TOX/2020/51

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Scoping Paper on Herbal Supplements Used in Pregnancy

Background

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, 2011a) 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. 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.

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. A provisional list of chemicals was proposed by SACN Members; however, this was subject to change following discussion by COT. A scoping paper was presented to the Committee (TOX/2020/45) to define the scope of the work from the 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 thought it would be useful to consider the use of dietary supplements during pregnancy. These are supplements that are not officially recommended by relevant authorities, but which are promoted by anecdotal evidence and unofficial sources as having various purported benefits.

4. This review is confined to herbal dietary supplements which 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).

Introduction

5. The use of herbal supplements in the support of health during pregnancy varies according to geographical location but is common in many cultures

worldwide. While limited data exists with respect the safety and efficacy of herbal supplements, they continue to grow in popularity.

6. The WHO defines traditional herbal medicines as follows: “Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products, that contain as active ingredients parts of plants, or other plant materials, or combinations”[i]. However, comparable products may also be available as food supplements.

7. Herbal supplements are dietary supplements containing one or more herbs or extracts thereof, are used to supplement the diet with a view of achieving some benefit to health. The amount of scientific evidence available is varied – some botanicals have had several extensive studies carried out, while limited information available for others, which can have safety implications for their use in populations including pregnant women.

8. In the UK, the MHRA determines whether a product is a medicinal product, which is done on a case by case basis. A medicinal product is determined as “Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; [the first/presentational limb] and” Any substance or combination of substances which may be used in, or administered to, human beings, either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis” [the second/functional limb]”. Therefore, products are classified on the basis of medicinal claims[ii]. Any product claiming to maintain or support a healthy lifestyle is not considered medicinal and is therefore considered a dietary supplement, for which the Department of Health and Social Care (DHSC) has the legislative lead, but with the FSA providing advice on safety and enforcement as dietary supplements are regulated under food law.

9. Herbal dietary supplements may be used in pregnancy, to support the mother and child, provide relief of undesirable symptoms associated with pregnancy, and to ease the process of childbirth. Such supplements may be used by pregnant women considering them a “safer” alternative to pharmaceutical products which may be thought to carry adverse effects that could increase the level of harm to the mother and/or child.

10. For example, pregnant women often consider the use of supplements such as ginger root or products such as peppermint tea as a natural alternative for the relief of pregnancy associated nausea and morning sickness.

[i] https://www.who.int/traditional-complementary-integrative-medicine/about/en/

[ii] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/872742/GN8_FINAL_10_03_2020__combined_.pdf

11. The NHS currently recommends that pregnant women should not consume more than 4 cups of herbal tea per day, however no further information is provided (NHS, 2020). No advice on specific herbal supplements is provided.

12. Some limited advice on the use of herbal medicines during pregnancy is provided. This covers herbal medicines, highlighting issues such as the lack of evidence on efficacy of these commodities as well as potential interaction with other medicines and generally includes pregnant and lactating women in the populations that should avoid herbal medicines (https://www.nhs.uk/conditions/pregnancy-and-baby/medicines-in-pregnancy/; https://www.nhs.uk/conditions/herbal-medicines/).

Search methodology:

13. A selection of popular pregnancy and maternity forums were searched to identify frequently recommended herbal supplements among forum members. AS search was then conducted, with the use of Google Scholar, MEDLINE and Science Direct databases, using a search terms including herbal supplements, pregnancy. The search was centred on papers published between 2010 and 2020. A lot of information has been taken from EMA reviews of individual herbal ingredients.

14. A list of the most popular supplements is set out below, along with notes for Members' consideration. Some animal studies have reported results for both male and female animals and the results for males have been included for completeness.

Popular supplements that may be used in pregnancy

Ginger Root (*Zingiber Officinale*)

15. Ginger (*Zingiber officinale*) is a flowering tropical plant originating in Southeast Asia and grown in warm climates including China, India, Africa and the Caribbean. The root of the ginger plant is well-known as a spice and flavouring. It has also been used as a traditional remedy in many cultures[iii].

Uses

16. Ginger is a common traditional treatment for prophylaxis of motion sickness, Digestive disorders, upset stomach and nausea[iv]. In pregnancy it is most used in the treatment of pregnancy-related nausea (NHS). Ginger is available in fresh root form, dried root powder, capsule form, and as a tea.

[iii] https://www.webmd.com/vitamins-and-supplements/ginger-uses-and-risks
[iv] https://www.nhs.uk/news/pregnancy-and-child/drugs-ginger-and-acupuncture-best-for-morning-sickness/

Constituents

17. There are over 100 compounds identified in ginger, most of them 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, curcumene, citral, terpineol, borneol) (EMA 2012). 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.

Mechanism

18. Animal models suggest that ginger and its constituents reduce emesis by inhibiting 5-hydroxytryptamin 3 (5-HT_3) receptors (Abdel-Aziz et al.2005; Abdel-Aziz et al. 2006) and possibly influence other peripheral receptors involved in smooth muscle contraction in the gastrointestinal tract.

Toxicology

19. 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 10-15 for an adult). There is some evidence that ginger root may cause testicular weight to increase by repeated high dosages of ginger root extract (2000 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."

20. More recently, the Norwegian Food Safety Authority have issued a warning[v] 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 where rats were treated with a fresh grated ginger preparation with ginger at concentrations of 20-50 g/L in water, found that even in the 20 g/L treatment group – the equivalent of 1784 mg/kg bw increased the incidence of abortion in rats. The Norwegian Food Safety Authority concluded that while a woman of 70 kg would consume less ginger (124 mg to 329 mg) there remains cause for concern and fetal risk cannot be excluded.

Repeated Dose Toxicity

21. 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[vi] and female rats were treated with 500, 1000 and

[v] https://www.nutraingredients.com/Article/2019/08/15/Norwegian-Authority-warns-pregnant-women-to-avoid-ginger-supplements

2000 mg/kg bw/day by gavage. The results demonstrated that 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. It was only at the highest dose tested (2000 mg/kg), that 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.

22. 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 and systemic toxicity (Alnaqeeb et al. 2003). Neither oral nor intraperitoneal administration resulted in mortality. Orally administered aqueous ginger extract resulted in increased levels of serum aspartate aminotransferase (AST) and decreased levels of alanine aminotransferase (ALT).

23. Reproductive and developmental toxicity has also been investigated in rat studies. In a study by Wilkinson (2000), three groups of pregnant Sprague-Dawley rats were administered a control (unspecified), 20 g/L or 50 g/L ginger tea - prepared by the infusion of grated ginger in water - during days 6 to 15. No further details were provided regarding specific compounds of interests. 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 that controls and showed no gross structural malformations. The results of this study suggest that in utero exposure to ginger tea results in early embryonic loss and increase growth in surviving foetuses.

24. The teratogenicity of EV.EXT 33, a patented Zingiber officinale extract (comprising 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 & Sigwart, 2001). The extracts were administered orally at concentrations of 100, 333 and 1000 mg/kg, to three groups of pregnant rats from days 6 to 15 of gestation. Their bodyweight, food and water monitored during the treatment period. The study 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 1000 mg/kg bw.

25. Dissabandara & Chandrasekara (2007) also examined the effect of powdered ginger extract administered prenatally on the postnatal development of rats. A period of administration of the dry powdered extract orally at doses of 500 mg/kg/day 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 the ginger treated group, suggesting that maternal administration of ginger during mid pregnancy resulted in reduced maternal weight gain and increased embryonic loss

without affecting the postnatal growth and physical maturation of the surviving offspring.

26. Mutagenic activity has been observed in bacterial models. The EMA discussed these in their evaluation of ginger.

27. In Salmonella typhimurium strains TA 98, TA 100 and TA 1535, an ethanol extract of ginger (Soudamini et al. 1995) and an essential oil from ginger (Sivaswami et al. 1991) demonstrated mutagenic activity at concentrations of 25-50 mg/plate and 5-10 mg/plate, respectively. Likewise, an ethanolic ginger extract at concentrations between 10 and 200 µg/plate, and gingerol and shogaol were mutagenic in strains TA 100 and TA 1838 with metabolic activation by rat liver S9 fraction, while zingerone did not display mutagenic effects (Nagabhushan et al. 1987). Nakamura & Yamamoto (19820 found that the juice of ginger rhizome contained both mutagen and anti-mutagen, and that 6-gingerol in particular was a powerful mutagen. The group could also demonstrate that 6-shogaol was much less mutagenic (strain Hs30 of Escherichia coli) than 6-gingerol, and that the active part of 6-gingerol was the hydroxylated aliphatic side chain moiety [Nakamura & Yamamoto 1983]. Capsaicin, the alkaloid present in chili, is structurally related to gingerol and shogaol, and was also found to be mutagenic (Nagabushan & Bhide 1985. The urine of rats fed diets containing 0.5, 1 and 5% powdered ginger for 1 month and exposed to benzo(a)pyrene was found to display a significant reduction in the mutagenicity as indicated by a reduced number of TA98 and TA100 revertants at all ginger concentrations (Nirmala et al. 2007.

