SCIENTIFIC VALIDATION ON SIDDHA SASHTRIC HERBOMINERAL FORMULATION “GENDHAGA VALLAATHI...”

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ABSTRACT

Siddha system were practised in traditional Tamil speaking people, where they exists beyond the continent also. The people were well in Physical and Mental health with the Siddha Medicines. When the infectious diseases were ruled over the world, people were looked for the conventional medicines. But the re-infectious threat, challenging non-communicable diseases has reverted back the people to Siddha system of Medicines. Rheumatic or Musculoskeletal conditions compromises over 150 diseases and syndromes which are usually progressive and associated with Physical disability. Rheumatoid arthritis is such a medical threat to the world due to its disability and mortality. Rheumatoid arthritis is a generalised disease affecting the connective tissues of the whole body with focalised involvement of the Musculoskeletal system. People have long feared rheumatoid arthritis as one of the most disabling type of arthritis. The clinical features of Rheumatoid arthritis were correlated well with Uthiravaatha Suronitham in Siddha system pathology. Uthiravaatha Suronitham were classified under 84 types of Vaatha diseases as per the saint Yugi. According to him, the features of Uthiravaatha suronitham were Pain and swelling in the ankle joints, dorsum of the foot, knee joint , smaller joints of the hands, loss of appetite , mental depression. These symptoms were due to the elevation of Vaatham with deranged Pitham. An emerging body of research is focussing on various treatment modalities for Rheumatoid arthritis. In Siddha literatures, various formulations were indicated for
Rheumatoid arthritis. Gendhaga Vallaathi, a formulatory Siddha medicine is one of the traditionally used drug for treating Rheumatoid arthritis. This leading study in collection of scientific reviews about the drug in hope of creating better treatment for Rheumatoid arthritis.

**KEYWORDS:** Siddha formulation, Gendhaga vallaathi, Pharmacological activities, Rheumatoid arthritis, Uthiravaatha suronitham.

**INTRODUCTION**

Rheumatoid arthritis being an autoimmune disease, its etiology is Multifactorial. Stress is probably a triggering factor. Stress impairs cellular immunity, decreases immune tolerance and stimulates humoral immunity exposing individuals to autoimmune diseases.[1] About 1% of the world's population is affected by Rheumatoid arthritis, women three times more often than men. The incidence of RA is of 3 cases per 10,000 population per annum. Around 40% of RA patients are registered disabled within 3 years; around 80% are moderately to severely disabled within 20 years; and 25% will require a large joint replacement.[2] In Siddha Sashtric text, “Agathiyar Gandhaga Vallaathi 600” Gendhaga Vallaathi, a herbomineral formulation is mentioned for Rheumatoid arthritis. This review focusses the in-vivo, in-vitro, traditional uses of the 40 ingredients of Gendhaga vallaathi to get better results in Clinical application in managing Rheumatoid arthritis.

