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

Statement on the potential health effects of raspberry leaf tea in the maternal diet

Introduction

1. The Scientific Advisory Committee on Nutrition (SACN) last considered maternal diet and nutrition in relation to offspring health in its reports on "The influence of maternal, fetal and child nutrition on the development of chronic disease in later life" (SACN, 2011) and on "Feeding in the first year of life" (SACN, 2018). In the latter report, the impact of breastfeeding on maternal health was also considered.

2. In 2019, 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. SACN agreed that, where appropriate, other expert committees would be consulted and asked to complete relevant risk assessments. A provisional list of chemicals was proposed by SACN Members. However, this was subject to change following discussion by the COT. A scoping paper was presented to the Committee to define the scope of the work from a toxicological safety perspective, and also requesting their input on the selection of candidate chemicals or chemical classes that could be added or removed.

3. As part of this work, the Committee decided it would be useful to consider the use of herbal supplements during pregnancy. A scoping paper reviewed the

commonly used herbal supplements during pregnancy. These were promoted by anecdotal evidence and unofficial sources as having various purported benefits. The review was confined to herbal dietary supplements which would be regulated under food law and which would not be considered to be traditional herbal medicines within the remit of the Medicines and Healthcare products Regulatory Agency (MHRA). Among those investigated was raspberry leaf, which is most commonly taken during pregnancy as a dietary supplement to stimulate and facilitate labour and to shorten its duration. Several raspberry leaf products are registered as traditional herbal medicines in the UK. However, these are directed at non-pregnant women for the symptomatic relief of menstrual cramps. Some clinics offer enemas containing raspberry leaf, though it is not clear whether any are aimed at pregnant women.

4. Following this review, the COT agreed that raspberry leaf required further consideration, noting that human, animal and *in vitro* data were available. The main areas of concern included general toxicity to the mother, effects on the development of the fetus or embryo and possible interactions with drugs. Others included potential effects on offspring and on uterine contractility.

5. Based on the COT's recommendations, a more extensive literature search was undertaken to evaluate the safety of raspberry leaf use during pregnancy (for full details of the search method, see Appendix 1). This statement summarises the conclusions drawn by the Committee.

Background

Uses

6. The red raspberry plant (*Rubus idaeus*) is native to Europe, North America and temperate Asia. However, it is mainly grown for commercial use in central and eastern Europe, especially Bulgaria, Macedonia and Romania (European Medicines Agency (EMA), 2014). Leaves of the plant have been used medicinally in Europe since as early as the sixth century (Beckett *et al*., 1954).

7. Traditionally, raspberry leaf has been used for a range of applications, including relieving menstrual cramps and diarrhoea, as an astringent mouthwash and as a treatment for conjunctivitis (EMA, 2014). However, it is most commonly consumed during pregnancy in an effort to stimulate and facilitate labour and to shorten its duration, with a prevalence of use among pregnant women as high as 38%, based on a recent survey in Australia (Farnaghi and Braniff, 2022). In a survey of herbal remedy use performed at the antenatal clinic at Norfolk and Norwich University hospital between November 2007 and February 2008, 23.7% of expectant mothers who responded to the survey reported taking raspberry leaf (Holst *et al*., 2011). Typically, it is taken as tea or tablets but occasionally as a tincture (Simpson *et al*., 2001). Other alleged benefits of raspberry leaf during pregnancy include alleviation of morning sickness; prevention of post-partum haemorrhage, miscarriage and Braxton Hicks contractions; and stimulation of breast milk production (Patel *et al*., 2004; EMA, 2014).

8. Raspberry leaf may also be mixed with other botanical constituents in some dietary supplements.

Health-Based Guidance Values

9. Despite its long history of use, limited research has been undertaken to investigate the safety, efficacy or mechanism of action of raspberry leaf (Bowman *et al*., 2021). Therefore, there are no health-based guidance values (HBGVs) for raspberry leaf.

Constituents

10. It is unclear what the active constituents of raspberry leaf might be (EMA, 2014). However, it is known to contain a range of different components. Some of the main groups of chemicals in raspberry leaf include hydrolysable tannins, such as gallotannins; flavonoids, such as kaempferol, quercetin and quercetin glycosides;

small quantities of volatile compounds, such as octanol; terpenoids, such as terpinolene; vitamins C and E; minerals, such as calcium, magnesium and zinc; and phenolic acids, such as caffeine and chlorogenic acid (Gudej and Tomczyk, 2004; EMA, 2014).

Existing authorisations

11. In their review on the safety of raspberry leaf, the EMA's Committee on Herbal Medicinal Products (HMPC) highlighted that while clinical studies had not found a higher incidence of adverse pregnancy outcomes associated with raspberry leaf use, treatment durations had generally been short and only a small number of pregnant women were included in the trials (EMA, 2014). It was also highlighted that there were insufficient data on genotoxicity, carcinogenicity, reproductive and developmental toxicity to assess safety.

12. The HPMC recognised the traditional medicinal uses of raspberry leaf for the symptomatic relief of dysmenorrhea, as an astringent gargle, and for the symptomatic treatment of mild diarrhoea, and considered that these could be recognised as safe based on a history of traditional use. However, the HPMC concluded that the evidence regarding the efficacy and safety of raspberry leaf during pregnancy and lactation was lacking and that raspberry leaf could not be recommended for pregnant or lactating women, or in children and adolescents under 18 years of age (EMA, 2014).

Mechanism of action

In vitro and animal studies

13. The mechanism by which raspberry leaf may exert its alleged therapeutic effects during pregnancy is poorly understood (Bowman *et al*., 2021). Hastings-Tolsma *et al*. (2022) hypothesised that raspberry leaf's role in promoting parturition may be related to: its inflammatory, vasodilatory and antioxidant effects; its ability to promote apoptosis in cervical and myometrial cells; and the effects of the isoflavone

genistein. However, limited and at times contradictory evidence was given to support these claims.

14. Six studies were identified, which had investigated the effects of raspberry leaf extract(s) on uterine and other types of smooth muscle *in vitro* and/or in animals (Burn and Withell, 1941; Beckett *et al*., 1954; Bamford *et al*., 1970; Rojas-Vera, Patel and Dacke, 2002; Zheng *et al*., 2010; Olson and DeGolier, 2016). However, results from these studies were highly variable, with some reporting a stimulatory effect and others reporting a relaxant effect. These differences have been attributed to differences in the composition of raspberry leaf preparations, dosages, extraction methods, animal tissue, the pregnancy status of the uterus/uterine tissue, baseline muscle tone, and whether or not the raspberry leaf was tested *in vitro* or *in vivo* (Bowman *et al*., 2021).

Human studies

15. A case series, by Whitehouse (1941), reported the effects of 1.30-2.59 g crude raspberry leaf extract or 20 oz. 5% raspberry leaf tea, administered via a uterine bag, on the uterine muscle of three post-partum women. Based on the findings, it was concluded that: “the main effect [of raspberry leaf was] relaxation of the uterine muscle.”

Toxicity studies

In vitro and animal studies

Acute toxicity

16. No adverse effects were observed in mice when aqueous raspberry leaf preparation containing the equivalent of 2 g extract, was orally administered to mice (Burn and Withell, 1941). However, following intraperitoneal administration of extract equivalent to 0.1 g of raspberry leaf to mice, severe cardiotoxicity was observed (extreme cyanosis and widely dilated hearts) (Beckett et al., 1954). When the extract

was administered intravenously to mice, deaths occurred, with an LD_{50} of 0.4 g raspberry leaf equivalents per mouse (Burn and Withell, 1941). Intravenous administration of extract equivalent to 0.1 g of raspberry leaf to chicks resulted in convulsions and death (Beckett *et al.*, 1954).

Subacute toxicity

17. Only one study was identified which had assessed the sub-acute toxicity of raspberry leaf (Yang *et al*., 2019). In this study, different raspberry leaf preparations were administered to eight-week old, ICR male mice by oral gavage over two weeks at a dose of 100 mg/kg/bw/day (containing 15-55 % gallic acid-equivalent polyphenols). The preparations included an ethanolic raspberry leaf extract (RLE); an ethanolic extract subjected to high temperature and high pressure treatment (RLE-H); and a raspberry leaf powder (RLP).