28. Qiu et. al. (2015) investigated 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 cytochrome 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 regulate the activity and expression of various human CYPs, resulting in alterations in drug clearance and response.

Studies in human volunteers

29. A systematic review by Ding et. al. (2012) examined the effectiveness of ginger on the treatment of pregnancy-induced nausea and vomiting. The review focused on four randomised controlled trials (three double-blind), published between 2000 and 2009. All trials used mono preparations of ginger, with daily doses ranging between 500 mg and 1050 mg. All participants were pregnant women of less than twenty weeks. Trial duration varied between four days and three weeks, with a mean duration of 1.5 weeks. Four studies found ginger to be safe and effective in improving pregnancy induced nausea when compared with a placebo. The authors stated that in no study was the safety of ginger consumption

explicitly addressed, nor was any study powered well enough to provide statistically significant results concerning safety.

30. The EMA highlighted the possible relationship between ginger and over-anticoagulation in patients being treated with oral anticoagulants phenprocoumon and warfarin. They identified cases of two women, both aged 76, exhibiting an elevated INR of up to 10, and requiring admittance for epistaxis (Krüth et al. 2004, Lesho et al. 2004). In both cases, the patients had been taking ginger in dried, powder and as a tea.

Raspberry Leaf Extract (*Rubus Idaeus*)

31. There are no official government dietary recommendations for pregnant women relating to raspberry leaf extract, however it has been recommended by some healthcare practitioners that raspberry leaf tea can be taken after 32 weeks. However, it is suggested that it should be avoided by a subset of women, including women who have previously had, or plan to have, a caesarean section, premature labour, a previous labour lasting less than 3 hours, complications during a previous pregnancy, including high blood pressure and those expecting twins[vii].

Uses

32. Red raspberry leaf *(Rubus idaeus*) has been used as a “uterine tonic” and general pregnancy tea for centuries (EMA, 2012). It is typically taken in tea form during pregnancy to treat morning sickness, prevent miscarriage; shorten and facilitate labour, and to aid birth. It is also used as a food flavouring agent (Briggs and Briggs, 1997). It is sometimes reported that it can be used during the whole time of pregnancy, sometimes it is stated that it should be used in the last trimester only.

Constituents

33. The main active compounds of raspberry leaves are not clear, but they are reported to contain a range of compounds, including: polypeptides, tannins, flavonoids (Yang et al. 2019), gallic acid, ellagic acid, rutin, fragrine, quercetin-3-O-glucuronide and kaempferol, citric acid oxalic acid. Raspberry leaf is also stated to be a good source of vitamins C, A, E, calcium and iron; and it contains smaller amounts of phosphorous, magnesium, B vitamins and vitamin D.

Mechanism

34. Raspberry leaf is reported to have both a stimulatory or spasmolytic effect on the uterus, possibly being dose and tissue dependant. There is no data on its mechanism of action (Dogua 2010).

[vii] http://www.boltonft.nhs.uk/services/maternity/information/complementary-therapies/raspberry-leaf-tea/

Toxicology

35. In their 2013 review, the EMA concluded that “Toxicological data on raspberry leaf are limited. In mice an oral dose of extract equivalent to 10% of body weight of dried raspberry leaves was considered nontoxic, but these data are not transferrable to humans. Nonetheless, neither the chemical composition nor the long-term widespread use in the European Union suggests that there is a high risk associated with the use of raspberry leaf preparations. Adequate tests on reproductive toxicity and tests on genotoxicity and carcinogenicity have not been performed.”

Animal data

36. No long term or teratogenicity toxicity studies have been reported for raspberry leaf.

37. In vitro studies testing the effect of a saline infusion of dried leaves (1 g/15 ml saline infused for 10 min) on the uterine strips of pregnant and non-pregnant rats had varied outcomes (Bamford et al., 1970). No effect was observed in uteri of non-pregnant rats. Contractions in uteri of pregnant rats were inhibited for 3-4 min. The extract also contracted strips of normal human uteri at 10-16 weeks of pregnancy for a few minutes. In both experiments, the intrinsic rhythm observed became more regular and contractions were less frequent.

38. Aqueous extracts of raspberry leaf of varying concentrations (1.5 – 50 mg) were tested on mouse uterine tissues to further observe and quantify contractile effects of raspberry leaf extracts (Olson and DeGolier 2016). The application of raspberry leaf extract to isolated uterine strips resulted in increases in contractile responses ranging from 01.59 mN (millinewtons) to 74.68 mN.

39. The effect of three forms of raspberry leaf (tea, capsules [no further information provided] and an extract with 35-40% ethanol) were tested on uterine contractility in non-pregnant and late pregnant rats (Zheng et al. 2010). Non-pregnant rats were injected with diethylstilbestrol (DES) 2 days prior to sacrifice to produce an oestrogen dominant state. Aqueous extracts (tea and capsule content at concentrations of 1.0-4.6 mg/ml) tested on pregnant uterine preparation and ethanolic extract at concentrations of 2.2 -10.1 mg/ml used on DES treated non-pregnant uterine preparations were examined. Furthermore, non-pregnant uterine preparations were also treated with both aqueous extracts. Raspberry leaf tea had varying effects on pre-existing oxytocin-induced contractions. It was shown that aqueous extracts (0.2 g/ml concentration) could trigger contractions in uterine strips of both pregnant and non-pregnant rat, while the ethanolic extract had no effect on contractility.

40. *In vivo*, two studies have been reported from the EMA on raspberry leaf. In a study by Johnson *et al*. (2009), 40 nulliparous Wistar rats were assigned to receive vehicle, raspberry leaf or specific flavonoids in raspberry leaf (kaempferol or

quercetin) at 10 mg/kg bw/d from first day of pregnancy to birth. The female offspring (F1) were followed up to the birth of their offspring (F2) and the F2 generation was followed up to weaning.

41. No effects on maternal weight gain during pregnancy, live birth index, litter size, birthweight, total litter weight, sex ratio, survival to postnatal day 4 (PND4), or survival to weaning were reported for group receiving raspberry leaf. Exposure to raspberry leaf was associated with statistically significant increase in gestation length. There was also an association with reduced pregnancy success when compared to control animals (78% success as opposed to 100% for controls) although this was not statistically significant. Exposure to quercetin was also associated with an increase in weight gain in pregnancy. No other effects were observed on pregnancy or birth outcomes.

42. For the F1 animals, raspberry leaf exposure during pregnancy also resulted in precocious puberty (i.e., lower age at vaginal opening) in the female offspring. There was no effect of fetal exposure to raspberry leaf on time to pregnancy, gestation length, mating success, pregnancy success, the live birth index, litter size, birthweight, total litter weight, sex ratio, or postnatal survival to PND4 or postnatal day 21 (PND21). The mean birthweight of F2 pups was not significantly different between raspberry leaf exposed and control dams, however there was a significant increase in the proportion of offspring that were growth restricted (i.e., had a birthweight that was more than 2 standard deviations below the mean birthweight of the control offspring). The authors concluded that fetal exposure to raspberry leaf has previously unidentified transgenic rational effects, and further safety assessment was strongly recommended.

