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Original article

The effect of 5% *Curcuma xanthorrhiza* extract gel on diabetic rat socket: A fibroblast analysis

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ABSTRACT

Background: *Predominant advanced glycation end products (AGEs) in diabetes mellitus (DM) patients lead to increased reactive oxygen species, causing oxidative stress and cell apoptosis, which hinders wound healing. Curcuma xanthorrhiza contains active compounds such as curcumin, flavonoids, and saponins, which can increase fibroblast cell production, the primary indicator of wound healing, and serve as AGE inhibitors.* ***Purpose:*** *This study aimed to determine the effect of 5% C. xanthorrhiza extract gel on the number of fibroblasts in diabetic Wistar rats during the healing of tooth extraction over a specific duration.* ***Methods:*** *The left mandibular incisor was extracted after using alloxan to induce diabetes in the rats. The socket was then treated with different compounds, including 5% C. xanthorrhiza extract gel, placebo CMC-Na, or Gengigel. A histopathological examination of the socket was conducted to assess the presence of fibroblasts on days one, three, and five after treatment.* ***Results:*** *The number of fibroblasts in the sockets treated with 5% C. xanthorrhiza extract gel was lower than in the Gengigel group but higher than in the placebo group ($p < 0.05$).* ***Conclusion:*** *5% C. xanthorrhiza extract gel can increase the number of fibroblasts, thereby potentially accelerating wound healing in DM.*

Keywords: *Curcuma xanthorrhiza; diabetes mellitus; fibroblast; tooth extraction; wound healing*
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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease caused by impaired insulin secretion, characterized by high glucose levels in the blood. DM has become a world health problem and has developed into the third leading cause of death in the world.[1] Indonesia ranks fourth worldwide with the most DM cases after India, China, and the United States.[2] Based on the 2018 Indonesia Basic Health Research,[3] an increase of 2.6% in DM's prevalence was noted compared to its 2013 findings. Of all DM categories, as much as 90% of cases are of diabetes mellitus type 2 (DMT2).[4] DMT2 results in reduced use of glucose by the body's cells because of the ineffective use of insulin, causing hyperglycemia. Long-term hyperglycemia may cause various complications, including disrupting the wound healing process. This condition becomes one of the risk factors for an unfavorable prognosis in tissue injury such as tooth extraction.[5] Tooth extraction is the last option if the tooth can no longer be treated.[6] Based on the 2018 Basic Health Research,[3] the rate of tooth extraction in Indonesia is still quite high, reaching 7.9%.

Tooth extraction in patients with DM poses a greater risk than in those without the condition. The socket's healing process after extraction will be slower and more susceptible to infection due to DM patients' high blood sugar levels.[5] The dominant number of advanced glycation end products (AGEs) found in DM patients can lead to dysfunction and increased regulation of programmed cell death in fibroblast cells, inhibiting wound healing after extraction.[7]

The wound healing process resulting from tooth extraction involves several interconnected processes, including the hemostasis, inflammation, proliferation, and remodeling phases.[8] Fibroblasts are the primary cells involved in the healing process and play a role in the proliferation phase; they are widely distributed in connective tissue, producing precursor substances such as collagen, elastic fibers, and reticular fibers. They migrate towards

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the wound site and proliferate, creating a collagen matrix during tissue inflammation to repair damaged tissue.[6]

Tooth extraction can result in tissue damage and pain. Therefore, post-tooth extraction management typically involves administering systemic non-steroidal anti-inflammatory drugs, which may have side effects, including gastrointestinal symptoms.[9] Common topical applications are drugs containing hyaluronic acid (HA). Even though it is effective in accelerating post-extraction healing, HA is classified as a synthetic material that may act as an antigen and trigger a hypersensitivity reaction.[10] The cost of this drug is also relatively high. Therefore, many studies have been conducted to find potential medicinal preparations from natural ingredients that may be used post-extraction with minimal side effects.[6,11]

