Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Statement on the Safety of Ginger Supplement Use in Pregnancy

Background

1. In 2019, the Scientific Advisory Committee on Nutrition (SACN) agreed to conduct a risk assessment on nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery; this would include the effects of chemical contaminants and excess nutrients in the diet.

2. SACN agreed that, where appropriate, other expert committees would be consulted and asked to complete relevant risk assessments e.g., in the area of food safety advice. This subject was initially discussed during the COT's horizon scanning item at their January 2020 meeting, with a scoping paper being presented to the COT in July 2020. This included background information on a provisional list of chemicals proposed by SACN.

3. Following discussion at the September 2020 meeting, the COT agreed that papers on a number of substances should be prioritised, including the use of dietary supplements during pregnancy.

4. A scoping paper (TOX/2020/51) was presented to the Committee in October 2020, in which the dietary supplements commonly used during pregnancy were reviewed. These were supplements that were not officially recommended by the relevant authorities, but which have been promoted by anecdotal evidence and unofficial sources as having various purported benefits. The review was confined to herbal dietary supplements that would be regulated under food law, and which would not be considered to be traditional herbal medicines, which are the responsibility of the Medicines and Healthcare Products Regulatory Agency (MHRA).

5. Paper TOX/2020/51 provided a detailed summary of ginger, chamomile, raspberry leaf, echinacea, peppermint oil and leaves, dandelion, and evening primrose oil, focusing where available, on studies relevant to pregnancy and maternal outcomes. The main areas of investigation were general toxicity to the mother, effects on the development of the fetus or embryo, and possible interactions with medicines. The COT agreed that ginger required further investigation, noting that both human and animal *in vitro* and *in vivo* data were available. The following paper provides the advice of the COT on whether exposure to ginger would pose a risk to maternal health.

6. In May 2021, the Committee considered the potential effects of ginger and ginger supplements during pregnancy and lactation. Paper TOX/2021/26 (Available on the COT website) reviewed the available data on toxicity to the mother, effects on the development of the fetus or embryo, and possible interactions with drugs, as well as data on potential exposure.

7. Overall, it was concluded that the data were limited. The human data presented were not strongly indicative of any toxicological concern but there were some indications of possible side effects in mothers and many uncertainties. Ginger did not appear to be systemically toxic but in studies in experimental animals there was some evidence for reprotoxic effects at high doses. The Committee suggested looking at the animal data in detail to try to identify a point of departure (POD) (No Observed Adverse Effect Level - NOAEL), followed by calculation of the potential exposure to ginger supplements to determine whether there was cause for concern.

8. Paper TOX/2021/51 provided further information with respect to animal studies, primarily centred on the effects of ginger on prostaglandin production, reproductive and developmental toxicity, the possible contaminants present in ginger, and exposure to ginger supplements.

9. Members noted that although the different ginger extracts were not comparable across animal studies, they did appear to exhibit some biological activity in the early stages of pregnancy at high doses.

10. The COT noted that intake of ginger in foodstuffs should also be considered because ginger was consumed not only as a supplement but also as part of the diet in foods such as ginger biscuits, tea and ginger beer. Therefore, aggregate exposures would need to be considered when addressing the safety of ginger supplement use during pregnancy.

Information on ginger

11. Ginger (*Zingiber officinale*) is a flowering tropical plant originating in Southeast Asia and grown in warm climates including China, India, Africa and the Caribbean. Ginger is commonly consumed as fresh root, dried root powder and capsule (encapsulated dried powder) forms, as a liquid extract, preserved in syrup or sugar and as a tea.

Uses

12. It is the rhizome (underground stem) of the ginger plant that is commonly used as a spice and flavouring, it is used in many countries around the world and is growing increasingly popular as a natural remedy, due to its purported immunomodulatory properties and also to alleviate motion sickness and post-operative nausea and vomiting. Ginger has been recommended as a possible nonpharmacological treatment for mild to moderate nausea and vomiting in pregnancy (NHS 2024; NICE 2021) and has also been used as a dietary supplement and a traditional remedy in many cultures for this and other purposes. Ginger is included in the official pharmacopoeias of some western countries.

Constituents

13. Over 100 compounds have been identified in ginger extracts, most being terpenoids - mainly sesquiterpenoids (α-zingiberene, β-sesquiphellandrene, β-bisabolene, α-farnesene, ar-curcumene (zingiberol)) and smaller amounts of

monoterpenoids (camphene, β-phellandrene, cineole, geraniol, citral, terpineol, borneol) (EMA, 2012).

14. The ginger rhizome contains two main classes of constituents: the essential oils responsible for the aroma, and the main pungent principles, gingerols and shogaols. Organic acids are also present in smaller amounts. Varying with the area of cultivation, gingerols make up 4-7.5% of the pungent principles, the main one being 6-gingerol. Gingerols of other chain lengths are also present in smaller amounts.

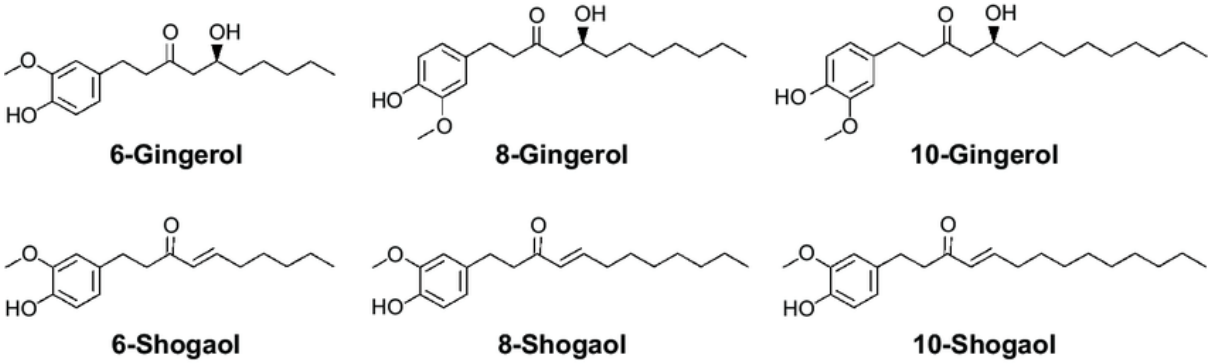

Figure 1. The structures of the main constituents of the ginger rhizome.

Reviews by other risk assessment bodies

15. Ginger is included in the official pharmacopoeias of several western countries. Ginger is classified as 'Generally Recognised as Safe' (GRAS) by the United States Food and Drug Administration (FDA). However, few specific studies have been carried out to evaluate the safety of ginger use during pregnancy and lactation. A report by the National Institute for Health and Care Excellence (NICE) cites a number of short duration trials which have been conducted in pregnant women (NICE, 2021).

16. In 2008, the Danish company Ferrosan A/S withdrew their product GraviFrisk – a product containing 6 g of dried ground ginger – from market, due to concerns

around the lack of safety data with respect to the use of supplements containing highly concentrated ginger extracts by pregnant women (Dietz *et al*., 2016).

17. In their 2012 report on ginger root in powdered form, the European Medicines Agency (EMA) concluded “The ginger extract dosages to provoke acute toxicity are high and much higher than usually administered dosages (factor of 10-15 for an adult). There is some evidence that ginger root may cause rodent testicular weight to increase by repeated high dosages of ginger root extract (2,000 mg/kg). Ginger root has mutagenic as well as antimutagenic properties in microbial test systems. Developmental toxicity studies in rats are difficult to interpret, however, it is probably not a cause for concern. In general, toxicity studies of ginger are considered inadequate at least regarding genotoxicity, carcinogenicity and, partially, reproductive and developmental toxicity.”

18. The Norwegian Food Safety Authority issued a warning regarding the use of ginger supplements and ginger-containing shots during pregnancy. This was based on a risk assessment carried out by the Danish Technical University and the Danish Veterinary and Food Administration (DTU, 2018). The assessment, based on animal studies, including one in which rats were treated with a freshly grated ginger preparation with ginger at concentrations of 20-50 g/L in water, found that even the lowest dose, 20 g/L – the equivalent of 1,784 mg/kg bw, increased the incidence of abortion in rats. The Norwegian Food Safety Authority concluded that while women would consume less ginger (124-329 mg, which is equivalent to 1.8-4.7 mg/kg bw, assuming a body weight of 70 kg), there remains cause for concern and fetal risk cannot be excluded.

19. Recently, the Finnish Food Authority issued a recommendation against the use of products containing ginger concentrate or extract, ginger tea and food supplements containing ginger by pregnant and breastfeeding women, infants and toddlers, schoolchildren, the elderly and individuals with weakened immunity (Finnish Food Authority, 2019). It was noted that the concentrates contained substances that may be harmful and safe consumption levels were unknown.

20. The Expert Panel for Cosmetic Ingredient Safety (U.S.) assessed the safety of ginger-derived ingredients for use in cosmetics and determined that they are safe in cosmetics in the present practices of use when formulated to be non-sensitising (Belsito, 2021). The report describes a number of human and animal studies where ginger was administered orally, including a short-term clinical study where seventy participants were given an oral dose of either steamed ginger extract (200 mg in capsule form; n = 36), or a placebo (n = 34), daily. All clinical test results were normal, and all participants completed the study. No extract-related adverse effects were observed.

Health-based guidance values

21. There are currently no health-based guidance values (HBGV) with respect to ginger or its main components.

22. The NHS recommends, among other suggestions, trying foods or drinks containing ginger to ease symptoms of morning sickness and state that during pregnancy a person should check with a pharmacist before taking ginger supplements (NHS, 2024). NICE also recommended that ginger in fresh, tea, capsule, or syrup form could be used as a non-pharmacological intervention for mild to moderate nausea and vomiting in pregnancy (NICE, 2021). Anecdotally, 1-1.5 g per day of ginger has been recommended during pregnancy from online sources such as Healthline and Mother and Baby (Healthline, 2020; Mother and Baby, 2022). It is advised that supplements should be used in pregnancy only under the advice and supervision of a medical professional.

Red ginger

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

24. The consumption of red ginger in the diet is not common due to the difference in taste when compared with common ginger. Available evidence suggests that red ginger is not commonly purchased or consumed in the UK.

25. Health claims from producers of red ginger supplements reference the benefits of its consumption for emesis and pain during and following pregnancy. Studies on this are primarily from hospital obstetrics settings in Asia (largely Indonesia), where red ginger is grown and readily available.

26. There are only 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 of red vs common ginger in the toxicological literature. In these studies, red ginger has an enhanced effect when compared to common ginger.

27. The Committee noted that only limited toxicological data on red ginger are available, and this is summarised in Annex C paragraph 27 and 28.

Toxicology Overview

28. It was noted that some studies reported effects of ginger on the testes and, though not relevant for females, they were nevertheless regarded as indicating a potential reprotoxic effect. Studies suggest that ginger affected the viability of pregnancy at high doses; however, with no strong human data, the COT concluded that more work was required. Further, possible fetotoxicity based on evidence from animal data, genotoxicity and possible drug interactions should be further investigated.

29. Discussion paper TOX/2021/26 reviewed the available studies on cytotoxicity, mutagenicity, acute, reproductive and developmental toxicity, lactation and possible drug interactions as well as data on potential exposure in pregnancy, covering both animal and human studies. The results from these reports were variable due to the

differences in the forms and extracts of ginger tested and as a result, some findings were contradictory.

30. Paper TOX/2021/51 provided further information with respect to animal studies, contaminants and exposure to ginger supplements, primarily centred on the effects of ginger on prostaglandin production, reproductive and developmental toxicity and the possible contaminants present in ginger. The Committee noted that the papers reviewed covered ginger in a range of forms including fresh, aqueous, dried and alcohol extracts.

31. The toxicological data in this report have been divided into two sections: the first includes studies in which ginger was administered in forms similarly to those in traditional culinary uses; and the second includes studies using ginger extracts and other concentrated forms.

32. Dry ginger powder was administered in some of the studies. Where the dose was ≤ 4 g/day (equivalent to approximately 2 teaspoons) they have been included in the section on traditional culinary uses, and if it was > 4 g/day they were included in the extracts section.

Toxicology of ginger root in traditional culinary uses

Reproductive and developmental toxicity

Animal studies

33. Reproductive and developmental toxicity has been investigated in studies in rats. In a study by Wilkinson (2000), three groups of pregnant Sprague-Dawley rats were administered either a control (unspecified), or 20 g/L or 50 g/L ginger tea - prepared by the infusion of grated ginger in water then filtered and administered via the drinking water - during days 6 to 15 of gestation. No further details were provided regarding specific compounds of interest. While no maternal toxicity was observed, embryonic loss in the treated groups was found to be twice that of the controls. Exposed fetuses were found to be significantly heavier than controls but showed no

gross structural malformations. The authors concluded that the results of this study suggest that *in utero* exposure to ginger tea results in early embryonic loss and increased growth in surviving fetuses.

Human studies - exposures in pregnancy

34. In a double-blind randomised crossover trial, 27 pregnant women were administered capsules containing either 250 mg ginger in powdered root form or 250 mg lactose as a placebo, four times per day, for four days followed by a wash out period of 2 days prior to a further 4 days administration of ginger or placebo alternative to the treatment during phase 1 (Fischer-Rasmussen et al., 1990). Two subjects did not carry to term: one subject from the ginger group had a spontaneous abortion, one elected. Of the remaining 25 subjects, no adverse effects were observed.

35. Of the available human studies, few explicitly addressed the safety of ginger consumption during pregnancy, most being incidental to other studies. In a double-blind study by Vutyavanich et al. (2001), 32 women were given 1 g of dried ginger in capsule form for 4 days. Of those in the ginger group, one spontaneous abortion was reported compared to 3 in the placebo group. Equally, for delivery by caesarean section, there was no difference between the groups. No congenital abnormalities were observed in any baby carried to term. The group concluded that there were no significant adverse effects of ginger on pregnancy outcome.

36. An observational study in humans examined 187 pregnant women who took ginger in their first trimester and compared them to 187 pregnant women exposed to nonteratogenic drugs that were not antiemetic drugs (Portnoi et al., 2003). Three major malformations were reported in the ginger group, ventricular septal defect (VSD), right lung abnormality, and kidney abnormality (pelviectasis) and one child was diagnosed with idiopathic central precocious puberty at age 2 years. The mother was reported to have taken 250 mg of ginger in capsules four times a day from 11 to 20 weeks of gestation in addition to dimenhydrinate and doxylamine/vitamin B6 (Diclectin) during the first trimester of pregnancy. In the comparison group, there were two major malformations, consisting of a VSD and bladder exstrophy. The

authors concluded that the results suggested ginger does not increase the rate of major malformations above the baseline rate of 1%-3%. No significant difference between the two groups in terms of live births, spontaneous abortions, stillbirths, therapeutic abortions, birth weight, or gestational age were reported, however the comparison group had more infants weighing less than 2,500 g (12 vs 3, P<0.001) and the ginger group had 8 sets of twins (i.e. approximately 4 in 100 births), compared with an expected background rate of 1 in 80 to 1 in 100 births. There were no twins reported in the control group.

