

Annex B - Summary of Studies

In this guide

[In this guide](#)

- 1. [Introduction - Second Draft Statement on the Safety of Ginger Supplement use in Pregnancy](#)
- 2. [Annex A - Second Draft Statement on the Safety of Ginger Supplement Use in Pregnancy](#)
- 3. [Annex A - Information on ginger](#)
- 4. [Annex A - Exposure](#)
- 5. [Annex A - Conclusions of the Committee](#)
- 6. [Annex A - References](#)
- 7. [Annex B - Summary of Studies](#)
- 8. [Annex C - Assessment of Exposure](#)

Human Studies

Author/Date	Study type	Study size/No. of Patients at End	Exposure (ginger dose/day)	Study period	Length of Treatment (days)	Main outcome measures	Main results
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Chittumma <i>et al.</i> , 2007	Randomized double-blind controlled trial.	126/123	Ginger powder capsules (325 mg ×2, 3x/d, = 1950 mg/day)	4 days	4	Change in nausea and vomiting scores (3 symptoms on Rhodes index); occurrence of side- effects	Results showed ginger signific more effectiv relievin than vit B6 (p <
Ensiyeh <i>et al.</i> , 2005	Double-blind randomised controlled trial.	70/69	Ginger powder capsules (500 mg 2×/d =1000 mg/day)	3 months	4	Severity of nausea (VAS 0–10); number of vomiting episodes; general response to treatment (5-item Likert scale); occurrence of side- effects or adverse pregnancy outcome	two spontane abortion ginger 1 in B6 no cong anomal observe babies to term

Fischer-Rasmussen <i>et al.</i> , 1991	Double-blind randomised crossover trial	30/27	Ginger powder capsules (250 mg 4 times per day = 1000 mg/day)	11 days	4	Preference of treatment period; relief scores (4- point scoring system); outcome of pregnancy	One spontaneous abortion elected adverse effects observed remain subject
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Portnoi, 2003	Not specified	187 pregnant women	Various, not specified	up to 12 months post birth	Minimum of 3 days	Safety and effectiveness of ginger for nausea and vomiting of pregnancy (NVP).	Three major congenital malformations were reported in the control group, ventricular septal defect (VSD), lung abnormality, and kidney abnormality (pelvic)
							One incident of idiopathic central precocious puberty at age 2 years. No significant differences between the two groups in terms of births, spontaneous abortions, stillbirths, therapeutic abortions, birth weight, or gestational age.

Smith, 2004	Randomized, controlled equivalence trial	291 women, less than 16 weeks pregnant	1.05 g ginger	3 weeks	3 weeks	Ginger versus B6 for the treatment of nausea or vomiting in pregnancy	Three spontaneous abortions; ginger reduced 9 abortions; B6 group
Vutyavanich, 2001	Double blind	32	Ginger powder capsules (250 mg 4x/day =1000 mg/day)	5 months	4	Severity of nausea (VAS 0-10); number of vomiting episodes; general response to treatment after 1 week (5-item Likert scale); occurrence of side-effects and adverse pregnancy outcomes	Ginger significantly more effective than the placebo in relieving severity of nausea; p = 0.014

Willetts <i>et al.</i> , 2003	Double-blind randomised placebo-controlled trial	120/99	Ginger extract capsules (125 mg 4x/d =1000 mg/day)	8 months ⁴	Used RINVR to measure frequency, duration, distress caused by nausea, vomiting and retching; long term follow-up for birth outcome	Three spontaneous abortions observed; ginger
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Human studies - Platelet Aggregation

Author/date	Study design	Population/study size	Study Duration	Exposure	Outcome
Bordia <i>et al.</i> , 1997	Placebo controlled trial	Patients with confirmed myocardial infarction N = 60	3 months. Outcomes measured at: baseline, 1.5 months and 3 months.	Dose: 4g per day Unstandardised capsules	Platelet aggregation- Agonist(s): A Epi;
Bordia <i>et al.</i> , 1997	No data.	No data.	No data.	No data.	Fibrinogen;
Bordia <i>et al.</i> , 1997	No data.	No data.	No data.	No data.	Fibrinolytic a

