TWO DAYS NATIONAL LEVEL CONFERENCE

ON

ROLE OF PHYTOCHEMICALS AND ADVANCED MATERIALS IN CANCER PREVENTION AND RESEARCH

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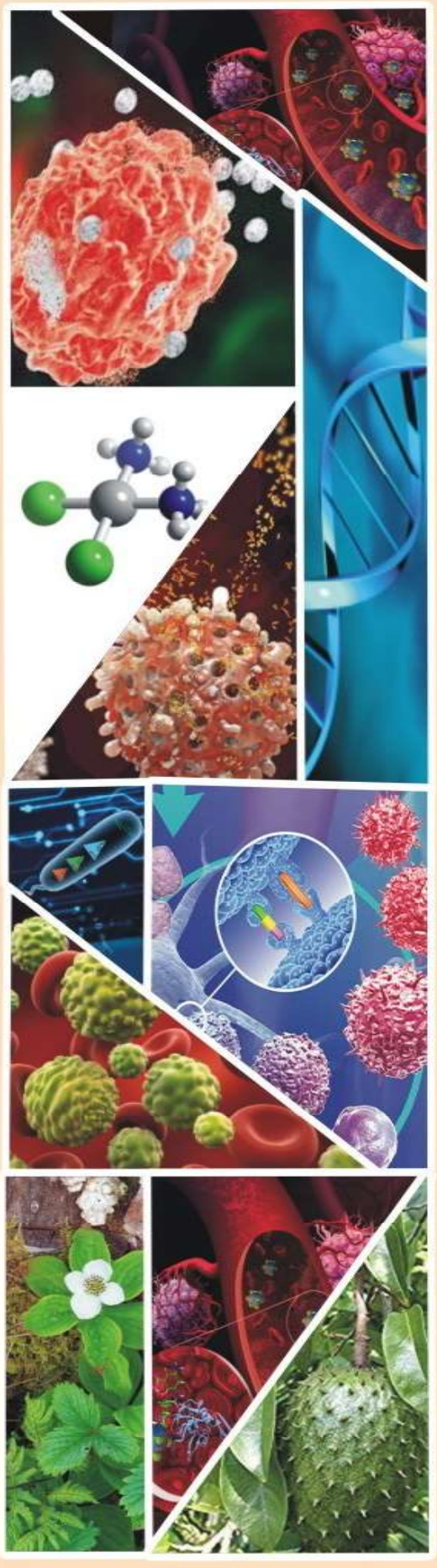

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CONTENT

S.No	Title	Page
1.	INTERESTING MORPHOLOGY OF La doped CuC_2O_4 and Na doped CuC_2O_4 SYNTHESISED VIA THERMAL DECOMPOSITION ***POONKODI K, ATHIRA. S, AKSHAYA, V. SAJANA. M.S. and SUBHAHARINI***	1
2.	EVALUATING PHARMACOGONOSTICAL AND PHYTOCHEMICAL CHARACTERS OF THREE IMPORTANT MEDICINAL PLANTS, *phyllanthus reticulatus* POIR., *AZIMA TETRACANTHA* LAM., AND *ZIZIPHUS OENOPLIA* L. INHABITING LOWER WESTERN GHATS OF POLLACHI TALUK, TAMILNADU, INDIA. ***A.M. ANANDAKUMAR, N. SASIKUMAR, R. RAKKIMUTHU and P. SATHISHKUMAR***	9
3.	ZNO/ ZN -AL LDH COMPOSITE MATERIAL WITH SUPER PHOTOCATALYTIC ACTIVITY FOR ENHANCED ADSORPTION OF CONGO RED DYE ***ANITHA VENKATASAMY and RAJALAKSHMI SUBRAMANIAN***	18
4.	A THERAPEUTIC APPLICATIONS OF NANOTECHNOLOGY IN CANCER DIAGNOSIS AND TREATMENT ***S.BAGYALAKSHMI***	30
5.	SPECTRAL CHARACTERIZATION OF 1-(5-AMINO-2, 4-DINITROPHENYL) PYRIDINIUM CHLORIDE MONOHYDRATE ***R.BABYKALA and DR.M. BUVANESWARI***	35
6.	WATER QUALITY INDEX AND CORRELATION STUDY FOR THE ASSESSMENT OF GROUNDWATER QUALITY AND ITS PARAMETERS OF MADATHUKULAM, TIRUPPUR DISTRICT, TAMIL NADU. ***R.CHITRADEVI***	37
7.	STRUCTURE AND BIOLOGICAL STUDIES ON SOME SUBSTITUTED PIPERIDINE PHENYL HYDRAZINES ***M. DINESH KUMAR and P. RAJESH***	43
8.	ISOLATION OF CARVONE AND OTHER PHENOLIC COMPOUNDS FROM *Nigella sativa - AN REVIEW* ***A. GEETHAMANI, N. GOMATHI and G. ASWINI***	58
9.	A REVIEW ON PHYTOCHEMICAL PROFILING OF *Couroupita guianensis* AUBL. ***VELLIANGIRI PRABHU and GOKILA PRIYA***	61

