Effect of Theobromine from *Theobroma cacao* L. on Cervical Cancer Treatment

Budi Santoso[1,2], *Josephine Eugenia* Wirianata[1,3], *Maria Louise Ulina* Dimu[1,4], *Rhiana Abigail* Katu[1,4], *Willyanto* Anggono[1,5], and *Edwin* Setiawan[6*]

[1]Center for Sustainable and Innovation Product Development, Petra Christian University, Surabaya, East Java, Indonesia
[2]SMA Negeri 1 Lumbang Pasuruan, East Jawa, Indonesia
[3]SMA Swasta Kristen Waikabubak, West Sumba, Indonesia
[4]SMA Negeri 1 Waikabubak, West Sumba, Indonesia
[5]Mechanical Engineering Department, Petra Christian University, Surabaya, East Java, Indonesia
[6]Biology Department, Institut Teknologi Sepuluh Nopember, East Java, Indonesia

Abstract. *Theobroma cacao* L. (Forastero variety) is a tropical plant widely cultivated in the Sumba region, Indonesia. Cacao beans contain theobromine, which has notable therapeutic potential. This study investigated the potential of cacao beans as a treatment for cervical cancer. Using a quantitative method, cacao beans were processed into three different formulations (F1, F2, and F3) and evaluated through an organoleptic test to determine the most preferred formulation. F3 was the most approved formulation in terms of aroma, color, texture, and taste. The 20 respondents did not experience any adverse side effects within 24 h of consumption. A clinical trial was conducted on F3 involving patients with early stage cervical cancer. Over 14 days, the patients showed improvements, including reduced vaginal discharge, bleeding, and pelvic pain. Laboratory results indicated an increase in hemoglobin from an average of 11.0 to 12.0 g/dL. Hematocrit also increased from 35.67% to 36.10%, and erythrocyte counts improved from 4.27 to 4.73 µL. Meanwhile, the neutrophil count decreased from an average of 67.5% to 63.25%, and the basophil count decreased from 0.95% to 0.65%. The anthocyanin reaction time increased from an average of 4.6 to 10.3 s, indicating reduced oxidative activity. These findings suggest that cacao beans have anticancer effects.

1 Introduction

Theobroma cacao L., or the cacao plant, is a small evergreen tree of the Malvaceae family. It thrives in tropical climates with 70-100% humidity, temperatures between 25-30°C, consistent rainfall, and fertile, well-drained soil. [1]. Cacao beans have attracted scientific attention because of their antioxidant, anti-inflammatory, and anticancer properties [2]. The bioactive compounds found in cacao beans are theobromine, flavonoids, and phenolic

*Corresponding author: edwin.setiawan@its.ac.id

compounds, which contribute to the prevention of various diseases [3]. Recently, global efforts have increased to integrate environmental sustainability into biomedical innovations.

Therefore, this study aimed to develop a *T. cacao* L. herbal-based beverage for cancer therapy, specifically for cervical cancer, which is the second most common malignancy among women and is primarily caused by Human Papillomavirus types 16 and 18. According to the World Health Organization, approximately 660,000 new cases and 350,000 deaths from cervical cancer were reported worldwide in 2022 [4]. In West Sumba Regency, East Nusa Tenggara Province, according to the Rumah Sakit Umum Daerah, 77 cases were reported from 2022 to the first semester of 2025. Currently, conventional chemotherapeutic drugs often generate chemical waste; if released untreated into wastewater or landfills, they can contaminate water sources, soil, and aquatic ecosystems, leading to bioaccumulation and long-term toxic effects. These drugs can harm aquatic organisms, disrupt biodiversity, and pose health risks if they contaminate drinking water and agricultural products, exposing people to carcinogens and mutagens [5]. Chemotherapy drugs may prolong a patient's survival, but they often cause severe side effects, including therapy resistance, cancer relapse, and recurrence [6, 7].

