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S.A. Razzaq [1],
BSC, MSc, lecturer of the Pharmacology and toxicology Department at the College of Pharmacy
N.A. Nasir [2],
DDS, MSc, assistance lecturer of the Clinical sciences Department at the College of Dentistry
K.A. Al-Salihi [2],
BVD, MSc, PhD, professor of the Basic science Department at the College of Dentistry, head of scientific and ethical committee

[1] Al-Muthanna University, 87QQ+3VG, Samawah, Iraq
[2] Al-Iraqia University, 9985+CRP, Baghdad, Iraq

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Extraction and evaluation of eugenol from *Syzgium aromaticum* as topical anesthetic for toothaches

Abstract. Objective — this study intends to extract and identify the eugenol from *Syzgium aromaticum* and evaluate its analgesic effects in laboratory animals and clinically in volunteer patients suffering from toothaches. **Materials and methods.** Direct stem distillation was used to extract eugenol from cloves, followed by chemical extractions. The extracted products were identified by thin-layer chromatography (TLC) and ^{1}H NMR spectroscopy, and tested clinically in 51 volunteer patients suffered from acute toothache. Those patients was divided into 3 equal groups: patients of the first (control) group (G1) was given the hydroxypropyl methylcellulose (HPMC) gel mixed with distilled water — placebo; patients of the second group (G2) received the prepared clove gel — eugenol previously extracted (2% in HPMC); patients of the third group (G3) received commercial "Orajel" containing benzocaine 10%. The patients were advised to apply a small amount of gel the size of a chickpea into the tooth cavity or the toothache area. **Results.** Eugenol was extracted as bright yellow oil (about 2.02 g, 5% recovery) with a solid particular clove smell from the clove. TLC revealed various Rf value spots ranging between 0.6 and 0.9. The ^{1}H NMR spectroscopy showed various analysis data, including 3.28—3.32 (3H), 5.5 (1H, C=C—H), 5.9 (aromatic 2H), and 6.6 (aromatics). All patients in G1 exhibited continuous toothache pain. In contrast, within G2 and G3, 14 (82%) and 15 (88%) of subjects, respectively, reported a reduction in toothache intensity within a 5-minute timeframe. The majority of patients in both G2 and G3, 13 (76%) and 12 (71%) patients, respectively, experienced a duration of pain relief of 72 hours. **Conclusion.** Clove-extracted products are as effective as benzocaine when used as intraoral topical anesthesia. The authors recommend future studies to investigate the analgesic effects mechanism of clove extract.

Key words: clove, eugenol, *Syzgium aromaticum*, toothaches, topical

С.А. Раззак [1],
преподаватель кафедры фармакологии и токсикологии Колледжа фармацевтики
Н.А. Насир [2],
доктор стоматологии, доцент кафедры клинической стоматологии
К.А. Аль-Салихи [2],
доктор наук, профессор кафедры фундаментальных наук Колледжа стоматологии, председатель научно-этического комитета

[1] Университет Аль-Мутанна, 87QQ+3VG, Эс-Самава, Ирак
[2] Иракский университет, 9985+CRP, Багдад, Ирак

ДЛЯ ЦИТИРОВАНИЯ:
Раззак С.А., Насир Н.А., Аль-Салихи К.А. Извлечение и оценка эвгенола из *Syzygium aromatum* в качестве местного анестетика при зубной боли. — *Клиническая стоматология*. — 2025; 28 (1): 92—97.
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Извлечение и оценка эвгенола из *Syzygium aromatum* в качестве местного анестетика при зубной боли