18. The study assessed body weight, adiposity, relative organ weights (heart, lung, liver, spleen, kidney, testis, fat pad) and time to exhaustion in a swimming test. None of the mice given RLP, RLE or RLE-H died or exhibited visible signs of toxicity over the two-week study period (Yang *et al*., 2019). Final body weight, adiposity index and body mass index in the RLE and RLE-H groups were statistically significantly decreased compared to the control and RLP groups. Relative weights of testes were statistically significantly increased in all treated groups compared to the control group. Exhaustion swimming times in the RLE and RLE-H group were statistically significantly increased compared to the control and RLP groups. Adverse intestinal flatulence (gaseous distention) was observed in the RLE and RLE-H groups, which the authors suggested may have been due to the high intakes of ellagic acid in these groups. In a repeated study, RLE with pectin and sodium alginate with boiling water was prepared into a gelled food for the mice. Similar effects were observed as for RLE in the initial study, except that body weight was not decreased and intestinal flatulence was not observed.

Cytotoxicity

19. Teo *et al*. (2021) investigated the toxicity of a traditional Chinese herbal medicine, “Five-seeds”, *in vitro*. The cytotoxicity of extracts of the constituent herbs, *Rubus idaeus* (raspberry leaf), *Lycium barbarum*, *Cuscuta chinensis* Lam, *Schisandra chinensis* and *Plantago asiatica* individually and in 1:1:1:1:1 ratio, as occurs in “Five-seeds”, was determined in human embryonic kidney (HEK-293) and Chang liver (now known to be HeLa derived) cells. All extracts, and the mixture showed some cytotoxicity in both cell lines, with IC_{50}s ranging from 18 to >100 mg/mL of extract. There was evidence that cytotoxicity was, at least in part, due to an increase in apoptosis (proportion of cells in subG1 phase).

Genotoxicity

20. No studies which had investigated the genotoxicity or carcinogenicity of raspberry leaf were identified in the scientific literature.

21. A European Public Assessment Report for one raspberry leaf product registered as a traditional herbal medicine (“Lydiva” capsules) reported that an Ames (bacterial reverse mutation) test and an *in vivo* micronucleus assay in mice had been conducted on the aqueous raspberry leaf extract contained in this product (BASG, 2014). A positive result was reported in the Ames test in *Salmonella typhimurium* strain TA98 in the presence of metabolic activation. It was suggested that this result may be due to flavonoids (e.g. quercetin) in the extract, which are generally considered to be non-genotoxic *in vivo*. The extract was reported to be negative in the *in vivo* micronucleus test in mice.

Reproductive and developmental toxicity

22. Limited numbers of studies were available which had investigated the reproductive or developmental effects of raspberry leaf during pregnancy. Of those identified, three involved pregnant mice or rats given raspberry leaf extracts orally, from the point mating was confirmed until parturition (Johnson *et al.*, 2009; Makaji *et al.*, 2011; Hastings-Tolsma *et al.*, 2022). A range of effects was reported in these studies.

23. In the first study, female Wistar rats were administered 10 mg/kg bw/day commercially available raspberry leaf extract from Canada or an equivalent dose of the raspberry leaf components kaempferol or quercetin (Johnson *et al*., 2009) throughout pregnancy until parturition. Pregnancy outcomes were assessed in the parental (P) generation, and reproductive development and fertility were then assessed in the female F1 offspring. Raspberry leaf exposure during pregnancy in the P generation was associated with a significant increase in the length of gestation by 1.6 days. There was also a non-statistically significant reduction in pregnancy success rate (78% compared to 100% in the control group). A significant reduction in time to vaginal opening was observed in the F1 offspring. In the F2 offspring, although there was no significant difference in birthweight, the proportion of pups considered to be growth restricted (having a birthweight more than 2 standard deviations below the mean birthweight of the control group) was significantly increased, at 9.8% compared to 0%. Compared with the control group, dams given quercetin had significantly increased weight gain during pregnancy. Johnson *et al*. (2009) concluded that: "in Wistar rats, exposure to raspberry leaf extract throughout pregnancy increases gestation length and results in altered reproductive development and function in the offspring…[which] raise concerns about the safety of this herbal preparation for use during pregnancy."

24. In the second study, from the same laboratory as the first, female Wistar rats were given 10 mg/kg bw/day of raspberry leaf extract from the same commercial source as used by Johnson et al. (2009) or an equivalent dose of the raspberry leaf components kaempferol, ellagic acid or quercetin from the day of mating to the day of parturition (Makaji *et al.*, 2011). Hepatic microsomes were prepared from offspring on postnatal days (PND) 1, 21, 65 and 120 and used to test the biotransformation rates of eight substrates representing the most common hepatic P450 enzymes (CYPs). Maternal consumption of raspberry leaf tea extract resulted in slightly increased biotransformation rates for three of the substrates by female offspring at PND120. Similar results were also observed for quercetin and kaempferol. These were considered to be more male profiles, since biotransformation rates for these three enzymes were higher in control male than control female offspring. The

authors concluded that maternal consumption of either raspberry leaf or some of its components lead to long term alterations in the CYP activity of female offspring.

25. In the third study, C57BL/6N Tac mice received *ad libitum* access to water bottles containing 1.78 or 2.66 mg/mL raspberry leaf extract, from the day of mating throughout pregnancy (Hastings-Tolsma *et al*., 2022). Compared with untreated controls, both raspberry leaf groups exhibited significant reductions in litter size (viable and non-viable). The high-dose group also exhibited increased fluid consumption and significant reductions in pup weight gain at postnatal days four and five. According to the authors, the changes in the high-dose group were accompanied by a trend towards reduced gestation length, although this was not statistically significant. There were no statistically significant differences in measures of neurodevelopment, assessed through pup locomotor activity, including time to righting, orienting response, cliff avoidance and swimming development. However, the authors suggested there were trends towards effects with maternal raspberry leaf consumption, which were more marked in the high dose group. The authors concluded that when ingested throughout gestation in mice, raspberry leaf may impact length of gestation, fluid intake during pregnancy, litter size and viability, as well as pup development.

26. A fourth reproductive study was identified, involving immature Sprague-Dawley rats, in which possible mechanisms for the reported contraceptive effect of raspberry leaf were investigated (Graham and Noble, 1955). Extracts of fresh or dried raspberry leaf (equivalent to 0.8 - 18 mg raspberry leaf) were mixed *in vitro* with pregnant mares' serum diluted to a concentration of 100 I.U. per 0.1 mL gonadotrophin and the mixtures incubated for two hours at 37^{o}C. The authors reported that when rats were injected subcutaneously with 0.5 mL of the extracts, containing the equivalent of 100 I.U. of mare's gonadotrophin, they exhibited marked reductions in ovarian weight within three days compared with the controls (given pregnant mare's serum only). Based on the findings, the authors concluded that raspberry leaf "possessed an appreciable amount of [*in vitro* anti-gonadotrophic] activity." It should be noted that GnRH antagonists have been developed clinically due to their potential benefit in assisted reproduction. GnRH antagonism can also

have other varied biological effects, dependant on exposure and stage of pregnancy. There is no significant evidence of major congenital malformations in fetuses caused by GnRH antagonists or GnRH agonists.

Drug-herb interactions

27. A study by Langhammer and Nielsen (2014) found that ethanolic raspberry leaf extracts prepared from commercially available capsules were capable of inhibiting recombinant human CYP enzymes *in vitro*. These included CYP1A2, CYP2D6 and CYP3A4, with IC_{50} constants ranging from 44-81 µg/mL. The authors concluded that clinically relevant systemic CYP inhibition could be possible for raspberry leaf, and that it might cause clinically relevant inhibition of intestinal CYP3A4. If raspberry leaf inhibits these CYPs *in vivo* it may affect drugs that are metabolised by these enzymes.