Theobromine, a caffeine analog (3,7-dimethylxanthine), is found abundantly in Forastero cacao beans at approximately 13.83 mg/g [8, 9]. Theobromine has demonstrated strong cytotoxic effects against cervical cancer cells by inhibiting cell migration, invasion, and proliferation by 70–80% without harming the healthy cells. These results suggest that theobromine can suppress tumor aggressiveness. [10]. Molecular analyses revealed that theobromine downregulated key oncogenic and stemness-related genes in cervical cancer, including HIF-1α, VEGF, CD24, and Bcl-2, and reduced the expression of the stem cell marker ALDH1A1 [11]. These findings indicate that theobromine interferes with hypoxic adaptation, angiogenesis, and the maintenance of cancer stem cells. Furthermore, it induces both apoptotic and ferroptotic cell death [12, 13]. Hence, this study provides a foundation for further exploration of the bioactive potential of cacao and contributes to sustainable utilization and eco-friendly alternative resources in cancer-related applications.

2 Experimental Method

This study used a quantitative experimental method to evaluate the therapeutic effect of *Theobroma cacao* L. (Forastero variety) herbal beverage containing theobromine as a conventional treatment for cervical cancer. All experimental procedures were conducted at the Lingkungan Hidup Agency laboratory and Rumah Sakit Umum Daerah of Waikabubak, West Sumba Regency, Indonesia with official permitted research from the Hospital (Number: P.1623/RSUD.445/53.12/08/2025).

Three formulations (F1, F2, and F3) were designed to evaluate natural flavoring agents such as cinnamon powder and honey, while maintaining the same proportions of cacao powder, soymilk powder, stevia, and water in each formulation. The materials and proportions used for each formulation are listed in Table 1.

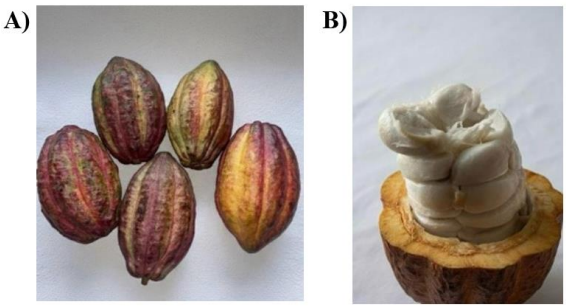

Fig. 1. *T. cacao* L. fruits. (A) Pods. (B) Beans

Table 1. Materials and formulations

Materials	Formulations		
	F1	**F2**	**F3**
Cacao bean powder (*Theobroma cacao* L.)	18.07 g	18.07 g	18.07 g
Soy milk (*Glycine max*)	10 g	10 g	10 g
Cinnamon (*Cinnamomum burmannii)*	0 g	0.015 g	0.015 g
Honey (*Apis dorsata*)	30 mL	0 g	30 mL
Stevia (Beeru™)	0.05 mL	0.05 mL	0.05 mL
Water	200 mL	200 mL	200 mL

For the beverage, water was heated to 100°C to dissolve the soymilk powder. The mixture was then filtered through a 200-mesh sieve to remove undissolved soymilk residues. Cacao bean powder was then added and stirred until homogeneous. Subsequently, a drop of stevia was added to the mixture. Finally, honey and cinnamon powder were added and mixed thoroughly, depending on the formulation [14].

Each formulation was then subjected to organoleptic evaluation with 20 female respondents aged 19-50. Adults within this range generally have reliable sensory evaluations [15]. The sensory attributes assessed included color, aroma, taste, and texture, using a five-point scale from strongly dislike, dislike, neutral, like, and strongly like [16]. To monitor product safety, respondents were observed for 24 h after consumption for any negative side effects.

After determining the most preferred formulation, a clinical trial was conducted to evaluate the treatment effect of the cacao beverage. The study was conducted with ethical approval and medical supervision from the Rumah Sakit Umum Daerah of West Sumba Regency. Patients were selected based on a confirmed diagnosis of cervical cancer and provided informed consent. Symptoms such as vaginal discharge, abnormal bleeding, and pelvic pain were recorded before and continuously during the intervention for 14 days. Laboratory assessments, including Complete Blood Count (CBC) and anthocyanin reaction tests, were conducted only before and after the intervention. CBC was performed using a hematology analyzer to measure hemoglobin (Hb), leukocyte (WBC), erythrocyte (RBC), hematocrit (HCT), basophils (BASO), and neutrophils (NEU). Blood serum was also obtained using a centrifuge tube and spun at 3,000 rpm for 5 min [17]. The serum sample was used to indicate the antioxidant effect by measuring the concentration of anthocyanin extract required to produce a color change and the reaction time. All acquired data were analyzed using descriptive statistics. The flowchart of the experimental procedure is shown in Figure 2.

