Annex C: Red ginger (Zingiber officinale var. Rubrum)

Background

1. A recent review (Zhang et al., 2022) summarises the constituents found in red ginger (also known as *Zingiber officinale* var. rubrum and *Alpinia purpurata*) and its potential medical uses. No information was available on the use of red ginger by pregnant women. The major bioactive compounds in red ginger are vanilloids and based on the chemistry of the side chain they are divided into groups including gingerols and shogaols. (Zhang et al., 2022).

2. Ghasemzadeh et al. reported that the total number of phenolics and flavonoids in red ginger is greater than in common ginger (Ghasemzadeh et al., 2010). Several studies have compared red ginger and white ginger and, at the same concentrations, red ginger is able to elicit stronger effects for the given end point. (See section: Studies comparing red ginger and common ginger). The visual difference between the plants is shown in Figure 1.

3. The consumption of red ginger in the diet is not common due to the difference in taste when compared to common ginger. Red ginger has a strong aroma and more distinctive heat and spiciness than common ginger. Red ginger is more commonly used for health applications and supplementation. Red ginger extract tablets are purported to have anti-inflammatory and anti-nausea effects.

4. The availability of red ginger in the UK is mostly via ecommerce as a root powder and it appears to have a greater presence in the US currently than in the UK. It cannot be ruled out that it is available to purchase from Asian markets/grocery stores but there is no evidence on this. Red ginger root can be purchased online for the cultivation of the plant but it appears difficult to grow in the UK climate.

5. Marketing of supplements/powders is targeted in some instances at pregnant women (dried root extract capsule and powder) for morning sickness and inflammation/pain. There is literature describing its use to manage pain and

wound healing post-partum (Fikriyani, 2023).

Figure 1: Photographs of (A) Red ginger (Zingiber officinale var. rubrum), (B) common ginger, and (C) whole plant of Zingiber officinale var. rubrum.

Biological activity

6. In traditional medicine, red ginger is used for treating headaches, indigestion, nausea, vomiting, and cancer. In addition, it is widely used to treat autoimmune diseases (psoriasis), hypertension, hypercholesteremia, hyperuricemia and bacterial infections (Zhang et al., 2022).

Studies related to pregnancy

7. Hutabarat reported a study that aimed to determine the effects of red ginger extract on reducing blood pressure among pregnant women with gestational hypertension. (Hutabarat et al., 2020) Thirty-four patients were recruited and divided into an experimental and control group. The experimental group received antihypertensive drugs plus red ginger extract at a dose of 500 mg for 14 days and the control group was given antihypertensive drugs with a placebo. There was a significantly greater decrease in blood pressure in the group receiving ginger than in the placebo group. The paper is limited to the effects of interest, and there is no mention of adverse or unexpected effects.

Studies comparing red ginger to common ginger

8. Malondialdehyde (MDA) is the end-product of lipid peroxidation and is used as a biomarker to measure the level of oxidative stress in an organism. A study carried out by Obah et al. compared the protective properties of two varieties of red and common ginger on Fe^{2+}-induced lipid peroxidation in rat brain *in vitro*. (Oboh et al., 2012). Incubation of brain tissue homogenate in the presence of Fe caused a significant increase in the malondialdehyde (MDA) content of the brain. An aqueous extract from both varieties of ginger caused a significant decrease in the MDA concentration of the brain in a dose-dependent manner. The aqueous extract of red ginger had a significantly greater inhibitory effect on Fe2+-induced lipid peroxidation than that of common ginger. The greater inhibitory effect of red ginger might be attributable to its significantly higher phytochemical content.

9. The aim of a study carried out by Handayani et al. was to determine the antibacterial effectiveness of red ginger extract compared to that of common ginger extract in S*treptococcus mutans in vitro*. (Handayani et al., 2018) Both ginger extracts had antibacterial effects on *Streptococcus mutans.* Red ginger extract had greater antibacterial effect against *Streptococcus mutans* than white ginger extract.