Аннотация. Цель — извлечение и идентификация эвгенола из *Syzgium aromatum* и оценка его анальгетического действия на лабораторных животных и клинически на пациентах-добровольцах, страдающих зубной болью. **Материалы и методы.** Для получения эвгенола из гвоздики использовали прямую перегонку стебля с последующей химической экстракцией. Извлеченные продукты были идентифицированы с помощью тонкослойной хроматографии (ТСХ) и ЯМР-спектроскопии и протестированы клинически на 51 пациенте-добровольце с острой зубной болью. Пациенты были разделены на 3 равные группы: в I (контрольной) применяли водный гель гидроксиметилцеллюлозы (плацебо); во II — полученный эвгенол (2% в геле гидроксиметилцеллюлозы); в III пользовались 10%-ным бензокаиновым гелем Orajel. **Результаты.** Эвгенол был извлечен из гвоздики в виде ярко-желтого масла (около 2,02 г, выход 5%) с твердым специфическим запахом гвоздики. ТСХ выявила различные пятна со значением Rf в диапазоне от 0,6 до 0,9. ЯМР-спектроскопия показала различные пики, включая 3,28—3,32 (3H), 5,5 (1H, C=C—H), 5,9 (ароматический 2H) и 6,6 (ароматическое кольцо). У всех пациентов I группы наблюдалась постоянная зубная боль. Напротив, во II и III группе 14 (82%) и 15 (88%) субъектов соответственно сообщили об уменьшении интенсивности зубной боли в течение 5 минут. У большинства пациентов как во II, так и в III группе, 13 (76%) и 12 (71%) человек соответственно, облегчения боли продолжалось в течение 72 ч. **Заключение.** Продукты, извлеченные из гвоздики, так же эффективны, как бензокаин, при использовании в качестве интраоральной местной анестезии. Авторы рекомендуют провести будущие исследования для изучения механизма анальгетического действия экстракта.

Ключевые слова: гвоздика, эвгенол, *Syzygium aromatum*, зубная боль, местное применение

INTRODUCTION

Syzygium aromaticum (syn. Eugenia caryophyllata) comes from the Greek word "*κἄρῠόφῠλλον*" and is called as Clove in English language, and Qaranful in Arabic language. Clove is imported from Amboina, Honimoa, Moussalaut, and Celebes to India. Then, a native Indian doctor used Clove as an aromatic. Consequently, many western parts of the Archipelago of India were cultivated clove. Al-Kindi was the first pioneer to use the Clove in a nosh-dārû electuary, in a dentifrice to treat rotting teeth and bad breath, in a collyrium, as a drug to strengthen breathing, and in stomachics. In Iraq and Iran, for centuries, clove has been used as a carminative and stimulant to relieve irritation of the throat, while its oil is used to relieve headache and toothache. Moreover, clove is imported from Molucca and Sumatra in Egypt and is also used as carminative and aromatic.

Eugenia caryophyllata is traditionally called clove herb. It is classified within the Myrtaceae family — the dried flower of Clove known for its wealthy components, such as potent antimicrobials and antioxidants [1]. Clove essential oil (CEO) mainly comprises phenylpropanoids called eugenol derivatives and low humulene and caryophyllene chemical constituents. Many scientists worldwide reported that CEO's biological constituents have antioxidant, antibacterial, antifungal, antiseptic, pesticide, analgesic, and anticarcinogenic activity [2]. Consequently, CEO is used in food [3], biomedical [4], packaging, sanitary, cosmetic, and pharmaceutical industries [5]. A low CEO concentration is accepted as a secure anesthetic in vertebrates [6], and invertebrates. Clove oil has shown a potential effects for treating vaginal candidiasis and neuropathic pain. The FDA considers Clove oil safe (GRAS) in food additives and dental cement. The synthesis of prostaglandins is assumed to be inhibited by clove oil, which lowers painful symptoms [7].

Traditionally, cloves are used as seasoning in cooking. On the other hand, it is a topical remedy for treating toothache as it contains eugenol. This oil liquid is used in dentistry for analgesic and antiseptic properties. The effects of eugenol, iso-eugenol, and vanillin have been approved by some researchers. In India, Clove has a multi-medical purpose. It is used to manage blood disorders, thirst, vomiting, pain, hiccups, and abdominal distension. It has also been used to beat toothache and tooth-related troubles for more than a decade by most Indian families [8].