28. Holst *et al*. (2011) administered a self-completed survey of herbal remedy use during pregnancy, which looked at parallel use of other pharmaceuticals. The survey was given to 1,037 expectant mothers who were at least 20 weeks pregnant and who presented at an antenatal clinic at Norfolk and Norwich University Hospital. Of the 578 respondents (response rate 55.7%), 232 (40.1%) reported using both herbal remedies and pharmaceuticals during pregnancy. It is unclear what the other pharmaceuticals were or whether the women experienced any adverse effects. However, the authors commented that four women reported simultaneous use of iron and a tannin-containing herb (raspberry leaf, chamomile or valerian). They noted that tannin-containing supplements may interfere with iron absorption, which should be taken into account in anaemic patients. However, no studies were identified in the present review which had evaluated the effects of raspberry leaf tea on iron absorption.

Human studies

29. Several human studies on the safety of raspberry leaf use during pregnancy were identified (Parsons *et al.*, 1999; Simpson *et al.*, 2001; Nordeng *et al.*, 2011). This included several case reports of adverse effects experienced by pregnant women or their newborns after taking raspberry leaf, ranging in severity from petechiae to acute liver injury (UKTIS data; MacPherson and Kilminster, 2006; Wedig and Whitsett, 2008; EMA, 2014; Cheang *et al.*, 2016; Koenig, Callipari and Smereck, 2021). However, limited information was available in these case reports about the doses taken, and it was uncertain whether the adverse effects described were related to raspberry leaf consumption or to other factors, such as the use of other herbal products described in several of them (MacPherson and Kilminster, 2006; Wedig and Whitsett, 2008; Koenig *et al.*, 2021). In some cases, the authors attributed the adverse effects to other products consumed, such as evening primrose oil (Wedig and Whitsett, 2008) or blue cohosh (MacPherson and Kilminster, 2006).

30. Two publications noted that there had been some suggestion in the lay press that raspberry leaf might promote human miscarriage or abortion (Simpson *et al.*, 2001; Johnson *et al.*, 2009). However, the authors of both papers concluded that the evidence to support this was very limited.

31. One of the main human safety studies that the COT considered in its evaluation was a retrospective cohort study by Parsons *et al.* (1999). The study was conducted at hospitals in Sydney, Australia. It included a convenience sample of 57 postnatal women who reported using raspberry leaf during pregnancy and a control group of 51 women randomly selected from the hospital database who stated that they had not used raspberry leaf during pregnancy. The groups were otherwise considered comparable. The women in the study who consumed raspberry leaf reported having done so either as tea (56.1%), tablets (40.4%) or a combination of all three - tea, tablets and tinctures (3.5%) - from as early as eight weeks' gestation for 1-32 weeks. Doses ranged from 1-8 cups of tea or tablets daily, but the tincture appears to have been a single dose, possible taken by one woman (this information is unclear in the paper). No further information was provided about the doses taken or how they were prepared.

32. Parsons *et al.* (1999) identified no adverse effects associated with raspberry leaf consumption, based on information from the hospital obstetric database and participants' medical records. There was no significant difference in maternal blood loss, babies' Apgar scores at five minutes of age, pre-labour maternal diastolic blood pressure or transfer to a special/intensive care baby unit. Nor was there any significant difference in the length of gestation, likelihood of labour augmentation, incidence of meconium liquor, need for an epidural or length of each of the three stages of labour. Raspberry leaf users had a shorter mean duration of the first stage of labour compared with the control group, though this was not statistically significant. There was also a trend towards raspberry leaf users being less likely to require an artificial membrane rupture, caesarean section, forceps or vacuum birth. The authors concluded that: "the findings suggest that the raspberry leaf herb can be consumed by women during their pregnancy…to shorten labour with no identified side effects for the women or their babies" (Parsons *et al.*, 1999).

33. The other main human safety study that the COT considered was a double-blind, randomised, placebo-controlled trial carried out by Simpson *et al*. (2001). The study, which was carried out by the same group, in Sydney, Australia, aimed to evaluate the safety and efficacy of raspberry leaf tablets in shortening and easing labour when consumed from 32 weeks' gestation. The sample consisted of 192, low-risk nulliparous women (mostly Caucasian) with a healthy pregnancy, who were randomised to receive either a placebo or raspberry leaf tablets containing 2.4 g extract daily with food in two separate, 1.2 g doses (n=96 women per group).

34. There were no adverse effects that could be directly attributed to the raspberry leaf, except possibly constipation, which was exclusively observed in four of the raspberry leaf participants (Simpson *et al.*, 2001). Similarly, there were no significant differences between the raspberry leaf and placebo groups with respect to other safety outcomes, including maternal blood loss; maternal diastolic blood pressure; newborn Apgar score at five minutes; presence of meconium-stained fluid; or newborn birth weight (Simpson *et al.*, 2001). The babies in the placebo group tended to have a higher average Apgar score at five minutes, with a narrower spread of measures, but this difference was not statistically significant. A slightly higher

proportion of babies from the raspberry leaf group was admitted to the Neonatal Intensive Care Unit or Special Care Nursery within 24 hours of birth (5.2% compared to 3.7%). No statistical evaluation of this difference was presented; however, chi-square analysis shows that there was no statistical difference between the two groups (P=0.4). The authors noted that the frequency of admissions in the raspberry leaf group was still below the average admission rate for term babies born within the participating hospital at the time of the study.

35. There were no statistically significant differences reported with respect to any of the efficacy outcomes, such as emergency caesarean rate (Simpson *et al.*, 2001). However, based on the findings, it was concluded that a raspberry leaf dose of 2.4 g/day appeared to be safe for mother and baby.

36. The COT also considered data collected by the UK Teratology Information Service (UKTIS) to be of importance in its evaluation. Since its inception in 1983, UKTIS had received six reports of accidental or “therapeutic” raspberry leaf exposure (tea or tablets) during pregnancy. Limited information was available about the dose or timing of exposure but pregnancy outcomes for the six women were normal, except for one, who gave birth to a child with cerebral palsy following a delayed delivery. This would have been incidental, and not due to the consumption of raspberry leaf. One of the women had accidentally consumed large quantities of 400 mg raspberry leaf tablets after mistaking them for sweets (no further information is available on the dose taken), and experienced nausea and diarrhoea but no pregnancy-related effects. She gave birth to a normal, liveborn infant at 40 weeks.

Contaminants

37. Few studies were found which had investigated potential contaminants in raspberry leaf.

38. As part of a screening study by Veatch-Blohm *et al*. (2021), Pb, Ni and Cu were not detected in a commercial raspberry leaf supplement sold in the USA. However, Cr (0.42 µg/g) and Zn (1.90 µg/g) were detected, each in one of the two

samples tested. The authors noted that intakes of Zn would be within the tolerable upper intake level (TUL) established by the Institute of Medicine US Panel on Micronutrients in 2001 (40 mg/day). The metal levels in this study were compliant with the limits laid down for supplements within retained EU Commission Regulation (EC) No.1881/2006, as amended.

39. Several fungal species were detected in the raspberry leaf supplement, (*Aspergillus fumigatus*, *Microsporum* sp. and *Nocardia brasiliensis*), of which the authors suggested *Microsporum* sp. may be of concern in immunocompromised individuals (Veatch-Blohm *et al*., 2021).

40. In one study of plant materials collected from farms located in eastern Poland between 2015 and 2018, the heavy metals Cd, Hg and Pb were detected in raspberry leaf at concentrations ranging from <0.005-0.613 mg/kg, while As was not detected (<0.1 mg/kg) (Kowalska, 2021). Levels of lead were well within the WHO-recommended limit of 10 mg/kg, whereas levels of Cd, at 0.211-0.613 mg/kg, in some samples slightly exceeded the WHO recommended limit of 0.3 mg/kg (Kowalska, 2021). Levels of Hg (0.005–0.010 mg/kg) were just above the LOQ. The levels of Cd, Pb and Hg were all within the legal limits for supplements established by retained EU Commission Regulation (EC) No. 1881/2006, as amended.

