-20 years.

The interest / awareness among citrus growers in the adoption of the latest technologies for commercial citrus cultivation is increasing. The National Citrus Research Centre, Nagpur, has released a set of cultivation practises for citrus in different regions of the country. The NRC 's guidelines on citrus and the experiences of citrus growers and their experience have been taken into account in the latest bankable citrus project [9].

Distribution

In India, *Citrus* is the third largest fruit crop, after banana and mango, in terms of the region under cultivation. Compared to other developing countries, such as Indonesia, Turkey, Brazil and the USA, the average citrus fruit yield in India is alarmingly low (8.8t/ha). Among mandarins, India 's commercial cultivars are Nagpur mandarin (Central India), Kinnow mandarin (North West India), Coorg mandarin (South India) and Khasi mandarin (North East India). Whereas the sweet orange cultivars traditionally grown are Mosambi (Maharashtra), Sathgudi (Andhra Pradesh) and Malta and Jaffa (Punjab) [10].

Figure 1: Fruit of *Citrus paradisi*Figure 2: Flower of *Citrus paradisi*Figure 3: Leaves of *Citrus paradisi*Figure 4: Tree of *Citrus paradisi*Table 1: % Distribution of *Citrus* Fruits

<i>Citrus</i> Fruits	Global Scenario	National Scenario
Mandarin	13%	44%
Lime & lemon	10%	28%
Sweet orange	71%	18%
Others	6%	10%

Climate

Citrus fruits are grown in India under various agro-ecological conditions, ranging from arid and semi-arid regions in the southwestern region to the humid tropical climate of north-eastern India. *Citrus* trees are evergreen, grown in the world's genuinely subtropical climates, although they tend to generate cyclic growth flushes in tropical regions and thus control cropping in tropical areas to push them into concentrated bloom, requiring judicious management of water deficit stress according to soil type and growing season.

Citrus fruits grow best between 13 ° C to 37 ° C temperature levels. Temperatures below 40 ° C for young plants are dangerous. For root growth, soil temperatures around 25 ° C appear to be ideal. Low humidity encourages the emergence of many diseases. Frost is particularly injurious. During the

summer, hot wind results in flowers and fruits being desiccated and falling. In both subtropical and tropical areas of the world, citrus is cultivated without these restrictions. The sub-tropical climate is most suitable for the growth and production of *Citrus*. As it is suited to a cooler climate, Khasi and Darjeeling mandarins are cultivated at high altitudes up to 2000 m ^[11].

Soil

Citrus plants are grown in a wide variety of soils in the Deccan plateau and north-eastern hills, ranging from sandy loam or alluvial soils of north India to clay loam or deep clay loam or lateritic / acidic soils. In light soils with strong drainage properties, citrus orchards thrive well. Deep soils with a 5.5 to 7.5 pH range are considered suitable. However, they can also be grown in the 4.0 to 9.0.0 pH range. The high concentration of calcium carbonate in the feeder root zone can adversely affect development ^[12].

Chemical Constituent

Naringin [naringenin 7- β -neohesperidoside (4', 5, 7-trihydroxiflavanone)] is present in citrus plants and is most abundant in the species of

Citrus paradisi. The essential oil reveals the presence of 23 constituents from which several constituents are analysed by gas chromatography (GC) and mass spectroscopy (MS) were identified as alphapinene (0.44%), beta-pinene (2.51%), limonene (81.6%), p-cymene (3.6%), linalyl acetate (5.20%), sabinene (1.02%), 4-terpineol (0.389%), alpha-terpineol (0.31%), alpha-thugene (0.28%), ctanol (0.26%), 1,8- cineol (0.42%), Geraniol (0.21%) and decanal (0.16%) [13]. Important amounts of vitamin C, potassium, folate, calcium, and iron are present in grapefruit pulp. Beta-carotene and lycopene, antioxidants that the body may transform to vitamin A, are also found in the pink and red varieties. Phenolic acid, limonoids, terpenes, monoterpenes, D-glucaric acid and flavonoids, including hesperetin and naringenin, are other defensive plant chemicals present in grapefruits. Grapefruit oil contains the following substances: nonanal, nootkatone, beta-pinene, alphaphellandrene, 3-carene, ocimene, octanol, cis-p-mentha-2, 8-dien-1-ol, alpha-pinene, limonene, linalool, geraniol, citronell, alphaterpineol, neral, dodecanal and

alphahumulene. [14].Limonene (50.8 percent, 53.8 percent and 65.5 percent), β -myrcene (3.51 percent, 3.57 percent and 3.60 percent), linalool oxide (2.29 percent, 6.52 percent and 4.03 percent) and nootkatone (25.40, 8.47 percent and 10.90 percent) were the main constituents of *Citrus paradisi* fresh, ambient-dried and oven-dried peel essential oils. The large portion (56.92-70.58 percent) of these oils were monoterpene hydrocarbons among the chemical compound groups, with limonene and β -myrcene as the key components. 17.67, 21.85 and 21.74 percent of the new, ambient-dried and oven-dried *Citrus paradisi* peel essential oils were hydrocarbons of oxygenated monoterpenes, respectively.