Dental pain occurs around a tooth and is caused by abscesses of the tooth, tooth fractures, tooth decay, damaged filling, and repetitive motion, like grinding teeth and chewing gum. Tooth pain can be a constant or sharp pain, and it is sometimes very confusing to recognize if it comes from the lower or upper jaw or if it even feels like it originates from the ear. The most common type of toothache is severe orofacial pain, referred to as a dental emergency. The tooth is built of outer hard calcified tissues (enamel layer followed by dentin and cementum) and the inner soft tissue core (the pulp system). The typical sensation exhibited by gum and teeth is sharp and lasting as long as the stimulus. There is a distinction between normal physiological sensation and pain in disease. Pain is defined as unpleasant emotional and sensory experiences originating from peripheral stimuli and continuing physiological processes resulting in pain perception. The odontogenic pain or toothache is a compound mechanism comprising numerous pathways that lead to the sensation of pain [9]. In the case of toothache, the brain and spinal cord receive signals from destructive stimuli. These stimuli include thermal, mechanical, and chemical, which deal with dental pulp and periodontal pain. In the case of dental caries, inflammatory mediators such as prostaglandins, bradykinin, and cytokines are released, amplifying the pain response by sensitizing nociceptors and lowering their activation. However, in the case of dental pulp and dentine sensitivity, the hypodynamic theory is more accepted, which is based on changes in fluid flow in dentinal tubules due to external stimuli and leading to activation of dental pulp nerve ending and starting pain [10]. Pulpal inflammation (pulpitis), neurogenic inflammation, periodontal ligament and surrounding tissue (tension, pressure, and inflammation), and central sensitization are all stimulate toothache. The pain mechanism is transmitted via myelinated and unmyelinated cranial nerve fibers of the trigeminal nerve [10].

The major constituent of clove essential oil is eugenol, a phenylpropanoid officially derived from guaiacol through an allyl chain substituted para to the hydroxy group. Its molecular formula is $C_{10}H_{12}O_2$ (fig. 1) [11].

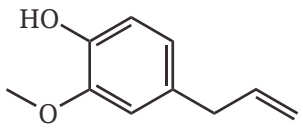

Fig. 1. Chemical structure of eugenol

Clove oil offers the greatest value for toothaches because it has natural analgesic, antiseptic, and antibacterial properties. Consequently, it was used in the preparation of some toothpaste and a local anesthesia, the Clovacaine solution, applied for oral ulceration and inflammation.

A literature review revealed no publications regarding the investigation of clove (Syzgium aromaticum) as an anesthetic agent in Iraq. The null hypothesis in this study is the clove extracted eugenol has no significant effect compared to benzocaine the standard anesthetics in offering local anesthesia. Therefore, the purpose of this study was to extract and identify eugenol from Syzgium aromaticum and evaluate its effectiveness as topical anesthetic for ameliorating toothaches.

MATERIALS AND METHODS

All methods were done according to the Helsinki Declaration and later amendments for human research. Before attending this study, the patients received complete information about the type and aims of the research and henceforth signed an informed consent form. This study has been approved by the ethical and research committee (ESA & HER-04-29-074-24).

Preparation and extraction of active clove substance (Eugenol)

Cloves were purchased from an herbal shop in Al-Shorja marketing area (a famous local market in the heart of Baghdad city). The purchased clove was a dried flowering bud. Initially, the dried clove was selected and washed with water to remove unwanted particles such as dust. Then, they ground to fine powder with a Cardamom grain grinder to increase the Extraction of clove active ingredients. Then, clove powder was kept in sterile plastic bags and stored at 2—8°C until further processing.

The extraction and identification of eugenol from clove were done according to the method described previously by DeFrancesco (2021) [11]. The extraction procedure started by placing 40 grams of clove fine powder in a 1000 ml round bottom volumetric flask containing 600 ml of distilled water and connected to the distillation apparatus. Then, the flask was distilled intensely by Bunsen burner until 300 ml of yellow oily solution (S1) was accumulated. Subsequently, a chain of chemical extraction was done. The S1 was kept in a separating funnel, and 50 ml of dichloromethane was added and stirred well in a magnetic stirrer to prepare solution 2 (S2). Then, S2 was allowed to settle, and two different layers formed. The organic lower layer (OLL) was colorless, while the cloudy upper layer (CUL) was aqueous. The OLL was transferred into a 500 ml conical volumetric flask. Then, 50 ml of dichloromethane was added to S1 and shaken well. Again, two layers appeared, and the oil was collected and placed into the same volumetric flask with the previously collected organic layer. At the same time, the CUL was kept in another 500 ml volumetric flask. Afterward, the OLL was transferred into a clean separating funnel, and 40 ml of 10% NaOH solution was added to separate the eugenol acetate; then, to collect all probable eugenol acetate, more than 40 ml of 10% sodium hydroxide was added.

