

Analgesic and Anti-inflammatory Effects of Ginger Oil

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Abstract: **Objective** Ginger (*Zingiber officinale*) is widely used as a spice in cooking and as a medicinal herb in traditional herbal medicine. The present study was to investigate the analgesic and anti-inflammatory activities of ginger oil in experimental animal models. **Methods** The analgesic effect of the oils was evaluated by the “acetic acid” and “hot-plate” test models of pain in mice. The anti-inflammatory effect of the oil was investigated in rats, using rat paw edema induced by carrageenan, adjuvant arthritis, and vascular permeability induced by bradykinin, arachidonic acid, and histamine. Indomethacin (1 mg/kg), Aspirin (0.5 g/kg) and Dexamethasone (2.5 mg/kg) were used respectively as reference drugs for comparison. **Results** The ginger oil (0.25–1.0 g/kg) produced significant analgesic effect against chemically- and thermally-induced nociceptive pain stimuli in mice ($P < 0.05$, 0.01). And the ginger oil (0.25–1.0 g/kg) also significantly inhibited carrageenan-induced paw edema, adjuvant arthritis, and inflammatory mediators-induced vascular permeability in rats ($P < 0.05$, 0.001). **Conclusion** These findings confirm that the ginger oil can be used to treat pain and chronic inflammation such as rheumatic arthritis.

Key words: analgesic activity; anti-inflammatory activity; ginger oil; *Zingiber officinale*; Zingiberaceae

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Introduction

Ginger, the rhizome of *Zingiber officinale* Roscoe (Zingiberaceae), is a common edible composition of diet worldwide and it has been reported that its extracts presented some pharmacological activities (Peng, 1992; Song *et al.*, 2007), and were used to treat many inflammatory conditions (Srivastava and Mustafa, 1992; Penna *et al.*, 2003) and their associated pain (Suekawa *et al.*, 1984). Some studies have shown that the extracts of ginger obtained using different methods or the components of these extracts had anti-oxidative activity, inhibition of thromboxane formation and cholesterol biosynthesis, anti-inflammation, antitumor and interference with the process of apoptosis of tumor cells, *etc.* The extracts from Chinese ginger have excellent effect on anti-emetic or control of nausea and vomiting,

prevention of coronary artery disease, and healing and prevention of both arthritic conditions and stomach ulcers.

Our previous studies have shown that the ginger oil significantly inhibited T lymphocyte proliferation, decreased the number of the total T lymphocytes and T helper cells, but increased the percentage of T suppressor cells to the total T lymphocytes in mice. And the ginger oil inhibited IL-1 α secretion by the murine peritoneal macrophages. *In vivo*, ig administration of the ginger oil weakened the delayed type of hypersensitivity response to 2,4-dinitro-1-fluorobenzene in the sensitized mice (Zhou, Deng, and Xie, 2006). This indicated that the ginger oil is clinically useful for the treatment of inflammatory and immunological diseases (Srivastava and Mustafa, 1992), such as asthma and

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arthritis (Tjendraputra *et al.*, 2001). The chemical investigations carried out in the past showed that the essential oil, normally extracted by steam distillation of the rhizomes, contained a high content of sesquiterpene hydrocarbons, in particular, 6-gingerol, *ar*-curcumene, β -bisabolene, and β -sesquiphellandrene, and the monoterpenoids geranial, neral, and camphene in ginger oil (Martins *et al.*, 2004; Gong, Fung, and Liang, 2004; Rui *et al.*, 2008). However, up to now, there are few reports about the analgesic and anti-inflammatory effects of ginger oil obtained with supercritical fluid extraction.

We performed a pharmacological investigation on the anti-inflammatory and analgesic activity of ginger volatile oil on classical models of inflammation and pain.

Materials and methods

Animals

Male Sprague-Dawley rats, (50–70) and (150–250) g, and either male or female ICR mice (20–25) g were used. These animals were obtained from the Laboratory Animal Center of Zhejiang University, China. The animals were housed in groups of 6–10 under environmentally controlled conditions with food and water *ad libitum*. The handling and use of animals were in accordance to the institutional guidelines.