Bordia <i>et al.</i> , 1997	No data.	20	1 day. Outcomes measured at: baseline, 4 hours post- consumption	10 g single dose. Unstandardised capsules	Platelet aggregation - Agonist(s): AA; Epi
Jiang <i>et al.</i> , 2004	Randomized, open label, three-way crossover trial	Healthy male volunteers Age: 20-36 N =12	Total study period: 3x13 days, 14 days washout period between each study period.	Dose: 3.6g (3x 0.4g, 3x per day) Unstandardized capsules Consumed with 25 mg dose of rac-warfarin, consumed once per study period.	Platelet aggregation Agonist: AA; Plasma warfarin enantiomer p binding & wa enantiomer concentration Urinary S- 7-hydroxywa
Lumb. 1994	Randomised, double- blinded placebo- controlled crossover trial	Healthy male volunteers N=8	Total study period: 2 x 1 day, at least 14 days washout period. Outcomes measured immediately before, 3 hrs, and 24 hrs post consumption of ginger	Dose: 2g (4 x 500 mg) dried ginger per day Unstandardized capsules	Platelet aggregation - Agonist(s): AA; collagen, ristocetin ADP; Bleeding time Platelet count Thromboelastography

Rubin <i>et al.</i> , 2019	Case report	Female, 70 yrs	No data.	48 mg daily Chewable ginger supplement for approx. 1 month	INR - 8.0 approx. month after t ginger suppl
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Srivastava 1989	Open-label single-arm trial	Healthy female volunteers, N = 7	Total study period: 7 days. Outcomes measured at baseline and 7 days post- consumption	Dose: 5g raw ginger per day	Platelet thromboxane B2 production
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Verma <i>et al.</i> , 1993	Randomised placebo controlled trial	Healthy male volunteers; N = 20	Total study period: 14 days, high calorie diet for first 7 days, high- calorie diet and ginger/placebo consumed for next 7 days. Outcomes measured at baseline, 7, and 14 days	Dose: 5g (4 x 625 mg, twice per day); dry ginger powder - Unstandardized capsules Consumed with 100g (2x50g) butter, 2 cups of milk, 8 slices of bread.	Platelet aggr Agonist(s): A Epi
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Young <i>et al.</i> , 2006	Not specified	20	72 days	1 g ginger (+ 10 mg nifedipine)	Synergistic e ginger and n on anti-plate aggregation normal huma volunteers an hypertensive patients.
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***In vitro* studies**

Author	Test System	Exposure	Characterisation of test substance	Main outcome measure	Outco
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No data.	No data.	No data.	No data.	No data.	Characterization of cellular and protein content dose manner (concentration μ M)
No data.	No data.	No data.	No data.	No data.	Significant decrease in cardiomyocyte differentiation for a concentration exceeding 100 μ M in ES cells
No data.	No data.	No data.	No data.	No data.	Significant decrease in cellular and protein content cell-cultured cardiomyocytes with 6-gingerol concentration exposure
Nakamura & Yamamoto (1982)	Escherichia coli Hs30	Not specified	Juice of ginger rhizome, 6-gingerol	Mutagenicity	gingerol suppresses spontaneous mutagenesis of gingerol mutagenesis isolates

Nakamura & Yamamoto 1983	Escherichia coli Hs30	Not specified	6-shogaol, 6-gingerol	Mutagenicity	[6]-S 104 t muta conc 700u [6]-g
Nirmala <i>et al.</i> , 2007	Wistar rats, male	Salmonella typhimurium strains TA 98 and TA 100	Ginger paste and powder, unboiled, boiled, unfried, fried Ames test: Ginger paste: 1, 2 and 3 mg; powder: 0.5, 1 and 1.5 g	Anti-mutagenicity	Anti-poten unalt treat ginger
Plengsuriyakarn <i>et al.</i> , 2012	Cholangiocarcinoma (CCA) cell line 6 (CL-6), hepatocarcinoma (HepG2) and normal human renal epithelium (HRE)	1.95, 3.90, 7.81, 15.62, 31.25, 62.5, 125, and 250 µg/ml	Crude ethanolic ginger extract	Cytotoxicity	IC50 cytot 10.9 53.1
Sivaswami <i>et al.</i> , 1991 (Abstract)	Salmonella typhimurium strains TA 98, TA 100 and TA 1535	Unknown	Essential oil from ginger	Mutagenicity	Non
Soudamini <i>et al.</i> , 1995	Salmonella typhimurium strains TA 100, 98 and TA 1535	25 and 50 mg/plate	ethanolic mixture of powdered ginger	Mutagenicity	muta both and both conc

Zaeoung <i>et al.</i> , 2005	breast (MCF7) and colon (LS174T) cell lines	Not specified	aqueous extract and volatile oils	Cytotoxicity	IC50 µg/m
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In vivo studies

Author	Test System	Study size	Exposure	Characterisation of test substance	Duration
Alnaqeeb <i>et al.</i> , 2003 (abstract)	Rats, female	Unknown	Oral and intraperitoneal. 50 mg/kg and 500 mg/kg	Aqueous ginger extract	28 days
Dissabandara & Chandrasekara, 2007	Sprague-Dawley rats	15 in 3 groups, otherwise not specified	Oral: 500 mg/kg/day and 1000 mg/kg/day during days 5 to 15 of gestation	Powdered ginger extract	Animals treated with ginger for 10 days