37. Ensiyeh et al. (2009), investigated the effectiveness of ginger versus vitamin B6 for treatment of nausea and vomiting in pregnancy (NVP) in women before 17 weeks' gestation. Seventy women were randomised to receive either ginger at a dose of 1 g per day or B6 at 40 mg per day for 4 days. The ginger group reported 2 spontaneous abortions, compared to one in the B6 group. Of the babies brought to term, no congenital anomalies were observed, and all babies were discharged in good health.

38. Whilst also examining the use of ginger in the treatment of nausea and vomiting in pregnancy, Smith et al. (2004) noted 3 spontaneous abortions in the group taking 1.05 g ginger compared to 9 in the group taking 75 mg B6 daily for 3 weeks, however the overall risk of pregnancy complications did not differ by study group.

39. Chittumma (2007) compared the effectiveness of ginger and vitamin B6 for treatment of nausea and vomiting in pregnancy. One hundred and twenty-six pregnant women, with a gestational age of < 16 weeks received either 650 mg of ginger or 25 mg of vitamin B6 three times per day for 4 days. Ginger and vitamin B6 significantly reduced nausea and vomiting scores from 8.7 ± 2.2 to 5.4 ± 2.0 and 8.3 ± 2.5 to 5.7 ± 2.3 respectively, ($p < 0.05$). There were some minor side effects in both groups, 25.4% and 23.8% ($p = 0.795$) respectively, such as sedation, heartburn, arrhythmia.

40. Heitmann et al. (2013) analysed data on ginger use during pregnancy from the Norwegian Mother and Child Cohort study. Among the 68,522 women in the study, 1,020 (1.5 %) women reported using ginger during pregnancy. The use of ginger during pregnancy was not associated with any increased risk of congenital malformations. No increased risk for stillbirth/perinatal death, preterm birth, low birth weight, or low Apgar score was detected for the women exposed to ginger during pregnancy compared to women who had not been exposed.

41. The COT considered the possible mode of action of the purported benefits of ginger on nausea. It was theorised that ginger might decrease prostaglandin levels, which were linked to nausea. The effects on prostaglandin levels are covered from paragraph 105 onwards.

42. Overall, it was concluded that there were limited data on the effects of ginger in traditional culinary uses during pregnancy. The human data presented were not strongly indicative of any toxicological concern but there were many uncertainties. Ginger did not appear to be systemically toxic but reprotoxic effects have been reported in animal studies. However, there is no convincing evidence for such effects in human studies.

Lactation

43. With respect to lactation, the focus of available studies (Lamxay *et al.*, 2011; Kaygusuz *et al.*, 2021; Dilokthornsakul *et al*., 2022) was on the effect of ginger on milk production and volume rather than safety and therefore, the effect of exposure during lactation has not been fully investigated.

Effect on P450 (CYP) Enzymes and Herb-Drug Interactions

44. Ginger was found to have a significant inhibitory effect on CYP3A4, CYP2C9, and P-glycoprotein activities in vitro (Kimura *et al*., 2010; Zhang et al. 2008). It was this effect that was thought to be responsible for reported hepatic cytolysis in a 48-year-old woman being treated with crizotinib. The patient, who was being treated with 250 mg crizotinib twice a day, had been taking ginger as a tea (amounts

unknown) concomitantly during treatment. A subsequent diagnostic evaluation showed an increased crizotinib concentration, 1.8-fold higher than that measured two months prior.

Anti-platelet aggregation activity

Human studies

45. Krüth *et al.* reported possible over-anticoagulation resulting from a ginger-phenprocoumon interaction (2004). A 76-year-old woman on long-term phenprocoumon therapy presented with epistaxis and an international normalized ratio (INR) of >10. Partial thromboplastin time (PTT) was also found to be prolonged (84.4 seconds; normal <35). For several weeks prior to the event, the woman had a regular ginger intake of dried ginger pieces and tea from ginger powder. Following treatment with vitamin K, the patient's INR and PTT returned to within therapeutic range.

46. Young et al. (2006) investigated the synergistic effect of ginger and nifedipine on anti-platelet aggregation in healthy volunteers aged 25-60 years old and hypertensive individuals aged 35-60 years old. In a five-part study, the two groups comprising 10 males and 10 females, were administered 75 mg of acetylsalicylic acid (ASA), 1 g of ginger, 10 mg nifedipine, 1 g dried ginger and 10 mg nifedipine in combination and 1 g dried ginger and 75 mg ASA in combination daily for one week each following a washout period (7 days following ASA administration, 10 days thereafter).

47. Young et al. found that platelet aggregation in the presence of collagen, ADP and epinephrine was 44.1%, 44.5% and 42.1% in normal subjects, compared to 64.2%, 67.7% and 62.9% in hypertensive patients. Following administration of ginger alone to normal subjects, the percentage inhibition of platelet aggregation induced by collagen, ADP and epinephrine was 35.2%, 37.8%, 35.9%, respectively. Following nifedipine administration to such subjects, platelet aggregation induced by collagen, ADP and epinephrine was inhibited by 20.2%, 22.6% and 23.4 %, respectively. When normal subjects were administered ginger and nifedipine in combination

platelet aggregation induced by collagen, ADP and epinephrine was inhibited by 79.8%, 75.2%, 69.3%, respectively, which values were significantly different from those with either ginger or nifedipine alone, suggesting a synergistic effect of the combined treatments. This synergistic effect was also seen in hypertensive patients. The authors concluded that ginger could potentiate the anti-platelet effect of nifedipine.

48. AlAskar *et al.* (2020) investigated the effect of ginger on platelet aggregation using ADP, arachidonic acid, collagen, ristocetin and epinephrine as agonists. Forty healthy male and female participants (numbers of each not specified, presumably 20 of each) were randomized (20 per group) to consume ginger tea comprising either 4 g powered ginger in 150 ml of boiling water once daily or 4 g twice daily, for five days. Comparisons were with pre-treatment values. Administration of 4 or 8 g ginger powder daily for 5 days as a tea had no effect on platelet aggregation induced by any of the agonists, or than modest inhibition in the 4 g per day group with epinephrine as agonist (by 12%), Essentially, ginger had no effect on platelet aggregation in this study.

49. Srivastava (1989) investigated the effect of fresh ginger on blood platelet thromboxane synthesis in humans. In a study on 7 women aged between 25-65 years, where volunteers consumed ~5 g of fresh ginger for 7 days, ginger was found to inhibit thromboxane B_2 biosynthesis *in vivo* by 36%.

50. Lumb (1994) found that after a single dose of 2 g of dried ginger in powder form there were no significant differences in platelet aggregation/function at 3 and 24 hours post-dose compared to those after a lactose placebo. The authors concluded that previously reported effects of ginger on thromboxane synthetase activity may have been due to the use of higher doses or fresh ginger.

51. Bordia *et al.,* (1997) found that 4 g powdered ginger administered daily over the course of 1.5 and 3 months had no effect on ADP and epinephrine-induced platelet aggregation in individuals with coronary artery disease (CAD) (who were all taking nitrates and aspirin). However, a single 10 g dose of powdered ginger,

administered to CAD patients resulted in a significant decrease in induced platelet aggregation (by approx 30%).

Toxicology of ginger extracts and other concentrated forms

Cytotoxicity

52. The cytotoxicity of ginger extracts has been investigated with varied results. Plengsuriyakarn *et al*. (2012) examined the cytotoxicity of ethanolic ginger extracts in a cholangiocarcinoma (CCA) cell line 6 (CL-6) model, compared to hepatocarcinoma (HepG2) and normal human renal epithelium (HRE) models, using calcein-AM release and Hoechst 33342 assays to assess cell viability and apoptotic activity, respectively. The median inhibitory concentration, (IC_{50}) values, for cytotoxicity of the crude ethanolic extract of ginger ranged from 11 – 245 µg/mL across the 3 cell lines and the two assays.

53. Zaeoung *et al.* (2005) reported that the IC_{50} of aqueous and methanolic extracts of ginger was greater than 39.2 µg/ml against breast (MCF7) and colon (LS174T) cell lines.

54. Abudayyak *et al*. (2015) found that aqueous and methanolic extracts of ginger exhibited no cytotoxic activity when assessed using an MTT test (a colourimetric assay for assessing cell metabolic activity) in the rat kidney, NRK-52E cell line. A chloroform extract resulted in an IC_{50} value of 9.1 mg/mL.

55. However, it was noted by the COT that the inhibitory concentration (IC_{50}) values presented in the studies reviewed were based on limited data, from only a few different cell lines and therefore firm conclusions could not be drawn. Also, the purpose of most of these studies was an attempt to identify possible anti-cancer agents, rather than as an assessment on the safety of ginger as a supplement and therefore relevant endpoints were often not assessed.

Mutagenicity

56. Nakamura and Yamamoto (1982) found that the juice of ginger rhizome contained both mutagenic and anti-mutagenic substances, and that 6-gingerol in particular was a powerful mutagen. Ginger juice itself had anti-mutagenic activity. The group also demonstrated that 6-shogaol was much less mutagenic (strain Hs30 of *Escherichia coli*) than 6-gingerol and zingerone was much weaker still (Nakamura & Yamamoto 1983). In a *Salmonella typhimurium* reverse mutation (Ames) assay, the urine of rats fed diets containing 0.5, 1 and 5% powdered ginger for 1 month showed no mutagenicity with either strain TA98 or TA100. The rats were then treated with a single intraperitoneal injection of benzo(a)pyrene. The urine from benzo(a)pyrene-treated animals caused an increase in the number of revertants in both strains of *Salmonella*, with and without metabolic activation. Urine from those rats that had also received ginger was found to display a significant reduction in mutagenicity, at all ginger concentrations, when tested in the Ames assay (Nirmala *et al*. 2007).

57. The mutagenicity of aqueous and DMSO extracts of fresh, boiled and fried ginger paste and powder was assessed in an Ames test using *S. typhimurium* strains TA98 and TA100 with and without metabolic activation, at concentrations of 1, 2 and 3 mg/plate of ginger paste and 0.5, 1 and 1.5 mg/plate of ginger powder, respectively. None of the preparations caused any increase in the number of revertants. All of the ginger preparations reduced the mutagenicity of benzo(a)pyrene *in vitro* (Nirmala *et al*. 2007).

58. In other Ames assays, an ethanolic extract of ginger (Soudamini *et al.* 1995) demonstrated mutagenic activity in *S. typhimurium* strains TA100 and TA1535 at concentrations of 25-50 mg/plate and 5-10 mg/plate, respectively. Similarly, an ethanolic ginger extract at concentrations of between 10 and 200 µg/plate, gingerol at concentrations between 5 and 200 µg/plate, and shogaol at concentrations between 5 and 200 µg/plate, were mutagenic in strains TA100 and TA1538 with metabolic activation by rat liver S9 mix, while zingerone (5 and 200 µg/plate) did not display mutagenic effects (Nagabhushan *et al*. 1987).

59. Abudayyak *et al*. (2015) found that an aqueous ginger extract exhibited mutagenic activity when assessed using the Ames assay on *S. typhimurium* TA98 strain (in the presence of S9 mix) over a concentration range of 0.78–25 ug/mL. However, no activity was exhibited on the TA100 strain. No activity was observed with chloroform and methanolic extracts.

60. Based on the available data, ginger showed some mutagenicity in TA100, TA1535, and TA98 strains, but this is low compared with established mutagens. An aqueous extract of ginger did not show any mutagenicity *in vivo* (Nirmala et al. 2007).

Acute toxicity

61. An acute toxicity study (Malik and Sharma, 2011) in male Wistar rats showed no signs of toxicity or mortality with ginger. The animals were administered doses of 250, 500 and 1000 mg/kg lyophilised ginger powder by gavage. The authors stated that the three dose levels used in the study corresponded to 5, 10 and 20% of the NOAEL of the powder (5000 mg/kg).

62. Preliminary to a study of the effects of an aqueous extract of ginger rhizomes on sexual parameters in rats, Peneme et al. (2023) (see below) determined the acute toxicity of the extract in accordance with The Organisation for Economic Co-operation and Development (OECD) guideline no. 423. Mice received 5000 mg/kg aqueous ginger extract by gavage. No change in the general condition or behaviour of the mice compared with the control animals was observed. No mortality was observed after 48 hours or 14 days of observation. Hence, the LD50 was above 5000 mg/kg.

Short term repeat dose studies

63. Rong et al. (2009) evaluated the safety of powdered Japanese ginger (mainly containing 6-gingerol galanolactone and 6-shogaol) by conducting a 35-day toxicity study in rats. Both male and female rats were treated with 500, 1000 and 2000 mg/kg bw/day by gavage. Oral administration of up to 2000 mg/kg to male and

female rats did not result in any increase in mortality, or changes to behaviour, growth, the general condition of the animals (including: changes in skin, fur, eyes, and mucous membranes, occurrence of secretions, excretions and autonomic activity), food and water consumption. At the highest dose tested (2000 mg/kg), ginger led to slightly reduced absolute and relative weights of testes (by 14.4% and 11.5%, respectively). No effects were apparent in the females.

64. The effect of oral and intraperitoneal administration of aqueous extracts of ginger root over 28 days in female rats at two dose levels (50 mg/kg and 500 mg/kg) was examined for haematological, serum enzymes and systemic toxicity (Alnaqeeb et al. 2003). Neither oral nor intraperitoneal administration resulted in mortality. Orally administered aqueous ginger extract resulted in increased serum levels of serum aspartate aminotransferase (AST) and decreased levels of alanine aminotransferase (ALT) at 500 mg/kg. Intraperitoneal administration had no effect on either AST or ALT levels.

65. Jeena et al. (2011) conducted a sub chronic toxicity study of essential oil of ginger in Wistar rats following oral administration at doses of 100, 250, and 500 mg/kg per day once daily for 13 weeks to assess the oral safety of ginger oil. No mortality was observed. No unusual changes in behaviour or locomotor activity were observed during the period of the study, nor were any abnormal changes observed in the relative organ weights of liver, kidney, spleen, lungs, brain, and stomach with respect to body weight in ginger oil-treated animals when compared to vehicle control animals.