Active compounds such as curcumin, flavonoids, terpenoids, steroids, saponins, alkaloids, tannins, and phenols are commonly found in plants. These compounds have beneficial properties, such as anti-inflammatory, antioxidant, analgesic, and antimicrobial agents supporting wound healing.[12] One of the plants that contains these compounds is *Curcuma xanthorrhiza*.[13,14] *C. xanthorrhiza* is a native Indonesian spice plant that has been commercially cultivated in Southeast Asia countries. In 2019, Indonesian *C. xanthorrhiza* cultivation was conducted on a very large scale.[15]

The primary active substance in *C. xanthorrhiza* is curcuminoid, specifically curcumin, which can accelerate wound healing by stimulating increased proliferation and migration of fibroblasts to the wound area.[15] Curcumin has also been proven to have significant potential as a protective agent against the formation of AGEs and AGEs-induced disorders through various potential mechanisms.[16] The curcumin content in *C. xanthorrhiza* is higher than that of black or white turmeric.[12] Flavonoids and saponins, active compounds present in *C. xanthorrhiza* rhizomes, can stimulate an increase in the number of fibroblasts through the production of TGF-β (transforming growth factor-β).[17,18] Kesumayadi et al.'s[14] study showed that a 5% concentration of *C. xanthorrhiza* gel extract accelerated the wound-healing process compared to concentrations of 1% and 3%. Based on the preceding information, the researcher is interested in investigating the effects of a 5% *C. xanthorrhiza* extract gel on the number of fibroblasts in the wound-healing process after tooth extraction in Wistar rats (*Rattus norvegicus*) with DMT2.

MATERIALS AND METHODS

This study utilized a true experimental post-test-only control group design, employing male Wistar rats. The Research Ethics Commission of the Faculty of Veterinary Medicine, University of Udayana (ethical clearance number B/260/UN14.2.9/PT.01.04.2022) approved the research protocol.

The study included a total of 45 male Wistar rats aged 3–4 months and weighing between 200 grams and 260 grams. All rats underwent a 7-day adaptation period during which they were housed in standard cages, provided with a standard diet, and given unrestricted access to water. DM was induced through an intraperitoneal injection of alloxan at a dosage of 150 mg/kg of body weight. Diabetes was confirmed based on random blood glucose measurements using a glucometer; a reading of ≥ 200 mg/dl on the third day following alloxan injection indicated the presence of diabetes.[19]

C. xanthorrhiza rhizomes, aged between 9–12 months and exhibiting a branched structure with various colorations (reddish-brown, dark green, or dark yellow), were identified and confirmed; the species were from the Bali Botanic Garden under the Indonesian Institute of Sciences, ELSA

Table 1. The component identification procedure

Component	Methods
Flavonoid	The extract was added to oxalic acid, boric acid, and 2 ml of acetone. The presence of flavonoids was confirmed by observing yellow fluorescence under 366 nm ultraviolet light.[20]
Phenols	The extract was added to a 2% ferric chloride (FeCl3) solution, and the presence of phenols was confirmed by observing the formation of a blue-black precipitation.[20]
Terpenoids	The extract was added to 1 ml of 5% sulfuric acid and vanillin; a brownish ring confirmed the presence of terpenoids.[20,21]
Saponins	The extract was added to distilled water and then shaken vertically for 10 seconds; observing a stable foam of 1–10 cm in height after 10 minutes confirmed the presence of saponins.[12,22]
Steroid	The Liebermann-Burchard reaction was induced by adding anhydrous acetic acid and concentrated sulfuric acid. A greenish-blue color indicated the presence of steroids.[12,22]
Alkaloids	The extract was added to 10% hydrochloric acid, followed by ethyl acetate. Alkaloids were detected by white, orange, or red precipitates.[12,22]
Tannins	The extract was added to 10% lead acetate reagent, forming a blue-black solution, confirming the presence of tannins.[12,22]
Curcumin	The extract was dissolved using hexane and methanol solvents (1:1; v/v) and then extracted using chloroform. A TLC plate (Silica GF 254) was used to analyze the curcumin content under UV light (366 nm wavelength). The appearance of a yellow color indicated a positive result for curcumin, followed by measurement of the retention factor (Rf) value.[23,24]

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ID #6795 (https://elsa.brin.go.id/verifikasi). The rhizomes were cleaned, dried in an oven, and ground into a 500-gram powder (60 mesh) to prepare the extract. This powder was macerated in 96% ethanol for 24 hours, filtered, and evaporated at 60°C using a rotary evaporator. The extract underwent further evaporation with a water bath for two hours, followed by 24 hours in an oven to minimize solvent residue.[20,21]

Phytochemical screening was conducted to assess the presence of active compounds, including flavonoids, phenols, terpenoids, saponins, steroids, alkaloids, and tannins. The identification methods are described in Table 1.