ElMazoudy and Attia, 2018 (abstract only)	ICR mice	Unknown	250, 500, 1000, or 2000 mg/kg bw/d aqueous ginger extract.	Powdered dried ginger root	35-day treatment study; 20 day study (antifertility and abortifacien loss)
Hosseini <i>et al.</i> , 2015 (abstract only)	Rats, female and male offspring	72 (groups of 9)	Oral: 50, 100 and 200 mg/kg bw during neonatal and perinatal periods	Alcoholic ginger extract	Unknown

Jeena <i>et al.</i> , 2011	Wistar rat	30	Oral: 100, 250, and 500 mg/kg Ginger essential per day once oil daily	13 weeks
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Malik and Sharma, 2011	Wistar rat, male	Not specified	gastric gavage: 250, 500 and 1000 mg/kg, (corresponding to 5, 10 and 20% of the NOAEL of the lyophilised ginger powder (5000 mg/kg)	Lyophilised ginger juice powder	Experiment 2: 8 weeks. Exp 1&2 not specified
Plengsuriyakarn <i>et al.</i> , 2012	OV and nitrosamine (OV/DMN)-induced CCA hamsters	90	1000, 3000, and 5000 mg/kg bw/d	No data.	30 days
Rong <i>et al.</i> , 2009	Sprague-Dawley rats, male and Female	40	Gavage: 500, 1000 and 2000 mg/kg bw/day	Powdered Japanese ginger,	37

Shalaby and
Hamowieh,
2010

Sprague Dawley 120
rats,

Oral, 5 to 17.5
g/kg bw

water or
methanolic ginger 65 days
extract

No data. No data. No data. No data. No data. No data.

No data.	No data.	No data.	100 and 200 mg/kg bw for 65 consecutive days and water extracts at doses of 150 and 300 mg/kg bw	No data.	No data.
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Weidner & Sigwart, 2001	Wistar rats, pregnant female	176 (88 Females)	Gastric intubation: 100, 333 and 1000 mg/kg from days 6-15	EV.EXT 33, a patented Zingiber officinale extract (comprising 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol, and 8-shogaol (1.9 w/w of the extract))	21 days
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Wilkinson 2000	Sprague-Dawley rats, F	43	Oral, drinking water on days 6-15	20 g/L or 50 g/L ginger tea	20 days
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Effect on CYPs and prostaglandin activity

Author	Test System	Exposure	Characterisation of test substance	Main outcome measure	Outcome
Dugasani <i>et al.</i> , 2010	Mouse leukaemic monocyte (RAW 264.7) macrophages and human polymorphonuclear neutrophils (PMN)	1, 3 and 6 uM	[6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol	Compare the antioxidant and antiinflammatory activities of gingerols and their natural analogues to determine their structure-activity relationship and molecular mechanisms.	Dose dependant inhibition of activated PGE2 release. Inhibition reached 56, 66, 73 and 87%, respectively at 6uM

Jolad et al., 2004	HL-60 cells	Not specified	Ginger constituents: gingerols, shogaols, 3-dihydroshogaols, gingerdiols	Effects of ginger components on LPS-induced PGE2 production	No cytotoxicity demonstrated
Jolad et al., 2005	HL-60 cells	Not specified	Ginger constituents containing gingerols, shogaols, 3-dihydroshogaols, gingerdiols	Effects of ginger components on LPS-induced PGE2 production	Inhibition of LPS-stimulated PGE2 production (IC50 = 0.008 ug/ml with Ginger fractions)
Kim et al., 2012	Human liver microsomes	0.05–5 ug/ml	Aqueous ethanolic ginger extract (30% EtOH)	Inhibitory effect on CYP450-mediated drug metabolism	Concentration dependent inhibitory effects on CYP2C19; IC50 value 3.8 g/ml
Kimura et al., 2010	Human CYP3A4 and CYP2C9 microsomes	Not specified		Inhibitory effect on CYP3A4 and CYP2C9 activity	significant inhibition of CYP3A4 IC50 5.1ug/ml CYP2C9 IC50 (10ug/ml) activity

Lantz <i>et al.</i> , 2007	U937 cells	0.1 ug/ml for 6 hrs	Ginger extract and mixtures of 6- , 8- 10-gingerols and 6-, 8-, 10- shogaols	Effect on inflammatory mediator production	No effect on COX-2 expression
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Mukkavilli
et al.,
2014

Human liver
microsomes

Ginger
extract: 500
mg/ml
(containing
15 mg/
ml 6G, 3.4
mg/ml 8G,
3.9 mg/ml
10G, 3.0
mg/ml 6S);
All
individual
components
of gingerols
assessed at
100 mM
(equivalent
to 29 mg/ml
6G, 32
mg/ml 8G,
35 mg/ml
10G and
28 mg/ml of
6S)

Ginger extract:
(containing 6-
Gingerol, 8-
Gingerol, 10-
Gingerol, 6-
Shogaol). All
individual
components of
gingerols were
assessed at 100
mM
equivalent to 29
mg/mL 6G, 32
mg/mL 8G, 35
mg/mL 10G and
28 mg/mL of 6S.