Studies on male reproduction

10. Aprilia carried out a study in mice which aimed to determine the effect of administering red ginger ethanol extract on the sperm quality of mice exposed to monosodium glutamate (MSG).(Aprilia et al., 2024) Male mice were randomly divided into groups of 5: (control), MSG 4 mg/g bw and MSG 4 mg/g bw with *Z. officinale* extract 0.4 mg/g bw; all extracts were administered orally for 30 days. Red ginger extract at a dose of 0.4 mg/g body weight was effective in increasing the quality of spermatozoa in mice exposed to MSG. The toxicity of red ginger and MSG was not assessed.

11. A study looking at the effects of red ginger on testicular function in rats was carried out by Sutyarso et al (2016). Using a randomised trial design 24 male rats were split into four groups each consisting of 6 rats. Group 1 received 1 ml of distilled water; group 2 was given 500 mg/kg of ginger extract; group 3 was treated with 500 mg/kg of the extract and 0.5 mg/kg zinc sulfate; and group 4 was fed with 500 mg/kg of extract and 1 mg/kg of zinc. Testosterone levels increased in the ginger extract group, and this was enhanced with the coadministration of zinc.

Studies on antibacterial properties

12. See above for study comparing anti-bacterial testing of red vs common ginger.

13. An antimicrobial study showed that red ginger ethanol extract can inhibit the growth of *Salmonela thyphi*, *Staphylococcus epidermidis*, and *Streptococcus mutans* at a concentration of 500 µg/mL, while *Pseudomonas aeruginosa* was inhibited at a concentration of 250 µg/mL. (Juariah et al., 2023) Further observation of bacterial cell leakage showed that the higher the red ginger ethanol extract concentration, the higher the bacterial cell leakage.

14. A separate study claimed limited antimicrobial activity of red ginger extract when compared to oil and concluded that red ginger extract did not inhibit bacterial activity, whereas red ginger essential oil at a concentration of 100% inhibited the growth of *E. coli* and *S. aureus* bacteria. (Kapelle et al., 2024) The paper commented on the significant difference in constituents of the two test items.

15. There are several studies in addition to the ones described which claim antimicrobial effects of red ginger.

Studies on blood glucose

16. A study on mice by Dewi & Jumain aimed to determine the effectiveness of red ginger extract in decreasing blood glucose levels. (Dewi & Jumain, 2023) This study was conducted using alloxan as a diabetes inducer, Na carboxymethyl cellulose 1% as a negative control, glibenclamide as a positive control, and red ginger extract doses of 2 %, 5 % and 7 % orally for 7 days in 5 groups of male mice as test animals. It was concluded that the administration of red ginger extract significantly reduced blood glucose levels in alloxan-induced diabetic mice at concentrations of 2%, 5% and 7% (most effective) (p0.05).

Other studies

17. An *in vitro* study was carried out to determine the inhibitory activity of red ginger rhizome extract on the rate of prostaglandin production. (Fikri et al., 2016) This research was conducted using commercial Colorimetric COX Inhibitor Screening Assay kits from Cayman Chemical Company, with ovine COX-1 and human COX-2. The rate of prostaglandin formation was inhibited by red ginger extract, the potency being greater with COX-2 than COX-1. Red ginger extract was a much less potent inhibitor of COX-1 and COX-2 than aspirin (acetosal).

18. A study carried out by Sarmoko et al. aimed to determine the effect of red ginger extract as a co-chemotherapy agent with 5-fluorouracil (5-FU) on WiDr colon adenocarcinoma cells using an MTT assay. (Sarmoko et al., 2020) It was concluded that red ginger extract increases the cytotoxic activity of 5-FU, therefore it has the potential to act as a nutraceutical agent in the treatment of colon cancer. Red ginger alone reduced cell viability when compared to that of the control group at all concentrations (15-500 µg/ml), with an IC50 between 62.5 and 125 µg/ml.

19. Research has shown that red ginger plants growing in different places or locations have different tolerances, which leads to differing content in their constituent metabolites. This was demonstrated by Febriani et al. by determining the LC50 in zebra fish of methanolic extracts of red ginger harvested from three different geographical locations in Indonesia. (Febriani et al., 2023) The LC50 differed relative to the location from which the plant was harvested, although not by very much.