A 5% *C. xanthorrhiza* extract gel was prepared by mixing 5 g of *C. xanthorrhiza* extract with a gel base containing 1.5 g of CMC-Na (carboxymethylcellulose sodium). 1.5 g of CMC-Na powder was dispersed in 100 ml of warm distilled water and continuously stirred until a uniform gel base was obtained, creating the CMC-Na gel base. Subsequently, 5 g of *C. xanthorrhiza* extract was added to the 100 grams of the gel base. The mixture was stirred using a magnetic stirrer at 400 RPM until homogeneity was achieved. The gel preparation was conducted at 25°C.[25]

The Wistar rats underwent mandibular left incisor tooth extractions using a needle holder after the 5% *C. xanthorrhiza* extract gel was prepared. During the procedure, all the rats were under anesthesia using a combination of ketamine (50 mg/kg body weight) and xylazine (4 mg/kg body weight), administered intramuscularly. After the extraction, each animal was treated using different protocols. The first group was treated using a CMC-Na placebo, the second group received Gengigel, and the third group used 5% *C. xanthorrhiza* extract gel; all three groups received their respective treatment in the socket twice daily.[26] After 1, 3, and 5 days of treatment, each group was sacrificed using ketamine (60–75 mg/kg body weight), and the mandibular tissue was collected.[26,27] This was decalcified using 10% formic acid for 7 days.[21,28] The tissue was then processed for histopathology sections with 6 um thicknesses and stained using Harris hematoxylin-eosin.[26,29] The fibroblast cells in the socket appeared dark purple with a pinkish cytoplasm and exhibited a round oval shape. The fibroblast cells counted were active cells with a round nucleus, smooth chromatin, large cytoplasm, and a clearly visible nucleus that were the same for all groups. The observation of fibroblast cells was accomplished using an Olympus light microscope with a digital Optilab camera at 400x magnification. Cell counting was performed in three different fields of view, then summed and divided by three to obtain the average.[29]

The data were analyzed using SPSS 26.0 (IBM, Armonk, New York) for Windows. The data that met the requirements were then processed and analyzed quantitatively using bivariate one-way ANOVA analysis followed by a post-hoc LSD test. Data that did not meet the criteria was subjected to the Kruskal–Wallis test, followed by the Mann–Whitney test. A P-value of < 0.05 indicated a significant difference.

RESULTS

C. xanthorrhiza rhizome samples were identified using direct identification and literature comparison methods, which confirmed the rhizome's authenticity. Phytochemical screening and TLC tests detected several compounds in the rhizome extract, including curcumin, flavonoids, terpenoids, steroids, saponins, alkaloids, tannins, and phenols (Figure 1).