66. An increase in serum sodium levels was observed in the male rats treated with 500 mg/kg per day but in the absence of changes in sodium levels in females, this change was not considered significant. A slight increase in total bilirubin level was observed in female rats treated with ginger oil along with a decrease in AST and ALT levels, however, there were no significant changes in hepatic function parameters such as alkaline phosphatase, total protein, albumin, and globulin content.

Reproductive and developmental toxicity

In vitro studies

67. Mohammed et al. (2016) investigated the effects of herbal extracts, including ginger and 6-gingerol, on primary chick embryonic cardiomyocyte micromass and mouse D3 embryonic stem cell (ESD3) systems. Primary embryonic chick cardiomyocytes treated with 6-gingerol at concentrations of 0.75–6 μM showed no significant changes in contractile or cellular activity or changes in total protein content in comparison to the control. At concentrations of 12.5–50 μM, inhibition in contractile activity was observed at 48h. All high 6-gingerol concentrations, 12.5–100 μM, tested in micromass, significantly altered both cellular activity and protein content in a dose-dependent manner.

68. The same concentrations of 6-gingerol used in the micromass system were used to treat the ESD3, which showed a significant decrease in cardiomyocyte differentiation with all tested concentrations above 0.75 μM. The cellular activity and protein content of stem cell-derived cardiomyocytes also exhibited a significant decrease with exposure to increasing 6-gingerol concentrations.

Animal studies

69. To date, the number of studies on the safety of the use of ginger supplements during pregnancy is limited. The ginger component, 6-gingerol, was shown to affect some essential embryonic developmental processes, such as the disruption of angiogenesis. Kim *et al*, demonstrated the ability of 6-gingerol (10 μM) to inhibit proliferation and capillary-like tube formation of primary cultured human endothelial cells in rat aorta by down regulation of cyclidin D and the ability to inhibit tumour growth in mice (3 mg/kg) through its anti-angiogenic activity (Kim et al., 2005).

70. The teratogenicity of EV.EXT 33, a patented ethanol extract of dry rhizomes of *Zingiber officinale* Roscoe (comprising largely 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol, and 8-shogaol, which made up 1.9 w/w of the extract) was investigated in Wistar rats (Weidner and Sigwart, 2001). The extract was administered orally by

gastric intubation at concentrations of 100, 333 and 1000 mg/kg, to pregnant rats from days 6 to 15 of gestation. Their bodyweight, food and water were monitored during the treatment period. The study authors concluded that treatment with EV.EXT 33 during the period of organogenesis resulted in neither maternal nor developmental toxicity at daily doses of up to 1,000 mg/kg bw.

71. Shalaby and Hamowieh, (2010) investigated the acute toxicity, effects on fertility and on serum testosterone levels of ginger in rats. One hundred and twenty male Sprague Dawley rats, separated into groups of 10, were orally administered either water or methanolic extracts of dry ginger roots in graded doses ranging from 5 to 17.5 g/kg bw (gavage doses were not specified). Following dosing, the number of dead mice in each group after 48 hours of observation was recorded. The oral lethal doses (LD_{50}) of the methanolic and water extracts were calculated to be 10.3 and 11.8 g/kg bw respectively. No signs of toxicity were observed at doses up to 5 g/kg bw. Both extracts increased the fertility index, sexual organ weight, and sperm motility and count after 65 days of dosing (see below).

72. To investigate the effects of ginger extracts on serum testosterone levels, male rats had their fertility reduced by inducing diabetes, a condition shown to reduce male fertility (Shalaby and Hamowieh, 2010). The aim was to see whether ginger, with its antioxidant and androgenic effects, would restore fertility. Rats rendered diabetic by subcutaneous injection of 120 mg/kg bw alloxan for 3 days, were administered methanolic extracts of ginger for 65 days at doses of 100 and 200 mg/kg bw/d. Testosterone levels increased to 4.08 ± 0.10 and 7.13 ± 0.14 ng/dL (both significant at $P < 0.001$) in the ginger treated groups compared to the diabetic control group, which had levels of 3.30 ± 0.03 ng/dL. Serum testosterone levels also increased in rats given water extracts of ginger (150 and 300 mg/kg bw) to 4.06 ± 0.03 and 5.04 ± 0.08 ng/dL (both significant at $P < 0.001$ when compared to the diabetic control group), respectively.

73. The study also investigated fertility as assessed by the fertility index (for each male this was calculated as the percentage of the number of females that become pregnant in relation to the number of mated females) and spermatogenesis. Rats

were orally administered methanolic extracts of ginger at doses of 100 and 200 mg/kg bw for 65 days and water extracts at doses of 150 and 300 mg/kg bw and compared to a diabetic control group.

74. Histopathological examination of the testes of the diabetic rats showed mild to moderate degenerative changes of spermatogenic cells, diffuse oedema and incomplete arrest of spermatogenesis compared to normal control rats. The testes of rats orally administered 300 mg/kg bw of water extract of ginger root showed less changes in the testes, with mild degeneration of spermatogenic cells and slight oedema of interstitial cells. The testes of rats receiving orally 200 mg/kg bw of methanolic extract of ginger root showed nearly normal seminiferous tubules, with fewer signs of degradation, suggesting a LOEL of 200 mg/kg bw/day for the methanolic extract. The study concluded that the results suggest the intake of ginger root extract as a drink may be useful for diabetic patients suffering from sexual dysfunction.

75. The above study has been included for completeness and as any general mechanisms may be more widely relevant: The findings are consistent with those of Hosseini et al (2015)

76. Hosseini et al. (2015, abstract only) investigated the effect of ethanolic ginger extract on serum levels of testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH), as well effects on numbers of spermatogenic cells in male mature offspring rats. In this study, 72 female rats, divided into 9 groups, were orally administered an alcoholic extract of ginger at doses of 50, 100 and 200 mg/kg bw, during their neonatal and perinatal periods, with saline as a control. Following puberty, serum levels of testosterone, LH and FSH, and testicular numbers of Sertoli cells, spermatogonia, spermatocytes and spermatids were counted in 8 male offspring from each group after puberty. Treatment with ginger significantly, and dose-dependently, increased testosterone levels and the number of spermatogenic cells and at doses of 100 and 200 mg/kg bw, significantly reduced the FSH and LH levels compared to control groups. The authors concluded that “the oral consumption of ginger during pregnancy and lactation dose-dependently increase the level of testosterone and the number of spermatogenic cells.”

77. Dissabandara & Chandrasekara (2007) examined the effect of powdered ginger extract administered prenatally on the postnatal development of rats. Administration of the dry powdered extract orally at doses of 500 or 1000 mg/kg/day (control not specified) during days 5 to 15 of gestation resulted in a lower intake of food and water and lower weight gain in dams in the ginger treated group, with some embryonic loss. Growth and physical maturation of the offspring were unaffected. It was concluded that maternal administration of ginger during mid pregnancy resulted in reduced maternal weight gain and increased embryonic loss without affecting the surviving offspring.

78. ElMazoudy and Attia (2018) investigated the effect of powdered dried ginger root on the oestrus cycle and implantation in female mice. ICR mice were orally dosed with 250, 500, 1000, or 2000 mg/kg bw/d aqueous ginger extract. There were four different experiments: (i) treatment for 90 days and throughout mating and gestation; (ii) 35-days of treatment evaluating the effects on the oestrous cycle; (iii) treatment for 20 days and throughout mating to evaluate pre-implantation loss (antifertility); and (iv) treatment for 20 days and throughout gestation to evaluate post-implantation loss (abortifacient). In the 90-day study, the dams were terminated on gestation day 20. In the mothers, one mortality was recorded in the 1000 mg/kg bw/d group on gestation day 18 and two in the 2000 mg/kg bw/d group at gestational day 16. There was a significant reduction in body weight changes in these two dose groups compared to the control group; however, food consumption was comparable.

79. In the study investigating the oestrus cycle, a significant reduction in the numbers of oestrus cycles was observed at the highest dose, with the length of the oestrus cycle in this group being significantly prolonged, 10.05 ± 0.8 days compared with 4.99 ± 0.5 days recurrent and successive oestrous cycles in control mice. At the highest dose level, there was a significant decrease in the duration of diestrous-metestrus (luteal) phase and prolonged proestrus-estrus (ovulatory) phase. In the study investigating pre-implantation loss, a significant decrease in the number of corpora lutea was observed at the highest dose. Implantation failure was also increased by 36% compared to the control group and pre-implantation loss in this

dose group was also 16.6% higher than in the control group. The authors considered that this may reflect a dose-dependent antifertility (anti-implantation) effect.

80. Regarding fertility and developmental outcomes, the female copulation index was significantly reduced at 2000 and 1000 mg/kg bw/d, whereas the female pregnancy index was significantly decreased only at the highest dose. The number of implantation sites and live fetuses in the 2000 mg/kg bw/d group was lower than in the other treated and control groups. An increase in fetal resorption and post implantation loss was also seen in the highest dose group. There was no evidence of fetal malformations, however growth retardation, reduced pup weight and delay in the crown-rump length were observed in this dose group as well. Finally, changes in ovarian histopathology were observed at 2000 mg/kg bw/d, following 90 days of treatment. Ovarian follicle atresia was observed. The atretic follicles contained cell debris and there was haemorrhage in the antral cavity.

81. Additionally, degenerated primordial follicles with pyknotic nuclei forming polycystic ovaries were noted. Deteriorated follicles were observed as a detaching of layers of granulosa cells from the basal membrane by dilation of zona pellucida and with evidence of apoptosis; non-visibility of the follicular nuclei was also evident in damaged ova. The authors considered the above observations as evidence that ginger possesses anti-ovulation properties. Overall, the authors concluded that ginger impairs the normal growth of the corpus luteum because of progesterone insufficiency during early pregnancy and that the results suggested that ginger can disrupt the oestrous cycle and blastocyst implantation without teratogenesis. They considered the lowest NOAEL to be 250 mg/kg bw.

82. Peneme et al. (2023) investigated the effects of an aqueous extract of ginger rhizomes on sexual parameters in rats, after first determining the acute toxicity of the extract in mice (see above). The extract was administered at doses of 300 and 600 mg/kg, 17β-oestradiol at a dose of 1 mg/kg or distilled water at an equivalent volume, orally to rats by gavage daily for 14 days. A non-significant increase and decrease in body weight was observed at doses of 300 and 600 mg/kg, respectively. Similarly, there was no significant change in body weight on treatment with 17 β-oestradiol.

Based on the eosinophil indices, treatment with 600 mg/kg of the extract blocked the sexual cycle at the estrus stage as did 17β-oestradiol. There was no effect at 300 mg/kg of the extract. A significant increase in oestradiol levels was observed in the rats treated at 300 mg/kg compared with the control group, but treatment with 600 mg/kg or 17β-oestradiol had no significant effect.

83. ElMazoudy and Attia (2018) noted reductions in bodyweight and deaths in mice dosed with up to 2000 mg/kg bw/day ginger extract and Alnaqeeb *et al.,* (2003), observed increases in serum aspartate aminotransferase (AST) in female rats dosed with up to 500 mg/kg ginger extract.

84. However, the Committee noted that the database was limited, and the extraction and concentration of ginger varied between the studies. The Committee considered the animal studies to be inconclusive. On the basis of the available information, more data would be needed in order to allow for a robust investigation of the effects described above. Therefore, at present, the Committee are unable to determine a point of departure.

Human studies - exposures in pregnancy

85. Willetts et al. examined the effect of ginger on pregnancy induced nausea (2003). 120 women less than 20 weeks pregnant, were given 125 mg ginger extract (EV.EXT35; equivalent to 1.5 g of dried ginger) or a placebo four times per day for 4 days. However, there is some lack of clarity in the description of this study as it is stated in the discussion "Women in the treatment arm of this trial took ginger for 8 days and those in the placebo arm took ginger for 4 days." It is not clear whether this refers to the trial described. Three spontaneous abortions were observed in the group receiving ginger, although one of these had not started taking ginger at the time of abortion. One spontaneous abortion was observed in the placebo group.

86. In a clinical feasibility study on the use of ginger during pregnancy conducted by Laekeman et al. (2021), 51 pregnant women could freely use ginger tablets with a maximum of 2 tablets of 50 mg EXT.GR10 a day in case of gastrointestinal discomfort during pregnancy. EXT.GR10 is a 10-times concentrated ethanolic extract

of ginger root. No strict minimum number of tablets was set, and 44 out of 51 patients (86.3%) took the ginger tablets. The 44 patients took 544 tablets or a mean of 12.4 tablets per patient, with a minimum of 1 and a maximum of 55 tablets. The incidences of stillbirth, prematurity, hypertension, and gestational diabetes were reported. There were no serious complications at birth. Four cases of dysplasia of the hip and two minor malformations were recorded in the offspring. Outcomes were compared to the rates in a Flemish population delivering during the same period. Hypertension, low birth weight and premature delivery were 15.9%, 13.6% and 20.5 % respectively in the ginger cohort compared to the representative population where the rates were 5.4%, 5.6% and 5.8% respectively. The author concluded that there was no qualitative or quantitative relationship between complications in the mother during pregnancy or malformations or complications in the newborn at delivery and the use of EXT.GR10 but emphasised that this was a pilot study with small numbers.

Effect on P450 (CYP) Enzymes and Herb-Drug Interactions

87. CYPs are a family of enzymes responsible for the biotransformation of numerous drugs. Induction or inhibition of CYP enzymes is a major determinant of the occurrence of drug-drug interactions.

In silico

88. Qiu *et al.* (2015) estimated the molecular interactions between 12 main active components (6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol, 8-shogaol, 10-shogaol, ar-curcumene, β-bisabolene, β-sesquiphelandrene, 6-gingerdione, (-)-zingiberene, and methyl-6-isogingerol) and human P450 (CYP) 1A2, 2C9, 2C19, 2D6, and 3A4 and attempted to predict the absorption, distribution, metabolism, excretion, and toxicity (ADMET) of the 12 ginger components using computational methods and literature searches. This study suggests that ginger components may have the potential to regulate the activity and expression of various human CYPs, resulting in alterations in drug clearance and response with a high risk of inhibition of CYP2C9 and CYP3A4.

In vitro studies

89. Ginger extracts and the major components thereof: 6-gingerol (6G), 8-gingerol (8G), 10-gingerol (10G) and 6-shogaol (6S) were investigated in *in vitro* models and shown to have inhibitory effects on CYP enzymes CYP3A4, CYP2C9 (Kimura *et al.*, 2010), CYP2C19 (Kim *et al.*, 2012), and CYP1A2 and CYP2C8 with IC_{50} values as low 1 μM, (e.g., 6-shogaol on CYP1A2; Mukkavilli *et al.*, 2014).