**STUDIES ON INGREDIENTS OF GENDHAGA VALLAATHI**

<table>
<thead>
<tr>
<th>Tamil Name</th>
<th>botanical name /Family/parts used</th>
<th>Chemical constituents</th>
<th>Traditional uses</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>serankottai</td>
<td><em>Semecarpus anacardium</em>, Linn. Anacardiaceae -Fruit</td>
<td>Bilawanol, semecarpol, fixed oil, catechol,[3], semecarpus biflavone B, galuflavone, jeediflavonone,[4]</td>
<td>Leprosy, ulcer, hemorrhoids, scabies, arthritic pain.[5]</td>
<td>Hypoglycemic[7], Anticancer[8], Antiinflammatory[9], Neuroprotective[10,11], Antioxidant[12], Antimicrobial[13], Antiatherogenic[14]</td>
</tr>
<tr>
<td>kodivel</td>
<td><em>Plumbago zeylanica</em>, Linn. Plumbaginaceae -Root bark</td>
<td>2 new quinines zeylanone, plumbagic acid, isozeylanone, Plumbagin, b-sitosterol, vanilic acid, Steroidal glycoside[6].</td>
<td>Sinusitis, headache, vaginalcancer, ulcer, dysentry.</td>
<td>Antiinflammatory[15], Antidiabetic[16], Antibacterial[17], Anticancer[18]</td>
</tr>
<tr>
<td>Common Name</td>
<td>Scientific Name</td>
<td>Active Principles</td>
<td>Medical Uses</td>
<td></td>
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<td>------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Kadukkai</td>
<td><em>Terminalia chebula</em>, <em>Retz.</em> Combretaceae - Fruit</td>
<td>Chebulinic acid, chebulagic acid, tannic acid, arachidic acid, linoleic, oleic acid, behenic, palmitic, stearic acid [6]</td>
<td>Ulcer, haemorrhoids, heart diseases, eye diseases, liver diseases, fever, scrotal swelling, leucoderma, Antidiabetic [38]</td>
<td></td>
</tr>
<tr>
<td>Plant Name</td>
<td>Scientific Name</td>
<td>Active Constituents</td>
<td>Medical Applications</td>
<td>Phytochemical Properties</td>
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<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Lavanga-pattai</td>
<td>Cinnamomum verum, Presl Lauraceae Barker</td>
<td>Linalool, benzyl acetate, cinnamic aldehyde, eugenyl acetate, cinnamyl acetate, benzyl benzoate, cinnamaldehyde, eugenol, pinene, cymene, cinnaryl alcohol</td>
<td>Abdominal discomfort, dysentry, ulcer, insect bite, cough.</td>
<td>Antioxidant[^44], Antimicrobial[^45]</td>
</tr>
<tr>
<td>Nelli</td>
<td>Phyllanthus emblica, Linn Euphorbiaceae Fruit</td>
<td>A good source of vitamin C, carotene, nicotinic acid, tannins, riboflavin, myoinositol, polyphenolic compounds, ellagic acid, alkaloids, phyllantidine, indole acetic acid, 4 other auxins[^6]</td>
<td>Liver diseases, eye diseases.</td>
<td>Anticancer[^50], Cardioprotective[^51]</td>
</tr>
<tr>
<td>Omam</td>
<td>Carum copticum Benth &amp; Hook.f Umbelliferae Fruit</td>
<td>Essential oil, thymol[^3]</td>
<td>Cholera, tooth disease, asthma, cough, indigestion.</td>
<td>Antiulcer[^53], Antispasmodic[^54]</td>
</tr>
<tr>
<td>Parangi – pattai</td>
<td>Smilax china, Linn Liliaceae Bark</td>
<td>Fat, sugar, glucoside, colouring matter, saponin, gum, starch[^3]</td>
<td>Skin diseases, arthritic pain.</td>
<td>Antidiabetic[^56], Anti-HIV-1[^57]</td>
</tr>
<tr>
<td>Perumarun -thu</td>
<td>Aristolochia indica, Linn. aristolochiacea root bark</td>
<td>Aristolochic acid, aristololactam, aristolic acid, allantoin, b-sitosterol, b-coumaric acid, glycerides of palmitic, stearic, lignoseric, cerotic, oleic, linoleic acids[^6]</td>
<td>Snake poison, heart disease, anaemia, diarrhoea, fever.</td>
<td>Antimicrobial[^59], Antiimplantation[^60], Abortifacient[^61]</td>
</tr>
<tr>
<td>Area</td>
<td>Species</td>
<td>Description</td>
<td>Medicinal Uses</td>
<td>Other Uses</td>
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<tr>
<td>Sangam</td>