Extraction and analysis of ginger oil

Extraction Powder of the ginger sieved through 40–60 mesh was accurately weighed after washing to dried form. Supercritical fluid extraction was performed with the flow rate of 380 kg/h at 45 °C for 2.5 h under the extraction pressure of 30 MPa.

Analysis Analytes were carried out on an HPLC system. The Hypersil ODS column (25 cm \times 4.6 mm, 5 μ m) was maintained at 25 °C. Solvents used for separation were 65% Methyl Cyanides in water. The flow rate was 1.0 mL/min. Detection wavelength was 330 nm. The theoretical plate number was 1000 according to 6-gingerol.

Preparation of standard solution Standard solutions were prepared by accurately weighing 5 mg of 6-gingerol into separate 10-mL brown volumetric flask and dissolving in methanol, then diluting to the concentration of 0.5 mg/mL and stored away from light under a low temperature.

Sample preparation Ginger oil (0.2 g) was

weighed accurately, transferred into a 10-mL brown volumetric flask, added with methanol, and diluted to the scale. Above-mentioned solution (1 mL) was transferred to separate 5-mL brown volumetric flask, then filtered with microporous membrane prior to injection for HPLC analysis.

Determination of sample Standard solution (20 μ L) and sample solution (20 μ L) were injected into HPLC, respectively. The result demonstrated that the content of 6-gingerol in ginger oil was 1.1% calculated by the external standard method.

Tween-80 (1%) was used as solvent to get different concentrations of ginger oil before experiment.

Chemicals and reagents

The following drugs and chemicals were used: histamine acid phosphate (Shanghai Biochemical Research Institution of Academy of Science, China), bradykinin (Guaranteed Reagent, Nakarai Chemical Ltd., Japan), arachidonic acid (AA, Fluka AG, CH-9470 Buchs, packed in Switzerland), Aspirin (Maidisen Pharmaceutical Co., Ltd., Suzhou, China), Dexamethasone sodium phosphate (DXM, The No. 2 Pharmaceutical Factory, Suzhou, China), Indomethacin (The No. 3 Pharmaceutical Factory, Zhejiang, China), carrageenan (Pharmaceutical Research Institution of Liaoning Province, China), *Mycobacterium butyricum* (Biological Products Institution of Beijing, China), Evans blue dye (Aldrich Chemical Co., USA). All other chemicals were of analytical grade.

Acute toxicity

Six groups of 10 ICR mice (five males and five females) were ig administrated with a single dose of 0, 2.0, 2.5, 3.125, 3.906, and 4.883 g/kg. The number of deaths was counted at 48 h after treatment. LD₅₀ (95% confidence limits) value was calculated by weighted probit analysis of Bliss method.

Analgesic activity

Acetic acid-induced writhing in mice The writhing acetic acid test was performed in mice as originally described by Siegmund *et al.* (1957). Groups of 14 mice were fasted overnight while given free access to water prior the start of the experiment. The ginger volatile oil (0.25, 0.5, and 1.0 g/kg), Indomethacin (10 mg/kg), or equivalent volumes of vehicle (1% Tween-80) were ig injected daily for 2 d, and ip injected of acetic acid (0.6% and 10 mL/kg) 1 h after the next administration. The mice were then

placed in an observation box, and the number of writhes was counted for 10 min after acetic acid injection.

Hot-plate test in mice

Groups of 12 mice were fasted overnight while given free access to water prior to the start of the experiment. The ginger volatile oil (0.25, 0.5, and 1.0 g/kg), Indomethacin (10 mg/kg), or equivalent volumes of vehicle (1% Tween-80) were ig administrated 1 h prior to the test, each animal was then placed gently on a 55 °C hot-plate. Latency to exhibit nociceptive responses, such as licking paws or jumping off the hot-plate, was determined after administration of the test substances or vehicle (MacDonald *et al.*, 1946).