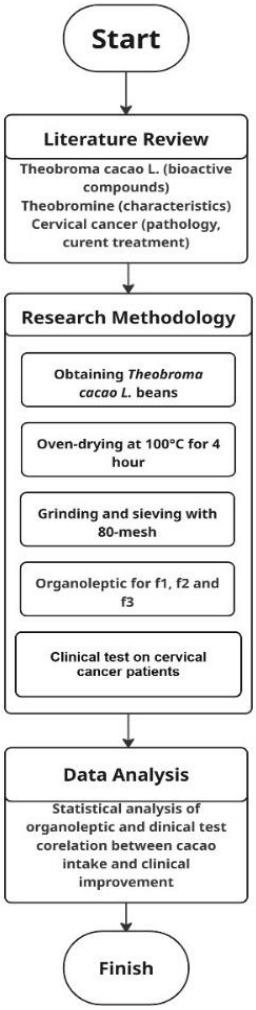

Fig. 2. Flowchart containing experimental procedures

3 Results and Discussion

The organoleptic evaluations of the cacao beverage formulations showed differences in sensory acceptance among the respondents. For aroma in Figure 3 (A), the F1 formulation received 3 “neutral,” 4 “like,” and 13 “strongly like” responses. Meanwhile, the F2 formulation received 4 respondents choosing “dislike,” 11 “neutral,” and 5 “like.” The F3 formulation gained the highest acceptance, with 13 respondents selecting “strongly like,” 4 “like,” and 3 “neutral.” These results indicate that the F3 formulation was the most appealing among the three.

For the color shown in Figure 3 (B), the F1 formulation received 3 respondents choosing “dislike,” 8 “neutral,” 5 “like,” and 4 “strongly like” responses. F2 received lower scores, with 3 respondents choosing “dislike”, 8 “neutral”, 8 “like,” and 1 “strongly like, whereas F3 had 5 respondents choosing “neutral,” 6 “like,” and 9 “strongly like,” indicating that F3 produced the most attractive color among the samples.

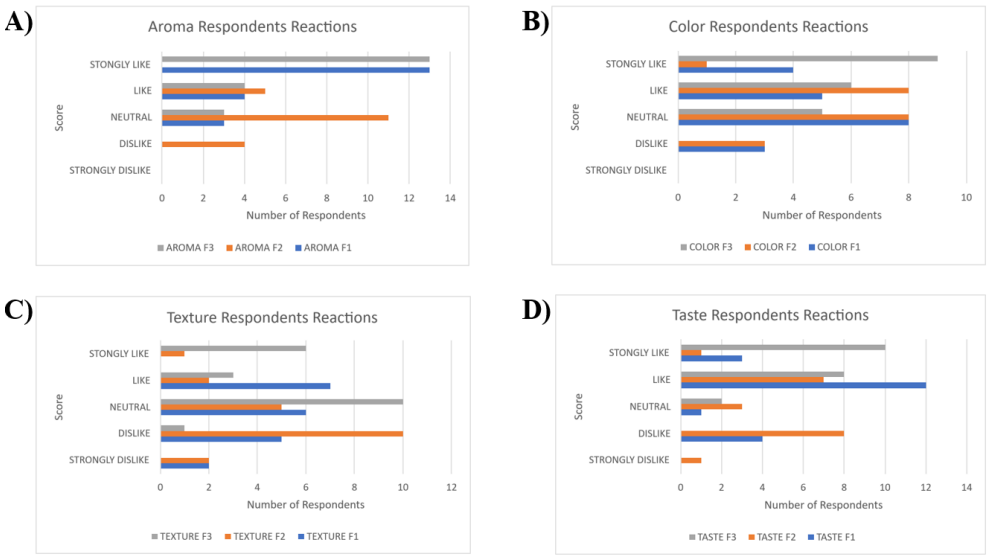

Fig. 3. Respondent ratings for F1, F2, and F3 formulations. (A) Aroma. (B) Colour. (C) Texture. (D) Taste

According to Figure 3 (C), the F1 formulation received two respondents choosing "strongly dislike," 5 "dislike," 6 "neutral, and 5 "like" responses. The F2 formulation showed improved ratings, with 3 respondents choosing "strongly dislike," 1 "dislike," 5 "neutral," 10 "like," and 1 "strongly like." Meanwhile, the F3 formulation achieved the best overall acceptance, with only 1 "dislike," 10 "neutral," 3 "like," and 6 respondents choosing "strongly like."