Effect of ginger
extract and
major
constituents on
CYP P450
enzyme activity

Inhibition of
CYP1A2 (IC₅₀ =
-
221.5 mg/
by ginger
extract. No
effect on
CYP2A6;
maximum
inhibition of
CYP2B6: IC₅₀ =
- 22 mg/ml
IC₅₀ - 122
mg/mL
against
CYP2C8
in the
presence of
amodiaquin
IC₅₀ - 93.5
mg/mL
against
CYP2C9,
in the
presence of
diclofenac
Inhibition of
CYP3A in the
presence of
testosterone
no effect in
the presence
of midazolam

Effect on Platelet Aggregation

Author	Test System	Study size	Exposure	Characterisation of test substance	Main outcome measure	Outcomes
Srivas, 1984	Human platelets and rat aorta	No data.	15-20 ul (concentrations not given)	Ginger extracts in water, n-hexane, chloroform, and ethyl acetate	Effect of ginger extracts on <i>in vitro</i> platelet aggregation	Inhibition of arachidonic acid epoxide formation (ADP, collagen induced platelet aggregation)
Srivastava, 1986	Platelet rich plasma (no further information given)	No data.	10-20 ul (concentrations not given)	No data.	Effect of ginger and components on platelet aggregation and eicosanoid biosynthesis	Reduction of thromboxane formation from exogenous AA; inhibition of ADP, collagen induced platelet aggregation

Srivastava 1989	Open-label single-arm trial	Healthy female volunteers, N = 7	Total study period: 7 days. Outcomes measured at baseline and 7 days post- consumption	Dose: 5g raw ginger per day	Platelet thromboxane B2 production	Ginger cons resu 37% inhib thro B2 proc (p<
Suekawa <i>et al.</i> , 1986 (abstract only)	Rat hind paw and aorta, rabbits	Unknown	Unknown	6-shogaol	Effect of 6- shogaol on arachidonic acid cascade	Inhib carn indu swe hinc rats arac acid indu plat agg in ra Inhib pros 12 (rele rat a Poss caus COX inhib

Thomson <i>et al.</i> , 2002	Sprague- Dawley rats, Adult, F; <i>ex vivo</i>	36	50 mg/kg or 500 mg/kg daily by gavage or intraperitoneally (IP) for 4 weeks	Aqueous ginger extract, equivalent of 500 mg/ml	<i>ex vivo</i> effect of aqueous extract of ginger on the synthesis of thromboxane- B2, prostaglandin- E2, and cholesterol, triglyceride levels in the serum of normal rats	Serum reduced both levels dose- signifi- cantly reduced serum both and non- signifi- cantly reduced the TXB2 observed when was IP by signifi- cantly different from group
No data.	No data.	No data.	No data.	No data.	No data.	Signifi- cantly reduced levels cholesterol rats highly No s char trigly levels either either or IP

Herb-drug interactions

Author	Test System	Study size	Exposure	Characterisation of test substance	Duration	Main outcome measure	Outcome
Al-Omari <i>et al.</i> , 2012	Albino rat, M	30: 5 groups of 6; 72: 12 groups of 6;	25, 50 and 100 mg/kg bw by gavage; single dose (50 mg/kg bw)and up to one week	Ginger crude extract	Multiple dose: 2 weeks; single dose: 1 week	Effect on glibenclamide and insulin; hypoglycaemic and antihyperglycemic effects in normoglycemic- and streptozotocin-induced (STZ) diabetic rats	Significant decrease in blood glucose levels in normoglycemic rats; significant decrease in blood glucose levels in STZ diabetic rats
Egashira <i>et al.</i> , 2012	Sprague-Dawley rat, M (7 weeks old)	Not specified	10 mL/kg orally	50% ginger juice	1-3 days	interaction between ginger juice and tacrolimus	Significant increase in tacrolimus blood concentration in rats with ginger juice compared to those without oral

Okonta
et al.,
2008

Rabbits
(3F, 2M) 5

1 ml/kg,
orally

Ginger extract

3 days

Effect of ginger on
the
pharmacokinetics
of metronidazole

Sig
inc
abs
pla
life
dec
the
rat
and
of
me