Annex C

Annex D: Red ginger

Red ginger (Zingiber officinale var. rubrum)

Background

1. A recent review (Zhang et al., 2022) on red ginger (also known as *Zingiber officinale var. rubrum* and Alpinia purpurata) summarises the constituents found in red ginger and its potential medical uses. This review does not describe the use of red ginger during pregnancy. 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 phenolic and flavonoids in red ginger is higher than in common ginger (Ghasemzadeh et al., 2010). Several studies compare 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 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 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. Red ginger extract tablets are a purported to have anti-inflammatory and anti-nausea effects.

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

5. Marketing 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 presents a study which aimed to analyse 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 significant decrease in blood pressure. The paper is limited to the effects of interest, and 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 compares the protective properties of two varieties of red and common ginger Fe^{2+} induced lipid peroxidation in rat brain *in vitro*. (Oboh et al., 2012) Incubation of the brain tissue homogenate in the presence of Fe caused a significant increase in the malondialdehyde (MDA) contents of the brain. The 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 higher inhibitory effect on both Fe2+-induced lipid peroxidation than that of common ginger. The higher

inhibitory effect of red ginger could be attributed to its significantly higher phytochemical content.

9. The aim of a study carried out by Handayani was to determine the antibacterial effectiveness of red ginger extract compared to common ginger extract in S*treptococcus mutans in vitro*. (Handayani et al., 2018) Red ginger extract and white ginger extract had an antibacterial effect on *Streptococcus mutans.* Red ginger extract at concentration of 60% has greater antibacterial effect against *Streptococcus mutans* compared to 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 of on the sperm quality of mice exposed to MSG.(Aprilia et al., 2024) This study used male mice which were randomly divided into groups of 5: (control), MSG 4 mg/g bw and MSG 4 mg/g bw and Z. officinale extract 0.4 mg/g bw, and all extracts were administered orally for 30 days. Red ginger extract at a dose of 0.4 mg/g body weight proves to be effective in increasing the quality of spermatozoa 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. (Sutyarso et al., 2016) Using a randomised trial design 24 male rats were split into four groups consisting of 6 rats. Group 1 received 1ml of distilled water; group 2 given 500 mg/kg of ginger extract; group 3 treated with 500 mg/kg of the extract and 0.5 mg/kg zinc sulfate; and group 4 fed with 500 mg/kg of extract and 1 mg/kg of zinc. Testosterone levels increased in the ginger extract group and this is 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 thypi*, *Staphylococcus epidermidis*, and *Streptococcus mutans* at a concentration of 500 µg/mL, while *Pseudomonas aeruginosa* 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 not inhibit bacterial activity, whereas red ginger essential oil at a concentration of 100% provided inhibition of 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 was carried out to determine the effect of the dried red ginger powder on fasting blood glucose (FBG) and 2-hour postprandial blood glucose patients with type 2 diabetes mellitus. (Almasdy et al., 2022) 33 patients divided into two groups: the control group and the treatment group. Exclusion criteria included pregnant and lactating mothers. The treatment group received 3g of red ginger powder per day with standard medicines while the control group received a standard drug without red ginger powder. Dried red ginger powder at a dose of 3 grams per day, significantly affected the decline in fasting blood glucose. Dried red ginger powder 3 grams a day, did not influence the 2-hour postprandial blood glucose (diet was not controlled and this may have had an effect).

17. This study discussed adverse effects which would be considered self-limiting. The article states “the use of dried red ginger powder 3 x 2 capsules daily after every meal for a month showed that no adverse events reported by patient’s irritation. Irritation of the stomach is the major side effects that have been reported by previous researchers. Other side effects that arise during the study were diarrhoea though only 2 of 16 patients who received treatment. Ginger can increase intestinal peristalsis thus estimated diarrhoea in patients caused by it. In addition, some patients also feel a headache, burning sensation in the throat. This reaction causes one patient withdrew from the study on the second day of use. Yet another patient recognizes that this reaction only occurs in the first three days of drug consumption capsule that researchers provide. Then the reaction goes away by itself after 3-7 days of use”. Note that no references are given for these “major side effects” and that these statements may be referring to common ginger. No other studies found referred to any adverse effects as a result of red ginger administration.

18. A study on mice by Dewi aimed to determine the effectiveness of Red Ginger extract against decreasing blood glucose levels. (Dewi & Jumain, 2023)

This study was conducted using alloxane as a diabetes inducer, Na CMC 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 test animals. It was concluded that the administration of red ginger extract has been shown to significantly reduce blood glucose levels in alloxane-induced mice at concentrations of 2%,5% and 7% (most effective) (p 0.05).

Other studies

19. A study carried out by Devia to determine the effect of the consumption of red ginger stew on dysmenorrhea in high school adolescents. (Rahayu et al., 2018) The process in formulating the red ginger stew included 15 mg of red ginger boiled with 400 ml of water reducing to 200 ml then add. This is administered as a drink to participants. The quasi-experiment with non-equivalent control group design was carried out by purposive sampling on 54 respondents. It was concluded that consumption of red ginger stew (Zingiber Officinale var. Rubrum) reduced the symptoms of dysmenorrhea. There is no information on dosing and results are obtained from questionnaires which did not request the reporting of adverse effects.