10. INVITRO ANTICANCER ACTIVITY OF *Plectranthus amboinicus* LEAVES ESSENTIAL OIL AGAINST CHANG LIVER CELL LINE 67
K.VIMALADEVI, R. MINI and N. MALATHI

11. PHYTOCHEMICAL AND PHARMACOLOGICAL STUDIES OF *Orthosiphon stamineus*- AN UPDATED REVIEW 72
SARANYA K. S, KARTHIGAIPRIYA. M and POONKODI. K

12. NOVEL TRANSITION METAL COMPLEXES WITH AMINOGUANIDINE AND 3-HYDROXY-2-NAPHTHOIC ACID AS LIGANDS – SYNTHESIS AND CHARACTERIZATION 79
PRABHA DEVI.B, KANCHANA.P, ARUNADEVI.N, M.SWATHIKA

13. SYNTHESIS, DOPING AND CHARACTERIZATION OF N-GRAPHENE 80
KANDEEBAN, RAJAGOPALAN, S.DURGANANDINI, K.MANOJKUMAR, R.SUBHASINI, K. SAMINATHAN

14. PHYTOCHEMICAL AND PHARMACOLOGICAL ACTIVITIES OF *Eupatorium adenophorum* SPRENG- *A REVIEW* 84
KARTHIGAIPRIYA, M. SARANYA K. S, and POONKODI. K

15. CANCER FIGHTING FRUITS AND VEGETABLES 91
A. LOGAMADEVI

16. ROLE OF PHYTOCHEMICALS IN MEDICINAL PLANT 96
N.SOUNDARRAJ, C.PRIYADHARSINI and K. KOUSALYA

17. CHEMICAL COMPOSITION OF METHANOL EXTRACT OF *Physalis minima* 99
VELLIANGIRI PRABHU and MONIKA B

18. A COMPARATIVE STUDY ON DEGRADATION EFFICIENCY OF PHENOL RED USING ZNO NANOPARTICLE 103
MUTHULINGAM. S, GREESHMA .K. P, HASEENA. Z, VARSHA SRI.G, JANANI.J, JEEVITHA.T

19. METAMORPHOSIS OF FLORAL WASTE IN TO VALUABLE (ZnO) FABRICATED CQDS AND THEIR IMPACT ON CATALYTIC DEGRADATION OF INDUSTRIAL EFFLUENTS & PLANT GROWTH ENHANCEMENT - DIVINE FLOWERS WITH SOCIETAL APPLICATIONS. 104
S.MUTHULINGAM, K.P.GREESHMA and S.NITHISH

20. INHIBITIVE ACTION OF HYDROXY PYRAZOLINE DERIVATIVES ON THE CORROSION OF MILD STEEL IN SULPHURIC ACID MEDIUM TOGETHER WITH QUANTUM CHEMICAL STUDIES 105
N.ANUSUYA, J SARANYA and S.CHITRA

PHYTOCHEMICAL AND PHARMACOLOGICAL STUDIES OF *Orthosiphon stamineus*- AN UPDATED REVIEW