Decanal and linalool oxides were the two main hydrocarbons found by oxygenated monoterpenes. Sesquiterpenoides, another chemical category, included 9.83, 6.50 and 2.59 percent of the essential oils from *Citrus paradisi* fresh, ambient-dried and oven-dried peels, respectively. The two main components included in this class were β -caryophyllene and δ -cadinene [15].

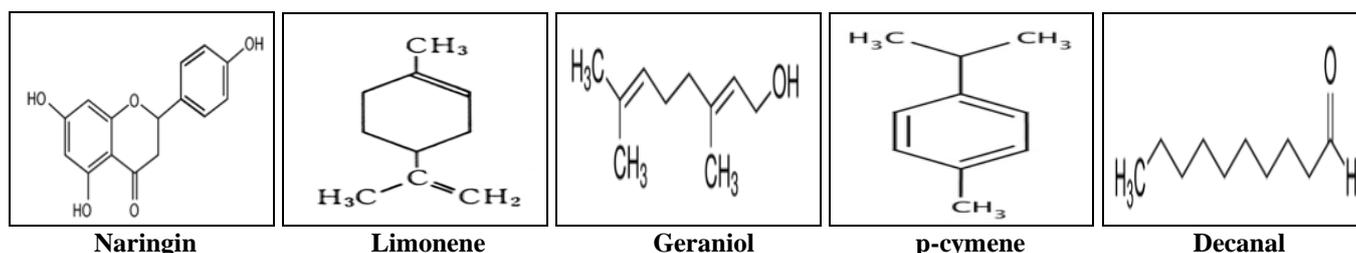


Figure 5: Major Chemical Constituents of *Citrus paradisi*

Medicinal Use

There are excellent medicinal qualities for *Citrus paradisi* which are valuable treatments for many diseases such as toothache, constipation, diarrhoea, which vomiting. It has also been used in the prevention of cancer, cell regeneration, cholesterol lowering, washing, detoxification and weight loss. The flesh of this fruit is used as a cure in poisoning and used to refresh the break. The seed extract of *Citrus paradisi* have been used for the treatment of ulcer, cataracts, urinary and alimentary tract infection. The oil from the peel of grapefruit has been used as insecticide and antifeedant [16].

Pharmacological Activities

Anticancer Activity

The ability of *Citrus species* as an anticancer agent in mice has been shown to induce large amounts of glutathione-S - transferase (GST)

in the liver and intestinal mucosa from five limonoid glycones (limonin, nomilin, obacunone, isobacunoic acid, ichangin). GST is a major detoxifying enzyme system which catalyzes the conjugation of glutathione with many potentially carcinogenic compounds which are highly electrophilic in nature.

A analysis of the inhibitory effects of two limonoidaglycones (limonin and nomilin) on the development of neoplasia induced by benzo pyrene in the fore stomach of ICR / Ha mice showed that at 10 mg / dose, tumour incidence could be reduced by more than 50%. Due to their inhibitory effect on breast cancer cell lines, the use of *Citrus flavonoids* in cancer care has been proposed [17]. The antimutagenicity and anticancer activity of fruit juice from *Citrus paradisi*. In order to consider its anticancer effect, they perform the vital ability test and Ames test with special focus

on the application of *Salmonella typhimurium* to determine the level of anti-mutagenesis and anticancer chemicals. In this analysis, half-ripe and ripe fruit juice showed an anti-cancer and anti-mutagenesis effect, which was more effective than ripe fruit juice with half-ripe fruit juice. In-vitro studies on the impact of fruit juice on cancer cell culture showed that fruit juice severely repressed cancer cell division, which in this study had more than one mature impact of half-ripe *Citrus paradisi* fruit juice [18]. Vitamin C, β -carotene, flavonoids, limonoids, dietary fibres and folic acid are the bioactive components found in citrus fruits that are implicated in degenerative disease prevention.

Vitamin C, flavonoids and β -carotene are potential antioxidants that protect biomolecules such as DNA, protein and lipid membranes from oxidation, thereby reducing the risk of cardiovascular diseases, cataracts and cancers. By inducing GST activity to neutralise carcinogenic free radicals, limonoids can protect against a variety of cancers. Folic acid plays an essential function in the synthesis of amino acids and is thus a vital growth factor [19]. Grapefruit juice provides the diet with a high amount of putrescine, which may slow the process of cancer [20].