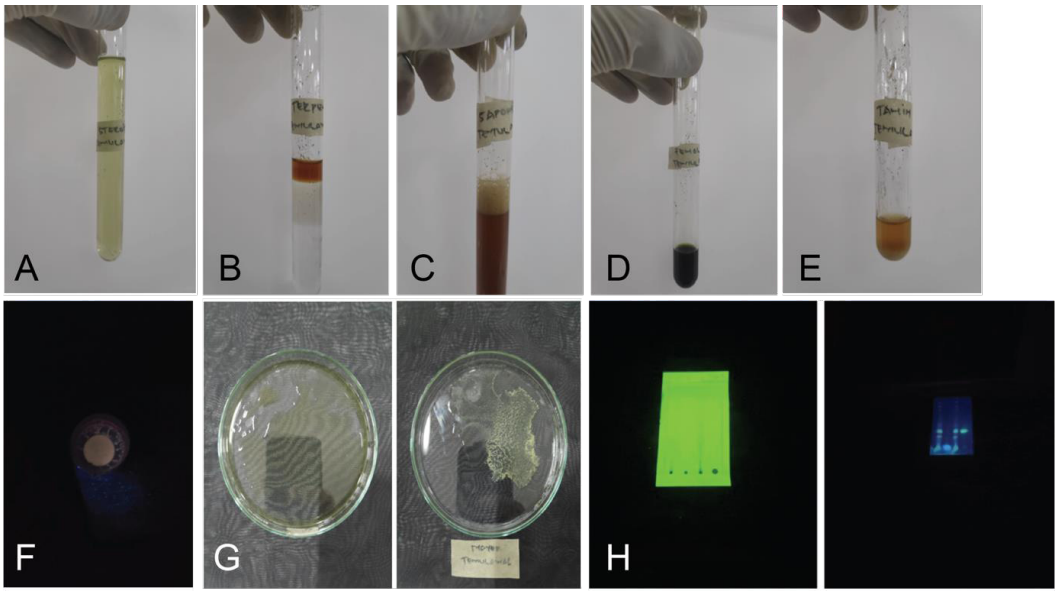

Figure 1. Phytochemical tests with respective reagents showing the presence of (A) steroids, (B) terpenoids, (C) saponins, (D) phenols, (E) tannins, (F) alkaloids, and (G) flavonoids. The curcumin content is shown as spots formed on a flat KLT under UV light at 254 nm and 366 nm (H) wavelengths.

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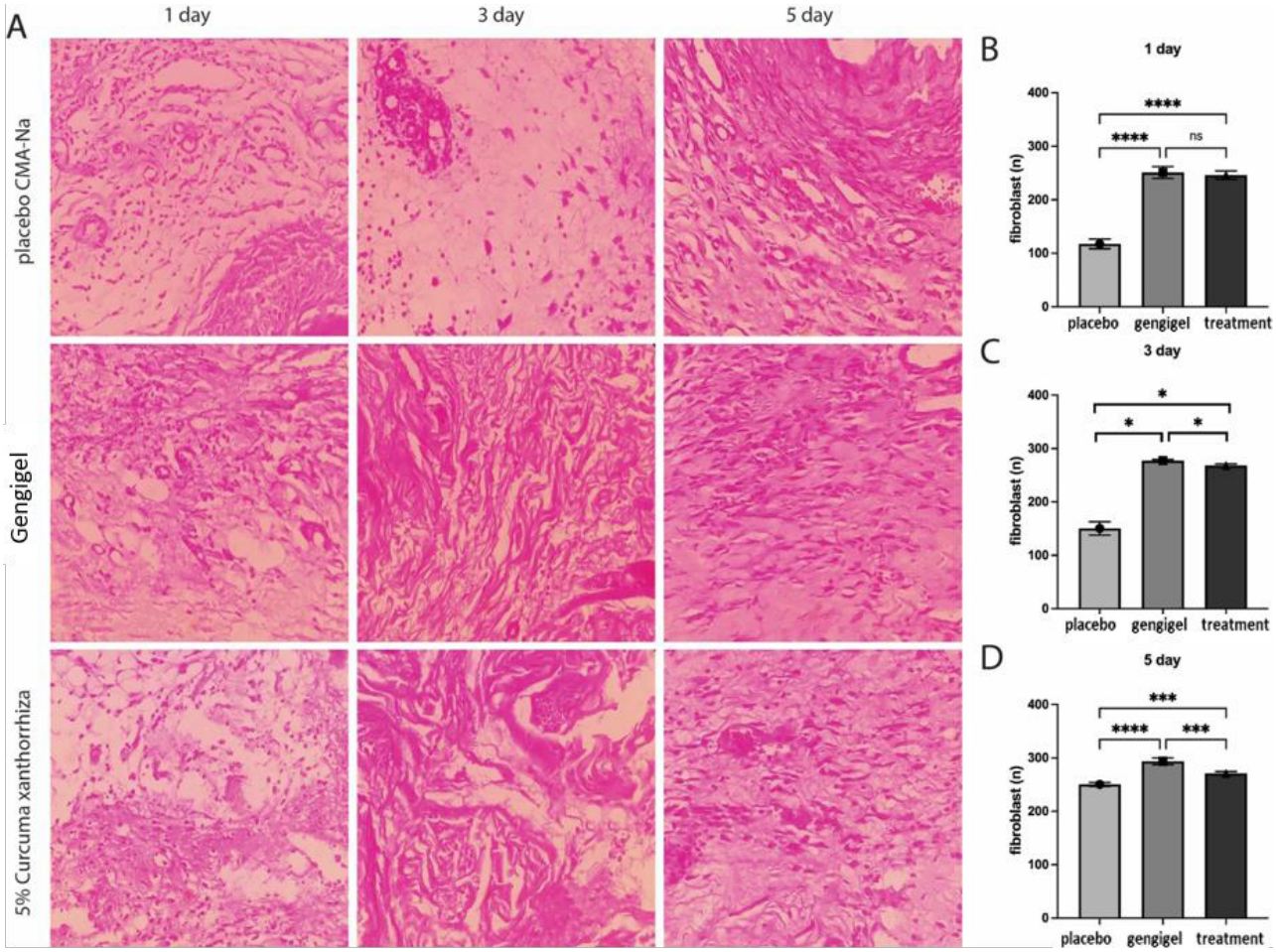