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Abstract

Orthosiphon stamineus Benth is a medical herb belonging to the Family Lamiaceae, a valued medicinal plant in traditional folk medicine. Phytochemical studies reported about 116 compounds that isolated from this plant classified as monoterpenes, diterpenes, triterpenes, saponins, flavonoids, essential oil and organic acids. Pharmacological studies for whole extract, or pure compounds isolated from the plant showed antioxidant, antitumor, diuretic, nephroprotective, antilipidemic, antipyretic, anticancer antidiabetic, antihypertensive, antiinflammation,Gastro protective activity, antimicrobial, Antisebum and hepatoprotective. Traditional uses of *O. stamineus* meets its scientific evidence in aspects of phytochemical, pharmacological, toxicological as well as clinical. The present review reportedthe chemical and pharmacological investigations of important medicinal *O. stamineus*

Keywords : *Orthosiphon stamineus*, flavonoids, antimicrobial, nephroprotective, organic acids.

Introduction

Orthosiphon stamineus Benth is commonly known as misaikucing and kumis kucing. *O. stamineus* is widely grown in Southeast Asia and the tropical countries. The leaves of this plant are known as "Java tea" and are mainly used for the purpose of making herbal tea commonly in Southeast Asia and European countries (Indubala., 2000). Other names for *O. stamineus* include *Orthosiphon aristatus*, *Orthosiphon spicatus*, *Orthosiphon blaetter* and *de Java*. *Orthosiphon* species is categorized into two varieties: one with the white flowers (white variety) and the other with the light purple flowers (purple variety). Purple variety contains more bioactive compounds than the white one. Normally, the leaves and stem tips have medicinal values. Due to this property, this plant has extensively been subjugated traditionally to treat several human ailments and conditions such as diuretic, rheumatism, abdominal pain, kidney and bladder inflammation, edema, gout, and hypertension (Hegnauer., 1966; Eisai.,1955;Wangner., 1982).

The leaves of *O. stamineus* exhibit excellent pharmacological activities such as antioxidant, antibacterial, hepatoprotective, anti-inflammatory, cytotoxic, antihypertensive, and vasodilatation(Chung,*et al.,* 1998, Masuda,*et al.,*Beaux, *et al.,* 1993). Many pharmacopoeias such as French, Indonesian, Dutch, and Swiss have listed this plant for the treatment related to renal cleansing and function, and related disorders that include nephritis, cystitis, and urethritis. In Europe, people use the leaves of *O. stamineus* extract as a tonic for kidney and bladder stones, liver and gallbladder problems, and urinary tract infections. This can be used to reduce cholesterol and blood pressure. Earlier report showed that this plant contains high amount of flavones, polyphenols, bioactive proteins, glycosides, a volatile oil, and vast quantities of potassium (Tezuka, *et al.,* 1993).

Phytochemical study

The phytochemical study of *O. stamineus* grown in Asia has been conducted extensively since the 1930s. The scientists have identified more than hundreds of chemical compounds and classified them as monoterpenes, diterpenes, triterpenes, saponins, flavonoids, organic acids, and so on. Moreover, earlier study has recognized 69 chemical compounds in the essential oil extracted from the leaves of *O. stamineus*. They were 1-octen-3-ol, β-bourbene, β-caryophyllene, α-humulene, β-elemene, phenylacetaldehyde, caryophyllene oxide, β-pinene, camphene, 3-octanol, limonene, cis-2-octenal, 2-heptenal, trans, cis-octa-3-5-dien-2-one, 1-methylnaphthalene, α-muniolene, trans, trans-octa-3-5-dien-2-one, 2-amylfuran, menthone, carvone, methyl chavicol, α-pinene, tridecane, ρ-cymene, pentenylfuran, hexanal, naphthalene, benzaldehyde, eugenol, linalool, trans-linalool oxide, δ-cadinene, trans-2-(cis)-6-nonadienale, methyl eugenol, trans-2-hexanal, camphor, citronellol, α-copaene, borneol, dodecane, α-cubebene, geranylacetane, δ-terpineol, acetophenone, trans-anethole, germacrene D, decanal, δ-elemene, 1,8-cineol, 4-heptenal, isomenthone, β-cyclocitral, damascenone, dehydroionone, cis-linalool oxide, undecane, bornyl acetate, 2-methyl naphthalene, β-ionone, perillen, safranal, hexahydrofamesylacetone, hexan-1-ol, 2,6,6-trimethyl-2-cyclohexene-1,4-dione, isobornyl acetate, trans, trans-deca-2,4-dienal, cis-caryophyllene, germacrene, and cis-3-hexen-1-ol (Eisai.,1955; Wangner., 1982; Chung, *et al.,* 1998) .