Animal studies

90. Several reports have been published on the pharmacological properties of ginger, with varying findings. Studies have examined the herb-drug interaction in animal models, (Okonta *et al.*, 2008; Egashira *et al.*, 2012) although the results of some studies are questionable.

91. A study into the effect of ginger on the pharmacokinetics of metronidazole was reported by Okonta *et al.*, using rabbits (2008). In a two-phase study, five healthy local strain rabbits (3 females, 2 males) were each given 3 mg/kg oral metronidazole. Following a 2-week washout period, the rabbits were given 1 ml/kg of ginger extract orally daily for 3 days and immediately given 3 mg/kg metronidazole on the third day. Ginger significantly increased the absorption and plasma half-life and significantly decreased the elimination rate constant and clearance of metronidazole.

92. Egashira *et al.*, reported the interaction between ginger juice and tacrolimus in rats (2012). Tacrolimus (0.6 mg/kg) was administered intraduodenally in male Sprague-Dawley rats 1 h following oral administration of 10 mL/kg 50% ginger juice or water. CYP3A enzymes metabolize tacrolimus in the intestine as well as in the liver and the author states that ginger has been reported to change the activity of CYP3A4. Pre-treatment with ginger juice was found to significantly increase tacrolimus blood concentrations compared to those in animals pre-treated with water or orange juice.

93. The possible herb-drug interaction of ginger crude extract (GCE) on glibenclamide and insulin was investigated by Al Omari *et al.*, along with its hypoglycaemic and antihyperglycemic effects in normoglycemic- and streptozotocin-induced (STZ) diabetic rats (2012). Ginger crude extract was administered to normoglycemic male rats as a single dose (1 day) and as a daily dose for 1 week. STZ diabetic rats were treated with the same GCE concentrations (25, 50 and 100 mg/kg bw) together with glibenclamide (5 mg/kg bw) or insulin (1.2 IU/kg bw).

94. Single administration of ginger crude extract resulted in a significant decrease in blood glucose level (BGL) in normoglycemic rats after 1 and 2 hours (50 mg/kg bw). In STZ- diabetic rats ginger crude extract (25 and 50 mg/kg bw) decreased non-fasting BGL (N-FBGL) significantly at 1.5, 2.5, 3.5 and 4.5 hours. Glibenclamide (5 mg/kg bw) in combination with ginger crude extract at doses of 25 or 50 mg/kg bw resulted in a significant reduction in the N-FBGL by 26.3% and 25.1% respectively after 4.5 hours, compared to glibenclamide alone which exhibited a 7.9% reduction. The authors suggested that ginger crude extract may act by affecting the release of insulin from the ß-cells of the pancreas.

Human studies

95. Human data showed possible interactions of ginger with drugs, including antibiotics, immunosuppressants, and anticoagulant medications. Although, in some cases, multiple concomitant medications were being used by the subjects, therefore, the effects observed cannot necessarily be directly attributed to ginger supplementation (Rubin *et al.*, 2019).

96. Conversely, whilst investigating the effects of ginger on the pharmacokinetics and pharmacodynamics of warfarin and the effect of ginger on clotting status, Jiang *et al.,* (2005), found that neither the pharmacokinetics nor pharmacodynamics of warfarin were affected in healthy males who were treated with a single 25 mg dose of warfarin, following 7 days of pretreatment with ginger tablets (3 tablets, 3 times per day, each capsule containing extract equivalent to 0.4 g of ginger rhizome powder). Furthermore, ginger treatment had no effect on INR or *ex vivo* platelet aggregation in response to arachidonic acid.

Anti-platelet aggregation activity

In vitro studies

97. Srivastava (1986) reported an effect of ginger extracts on *in vitro* platelet aggregation. Ginger extracts in water, n-hexane, chloroform, and ethyl acetate were shown to inhibit platelet aggregation using arachidonic acid (AA), epinephrine, adenosine diphosphate (ADP), and collagen as agonists. From the paper it was difficult to determine the concentrations of ginger equivalents used.

Animal studies

98. The effects of an aqueous ginger extract on platelet thromboxane-B_2 (TXB_2) and prostaglandin-E_2 (PGE_2) production was studied by Thomson *et al*. (2002). Adult female Sprague-Dawley rats were administered an aqueous extract of raw ginger at either 50 mg/kg or 500 mg/kg daily, by either oral gavage or intraperitoneally (IP) for a period of 4 weeks. A dose of 50 mg/kg ginger administered orally, or IP did not result in any significant reduction in serum TXB_2 levels when compared to the saline-treated control group but oral doses at 500 mg/kg significantly reduced TXB_2 levels in serum. There was no significant effect on serum TXB_2 levels when this dose (500 mg/kg) was administered IP.

99. Administration of either 50 or 500 mg/kg of the aqueous extract orally or by IP injection resulted in a significant reduction in serum PGE_2 levels (reduction with 50 mg/kg IP did not reach statistical significance), which was more marked after 500 mg/kg.

Human studies

100. Rubin *et al.* (2019) reported the possible effect of ginger supplementation on the INR in a woman taking warfarin. The 70-year-old female, who had been taking clonazepam 1 mg, metoprolol succinate 25 mg, paroxetine 10 mg, phenytoin 30 mg, rosuvastatin 20 mg, warfarin 7.5 mg daily except 10 mg on Wednesdays, for at least a month prior to presentation, presented with an INR of 8, an increase from 2.7, one month after taking a “Ginger Rescue,” a daily oral, chewable, 48 mg ginger

supplement that had no other herbal or active ingredients. A week following cessation of the ginger supplement, the INR declined to 2.6. Upon resuming warfarin at 7.5 mg daily, her INR remained in the therapeutic range.

101. The effects of ginger on platelet aggregation were investigated in healthy male subjects (n=20) whose diet was supplemented with 100 g butter per day for seven days. This significantly enhanced platelet aggregation. Ten of the subjects then received ginger, in powder form (5 g per day) and the other ten received a placebo. ADP- and epinephrine-induced platelet aggregation was significantly ($P<0.001$) reduced in the ginger-treated group, whilst there was no significant change in the placebo control group (Verma *et al.*, 1993). In addition, no change was observed in the fibrinolytic activity or fibrinogen levels in these subjects. All patients in this study were taking nitrates and aspirin; the latter was stopped 2 weeks before the start of the study. In contrast to the effects after 3 months, a single 10 g dose of powdered ginger, administered to CAD patients (n=10), resulted in a significant decrease in ADP- and epinephrine-induced platelet aggregation 4 h after dosing, as compared to that prior to treatment. There was no change in the placebo-treated controls (n=10).

Effects on blood pressure

Animal studies

102. Ghayur and Gilani (2005) reported that a crude extract of ginger administered intravenously, induced a dose-dependent (0.3–3 mg/kg) decrease in arterial blood pressure of anesthetized Sprague-Dawley rats with an EC50 value of 0.9 ± 0.1 mg/kg (mean ± SEM). In guinea pig paired atria, the crude extract exhibited cardio-depressant activity on the rate and force of spontaneous contractions with EC50 values of 0.57 ± 0.03 and 0.88 ± 0.07 mg/ml (mean ± SEM) for force and rate of contraction, respectively. In rabbit thoracic aorta preparations, when tested on the resting baseline, the ginger extract was devoid of any effect up to a dose of 10 mg/mL. The extract was then tested on high-potassium (K+) (80 mg/mL) and phenylephrine (1 µg/mL)-induced contractions. The extract relaxed the phenylephrine-induced vascular contraction at a dose 10 times that required against

K+ (80 mg/mL)-induced contraction with an EC50 of 0.92 ± 0.04 mg/ml, compared with an EC50 of 0.11 ± 0.01 mg/ml against K^+-induced contraction.

103. Ca^{2+} channel-blocking (CCB) activity was confirmed when the crude extract shifted the Ca^{2+} dose–response curves of thoracic aorta preparations to the right, the shift being similar to that obtained with verapamil. It also inhibited the phenylephrine (1 mg/mL) peak responses in normal-Ca^{2+} and Ca^{2+}-free solution, indicating that it acts at both the membrane-bound and the intracellular Ca^{2+} channels. When tested in endothelium-intact rat aorta, it again relaxed the K+-induced contraction (EC50 value of 0.091 ± 0.002 mg/ml) at a dose 14 times less than that required for relaxing the PE-induced contraction (EC50 value of 1.26 ± 0.08 mg/ml). The vasodilator effect of the crude extract was endothelium-independent because it was not blocked by N_ω-nitro-L-arginine methyl ester hydrochloride (L-NAME) (0.1 mg/mL) or atropine (1 mg/mL) and also was reproduced in endothelium-denuded preparations at the same dose range. These data indicate that the blood pressure-lowering effect of ginger is mediated through blockade of voltage-dependent calcium channels.

Effect on Prostaglandins

In vitro

104. Ginger extracts, along with many gingerols and shogaols, have been shown to suppress prostaglandin synthesis *in vitro,* through inhibition of cyclooxygenase (Jolad et al. 2005; Pan et al. 2008; Dugasani et al. 2010).

105. Lantz *et al.* (2007) investigated the anti-inflammatory effect of crude organic extracts (dichloromethane-methanol, 1:1 v/v) of ginger and the principal components thereof (6-, 8- 10-gingerols and 6-, 8-, 10-shogaols) in an *in vitro* model, U937 cells (a pro-monocytic cell line), differentiated and exposed to lipopolysaccharide (LPS) from *Escherichia coli* (1 µg/ml). Extracts containing predominantly gingerols were not cytotoxic, while shogaols were cytotoxic at concentrations above 20 µg/ml. Crude extracts of ginger inhibited LPS-induced PGE2 (IC50 < 0.1 µg/ml) production but were much less effective at inhibiting TNF-α production (IC50 > 30 µg/ml). Extracts containing either predominantly gingerols or shogaols were highly active at inhibiting

LPS-induced PGE2 production (IC50 < 0.1 µg/ml). Extracts containing predominantly gingerols inhibited LPS-induced COX-2 expression while shogaol containing extracts had no effect on COX-2 expression.

106. Jolad *et al.* also demonstrated the inhibitory effect of gingerols on LPS-induced PGE_2 production in HL-60 cells stimulated with 1 µg/ml of LPS (2004). None of the compounds tested was shown to be cytotoxic.

107. The Committee noted the potential effect of ginger on the prostaglandin pathway, in particular cyclooxygenase-1 (COX1) and cyclooxygenase-2 (COX2) inhibition, and how this may affect early pregnancy. It was noted that in Lantz *et al.* (2007), the half maximal inhibitory concentration (IC_{50}) values for a range of components in ginger were given, and it was demonstrated that these acted mainly on COX-2. The COT concluded that further studies would be needed to determine the role of decreased prostaglandin levels induced by ginger in the early termination of pregnancy.

Animal studies

108. The composition of ginger extracts appears to vary according to whether the ginger is fresh or dried. Suekawa *et al.,* (1986, only abstract in English) demonstrated that (6)-shogaol (140 and 280 mg/kg), a principal component found mainly in dried ginger, inhibited carrageenan-induced swelling of rat hind paw, arachidonic acid- and collagen-induced platelet aggregation in rabbit and ADP-induced platelet aggregation due to prostaglandin PGI_2 release in rat aorta. It was further shown that at micromolar concentrations (6)-shogaol inhibited cyclooxygenase activities in rabbit platelets and microsomal fractions of rat aorta in a concentration-dependent manner and was inhibitory to 5-lipoxygenase activity in RBL-1 cells. These studies suggested a potential inhibitory action of (6)-shogaol on cyclooxygenases (COX) in both platelets and aorta tissue.

Effect on animals with induced diabetes

109. Luo et al. (2022) investigated the effects of dried, ground ginger on gestational diabetes in rats. In this study, 40 adult female rats were divided into 4 equal groups: pregnant rats, pregnant rats with streptozotocin-induced diabetes, pregnant rats consuming ginger powder (100 mg/kg, by gavage), and pregnant rats with streptozotocin-induced diabetes consuming ginger powder. The results of this study showed that one of the mechanisms of physiological metabolic adaptation during pregnancy involves reduced expression of mTORc1, SREBP-1c, PPAR-g and GLUT4 genes, with increased PPAR-α expression. Disruption of their expression can lead to metabolic disorders and hyperglycaemia and, in advanced cases, even cause gestational diabetes. Administration of ginger to diabetic animals restored expression levels of mTORc1, SREBP-1c, PPAR-g, PPAR-α, and GLUT4 in liver to those in non-diabetic animals. Ginger had no effect in non-diabetic rats. The authors concluded that these results showed that ginger can significantly improve metabolic status in gestational diabetes by modulating the expression of these genes. There were no reported adverse effects resulting from the administration of ginger when compared to the control.

110. Streptozotocin-induced diabetic rats were utilized as a diabetic model and received 200 or 400 mg/kg/day ginger extract for eight weeks. (Raoufi et al., 2023). Ginger at both levels partially ameliorated the elevated levels of glucose, testosterone, and MDA caused by diabetes. In the higher dose group, the diabetes-induced reductions in the levels of insulin, 17β-oestradiol, progesterone, and ovarian 3β-hydroxysteroid dehydrogenase transcript were also partially offset.

Contaminants

111. Differences in cultivation conditions and extraction methods might lead to contamination of ginger from toxins, microbes, pesticides, heavy metals and residual solvents. Studies investigating contamination of ginger are limited, however of the few studies available, the main types of contamination reported are heavy metals (Wagesho & Chandravanshi, 2015; Getaneh *et al.,* 2021; Goroya *et al.,* 2019, Kilic & Soylak, 2019; Xu *et al.*, 2020) and mycotoxins (Ałtyn and Twarużek, 2020; Wen *et al., 2014;* Omotayo *et al., 2019;* Lippolis *et al., 2017*).

112. Ginger can become contaminated with mycotoxins during harvesting, storage and handling. Whilst information on mycotoxin contamination of ginger is limited, ginger has been demonstrated to be particularly exposed to aflatoxins and ochratoxin A (OTA). This is reflected in GB legislation, where maximum levels for these toxins for spices including ginger are established in Assimilated EU Law 1881/2006. Maximum levels are 5 µg/kg for aflatoxin B_1 (AFB_1), 10 µg/kg for all aflatoxins (sum of AFB_1, AFB_2, AFG_1, and AFG_2) and 15 µg/kg for OTA, for ginger and its products.