Lastly, for taste shown in Figure 3 (D), the F1 formulation received 12 respondents choosing "like," 3 "strongly like," 1 "neutral, and 4 "dislike" responses. F2 showed mixed results with 8 respondents choosing "dislike," 7 "like," 3 "neutral," 1 "strongly like," and 1 "strongly dislike." In contrast, F3 achieved the highest preference, with 10 respondents choosing "strongly like," 8 "like," and 2 "neutral."

The organoleptic evaluation results indicated that the F3 formulation was the most preferred in all sensory parameters. Adding honey contributed natural sweetness that balanced the bitterness of the cacao. Cinnamon is enriched with both fragrance and flavor [18]. The combined presence of these natural ingredients also enhanced the color of the beverage, resulting in a richer brown hue.

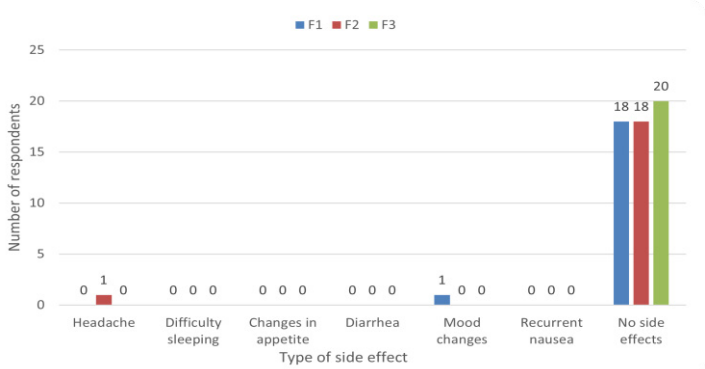

Fig. 4. Side effects reported after 24 hours of consuming F1, F2, and F3 formulations

Furthermore, all 20 respondents were observed for any negative side effects within 24 h of consuming each formulation. Among the 20 respondents, F1 formulation showed that only one respondent experienced slight mood changes. In the F2 formulation, only one respondent experienced irregular bowel movements. Meanwhile, in F3, all 20 participants reported no negative side effects were reported. These findings confirm that all beverage formulations, particularly F3, are safe for consumption. This supports the use of natural ingredients in the production of the beverage. The results are presented in Figure 4.

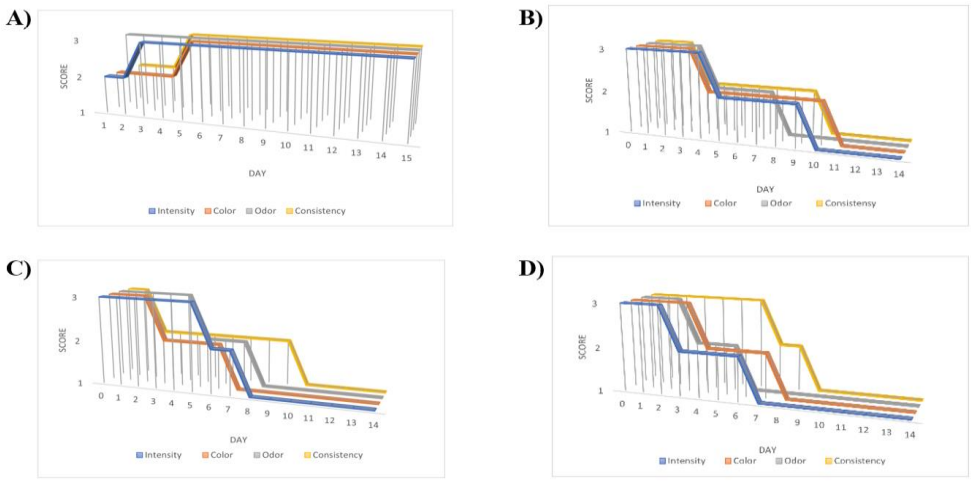

Fig. 5. Improvement in vaginal discharge within 14 days of consuming the F3 beverage. (A) Patient 0. (B) Patient 1. (C) Patient 2. (D) Patient 3.