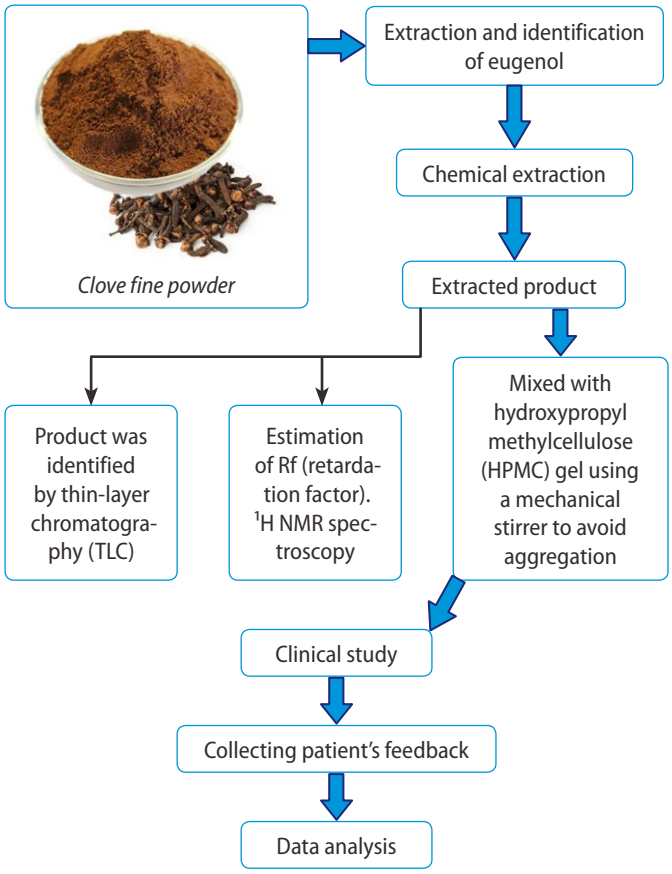

Fig. 2. Preparation and extraction procedures and clinical study

The CUL or aqueous layer kept in a volumetric flask was acidified to a *p*H of less than 2 by adding concentrated HCl. The *p*H was estimated using blue litmus paper; it turned red if the solution was adequately acidified. The aqueous layer was washed with sodium half-saturated chloride solution. Finally, 50 ml dichloromethane was added to the collected OLL, and the solution was dried with magnesium sulfate and filtrated over a filter paper. The solvent was evaporated at 60°C using a rotary evaporator to leave light yellow oil, pure eugenol.

The oil solution smelled solid and spicy.

The collected product was identified by thin-layer chromatography (TLC) using dichloromethane as an elution solvent. The Rf (retardation factor) value was estimated between 0.6 and 0.9. ^{1}H NMR spectroscopy was also used to characterize the extracted eugenol at room temperature in the absence of light; it was prepared in $CDCl_3$ according to the method described by [12].

Clinical evaluation of clove oil extract anesthetic effects topically in volunteers with toothache

Fifty-one volunteer patients participated in this study during the period extended from April 2020 to December 2020 and precisely during the COVID-19. Those patients suffered from acute toothache and could not reach the dentist's clinic because COVID-19 lockdown.

1) 17 patients of the first (control) group (G1) was given the hydroxypropyl methylcellulose (HPMC) gel mixed with distilled water — placebo;
2) 17 patients of the second group (G2) received the prepared clove gel — 2% received eugenol extracted oil prepared previously was added slowly to the HPMC gel and mixed by a mechanical stirrer to avoid aggregation;
3) 17 patients of the third group (G3) received commercial "Orajel" containing benzocaine 10% (weight).The patients were advised to apply a small amount of gel the size of a chickpea into the tooth cavity or the toothache area.

All information regarding the eugenol-extracted oil was explained to each patient, and all patients signed the consent form while receiving the tested material. The test materials were given to the patients in gel form.

The patients were instructed to rate their pain and send feedback according to modified McGill Pain Questionnaire (MPQ) [13]. Patients' feedback was collected and recorded regarding their experience in applying treated gel and reducing the toothache pain or pain near the tooth where they require a filling. Data were presented as a mean and percentages.

Preparation and extraction procedures and clinical study are shown in fig. 2.