41. Sadło *et al.* (2015) reported on the results of field studies of pesticides applied at a commercial raspberry plantation. Various pesticides were applied in accordance with current pest control programmes and according to the instructions on their labels, and residues in both the fruit and leaves were reported. Residues of boscalid, cypermethrin, pyrimethanil, pyraclostrobin and chlorpyrifos were detected in the leaves at concentrations ranging from 0.15-30.6 mg/kg on the first day of harvesting, and these residues decreased each week during the harvesting period (Sadło *et al.*, 2015). Pesticide residues in the fruit were within their respective maximum residue levels (MRLs), while residues in the leaves exceeded their respective MRLs for herbal infusions (leaves and herbs) established by EU Regulation (EC) No. 396/2005. Dietary intakes were estimated based on an assumed daily consumption of dry leaves equivalent to a fresh weight of 7 g, and a body weight for an adult

consumer of 76 kg. The highest estimated daily intake was for boscalid, which was up to 6.63% of its ADI established in the EU of 0.04 mg/kg bw, based on the analytical result for the first day of harvesting. Hence, at the levels found, pesticide residues in raspberry leaf do not pose a health concern to the consumer.

Exposure assessment

42. Raspberry leaf is typically consumed during pregnancy as tea (fresh or dried leaf preparations), tablets or tinctures (EMA, 2014; Bowman *et al.*, 2021). Different recommendations exist as to when women should commence raspberry leaf use during pregnancy; most online sources suggest taking it from the third trimester, typically as tea or tablets, while others suggest taking it from the second or even first trimester (Appendix 2).

43. While not specific to raspberry leaf, data from the National Diet and Nutrition Survey (NDNS) on chronic herbal and fruit tea consumption among women of childbearing age (16-49 years) may provide some indication of raspberry leaf tea intake during pregnancy and is provided in Tables 1a and 1b (without recipes). However, it should be noted that as raspberry leaf is specifically consumed during pregnancy, these are likely to be underestimates of exposure in this group. The data suggest that women within this age group consume a mean of 4.5 mL/kg bw/day or 16 mL/kg bw/day at the 97.5th percentile of herbal or fruit tea, as consumed. This corresponds to a mean of 0.045 g/kg/bw/day herbal or fruit tea or 0.16 g/kg/bw/day at the 97.5th percentile on a dried weight basis.

44. Significantly, it is still unclear as to what the active components in raspberry leaf are (Bowman *et al.*, 2021). However, some raspberry leaf components, such as polyphenolic compounds, may vary in concentration between different raspberry leaf preparations, depending on area of cultivation, in a way that may affect their bioactivity and potentially also their toxicity (Venskutonis *et al.*, 2007). In addition, as indicated above, the NDNS does not capture consumption data for pregnant or lactating women, nor does it capture data on raspberry leaf tea specifically, and so while the data in Tables 1a and 1b are based on women of childbearing age, they

may not be representative of the maternal diet. Therefore, consumption data for raspberry leaf tea, tablets and tinctures were also estimated during each trimester based on dose recommendations gathered from online sources by the FSA's exposure team. These are provided in Tables 2a and 2b.

45. Assuming that one teabag represents 2 g tea, that a single cup holds 350 mL fluid and that capsules contain 100% dried raspberry leaf, online sources suggest that raspberry leaf consumption ranges from 350-1,750 mL/person/day for tea, 16-24 mL/person/day for tinctures and 900-2,400 mg/person/day for tablets during pregnancy, as consumed. In terms of dried weight, this corresponds to 2-10 g/person/day for tea, 0.014-0.021 g/person/day for tinctures and 0.9-2.4 g/person/day for tablets.

46. A retrospective cohort study suggested that at least 3.5% of women may use a combination of all three of raspberry leaf tea, tablets and tinctures together during pregnancy (Parsons *et al.,* 1999). Therefore, the FSA's Exposure Team calculated consumption values for raspberry leaf during pregnancy, assuming combined use of tea, tablets and/or tinctures in order to cover different worst-case exposure scenarios. These values are provided in Table 3 and were based on online dose recommendations during the third trimester, which is when raspberry leaf appears to be taken most commonly. It is apparent that the consumption level resulting from combined use of raspberry leaf tea, tablets and tinctures may reach up to 12.4 g/person/day in extreme cases. It was noted that tinctures make very little contribution to estimated combined exposures.

Table 1a. Estimated chronic consumption of herbal and fruit teas as consumed (without recipes)*[ab.]

Consumers (n)	**Mean (mL/person/day)**	**97.5th percentile (mL/person/day)**	**Mean (mL/kg bw/day)**	**97.5th percentile (mL/kg bw/day)**	**Respondents in population group (n)**
364	290	1100	4.5	16	2556

*Rounded to 2 significant figures.

[a]Based on females aged 16-49 in NDNS years 1-11.

[b]Conversion factor of 0.99 used to convert tea from dry weight to as consumed.

Table 1b. Estimated chronic consumption of herbal and fruit teas dry weight (without recipes)[*ab.]

Consumers (n)	**Mean (g/person/day)**	**97.5th percentile (g/person/day)**	**Mean (g/kg bw/day)**	**97.5th percentile (g/kg bw/day)**	**Respondents in population group (n)**
364	2.9	11	0.045	0.16	2556

*Rounded to 2 significant figures.

[a]Based on females aged 16-49 in NDNS years 1-11.

[b]Conversion factor of 0.01 used to convert tea as consumed to dry weight.

Table 2a. Raspberry leaf-containing teas, tinctures and tablets summary table of suggested serving sizes on an as-consumed basis (data pooled from online sources in Appendix 2).

Stage of pregnancy	**Suggested serving size per day (as consumed). Tea (mL) *[a]**	**Suggested serving size per day (as consumed). Tincture (mL)**	**Suggested serving size per day (as consumed). Capsules/tablets (mg)**
1st trimester.	350	N/a	N/a
2nd trimester.	700	N/a	N/a
3rd trimester.	350 – 1,750	16 – 24	900 – 2,400

*Calculated on the assumption that 1 teabag contains approximately 2 g of tea.

[a]Calculated on the assumption that a large mug holds approximately 350 mL of tea.

N/a = no sources recommending consumption.

Table 2b. Raspberry leaf-containing teas, tinctures and tablets summary table based on dry weight of raspberry leaf consumed (data pooled from online sources in Appendix 2).

Stage of pregnancy	**Suggested serving size per day (as consumed). Tea (g)***	**Suggested serving size per day (as consumed). Tincture (g)[a]**	**Suggested serving size per day (as consumed). Capsules /tablets (g)[b]**
1st trimester.	2	N/a	N/a
2nd trimester.	4	N/a	N/a
3rd trimester.	2-10	0.014-0.021	0.9 – 2.4

*Calculated on the assumption that 1 teabag contains approximately 2 g of tea.

[a]Calculated on the assumption that the tincture was made 1:1 weight to volume ratio. Assumption that fresh leaf is 77.75 % moisture content of nettle leaves.

[b]Assumption that capsules contain 100% dried raspberry leaf tea.

Table 3. Combined consumption scenarios of raspberry leaf (dry weight) in the third trimester.

Estimated consumption of dry raspberry leaf (g per day)	**Estimated consumption of dry raspberry leaf (g per day)**	**Estimated consumption of dry raspberry leaf (g per day)**	**Estimated consumption of dry raspberry leaf (g per day)**
Tea	Tincture	Capsule	TOTAL consumed per day
2-10	0.014-0.021	0.9-2.4	2.914 – 12.421
2-10	0.014-0.021	N/a	2.014 – 10.021
2-10	N/a	0.9-2.4	2.9 – 12.4
N/a	0.014-0.021	0.9-2.4	0.914 – 2.421

Risk characterisation

47. The COT considered the breadth of evidence available on the safety of raspberry leaf during pregnancy, dating back to the 1940s. It was noted that the literature search identified only a limited number of animal studies and most of those on systemic toxicity were very old. Therefore, they did not meet current test guidelines, nor the requirements for reporting of botanicals or current animal welfare regulations and ethical standards. The Committee highlighted that it did not endorse these studies but considered that they were performed in accordance with the guidelines available at the time when they were published. Therefore, information from these studies was considered in the COT's assessment, but it was noted that there was considerable uncertainty associated with them.