<td><em>Azima tetracantha, Linn</em> Salvadoraceae-Root bark</td>
<td>Piperidine alkaloids, azzcarpine, friedelin, small quantity of carpaine[^4].</td>
<td>Fever, cough, worm infestations, arthritic pain, eczema.</td>
<td>Hepatoprotective Antioxidant[^66]</td>
</tr>
<tr>
<td>Seeragam</td>
<td><em>Cuminum cymturnum, Linn</em> Apiaceae-Seeds</td>
<td>Fatty oil, resins, mucilage, gum, malates, essential oil, cuminol or cumin aldehyde, cymene or cymol, terpenes[^3].</td>
<td>Viral fever, jaundice, leucorrhoea.</td>
<td>Anticancer[^69] Antiasthmatic[^70]</td>
</tr>
<tr>
<td>Chitra-rathai</td>
<td><em>Alpinia galangal (Linn) wild</em> Zingiberaceae-Rhizome</td>
<td>Essential oils, camph eride, galangin, alpinin, ethyl trans-cinnamate, ethyl 14-methoxy-trans-cinnamate[^4,6].</td>
<td>Eczema, head diseases, fever, cough.</td>
<td>Antiallergic[^76] Antibacterial[^77]</td>
</tr>
<tr>
<td>Thaanrik-kaai</td>
<td><em>Terminalia bellerica (Gaertn.)</em> Roxb. Combretaceae</td>
<td>Chebulagic acid, b-sitosterol, ellagic acid, galloyl derivative, tannins, mannitol, rhamnose, glucose[^4,6].</td>
<td>Asthma, sore throat, ulcers, tooth ache, cough.</td>
<td>Antiulcer[^79] Antidiarrhoeal[^80]</td>
</tr>
<tr>
<td>Thippili</td>
<td><em>Piper longum</em> Piperaceae</td>
<td>Piperlongumine, piperlongumine, n-</td>
<td>Cough, leucorrhoea, menorrhagia.</td>
<td>Antiasthmatic[^82]</td>
</tr>
<tr>
<td>Plant</td>
<td>Part</td>
<td>Chemical Constituents</td>
<td>Medical Uses</td>
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<td></td>
<td></td>
<td></td>
<td>Antidiabetic[85] Gastroprotective[86]</td>
<td></td>
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<tr>
<td></td>
<td>-Leaf</td>
<td></td>
<td>Antiinflammatory</td>
<td></td>
</tr>
<tr>
<td>Davasimur-ungai</td>
<td>-Fruits, Root</td>
<td>Luteolin, chrysoeriol, glucosides, isosalipurposide</td>
<td>Sinusitis, cough, rhinorrhoea.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-Root</td>
<td></td>
<td>Antiinflammatory Antiinflammatory[89]</td>
<td></td>
</tr>
<tr>
<td>Kaattumalli</td>
<td>-Fruits, Root</td>
<td>Glycosides kaempferol-3, rutinoside, oleoside, 7-ketologanin, oleuropein, liggrostoside</td>
<td>Diarrhoea, fever, dryness of tongue.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-Root</td>
<td></td>
<td>Antiinflammatory[90]</td>
<td></td>
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<td></td>
<td>-Root</td>
<td></td>
<td>Hepatoprotective Antioxidant[91]</td>
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<tr>
<td></td>
<td>-Root</td>
<td></td>
<td>Hepatoprotective[93] Antidiabetic[94]</td>
<td></td>
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<td></td>
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<td></td>
<td>Gastroprotective[95] Nephroprotective[96]</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Anxiolytic[98] Antithrombotic[99]</td>
<td></td>
</tr>
<tr>
<td>Then</td>
<td>-Fruits, Honey Mel</td>
<td>Fructose, glucose, maltose, sucrose, water, higher sugars, ash, vitamin C, minerals[101]</td>
<td>Asthma, eye diseases, fever, vomiting, eczema, ulcer[102]</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Antiallergic[103]</td>
<td></td>
</tr>
<tr>
<td>korosanam</td>
<td>Purified Ox gall, Fel bovinum purifactum.</td>
<td>Throat diseases, eye diseases, pox diseases,\textsuperscript{[102]} Skin diseases.</td>
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<tr>
<td>Ganthaga-</td>
<td>Sulphur</td>
<td>diarrhea, fever, poisons,\textsuperscript{[102]} Antiallergic,\textsuperscript{[104]} Anticancer,\textsuperscript{[105]}</td>
<td></td>
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</tbody>
</table>

