Annex B

Annex B: Summary of Studies

Traditional/culinary uses of ginger

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 result
Chittumma *et al.*, 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.	Result showe ginger signifi more effecti relievi than v B6 (p

Ensiyeh *et al.,* 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 sponta aborti ginger 1 in B6 no cor anoma observ babies to terr
Fischer-Rassmussen *et al*., 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 sponta aborti electe advers effects observ remain subjec

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 malfor were r in the group, ventric septal (VSD), lung abnorr and ki abnorr (pelvie One in of idio centra precoc puber age 2 No sig differe betwe two gr terms births, sponta aborti stillbir therap aborti birth w or ges age.

Smith, 2004	Randomized, controlled equivalence trial.	291 women, less than 16 weeks pregnant.	1.05 g ginger.	3 weeks.	3 weeks.	Ginger verses B6 for the treatment of nausea or vomiting in pregnancy.	Three sponta abortio ginger 9 abor B6 gro
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 signifi more effecti the pla relievi severi nause pregna = 0.01

Human studies – Platelet Aggregation

Author/date	Study design	Population/study size	Study Duration	Exposure	Outcome

Bordia *et al.,* 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 aggr Agonist(s): Al Epi;
Bordia *et al.,* 1997	NA	NA	NA	NA	Fibrinogen;
Bordia *et al.,* 1997	NA	NA	NA	NA	Fibrinolytic a
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 aggr Agonist(s): A collagen, rist ADP; Bleedin Platelet coun Thromboelas

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 thror B2 productio
Young *et al.,* 2006	Not specified.	20	72 days.	1 g ginger (+ 10 mg nifedipine).	Synergistic e ginger and ni on anti-platel aggregation i human volun hypertensive

In vitro studies

Author	Test System	Exposure	Characterisation of test substance	Main outcome measure	Outcome

In vivo studies

Author	Test System	Study size	Exposure	Characterisation of test substance	Duration	Main outcome measure	Outcom
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.	Reproductive and developmental toxicity.	Embryo loss in t treated groups 2 that of t controls Exposed foetuses found to significa heavier control. gross structur malform observe

Effect on CYPs and prostaglandin activity

Author	Test System	Exposure	Characterisation of test substance	Main outcome measure	Outcome

Effect on Platelet Aggregation

Author	Test System	Study size	Exposure	Characterisation of test substance	Main outcome measure	Outcome

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 consumptio resulted in a 37% inhibition of thromboxan B2 production (p<0.01).

Herb-drug interactions

Author	Test System	Study size	Exposure	Characterisation of test substance	Duration	Main outcome measure	Outcome

Extracts and concentrates of ginger

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

Laekman et al., 2021	Observational study, clinical trial.	51/44.	maximum of 2 tablets of 50 mg EXT.GR10 a day [limited data on actual amount administered].	During pregnancy.		Patient satisfaction pregnancy complication (including hypertension and diabetes and birth complication (including stillbirth, premature delivery, low birth weight)
Willetts *et al.,* 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.

Human studies – Platelet Aggregation

Author/date	Study design	Population/study size	Study Duration	Exposure	Outcome

Bordia *et al.,* 1997	NA	20	1 day. Outcomes measured at: baseline, 4 hours post-consumption.	10 g single dose. Unstandardised capsules.	Platelet aggregation Agonist(s): A and Epi.
Jiang *et al.,* 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) ginger extract Unstandardized capsules Consumed with 25 mg dose of rac-warfarin, consumed once per study period.	Platelet aggregation Agonist: AA Plasma warf enantiomer protein binding & warfarin enantiomer concentrati Urinary S-7-hydroxywar

Rubin *et al.*, 2019	Case report.	Female, 70 yrs.	NA	48 mg daily Chewable ginger supplement for approx. 1 month.	INR - 8.0 ap 1 month aft taking ginge supplement
Verma *et al.,* 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 aggregation Agonist(s): A and Epi

In vitro studies

Author	Test System	Exposure	Characterisation of test substance	Main outcome measure	Out
Abudayyak *et al.,* 2015	Ames: Salmonella typhimurium TA98 and TA100 strains; Cytotoxicity assay: Rat kidney NRK-52E cell line.	Cytotoxicity assay: (0.75, 1.50, 3.00, 6.00, 12.00, 25.00, 50.00, and 75.00 mg/ml, genotoxicity: 0.78, 1.56, 3.13, 6.25, 12.50, and 25.00 mg/ml.	Aq, chloroform and MeOH ginger extracts.	Cytotoxicity and genotoxicity.	Chlo extr IC50 mg/ extr mut conc agai strai pres mix.
Mohammed *et al.,* 2016	chick embryonic heart micromass; mouse D3 embryonic stem cell systems (ESD3).	0.75–100 uM Micromass assay: 6 days, ESD3: 12 days.	6-gingerol.	Embryotoxicity.	no s char cont cellu or cl tota cont ging prim emb card
NA	NA	NA	NA	NA	inhib cont activ 12.5

NA	NA	NA	NA	NA	Char cellu and cont dose man conc µM).
NA	NA	NA	NA	NA	Sign decr card diffe for a conc exce in ES
NA	NA	NA	NA	NA	Sign decr cellu and cont cell- card with 6-gi conc expo
Nakamura & Yamamoto (1982)	Escherichia coli Hs30.	Not specified.	Juice of ginger rhizome, 6-gingerol.	Mutagenicity.	ging supr spon mut ging mut isola