48. The Committee was unable to establish a point of departure for raspberry leaf due to the absence of suitable data and significant uncertainties associated with the few studies available. The main sources of uncertainty identified included: the lack of data available on the active components of raspberry leaf and on characterisation of the test material used; the potential for the method of sampling and preparation to affect the activity of the supplement, as well as unknown batch to batch variation; the large variation in the literature as to raspberry leaf's critical effects (smooth muscle relaxation vs. contraction (described in detail in TOX/2022/50)), which appeared to depend on numerous factors, such as the species, preparation and whether extracts were tested *in vitro* or *in vivo*; and the lack of clarity in the literature as to the most appropriate choice of animal model for studying raspberry leaf's effects in humans (see TOX/2022/50, TOX/2022/50 The Potential Health Effects of Raspberry Leaf in the Maternal for details).

49. Another source of uncertainty was the absence of any specific data on the pharmacokinetics of the constituents of raspberry leaf. However, it was noted that there were indications in the literature that it was less toxic when administered orally than parenterally in mice (Burn and Withell, 1941; Beckett et al., 1954), suggesting reduced oral bioavailability of the toxic constituents. Members also noted that there was limited data on the reproductive toxicity of raspberry leaf and that only one study, conducted in ICR male mice given one dose level of different extracts or

raspberry leaf over a two-week period (100 mg/kg bw/day), could be identified in which it had been evaluated it for sub-acute toxicity (Yang et al., 2019).

50. Limited data were available on levels of contaminants, such as heavy metals, and of pesticide residues.

51. The Committee considered the reproductive toxicity study conducted by Hastings-Tolsma *et al*. (2022). The authors of the study reported finding a statistically significant reduction in litter size among C57BL/6N Tac mice given 1.78 or 2.66 mg/mL aqueous raspberry leaf extracts orally throughout pregnancy, compared with untreated controls. Members noted that there were a number of limitations in this study. The mouse strain chosen (C57BL/6NTac) is known not to have good mothering behaviour and is associated with high spontaneous litter mortality. Animals were examined only in the morning, and as mice typically litter overnight the precise time of birth could not be determined. No necropsies were performed on the animals, so it was not possible to assess implantation rates and whether there might have been any maternal cannibalism of offspring. Few of the differences reported were statistically or biologically significant. The few differences reported as significant (pup weight, maternal fluid consumption and pup mortality) showed overlap of their standard error bars with those of the controls, and in the case of pup mortality, were not analysed appropriately (ANOVA was used for incidence data). It was unclear as to exactly how much raspberry leaf extract mice were exposed to, as the animals were given free access to water bottles containing the extract. The Committee concluded that, in view of these appreciable uncertainties, the results of this study in themselves do not give rise to undue health concern from consumption of raspberry leaf.

52. Although there was a high degree of uncertainty, Members considered that the available human data indicated that the risk associated with raspberry leaf consumption during pregnancy is low. This was based on the results of the two Australian human safety studies identified in the literature search. These included a retrospective cohort study by Parsons *et al.* (1999), involving a control group of 51 women and a group of 57 women who reported taking raspberry leaf for 1-32 weeks during pregnancy, including 1-8 cups/tablets and/or a single tincture. The other was

a double-blind, placebo-controlled, randomised trial by Simpson *et al*. (2001), involving 192 nulliparous women with a healthy pregnancy, who were randomised to receive either a placebo or raspberry leaf tablets containing 2.4 g extract daily with food from 32 weeks' gestation (as two separate 1.2 g doses).

53. Neither study reported adverse effects to mother or child associated with raspberry leaf consumption during pregnancy compared with controls. However, Members noted that the estimated consumption of raspberry leaf from tea (up to 10 g/person/day) or combined sources (up to 12.4 g/person/day), based on data collected from online sources by the FSA's exposure team, was up to four or more times higher than the raspberry leaf dose tested by Simpson *et al*. (2001). Simpson *et al.* (2001) stated that they selected a conservative dose level since this was the first study of its kind.

54. The Committee also took into account that there had been very few reports of adverse effects in pregnant women taking raspberry leaf or their children received by the UKTIS since its inception in 1983 to the present date, despite the reported high prevalence of use of raspberry leaf in pregnancy. Six reports were received altogether of women who had taken raspberry leaf during pregnancy following accidental or "therapeutic" consumption. Except for one woman, who gave birth to a child with cerebral palsy following a delayed delivery, which would not have been caused by raspberry leaf, all had normal pregnancy outcomes. Limited information was available in each case about the dose, timing or duration of raspberry leaf exposure but included in one case, a woman who had taken large quantities of 400 mg raspberry leaf tablets. She experienced nausea and diarrhoea but no pregnancy-related effects and gave birth to a normal, liveborn infant at 40 weeks.

55. Members considered that one of the other reasons that raspberry leaf appeared to be of low concern to human health was the apparent poor bioavailability of the toxic constituents (based on indirect evidence). However, concern was expressed that if raspberry leaf extracts were micronised, or otherwise formulated to increase bioavailability, they may need to be evaluated separately in terms of safety.

Conclusions

56. Overall, the COT concluded that the risk associated with raspberry leaf use during pregnancy was low but with high uncertainty. This was based on the results of two Australian human safety studies, comprising a retrospective cohort study and a double-blind, placebo-controlled, randomised trial. Neither reported adverse effects in mother or child following raspberry leaf consumption during pregnancy at doses of 1-8 cups of tea/tablets per day or a single dose of tincture, or 2.4 g extract daily, respectively. However, Members noted that the estimated combined consumption of raspberry leaf from tea (up to 10 g/person/day) or from tea, tinctures and capsules combined (up to 12.4 g/person/day), based on data collected from online sources by the FSA's exposure assessment team, was up to four or more times higher than the raspberry leaf dose tested in the randomised controlled trial.

57. The COT's conclusion was also based on the fact that there had been very few reports of adverse effects in pregnant women taking raspberry leaf or their children received by the UKTIS since its inception in 1983 to the present date, despite the reported high prevalence of use of raspberry leaf. Members considered that the apparent poor oral bioavailability of the toxic constituents of raspberry leaf (based on indirect information) might also be why it appeared to be of low concern to human health. However, it was recognised that micronised or other modified raspberry leaf products might exhibit increased bioavailability and may require a separate safety evaluation.

58. Members identified a number of significant uncertainties in the risk assessment of raspberry leaf. These underpinned the high level of uncertainty in their conclusion on its safety for use during pregnancy and prevented the Committee from establishing a health-based guidance value for raspberry leaf. The main sources of uncertainty identified included: the lack of data available on the active components of raspberry leaf; the potential for the method of sampling and preparation to affect the activity of the supplement; the large variation in the literature as to raspberry leaf's critical effects (smooth muscle relaxation vs. contraction), which appeared to depend on numerous factors, such as the species, preparation

and whether extracts were tested *in vitro* or *in vivo*; and the lack of clarity in the literature as to the most appropriate choice of animal model for studying raspberry leaf's effects in humans. Other sources of uncertainty included the lack of any specific information on pharmacokinetics of the key constituents, limitations on the amount of data available on the toxicity (including reproductive toxicity) of raspberry leaf, and on levels of contaminants and residues present.