**PHARMACOLOGICAL ACTIVITIES RELATED TO RHEUMATOID ARTHRITIS**

*Semecarpus anacardium* Linn.

**Antiinflammatory activity**

A Chloroform extract of the nut significantly reduced acute carrageenan induced paw oedema in rats and was active against the secondary lesion of adjuvant induced arthritis.\textsuperscript{[19]}

**Antioxidant**

Evaluation of antioxidant effects of *Semecarpus anacardium* Linn. nut extract on the components of Immune system in adjuvant arthritis.\textsuperscript{[20]}

*Plumbago zeylanica*, Linn

**Anti-inflammatory activity**

The root of *Plumbago zeylanica* extracted with methanol was used for determining the anti-inflammatory effects. The methanolic extracts at 300 and 500 mg/kg produced 31.03 and 60.3% inhibition of acute inflammation, respectively in carrageenan induced rat paw edema confirming that *Plumbago zeylanica* roots are effective against acute inflammation.\textsuperscript{[21]}

**Antioxidant activity**

Antioxidant effects of the aqueous alcoholic extracts of root, corresponding to the medicinal preparations, and the active ingredient, *Plumbagin*, were studied by Tilak et al Methods used included: Ferric reducing antioxidant power (FRAP), radical scavenging of 1,1-diphenyl-2-picryl hydrazyl (DPPH) and 2,2’-azobis-3-ethylbenzthiazoline-6-sulfonic acid (ABTS), lipid peroxidation in rat liver mitochondria induced by different agents and estimating phenolic and flavonoid content. In FRAP/DPPH assays, boiled ethanolic extracts was the most effective while in ABTS assays, boiled aqueous extract was the most efficient. These extracts also significantly inhibited lipid peroxidation induced by cumene hydroperoxide, ascorbate – Fe$^{2+}$ and peroxynitrite and contained high amounts of polyphenols and flavonoids.\textsuperscript{[22]}
**Aristolochia bracteolate, Retz.**

**Antiinflammatory**
The ethanolic extract of the shade dried leaves of Aristolochia bracteolate was evaluated anti-inflammatory activities in wistar rats by using the carrageenan induced left hindpaw edema method.\[27\]

**Antiarthritic activity**
Antiarthritic activity was demonstrated using Freund’s complete adjuvant in rats. Treatment of FCA induced rats with Aristolochia bracteolata extracts shown (P<0.05) increase in pain threshold, weight bearing ability, ambulation and also decline in scratching, defecation, urination, were observed as a sign of improvement in behavioural pattern.\[28\]

**Zingiber officinale, Roscoe**

**Antiinflammatory**: The crude extract of zingiber officinale was able to reduce rat paw and skin edema induced by carrageenan, 48/80 compound and serotonin. The antiedematogenic activity seems to be related atleast partially to an antagonism of the serotonin receptor.\[32\]

**Analgesic, antipyretic**: An ethanolic extract of the rhizomes of zingiber officinalebwas investigated for anti-inflammatory, analgesic, antipyretic, antimicrobial, hypoglycaemic activities.\[31\]

**Clerodendrum inerme, Gaertn**

**Antioxidant**: The active isolate jinoside D were fond to possess significant antioxiadant activity.\[36\]

**Antiinflammatory**: The flavonoid glycosides in it showed modulation in calcium transport in rat liver and there by showed reduction in inflammation.\[37\]

**Terminalia chebula, Retz**

**Immunomodulatory**: Vaibhav aher, et al studied the immunomodulatory activity of alcohol extracts of terminalia xhebula.\[40\]

**Carissa carandus, Linn**

**Analgesic, anti-inflammatory, antipyretic**
The ethanolic and aqueous extracts from roots of Carissa carandas exhibited significant analgesic activity at the dose of 100mg/kg body weight. It also found to reduce significantly
the formation of edema induced by carrageenan after 2 hrs. It also showed significantly competent on yeast induced hyperpyrexia in rats after 2 hrs.\textsuperscript{41}