Antimicrobial Activity

Antimicrobial activity of commercial natural extracts based on Citrus against *E. coli* isolates and mutant strains. For antimicrobial activities against *E. coli*, all these seven essential oils were evaluated. Strains of *E. coli*. Limonene is the most vulnerable to Strains of *E. coli*, which did not vary substantially from Strains of *E. coli*. With inhibition zones of 14.5 ± 0.7 mm and 13.5 ± 0.7 mm. All other *E. coli* strains yielded significantly smaller inhibition zones 10.3 [21].

Antimicrobial activity of carotenoid extracts against *Staphylococcus aureus*, *Bacillus subtilis*, *E. coli* also clarified were *coli*, *Aspergillus niger*, *Aspergillus flavus*, *Penicillium chrysogenum*, *Rhizopus oryzae* and *Saccharomyces cerevisiae*. The results showed that at a temperature of 50°C , the optimal extraction condition was a solvent-oil ratio of 10:1 and a period of 40 minutes. The method of disc diffusion and the determination of minimum inhibitory concentration showed that the extract has a broad spectrum of anti-microbial

activities against *S. aureus*, *Bacillus subtilis*, *Saccharomyces cerevisiae*, *Rhizopus oryzae* [22].

Antioxidant Activity

In the investigation, domestic (gooseberry, apples, plums) and imported (watermelon, lemon, grapefruit, kiwi fruit, melon, lime, grapefruit) seeds and peels of commercially available fruits were used. The highest antioxidant activity was observed in the peels of the sampion cultivar and white grapes, and the seeds of the I dared cultivar and orange, among the fruit parts examined. White *Citrus paradisi* dried peels contain large concentrations of polyphenols, ascorbic acid and carotenoids that show the capacity for antioxidants [23].

Antifungal Activity

The goal of this research was to study the effect of grapefruit (*Citrus paradisi*) lemon (*Citrus lemon* L.) and mandarin (*Citrus reticulata* L.) essential oils on the growth of moulds commonly associated with food spoilage: *Aspergillus Niger*, *Aspergillus flavus*, *Penicillium chrysogenum* and *Penicillium verrucosum*, using the method of agar dilution. Against all the moulds, the oil showed antifungal activity. The most successful of these was orange essential oil against *A. niger*. The most successful reduction of *Aspergillus flavus* growth was, mandarin essential oil, while grapefruit was the best inhibitor of the *P. chrysogenum* and *P. verrucosum* moulds. Suitable alternatives to chemical additives for use in the food industry may be considered to be essential citrus oils [24].

Anti-inflammatory Activity

The anti-inflammatory effect of the drug *A. occidentale*. On fresh egg albumin-induced rat paw edoema, stem-bark aqueous extract was investigated alone and in combination with grapefruit (*Citrus paradisi*) juice. Like the aqueous extract of diclofenac from *A. occidentale*. The time-related, sustained and important reduction of the fresh egg albumin-induced acute inflammation of the rat hind paw was provided by *A. occidentale* stem-bark.

However, it was found that the plant extract's anti-inflammatory activity was approx. 8-15 times less than that of diclofenac. Grapefruit juice co-administration with *A. occidentale*. The anti-inflammatory effects of crude plant extract and diclofenac on fresh egg albumin-induced rat paw

edoema were substantially potentiated by occidentale stem-bark aqueous extract or diclofenac [25].

Apoptotic Activity

Limonene is a primary component of the essential oils of *Citrus* and has been reported to induce tumour cell apoptosis. The activation of apoptosis by *Citrus* EOs is little understood. We investigated the induction of apoptosis by *Citrus aurantium* var. in this report. EO, *Citrus paradisi* (grapefruit) EO and *Citrus limon* (lemon) EO. Dulcis (sweet orange). The operation of apoptosis was correlated with the limonene content of the EOs. In addition, sweet orange EO and grapefruit EO may contain components that have apoptotic activity besides limonene. Strong apoptotic activity was demonstrated, indicating that the aldehyde compounds strongly induced apoptosis in HL-60 cells [26].

Antibacterial Activity

Citrus paradisi peels were successively extracted using a Soxhlet extractor for 8 h each with hexane, chloroform, acetone and methanol. Thin layer chromatography (TLC) revealed three spots with separate concentrations of hexane and chloroform extracts. The antibacterial activity of these fractions against different bacteria was assessed. Maximum activity followed by hexane extract was found to contain the alcohol soluble fraction. Extracts were more effective against Gram-positive than Gram-negative bacteria [27].