COT Statement 2024/06
November 2024

Abbreviations

ADI	Acceptable daily intake
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMMC	3-[2-(N,N-diethyl-N-methylammonium)ethyl]-7-methoxy-4- methylcoumarin
API	Adiposity percentage
AST	Aspartate transaminase
BFC	7-benzyloxy-4-(trifluoromethyl)-coumarin
BMI	Body mass index
BQ	7-benzyloxyquinoline
bw	Body weight
CEC	3-cyano-7- ethoxycoumarin
CI	Confidence interval
CYP	Cytochrome P450
DES	Diethylstilbestrol
DMSO	Dimethylsulfoxide
EC_{50}	Half-maximal effective concentration
EFC	7-ethoxy-4-trifloromethyl-coumarin
EMA	European Medicines Agency
ERES	Ethoxyresorufin
FSA	Food Standards Agency
GDM	Gestational diabetes mellitus
HBGV	Health-based guidance value
HPLC	High-performance liquid chromatography
IC_{50}	Half-maximal inhibitory concentration
LCMS/MS	Liquid chromatography mass spectrometry/mass spectrometry

LOQ	Limit of quantification
MFC	7-methoxy-4-(trifuoromethyl)-coumarin
MHRA	Medicines and Healthcare products Regulatory Agency
MRES	Methoxyresorufin
MRL	Maximum residue level
NDNS	National Diet and Nutrition Survey
NOAEL	No-observed-adverse-effect level
NP	Non-pregnant
RLE	Raspberry leaf extract
RLE-H	High-temperature, high-pressure raspberry leaf extract
RLP	Raspberry leaf powder
SACN	Scientific Advisory Committee on Nutrition
TG2	Transglutaminase 2
TDI	Tolerable daily intake
TUL	Tolerable upper intake level
UKTIS	UK Teratology Information Service
WHO	World Health Organization

References

Amuse Projects (no date). The benefits of raspberry leaf tea during pregnancy. The Benefits of Raspberry Leaf Tea During Pregnancy – A.muse Projects (Accessed: 21 April 2022).

Bamford, D.S., Percival, R.C. and Tothill, A.U. (1970). Raspberry leaf tea: a new aspect to an old problem, **British Journal of Pharmacology**, 40(1), p. 161P+. Raspberry leaf tea: a new aspect to an old problem - PMC.

BASG (2014). Public Assessment Report: Scientific discussion: Ladiva Kapseln, Rubi idaei folium. Bundesamt für Sicherheit im Gesundheitswesen, 10 March 2020. Available at: updated_PAR_AT_H_0744_001_Ladiva Kapseln_Feb2021 (2).pdf (Accessed: 26 July 2024).

Beckett, A.H., Belthle, F.W. and Fell, K.R. (1954). The active constituents of raspberry leaves; a preliminary investigation, **The Journal of Pharmacy and Pharmacology**, 6(11), pp. 785–796.

Bellybelly (2011). Red raspberry leaf tea - benefits for pregnancy and labor. Available at: Red Raspberry Leaf Tea - Benefits For Pregnancy And Labor (Accessed: 21 April 2022).

Birth Eat Love (2019). Raspberry Leaf Tea Benefits for Pregn ancy - Does It Really Work??? (Accessed: 21 April 2022). Does Red Raspberry Leaf Tea Work??? Plus Labor Stories! - Birth Eat Love.

Bonet, A. (2021) **Raspberry leaf tea health benefits, backed by research, Netdoctor**. Raspberry leaf tea: pregnancy, health benefits, side effects and uses (Accessed: 4 July 2024).

Bowman, R., Taylor, J., Muggleton, S., Davis, D. (2021). Biophysical effects, safety and efficacy of raspberry leaf use in pregnancy: a systematic integrative review, BMC Complementary Medicine and Therapies, 21(1), p. 56. https://doi.org/10.1186/s12906-021-03230-4.

Burn, J.H. and Withell, E.R. (1941). A principle in raspberry leaves which relaxes uterine muscle, **The Lancet**, 238(6149), pp. 1–3.

Cambridge Naturals (no date). Raspberry: beyond the fruit (*Rubus* idaeus/rosaceae). maternal — Blog — Cambridge Naturals (Accessed: 21 April 2022).

Cancer Care of Western New York (no date). Red raspberry. Red Raspberry - Cancer Care of Western New York (Accessed:4 July 2024).

Cheang, K.I., Nguyen, T.T., Karjane, N.W., Salley, K.E.S. (2016). Raspberry Leaf and Hypoglycemia in Gestational Diabetes Mellitus, **Obstetrics and Gynecology,** 128(6), pp. 1421–1424.

Cleveland Clinic (2018). 8 Ways to Start Labor Naturally. What Is a Guaranteed Way To Induce Labor? (Accessed: 21 April 2022).

Darby, D. (no date). **Red Raspberry Leaf Tea, Dear Darby**. BirthAcademy - Etsy UK (Accessed: 21 April 2022).

Edwards, S.E., Da Costa Rocha, I., Williamson, E.M., Heinrich, M. (2015). Phytopharmacy: An Evidence-Based Guide to Herbal Medicinal Products. John Wiley & Sons.

Ellis, L. (no date). The benefits of red raspberry leaf tea for pregnant ladies – BABYGO. The Benefits of Red Raspberry Leaf Tea For Pregnant Ladies – BABYGO® (Accessed: 21 April 2022).

EMA (2014). Assessment report on **Rubus idaeus L., folium'**. Assessment report on Rubus idaeus L., folium (Accessed: 23 April 2024).

Expectancy (2022). Raspberry Leaf Tea in Pregnancy. 2581508 v3.indd (Accessed: 21 April 2022).

Farnaghi, S., Braniff, K. (2022). Survey of raspberry leaf tea in pregnancy, **Australian and New Zealand Journal of Obstetrics and Gynaecology**, 62(4), pp. 506–510.

Gentle Nursery (2021). Red raspberry leaf tea for pregnancy: all you need to know. Red Raspberry Leaf Tea for Pregnancy: Benefits and Usage (Accessed: 21 April 2022).

Graham, R.C. and Noble, R.L. (1955). Comparison of *in vitro* activity of various species of *Lithospermum* and other plants to inactivate gonadotrophin, *Endocrinology*, 56(3), pp. 239–247.

Greatist (2022). Brewing a baby? How red raspberry leaf tea benefits your pregnancy and more. Does Raspberry Tea Have Caffeine? Benefits and Risks (Accessed: 21 April 2022).

Grow a Good Life (2015). How to harvest and preserve red raspberry leaf tea. How to Harvest & Preserve Red Raspberry Leaf Tea (Accessed: 21 April 2022).

Gudej, J., Tomczyk, M. (2004). Determination of flavonoids, tannins and ellagic acid in leaves from *Rubus* L. species', **Archives of pharmacal research, 27**, pp. 1114–9.

Hastings-Tolsma, M., Stoffel, R.T., Quintana, A.S., Kane, R.R., Turner, J., Wang, X. (2022). Effect of **Rubus idaeus** L. consumption during pregnancy on maternal mice and their offspring, **Journal of Medicinal Food**, 25(2), pp. 183–191.

Healthline (2018). Red raspberry leaf tea: pregnancy, benefits and side effects. Red Raspberry Leaf Tea: Pregnancy, Benefits, and Side Effects (Accessed: 21 April 2022).

Hearth and Home Midwifery (2022). Red Raspberry Leaf Tea. Red Raspberry Leaf Tea — Portland Midwives | Hearth and Home Midwifery | Portland OR (Accessed: 21 April 2022).

Holst, L., Wright, D., Haavik, S., Nordeng, H. (2011). Safety and efficacy of herbal remedies in obstetrics—review and clinical implications, **Midwifery**, 27(1), pp. 80–86.

Jester, J. (no date). Herbs in pregnancy. A thoughtful approach. Herbs-in-Pregnancy-Handout.pdf (Accessed: 13 April 2022).

Jester, J. (no date). Red Raspberry Leaf. Red-Raspberry-Leaf-Handout.pdf (Accessed: 21 April 2022).

Johnson, J.R., Makaji, E., Ho, S., Xiong, B., Crankshaw, D.J., Holloway, A.C. (2009). Effect of maternal raspberry leaf consumption in rats on pregnancy outcome and the fertility of the female offspring, **Reproductive Sciences**, 16(6), pp. 605–609.