113. A study evaluating the heavy metal content of ginger from Turkey found that the permissible limit values in edible plants determined by FAO/WHO were exceeded for Fe, Zn, Cd, Pb and Cu (Karagözoğlu, 2023).

114. The Committee discussed the potential presence of contaminants in ginger and noted that the ginger products used in the studies reported were sourced locally in markets or from herbalists (Wagesho & Chandravanshi, 2015; Goroya *et al.*, 2019). Members queried whether there were any specific data on contaminants in ginger or ginger supplements available in the UK. However, no such information could be found.

115. The Committee noted that it was unknown how much ginger and particularly, highly concentrated juice extracts, would contribute to overall exposure to contaminants in the UK.

Exposure

116. TOX/2021/26 discussed exposure to ginger via the diet and in supplement form. TOX/2020/51 examined in more detail exposure to ginger in the form of highly concentrated juices (‘shots’). This statement reviews exposure to ginger from all sources described previously.

117. A number of ginger supplements (Annex B, Tables 1 and 2), many of which are purported to support digestive and joint health, alleviate nausea, upset stomach, and travel sickness, are available. Currently, a number of commercially available pregnancy supplements, including ‘Seven Seas Pregnancy’ and ‘Seven Seas Pregnancy Plus Follow On’, contain ginger extracts in their formulations.

118. The availability of supplements in different forms, along with a lack of information with regards to the extraction processes involved and therefore composition of the extracts, meant that it was not possible to assess aggregate exposures. As such, ginger exposure from the diet and from supplements were considered separately.

119. In addition to supplements, pregnant women may also consume ginger as part of their general diet to various degrees. There are anecdotal reports of women consuming ginger products (Annex B, Table3), such as ginger biscuits and ginger ale, to alleviate morning sickness and nausea. Some may use these in combination with juice shots or tinctures (Annex B, Table 4).

120. Table 1 shows estimated exposures from the diet, supplements and drinks (including teas and shots). Mean estimated acute ginger exposure from the diet in women aged 16-49 years old was 0.026 g/kg bw/day, and 97.5th percentile exposure was 0.16 g/kg bw/day. The corresponding mean and 97.5th percentile chronic exposures were 0.0083 and 0.058 g/kg bw/day, respectively. The upper value of the range of daily exposure from drinks and supplements was more than double that estimated for 97.5th percentile acute exposure from the diet, and 8-10 times that for chronic consumption from the diet.

Table 1: Estimated mean and 97.5th percentile acute and chronic ginger exposures from a variety of sources in women aged 16 – 49 years old.

Sources	**Range of daily exposures (g/day)**	**Range of daily exposures (g/kg bw/day)**	**Mean acute exposure * (g/day)**	**Mean acute exposure * (g/kg bw/day)**	**97.5th percentile acute exposure * (g/day)**	**97.5th percentile acute exposure * (g/kg bw/day)**	**Mean chronic exposure * (g/day)**	**Mean chronic exposure * (g/kg bw/day)**	**97.5th percentile chronic exposure * (g/day)**	**97.5th percentile chronic exposure * g/kg bw/day**
Food[a]	NA	NA	1.7	0.026	11	0.16	0.55	0.0083	3.4	0.058
Drinks (Including tea and shots) [b1,b]	0.5 - 32.5	0.0071 - 0.46	NA	NA	NA	NA	NA	NA	NA	NA
Supplements [c]	0.010 - 24	0.00014 - 0.34	NA	NA	NA	NA	NA	NA	NA	NA

[1]This assumes only one serving is consumed per day.

[a] Data obtained from the National Diet and Nutrition surveys years 1-8 calculated from women of a childbearing age (16-49 years). (Bates *et al*., 2014; 2016; Roberts *et al*., 2018).

[b] Data obtained online from retailers, see Appendix 1 for further details.

c Data obtained online from retailers, see Appendix 1 for further details.

*Rounded to 2 significant figures.

121. As previously mentioned, if used during pregnancy, 1 - 1.5 g per day of ginger is advised (NHS, 2022, Healthline, 2020; Mother and Baby, 2022). Some highly concentrated ginger shots commercially available contain up to 30 g of fresh ginger per serving, over 30 times that recommended by healthcare professionals.

122. As the National Diet and Nutrition Survey (NDNS) does not provide data for pregnant women, there was uncertainty as to whether the data presented an accurate reflection of consumption during pregnancy. This uncertainty also extended to data presented for drinks and supplements, as the pattern of consumption during pregnancy to alleviate symptoms of sickness is unknown.

Toxicology conclusions

Reproductive and developmental toxicity

123. The COT considered a number of epidemiological studies investigating the use of ginger during pregnancy (TOX/2021/26). For the most part, few of these studies explicitly addressed the safety of ginger consumption. Most were focused on the use of ginger as a treatment for nausea (Fischer-Rasmussen *et al.*, 1990; Smith *et al.*, 2004; Ensiyeh *et al.*, 2009), age-related neurological disorders or pregnancy-induced sickness and therefore focused on efficacy (Willetts *et al.*, 2003; Stanisiere *et al.*, 2018). However, safety was considered in a few studies. The studies considered by the Committee included observational and randomised clinical studies, lasting from 4 days to 20 weeks in duration (Vutyavanich *et al.*, 2001; Portnoi *et al.*, 2003). Ginger in various forms was investigated in doses ranging from 750 mg/day to the equivalent of 7 g/day.

124. The animal studies on reproductive toxicity considered in TOX/2021/26 reported a number of findings, including reduced maternal weight gain, increased fetal weight, increased serum testosterone levels in F1 generation males and an increase in embryonic loss.

125. The study results in pregnant women were also varied and overall were inconclusive. Findings reported included abdominal discomfort, vomiting and diarrhoea. There were reports of incidences of spontaneous abortion (Portnoi *et al*., 2003, Ensiyeh *et al.*, 2009), however, this effect was observed in both the treated and control groups and therefore, cannot be attributed directly to the consumption of ginger. Portnoi *et al*., reported 8 spontaneous abortions in the comparator group, compared to 3 occurring in the group taking ginger and Ensiyeh *et al.*, reported 2 spontaneous abortions in the ginger group compared to 1 in the group taking vitamin B6. This study reported no congenital abnormalities post-partum following exposure to ginger.

126. In their 2015 review of interventions for nausea and vomiting in early pregnancy (first trimester), Matthews concluded high-quality consistent evidence is lacking to support advice regarding the safety of ginger during pregnancy (Matthews et al., 2015). However, it was noted that a review by Bryer et al. (2005) concluded that maternal consumption of ginger shows no evidence of teratogenicity in infants. More recently, Stanisiere et al. (2018) conducted a review of the safety and efficacy of ginger rhizome for decreasing nausea and vomiting in women during early pregnancy, based on systematic literature searches until the end of December 2017. The group concluded that the *in vivo* results do not suggest any major concerns with respect to reproductive and developmental safety of ginger root, as no associations were found between the use of ginger and malformations in humans. *In vitro* results could not be extrapolated to humans due to the lack of representativeness of the preparations and/or concentrations used. The authors concluded that, overall, the available evidence suggested that the use of ginger for treatment of nausea in pregnancy is safe, but that ginger quality is important from the perspective of safety. The majority of the studies included in Stanisiere et al. (2018) have already been included in this draft statement. Some recent studies have been conducted evaluating the effectiveness and safety of ginger in pregnancy and are discussed in detail. Overall, most studies reported gastrointestinal effects such as abdominal discomfort/heartburn, vomiting and diarrhoea. Other effects included dizziness, headaches and drowsiness. The review by Jewell and Young (2003) focuses on the reported effects rather than statistical significance, therefore more details on the studies reporting more serious effects were given in this statement.

Anti-platelet aggregation activity

127. Several reports have been published on the pharmacological properties of ginger, with varying results. The potential effect of ginger extract and components thereof on the reduction of platelet aggregation and their potential antithrombotic activity has been noted as a concern both in the literature and by health professionals.

128. Ginger was reported to have antiplatelet activity (Srivastava, 1986,1989; Young *et al.*, 2006), with some studies reporting effects in animals at doses of 500 mg/kg bw (Thomson *et al.*, 2002). Ginger was found to inhibit the formation of thromboxane and prostaglandin endoperoxides ($PGF_{2\alpha}$, PGE_2 and PGD_2) in human platelets *in vitro*, in a dose-dependent manner (Srivas, 1984).

129. With regards to the relevance of such effects in pregnancy, literature reports note that pregnancy is associated with an increased incidence of thrombotic events; mainly related to a pro-thrombotic state, physiologically useful to reduce bleeding at delivery. These changes are more pronounced in the third trimester (Patti *et al.,* 2014). It has also been hypothesised that antiplatelet agents might prevent or delay the development of pre-eclampsia (Duley *et al.*, 2019). The implications and clinical significance of the anti-platelet activity of ginger during different stages of pregnancy remain undetermined.

130. This further highlighted the need to differentiate exposure from the normal diet to that from supplements. Members noted that associations with haemorrhagic effects had been reported mainly as the result of a herb-drug interaction following supplemental exposure to ginger, (Kruth *et al.*, 2003; Rubin *et al.*, 2019; AlAskar *et al.*, 2020). though these were inconclusive.

Conclusions of the Committee

131. Ginger is commonly used as a spice and flavouring in many countries worldwide and is growing increasingly in popularity as a natural remedy, due to its purported immunostimulatory properties, for easing motion sickness and post-operative nausea and vomiting, and pregnancy related nausea.

132. Several ginger supplements are commercially available, ranging from dried root in capsule form to tincture form, all with varying amounts of ginger. In addition to this, concentrated ginger shots (liquid form), containing large amounts of pressed ginger, are becoming increasingly popular. The variability in the composition of these supplements adds uncertainty to the amount of active ginger actually being consumed.

133. A number of the studies noted that the toxicity observed varied according to the nature of extraction solvent; organic solvent extracts exhibited more toxicity than aqueous extracts, which presumably indicates extraction of differentially toxic compounds.

134. Overall, the Committee concluded that based on the available information it was not possible to determine a point of departure to use in the risk assessment of ginger when used as a supplement.

135. Members noted that although the different ginger extracts were not comparable across animal studies, there was evidence for some biological effects in the early stages of pregnancy. It was stressed that in general there was no indication of systemic toxicity in pregnant women or to the fetus from the use of ginger in the diet as food.

136. The lack of safety and toxicological information available on ginger use in pregnancy overall make it difficult to fully characterise the risks in this respect. The committee noted that while there was some equivocal evidence for effects of ginger on reproduction in experimental animals, it was not possible to characterise this based on the data available.

137. Also, consumption data was based on women of childbearing age and therefore may not be representative of the maternal diet, leading to an under/overestimation of the actual exposure. The Southampton Women's Survey assessed the diet of a large group of non-pregnant women aged 20 to 34 years living in the city of Southampton (Inskip, 2006). Women (n=12,583) were recruited between April 1998 and December 2002. For the women who subsequently became pregnant similar information was collected. Compared with the period before pregnancy, there were marked decreases in alcohol and caffeinated drink intake, however, there was little change in overall levels of fruit and vegetable consumption. It is unlikely that this captures potential supplement use or specific dietary modifications to address pregnancy-related conditions such as nausea, but it does indicate that there is overall similarity between the diets of women of childbearing age and pregnant women (Crozier, 2009).

138. There is no clear indication that ginger is detrimental to pregnant women or the developing fetus or embryo, although there are some signals for potential adverse effects. Generally, consumption of ginger in a traditional culinary manner within a diet is not considered a health concern. The Committee noted that from the evidence presented, the potential for contamination of ginger with heavy metals and/or mycotoxins cannot be excluded.

139. The COT concluded that there is no evidence to support changing the current NHS advice to pregnant women. The NHS currently recommends trying foods or drinks containing ginger as one of the approaches that might ease symptoms of morning sickness but emphasises that during pregnancy a person should check with a pharmacist before taking ginger supplements (NHS, 2024).

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COT/2025/01 Annex A

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Annex A: Summary of Studies

Traditional/culinary uses of ginger

Human Studies

Author/Date	Study type	Study size/No. of Patients at End	Exposure (ginger dose/day)	Study period	Length of Treatment (days)	Main outcome measures	Main results
Chittumma *et al.*, 2007	Randomized double-blind controlled trial.	126/123	Ginger powder capsules (325 mg ×2, 3x/d, = 1950 mg/day).	4 days	4	Change in nausea and vomiting scores (3 symptoms on Rhodes index); occurrence of side-effects.	Only minor side effects observed. No difence between the groups.

Ensiyeh *et al.,* 2005	Double-blind randomised controlled trial.	70/69	Ginger powder capsules (500 mg 2×/d =1000 mg/day)	3 months	4	Severity of nausea (VAS 0–10); number of vomiting episodes; general response to treatment (5-item Likert scale); occurrence of side-effects or adverse pregnancy outcome.	Two spontaneous abortions in ginger group, 1 in B6 group; no congenital anomalies observed in babies brough to term.
Fischer-Rassmussen *et al*., 1991	Double-blind randomised crossover trial.	30/27	Ginger powder capsules (250 mg 4 times per day = 1000 mg/day).	11 days	4	Preference of treatment period; relief scores (4-point scoring system); outcome of pregnancy.	One spontaneous abortion, One elected. No adverse effects were observed in remaining 25 subjects.
Portnoi, 2003	Not specified.	187 pregnant women.	Various, not specified.	up to 12 months post birth.	Minimum of 3 days.	Safety and effectiveness of ginger for nausea and vomiting of pregnancy (NVP).	Three major malformations were reported in the ginger group, ventricular septal defect (VSD), right lung abnormality, and kidney abnormality (pelviectasis). One incidence of idiopathic central precocious puberty at age 2 years. No significant

							difference between the two groups in terms of live births, spontaneous abortions, stillbirths, therapeutic abortions, birth weight, or gestational age.
Smith, 2004	Randomized, controlled equivalence trial.	291 women, less than 16 weeks pregnant.	1.05 g ginger.	3 weeks.	3 weeks.	Ginger verses B6 for the treatment of nausea or vomiting in pregnancy.	Three spontaneous abortions in ginger group, 9 abortions in B6 group.
Vutyavanich, 2001	Double blind	32	Ginger powder capsules (250 mg 4x/day =1000 mg/day).	5 months.	4	Severity of nausea (VAS 0–10); number of vomiting episodes; general response to treatment after 1 week (5-item Likert scale); occurrence of side-effects and adverse pregnancy outcomes.	No significant adverse effects of ginger on pregnancy outcome.