20. An *in vitro* study was carried out to determine the inhibitory activity of red ginger rhizome infusion on the rate of prostaglandin production. (Fikri et al., 2016) This research was conducted by colorimetric COX Inhibitor Screening Assay method. The rate of prostaglandin formation by red ginger infusion in COX-1 was slower than COX-2. Inhibitory strength of red ginger infusion in COX-1 and COX-2 is weaker than acetosal (aspirin).

21. A study carried out by Sarmoko 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 acts as a nutraceutical agent in the treatment of colon cancer. Red ginger alone reduced cell viability when compared to the control group at all concentrations.

22. 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 by determining the LC50 of 3 different red ginger methanolic extracts in zebra fish. (Febriani et al., 2023) The LC50 differed relative to location from which the plant was harvested.

23. Nirvana *et al.* present a study on the anti-hypercholesterolemia 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. Before the treatment rats were induced a on a high fat diet. The treatment of red ginger extract and simvastatin were carried out for 2 weeks. The results of *in vivo* test showed that red ginger extract had a significant effect on lipid profile and body weight changes in hyperlipidemia rats at a dose of 200 mg/kg bw and was comparable to the positive control of simvastatin. Data was only presented on the lipid profile and body weight of the animals with no discussion on the higher dose groups.

24. An *in vitro* model of epidermal inflammation indicated that red ginger extract (chloroform) samples directly inhibited keratinocyte proliferation and the production of IL-20 and IL-8, both are key psoriasis-promoting cytokines. (Nordin et al., 2013) The author 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.

25. Razali evaluated vasorelaxant and vasoconstriction effects of red ginger extract on live rats and isolated aortic rings of spontaneously hypertensive rats (SHRs). (Razali et al., 2020) This demonstrated that red ginger extract (petroleum ether) when dosed at 250 mg/kg body weight per day may exert an antihypertensive effect in the SHR model. Possible active compounds that contribute to the vasorelaxant effects are 6-gingerol, 8-gingerol and 6-shogaol.

26. Treatment with gentamicin can lead to cell membrane damage and the release of SGOT and SGPT. This increase can be measured in serum. A study demonstrated that red ginger ethanol extract can inhibit the increase in SGOT levels in white rats induced by Gentamicin 80 mg/kg BW with an effective dose of 400 mg/kg BW and can inhibit the increase in SGPT levels in white rats induced by Gentamicin 80 mg/kg BW with an effective dose of 200 mg/kg BW. (Humairo et al., 2024).

Summary

27. There is limited evidence to suggest that red ginger is commonly purchased or consumed in the UK. Health claims relating to red ginger reference the benefits of consuming red ginger for 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 in primarily in Indonesia and Malaysia comment on the frequent and common use of red ginger for medicinal purposes.

28. There is limited toxicological data available on red ginger and studies looking at the medicinal potential of red ginger do not assess or comment on effects outside of those of interest. There are some examples of comparisons or red vs common ginger on toxicological literature. In these studies, red ginger has an enhanced effect when compared to common ginger. This demonstrates that the constituent profile of the two differ.

References

Almasdy, D., Martini, R. D., & Arman, E. (2022). **The effect of dried red ginger powder *zingiber officinale var rubrum)* on patients with type 2 diabetes *mellitus*.**

Aprilia, N. H. L. A., Rahayu, S., & Marhendra, A. P. W. (2024). Effect of Curcumin (Curcuma xanthorriza) and Red Ginger (Zingiber officinale var. Rubrum) Ethanol Extract on Improvement of Mice Sperm Quality Exposed by Monosodium Glutamate. **The Journal of Experimental Life Science**, *14*(1), 18–24.

Dewi, S. T., & Jumain, J. (2023). The Effectiveness of Red Ginger Extract (Zingiber Officinale Var. Rubrum) on Decreased Blood Glucose Levels in Mice (Mus Musculus). **Indonesian Health Journal**, *2*(1), 16–21.

Febriani, E. F., Widodo, M. S., & Faqih, A. R. (2023). Phytochemical Analysis from Three Different Methanolic Extracts of Red Ginger (Zingiber officinale var. Rubrum) Against LC50 Treatment of Zebra Fish as Model Fish. **Journal of Aquaculture and Fish Health, 12**(2), 179–190. https://doi.org/10.20473/jafh.v12i2.36747.

Fikri, F., Saptarini, N. M., & Levita, J. (2016). The inhibitory activity on the rate of prostaglandin production by Zingiber officinale var. Rubrum. **Pharmacology and Clinical Pharmacy Research, 1**(1), 33–41.

Fikriyani, E. S. (2023). The Effect of Consumption of Red Ginger Extract on the Pain Scale Intensity of Perineal Laceration Wounds in Postpartum Mothers in the Working Area of Jalancagak Health Center, Subang Regency, Indonesia. **Archives of The Medicine and Case Reports, 4**(5), 492–496.