A clinical test was performed for F3 in four female patients diagnosed with early stage cervical cancer. As presented in Figure 5, Patient 0, as the control variable, showed no improvements in vaginal discharge, while Patients 1, 2, and 3 initially experienced severe symptoms (score = 3) before the intervention (e.g., thick, blood-tinged discharge with a strong odor and sticky consistency). Improvements were observed between Days 3 and 5, where the discharge color began to change from reddish-brown to yellowish, and the odor intensity decreased from severe to moderate (score = 2). By Days 7–10, most patients showed a transition to mild discharge (score = 1) with clear or white color, no odor, and a watery consistency. Complete normalization occurred from Day 11-14.

The trend presented in Figure 6 (A) shows that patient 0 (control variable) experienced heavy flow bleeding without any improvements. However, for patients 1, 2, and 3, before the intervention to Day 3, the patients initially experienced severe heavy menstrual-like flow bleeding (score = 3). Noticeable improvement began between days 4 and 6, during which three patients transitioned from severe to moderate bleeding (score = 2). Patient 2 experienced severe bleeding until day 6. By Days 7–9, most patients experienced reduced bleeding flow, and by Day 10, all patients had mild bleeding (score = 1). From Day 10 onward, all patients experienced mild or absent bleeding.

A steady decline in pelvic pain is shown in Figure 6 (B). Before the intervention, all patients reported severe pain (score = 6), which significantly interfered with their daily activities. Improvement was first observed between days 3 and 5, when the pain intensity decreased to a moderate level (score = 5) across most patients. By days 6–7, pain was reported as “slightly moderate” or “slightly mild” (scores = 4–3). From Days 8–10, all patients reported mild to very mild discomfort (scores = 2–1), and by Days 13–14, the pelvic pain had disappeared (score = 0).

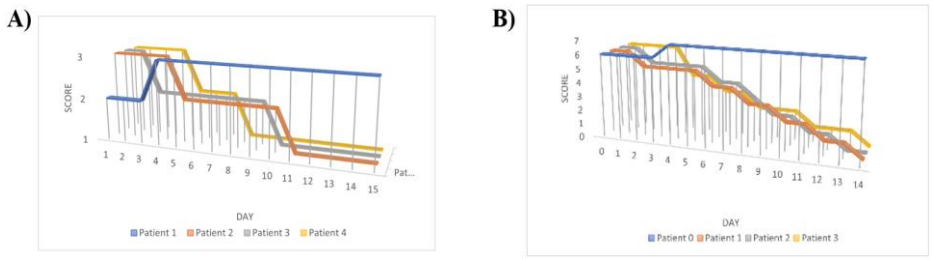

Fig. 6. Improvement in bleeding intensity (A) and pelvic pain (B) within 14 days of consuming the F3 beverage in all four patients.

Table 2. Haematology levels during pre-test and post-test (day 14) of consuming the F3 beverage.

Patient	Test Type	Hb (12-15 g/dL)	HCT (36-46 %)	WBC (4-10 µL)	RBC (4.0-5.5 µL)	NEU (40-60%)	BASO (0-1%)
0	Pre-test	10.5	34.1	6.8	4.25	70	1.1
	Post-test	10.7	34.0	6.5	4.28	69	1.0
1	Pre-test	10.4	30.5	6.0	4.64	73	1
	Post-test	11.0	31.9	6.1	4.75	65	0.5
2	Pre-test	11.2	34.8	4.0	4.10	68	1.0
	Post-test	12.6	34.5	5.9	4.70	61	0.6
3	Pre-test	10.8	36.5	4.5	4.25	72	1.1
	Post-test	12.2	40.2	6.4	4.83	64	0.7

Table 2 shows the laboratory assessments of each patient, including the normal values at the top. Hemoglobin (Hb) levels increased in all patients, rising from 11.0 to 12.0 g/dL. Haematocrit (HCT) also increased from 35.67% to 36.10%, and erythrocyte (RBC) counts improved from 4.27 to 4.73 µL. The proportion of neutrophils (NEU) decreased from an average of 67.5% to 63.25%, and that of basophils (BASO) decreased from 0.95% to 0.65%. These changes indicate enhanced oxygen transport, improved blood regeneration, and a lower inflammatory response, suggesting the restoration of immune balance after the consumption of the F3 beverage.