43. In the second study (abstract only), female rats injected subcutaneously. with aqueous Pregnant Mares´ Serum (PMS) gonadotrophin at 300 IU/mg PMS were administered raspberry leaf extract (no further details available). Ovarian weight gain was reduced. Some of the extracts were made from fresh green leaves, and others from the dried plant. All the extracts that were made from dried plants were found to be active on 10-18 mg dried herbal substance per dose (~230 mg/kg b.w.) dose level and the activity was seasonally variable and fell after storage of the dried leaves for 15 months (Graham and Noble 1955)

Human data

44. Two small studies were reported in the EMA evaluation. In a retrospective observational study in hospitals in Sydney, 57 women were exposed to either raspberry leaf tea or tablets (up to 6 cups or 8 tablets or 1 dose of tincture per day, no further details given) for continuous a period of 1-32 weeks, with some women commencing as early as 8 weeks of pregnancy (Parsons et al. 1999). In a second double-blind, randomized, placebo-controlled study conducted at a hospital in Sydney, a total of 96 nulliparous women were exposed to raspberry leaf tablets (2 x 1.2 g/d) from week 32 of pregnancy to labour (Simpson et al. 2001). In both studies,

there were no clinically significant differences between controls and treatment groups (maternal blood loss, babies' Apgar score at 5 min of age, maternal diastolic blood pressure pre labour or transfer of baby to special care unit). Furthermore, there was no effect on length of gestation, medical augmentation of labour, need for pain relief during labour or time of the three stages of labour (in the first study the first stage of labour was shorter whereas in the second study a shorter second stage in the raspberry leaf group was reported).

45. Raspberry leaf used orally for two months to "precipitate labour" firstly once weekly and then daily for 30 days resulted in convulsions in a new-born boy, based on a report in the World Health Organization's Uppsala Monitoring Centre (WHO-UMC). Other adverse reactions reported were diarrhoea and increased frequency of Braxton Hicks contractions in the retrospective study. The authors reported that these could be avoided by lowering the raspberry leaf dose. In the study by Simpson *et al.* the side effects reported were most likely related to common pregnancy ailments, mainly nausea, vomiting, diarrhoea, constipation and changes in blood pressure however there were no significant differences between groups.

46. The use of herbal drugs during pregnancy in relation to concurrent use of conventional drugs, delivery and pregnancy outcome was studied by Nordeng *et al.* (2011). In the study, 600 Norwegian women were interviewed using a structured questionnaire within five days after delivery. Medical birth charts were reviewed with respect to pregnancy outcome. 39.7% of women reported using herbal drugs during pregnancy, raspberry leaf being amongst those most commonly used. 86.3% of the women reported having used conventional drugs during pregnancy, however there were few potential interactions between herbal drugs and conventional drugs. Conversely, these are: ginger and acid suppressants (may decrease the effect of acid suppressant), chamomile and psychotropic drugs (may increase CNS effects), iron-rich herbs and acid suppressants (may result in mutual decreased effect), dandelion and furosemid. Regarding the use of raspberry leaf, the authors reported a significant association between the use of the leaf and caesarean delivery (23.5% vs. 9.1% among women with no use of herbal drugs, crude odds ratio = 3.18;95%CI;1.37-7.38). This association remained significant even after controlling for maternal age, parity, marital status, education and conventional drug use (adjusted odds ratio = 3.47; 95% CI 1.45-8.28). The authors speculated that women using raspberry leaves have to a greater extent underlying conditions that increase the risk of a caesarean section and that the finding is due to confounding by indication. They did not rule out the possibility that there may be active substances in raspberry leaves that act directly on the pregnant uterus in a negative way. They proposed that their findings supported the view that raspberry leaves should not be recommended due to very limited documentation on the safety and efficacy of raspberry leaves in pregnancy. They also highlighted that it is important to recognise that the fact that a herb has been used for decades does not constitute evidence and is not a sufficient guarantee for safety or efficacy

Chamomile (*Matricaria Recutita L.*)

Uses

47. Chamomile, one of the more popular herbal supplements, is traditionally used as a mild sedative, to aid digestion and in the treatment of inflammation. Chamomile is available in flower, essential oil, liquid extract and dry extract forms.

Constituents

48. The main constituents of chamomile include essential oil, flavonoids, sesquiterpene lactones, coumarins, spiroethers (cis- and trans en-in-dicycloethers), phenolic acid, polysaccharides, amino acids and choline (Schilcher et al 2005).

Use in Pregnancy

49. In a study of 400 Norwegian women by Nordeng and Havnen (2004) chamomile was amongst the 10 most commonly used herbal drugs, overall applied by 9% (n=13) of the herbal drugs using women.

50. Cuzzolin *et al.* (2010) investigated the use of herbal products among pregnant Italian women (n=392) and the possible influence of herbal consumption and pregnancy outcome (abstract only). The study was conducted over a 10-month period (2 days a week). Data were collected through a face-to-face interview on the basis of a pre-structured questionnaire including socio-demographic characteristics of the enrolled subjects, specific questions on herbal use, information about pregnancy and the newborn. 109 out of the 392 women reported having taken herbal drugs during pregnancy; chamomile was one of the more common supplements taken.

51. Holst et al. (2011) conducted a study where 1,037 women, at least 20 weeks pregnant, were given a questionnaire regarding the use of herbal products. Of the 578 women who answered, 76 had used chamomile. No risk was documented.

52. In the study by Facchinetti et al. (2012), 700 women were interviewed in three hospitals around the time of labour. 35.7% had taken chamomile via oral administration. A correlation between use of chamomile and low body weight of the infant was not statistically significant.

53. Bishop et al. (2011) carried out an observational population-based cohort study of 14,541 pregnant women residing within the former county of Avon in the UK. Data were available from 14,115 women. Chamomile was used by 551 women throughout pregnancy (14.6%).

54. In a study by Forster et al. (2006) a questionnaire was answered by 588 Australian pregnant women during the 36-38th weeks of pregnancy, 11% used chamomile tea during pregnancy. Information on pregnancy outcome was not part of the questionnaire.

55. In Canada a questionnaire was submitted to 8,505 women who gave birth to a live born between January 1998 and December 2003 were selected from a Quebec pregnancy registry (Abstract only). The questionnaire was answered by 3,354 women of which, chamomile was used by 122 women. The same data set was used to perform a case control study regarding premature delivery (<37th week), identifying 623 preterm births: 62 women had used herbal products, a third of those, chamomile. Adjusting to cofounders found no relation between the use of chamomile during the last two trimesters of pregnancy and preterm delivery (Moussally et al. 2009).

Toxicology

56. In their 2015 report, the EMA concluded: "The non-clinical data support the plausibility of the traditional use. Anti-inflammatory effects and effects on wound healing and on gastrointestinal tract were seen in vivo. Unfortunately, most of the studies do not provide exact extract specifications or dosages/concentrations… Non-clinical information on the safety of matricaria preparations is scarce. Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed."

57. The EMA reported a genotoxicity study by Kalantari et al. (2009), who studied a chamomile containing preparation (no further details available) from Iran in a short-term mouse peripheral blood micronucleus test. 2.5, 5 and 10 ml/kg doses were used for test groups. Mitomycin C at the dose of 0.5 mg/kg, Hypiron (St John's wort) were administered twice in 24 hours intervals. Blood samples were prepared 48 hours after first administration and kept on precoated Acridine orange slides. The scoring of micronucleated reticulocytes were carried out per 2,000 counted reticulocytes in each slide by fluorescent microscope. For the chamomile treated groups the micronuclei increased from 2 to 4.5.

58. Ganzera et al. (2005) studied the effect of the essential oil and its major constiutents (chamazulene, farnesene, α-bisabolol, bisabololoxide A, bisabololoxide B, trans-(Z)-spiroether and cis-(E)-spiroether) of chamomile on four selected cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2D6 and CYP3A4). Varying concentrations of essential oil (up to 200 µM) and the individual extracts (up to 100µg/ml) were tested against individual, recombinant CYP isoforms. The essential oil extract and in particular chamazulene, was found to demonstrate inhibition of all four enzymes, with CYP1A2 being the most sensitive to the action.

59. Anter et al. (2011) evaluated the genotoxic, antigenotoxic, tumoricidal, and apoptotic effect of apigenin, bisabolol and protocatechuic acid from chamomile and cat's claw. The wing spot test of Drosophila melanogaster was used to evaluate the genotoxicity and antigenotoxicity. The human model of HL-60 leukaemia cells was used to assess cytotoxicity, growth, and cellular viability. The apoptotic effect was evaluated using a DNA fragmentation assay based on the formation of internucleosomal units. Protocatechuic acid (0.25 and 1 mM), apigenin (0.46 and 1.85 mM), and bisabolol (0.56 and 2.24 mM) were not found to have a genotoxic effect (abstract only).

60. Related allergic reactions to food, pollen and others was investigated in 14 patients with a positive skin prick test/RAST (abstract only). IgE-binding patterns were determined by immunoblotting, inhibition tests and deglycosylation experiments. Ten of the 14 patients had a clinical history of immediate-type reactions to camomile, in some cases life threatening. (Reider et al. 2000).