Figure 2. Histopathology of the diabetic rat socket stained with hematoxylin and eosin and visualized under a light microscope at 400x magnification (A). Quantification of fibroblasts at various time points (1, 3, and 5 days) is presented in panels (B–D). The fibroblast analysis at 1 and 5 days was performed using ANOVA and a post-hoc LSD test, while the fibroblast analysis at 3 days used Kruskal–Wallis and Mann–Whitney tests. *$p < 0.05$; ***$p < 0.001$; ****$p < 0.0000$ and ns = not significant.

The histopathological analysis of fibroblast counts in each group is shown in Figure 2A. After 1 day of treatment, the 5% *C. xanthorrhiza* group exhibited similar fibroblast numbers compared to the Gengigel group ($p = 0.457$) but significantly higher counts than the placebo group ($p < 0.0001$) (Figure 2B). On day 3 post-treatment, the 5% *C. xanthorrhiza* group had fewer fibroblasts compared to the Gengigel group ($p < 0.05$) but still significantly more than the placebo group ($p < 0.05$) (Figure 2C). This trend persisted on day 5 post-treatment, with the 5% *C. xanthorrhiza* group displaying fewer fibroblasts than the Gengigel group ($p < 0.001$) but more than the placebo group ($p < 0.01$) (Figure 2D).

DISCUSSION

This investigation is an in vivo true experimental study; the dependent variable is the number of fibroblasts, and the independent variable is the 5% *C. xanthorrhiza* gel extract. Prior to the study, a determination test was conducted on the rhizomes to ensure the correct identification of the plant species, thus avoiding any errors related to plant selection.[21] The results of the determination test indicated that the rhizome used was indeed *C. xanthorrhiza*.

Phytochemical and TLC analyses were conducted to qualitatively determine the number of active compounds in the *C. xanthorrhiza* extract. The results of the phytochemical test showed findings consistent with Suwardi and Ranggaini's study,[30] indicating the presence of active compounds such as flavonoids, phenols, terpenoids, steroids, saponins, alkaloids, and tannins in the *C. xanthorrhiza* extract. The TLC test was also performed, which revealed the formation of greenish-yellow spots with Rf values matching the Rf profile of the standard compound curcumin, indicating the number of active compounds, specifically curcumin, in the *C. xanthorrhiza* extract, as Suharsanti et al. suggested. [24]

The study utilized 36 out of 45 samples of Wistar rats' left mandibular incisor tooth sockets. Some samples were found to have died during the experiment, presumably due to fighting, and it is suspected that a few samples expired

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as a result of high glucose levels following DM induction, leading to complications.[31,32]

Descriptive analysis data shows the mean number of fibroblast cells in the treatment group is higher than the negative control group but lower than the positive control group on each observation day. Data analysis using a one-way ANOVA test and the alternative Kruskal–Wallis test shows a significant difference in the number of fibroblast cells among groups ($p < 0.05$). The results of the LSD post hoc test and Mann-Whitney test indicate significant differences in each pair of groups, except for the treatment and positive control groups, which did not show statistically significant differences on day 1 ($p > 0.05$).