Few years ago, seven triterpenes namely, ursolic acid, oleanolic acid, betulinic acid, hydroxyl betulinic acid, maslinic acid, a-amyrin, and b-amyrin have been isolated from the leaves of *O. stamineus*. Recently, one compound a-amyrin was isolated for the first time from this plant. Some other compounds detected were b-caryophyllene, a-humulene, b-elemene, 1-octen-3-ol, b-bourbonene, b-pinene, caryophyllene oxide, camphene, and limonene. These are all major compounds obtained from the hydro distilled essential oils of the leaves and stems of *O. stamineus*. Alternatively, a-pinene, 1,8-cineol, borneol, linalool, camphor, eugenol, p-cymene, carvone, bornyl acetate, and d-cadinene were reported as minor components of *O. stamineus* leaf and stem oils (Tezuka, *et al.,* 1993; Hossain, *et al.,* 2008; Ameer, *et al.,* 2012)

PHARMACOLOGICAL PROPERTIES

Anti-inflammatory activity:

Mostly 60-75% of the medicinal species of *Orthosiphon* reported traditionally used for treatment of inflammation and diseases like arthritis, bronchitis and rheumatoid. The pharmacological activity of the species of genus *Orthosiphon* provides primarily *in vivo* information for anti-inflammatory effects.

Hossan *et al.,* 2008 reported in different studies on *O. stamineus* methanolic extract on various amount model suggested that oral administration of methanolic extract of *O. stamineus* exerted significant anti-inflammatory activity from 250-1000 mg kg^{-1} of dose.

Ameer *et al.,*2012 investigated the anti-inflammetory chloroform extract was studied on various models like anti-peritoneal capillary permeability, carrageenan-induced rat paw edema along with *in vitro*radical scavenging activity. It was found that oral administration of chloroform extract at 500-1000 mg kg^{-1} reduced edema and no dye leakage to the peritoneal cavity.

Akowuah and Zhari 2010 carried out both anti-inflammatory and analgesic activities of standardized 50% methanol extract of *O. stamineus*. The result showed that oral administration of up to 1000mg/kg of the extract produced an anti-inflammatory effect as established by a reduction in the hind paw edema in rats pretreated with carrageenan.

Masuda *et al*., 1992 evaluated the isolation of*Orthosiphol*A and B showed strong inhibitory activity against the inflammation induced by a tumor promoter on the ears gene targated mice (Masuda, *et al*., 1992).

Antioxidant activity:

Several *Orthosiphon* species traditionally used for expectorant and rheumatism indicated antioxidant activity. Antioxidant activity was investigated using DPPH, superoxides and xanthin oxidase. *O. stamineus* extract showed potential antioxidant activity. The highest activity was found in hydroacetone extract. Other study found that all the extract had potential antioxidants comparable to that of some standard antioxidants BHA and quercetin. (Adnyana, *et al*., 2013). In another study the antioxidant activity was determined by 2, 2-diphenyl-1-picrylhydrazyl radical scavenging method, whereas the antibacterial effectiveness was carried out by both disc diffusion method and minimum inhibitory concentration (MIC) against four bacterial strains (gram-positive and gram-negative. The result showed that the aqueous extract of *O. stamineus* exhibited significant free radical scavenging activity with IC_{50} of 9.6 µg/mL, whereas the IC_{50} for the ethanol extract was 21.4 µg/ml (Alshawsh, *et al.,* 2012).