\textit{Costus speciosus, Sm}

\textbf{Antiinflammatory, Analgesic, Antipyretic activities}

The anti-inflammatory activity of methanol extracts of species (400&800 mg/kg,p.o.) was evaluated using carrageenan induced paw edema test. Analgesic effects was evaluated using acetic-acid induced writhing & Eddy's Hot plate models and anti-pyretic activity was assessed by Brewer's yeast induced pyrexia in rats.\textsuperscript{43}

\textit{Cinnamomum verum, Pers}

\textbf{Antiinflammatoyr, Antiarthritic activity}

Type –A procyanidine polyphenols (TAPP) showed significant anti-inflammatory effect at dose of 4,8,25 mg/kg ,p.o but not at 2mg/kg,p.o dose in Carrageenan induced rat paw edema model. The dose of 8mg/kg ,p.o was selected for the evaluation of anti-arthritic activity in AIA model. TAPP (8mg/kg,p.o.daily from day 12 to day-21) treatment in established arthritic rats showed significant reversal of changes induced in AIA with respect to body weight drop, ankle diameter, arthritic score, serum C-reactive protein levels.\textsuperscript{46}

\textit{Toddalia asiatica, Linn}

\textbf{Antiinflammatory & Analgesic activities}

The administration of alkaloids of Toddalia asiatica had function of inhibiting the auricle swelling caused by Xylol and joint swelling caused by agar and leukocytes migration caused by CMC-Na decreasing the body distortion of the rats. Toddalia asiatica has anti-inflammatory and analgesic effects and there is no injury to the liver after long administration in rats.\textsuperscript{48}

\textit{Piper nigrum, Linn}

\textbf{Antiinflammatory activity}

The extracts of piper nigrum had the inhibitory effects on cyclooxygenase enzyme thus reduces the inflammation.\textsuperscript{49}

\textit{Phyllanthus emblica, Linn}

\textbf{Antioxidant Activity}

Prakash D, et al have showed the wild edible fruits of phyllanthus emblica for antioxidant effects.\textsuperscript{52}
Carum copticum, Benth Hook
Antioxidant Activity
The methanol fraction showed highest antioxidant activity by phosphomolybdenum (2087.7 micromol) and DPPH assay (90.2%) followed by other fractions comparable to ascorbic acid and BHT. The methanolic fraction showed no sign of mutagenicity at tested concentrations (25-100 microg/plate) [55]

Smilax china, Linn
Antiinflammatory and Analgesic Activities
The aqueous extract of tuber of Smilax china L, was tested for its anti-inflammatory activities in rats by egg-albumin induced edema and antinociceptive effects in mice using hot plate test and acetic-acid induced abdominal constriction test respectively. The aqueous extract in dose of 1000mg/kg (i.g.) had a significant antinociceptive and anti-inflammatory effect compared to physiological saline. [58]

Streblus asper, Linn
Anti-inflammatory Activity
The Streblus asper leaf ethanolic (SAE) extract at all given doses caused a significant dose-dependent inhibition of edema (p<0.05). The significant and dose dependent LPS-induced cyclooxygenase (COX)-2 and inducible nitric oxide synthase (iNOS) mRNA expression were demonstrated in RAW 264.7 cells treated with SAE. The inhibition is selective, since COX-1 mRNA expressions did not change in presence of SAE. [64]

Myristica fragrans Houtt, Arillus
Anti-inflammatory Activity
The methanol extracts (1.5g/kg) ether fraction (0.98g/kg), n-hexane fraction (0.5g/kg), Fr-I(0.19g/kg) and Fr-VI (0.17g/kg) showed a lasting anti-inflammatory activity and potencies of the fraction were approximately the same as that of Indomethacin (10mg/kg) Fr-VI was determined to be Myristicin. [65]