RESULTS

The clove extraction procedure was done ordinarily as the designed plan of the experiment with no unpredicted physical losses. About (2.02 g, 5% recovery) eugenol was extracted as bright yellow oil with a solid particular clove smell from 40 g of clove. The result of TLC revealed various Rf value spots ranging between 0.6 and 0.9. The ^{1}H NMR spectroscopy prepared in $CDCl_3$ showed various analysis data, including: 3.28–3.32 ppm (3H), 5.5 ppm (1H and C=C–H), 5.9 ppm and 6.6 ppm (aromatic H; table 1).

Table 1. Analysis of ^{1}H NMR data for eugenol

No	Peak at PPM	Analysis of data
1	3.28–3.32	CH–O (ether)
2	5.5	C=C–H
3	5.9	Aromatic H
4	6.6–6.9	Aromatic H
5	6.95	$CDCl_3$

All recordings of the clinical study were done according to plan. In total, 255 records were recorded by 51 volunteer participants. Each participant gave 5 feedbacks for the tested agents, including the duration of reduction of toothache pain, and the lasting duration time after application. The feedbacks of patients in control group that received the gel with placebo were no relieving of pain. While, the percentages of G2 (received 2% eugenol extracted oil) and G3 (received benzocaine 10% gel) were 82% and 88% patients relieving of pain at 5 minutes (table 2).

The participants also gave feedback regarding the duration of time spent reducing toothache pain in treatment groups. The percentage of G1 was zero, while the percentages of lasting duration for G2 and G3 were 13 (76%.), 2 (12%), 1 (6%) 2 (12%), and 12 (71%), 3 (17%), 1 (6%), and 1 (6%) for 72, 24, 12, and 6 hours respectively (table 3).

in the clove-dried flowering bud at a concentration of 5% recovery (2.02 g from 40 g) of clove. Likewise, the extracted product was bright yellow oil with a clove's smell. These results are compatible with previously published research by Bisergaeva et al. (2021) [12], who found that eugenol was extracted as a light yellow oil with a strong smell of clove [16].

Both TLC and ^{1}H NMR were used in this study to identify the extracted product. The results of the current study showed that Rf value spots ranged between 0.6 to 0.9. In contrast, ^{1}H NMR spectroscopy results showed various peak at part per million, which included 3.28–3.32 (3H), 5.5 (1H, C=C–H), 5.9 Aromatic (2H), and 6.6 aromatic. These results of identification of the extracted product agree with previously reported studies [11, 12, 17, 18].

Fabry et al., (2024) prepared three essential oil from cloves; the isoeugenol was found in 2 samples and detected by 1H NMR spectrometry. Moreover, they confirmed that using steam distillation in extraction led to sharper

Table 2. Time to onset of toothache relief in treatment groups

Time (minutes)	Group 1 (placebo, *n*=17)		Group 2 (eugenol extracted oil, *n*=17)		Group 3 (benzocaine 10%, *n*=17)	
	abs.	%	abs.	%	abs.	%
5	0	0	14	82	15	88
10	0	0	1	6	2	12
15	0	0	1	6	0	0
20	0	0	1	6	0	0

Table 3. Duration of pain reduction for toothache in the treatment groups

Duration (hours)	Group 1 (placebo, *n*=17)		Group 2 (eugenol extracted oil, *n*=17)		Group 3 (benzocaine 10%, *n*=17)	
	abs.	%	abs.	%	abs.	%
72	0	0	13	76	12	71
24	0	0	2	12	3	17
12	0	0	1	6	1	6
6	0	0	1	6	1	6

DISCUSSION

Due to its medicinal properties, such as antioxidants, antibacterial, and analgesic, clove has been used for centuries. Additionally, it is also used as a seasoning and food preservative. Likewise, many publications confirmed various properties of clove, such as antiviral, antibacterial, and antifungal [14]. It is also attracted researchers as a potent antioxidant activity among the other spices [15].

Clove is the primary vegetable source of phenolic compounds, and eugenol is the main bioactive component with a concentration ranging from 9.381 to 14.650 g per 100 g of fresh clove material. Clove flower buds contain up to 18% of essential oil, approximately 89% is eugenol, and 5% to 15% is eugenol acetate and ß-caryophyllene. At the same time, the concentration of α-humulene is 2.1% [16]. The results of the extraction experiment of clove components by steam distillation revealed the existence of eugenol and obviously recognizable signals of isoeugenol, contrary to the spectrum of solvent extraction. They also mentioned that increasing stem distillation led to increasing concentration, and these observations are compatible with the steam distillation that used in current study for extraction of eugenol from clove [18].