Human studies – Platelet Aggregation

Author/date	Study design	Population/ study size	Study Duration	Exposure	Outcome	Results	Comment

Bordia *et al.,* 1997	Placebo controlled trial.	Patients with confirmed myocardial infarction N = 60.	3 months. Outcomes measured at: baseline, 1.5 months and 3 months.	Dose: 4g per day Unstandardised capsules.	Platelet aggregation— Agonist(s): ADP and Epi.	Ginger had no significant effect on both measures of aggregation.	Ginger had no significant effect on blood lipids or blood sugar.
Bordia *et al.,* 1997	NA	NA	NA	NA	Fibrinogen;	NA	No mention of randomisation.
Bordia *et al.,* 1997	NA	NA	NA	NA	Fibrinolytic activity.		P value not reported.
Lumb. 1994	Randomised, double-blinded placebo-controlled crossover trial.	Healthy male volunteers N=8.	Total study period: 2 x 1 day, at least 14 days washout period. Outcomes measured immediately before, 3 hrs, and 24 hrs post consumption of ginger.	Dose: 2g (4 x 500 mg) dried ginger per day Unstandardized capsules.	Platelet aggregation; - Agonist(s): AA, ADP, collagen, ristocetin, ADP; Bleeding time; Platelet count; Thromboelastography.	No significant changes in any outcome at any time point.	NA
Srivastava 1989	Open-label single-arm trial.	Healthy female volunteers, N = 7.	Total study period: 7 days. Outcomes measured at baseline and	Dose: 5g raw ginger per day.	Platelet thromboxane B2 production.	Ginger consumption resulted in a 37% inhibition of thromboxan	NA

			7days post-consumption.			e B2 production ($p<0.01$).	
Young *et al.,* 2006	Not specified.	20	72 days.	1 g ginger (+ 10 mg nifedipine).	Synergistic effect of ginger and nifedipine on anti-platelet aggregation in normal human volunteers and hypertensive patients.	Ginger and nifedipine had synergistic effect on anti-platelet aggregation; Ginger increased anti-platelet aggregation effect of nifedipine in all patients.	NA

In vivo studies

Author	Test System	Study size	Exposure	Characterisation of test substance	Duration	Main outcome measure	Outcome

Wilkinson 2000	Sprague-Dawley rats, F.	43	Oral, drinking water on days 6-15.	20 g/L or 50 g/L ginger tea.	20 days.	Reproductive and developmental toxicity.	Embryonic loss in the treated groups 2 times that of the controls. Exposed fetuses found to be significantly heavier than control. No gross structural malformations observed.

Effect on Platelet Aggregation

Author	Test System	Study size	Exposure	Characterisation of test substance	Main outcome measure	Outcome
Srivastava 1989	Open-label single-arm trial.	Healthy female volunteers, N = 7.	Total study period: 7 days. Outcomes measured at baseline and 7 days post-consumption.	Dose: 5g raw ginger per day.	Platelet thromboxane B2 production.	Ginger consumption resulted in a 37% inhibition of thromboxane B2 production ($p<0.01$).

Extracts and concentrates of ginger

Human Studies

Author/Date	Study type	Study size/No. of Patients at End	Exposure (ginger dose/day)	Study period	Length of Treatment (days)	Main outcome measures	Main results
Laekeman et al., 2021	Observational study, clinical feasability trial.	51/44	maximum of 2 tablets of 50 mg EXT.GR10 a day [limited data on actual amount administered]	During pregnancy.	NA	Patient satisfaction pregnancy complications (including hypertension and diabetes) and birth complications (including stillbirth, premature delivery, low birth weight).	Incidence of premature birth, low birth weight and hypertension in treatment group higher than in general population. Pilot study but not considered to indicate a safety concern.
Willetts *et al.,* 2003	Double-blind randomised placebo-controlled trial.	120/99	Ginger extract capsules (125 mg 4x/d =1000 mg/day).	8 months.	4	Used RINVR to measure frequency, duration, distress caused by nausea, vomiting and retching; long term follow-up for birth outcome.	Three spontaneous abortions observed in ginger group.

Human studies – Platelet Aggregation

Author/date	Study design	Population /study size	Study Duration	Exposure	Outcome	Results	Comment
Bordia *et al.,* 1997	NA	20	1 day. Outcomes measured at: baseline, 4 hours post-consumption.	10 g single dose. Unstandardised capsules.	Platelet aggregation. - Agonist(s): ADP and Epi.	Reduction of both measures of platelet aggregation when compared to placebo ($p < 0.05$).	NA
Jiang *et al.,* 2004	Randomized, open label, three-way crossover trial.	Healthy male volunteers Age: 20–36 N =12.	Total study period: 3x13 days, 14 days washout period between each study period.	Dose: 3.6g (3x 0.4g, 3x per day) ginger extract Unstandardized capsules consumed with 25 mg dose of rac-warfarin, consumed once per study period.	Platelet aggregation, Agonist: AA; INR; Plasma warfarin enantiomer protein binding & warfarin enantiomer concentrations Urinary S-7-hydroxywarfarin.	No significant changes in any outcome.	P value not reported.
Rubin *et al.*, 2019	Case report	Female, 70 yrs	NA	48 mg daily Chewable ginger	INR - 8.0 approx. 1 month after taking	INR reduced to 2.6 following cessation of	Patient also taking clonazepa

				supplement for approx. 1 month.	ginger supplement.	ginger supplementation and pause in warfarin administration. Remained within normal range on resumption of warfarin.	m 1 mg, metoprolol succinate 25 mg, paroxetine 10 mg, phenytoin 30 mg, rosuvastatin 20 mg, warfarin 7.5 mg, and warfarin 10 mg 10 mg.
Verma *et al.,* 1993	Randomised placebo controlled trial.	Healthy male volunteers; N = 20.	Total study period: 14 days, high calorie diet for first 7 days, high-calorie diet and ginger/placebo consumed for next 7 days. Outcomes measured at	Dose: 5g (4 x 625 mg, twice per day); dry ginger powder - Unstandardized capsules Consumed with 100g (2x50g) butter, 2 cups of milk, 8 slices of bread.	Platelet aggregation. Agonist(s): ADP and Epi.	Ginger significantly reduced platelet aggregation using both agonists when compared to placebo group ($p<0.001$).	Platelet aggregation reduced close to baseline but did not decrease further.

			baseline, 7, and 14 days.				

In vitro studies

Author	Test System	Exposure	Characterisation of test substance	Main outcome measure	Outcome
Abudayyak *et al.,* 2015	Ames: Salmonella typhimurium TA98 and TA100 strains; Cytotoxicity assay: Rat kidney NRK-52E cell line.	Cytotoxicity assay: (0.75, 1.50, 3.00, 6.00, 12.00, 25.00, 50.00, and 75.00 mg/ml, genotoxicity: 0.78, 1.56, 3.13, 6.25, 12.50, and 25.00 mg/ml.	Aq, chloroform and MeOH ginger extracts.	Cytotoxicity and genotoxicity.	Chloroform extract cytotoxic: IC_{50} = 9.08 mg/ml; aqueous extract mutagenic at all concentrations against T98 strain, in presence of S9 mix.
Mohammed *et al.,* 2016	chick embryonic heart micromass; mouse D3 embryonic stem cell systems (ESD3).	0.75–100 uM Micromass assay: 6 days, ESD3: 12 days.	6-gingerol	Embryotoxicity	no significant changes in contractile and cellular activity or changes in total protein content in 6-gingerol-treated primary embryonic chick cardiomyocytes.

NA	NA	NA	NA	NA	Inhibition in contractile activity at 12.5–50 µg/mL.
NA	NA	NA	NA	NA	Change in both cellular activity and protein content in a dose-dependent manner at high concs (12.5–100 µg/mL).
NA	NA	NA	NA	NA	Significant decrease in cardiomyocyte differentiation for all tested concentrations except 0.75 µg/mL in ESD3.
NA	NA	NA	NA	NA	Significant decrease in cellular activity and protein content of stem cell-derived cardiomyocytes with increased 6-gingerol concentration exposure.

Nakamura & Yamamoto (1982)	Escherichia coli Hs30.	Not specified.	Juice of ginger rhizome, 6-gingerol.	Mutagenicity	ginger juice supressed spontaneous mutation; 6-gingerol mutagenic in isolation.
Nakamura & Yamamoto 1983	Escherichia coli Hs30.	Not specified.	6-shogaol, 6-gingerol.	Mutagenicity.	[6]-Shogaol was 10^4 times less mutagenic, at a concentration of 700uM, than [6]-gingerol.
Nirmala *et al.,* 2007	Wistar rats, male	Salmonella typhimurium strains TA 98 and TA 100.	Ginger paste and powder, unboiled, boiled, unfried, fried. Ames test: Ginger paste: 1, 2 and 3 mg; powder: 0.5, 1 and 1.5 g.	Anti-mutagenicity.	Anti-mutagenic potential unaltered by treatment of ginger.
Plengsuriyakarn *et al.,* 2012	Cholangiocarcinoma (CCA) cell line 6 (CL-6), hepatocarcinoma (HepG2) and normal human renal epithelium (HRE).	1.95, 3.90, 7.81, 15.62, 31.25, 62.5, 125, and 250 µg/ml.	Crude ethanolic ginger extract.	Cytotoxicity	IC_{50} and cytotoxicity 10.95 and 53.15 µg/ml.

Soudamini *et al.,* 1995	Salmonella typhimurium strains TA 100, 98 and TA 1535.	25 and 50 mg/plate.	ethanolic mixture of powdered ginger.	Mutagenicity	mutagenicity in both TA 1535 and TA 100 at both concentrations.
Zaeoung *et al.,* 2005	breast (MCF7) and colon (LS174T) cell lines.	Not specified.	aqueous extract and volatile oils.	Cytotoxicity	IC_{50} > 39.2 µg/ml.

In vivo studies

Author	**Test System**	**Study size**	**Exposure**	**Characterisation of test substance**	**Duration**	**Main outcome measure**	**Outcome**
Alnaqeeb *et al.,* 2003 (abstract)	Rats, female	Unknown	Oral and intraperitoneal. 50 mg/kg and 500 mg/kg	Aqueous ginger extract	28 days	NA	Increased levels of serum aspartate aminotransferase (AST) and decreased levels of alanine aminotransferase (ALT) in orally dosed rats.
Dissabandara & Chandrasekara, 2007	Sprague-Dawley rats.	15 in 3 groups, otherwise not specified.	Oral: 500 mg/kg/day and 1000 mg/kg/day during days	Powdered ginger extract.	Animals treated with ginger for 10 days.	Effect of powdered ginger extract administered prenatally on	Lower intake of food and water and lower weight gain in

			5 to 15 of gestation.			postnatal development .	ginger treated group.
ElMazoudy and Attia, 2018 (abstract only)	ICR mice	Unknown	250, 500, 1000, or 2000 mg/kg bw/d aqueous ginger extract.	Powdered dried ginger root	35-day treatment study; 20 day study (antifertility and abortifacient loss).	Effect on oestrus cycle and implantation in female mice.	Female copulation index was significantly reduced at 2000 and 1000 mg/kg bw/d groups; female pregnancy index significantly decreased at the highest dose. No. of implantation sites and live fetuses in the 2000 mg/kg bw/d group lower than the other treated and control groups.
Hosseini *et al.,* 2015 (abstract only)	Rats, female and male offspring	72 (groups of 9)	Oral: 50, 100 and 200 mg/kg bw during neonatal and	Alcoholic ginger extract	Unknown	Serum testosterone, LH and FSH. Effect on spermatogen ic cell lines	Significant increase in testosterone levels and number of spermatogenic

			perinatal periods.			in male mature offspring rats.	cells. Significant reduction in FSH and LH at doses of 100 and 200 mg/kg bw compared to control.
Jeena *et al.*, 2011	Wistar rat	30	Oral: 100, 250, and 500 mg/kg per day once daily.	Ginger essential oil.	13 weeks.	Oral Toxicity.	No mortaility or abnormal changes observed in relative organ weights w.r.t. body weight. Increase in serum Na levels in male rats treated with 500 mg/kg/d. slight increase in total bilirubin in female rats, along with a decrease in AST and ALT levels. No significant changes in hepatic function parameters (alkaline phosphatase,

							total protein, albumin and globulin content).
Malik and Sharma, 2011	Wistar rat, male.	Not specified.	gastric gavage: 250, 500 and 1000 mg/kg, (corresponding to 5, 10 and 20% of the NOAEL of the lyophilised ginger powder (5000 mg/kg).	Lyophilsed ginger juice powder.	Experiment 2: 8 weeks. Exp 1&2 not specified.	Acute Toxicity.	no signs of toxicity or mortality.
Peneme et al., 2023	Swiss mice.	6	5000 mg/kg aqueous ginger extract.	Ginger powder extracted into water.	OECD guideline no. 423.	Acute toxicity.	no signs of toxicity or mortality.
NA	NA	20	17 β-oestradiol, (1 mg/kg) or ginger extract	Ginger powder extracted into water.	2 weeks.	Effect on oestrus cycle and plasma oestradiol levels.	Changes in body weight and eosinophil indices for 600 mg/kg bw

			(300 or 600 mg/kg) per day.				indicated disruption of oestrus cycle.
Plengsuriyakarn *et al.,* 2012	OV and nitrosamine (OV/ DMN)-induced CCA hamsters.	90	1000, 3000, and 5000 mg/kg bw/d.	NA	30 days	Acute Toxicity.	NA
Rong *et al.*, 2009.	Sprague–Dawley rats, male and Female.	40.	Gavage: 500, 1000 and 2000 mg/kg bw/day.	Powdered Japanese ginger.	37	35 day repeat dose.	No increase in mortality. Slightly reduced absolute and relative weights of testes (by 14.4% and 11.5%, respectively) at highest dose.
Shalaby and Hamowieh, 2010	Sprague Dawley rats.	120	Oral, 5 to 17.5 g/kg bw.	Water or methanolic ginger extract.	65 days.	Fertility, serum testosterone and acute toxicity.	oral Lethal Doses (LD50) of the methanolic and water extracts - 10.25 and 11.75 g/kg bw respectively. No symptoms of toxicity

							observed at doses up to 5 g/kg bw. Both extracts increased fertility index, sexual organ weight, and sperm motility and count after 65 days.
NA	NA	NA	NA	NA	NA	NA	Methanolic extract: Testosterone levels increased to 4.08 ± 0.10 and 7.13 ± 0.14 ng/dL (both significant at $P < 0.001$); Water extract (150 and 300 mg/kg bw): Serum testosterone levels increased 4.06 ± 0.03 and 5.04 ± 0.08 ng/dL (both significant at $P < 0.001$).