This study was aimed at determining the effectiveness of the essential oil of Grapefruit (*Citrus paradisi*) in inhibiting the growth of wild food-borne spoilage and pathogenic strains of bacteria. The effect of this oil on the growth of wild strains was determined by total count and spectrophotometric absorption at different times. These findings show that, when compared with and without the addition of essential oil, oil has a bactericidal effect. This essential oil has a very strong potential for use as a natural antibacterial agent for the food industry, particularly for the production of pasta that faces serious problems of spoilage due to lactic bacteria activity [28].

Hematopoietic Activity

The blood-forming effects of *Citrus paradisi* in adult Wistar rats (100 percent methanol seed extract) for 30 days were a way of

testing its conventional use in the treatment of blood deficiencies. In total leukocyte count, lymphocyte differentials, red blood count, haemoglobin concentration, packed cell count, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration and platelet count, important progressive and dose-dependent elevations were shown. Reversed effect was recorded for the neutrophil and monocyte differentials which were significantly decreased in the treated rats [29].

Anti-HIV Activity

The 6, 7-dihydroxy-bergamottin of *Citrus paradisi* enhances bioavailability of HIV protease inhibitor by inhibiting cytochrome P450 isoenzyme 3A4 in liver and gut [30].

Antiatherogenic Activity

Naringenin belongs to the flavonoid class known as flavanones. *Citrus* fruits such as grapefruit (*Citrus paradisi*) and oranges (*Citrus sinensis*) abound with flavanones. Significant attention has recently been paid to the function of naringenin and related citrus flavanones, hesperetin, in the prevention and treatment of disease, with particular interest in the use of these flavanones as anticancer and antiatherogenic compounds [31].

Apoptotic Activity

The aldehyde compounds of *Citrus paradisi* essential oil have been reported to induce apoptosis strongly in HL-60 cells [32].

Hepatoprotective Activity

To test its protective utility on the liver against paracetamol-induced liver injury, the ethanol seed extract of *Citrus paradisi* (grapefruit) Macfad was carried out. Extracts substantially decreased the dose-dependent behaviour of ALP, ALT and AST relative to negative controls. All blood parameters except for neutrophil differentials were significantly elevated by the extract. The seed extract of *Citrus paradisi* (grapefruit) has hepatoprotective potential and can be used as an antidote to against paracetamol-induced hepatotoxicity [33].

Arterial Pressure Activity

In the Langendorff isolated and perfused heart model and in the heart and lung dog preparation, the coronary vasodilator and hypertensive effects of the *Citrus paradisi* peel

extract were evaluated. *Citrus paradisi* peel extract reduced coronary artery resistance and average arterial pressure relative to control values in both models. When isolated and perfused hearts and mongrel dogs were pre-treated with L-NAME, the decreases in coronary vascular resistance and mean arterial pressure were blocked. In humans, *Citrus paradisi* juice decreased diastolic arterial pressure and systolic arterial pressure both in normotensive and hypertensive subjects [34].

Antidiabetic Effect

For these rats were used and divided into five groups. At the dose amounts of 10 ml / kg / day of distilled water, 10 ml / kg of body weight / day of dimethyl sulphoxide (DMSO), 100, 300 and 600 mg / kg of body weight / day of the extract dissolved in 10 ml / kg of DMSO for a duration of 30 days, the rats were administered. The fasting plasma glucose (FPG), total cholesterol (TC), high density lipoprotein (HDL-c), low density lipoprotein (LDL-c) and very low density lipoprotein (VLDL-c) blood samples collected on day 31 were assayed using normal procedures [35].

Risk assessment factors such as obesity or body mass index (BMI), atherogenic index (AI), and coronary risk index (CRI) were calculated for cardiovascular disease. The findings showed substantial ($p < 0.05$, $p < 0.001$) dose-related lowering effects of the extract on FPG, risk assessment of cardiovascular disease indices and lipid parameters with the exception of significantly elevated HDL-c fraction ($p < 0.05$, $p < 0.001$). The extract also induced significant ($p < 0.05$) dose related weight loss in the treated rats in the latter 15 days of their treatment. This research lend support to its therapeutic potentials in the management of suspected type-2 diabetic patients [36].

CONCLUSION

As well as Ayurveda, *Citrus paradisi* is a big medicine of the western method. In preparing herbal medicines, almost all parts of the plant are used. Anti-cancer, antimicrobial, antifeedant, anti-inflammatory, anti-hyperpigmentation, hepato-protective, antihistaminic, analgesic and related activities are known to occur in the plant. The aim of this review is to cover the literature available on *Citrus paradisi* with regard to its traditional uses, its chemical constituents and the summary of

its different pharmacological activities. *Citrus paradisi* has various biological functions that have been shown by several experimental studies. It is a class of herbal drugs with a very good philosophical foundation for their use. Therefore, this plant has great potential to be developed by the pharmaceutical industry as a drug, but there is a need to perform clinical trials to prove its clinical effectiveness before approving it for clinical use in these conditions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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