61. It is noted chamomile can have interactions with conventional medicines, although reports are inconsistent.

Dandelion (Taraxacum Officinale)

Uses

62. Dandelion in tea form has been recommended as a diuretic and is traditionally used for the relief of fluid retention in the later stages of pregnancy. It is also used as a salad green, in soups, wine and tea. the roasted root is used as a coffee substitute.

Constituents

63. The root, herb and leaves of dandelion consist of various phenolic compounds including chicoric acid, chlorogenic acid, monocaffeyltartaric acid, cichoriin and esculin (Wolbis M and Krolikowska M 1985; Wolbis M et al. 1993; Williams CA et al. 1996; Budzianowski J 1997; Kristó ST et al. 2002), potassium (Tsialtas JT et al. 2002) and trace metals cadmium, chromium, copper, lead and zinc (Keane B et al. 2001).

Toxicology

64. The initial, broad literature search did not identify any relevant papers regarding the safety of dandelion use during pregnancy.

65. In their 2009 report, the EMA concluded: “Reliable data on acute toxicity are only available for whole crude drug and some extracts. Oral administration of preparations from Taraxaci radix cum herba can be regarded as safe at traditionally used doses with the exception of patients with renal failure and/or diabetes, and/or heart failure. In those conditions, the use should be avoided because of possible complications due to hyperkalaemia.

66. Although toxicological data on dandelion are very limited, neither the European traditional use nor known constituents suggest that there is any risk associated with the use of dandelion root and herb.”

67. In a study by Akhtar et al. (1985), no visible signs of acute toxicity observed after oral administration of dried whole dandelion plants at 3–6 g/kg body weight in rats. Following a single dose administration, rats were observed for up to 8 hours

for signs of toxicity and behavioural changes and remained under observation for seven days.

68. The EMA report included cytotoxicity studies where an herb water decoction caused a time-dependent and partially dose-dependent reduction of human hepatoma cell lines viability by 26% (Koo *et al.* 2004).

69. Dandelion extract was not found modify the metastatic process when it was used alone, but potentiated the efficiency of cytostatic therapy, as demonstrated on mice with subcutaneously transplanted tumours (Ehrlich adenocarcinoma, Lewis lung carcinoma - LLC) (Goldberg et al. 2004, Lopatina et al. 2007).

70. The water extract of dandelion leaf (DLE) decreased the growth of MCF-7/AZ breast cancer cells in an ERK-dependent manner (extracellular signal-regulated kinases), whereas the extracts of dandelion flower and root had no effect on the growth of either cell line (Sigstedt SC et al. 2008).

71. Ethanolic extracts of dandelion root were found to cause a dose-dependent inhibition of Adenosine Diphosphate (ADP)-induced human platelet aggregation, with a maximal inhibition of 85% observed at a concentration corresponding to 0.04 g dried root/ml (Abstract only available). Arachidonic- and collagen-induced platelet aggregation was not affected. High molecular weight fraction (Mr > 10,000) showed a 91% inhibition of platelet aggregation, while a lower fraction (Mr < 10,000) containing triterpenes and steroids caused an 80% inhibition, both at a concentration equivalent to 0.04 g crude material/ml Platelet Rich Plasma (Neef et al. 1996).

72. In a study by Saulnier P et al. (2005), aqueous extract of dandelion exhibited no inhibitory effect on ADP-induced platelet aggregation in samples from healthy volunteers.

Echinacea *(Echinacea Purpurea)*

Uses

73. Echinacea, listed as an herbal medicinal product by the EMA, is also promoted as a dietary supplement for the treatment of the common cold and other infections (National Centre for Complementary and Integrative Health, 2020).

Constituents

74. The number of species of echinacea varies depending on the source, but there are at least ten accepted species (McKeown 1999). While the exact concentration of the components varies with plant species, echinacea consists of caffeic acid derivatives, alkamides, melanins, polysaccharides, lipopolysaccharides and lipoproteins.

Mechanism

75. It is thought that echinacea may work by stimulating the immune system, although the mechanism is not known (EMA 2014).

Toxicology

76. In their 2014 report, the EMA concluded: “Substantial amount of toxicological investigations were performed, including genotoxicity. They indicate no safety concern for the use of Echinacea preparations at recommended doses and duration. Studies on reproductive toxicity and carcinogenicity are not available, therefore the use during pregnancy and lactation is not recommended.”

77. It is worth noting that, following a review of *in vitro,* animal and human studies, the EMA concluded that there was some (including statistically significant) inhibition of CYP activities by alkamides and extracts from Echinacea purpurea which may affect the CYP450-mediated metabolism of other concurrently ingested pharmaceuticals. Furthermore, it appeared that Echinacea may modulate the catalytic activity of CYP3A at hepatic and intestinal sites and inhibit CYP1A2 and CYP2C9 at high doses. It was concluded that further pharmacokinetic testing is necessary before conclusive statements could be made about Echinacea puprurea herb juice interactions in concomitant use of Echinacea and CYP3A4, CYP1A2 and/or CYP2C9 substrates. (EMA, 2014).

In vitro

78. In animal and human cell lines as well in bacterial tests, Echinacea extracts did not show any genotoxic activity (EMA, 2014).

Animal Studies

79. Mengs et al. (1991, abstract only) demonstrated oral and intravenous doses of the expressed juice of echinacea was found to be virtually non-toxic to both rats and mice. Following a single oral application of juice at doses of 15000 mg/kg in rats or 30000 mg/kg in mice resulted in no observed abnormalities. Mutagenicity tests carried out on mammalian cells in vitro and in mice yielded negative results and in vitro carcinogenicity studies on hamster embryonic cells resulted in no malignant transformation (no further details available).

80. Following 4 weeks of oral administration of echinacea expressed juice at doses of 800 mg/kg, 2400 mg/kg or 8000 mg/kg per day, male rats (2400 mg/kg and 8000 mg/kg) showed a statistically significant fall in plasma alkaline phosphatase compared to control group of rats, while the females (2400 mg/kg and 8000 mg/kg) showed a rise in prothrombin time compared to control (Mengs et al., 1991).

81. In a study conducted by Chow et al., (2006) where pregnant mice were fed echinacea from pregnancy onset to gestation days 10,11, 12, 13 and 14 showed consuming echinacea during pregnancy reduced the number of viable foetuses. The study also demonstrated a diet of echinacea resulted in a reduction in pregnancy-induced elevation in splenic lymphocytes.

82. A study conducted by Barcz et al. (2007), where mice were administered 0.6 mg of three types of echinacea extract dissolved in water orally from day 1 of fertilisation to day 18 of pregnancy, demonstrated a reduction in tissue vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) production of their foetuses. Angiogenic activity of tissue homogenates gave varied results for the echinacea treated groups, suggesting echinacea might influence fetal development and embryonal angiogenesis.

Human data

83. No prospective interventional studies on pregnant or lactating women were available, neither was any fertility data identified.

84. The EMA review reported a study from Canada (Gallo *et al., 2000)* where 206 women were prospectively followed up for use of Echinacea in pregnancy. The women were using either *E. purpurea* or *E. angustifolia* (no information on numbers), with one woman using *E. palida.* Women were exposed to tablets or capsules (58%, 200-1000 mg/d) or tincture (38%, 5-30 drops/d). 112 women used the preparations in the first trimester and 17 were exposed for all trimesters. No information was provided on the part of the plant used in these preparations. The cohort was disease-matched to women exposed to non-teratogenic agents by maternal age, alcohol and cigarette use. 206 women were used as controls. No statistically significant differences were reported between the study and control groups in the number of live births (195 vs 198 in control group), spontaneous abortions (13 vs 7 in control group), major malformations (6 including 1 chromosomal abnormality vs 7 in control group)- it was noted that 4 of the malformations for Echinacea occurred in women exposed in the first trimester). The authors concluded that gestational use of Echinacea during organogenesis is not associated with an increased risk for major malformations.

85. In the study on Norwegian women (Nordeng *et al*., 2011- see para. 49) Echinacea (no information on the part of the plant or species) was one of the most commonly used herbal medicines during pregnancy. No significant differences were reported for women using Echinacea during pregnancy and any of the outcomes investigated in the study.

86. In the study by Cuzzolin *et al. (*see para 51) Echinacea was reported as one of the most commonly used herbal medicines during pregnancy. Although no specific information on the effect of Echinacea on pregnancy outcomes is reported in the abstract, the authors concluded that “Users were more often affected by

pregnancy-related morbidities and their neonates were more frequently small for their gestational age".