As shown in Table 3, the anthocyanin reaction occurred rapidly during the pre-test, with a reaction time of 4.6 s and a required concentration of 0.17 mL, producing a pink to purple color, as shown in Figure 7. After 14 days, the post-test reaction slowed to 10.3 s and 0.25 mL concentration with the same purple color, indicating reduced oxidative activity and greater serum stability (e.g., slower reaction time and higher concentration requirement). Elevated Cu^{2+} ion levels in cervical cancer patients are 132.92 ± 64.39 µg/dL compared to healthy controls (111.23 ± 37.54 µg/dL) [19, 20]. The slower anthocyanin reaction suggests a lower Cu^{2+} concentration in the sample.

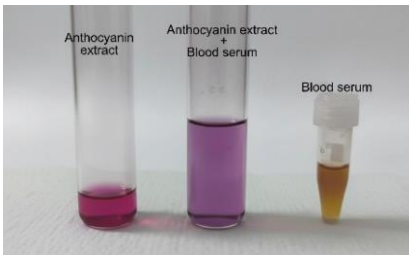

Fig. 7. Anthocyanin reaction test. (A) Anthocyanin extract showing pink colouration. (B) Anthocyanin extract after reacting with blood serum showing purple colouration. (C) Blood serum.

Table 3. Anthocyanin reaction test result during pre-test and post-test (day 14)

Patient	Test Type	Concentration	Time	Colour
0	Pre-test	0.15mL	4.4s	Purple
	Post-test	0.20mL	4.3s	Purple
1	Pre-test	0.15mL	4.7s	Purple
	Post-test	0.25mL	10.06s	Purple
2	Pre-test	0.20mL	5.1s	Purple
	Post-test	0.25mL	10.05s	Purple
3	Pre-test	0.20mL	4.3s	Purple
	Post-test	0.25mL	11,2s	Purple

Overall, Theobromine compounds in *Theobroma cacao* L. show anticancer activity against cervical cancer. Based on a study, it inhibits cell proliferation, migration, and invasion while suppressing oncogenic and stemness-related genes (HIF-1α, VEGF, CD24, and Bcl-2) and the stem cell marker ALDH1A1, which demonstrates its potential as a natural therapeutic agent [21]. This compound impairs tumor adaptation and stemness, triggering apoptosis and ferroptosis in cervical cancer cells [22]. These findings align with clinical observations, such as reduced vaginal discharge, clearer secretions, and absence of odor, along with decreased vaginal discharge, bleeding intensity, and pelvic pain [23, 24, 25]. These improvements were supported by haematological findings, where hemoglobin, erythrocyte, and hematocrit values increased, suggesting enhanced oxygen transport and blood regeneration. Stable leukocyte and platelet levels, along with reduced neutrophil and basophil percentages, reflect decreased inflammation and balanced immune activity. The slower anthocyanin reaction during the post-test also suggests an improved antioxidant capacity.

This study only involved a small sample size and a short intervention period of 14 days. Further studies with larger sample sizes, molecular biomarkers, and longer observation periods are required to confirm the long-term effects of *Theobroma cacao* L. as a cervical cancer treatment.

4 Conclusion

This study suggests that *Theobroma cacao* L. (Forastero variety) beverage enriched with honey and cinnamon powder effectively improved the patients' clinical condition. In the organoleptic test, all 20 respondents approved the F3 formulation in terms of aroma, color, texture, and taste, with no adverse side effects experienced after 24 h of consumption. A clinical trial conducted on cancer patients for over 14 days showed a significant improvement, such as a decrease in abnormal vaginal discharge from severe to mild by Day 10–14. The bleeding intensity also began to decrease from severe to mild, and the pelvic pain reduced from severe to none. Haematological results showed a measurable increase in hemoglobin from 11.0 to 12.0 g/dL and hematocrit from 34.5 to 37.6%, accompanied by a stable leukocyte count from 4 to 6 μL, a decrease in neutrophils from 70 to 63%, and basophils from 1.0 to 0.6%. The anthocyanin reaction time increased from an average of 4.6 s to 10.3 s. These findings indicate that the bioactive compounds in cacao beans contribute to the anticancer effect and promote cervical tissue healing with no negative side effects. The use of locally cultivated cacao supports eco-sustainable biomedical innovation, reducing dependence on synthetic drugs that contribute to chemical waste and ecological degradation.

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