Koenig, G., Callipari, C. and Smereck, J.A. (2021). Acute liver injury after long-term herbal “liver cleansing” and “sleep aid” supplement use, **Journal of Emergency Medicine**, 60(5), pp. 610–614.

Kothari, S. (no date). Should I take Raspberry Leaf Tea in Pregnancy? – my little Bubba. Available at: Should I take Raspberry Leaf Tea in Pregnancy? – my little Bubba (Accessed: 4 July 2024).

Kowalska, G. (2021). The Safety Assessment of Toxic Metals in Commonly Used Herbs, Spices, Tea, and Coffee in Poland, **International Journal of Environmental Research and Public Health**, 18(11), p. 5779.

Langhammer, A.J., Nilsen, O.G. (2014). *In vitro* inhibition of human CYP1A2, CYP2D6, and CYP3A4 by six herbs commonly used in pregnancy, ***Phytotherapy research*: PTR**, 28(4), pp. 603–610.

MacPherson, R.D., Kilminster, I. (2006). Neonatal epilepsy associated with maternal ingestion of blue cohosh, **Journal of Pharmacy Practice and Research**, 36(4), pp. 302–305.

Makaji, E., Ho, S.H.Y., Holloway, A.C., Crankshaw, D.J. (2011). Effects in rats of maternal exposure to raspberry leaf and its constituents on the activity of cytochrome p450 enzymes in the offspring, **International Journal of Toxicology**, 30(2), pp. 216–224.

Marie Fortier (no date). Raspberry herbal tea and pregnancy. Raspberry Herbal Tea and Pregnancy - Marie Fortier & Prenato (Accessed: 21 April 2022).

McFarlin, B.L., Gibson, M.H., O'Rear, J., Harman, P. (1999). A national survey of herbal preparation use by nurse-midwives for labor stimulation. Review of the literature and recommendations for practice, **Journal of Nurse-Midwifery**, 44(3), pp. 205-216.

Medical News Today (2021). *Red raspberry leaf tea:* **Nutrition, benefits, and how to use**. Red raspberry leaf tea: Nurition, benefits, and how to use (Accessed: 21 April 2022).

Mills, S.Y. and Bone, K. (2004). **The Essential Guide to Herbal Safety**. Elsevier Health Sciences.

Mommypotamus (2019). Red raspberry leaf pregnancy tea – a nourishing tonic for two. Benefits of Red Raspberry Leaf Tea for Pregnancy (Plus A Recipe) (Accessed: 21 April 2022).

Mumsnet (no date). Raspberry leaf tea - yes or no? Raspberry leaf tea - yes or no? | Mumsnet (Accessed: 13 April 2022).

Netmums (no date). Raspberry leaf tea? Please share your experiences! Raspberry leaf tea? Please share your experiences! (Accessed: 21 April 2022).

Nordeng, H., Bayne, K., Havnen, G.C., Paulsen, B.S. (2011). Use of herbal drugs during pregnancy among 600 Norwegian women in relation to concurrent use of conventional drugs and pregnancy outcome, **Complementary Therapies in Clinical Practice**, 17(3), pp. 147–151.

Olson, A.E., DeGolier, T.F. (2016) 'Research Article: Contractile activity of *Rubus idaeus* extract on isolated mouse uterine strips', **BIOS**, 87(2), pp. 39–47.

Palmer, J. (2018). Raspberry leaf, *Pregnancy* **Birth and Beyond**. Raspberry Leaf – Pregnancy Birth and Beyond (Accessed: 21 April 2022).

Parsons, M., Simpson, M. and Ponton, T. (1999). 'Raspberry leaf and its effect on labour: safety and efficacy, **Australian College of Midwives Incorporated Journal**, 12(3), pp. 20–25.

Patel, A.V., Rojas-Vera, J. and Dacke, C.G. (2004). Therapeutic constituents and actions of *Rubus* species, **Current Medicinal Chemistry**, 11(11), pp. 1501–1512.

Pregnancy, Birth and Baby (2021). Herbal teas during pregnancy and breastfeeding. Herbal teas during pregnancy and breastfeeding | Pregnancy Birth and Baby (Accessed: 21 April 2022).

Raspberry Leaf - Drugs in Pregnancy and Lactation: Tenth Edition (no date). doctorlib.info,pregnancy,drugs,pregnancy,lactation (Accessed: 21 April 2022).

Rojas-Vera, J., Patel, A.V. and Dacke, C.G. (2002). Relaxant activity of raspberry (*Rubus* idaeus) leaf extract in guinea-pig ileum *in vitro*, **Phytotherapy Research**, 16(7), pp. 665–668.

SACN (2011). The influence of maternal, fetal and child nutrition on the development of chronic disease in later life. Scientific Advisory Committee on Nutrition. TSO, London.

SACN (2018). Feeding in the first year of life. Scientific Advisory Committee on Nutrition.

Sadło, S., Szpyrka, E., Piechowicz, B., Grodzicki, P. (2015). A case study on toxicological aspects of the pest and disease control in the production of the high-quality raspberry (*Rubus idaeus* L.)', **Journal of Environmental Science and Health, Part B,** 50(1), pp. 8–14.

Simpson, M., Parsons, M., Greenwood, J., Wade, K. (2001). Raspberry leaf in pregnancy: its safety and efficacy in labor, **Journal of Midwifery & Women's Health**, 46(2), pp. 51–59.

Tea-and-Coffee.com (2020). Raspberry Leaf Tea Pregnancy Benefits. Raspberry Leaf Tea Pregnancy | Kent Tea & Coffee Co (Accessed: 21 April 2022).

Teacurry Herbals (no date). Red raspberry leaf tea - benefits, pregnancy, labor, and side effects. Red Raspberry Leaf Tea - Benefits, Pregnancy, Labor, and Side Effects (Accessed: 21 April 2022).

Teatoxlife (no date). Red raspberry leaf tea - precautions & side effects. Red Raspberry Leaf Tea - Precautions & Side Effects (Accessed: 22 April 2022).

Teo, Y.M., Er, Y.H., Chye, S.M., Wong, N. (2021). Toxicity effects of Chinese herbal 'five-seeds' formulation on human kidney HEK-293 and Chang liver cells, **ASM Sc J** 15, 2021. Available at: https://doi.org/10.32802/ASMSCJ.2021.637.

Veatch-Blohm, M.E., Chicas, I., Margolis, K., Vanderminden, R., Gochie, M., Lila, K. (2021). Screening for consistency and contamination within and between bottles of 29 herbal supplements, **PloS One**, 16(11), p. e0260463.

Vegan Momma (no date). Red raspberry leaf tea during pregnancy tones your uterus. Vegan-momma.com.Red-raspberry-leaf tea (Accessed: 21 April 2022).

Venskutonis, P.R., Dvaranauskaite, A. and Labokas, J. (2007). Radical scavenging activity and composition of raspberry (*Rubus idaeus*) leaves from different locations in Lithuania, *Fitoterapia*, 78(2), pp. 162–165.

Vyne Health (no date). Red Raspberry Leaf Tea Pregnancy: Benefits and Uses. Red Raspberry Leaf Tea Pregnancy: Benefits and Uses | Vyne Health Acupuncture Gold Coast (Accessed: 4 July 2024).

Wedig, K.E. and Whitsett, J.A. (2008). Down the primrose path: petechiae in a neonate exposed to herbal remedy for parturition, **The Journal of Pediatrics**, 152(1), pp. 140-140.e1.

Whitehouse, B. (1941). Fragarine: an inhibitor of uterine action, *British Medical Journal*, 2(4210), pp. 370–371. Fragarine: An Inhibitor of Uterine Action - PMC (Accessed: 4 April 2022).

Yang, J., Cui, J., Han, H., Chen, J., Yao, J., Liu, Y. (2019). Determination of active compounds in raspberry leaf extracts and the effects of extract intake on mice, *Food Science and Technology*, 40, pp. 124–131.