87. Perri *et al.* (2006) conducted a review on the safety of Echinacea in pregnancy and lactation. Of the available studies, the authors considered that the Gallo *et al.* study (paragraph 84) had provided good scientific evidence that consumption of Echinacea during the first trimester did not increase the risk of major malformations. They considered that low evidence, based on expert opinion showed that Echinacea consumption in the recommended doses was safe for use in pregnancy and lactation, that Echinacea was not teratogenic and advised caution for use of Echinacea during lactation until further high quality human studies can determine its safety.

Evening Primrose Oil (*Oenothera Biennis L.)*

Uses

88. Evening primrose oil is recommended for atopic eczema, rheumatoid arthritis, premenstrual syndrome (PMS), breast pain, menopause symptoms, and other conditions. In pregnancy, evening primrose oil is commonly used as a means of cervical ripening and inducing labour. There is no standard dosage, however a dose of 500 to 2000 mg daily at the 38th week of pregnancy has been suggested by some sources [viii].

Constituents

89. Evening primrose oil is high in fatty acids linoleic acid (LA), γ-linolenic acid (GLA). It also contains oleic, stearic and palmitic acids.

Mechanism

90. The mechanism of action of evening primrose oil is unclear.

Toxicity

91. In their 2018 report, the EMA concluded: "There was no repeated-dose, carcinogenic or teratogenic effect observed in a limited number of studies. As there is only limited information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended."

92. Everett et al. (1988a) studied long term toxicity of evening primrose oil on dogs and rats lasting 52 and 53 weeks respectively. A group of male and female beagle dogs were administered a daily dose of 5 ml/kg evening primrose oil, supplemented with vitamin E oil. Four groups were administered varying doses of evening primrose oil (0, 1, 3, 5 ml/kg) supplemented with corn oil. Haematology analysis, clinical chemistry analysis and urinalysis were carried out at 0, 12, 26 and 50 weeks. A post-mortem examination was carried out after 52 weeks. No significant differences were found in food consumption, clinical signs or body weight

[viii] https://www.healthline.com/health/pregnancy/does-evening-primrose-oil-induce-labor

changes neither in haematology, urinalysis nor clinical chemistry. No differences were found in the necroscopical or histopathological examination.

93. Male and female Sprague-Dawley rats (100 in each group), were administered a daily dose of 2.5 ml/kg of oil, containing either 0, 0.3, 1 or 2.5 ml/kg of evening primrose oil the ophthalmoscopic examination was carried out at 0 and 50 weeks and the post-mortem was carried out at 53 weeks. Six rats in the evening primrose oil group died compared to five in the control group. An increase in potassium level was observed in female rats.

94. The EMA described a study by Everett et al. (1988b), who also performed a long-term carcinogenicity study on Sprague-Dawley rats:

95. “Everett et al. (1988b) performed a long-term study on a total number of 500 rats randomly assigned to 4 treatment groups and 1 placebo group. Two hundred male and 200 female Sprague-Dawley rats were administered with 2.5 ml/kg/day oil during 5-6 weeks, 50 animals from each gender received a daily dose of 0.3 ml/kg, 1 ml/kg or 2.5 ml/kg Oenothera oil. The lower doses were diluted to 2.5 ml with corn germ oil. The remaining 50 males and females were given 2.5 ml corn germ oil as a control. Fifty other animals from each gender received a normal laboratory diet. After 104 weeks, the surviving and deceased animals were subjected to a post mortem histopathologic examination. An identical experiment with CD-1 mice, where the post-mortem histopathologic examination was conducted after 78 weeks because of the short life expectation of the animals, showed the same results. These experiments did not find any significant difference in the nature and the frequency of the tumours between the animals with a different dose of Oenothera and the control animals (Hänsel et al., 1993)”.

96. Dove & Johnson studied the effect of oral evening primrose oil on the length of pregnancy and selected intrapartum outcomes in low-risk nulliparous women (1999). 54 women were administered a dose of evening primrose oil from the 37th gestational week until birth. The study determined oral administration of evening primrose oil did not shorten gestation or the length of labour and furthermore orally administered evening primrose oil may result in an increase in the incidence of prolonged rupture of membranes, oxytocin augmentation, arrest of descent, and vacuum extraction.

Peppermint (*Mentha Piperita*)

Uses

97. Peppermint is one of the herbs used most commonly in pregnancy for treating nausea/morning sickness and other gastrointestinal issues such as flatulence. Traditionally, its leaves are used in tea, however it is also available as an oil, and can be consumed in that form, or in capsules.

Constituents

98. The main fatty acids in the leaves are palmitic, linoleic and linolenic acids. Additionally, flavonoids are present including luteolin and its 7-glycoside, rutin, hesperidin, eriocitrin (eriodictyol 7-O-rutinoside) and highly oxygenated flavones. Other constituents include phenolic acids and small amounts of triterpenes. Phenolic compounds have also been reported, with eriocitrin as the dominant phenolic secondary metabolite; luteolin 7-0-rutinoside, hesperidin and phenolic acid derivatives such as rosmarinic acid were also detected. Sullivan et al. (1979) stated that pulegone is found in young peppermint leaves and is metabolized to menthol as the leaves mature.

99. Peppermint oil is comprised mainly of menthol and menthone. Menthyl acetate and small amounts of cine- ole and other terpenes are also found in Peppermint Oil. Other identified components are acetaldehyde, amyl alcohol, menthyl esters, limone, pinene, phellandrene, cadinene, and dimethyl-sulphide. Traces of α-pinene, p-menthane, sabinene, terpinolene, ocimene, gamma-terpinene, fenchene, α-thujone, β-thujone, citronellol, α-cadinene, α-amorphene, α-gurjunene, and ¯β-copaene have also been reported.

100. Other possible constituents include pulegone, menthofuran, and limonene.

Mechanism of action

101. Most of the available data are on peppermint oil. Various sources[ix] report the use of peppermint as a smooth muscle relaxant, via a calcium blocking mechanism. The EMA reports a similar effect in animal models for the peppermint leaves. It has therefore been proposed that peppermint can help combat nausea and vomiting during pregnancy by reducing oesophageal dysmotility.

Toxicology

102. Overall, the EMA report concluded that “on the basis of its long-standing use, these peppermint leaf preparations can be used for relief of digestion-related problems such as indigestion and flatulence. They should only be used in adults and children over the age of 4 years. Preparations of peppermint leaves demonstrated a relaxant and antispasmodic effects on gastrointestinal tissue and antinociceptive effect on animal models. Mixed flavonoids showed choleretic activity in dogs. Also, the peppermint oil presents a similar action in animal and clinical

---

ix

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5814329/#:~:text=Effects%20on%20Gastrointestinal%20Tract%20Neuromotor,as%20a%20smooth%20muscle%20relaxant.&text=Hawthorn%20et%20al.,capable%20of%20blocking%20calcium%20channels.

https://www.gastrojournal.org/article/0016-5085(91)90459-X/pdf

https://www.healthline.com/health/benefits-of-peppermint-oil

https://bnf.nice.org.uk/treatment-summary/antispasmodics.html

studies. The special warnings advise patients with cholangitis, gallstones and any other biliary disorders to be cautious using peppermint leaf preparations. Patients with gastroesophageal reflux (heartburn) should avoid peppermint leaf preparations. There are no reports on interactions. There is no adequate data available with children under 4 years old and in fertility, pregnancy and lactation."

103. Data on the safety of menthol, pulegone and menthofuran are also presented as these are compounds with known potential adverse effects to health.

Peppermint (oil and leaves)

Acute toxicity

104. Both the leaves and oil are of low acute toxicity with LD50s greater than 4000 mg/kg bw/d for the dry leaf extract and 4441 ± 653 mg/kg after 24 hours and 2426 mg/kg after 48 hours for the oil.

Short term toxicity

105. For peppermint oil, the final report on the Safety Assessment (CIR, 2001) of *Mentha piperita* lists a number of short-term animal studies, at doses up to 500 mg/kg bw/d. The lowest NOAEL reported was 10 mg/kg bw/d in two separate studies in Wistar rats. A content of 38.1% menthol, 33.7 menthone and 1.7% pulegone content was reported in one of the studies whereas in the second study the composition is unknown. The NOAEL was based on cyst like spaces in the white matter of the cerebellum of the animals as well as a non-dose related dissociation and vacuolisation of the hepatocytes in the mid (40 mg/kg bw/d) and high (100 mg/kg bw/d) dose groups. This was consistent with the observations in the second study, where encephalopathy developed in the high dose group (100 mg/kg bw/d), with dose-related cyst-like spaces in the white matter of rats in the mid (40 mg/kg bw/d) and high dose groups.