Cuminum cyminum, Linn
Anti-osteoporotic
In animals receiving a methanolic extract of cuminum cyminum, significant reduction in urinary calcium excretion and augmentation of calcium content and mechanical strength of bones was found. [71]
Immunomodulatory Activity
Oral treatment with cumin showed immunomodulatory properties in normal and immune suppressed animals via modulation of T lymphocytes expression in a dose dependent manner. It stimulated the T cells (CD4, CD8) and Th1 cytokines expression in normal and cyclosporine A induced immune suppressed mice.[72]

Michelia champaca, Linn
Antiinflammatory activity
Michelia champaca showed significant stabilizing activity of 57.4% at concentration of 300 microg/ml. The percentage membrane stability exhibited by extract was concentration dependent. It concluded that the methanolic extract of Michelia champaca possess significant invitro antiinflammatory activity.[75]

Alpinia galangal
Antiinflammatory and Analgesic activities
Antiinflammatory and analgesic effects of Alpinia galangal in a variety of rheumatological conditions have been studied by several authors. YU, et al isolated p-coumaryl alcohol-0-methyl ether (CAME) having phenylpropanoid structure, which selectively and substantially suppressed IFN gamma production in CD4 and Th cells.[78]

Terminalia belerica, Roxb
Analgesic
The crude extracts of terminalia bellerica dose-dependently (50-100mg/kg) reduced the numbers of acetic acid mediated in mice.[81]

Piper longum, Linn
Antiinflammatory activity
The fruit decoction showed anti-inflammatory activity against carrageenan induced rat paw edema.[84]

Cinnamomum tamala, Fr.Nees
Antiinflammatory, Analgesic, Antipyretic
The methanolic extracts of Cinnamomum tamala leaves showed significant analgesic activity (p<0.05) which was evaluated in mice by Hot plate method, acetic acid induced writhing movement and tail flick test. Also anti-inflammatory activity in Swiss albino mice by carrageenan and antipyretic activity by brewer’s yeast.[87]
**Jasminum angustifolium, Vahl**

**Antiinflammatory and Analgesic**

The aqueous extract of Jasminum angustifolium Linn. by oral administration at dose of 500mg/kg/day of body weight to healthy albino rats and mice showed a greater anti-inflammatory and analgesic effect by carrageenan induced hind paw edema in rats and analgesic by Eddy’s Hot plate method.\(^{[90]}\)

**Sphaeranthus indicus, Linn**

**Immunomodulatory**

Administration of methanol extract in fraction (100 and 200mg/kg,p.o.) showed immunostimulating activity by increasing the phagocytic activity,hemagglutination antibody titre and delayed type hypersensitivity in cyclophosphamide induced myelosuppression in mice.\(^{[92]}\)

**Nigella sativa, Linn**

**Antiinflammatory and Analgesic**

The analgesic and anti-inflammatory effects of polyphenols from seeds were studied in mice and rats using the acetic-acid induced writhing, formalin light tail flick, carrageenan induced paw edema and croton oil induced ear edema in rats. These results suggests that NS polyphenols have potent analgesic and anti-inflammatory effects.\(^{[97]}\)

**Withania somnifera, Dunal**

**Antiinflammatory**

Administration of Withania somnifera root powder (600mg/kg) to the arthritic rats significantly decreased the severity of arthritis by effectively suppressing the symptoms of arthritis and improving the functional recovery of motor activity and radiological survey.\(^{[100]}\)

**Sulphur**

**Antiinflammatory**

Anti - inflammatory activity of sulphur containing phenolic Antioxidants in vivo is mediated by their effect on Redox-Sensitive Transcription Factors.\(^{[106]}\)

Oxidative Stress, Haemoglobin content, Superoxide Dismutase and Catalase activity influenced by Sulphur baths and Mud packs in patients with Osteoarthritis.\(^{[107]}\)
CONCLUSION
This review especially exposes that ingredients of Gendhaga Vallaathi have anti-inflammatory, analgesic, antipyretic, antioxidant and immunomodulatory activity. These pharmacological activities contribute mainly in the treatment of Rheumatoid arthritis.

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