Akowuah, *et al*., 2005 evaluated the antioxidative potency of various fractions of *O. stamineus* extract using an *in vitro* model of 1, 1-diphenyl-2-picrylhydrazyl scavenging. The results showed antioxidant potency comparable to that of some standard antioxidants, including quercetin and butylatedhydroxyanisole. The highest antioxidant activity showed by acetone extract was more than that of the aqueous methanol, methanol, and chloroform extracts.

Hepatoprotective activity:

Yam,*et al.,*2009 reported that pretreatment with methanolic extract of *O. stamineus* to hepatoprotective activity in CCl_4 induced liver damage in rats. It was investigated that hepatoprotective effects caused by antioxidants properties. Moreover *O. Storminess* showed hepatoprotective activity on paracetamol-induced rats. Further, they proposed that there quality of medicinal plant due to ability to prevent the depletion of the tissue GSH (Maheswari, *et al.,*2008).

Anticancer activity:

Stampoulis,*et al.,* 1999 proposed cytotoxic activity of methanol extract of *O. stamineus*against liver methanolicclon 26-LS carcinoma cells. The isolated compound stamina lactones A and B and norstaminal a showed mild cytotoxic activity against high malignant live metal stalic clone carcinoma cells.

Another study Adnyana,*et al*.,investigated the possible cytotoxic activity a compound isolated from Japan *O. stamineus* against highly malignant liver metastatices murine colon 26-LS carcinoma and human HT-1080 fibrosarcoma cell line (Adnyana, *et al*., 2013).

Antihypertensive activity:

The antihypertensive activity of aqueous extract of leaves and isolated from *O. stamineus*benth was examined by Adnyana, *et al.,* andAmmer, *et al.,*Methylripariochromene A (from aqueous extract of leaves), *Orthochromene*A, *Orthosiphonone* A and B and neoorthosiphol A and B (from $Chcl_3$ fraction of leaves), tetramethylscutell are in possess diuretic action. These constituents led to decrease in blood pressureand cardiac output. Subcutaneous administration of aqueous decoction of leaves led to decrease in systolic blood pressure conscious SHRSP. Does dependent decrease in urinary volume was observed ofter oral administration of isolated constituents of *O.stamineus*urinary excretion of electrolytes was increased 2-3 times. These results confirmed that flavonoids and isopimarane-type compounds contributes significant antihypertensive activity (Adnyana, *et al.,* 2013; Ammer, *et al.,* 2012).

Koay and Amir investigated antihypertensive activity of *O. stamineus*benth in combination with folic acid, coenzyme-Q, policosanol which indicated effective control of high blood pressure in patients with metabolic syndrome(Koay and Amir., 2012).

Matsubara, *et al.,* studied methylripariochromene A (100mg/kg) isolated from the leaves of *O. stamineus* decreased systolic blood pressure and heart rate, when it was injected subcutaneously into conscious male spontaneously hypertensive rats (Matsubara, *et al.,* 1999).

Gastro protective activity:

Yam, *et al*., investigated the methonalic extractof leaves of *O. stamineus*benthpossess significant effects for treatment gastric ailments. Fifty percentage of methanolic extractled to decrease in ulcer index, gastric mucosa mucosal damage, lipid peroxidationwith an increase in mucus secretion. The antiulcerogenic activity was investigated in male Sprague Dawley rats against ethanol-induced ulcers. The traces of histological changes, mucosal secretion, Ulcer index and lipid. Peroxidation level was estimated using both *in vitro*and *ex vivo* models. The results showed significant does dependent gastro protective responces (125-1000 mg kg^{-1} (Yam, *et al*., 2009).

Hyperlipidemicacivity:

The aqueous extract of *O. stamineus*showed significant hyperlipidemic activity. Mariam,*et al*., investigated the oral admnistration of aqueous extract *of O. stamineus* on lipid profilein normal and Streptozotocic induced diabetic male wistar rats. (Mariam, *et al*., 1996).

