Annex A - Drug-herb interactions

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26. 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 IC50 constants ranging from 44-81 µg/mL. The authors concluded that clinically relevant systemic CYP inhibitions could be possible for raspberry leaf, and that it might cause clinically relevant inhibition of intestinal CYP3A4.

27. 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

28. Several human toxicity studies were identified on the safety of raspberry leaf use during pregnancy (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).

29. 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 there was limited evidence to support this.

30. One of the main human toxicity studies which 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 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 only included a single dose of tincture, taken by one woman. No further

information was provided about the doses taken or how they were prepared.

31. 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 [suggested] that the raspberry leaf herb [could] be consumed by women during their pregnancy…to shorten labour with no identified side effects for…women or their babies" (Parsons et al., 1999).

32. The other main human toxicity study that the COT considered was a double-blind, randomised, placebo-controlled trial carried out by Simpson et al. (2001). The study, which was also carried out 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).

33. 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 pressures; 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 were admitted to the Neonatal Intensive Care Unit or Special Care Nursery within 24 hours of birth (5.2% compared to 3.7%). However, no statistical evaluation of this difference was presented. 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.

34. 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.

35. 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. One of the women had accidentally consumed large quantities of 400 mg raspberry leaf tablets and experienced nausea and diarrhoea but no pregnancy-related symptoms. She gave birth to a normal, liveborn infant at 40 weeks.