NA	NA	NA	100 and 200 mg/kg bw for 65 days and water extracts at doses of 150 and 300 mg/kg bw.	NA	NA	Fertility Index	Mild to moderate degenerative changes of spermatogenic cells, diffuse oedema and incomplete arrest of spermatogenesis. Mild degeneration of spermatogenic cells and slight oedema of interstitial cells in testes of rats orally administered 300 mg/kg bw water extract. LOAEL of 200 mg/kg bw/day for the methanolic extract suggested.

Weidner & Sigwart, 2001	Wistar rats, pregnant female.	176 (88 Females).	Gastric intubation: 100, 333 and 1000 mg/kg from days 6-15.	EV.EXT 33, a patented Zingiber officinale extract (comprising 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol, and 8-shogaol (1.9 w/w of the extract).	21 days.	Teratogenicity.	No maternal or developmental toxicity observed.

Effect on CYPs and prostaglandin activity

Author	Test System	Exposure	Characterisation of test substance	Main outcome measure	Outcome
Dugasani *et al.*, 2010	Mouse leukaemic monocyte (RAW 264.7) macrophages and human polymorphonuclear neutrophils (PMN).	1, 3 and 6 uM.	[6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol.	compare the antioxidant and antiinflammatory activities of gingerols and their natural analogues to determine their structure–activity relationship	Dose dependant inhibition of activated PGE2 release. Inhibition reached 58, 66, 73 and 87%, respectively, at 6uM.

				and molecular mechanisms.	
Jolad *et al.*, 2004	HL-60 cells.	Not specified.	ginger constituents: gingerols, shogaols, 3-dihydroshogaols, gingerdiols.	Effects of ginger components on LPS-induced PGE2 production.	No cytotoxicity demonstrated.
Jolad *et al.*, 2005	HL-60 cells.	Not specified.	Ginger constituents containing gingerols, shogaols, 3-dihydroshogaols, gingerdiols.	Effects of ginger components on LPS-induced PGE2 production.	Inhibition of LPS-stimulated PGE2 production (IC_{50} = 0.05 0.08 ug/ml) with Gingerol fractions.
Kim *et al.*, 2012	Human liver microsomes.	0.05–5 ug/ml.	Aqueous ethanolic ginger extract (30% EtOH).	Inhibitory effect on CYP450-mediated drug metabolism.	Concentration-dependent inhibitory effects on CYP2C19; IC_{50} value of 3.8 g/ml.
Kimura *et al.*, 2010;	Human CYP3A4 and CYP2C9 microsomes.	Not specified.	NA	Inhibitory effect on CYP3A4 and CYP2C9 activity.	significant inhibition of CYP3A4 IC_{50} 5.1u g/ml or CYP2C9 IC_{50}

					(10ug/ml) activity.
Lantz *et al.*, 2007	U937 cells	0.1 ug/ml for 6 hrs.	Ginger extract and mixtures of 6-, 8- 10-gingerols and 6-, 8-, 10-shogaols.	Effect on inflammatory mediator production.	No effect on COX-2 expression.
Mukkavilli *et al.*, 2014	Human liver microsomes.	Ginger extract: 500 mg/ml (containing 15 mg/ ml 6G, 3.4 mg/ml 8G, 3.9 mg/ml 10G, 3.0 mg/ml 6S); All individual components of gingerols assessed at 100 mg/mL (equivalent to 29 mg/ml 6G, 32 mg/ml 8G, 35 mg/ml 10G and 28 mg/ml of 6S).	Ginger extract: (containing 6-Gingerol, 8-Gingerol, 10-Gingerol, 6-Shogaol). All individual components of gingerols were assessed at 100 mg/mL equivalent to 29 mg/mL 6G, 32 mg/mL 8G, 35 mg/mL 10G and 28 mg/mL of 6S.	effect of ginger extract and major constituents on CYP P450 enzyme activity.	Inhibition of CYP1A2 (IC_{50} - 221.5 mg/ml) by ginger extract. No effect on CYP2A6; maximum inhibition on CYP2B6: IC_{50} - 22 mg/ml; IC_{50} - 122.5 mg/mL against CYP2C8 in the presence of amodiaquine; IC_{50} - 93.5 mg/mL against CYP2C9, in the presence of diclofenac; Inhibition of CYP3A in the presence of testosterone: no

					effect in the presence of midazolam.

Effect on Platelet Aggregation

Author	Test System	Study size	Exposure	Characterisation of test substance	Main outcome measure	Outcome
Srivas, 1984	Human platelets and rat aorta.	NA	15-20 ul (concentrations not given).	Ginger extracts in water, n-hexane, chloroform, and ethyl acetate.	Effect of ginger extracts on *in vitro* platelet aggregation.	Inhibition of arachidonic acid (AA), epinephrine, adenosine diphosphate (ADP), and collagen-induced platelet aggregation.
Srivastava, 1986	Platelet rich plasma (no further information given).	NA	10-20 ul (concentrations not given).	NA	Effect of ginger and components on platelet aggregation and eicosanoid biosynthesis.	Reduced thromboxane formation from exogenous AA; Inhibition of AA, epinephrine, ADP and collagen-induced platelet aggregation.
Suekawa *et al.*, 1986 (abstract only)	Rat hind paw and aorta, rabbits.	Unknown.	Unknown.	6-shogaol.	Effect of 6-shogaol on arachidonic acid cascade.	Inhibition of carrageenin-induced swelling of hind paw in rats and arachidonic acid (AA)-induced platelet aggregation in rabbits. Inhibition of prostaglandin 12 (PGI2) release in rat

						aorta. Possibly caused by COX inhibition.
Thomson *et al.,* 2002	Sprague-Dawley rats, Adult, F; *ex vivo*.	36	50 mg/kg or 500 mg/kg daily by gavage or intraperitoneally (IP) for 4 weeks.	Aqueous ginger extract, equivalent of 500 mg/ml.	*ex vivo* effect of aqueous extract of ginger on the synthesis of thromboxane-B2, prostaglandin-E2, and cholesterol, triglyceride levels in the serum of normal rats.	Serum PGE2 reduced and both dose levels; high dose significantly reduced serum TXB2 both orally and IP; A non-significant reduction in the level of TXB2 observed when ginger was injected IP but not significantly different from saline group.
NA	NA	NA	NA	NA	NA	significant reduction in levels of cholesterol in rats given high dose; No significant change in triglyceride levels with either dose either orally or IP.

Herb-drug interactions

Author	**Test System**	**Study size**	**Exposure**	**Characterisation of test substance**	**Duration**	**Main outcome measure**	**Outcome**

Al-Omari *et al.*, 2012	Albino rat, M	30: 5 groups of 6; 72: 12 groups of 6.	25, 50 and 100 mg/kg bw by gavage; single dose (50 mg/kg bw) and up to one week.	Ginger crude extract.	Multiple dose: 2 weeks; single dose: 1 week.	Effect on glibenclamide and insulin; hypoglycaemic and antihyperglycemic effects in normoglycemic- and streptozotocin-induced (STZ) diabetic rats.	Significant decrease in blood glucose level (BGL) in normoglycemic rats after 1 & 2 hrs (50 mg/kg). Significant decrease in non-fasting BGL (N-FBGL) in STZ- diabetic rats.
Egashira *et al.*, 2012	Sprague-Dawley rat, M (7 weeks old)	Not specified.	10 mL/kg orally.	50% ginger juice.	1-3 days.	interaction between ginger juice and tacrolimus.	Significant increase in tacrolimus blood concentrations in rats treated with ginger juice, compared to those treated with water or orange juice.
Okonta *et al.*, 2008	Rabbits (3F, 2M)	5	1 ml/kg, orally.	Ginger extract.	3 days.	Effect of ginger on the pharmacokinetics of metronidazole.	Significant increase in absorption and plasma half-life; significant decrease in the elimination rate constant and

							clearance of metronidazole.

COT/2025/01 Annex B

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Annex B: Assessment of Exposure

1. The active components of ginger – gingerols, shogaols and α-curcumene, occur in varying amounts and relative proportions, depending on the variety of rhizome and the area of cultivation.

2. Many ginger supplements (Tables 1 and 2) are recommended to support digestive and joint health, alleviate nausea, upset stomach, and travel sickness. Currently, two commercially available pregnancy supplements – 'Seven Seas Pregnancy' and 'Seven Seas Pregnancy Plus Follow On' – contain 10 mg ginger extract.

Table 1. Sample of ginger supplements in capsule and tablet form commercially available.

Commercial Product Name	**Form**	**Composition**	**Daily dose recommended by vendor or website**
Seven Seas Pregnancy	Tablet	Ginger extract 10 mg	1 tablet a day.
Seven Seas Pregnancy Plus Follow-On	Tablet, capsule	Ginger extract 10 mg	One tablet and one capsule/ day.
Supplemented	Tablet	Ginger Extract 3,000 mg (20:1)	1-2 tablets daily.
Good n Natural	Capsule	Powdered root 550 mg	2 capsules daily.
Woods Supplements	Tablet	Ginger extract 500 mg	1 tablet daily.
Solgar	Capsules	Ginger (Zingiber officinale) Root Powder 150 mg, Standardised Ginger (Zingiber officinale) Root Powdered Extract (5% ginger gingerols) 300 mg.	1-2 capsules daily.

Solgar	Capsules	Ginger (Zingiber officinale) Root Powder 500 mg. Ginger (Zingiber officinale) Root Powdered Extract (4:1) 5 mg.	1-3 capsules daily.
Swanson	Capsules	Ginger Root 540 mg.	2 capsules daily.
Bio Health	Capsules	Ginger Root 500 mg.	None given.
Biovea	Capsules	Ginger (root) (std. to 5% gingerols, 12.5 mg) 250 mg.	1-3 daily.
Jarrow Formulas	Capsules	Ginger root (concentrate) (Zingiber officinale) 500 mg.	1 daily.
Nature's Best	Capsule	Ginger Root 14,400 mg (provided by 120 mg of a 120:1 extract) providing 24 mg gingerols.	1 daily.
NeuLife	Tablets	Ginger Extract 12000 mg.	1-2 tablets daily.
Lifeplan	Capsule	Ginger 12:1 Extract.	1-2 tablets daily.
ALPHA01	Capsules	Ginger root powder 1100 mg.	2 capsules daily.
	Tablet	Ginger Extract 12,000 mg (20:1) standardised to 600mg 12,000 mg.	1-2 tablets daily.
Now Foods Capsules Superfood World	Capsules	Ginger Extract (Zingiber officinale) (Root) (Standardized to min. 5% Gingerols) 250 mg: Ginger Powder (Zingiber officinale) (Root) 225 mg.	1-3 capsules daily.
Viridian Ginger	Capsules	One vegetarian capsule provides: Certified organic Ginger root 400 mg.	1-3 capsules daily.

Table 2: Sample of ginger supplements in liquid and powder forms commercially available.

Commercial Product Name	**Form**	**Composition**	**Daily dose recommended by vendor or website**
Indigo Herbs	Tincture	Zingiber officinale, Alcohol, Water. Extraction Ratio: 1:3, Alcohol Volume: 25%.	1-2 ml, 2-3 times daily 20 drops from the glass dropper equals ~ 1ml.
Nature's Answer	Tincture	Ginger (Zingiber officinale) root extract: 145 mg.	1 ml (28 drops) three times per day.

Herb Pharm	Tincture	Ginger rhizome (Zingiber officinale) extract 598 mg (Extraction rate 140 mg herb per 0.7 ml).	“1 full squeeze of the dropper bulb to 2 oz. of water or juice, 2 - 5 times per day.
Indigo Herbs	Powder	100% Pure Zingiber officinale Powder.	1/3 teaspoon powder in water 3 times a day. (1 tsp = 3g).
Organic Herbal Remedies	Tincture	Herb to pure grain alcohol of 1:3. 1ml is the equivalent of 333mg of dried ginger root. W.	0.2ml to 0.4ml three times a day in a little water. Children 6-12 years old 0.1ml to 0.2ml three times a day.
Biovea	Tincture	Fresh Organic Ginger (root) (667 mg per 1 ml serving).	30 drops (~ 1 ml), 1-3 times daily or as needed.
Epigenar	Tincture	Purified water, organic alcohol, organic ginger (Zingiber officinale) (amounts not specified).	15 drops, 3 times daily Max 60 drops per day unless otherwise advised. Children aged 4-15 years, 3 times daily, one drop per number of years of age.

Consideration of ginger from other sources

3. In addition to supplements, pregnant women may also consume ginger as part of their general diet to various degrees. There are anecdotal reports of women using ginger products such as ginger biscuits and ginger ale, to alleviate morning sickness and nausea. Some may use these in combination with juice shots or tinctures.

Table 3: Sample of ginger-containing foods commercially available.

Commercial product name	Form	Composition
Border Biscuits Dark Chocolate & Ginger	Ground ginger	Ground ginger 1.5 %
Sainsbury's Stem Ginger Cookies, Taste the Difference	Stem ginger	Candied Stem Ginger (17%) (Australian Stem Ginger, Sugar); ginger powder.
Sainsbury's Dark Chocolate & Ginger Cookies, Taste the Difference	Stem ginger	Candied Stem Ginger (13%) (Australian Stem Ginger, Sugar); ginger powder.
Nairn's Wheat Free, Ginger Biscuits	Stem ginger	Stem Ginger (6.4%) (Stem Ginger, Sugar); Ground Ginger.
Sainsbury's Ginger Nut Biscuits, SO Organic	Powdered ginger	Ginger Powder (0.6%).
Nooro Lemon + Ginger CBD Bar	NA	Ginger (0.5%).
Rhythm 108 Lemon, Ginger & Chia Biscuit Share Bag	Dried ginger powder	Organic gluten free oat flour (33%), organic coconut oil (24%), organic coconut flower sugar, organic almonds, organic chia seeds (5%), organic lemon zest (1.3%), organic lemon oil, organic ginger powder (0.4%).

Table 4: Ginger containing teas, juices and drinks commercially available.

Commercial Product Name	Form	Composition
Gimber	liquid concentrate	38% organic and high-quality ginger, organic lemons, herbs and spices.
Moju	liquid	Apple, Ginger Root (25%), Lemon, Antioxidant: Ascorbic Acid.