Antipyretic activity:

Yam,*et al.,* reported antipyretic study of *O. stamineus* hydrochloric extract executed a profound effect from a dose range of 50-1000 mg kg^{-1} b.wt. The yeast induced pyrexia model was employed to investigate the effect. Similarly the effect was observed in 50% methaniolcextact of *O. stamineus* in yeast-induced pyrexia in Sprague Dawley rats was investigated. The study showed that oral administration of the extract in the range from 450-1000 mg kg^{-1} led to no reduction in body temperature, but a significant alleviation of the pyrexia induced by yeasts was observed (Yam, *et al.,* 2009).

Antibacterial activity:

Hossain,*et al.,* investigated *O.stamineus* methanolic extractat concentration of 50% inhibited *Bacillus subtilis*, *Bacillus cereus*, *Litseriamonocytogenes*, *Staphylococcus aureus*, *Escherichia coli*, *Vibriparahaemolyticus*, *Salmonella enteritidis*, *Salmonella typhimurium*and *Klebsiellapneumoniae*. This antibacterial activities of *O. stamineus*may be due to the high concentration of rosmarinic acid (Hossain,*et al.,* 2013).

Ho, *et al.,* investigated the whole *O. stamineus*powderedmethanolic extractdemonstrated inhibitory activity against vibrio parahaemolyticus*in vitro*. The inhibition showed with *O. stamineus*extracts was comparable to the inhibition seen with that of 5% lactic acid; this may be likely due to high concentration of rosmarinic acid found in the *O. stamineus*extracts Ho, *et al.,* 2010).

Antidiabetic activity:

Sriplang,*et al.,* investigated the oral glucose tolerance test, the water extract at doses of 0.2-1.0 g kg^{-1} significantly decreased plasma glucoseconcentration in dose-dependent manner for both normal and diabetic rats. At a dose of 1.0 g kg^{-1} showed similar effect with glibenclamide (5 mg kg^{-1}). In diabetic rats, after they were given the extract orally (0.5 g kg^{-1}) for 14 days, concentrations were reduced significantly. In addition, plasma triglyceride concentration was also lower in the extract-treated diabetic rats than that of untreated group. Furthermore, plasma HDL-cholesterol concentration was significantly increased in diabetic rats treated with the extract. In perfused rat pancreas, 100 μg ml^{-1} extract potentiated the glucose-induced insulin secretion.

Mohamed, *et al.,* investigated the antidiabetic effects of the chloroform, methanol, petroleum ether and water extracts of *O.stamineus*was studied. Chloroform extract at a dose of 1 g kg^{-1} b.wt., significantly reduced blood glucoselevel. Further, this extract was fractionated and finally one subfraction showed similar antidiabetic effect with metformin.

Diuretic activity:

Arafat,*et al.,*studied the diuretic and hypouricemic activity of different *O. stamineus*methanol extracts by Sprague, Dawley rats model. A single dose infusion (2 g kg^{-1}) of methanol and methanol: Water (1:1) extracts possesses significant diuretic action, where the effect was quantitatively similar to the control, hydrochlorothiazide. Repeated dose of 0.5 g kg^{-1} of methanol: water (1:1) extracts showed an increase in diuresis from the third day of treatment. Oral administration of 0.5, 1.0 and 2.0 g kg^{-1} of methanol: water (1:1) extracts significantly reduced serum urate level of hyperuricemic rats.

Adam,*et al.,*investigated the diuretic effects of *O.stamineus*aqueous extract. Orally at doses of 5 and 10 mg kg^{-1} to Sprague, Dawley rats and was compare with furosemide or hydrochlorothiazide at 10 mg kg^{-1}. Urine pH, urine volume, urine density and urine electrolytes were determined every hour for 4 h. Blood was assayed for albumin, glucose, Blood Urea Nitrogen (BUN) and creatinine. *O. stamineus*extract exhibited dose-dependent diuretic activity.

CONCLUSION

O. stamineus is a valued medicinal plant, growing well in many countries, especially Southeast Asian countries. This plant has a great potential value for cultivation because it contains secondary metabolites with interesting biological activities. Numerous compounds have been isolated from this plant, and this species has been used in the treatment and prevention of several illnesses such as diabetic, inflammation, and diuretic activities. Many experiments have been conducted to validate its pharmacological uses. This review has presented a phytochemical and pharmacological activies of *O. stamineus*.

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