Ghasemzadeh, A., Jaafar, H. Z. E., & Rahmat, A. (2010). Antioxidant Activities, Total Phenolics and Flavonoids Content in Two Varieties of Malaysia Young Ginger (Zingiber officinale Roscoe). Molecules, 15(6), 4324–4333. https://doi.org/10.3390/molecules15064324.

Handayani, H., Achmad, H., Suci, A. D., Firman, M., Mappangara, S., Ramadhany, S., Pratiwi, R., & Wulansari, D. P. (2018). Analysis of antibacterial effectiveness of red ginger extract (Zingiber Officinale Var Rubrum) compared to white ginger extract (Zingiber Officinale Var. Amarum) in mouth cavity bacterial streptococcus mutans (In-Vitro). **Journal of International Dental and Medical Research, 11** (2), 676–681.

Humairo, A. W., Sukmanadi, M., Yuliani, M. G. A., Sudjarwo, S. A., Santoso, K. P., & Luqman, E. M. (2024). **Effect of red ginger extract (Zingiber officinale var. Rubrum) of SGOT and SGPT levels in white rats (Rattus norvegicus) induced by Gentamicine**.

Hutabarat, N. C., Supriyana, S., & Suhartono, S. (2020). The Effect of Extract Red Gingger (Zingiber Officinale Var. Rubrum) on Reducing the Blood Pressure Level among Maternal with Gestasional Hypertension. **International Journal of Nursing and Health Services (IJNHS), 3**(4), Article 4. https://doi.org/10.35654/ijnhs.v3i4.219.

Juariah, S., Bakar, F. I. A., Bakar, M. F. A., Endrini, S., Kartini, S., & Ningrum, R. S. (2023). Antibacterial Activity and Inhibition Mechanism of Red Ginger (Zingiber officinale var. Rubrum) Ethanol Extract Against Pathogenic Bacteria. **Journal of Advanced Research in Applied Sciences and Engineering Technology, 30** (1), Article 1. https://doi.org/10.37934/araset.30.1.145157.

Kapelle, I. B. D., Mauhurry, M. F., & Neite, P. N. (2024). Testing the Antibacterial Activity of Red Ginger Essential Oil and Red Ginger Methanol Extract. **EKSAKTA: Berkala Ilmiah Bidang MIPA, 25(**01), Article 01. https://doi.org/10.24036/eksakta/vol25-iss01/469.

Nirvana, S. J., Widiyani, T., & Budiharjo, A. (2020). Antihypercholesterolemia activities of red ginger extract (Zingiber officinale Roxb. Var rubrum) on wistar rats. **IOP Conference Series: Materials Science and Engineering, 858**(1), 012025. https://doi.org/10.1088/1757-899X/858/1/012025.

Nordin, N. I., Gibbons, S., Perrett, D., & Mageed, R. A. (2013). **Immunomodulatory effects of *Zingiber officinale Roscoe var. Rubrum* (Halia Bara) on inflammatory responses relevant to psoriasis. 4**(1).

Oboh, G., Akinyemi, A. J., & Ademiluyi, A. O. (2012). Antioxidant and inhibitory effect of red ginger (Zingiber officinale var. Rubra) and white ginger (Zingiber officinale Roscoe) on Fe2+ induced lipid peroxidation in rat brain in vitro. **Experimental and Toxicologic Pathology, 64**(1–2), 31–36. https://doi.org/10.1016/j.etp.2010.06.002.

Rahayu, K. D., Guite, I., & Syafrulloh, H. (2018). The Effect Of Red Ginger Release Consumption (Zingiber Officinale Var. Rubrum) Against Dismenore In Adolescent High School. **Journal of Maternity Care and Reproductive Health, 1**(2).

Razali, N., Dewa, A., Asmawi, M. Z., Mohamed, N., & Manshor, N. M. (2020). Mechanisms underlying the vascular relaxation activities of Zingiber officinale var. Rubrum in thoracic aorta of spontaneously hypertensive rats. **Journal of Integrative Medicine, 18**(1), 46–58. https://doi.org/10.1016/j.joim.2019.12.003.

Sarmoko, S., Solihati, I., Setyono, J., Ekowati, H., & Fadlan, A. (2020). Zingiber Officinale Var. Rubrum Extract Increases the Cytotoxic Activity Of 5-Fluorouracil In Colon Adenocarcinoma Widr Cells. **Indonesian Journal of Pharmacy,** 266–272. https://doi.org/10.22146/ijp.859.

Sutyarso, S., Muhartono, M., Busman, H., & Kanedi, M. (2016). Testicular function of rats treated with water extract of red ginger (zingiber officinale var. Rubrum) combined with zinc. **Journal of Food and Nutrition Research, 4**(3), 157–162.

Zhang, S., Kou, X., Zhao, H., Mak, K.-K., Balijepalli, M. K., & Pichika, M. R. (2022). Zingiber officinale var. rubrum: Red Ginger’s Medicinal Uses. **Molecules, 27**(3), 775. https://doi.org/10.3390/molecules27030775.