106. For peppermint leaves, *M piperita* tea was given to rats at 20g/L for 30 days in a series of studies in different tissues. The findings included reduced serum iron and ferritin levels, increased unsaturated iron-binding capacity, increased AST and ALT levels (although not statistically significant), minimal hepatocyte degeneration (dose dependent damage) as well as hydropic degeneration of tubular epithelial cells, epithelial cells with pyknotic nuclei and eosinophilic cytoplasm, enlargement of bowman capsules in the kidneys (despite overall no evidence of nephrotoxicity being reported) were the effects observed.

Carcinogenicity

107. Only one study has been reported, this was for peppermint oil in toothpaste (CIR, 2001). Male pathogen-free CFLP (ICI-rede. ned) mice were dosed by gavage with 4 or 16 mg peppermint oil/kg per day, 6 days a week for 80 weeks, with a 16- to 24-week observation period. Body weight gain was initially reduced in animals of the 16-mg/kg per day group. At least one neoplasm at any site was observed in

73%, 69%, 65%, and 71% of mice of the low dose, high-dose, untreated-control, and vehicle-control groups, respectively. Malignant neoplasms were noted in 39%, 35%, 23%, and 31% of mice of the low-dose, high-dose, untreated control, and vehicle-control groups, respectively. The incidence of neoplasms of the lungs and kidneys were comparable among mice of the treated and non-treated groups. In a separate study, by Roe et al., (1979), hepatic cell tumour incidence for peppermint oil–dosed mice (25%) was comparable to the incidence for mice of the vehicle-control group (27%); the incidence for the untreated group was 19%. Malignant lymphoma was found in 25%, 21%, 10%, and 14% of mice of the low-dose, high-dose, untreated, and vehicle-control groups, respectively. The researchers did not discuss whether the difference in the incidence rate was significant. The EMA and CIR reports note that a review of the study by the British Industrial Biological Research Association (1992) noted that it was not designed to examine the carcinogenic potential of peppermint oil and thus "would have had only a very limited sensitivity to this particular component".

Reproductive/Developmental toxicity

108. No studies on either the leaves or the oil have been reported on female rats. The EMA reported one study on male Wistar albino rats. The level of follicle stimulating hormone was increased and total testosterone levels decreased at 20g/L *M. piperita.*

109. It is worth noting that various sources[x] caution against the use of peppermint tea and oil in the first trimester, especially in women with a history of miscarriages because of its emmenagogue effects, due to the potential presence of thujone and betaine. However, the reports on the presence of these compounds in either the herb or the oil are contradictory. (Westfall, 2004).

Genotoxicity

110. Peppermint oil was negative in two in vitro genotoxicity tests, the mouse lymphoma assay and in the in vivo combined micronucleus/Comet assay (liver, kidney and bladder mucosa cells) in female rats.

Clinical studies

111. The EMA reported a range of human studies investigating the efficacy of peppermint for various uses including the alleviation of IBS symptoms/ abdominal pain, nausea (post-operative or chemotherapy induced), and dyspepsia. No severe adverse effects have been reported at doses ranging from 180 to 225 mg/ dose (up to 6 doses per day) at up to 12 weeks. Although in some studies questionnaires were used to record scores of the effectiveness of peppermint, it is unclear whether

[x] https://www.leaf.tv/6726061/can-peppermint-oil-cause-a-miscarriage/

https://www.insider.com/worst-tea-during-pregnancy-2018-2#think-twice-before-drinking-peppermint-or-chamomile-tea-in-your-first-trimester-4

https://www.momjunction.com/articles/peppermint-tea-during-pregnancy_00358491/

the adverse effects discussed below were self-reported or included as part of the questionnaire.

112. In some cases, heartburn, perianal burning, dry mouth, dizziness, headache and nausea have been reported, however these side effects were considered “mild and transient”.

113. No studies on pregnant women have been identified.

Menthol

114. JECFA established an Acceptable daily intake of 0-4 mg/kg bw/d for menthol in 1998, which was reconfirmed in 2018 (JECFA, 2018). This was based on a reduced survival rate in mice at 600 mg/kg bw/d in a two-year study, with a NOAEL of 380 mg/kg bw/d and the application of an uncertainty factor of 100. Although no reproductive toxicity studies were reported, when tested at maximum doses of 190-430 mg/kg bw/d mice, rats, hamsters, and rabbits; no teratogenic effects were observed.

Pulegone

115. Pulegone is a known hepatotoxin. Pulegone is oxidized by cytochrome P450 to reactive metabolites such as menthofuran that are partly responsible for the toxicity observed in mice, rats, and humans (CIR, 2001). A NOAEL of 37.5 mg/kg bw was established in a 3-month toxicity study by the National Toxicology Programme in rats due to liver and kidney toxicity (EMA. 2020). Based on the results of this study and following the application of an uncertainty factor of 50, the EMA stated that “an intake of pulegone + menthofuran up to 37.5 mg/person per day, for an adult of 50 kg body weight, can be accepted for herbal medicinal products as a lifetime intake”. Carcinogenicity studies were also reported in both rats and mice, where evidence of carcinogenicity at 6 mg/kg bw/d were reported in female rats as well as in male and female mice at 3 mg/kg bw/d. The EMA noted that “the mechanism considered to be related to the formation of reactive metabolites and sustained cytotoxicity. These findings require a long-term exposure to pulegone and/or menthofuran at doses, which are not relevant in the human situation.”

116. The Committee of Experts on Flavouring Substances (CEFS) of the Council of Europe CEFS set a TDI of 100 µg/kg bw based on the NOEL of 20 mg/kg bw/d in the 28 days oral toxicity study in rats with a safety factor of 200 (Council of Europe, 1997). Regulation (EC) 1334/2008 sets the following limits for the use of pulegone in food and beverages: 100 mg/kg for mint/peppermint containing alcoholic beverages; 20 mg/kg for mint/peppermint containing non-alcoholic beverages; 2000 mg/kg for “micro breath freshening confectionery”; 350 mg/kg for chewing gum; and 250 mg/kg for mint/peppermint containing confectionery, except “micro breath” products.

Menthone

117. In a 28-day study in rats, a dose dependent increase in phosphatase alkaline and bilirubin were reported following oral exposure to 0, 200, 400 or 800 mg/kg bw/d. The no-effect level for menthone was <200 mg/kg bw/d. (EMA, 2020).

Summary

118. This paper has provided background information on a range of herbal supplements that may be used during pregnancy in addition to those recommended by healthcare professionals. While there are currently no official guidelines addressing the use and safety of herbal food supplements during pregnancy, there is government issued guidance, regarding the use of herbal medicines[xi]. The advice is limited and covers herbal medicines, highlighting issues such as the lack of evidence on efficacy of these commodities as well as potential interaction with other medicines and generally includes pregnant and lactating women in the populations that should avoid herbal medicines. However, women are advised to speak to a qualified practitioner should they choose to use these therapies. It should be noted that women may use herbal dietary supplements in a similar way, for some of the purported benefits of these herbals.

119. Generally, although these supplements are often regarded by consumers to "safer" natural alternatives, some adverse effects have been reported. Overall, there is a lack of compositional information and in many cases, studies specifically addressing effects on pregnancy are lacking.

Questions for the Committee

120. Members are asked to consider the information provided and consider:

I. Which, if any, of the herbal supplements described above does the Committee consider should be chosen for full review regarding their effects on the health of women of childbearing age who are or plan to become pregnant?
II. Which, if any, of the compounds selected, would be a priority?
III. Based on their knowledge, do the Members have suggestions for additional herbal supplements that should be considered?
IV. Does the Committee have any other comments on this scoping paper?

Secretariat

October 2020

[xi] https://www.nhs.uk/conditions/pregnancy-and-baby/medicines-in-pregnancy/

https://www.nhs.uk/conditions/herbal-medicines/

References

Abdel-Aziz H, Nahrstedt A, Petereit F, Windeck T, Ploch M, Verspohl EJ (2005): 5-HT3 receptor blocking activity of arylalkanes isolated from the rhizome of Zingiber officinale. *Planta Med*, 71: 609-616.