James White Drinks Organic Ginger Zinger Shot 70ml	liquid	Organic Apple Juice (73%), Organic Ginger Juice (27%), Water, Antioxidant: Ascorbic Acid.
James White Drinks Organic Xtra Ginger Zinger Shot 70ml	liquid	Organic Apple Juice (59.5%), Organic Ginger Juice (40%), Organic Chilli Flavouring (0.5%), Antioxidant: Ascorbic Acid.
Twinings Lemon & Ginger Tea	Tea	Ginger Root* (37%), Natural Lemon Flavouring with Other Natural Flavourings (25%), Lemongrass*, Blackberry leaves*, Lemon Peel, Sweet Fennel*, Natural Ginger Flavouring with Other Natural Flavourings (3.5%).
Pukka Organic Ginger, Galangal & Golden Turmeric Tea	Tea	Ginger Root (52%).
Belvoir Ginger Cordial	NA	Pressed Ginger Juice 2%, Ginger Extract.
Old Jamaica Ginger Beer	Drink	Ginger root extract.
Fever Tree Ginger Beer Light	Drink	Ginger Root, Natural Ginger Flavouring with other Natural Flavourings.
Fentimans Ginger Beer	Drink	Fermented Ginger Root Extract (Water, Glucose Syrup, Ginger Root, Pear Juice Concentrate, Yeast); Natural Flavourings (Ginger, Lemon, Capsicum).
Cawston Press Apple & Ginger Juice	Juice	1% Ginger Extract.
Pukka Lemon Ginger & Manuka Tea	Tea	Ginger Root (32%).

Twinings Spiced Ginger Tea	Tea	Ginger Root* (70%), Liquorice Root* (15%), Cinnamon* (10%), Cloves* (5%).
No.1 Kombucha Ginger & Turmeric	Tea drink	Kombucha (Filtered Water, Cane Sugar*, Green Tea*, Live Kombucha Cultures), Ginger Juice* (1.5%), Ginger* (0.14%), Turmeric* (0.14%), Black Pepper*.
Teapigs Lemon & Ginger Tea Bags	Tea	Ginger (65%), Lemongrass, Lemon Peel (5%), Liquorice Root.
MOJU Ginger Juice Shot 60ml	Juice	17.2g fresh ginger root'. Apple, Ginger Root (25%), Lemon, Antioxidant: Ascorbic Acid.
Innocent Shots Ginger Kick, Kicking Ginger & Spicy Turmeric 100ml	Juice shot	Apple Juice (54%), Carrot Juice (15%), Ginger Juice (10%), Red Pepper Juice, Lemon Juice, Orange Juice, Jalapeño Pepper Juice, Turmeric Juice (0.2%), Vitamin D.
Plenish Organic Ginger Immunity Juice Shot	Juice shot	Apple, Ginger (20%), Lemon, Apple Cider Vinegar (7%), Acerola Cherry Powder.
Lo Bros Organic Kombucha Gut Shot Ginger	Juice shot	Carrot Juice* (30%), Orange Juice*, Ginger Juice* (25%), Kombucha (14%) (Filtered Water, Kombucha Culture*, Green Tea*, Oolong Tea*, Raw Sugar*), Lemon Juice Concentrate", Living Cultures.
Belvoir Ginger Beer	Drink	Carbonated Spring Water, Sugar, Lemon Juice from Concentrate, Fresh Root Ginger Infusion 2%, Pressed Ginger Juice, Ginger Extracts, Lemon Extract, Capsicum Extract.

Grace Tropical Rhythms Sorrell Ginger	Drink	Water, Sorrel Cordial (Water, Sugar, Sorrel Flower (3%), Acid: Citric Acid), Rum Flavouring, Natural Sorrel Powder (0.13%), Ginger Emulsion (Water, Ginger Flavouring (.006%), Acid: Citric Acid, Capsicum, Stabilisers: Acacia Gum, Ester Gum), Colour: E129.

Background Exposure from the diet

Exposure estimates based on the NDNS

4. Table 5 provides exposure estimates for women of childbearing age (16 - 49 years) from years 1 – 8 of the NDNS survey (Bates *et al*., 2014; 2016; Roberts *et al*., 2018). The NDNS (Bates *et al*., 2014; 2016; Roberts *et al*., 2018) does not provide data for pregnant or lactating women so while the estimates are based on women of childbearing age, the data may not necessarily be representative of the maternal diet. The food groups used for the exposure assessment comprised all foods within the NDNS database which contained ginger (raw, powdered etc) except for alcoholic beverages. Mean estimated acute ginger exposure from the diet of women aged 16-49 years old was 0.026 g/kg bw/day, with a 97.5th percentile exposure of 0.16 g/kg bw/day. The corresponding mean and 97.5th percentile chronic ginger exposure estimates were 0.0083 g/kg bw/day and 0.058 g/kg bw/day.

5. Table 5 indicates the contribution of ginger to the diet of women aged 16-49 years is low, therefore, the main contributor to exposure for some could be from supplement use. This may vary however according to country of origin. For example, ginger is used more and in larger quantities in foods in Asian, African and Caribbean communities.

6. The NDNS does not provide data for pregnant women, therefore there would be uncertainty as to whether this gives an accurate reflection of exposure during

pregnancy, especially in women who use ginger drinks and teas or foods such as ginger biscuits to alleviate symptoms of pregnancy-associated sickness.

7. TOX/2021/26 concluded that the potential risks arising from exposure to ginger from food can be considered low compared to exposure from supplements and shots, which are available at much higher doses due to their concentrated nature.

8. The Committee highlighted that assumptions would have to be made on how many products, such as ginger shots, were consumed per day. The Committee noted that, as it is commonly understood that ginger suppresses morning sickness, it could not be ruled out that pregnant women would be using the supplements in this way. Diet plus supplement exposure would need to be considered, as well as diet plus shots depending on the exposure period of concern.

Consumption of ginger from food sources

9. The FSA Exposure team have sourced information on ginger intake in women of childbearing age from food. Due to the limited information on consumption amounts of supplements and drinks in pregnant women, exposure was estimated based on the compositional and usage information on widely available supplements and concentrated drinks. Full details of the ginger sources are given in Table 1 - 4.

Table 5: Estimated ginger exposures from a variety of sources in women aged 16 – 49 years old.

Source	**Range of daily exposures (g/day)**	**Range of daily exposures (g/kg bw/day)**	**Mean acute exposure * (g/day)**	**Mean acute exposure * (g/kg bw/day)**	**97.5th percentile acute exposure * (g/day)**	**97.5th percentile acute exposure * (g/kg bw/day)**	**Mean chronic exposure * (g/day)**	**Mean chronic exposure * (g/kg bw/day)**	**97.5th percentile chronic exposure * (g/day)**	**97.5th percentile chronic exposure * g/kg bw/day**
Food[a]	NA	NA	1.7	0.026	11	0.16	0.55	0.0083	3.4	0.058
Drinks (Including tea and shots) [b1,b]	0.5 - 32.5	0.0071 - 0.46	NA	NA	NA	NA	NA	NA	NA	NA
Supplements [c]	0.010 - 24	0.00014 - 0.34	NA	NA	NA	NA	NA	NA	NA	NA

[1]This assumes only one serving is consumed per day.
[a] Data obtained from the National Diet and Nutrition surveys years 1-8 calculated from women of a childbearing age (16-49 years) (Bates *et al*., 2014; 2016; Roberts *et al*., 2018).
[b] Data obtained online from retailers, see Appendix 1 for further details.
c Data obtained online from retailers, see Appendix 1 for further details.
*Rounded to 2 significant figures.

10. The upper value of the range of exposure from drinks and supplements was over double that estimated from 97.5th percentile acute exposure from food and 8-10 times that for chronic concumption from food (Table 5).

11. As the NDNS does not provide data for pregnant women, there would be uncertainty as to whether the data in Table 1 are an accurate reflection of consumption during pregnancy. This uncertainty also extends to data presented for drinks and supplements, as the patten of consumption during pregnancy to alleviate symptoms of sickness is unknown.

Further Information

Table 6: Ginger content in shots, teas and other drinks.

Shots	**Notes**
Ginger Shot | Pret A Manger	Contains 25% ginger in 110 ml shot, equivalent to 27.5 g fresh ginger.
Innocent Shots Ginger Kick, Kicking Ginger & Spicy Turmeric 100ml	Contains 10% ginger juice in 100 ml shot, equivalent to 10 g fresh ginger.
Hot Shot | Pret A Manger	Contains 2.5% ginger in 110 ml, equivalent to 2.75 g fresh ginger.
James White Drinks Organic Xtra Ginger Zinger Shot 70ml	Contains 26% organic ginger juice in 70 ml, equivalent to 18.2 g fresh ginger.
James White Drinks Organic Xtra Ginger Zinger Shot	Contains 40% organic ginger juice in 70 ml, equivalent to 28 g of fresh ginger.
MOJU Ginger Shots (12x60ml)	Contains 17.2 g of ginger in a 60 ml shot.
BumbleZest Ginger Turmeric Drink	Contains 16% ginger juice in 60 ml shot, equivalent to 9.6 g of fresh ginger.
Teas	**Notes**
Myrtle & Maude - Morning Sickness Herbal Tea - Peppermint & Ginger for Nausea Relief	Contains 25% ginger in each tea bag. Assuming that each bag is approximately 2 g, they will contain 0.5 g of dried ginger.
Pukka Lemon, Ginger and Manuka Honey 20 Herbal Tea Sachets 40g	Each tea bag contains ginger root 32%. Assuming each bag is 2 g, they will contain 0.64 g of dried ginger.
Twinings Lemon & Ginger 20 Tea Bags	Each tea bag contains 37% ginger root. Assuming each bag is 2 g, they will contain 0.74 g of dried ginger.
Pukka Organic Ginger, Galangal & Golden Turmeric Tea Bags	Contains 52% ginger root. For a 2 g tea bag, this is equivalent to1 g of dried ginger.

Twinings Spiced Ginger 20 Tea Bags	Contains 70% ginger root. For a 2 g tea bag, this is equivalent to 1.4 g of dried ginger root.
Lemon & Ginger | Herbal Tea | teapigs	Contains 65% ginger. For a 2 g tea bag, this is equivalent to 1.3 g of dried ginger.
Other drinks	**Notes**
Ginger Kombucha | Pret A Manger	Contains 2.2% ginger in 250 ml, equivalent to 5.5 g fresh ginger.
Belvoir Fruit Farms Ginger Cordial	Contains 11% fresh root ginger infusion and 2% pressed ginger juice in a 500 ml product. This is equivalent to 65 g fresh ginger and 32.5 g in a 250 ml serving.
Pure Pret Sparkling Ginger Beer | Pret A Manger	Contains 1% ginger juice in 330 ml, equivalent to 3.3 g of fresh ginger.

Please note the different forms of ginger (i.e., gingerols, ginger extract, dried ginger root, fresh ginger) which may not be directly comparable.

Table 7: Consumption of ginger from supplements.

Supplement	Maternal supplement?	Form of ginger	Recommended dose per person/day	Daily Consumption (g/kg bw)*	Notes
Seven Seas Pregnancy - 28 tablets	Yes	Ginger extract 10 mg.	0.010 g	0.00014	NA
Boots Pregnancy Essential Vitamins | 90 Tablets	Yes	Ginger root extract 58.5 mg.	0.05 9g	0.00084	NA
Boots Naturals Ginger | 60 Tablets	No	Dried ginger root 1.2 g	1.2 g	0.017	NA
Boots Pharmaceuticals DIGESTION SUPPORT TRAVEL with added Ginger 30 Capsules	No	Ginger Root Extract to 345 mg and Ginger root - 750 mg.	0.35 g extract + 0.75 g ginger root.	0.005 + 0.011	NA
Good n Natural Ginger Root Capsules 550mg | Holland & Barrett	No	Ginger root	1.1 g	0.016	2 capsules Daily.
Ginger 3000mg Tablets – Supplemented	No	Ginger extract	6.0 g	0.085	NA

Solgar Ginger Root Extract (60 Veg Caps)	No	Ginger root powder + Ginger root extract.	0.15 g + 0.30 g	0.0021 + 0.0043	NA
GINGER 250mg 120 Vegetarian Capsules by BIOVEA	No	Ginger root	0.75 g	0.011	NA
Jarrow Formulas Ginger (100 Capsules)	No	Ginger root concentrate	1.5 g	0.021	NA
High Strength Ginger Root Capsules | Nature's Best	No	24 mg gingerols equivalent to 14.4 g fresh ginger.	14.4 g	0.20	NA
Ginger 12000mg x 120 Tablets | Nausea - Stomach Settler - Aids Digestion | Neulife Health & Fitness	No	Ginger extract 600 mg equivalent to 12 g fresh ginger-.	24 g	0.34	1-2 capsules a day.
Lifeplan Ginger Root 1000mg 90 Tablets	No	Ginger Extract (equiv. herb powder 1000 mg) 50 mg.	2 g	0.028	2 tablets/day.

*Consumption per body weight based on recommended dose rounded to 2 significant figures.

is calculated from the daily recommended intake and the average body weight of women aged 16- 49 years (70.3kg).

^Indicates whether the supplement is marketed specifically to pregnant or breastfeeding women.

Please note the different forms of ginger (i.e., gingerols, ginger extract, dried ginger root, fresh ginger) which may not be directly comparable.

References

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COT/2025/01 Annex C

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

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).

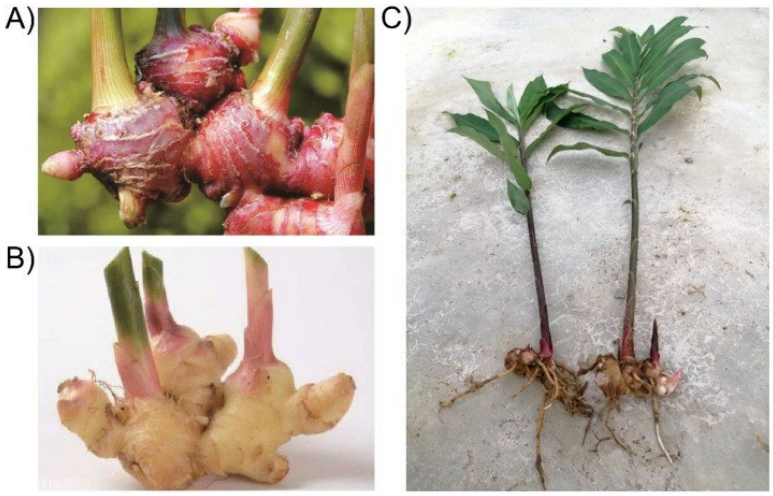

Figure 1: Photographs of (A) Red ginger (Zingiber officinale var. rubrum), (B) common ginger, and (C) whole plant of Zingiber officinale var. rubrum.

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) ($p<0.05$).

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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