Toxicology Overview

In this guide

28. It was noted that some studies reported effects on male testes and, though not relevant for females, they were nevertheless regarded as indicating a potential reprotoxic effect from ginger. Studies suggest that ginger affected the viability of pregnancy; however, with no strong conclusive human data, the COT concluded that more work was required, especially as these studies suggested a link between first trimester loss and ginger use. Further, the 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 varied due to the differences in the forms and extracts 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 effect of ginger on prostaglandins, 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 similarly to 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 is ≤4 g/day (equivalent to approximately 2 teaspoons) it has been included in traditional culinary uses, and if it is >4 g/day the study is included in the extracts section.

Toxicology of ginger root used traditionally

Reproductive and developmental toxicity

Animal studies

33. Reproductive and developmental toxicity has been investigated in rat studies. 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 double that of the controls. Exposed foetuses were found to be significantly heavier than controls and showed no gross structural malformations. The authors conclude that the results of this study suggest that in utero exposure to ginger tea results in early embryonic loss and increased growth in surviving foetuses.

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 groups. No congenital abnormalities were observed in all babies 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. The results suggested that the ginger group did not have an increased rate of major malformations above the baseline rate of 1%–3% (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. 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, investigated the effectiveness of ginger versus B6 for treatment of nausea and vomiting in pregnancy (NVP) in women before 17 weeks' gestation (2009). 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. 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 (2004).

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. p. 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. 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 prostaglandins are covered from paragraph 103 onwards.

41. Overall, it was concluded that there were limited data. The human data presented were not strongly indicative of any toxicological concern but there were some indications of possible effects and 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 this outcome in human studies.

Lactation

42. With respect to lactation, the focus of available studies (Lamxay *et al.*, 2011; Kaygusuz *et al.*, 2021; Dilokthornsakul *et al*., 2021) has been 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

43. Ginger was found to have a significant inhibitory effect on CYP3A4, CYP2C9, and P-glycoprotein activities in vitro (Kimura *et al*., 2010; Zhang and Lim, 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

44. Krüth *et al.* reported the possible over-anticoagulation resulting from a possible ginger-phenprocoumoun interaction (2003). 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.

45. Young *et al.* 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 (2006). In a five-part study, the two groups comprising of 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).

46. Platelet aggregation in the presence of collagen, ADP and epinephrine was 44.1%, 44.5% and 42.1% in normal subjects and 64.2%, 67.7% and 62.9% in hypertensive patients, respectively. Platelet aggregation induced by collagen, ADP or epinephrine was found to be higher in hypertensive patients than normal patients. Following administration of ginger alone, platelet aggregation was measured as 35.2%, 37.8%, 35.9% with collagen, ADP and epinephrine respectively. When administered ginger and nifedipine in combination, the percentage inhibition of platelet aggregation induced by collagen, ADP and epinephrine was 79.8%, 75.2%, 69.3% respectively.

47. Al Askar *et al.* (2020) investigated the effect of ginger on platelet aggregation using agonists adenosine diphosphonate, arachidonic acid, collagen, ristocetin and epinephrine. Forty healthy male and female participants were randomized (1:1) to consume ginger tea at an amount of 4 g powered ginger in

150 ml of boiling water once daily vs. 4 g twice daily for five consecutive days. Comparisons were with pre-treatment changes. Four grams of ginger powder administered daily resulted in reduced platelet aggregation in subjects using epinephrine only. No such effect was seen in the higher dose group. Essentially, ginger had no effect on platelet aggregation in this study. Platelet aggregation inhibition was found to be higher in women using arachidonic acid.

48. 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 ~5g of fresh ginger for 7 days, ginger was found to inhibit eicosanoid biosynthesis *in vivo*.

49. Lumb found that a dose of 2g of ginger in powder form daily produced no significant differences in platelet aggregation/function than the placebo. The authors concluded that previously reported effects on thromboxane synthetase activity may be dose dependent or attributed to fresh ginger (1994).

50. 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). However, a single 10g dose of powdered ginger, administered to CAD patients resulted in a significant decrease in induced platelet aggregation.