Abdel-Aziz H, Windeck T, Ploch M, Verspohl EJ (2006): Mode of action of gingerols and shagaols on 5-HT3 receptors: binding studies, cation uptake by the receptor channel and contraction of isolated guinea-pig ileum. *Eur J Pharmacol*, 530: 136-143.

Akhtar MS, Khan QM, Khaliq T. (1985): Effects of Portulaca oleracaea (kulfa) and Taraxacum officinale (dhudhal) in normoglycaemic and alloxan-treated hyperglycaemic rabbits. J Pakistan Med Assoc; 35:207-210.

Alnaqeeb MA, Thomson M, Al-Qattan KK, Kamel F, Mustafa T, Ali M. *(*2003): Biochemical and histopathological toxicity of an aqueous extract of ginger. *Kuwait J Sci Eng*, 30: 35-48.

Anter J, Romero-Jiménez M, Fernández-Bedmar Z, Villatoro-Pulido M, Analla M, Alonso-Moraga A, et al. (2011): Antigenotoxicity, cytotoxicity, and apoptosis induction by apigenin, bisabolol, and protocatechuic acid. J Med Food, 14(3):276-283

Bamford DS, Percival RC, Tothill AU. (1970): Raspberry leaf tea: a new aspect to an old problem. Br J Pharmacol, 161-162

Barcz, E., Sommer, E., Nartowska, J., Balan, B.J., Chorostowska-Wynimko, J., Ewa Skopińska-Różewska, E., (2007): Influence of Echinacea purpurea intake during pregnancy on fetal growth and tissue angiogenic activity. Folia Histochemica et Cytobiologica 45 Suppl 1(I): S35-9. DOI: 10.5603/4486

Bishop JL, Northstone K, Green JR, Thompson EA. (2011): The use of Complementary and Alternative Medicine in pregnancy: Data from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Complement Ther Med*, 19(6):303-310

Briggs CJ and Briggs K (1997): Raspberry. *Can. Pharm. J.*, **130** (ISS April), 41-43.

Budzianowski J. (1997): Coumarins, caffeoyltartaric acids and their artifactual methyl esters from Taraxacum officinale leaves. Planta Medica; 63:288.

Burn JH and Withell ER (1941). A principle in raspberry leaves which relaxes uterine muscle. *The Lancet*, **1**, 1-3.

Chow G, Johns T, Miller S, C (2006): Dietary Echinacea purpurea during Murine Pregnancy: Effect on Maternal Hemopoiesis and Fetal Growth. Biol Neonate; 89:133-138. doi: 10.1159/000088795

CIR (2001): Final Report on the Safety Assessment of Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, Mentha Piperita

(Peppermint) Leaf, and Mentha Piperita (Peppermint) Leaf Water, *International Journal of Toxicology*, 20(3_suppl), pp. 61–73. doi: 10.1080/10915810152902592.

Council of Europe (1997): Committee of Experts on Flavouring Substances 41st meeting – RD 4.2/8-41. Datasheet on pulegone.

Cuzzolin L, Francini-Pesenti F, Verlato G, Joppi M, Baldelli P, Benoni G. (2010): Use of herbal products among 392 Italian pregnant women: focus on pregnancy outcome. *Pharmacoepidemiol Drug Saf*, 19(11):1151-1158

Ding, M., Leach, M., Bradley, H (2013).; The effectiveness and safety of ginger for pregnancy-induced nausea and vomiting: A systematic review. *Women and Birth* 26 e26–e30

Dissabandara DLO, Chandrasekara MS. *(*2007): Effects of prenatal ginger rhizome extract treatment on pregnancy outcome and postnatal development of Sprague Dawley rats. *Ceylon J Med Sci* 50: 1-7

Dove D, Johnson P. (1999): Oral evening primrose oil: its effect on length of pregnancy and selected intrapartum outcomes in low-risk nulliparous women. J Nurse Midwifery; 44(3):320-324

DTU Food Institute, (2018), The safety of pregnant women when ingesting ginger shots made from the root from real ginger (Zingiber officinale Roscoe). Available at: https://www.matportalen.no/verktoy/advarsler/article55242.ece/BINARY/Danske%20Tekniske%20Universitet%20-%20Risikovurdering%20av%20ingef%C3%A6r

Dugoua, J.J. (2010): Herbal Medicines and Pregnancy*, J Popul Ther Clin Pharmacol*, Vol 17(3): e370-e378; October 26, 2010

EMA (2020): Assessment report on Mentha x piperita L., folium and aetheroleum, available at: https://www.ema.europa.eu/en/medicines/herbal/menthae-piperitae-folium

EMA (2018): Assessment report on Oenothera biennis L. or Oenothera lamarckiana L., oleum. Available at: https://www.ema.europa.eu/documents/herbal-report/final-assessment-report-oenothera-biennis-l-oenothera-lamarckiana-l-oleum-revision-1_en.pdf

EMA (2014): Assessment report on Echinacea Purpurea (L.) Moench., herba recens. EMA/HMPC/557979/2013

EMA (2012): Assessment report on Zingiber Officinale Roscoe, rhizome; EMA/HMPC/577856/2010

EMA (2015): Assessment report on Matricaria recutita L., flos and Matricaria recutita L., aetheroleum, EMA/HMPC/55837/2011

EMA (2014): Assessment Report on Rubus idaeus L., folium. EMA/HMPC/44209/2012

EMA (2009): Assessment report on Taraxacum Officinale Weber ex Wigg., radix cum herba, EMA/HMPC/212897/2008

Everett DJ, Greenough RJ, Perry CJ, et al. (1988a): Chronic toxicity studies of Efamol evening primrose oil in rats and dogs. Med Sci Res; 16:863-864

Everett DJ, Perry CJ, Bayliss P. (1988b): Carcinogenicity studies of Efamol evening primrose oil in rats and mice. Med Sci Res; 16:865-866

Facchinetti F, Pedrielli G, Benoni G, Joppi M, Verlato G, Dante G, et al. (2012) Herbal supplements in pregnancy: unexpected results from a multicenter study. Hum Reprod, 27(11): 3161-3167

Flemming Bager, DTU Food Institute, (2018), The safety of pregnant women when ingesting ginger shots made from the root from real ginger (Zingiber officinale Roscoe). Available at: https://www.matportalen.no/verktoy/advarsler/article55242.ece/BINARY/Danske%20Tekniske%20Universitet%20-%20Risikovurdering%20av%20ingef%C3%A6r

Forster DA, Denning A, Wills G, Bolger M, McCarthy E. (2006): Herbal Medicine use during pregnancy in a group of Australian women. BMC Pregnancy Childbirth, 6:21-30

Gallo M, Sarkar M, Au W, Pietrzak K, Comas B, Smith M, et al. (2000): Pregnancy outcome following gestational exposure to Echinacea: a prospective controlled study. *Arch Intern Med*, 160(20):3141-3143

Ganzera M, Schneider P, Stuppner H. (2006): Inhibitory effects of the essential oil of chamomile (Matricaria recutita L.) and its major constituents on human cytochrome P450 enzymes. Life Sci, 78(8):856-861

Goldberg ED, Amosova EN, Zueva EP, Razina TG, Krylova SG, Reikhart DV, (2004): Effects of Extracts from Medicinal Plants on the Development of Metastatic Process. Bull Exp Biol Med; 138(3):288-294.

Graham RCB, Noble RL. (1955): Comparison of in vitro activity of various species of Lithospermum and other plants to inactivate gonadotrophin. Endocrinology, 56:239-247

Hänsel R, Keller K, Rimpler H, Scheidner G. Hagers (1993): Handbuch der pharmazeutischer Praxis, Springer-Verlag, Berlin, 929-936

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

JECFA (2018): Evaluation of certain food additives, Eighty sixth report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series 1014. Available at: https://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=1519

Johnson JR, Makaji E, Ho S, Boya Xiong, Crankshaw DJ, Holloway AC. (2009) Effect of maternal raspberry leaf consumption in rats on pregnancy outcome and

the fertility of the female offspring. Reprod Sci. Jun; 16(6): 605-9. doi: 10.1177/1933719109332823.

Kalantari H, Dashtearjandi AA, Kalantar E. (2009): Genotoxicity study of Hypiran and Chamomilla herbal drugs determined by in vivo supervital micronucleus assay with mouse peripheral reticulocytes. Acta Biol Hung, 60(2):177-183

Keane B, Collier MH, Shann JR, Rogstad SH. (2001): Metal content of dandelion Taraxacum officinale leaves in relation to soil contamination and airborne particulate matter. Sci Total Environ; 281:63-78

Koo HN, Hong SH, Song BK, Kim CH, Yoo YH, Kim HM. Sci (2004): Taraxacum officinale induces cytotoxicity through TNF-and IL-1secretion in Hep G2 cells. Life; 74:1149-1157.