In the current study, the topical anesthetic effect of clove oil extract was evaluated clinically in volunteers suffering from toothache. The results of the current study reported five feedbacks for each participant. All G1 reported negative feedback, and they said that the toothache was continuous and not relieved by using locally tested medication. However, 14 (82%) and 15 (88%) participants in G2 and G3 experienced almost immediate pain relief for toothaches. At the same time, 13 (76%) and 12 (71%) patients reported 72 hours of pain-free lasting in G2 and G3, respectively. These results revealed the capability of both clove-extracted

essential oil and Benzocaine 10% to reduce toothache in volunteers compared with G1 with placebo during the COVID-19 lockdown and block the dentist service. However, no difference was seen in the pain reduction between G2 and G3.

In this study, all volunteer participants were suffering from severe pain, and they were very willing to participate in this study and get medication to resolve their toothache pain because absence of dentistry serving during COVID-19 lockdown. In the current randomized study, the results showed that the topical application of anesthetics on the buccal fold at the pain area led to relief it. These results are compatible with previously studies that clinically evaluated the topical anesthetics agents [19—21]. Additionally, Alqareer et al. (2006) mentioned the relief of toothache by application of topical anesthesia such as the home made clove gel and benzocaine 20% gels. They concluded that both agents were capable of diminishing pain associated with needle sticks compared with a placebo [19]. Aoshima and Hamamoto (1999) approved that eugenol was repressed and potentiated *N*-methyl-*D*-aspartate (NMDA) and ionotropic *γ*-aminobutyric acid (GABAA) receptors respectively [22]. They also explained that eugenol depressed both A and C fibers, compounding action potentials that are important in its analgesic effects. Moreover, Yang et al. (2003) approved that the chemical structure of eugenol is similar to capsaicin, and its influence on a vanilloid receptor should be considered [23]. Other researchers also approved that eugenol inhibits Na^+ current in rat dorsal root ganglion neurons [24].

In the current study, no participant was claimed to develop ulcers or side effects from using tested agents. However, according to previous studies, all anesthetic drugs have toxicity and side effects even if applied locally. For example, some researchers reported that benzocaine causes methemoglobinemia in some endoscopy cases when used in large amounts [24]. These results encouraged the researcher to look for another topical anesthesia, such as clove extracts or eugenol.

The topical intraoral application of eugenol in low concentration led to noticeable plasma concentration, which is related to the absorption of local anesthesia and leads to limiting the dose of injected anesthesia, especially in pediatric patients [19, 20]. Despite Syzgium aromaticum or clove being widely used as a spice and being found to have broad applications in alternative medicine in various countries around the world, its application at high doses may elicit adverse reactions. Some research mentioned that the extract influenced the reproductive indices in animal studies [25]. Other reports mentioned that the application of eugenol in therapeutic doses was neither implicated in causing serum enzyme elevations nor causing clinically apparent liver injury. Albeit, other publications mentioned that severe live injury occurs with ingestion of high doses (overdose) [26]. Additionally, Alqareer et al. (2006) mentioned that 4 participants (5.4%) of their study developed small ulcers with high concentrations of eugenol. However, they also recommended future studies to evaluate the side effects of the optimal low concentration [19].

A literature review showed that clove general effects possess antiplatelet activity, inhibiting lipid peroxidation. Furthermore, researchers approved that smoked clove in cigarettes or injected intravenously can cause severe pulmonary edema, and this was not reported during topical application. However, this issue needs further investigation [26].

CONCLUSION

This study revealed that clove gel was as effective as benzocaine when used as intraoral topical anesthesia. Both experimental animal and human studies approved the analgesic effects of clove oil extract or eugenol. This suggests that dentists could consider clove extract as an effective, cheaper substitute for benzocaine in dental practice. Also, applying clove extract locally could limit the dose of injected anesthesia. The authors recommend more future studies to investigate the exact mechanism of the analgesic effects of clove extract.

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