20. Nirvana *et al.* reported a study on the anti-hypercholesterolemic activity of red ginger. (Nirvana et al., 2020) In this study 25 rats were divided into 5 treatment groups receiving 0, 200, 350, or 500 mg/kg bw red ginger extract or simvastatin 7.2 mg/kg bw, as a positive control. Before treatment, hypercholesterolemia was induced in the rats by feeding a high fat diet and adding propylthiouracil to their drinking water to provide a dose of 2 mg/kg bw. Treatment with red ginger extract and simvastatin was carried out for 2 weeks. Red ginger extract had significant beneficial effects on the lipid profile and body weight changes in hyperlipidaemic rats at all doses, with little difference between doses, the effects being comparable to those with the positive control, simvastatin. Data were presented only on the lipid profile and body weight of the animals.

21. Studies with an *in vitro* model of epidermal inflammation (not specified) indicated that red ginger extract (chloroform) samples directly inhibited keratinocyte proliferation and the production of IL-20 and IL-8, both of which are key psoriasis-promoting cytokines. (Nordin et al., 2013) The authors stated that the experiments showed that the two identified compounds (6-shogaol and 1-dehydro-6-gingerdione) from the active fraction of the red ginger extract effectively inhibited nitric oxide (NO) and prostaglandin E2 (PGE2) production.

22. Razali evaluated the vasorelaxant and vasoconstriction effects of red ginger extract *in vivo on* spontaneously hypertensive rats (SHRs) and on isolated thoracic aortic rings from SHRs. (Razali et al., 2020) Red ginger extract (petroleum ether) when dosed at 250 mg/kg body weight per day (only dose tested)) for 28 days resulted in gradual attenuations of systolic blood pressure, mean arterial blood pressure and heart rate in SHRs over the period of treatment. Aqueous, chloroform and methanol extracts had no effect. All of the extracts produced significantly greater vasorelaxation compared to control *in vitro* in phenylephrine preconstricted aortic rings from SHRs. The petroleum ether extract was the most potent. Additional studies showed that the effects of the extract on vasorelaxation in rat aorta was both endothelium-dependent and -independent.

Chemical analysis of the extract suggested that 6-gingerol, 8-gingerol and 6-shogaol may be responsible for the antihypertensive effects of the extract of red ginger.

23. Treatment with gentamicin can lead to cell membrane damage and the release of SGOT and SGPT from the liver. This increase can be measured in serum. Humairo et al. studied the effects of red ginger extract on this response to gentamicin in white rats (no further information). Groups of 5 male rats were treated with 1% carboxymethyl cellulose Na and water as a negative control; 1% carboxymethyl cellulose Na and 80 mg/kg bw of gentamicin; 80 mg/kg bw of gentamicin and red ginger extract (no further details) at a dose of 100, 200, or 400 mg/kg bw. Treatment with gentamicin resulted in increased levels of SGPT and SGOT in the serum. Treatment with all doses of red ginger extract partially prevented the increase in SGOT levels, the effect being dose dependent. Treatment with red ginger extract also reduced the effect of gentamicin on SGPT levels, dose-dependently, and completely prevented it at 400 mg/kg bw. (Humairo et al., 2024)

Summary

24. There is limited evidence to suggest that red ginger is commonly purchased or consumed in the UK. Health claims by red ginger supplement manufacturers reference the benefits of its consumption for alleviating emesis and pain during and following pregnancy. However, studies in this area are primarily from hospital obstetrics settings in Asia (largely Indonesia) where red ginger is grown and readily available. Studies carried out primarily in Indonesia and Malaysia comment on the frequent and common use of red ginger for medicinal purposes.

25. There are limited toxicological data available on red ginger and in general studies looking at the medicinal potential of red ginger have not assessed or commented on effects outside of those of interest. There are some examples of comparisons of red (*Zingiber officinale* var. Rubrum) vs common (*Zingiber officinale*) ginger in the toxicological literature. In these studies, red ginger showed enhanced antimicrobial effects and a greater ability to inhibit oxidative damage when compared to common ginger. This demonstrates that the constituent profile of the two differ. However, there are no detailed studies that compare the bioactivities of red ginger and common ginger under the same experimental conditions that clearly explain why red ginger is preferred in some cultures for medicinal purposes (Zhang et al., 2022).

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