Kristó ST, Ganzler K, Apáti P, Szöke E, Kéry A. (2002): Analysis ofantioxidant flavonoids from Asteraceae and Moraceae plants by capillary electrophoresis. Chromatographia; 56:121-126

Krüth, P., Brosi, E., Fux,R, Klaus Mörike, K., Gleiter, C.H.,(2004): Ginger-associated overanticoagulation by phenprocoumon. *The Annals of Pharmacotherapy*, 38(2):257-60. doi: 10.1345/aph.1D225.

Mallory, J. (2018): Integrative Medicine (Fourth Edition) Pages 535-541.e1. Available online: https://doi.org/10.1016/B978-0-323-35868-2.00053-0

McKeown, K.A. (1999): A review of the taxonomy of the genus Echinacea. p. 482–489. In: J. Janick (ed.), Perspectives on new crops and new uses. ASHS Press, Alexandria, VA.

Mengs U, Clare CB, Poiley JA. (1991): Toxicity of Echinacea purpurea. Acute, subacute and genotoxicity studies. Arzneimittelforschung. Oct;41(10):1076-81. PMID: 1799389.

Moussally K, Oraichi D, Bérard A. (2009): Herbal products use during pregnancy: prevalence and predictors. Pharmacoepidemiol Drug Saf, 18(6):454-461

Nagabhushan M, Amonkar AJ, Bhide SV. (1987): Mutagenecity of gingerol and shagaol and antimutagenecity of zingerone in salmonella/microsome assay. Cancer Lett, 36: 221-233.
Nagabushan M, Bhide SV. (1985): Mutagenecity of chili extract and capsaicin in short-term trials. Environ Mutagen, 7: 881-888.

National Centre for Complementary and Integrative Health(2020): Dandelion: https://www.nccih.nih.gov/health/dandelion.

National Centre for Complementary and Integrative Health, (2020): https://www.nccih.nih.gov/health/echinacea. Accessed 09/10/2020

Neef H, Cilli F, Declerck PJ, Laekeman G. (1996): Platelet antiaggregating activity of Taraxacum officinale Weber. Phytother Res 10:138-140.

NHS (2020): Foods to Avoid in pregnancy. Available at: https://www.nhs.uk/conditions/pregnancy-and-baby/foods-to-avoid-pregnant/

NHS (2018): Herbal Medicines. https://www.nhs.uk/conditions/herbal-medicines/

NHS (2019): Medicines in pregnancy -Your pregnancy and baby guide. https://www.nhs.uk/conditions/pregnancy-and-baby/medicines-in-pregnancy/

Nirmala K, Krishna TP, Polasa K. (2007) In vivo Antimutagenic potential of ginger in the formation and excretion of urinary mutagens in rats. Int J Cancer Res, 3: 134-142.

Nordeng H, Havnen GC. (2004). Use of herbal drugs in pregnancy: a survey among 400 Norwegian women. Pharmacoepidemiol Drug Saf. 2004 Jun;13(6):371-80.

Nordeng H, Bayne K, Havnen GC, Paulsen BS. Use of herbal drugs during pregnancy among 600 Norwegian women in relation to concurrent use of conventional drugs and pregnancy outcome. Complement Ther Clin Pract (2011) , 17(3):147-151

Olson, A., DeGolier, T. (2016): Contractile activity of Rubus idaeus extract on isolated mouse uterine strips. Bios, Vol. 87, No. 2 (May 2016), pp. 39-47 https://www.jstor.org/stable/24878630

Perri D, Dugoua JJ, Mills E, Koren G. (2006): Safety and efficacy of Echinacea (Echinacea angustafolia, E. purpurea and E. pallida) during pregnancy and lactation. Can J Clin Pharmacol, 13(3): e262-267

Qiu JX, Zhou ZW, He ZX, Zhang X, Zhou SF, Zhu S. (2015): Estimation of the binding modes with important human cytochrome P450 enzymes, drug interaction potential, pharmacokinetics, and hepatotoxicity of ginger components using molecular docking, computational, and pharmacokinetic modelling studies. Drug Des Devel Ther. 9:841-866. Published 2015 Feb 16. doi:10.2147/DDDT.S74669

Reider N, Sepp N, Fritsch P, Weinlich G, Jensen-Jarolim E. (2000): Anaphylaxis to camomile: clinical features and allergen cross-reactivity. Clin Exp Allergy, 30(10):1436-1443

Roe, F. J. C., A. K. Palmer, A. N. Worden, and N. J. VanAbbe. (1979): Safety evaluation of toothpaste containing chloroform. I. Long term studies in mice. J. Environ. Pathol. Toxicol. 2:799–819.

Romero-Jiménez M, Campos-Sánchez J, Analla M, Muñoz-Serrano A, Alonso-Moraga A. (2005): Genotoxicity and anti-genotoxicity of some traditional medicinal herbs. Mutat Res. ;585(1-2):147-55. doi: 10.1016/j.mrgentox.2005.05.004. PMID: 16005256.

Rong et. Al (2009): A 35-day gavage safety assessment of ginger in rats, *Regul Toxicology Pharmacol*.;54(2):118-23. doi: 10.1016/j.yrtph.2009.03.002.

SACN (2011)The influence of maternal, fetal and child nutrition on the development of chronic disease later in life:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/339325/SACN_Early_Life_Nutrition_Report.pdf

Saulnier P, Crosbie L, Duttaroy AK. (2005): Inhibitory effect of aqueous extracts of some herbs on human platelet aggregation in vitro. Platelets; 8:469-473.

Schilcher H, Imming P, Goeters S (2005) Active chemical constituents of Matricaria chamomilla L. syn. Chamomilla recutita (L.) Rauschert. In: Franke R, Schilcher H (eds) Chamomile industrial profiles. CRC Press, Boca Raton, pp 65–8

Sigstedt SC, Hooten CJ, Callewaert MC, Jenkins AR, Romero AE, Pullin MJ, Kornienko A, Lowrey TK, Slambrouck SV, Steelant WF. (2008): Evaluation of aqueous extracts of Taraxacum officinale on growth and invasion of breast and prostate cancer cells. Int J Oncology; 32:1085-1090.

Sivaswami SN, Balachandran B, Balanehru S, Sivaramakrishnan VM. (1991): Mutagenic activity of South Indian food items. Indian J Exper Toxicol, 29: 730-737.

Soudamini KK, Unnikrishnan MC, Sukumaran K, Kuttan R. (1995): Mutagenecity and anti-mutagenecity of selected spices. Indian J Physiol Pharmacol, 39: 347-353.

Tsialtas JT, Kassioumi M, Veresoglou DS. (2002): Evaluating Leaf Ash Content and Potassium Concentration as Surrogates of Carbon Isotope Discrimination in Grassland Species. J Agronomy Crop Sci; 188:168-175.

UKTIS (2020): Best Use of Medicines in Pregnancy. https://www.medicinesinpregnancy.org/Medicine--pregnancy/

Weidner, M.S., Sigwart, K. 2001): Investigation of the teratogenic potential of a Zingiber officinale extract in the rat. *Reproductive Toxicology* 15, (75–80

Westfall RE. (2004): Use of anti-emetic herbs in pregnancy: women`s choices, and the question of safety and efficacy. Complement Ther Nurs Midwifery; 10: 30-36.

Wilkinson, J.M. (2000): Effect of ginger tea on the fetal development of Sprague-Dawley rats, *Reprod Toxicol*. Nov-Dec ;14(6):507-12. doi: 10.1016/s0890-6238(00)00106-4.

Wolbis M and Krolikowska M. (1985): Polyphenolic compounds of dandelion (Taraxacum officinale). Acta Pol Pharm; 42:215.

Wolbis M, Królikowska M, Bednarek P. (1993): Polyphenolic compounds in Taraxacum officinale. Acta Pol Pharm; 50:153-158.

Yang, J., Cui, J., Han, H., Chen, J., Yao, J., Liu. Y. (2020): Food Sci. Technol vol.40 no.1 Campinas

Zheng J, Pistilli MJ, A, Holloway AC, Crankshaw DJ. (2010): The effects of commercial preparations of red raspberry leaf on the contractility of the rat's uterus in vitro. Reproductive Sciences, (17)5:494-501