Anti-inflammatory activity

Carrageenan-induced inflammatory paw edema in rats Groups of 10 rats were ig administrated the ginger volatile oil (0.125, 0.25, 0.5, and 1.0 g/kg) or equivalent volume of vehicle (1% Tween-80) once per day for consecutive 4 d, Aspirin (0.5 g/kg) was used only once on the last day. One hour after the last administration, paw edema was induced by a single 0.1 mL subplantar injection of carrageenan (0.5%) into the right hind paw of conscious rats. Rat paw volume was measured at regular selected time intervals (1, 2, 4, and 6 h) after injection of carrageenan, using a plethysmograph. The edema rate and inhibition rate of each group were calculated as follows: Edema rate $E = V_t - V_0/V_0$. Inhibition rate $I = E_V - E_t / E_V$. Where V_0 is the volume before carrageenan injection (mL); V_t is the volume at t h after carrageenan injection (mL); E_V is the edema rate of vehicle group; and E_t is the edema rate of treated group.

Freund's adjuvant-induced arthritis Following anesthesia (140 mg/kg of ketamina chloride ip), adjuvant arthritis was induced by a single ip injection of 0.1 mL of Complete Freund's Adjuvant (CFA) in the palmar surface of the right hind paw for all experimental arthritis groups according to the well-known method (Tsai and Lin, 1999). The ginger volatile oil (0.125, 0.25, 0.5, and 1.0 g/kg), Dexamethasone 2.5mg/kg, or equivalent volume of vehicle (1% Tween-80) was ig administrated per day, beginning on the day 19 after injection of CFA for consecutive 10 d. Paw edema and secondary lesion were carefully and thoroughly measured and inspected

through day 21 to day 28 after CFA injection. The purpose is to evaluate the therapeutic effect of ginger volatile oil on the secondary lesion induced by CFA injection. The edema and inhibition rate were measured with the same method as described above.

Vascular permeability in rats Pretreatment with either ginger volatile oil (0.125, 0.25, or 0.5 g/kg), Indomethacin (10 mg/kg), or vehicle (1% Tween-80) alone ip administered (Brito *et al.*, 1997) per day for 3 d, 1 h after the last administration, the dorsal region of a rat was shaved and skin vascular permeability test was initiated by injection of bradykinin (0.01 mg/mL), histamine (0.1 mg/mL), or arachidonic acid (AA, 0.1 mmol/L) respectively in a total volume of 0.1 mL. After the injection of inflammatory stimulus, each rat received an iv injection of Evans blue dye (25 mg/kg in 2.5% PBS) immediately. The animals were sacrificed 20 min after the dye injection, and the skin was carefully dissected to reveal the blue spots of the invaded dye. Each spot was excised, and the Evans blue dye was extracted from the tissue with formamide (2 mL per spot) overnight at room temperature (Brito *et al.*, 1997). The concentration of Evans blue dye was assessed by spectrophotometry at 620 nm. The results were expressed as Evans blue dye extracted per gram of tissue/spot in each animal.

Statistical analysis

Results are expressed as $\bar{x} \pm s$. Statistical evaluations were made using ANOVA or Student's t -test, and values were considered significantly different when $P < 0.05$.

Results

Acute toxicity

LD₅₀ of the ginger oil was 3.197 (2.907–3.515) g/kg, and the maximum non fatal dose was 2.0 g/kg.

Analgesic effects of ginger volatile oil

The ginger oil (0.25, 0.5, and 1.0 g/kg, ig) significantly decreased the number of acetic acid-induced writhes in mice compared to the animals that received vehicle only. The writhe inhibitory effect of the oil ranged from 46.0% ($P < 0.05$) to 64.3% ($P < 0.01$) compared with vehicle group, ID₅₀ (95% confidence limit) was 0.309 (0.178–0.536) g/kg. By comparison, the writhe inhibitory effect of Indomethacin (10 mg/kg) was 81.3% ($P < 0.001$) in this

nociceptive model (Table 1).

In the hot-plate test, the ginger oil (0.25, 0.5, and 1.0 g/kg, ig) and Indomethacin (0.01 g/kg, ig) significantly prolonged the reaction time to 107.8%, 239.2% ($P < 0.05$), 243.2% ($P < 0.01$), and 274.5% ($P < 0.001$), respectively, compared to the corresponding vehicle groups (Table 2).