Zheng, J., Pistilli, M.J., Holloway, A.C., Crankshaw, D.J. (2010). The effects of commercial preparations of red raspberry leaf on the contractility of the rat's uterus *in vitro*, **Reproductive Sciences**, 17(5), pp. 494–501.

Appendix 1

Search Methodology

1. The following electronic databases were searched for relevant articles published from inception to Apr 2022: LitFetch (which includes material from PubMed, Scopus, Ebsco (Food Science Source) and Springer); ScienceDirect and Cochrane Library. Google and Google Scholar were also searched. The searches were conducted on various dates between 1st Apr 2022 and 22nd Apr 2022.

2. The search terms used included 'raspberry leaf' OR '*Rubus idaeus*' AND: ('safety' OR 'tox*' OR 'pregnan*' OR 'maternal' OR 'exposure' OR 'consumption' OR 'indications' OR 'uses' OR 'childbirth' OR 'transgenerational' OR 'transgenic' OR 'convulsion' OR 'uterine contract*' OR 'development' OR 'interactions' OR 'gestation' OR 'caesarean' or 'contaminant' OR 'heavy metal' OR 'mycotoxin' OR 'pesticide' OR 'residue').

3. The references from extracted papers were searched for citations not captured in the literature search. Only articles published in English were included, due to the linguistic abilities of the reviewer.

4. The UKTIS was also asked for information on any enquiries relating to maternal raspberry leaf use and any reports of adverse effects in pregnant women or their newborn infants received since its inception in 1983 to Apr 2022. This included information relating to the type, dosage, duration and timing of raspberry leaf taken and any pregnancy outcomes captured through follow-up.

Appendix 2

Online Dose Recommendations for Raspberry Leaf During Pregnancy

Source	Tea/Extract	Tablets	Tincture	Preparation
(Jester, no date)	Up to four cups daily.	N/a	N/a	N/a
(Edwards *et al.*, 2015)	4-8 g as an infusion daily.	N/a	4-8 mL (1:1 in 25 % alcohol) three times daily.	N/a
(Mumsnet, no date)	1-3 cups daily as tea after 36-37 weeks of gestation.	N/a	N/a	N/a
(Gerard, 1597, cited in McFarlin *et al.*, 1999)	N/a	N/a	N/a	Tea: 2 g steeped in 240 mL boiling water.
(Kothari, no date)	One cup daily at 32 weeks, increasing to 2-3 cups per day by 37 weeks.	N/a	N/a	N/a
(Birth Eat Love, 2019)	One cup daily, increasing to up to three cups per day in the third trimester, or at approx. 35 weeks.	N/a	N/a	N/a
(Grow a Good Life, 2015)	N/a	N/a	N/a	Tea: 1 tsp per 8-ounce cup of boiling water.
(Bonet, 2021)	1-3 cups daily.	N/a	N/a	N/a
(Cambridge Naturals, no date)	N/a	N/a	N/a	Tea: ‘1-2 teaspoons of dried leaf per cup of hot water’ OR ‘4 tablespoons dried herb in a quart of hot water’ OR ‘4 [tbsp] of the dried leaf in

				a quart of cold water.’
(Parsons, 1999, cited in Palmer, 2018)	Teabag cups: one cup daily during the first trimester; two cups daily during the second trimester; up to 4-5 cups during the last trimester. Loose leaf tea: 2-3 cups per day, especially after 28 weeks of pregnancy.	Two 300/400 mg tablets with each meal (three times daily) from 32 weeks.	Dose dependent on tincture strength.	Loose leaf tea: add 1 tsp of herb to a cup of boiling water, stir, sit for 10 minutes, strain and sip.
(Pregnancy, Birth and Baby, 2021)	1-2 cups daily	N/a	N/a	N/a
(Netmums, no date)	One cup of tea daily at 32 weeks, increasing every few days by one cup until taking 3-4 cups daily.	One tablet daily at 32 weeks, increasing every few days by one tablet until taking 3-4 tablets daily.	N/a	N/a
(Amuse Projects, no date)	One cup of tea per day from 27 weeks of gestation, increasing to 2-4 cups per day by week 35.	N/a	N/a	N/a
(Expectancy, 2022)	One cup daily at approx. 32 weeks, increasing gradually every few days to 3-4 cups.	One tablet (typically available as 300-400 mg doses) daily at approx. 32 weeks, increasing gradually every few days to 3-4 tablets.	N/a	N/a

(Bellybelly, 2011)	At least 2-3 cups (max 4-5) daily during the third trimester but one cup per day during the first trimester is 'fine.'	Two 300-400 mg tablets with each meal three times a day from 32 weeks.	N/a	Tea: add 1 tsp of raspberry leaf to a cup of boiling water.
(Vyne Health, no date)	One cup daily or if not experiencing any uterine sensations, increase to two cups per day (provided at due date or the 37th week).	N/a	N/a	Tea: steep 1-2 tsp raspberry leaf in a cup of boiling water.
(Ellis, no date)	One cup daily, gradually increasing to 4-5 cups a day.	Two tablets, three times daily from 32 weeks.	N/a	N/a
(The best raspberry leaf teas for pregnancy 2022, no date)	One cup daily. May increase gradually at 34 weeks to 2-3 cups.	N/a	N/a	N/a
(Mommypotamus, 2019)	One cup daily at 32 weeks, gradually increasing to three cups as the due date approaches.	N/a	N/a	N/a
(Hearth and Home Midwifery, 2022)	1-2 cups daily throughout the third trimester.	N/a	N/a	Tea: steep two handfuls of the dried herb in '1 qt cold water.'
(Vegan Momma, no date)	One cup daily during the first trimester, two cups daily in the second trimester and three cups daily during the third trimester.	N/a	N/a	Tea: add 2 tsp of dried tea into a strainer and pour one cup of boiling water over the top.
(Darby, no date)	1-3 cups daily starting in the second trimester.	N/a	N/a	N/a

(Marie Fortier, no date)	Three cups daily during the last 3-4 weeks of pregnancy.	N/a	N/a	N/a
(Jester, no date)	1-2 cups daily in the last 6-8 weeks of pregnancy. 'Drink plenty during labor…drink postpartum to cleanse the uterus and encourage healthy breastmilk production.'	N/a	N/a	N/a
(Cleveland Clinic, 2018)	1-2 cups daily from 32 weeks of gestation.	N/a	N/a	N/a
(Teatoxlife, no date)	1-2 cups daily, gradually increasing to three cups per day.	N/a	N/a	N/a
(Healthline, 2018)	1-3 cups daily.	N/a	N/a	N/a
(Medical News Today, 2021)	1-3 cups daily.	N/a	N/a	Tea: add 1 tsp crushed or dried raspberry leaves to a cup and pour over boiling water.
(Greatist, 2022)	'1-3 cups a day is safe…if…concerned about preterm labor…drink in the third trimester.'	N/a	N/a	N/a
(Raspberry Leaf - Drugs in Pregnancy and Lactation: Tenth Edition, no date)	'Typical doses…are 1.5–2.4 g/day.'	N/a	N/a	N/a
(Gentle Nursery, 2021)	One cup daily from as early as 14 weeks of gestation. Increase to two cups daily during the third trimester until due date.	N/a	N/a	Tea: add 1 tbsp of loose red raspberry leaf tea to every cup of boiling water.

(Cancer Care of Western New York, no date)	2-3 cups daily.	N/a	N/a	Tea: add one cup of boiling water to 1-2 tsp dried leaf.
(Teacurry Herbals, no date)	One cup daily from 32 weeks of gestation, gradually increasing to 2-3 cups daily until delivery.	N/a	N/a	N/a
(Mills and Bone, 2004)	12-24 g/day of dried leaf or by infusion. 12-24 mL/day of a 1:1 liquid extract. 4.5-1.4 mL/day of a 1:2 liquid extract or equivalent in tablet or capsule form.	N/a	N/a	N/a

For reference details, see main reference list.