Analysis data shows that treating with 5% *C. xanthorrhiza* extract gel exhibits a lesser effect than the positive control group on each observation day but matches the effect of Gengigel on day 1. Based on Kawano's (2021) study, the main content of hyaluronic acid in the positive control group showed an initial wound-healing effect on day 1.[33] The analysis also reveals that the administration of 5% *C. xanthorrhiza* extract gel has a significant effect on increasing the number of fibroblast cells compared to the negative control group at each observation time. According to Mardiyantoro et al.,[34] an increased number of fibroblast cells indicates an improvement in the rat sockets' wound healing process, suggesting that the 5% *C. xanthorrhiza* extract gel can enhance the wound healing process. Other studies, such as Kristianto's, [35] support these findings, showing a significant impact of *C. xanthorrhiza* extract administration on diabetic rat wound tissue, with more fibroblast cells in the treatment group than in the negative control group. The increased number of fibroblast cells is attributed to the active compounds present in the extract, such as curcumin, flavonoids, and saponins, which can enhance fibroblast cell proliferation and activate their forming factors.[14,15]

C. xanthorrhiza triggers an increase in the production of TGF-β, migration, proliferation of fibroblasts, and collagen matrix deposition.[36] TGF-β is a growth factor that plays a key role in wound healing by stimulating fibroblasts and is predominantly involved in increasing collagen synthesis.[37] In vivo studies have shown that curcumin mediates the infiltration of fibroblasts into the wound site, which naturally differentiates into myofibroblasts during granulation tissue formation. Treatment with curcumin also promotes the differentiation of fibroblasts into myofibroblasts, marking the initiation of wound contraction.[38] In this study, curcumin also plays a role in enhancing the extract's wound-healing potential in a diabetic rat model. This potential is consistent with the research conducted by Alizadeh and Kheirouri,[16] which states that curcumin can inhibit the formation of AGEs. High levels of AGEs in diabetic patients will increase reactive oxygen species, resulting in delayed wound healing and leading to fibroblast dysfunction and death.[7,39,40]

The active flavonoid in *C. xanthorrhiza* extract also directly affects the number of fibroblasts by increasing the number of macrophages.[41,42] Macrophages produce growth factors such as PDGF, FGF, EGF, and TGF-β. The TGF-β factor will impact blood vessel growth and fibroblasts, attracting more fibroblasts to the wound area and producing collagen. Flavonoids in the extract also help T cells to become active, differentiate, and develop into T helper cell 1 (TH1), T helper cell 2 (TH2), and T helper cell 3 (TH3). TH3 promotes fibroblast proliferation by producing more TGF-β.[13,41]

C. xanthorrhiza extract's saponin content, in addition to increasing macrophages by triggering monocyte increases, is also referred to as a growth factor.[18,41] This active substance's mechanism involves duplicating fibroblast proliferation, endothelial cell growth in blood vessels, and smooth muscle cell growth, which stimulate the formation of new cells and induce cellular growth for repair in damaged blood vessels.[18] Saponins also increase the secretion of cytokine IL-1β, which affects the increased proliferation of fibroblasts in the wound area. Additionally, saponins contribute to the activation of the TGF-β function. TGF-β's expression is enhanced by saponins, thereby inducing fibroblast migration and growth.[17,18]

Based on this study, it has been observed that the 5% *C. xanthorrhiza* gel extract has potential as an alternative treatment in accelerating the wound-healing process following tooth extraction in DM rats. It could be argued that although there is a smaller increase in the number of fibroblast cells in the treatment group compared to the positive control group, a significant increase of fibroblast cells could still be observed in the treatment group compared to the negative control group on each observation day. These findings are important as a reference for further research aiming to maximize *C. xanthorrhiza*'s potential as a natural resource to develop wound healing products for DM conditions after tooth extraction. However, this study's results have limitations for the following reasons. First, this study requires further testing on the modalities' toxicity. This is necessary to determine the right and safe dose for users. Secondly, this study used crude extracts as research material. Therefore, how many active compounds affect the number of fibroblasts cannot quantitatively be known.

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