Anti-inflammatory effects of volatile ginger oil

The rat's footpad became edematous soon after injection of carrageenan. Edema rate of the left footpad reached its peak at 4 h (49.7%). The ginger oil at doses of 0.25, 0.5, and 1.0 g/kg (ig) and Aspirin at a dose of 0.5g/kg (ig) significantly inhibited the development of pad swelling from 2 to 6 h after carrageenan injection (Table 3). The results showed that the ginger volatile oil inhibited the development of pad swelling by carrageenan in a dose-dependent manner. Aspirin (0.5 g/kg) was found to be more effective than ginger oil (0.5 g/kg).

Table 3 Inhibitory effect of ginger oil on rat hind paws induced by carrageenan ($\bar{x} \pm s, n = 10$)

| Groups | Dose / (g·kg ⁻¹) | Edema rate / % ^a | | | | | | | |
|------------|------------------------------|-----------------------------|--------------|------|--------------|------|---------------|------|---------------|
| | | 1 h | | 2 h | | 4 h | | 6 h | |
| vehicle | — | 29.0 | 7.0 | 38.9 | 5.5 | 49.7 | 5.3 | 43.0 | 5.5 |
| ginger oil | 0.125 | 23.5 | 4.9 (18.9) | 39.4 | 5.0 (-1.2) | 46.0 | 4.8 (7.4) | 37.6 | 4.5 (12.6) |
| | 0.250 | 27.9 | 4.0 (3.8) | 34.1 | 3.4 (12.3) | 33.8 | 5.5 (32.0) | 28.4 | 5.0** (34.0) |
| | 0.500 | 20.8 | 5.0 (31.0) | 27.9 | 5.4 (28.3) | 24.0 | 6.1** (51.7) | 15.9 | 3.3*** (63.0) |
| Aspirin | 1.000 | 6.8 | 1.5** (76.6) | 15.2 | 3.0** (60.9) | 17.9 | 3.0** (64.0) | 14.4 | 3.3*** (66.5) |
| | 0.500 | 20.6 | 3.4 (29.0) | 17.5 | 3.5** (55.0) | 14.1 | 2.0*** (71.6) | 8.4 | 1.9*** (80.5) |

a: Inhibitory rate (%) was listed in the bracket

** $P < 0.01$ *** $P < 0.001$ vs vehicle

The footpad injected with CFA became swollen gradually, edema reached its peak at day 25. The curves of edema rate vs time could be divided into two phases. In the first phase, edema rate of the injected footpad increased and reached a peak during the first three days. Thereafter, the swelling slowly subsided until the day 9 when the paw began to swell again and peaked in the 3rd week (second phase). Table 4 showed the time course of paw edema after the administration of CFA from day 21 to 28. Administration of the ginger oil at doses of 0.25, 0.5, and 1.0 g/kg (ig) significantly decreased joint swelling induced by CFA in a dose-dependent manner. Dexamethasone was found to be more effective than ginger oil.

The inhibitory ratios of the ginger oil at doses of 0.125, 0.25, and 0.5 g/kg (ig) on bradykinin-induced vascular permeability were 39.6 %, 52.8%, and 54.7% ($P < 0.05, 0.01$), respectively, and the ID₅₀ (95%

Table 1 Effect of ginger oil on acetic acid-induced writhes in mice ($\bar{x} \pm s, n = 14$)

| Groups | Dose / (g·kg ⁻¹) | Writhes number (10 min) | Reduction ratio / % |
|--------------|------------------------------|-------------------------|---------------------|
| vehicle | — | 19.4 ± 2.9 | |
| ginger oil | 0.25 | 10.5 ± 2.8* | 46.0 |
| | 0.50 | 8.0 ± 2.4** | 58.8 |
| | 1.00 | 6.9 ± 2.2** | 64.3 |
| Indomethacin | 0.01 | 3.6 ± 1.8*** | 81.3 |

* $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$ vs vehicle

Table 2 Effect of ginger oil on hot-plate test in mice ($\bar{x} \pm s, n = 12$)

| Groups | Dose / (g·kg ⁻¹) | Reaction time / s | Prolong ratio / % |
|--------------|------------------------------|-------------------|-------------------|
| vehicle | — | 5.1 ± 0.4 | |
| ginger oil | 0.25 | 10.6 ± 2.0* | 107.8 |
| | 0.50 | 17.3 ± 2.9** | 239.2 |
| | 1.00 | 17.5 ± 3.4** | 243.1 |
| Indomethacin | 0.01 | 19.1 ± 2.1*** | 274.5 |