Nakamura & Yamamoto 1983	Escherichia coli Hs30.	Not specified.	6-shogaol, 6-gingerol.	Mutagenicity.	[6]-S 104 mut conc 700 ging
Nirmala *et al.,* 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- pote unal trea ging
Plengsuriyakarn *et al.,* 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 cyto 10.9 53.1
Sivaswami *et al.,* 1991 (Abstract)	Salmonella typhimurium strains TA 98, TA 100 and TA 1535.	Unknown.	Essential oil from ginger.	Mutagenicity.	Non
Soudamini *et al.,* 1995	Salmonella typhimurium strains TA 100, 98 and TA 1535.	25 and 50 mg/plate.	ethanolic mixture of powdered ginger.	Mutagenicity.	mut both and both conc

Zaeoung *et al.,* 2005	breast (MCF7) and colon (LS174T) cell lines.	Not specified.	aqueous extract and volatile oils.	Cytotoxicity.	IC50 µg/m

In vivo studies

Author	Test System	Study size	Exposure	Characterisation of test substance	Duration
Alnaqeeb *et al.,* 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 *et al.,* 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 *et al.*, 2011	Wistar rat.	30.	Oral: 100, 250, and 500 mg/kg per day once daily.	Ginger essential oil.	13 weeks.

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).	Lyophilsed ginger juice powder.	Experiment 2: 8 weeks. Exp 1&2 no specified.
Peneme et al., 2023	Swiss mice.	6	5000 mg/kg aqueous ginger extract.	Ginger powder extracted into water.	OECD guideline no. 423.
NA	NA	20	17 β-oestradiol, (1 mg/kg) or ginger extract (300 or 600 mg/kg) per day.	Ginger powder extracted into water.	2 weeks.
Plengsuriyakarn *et al.,* 2012	OV and nitrosamine (OV/ DMN)-induced CCA hamsters.	90	1000, 3000, and 5000 mg/kg bw/d.	NA	30 days.

Rong *et al.*, 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 rats.	120	Oral, 5 to 17.5 g/kg bw.	water or methanolic ginger extract.	65 days.

NA	NA	NA	NA	NA

NA	NA	NA	100 and 200 mg/kg bw for 65 consecutive days and water extracts at doses of 150 and 300 mg/kg bw.	NA	NA
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.

Effect on CYPs and prostaglandin activity

Author	Test System	Exposure	Characterisation of test substance	Main outcome measure	Outcome
Dugasani *et al.*, 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 activated PGE2 relea Inhibition reached 5 66, 73 and 87%, respective 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 cytotoxicit demonstra
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 LPS-stimulated PGE2 production (IC50 = 0. 0.08 ug/m with Ginge 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.	Concentra dependen inhibitory effects on CYP2C19; IC50 value 3.8 g/ml.
Kimura *et al.*, 2010;	Human CYP3A4 and CYP2C9 microsomes.	Not specified.	NA	Inhibitory effect on CYP3A4 and CYP2C9 activity.	significant inhibition CYP3A4 IC 5.1u g/ml CYP2C9 IC (10ug/ml) activity.
Lantz *et al.*, 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 COX-2 expressio

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 CYP1A2 (IC - 221.5 mg by ginger extract. No effect on CYP2A6; maximum inhibition CYP2B6: IC - 22 mg/m IC50 - 122 mg/mL against CYP2C8 in the presence amodiaqui IC50 - 93.5 mg/mL against CYP2C9, in the presence diclofenac Inhibition CYP3A in t presence testostero no effect i the preser of midazol

Effect on Platelet Aggregation

Author	Test System	Study size	Exposure	Characterisation of test substance	Main outcome measure	Outc
Srivas, 1984	Human platelets and rat aorta.	NA	15-20 ul (concentrations not given).	Ginger extracts in water, n-hexane, chloroform, and ethyl acetate.	Effect of ginger extracts on *in vitro* platelet aggregation.	Inhibi arach acid (epine aden dipho (ADP) collag induc plate aggre
Srivastava, 1986	Platelet rich plasma (no further information given).	NA	10-20 ul (concentrations not given).	NA	Effect of ginger and components on platelet aggregation and eicosanoid biosynthesis.	Redu throm forma from exog AA; In of AA epine ADP a collag induc plate aggre

Suekawa *et al.*, 1986 (abstract only)	Rat hind paw and aorta, rabbits.	Unknown.	Unknown.	6-shogaol.	Effect of 6-shogaol on arachidonic acid cascade.	Inhibi carra induc swelli hind rats a arach acid (induc plate aggre in rab Inhibi prost 12 (P relea aorta Possi cause COX inhibi

Thomson *et al.*, 2002	Sprague-Dawley rats, Adult, F; *ex vivo.*	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.	*ex vivo* effect of aqueous extract of ginger on the synthesis of thromboxane-B2, prostaglandin-E2, and cholesterol, triglyceride levels in the serum of normal rats.	Serur reduc both levels dose signif reduc serur both and I non- signif reduc the le TXB2 obser when was i IP but signif differ from group
NA	NA	NA	NA	NA	NA	signif reduc levels chole rats g high No sig chang trigly levels eithe eithe or IP.

Herb-drug interactions

Author	Test System	Study size	Exposure	Characterisation of test substance	Duration	Main outcome measure	Ou
Al-Omari *et al.*, 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.	Sig de blo lev no rat hr mg Sig de no BG in dia
Egashira *et al.*, 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.	Sig inc tac blo co in wi jui co th wi ora

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 ab pla life de th ra an of me