* $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$ vs vehicle

confidence limit) was 0.276 (0.157—0.485) g/kg (Table 5). The inhibitory ratios on histamine-induced vascular permeability were 31.1%, 54.7%, and 60.4% ($P < 0.05, 0.001$), respectively, and the ID₅₀ was 0.264 (0.203—0.342) g/kg. The inhibitory ratios on arachidonic acid-induced vascular permeability were 26.1%, 33.3%, and 36.2% ($P < 0.01$), respectively. The inhibitory ratios of Indomethacin 0.01 g/kg (ig) on bradykinin, histamine, and arachidonic acid-induced vascular permeability were 56.6%, 47.1%, and 52.2% ($P < 0.001$), respectively. Indomethacin was found to be more effective than ginger oil.

Discussion

Previous studies indicated that alcoholic ginger extract (Mascolo *et al*, 1989) or 6-gingerol ip (Young *et al*, 2005) inhibited acetic acid-induced writhing. Acetic acid-induced writhing in mice was used to preferentially

Table 4 Therapeutic effect of ginger oil on Freund's adjuvant-induced arthritis in rats from day 21 to 28 ($\bar{x} \pm s$, $n = 12$)

| Group | Dose (g·kg ⁻¹) | Edema rate / % ^a | | | | | | | | |
|------------|-------------------------------|-----------------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--|
| | | day 21 | day 22 | day 23 | day 24 | day 25 | day 26 | day 27 | day 28 | |
| vehicle | — | 69.3±5.5 | 70.7±8.3 | 70.0±6.3 | 70.0±5.6 | 72.1±7.0 | 72.1±7.0 | 71.4±7.0 | 70.7±8.3 | |
| ginger oil | 0.125 | 65.8±6.3(5.1) | 70.0±6.5(1.0) | 67.2±8.4(4.0) | 67.2±7.7(4.0) | 70.0±6.3(2.9) | 67.9±7.7(5.8) | 69.3±5.5(2.9) | 70.7±5.6(0.0) | |
| | 0.250 | 55.8±4.8(19.5) | 55.8±4.2(21.1) | 55.2±3.0*(21.1) | 54.6±4.3*(22.0) | 55.8±5.4*(22.6) | 56.4±3.6*(21.8) | 56.4±4.8*(21.0) | 57.0±3.4(19.4) | |
| | 0.500 | 50.6±3.8*(27.0) | 51.2±4.4*(27.7) | 49.5±6.0*(29.3) | 48.9±4.9**(30.1) | 51.1±4.4**(29.1) | 51.2±3.8**(29.1) | 51.1±3.8**(28.4) | 52.3±3.3*(26.1) | |
| | 1.000 | 44.5±2.5**(35.8) | 45.0±3.5**(36.4) | 44.5±3.0**(36.4) | 45.0±3.5**(35.7) | 46.5±3.5**(35.5) | 45.5±2.5**(36.9) | 45.5±3.0**(36.3) | 45.5±3.5**(35.6) | |
| Dex | 0.0025 | 35.2±2.0*** (49.2) | 34.8±2.4*** (50.8) | 31.2±2.8*** (55.4) | 32.8±2.0*** (53.1) | 35.2±2.0*** (51.2) | 34.4±2.4*** (52.3) | 34.8±2.4*** (51.2) | 34.0±2.4*** (51.9) | |

a: Inhibition rate (%) was listed in the bracket

* $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$ vs vehicle

Table 5 Effect of ginger oil on vascular permeability induced by bradykinin, histamine, and arachidonic acid ($\bar{x} \pm s$, $n = 10$)

| Group | Dose / (g·kg ⁻¹) | Bradykinin (A_{620}) | Histamine (A_{620}) | Arachidonic acid (A_{620}) |
|--------------|------------------------------|--------------------------|-------------------------|--------------------------------|
| Vehicle | — | 0.053 ± 0.006 | 0.106 ± 0.009 | 0.069 ± 0.004 |
| Ginger oil | 0.125 | 0.032 ± 0.004* | 0.073 ± 0.008* | 0.051 ± 0.004** |
| | 0.250 | 0.025 ± 0.003*** | 0.048 ± 0.004*** | 0.046 ± 0.005** |
| | 0.500 | 0.024 ± 0.002*** | 0.042 ± 0.004*** | 0.044 ± 0.007** |
| Indomethacin | 0.010 | 0.023 ± 0.003*** | 0.056 ± 0.008*** | 0.033 ± 0.004*** |

* $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$ vs vehicle

evaluate possible peripheral effects, and hot-plate assay method was employed for the purpose of preferential assessment of possible centrally mediated analgesic effects (MacDonald *et al.*, 1946). In this study, the ginger oil showed the significant analgesic effects against chemically- and thermally- induced nociceptive pain stimuli in mice. Both results indicated that the oil possessed separately peripheral (writhing reduction) and central effects (thermal reaction time prolongation).

In the rat paw edema model, carrageenan could induce edema formation in three distinct phases according to the mediators involved (Di Rosa, Giroud, and Willoughby, 1971; Di Rosa, 1972). The initial phase occurring during the first hour after sc injection of carrageenan into rat hind paw is mediated by histamine and 5-hydroxytryptamine. After that the increased vascular permeability in the second phase is maintained by bradykinin release up to 2.5 h. Then the third phase, from 2.5 to 6 h, the involved mediators are prostaglandins. The biosynthesis of leukotrienes is suggested to be involved in the fourth phase of carrageenan-induced edema formation. The results of this study suggested ginger oil could inhibit the paw edema induced by carrageenan in different inflammatory phases, which indicated that ginger oil inhibit the release or activity of mediators mentioned above. Similar to our results that the alcoholic ginger extract and 6-gingerol by ip administration could significantly

inhibit carrageenan-induced paw swelling was found in some other researches (Penna *et al.*, 2003; Mascolo *et al.*, 1989; Young *et al.*, 2005).

Non-steroidal anti-inflammatory drugs inhibit the cyclooxygenase and corticosteroids are used to treat rheumatic disorders and osteoarthritis. Ginger was reported to treat rheumatic disorders (Srivastava and Mustafa, 1992), osteoarthritis (Altman and Marcussen, 2001), and gonarthrosis (Wigler *et al.*, 2003). Some patients suffering from such disorders were reported relief in pain and associated symptoms after ginger administration. 6-Gingerol, a component of ginger oil showed suppression of both cyclooxygenase and lipooxygenase metabolites of arachidonic acid (Jolad *et al.*, 2004) and anti-oxidative properties (Masuda *et al.*, 2004). Topical application of 6-gingerol inhibited PMA-induced cyclooxygenase-2 expression and activation of NF- κ B and p38 mitogen-activated protein kinase (Kim *et al.*, 2004). Freund's adjuvant-induced arthritis in rats has been used as a model of human rheumatoid arthritis. The model is of considerable relevance for the study of pathophysiological and pharmacological control of inflammatory processes, as well as the evaluation of analgesic potential or anti-inflammatory effects of drugs (Butler *et al.*, 1992; Fernihough *et al.*, 2004). The initial inflammatory response is developed within hours, but more critical clinical signals emerge from the post-inoculation day

10 and thereafter, and the alterations remain detectable for several weeks (Colpaert *et al*, 1982). According to Abbadie and Besson (1994), maximum arthritic response is obtained in three weeks. Many proinflammatory mediators and cytokines such as leukotrienes, prostaglandins, bradykinin, tumor necrosis factor- α , and interleukin-1 take part in the progression of inflammation. In present study, the ginger volatile oil showed inhibitory effect on edema formation and secondary lesion of the model of CFA-induced arthritis in rats. In accordance with our results, Sharma, Srivastava, and Gan (1994) also found ginger volatile oil, ig given for 26 d, caused a significant suppression of both paw and joint swelling. In addition, our results also indicated that the ginger volatile oil inhibited bradykinin, histamine, and AA-induced vascular permeability in rats.

All these data with our results indicate the ginger volatile oil has potent anti-inflammatory and/or anti-rheumatic property, and the mechanism of these effects at least has relationship with cyclooxygenase and lipoxygenase pathways. And further investigation is warranted for possible development of new classes of analgesic and anti-inflammatory drugs from effective monomer component of ginger oil.

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