Annex B - Summary of Studies

In this guide

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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

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	Results showed ginger significa more effectiv relievin than vit 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 spontan abortio ginger 1 in B6 no cong anomal observe babies to term

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 spontan abortio elected adverse effects observe remain subject

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 m malform were re in the g group, ventricu septal d (VSD), lung abnorm and kid abnorm (pelvie One inciden idiopath central precoci puberty age 2 y No sign differen betwee two gro terms o births, spontan abortio stillbirth therape abortio birth w or gest 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 spontan abortio ginger 9 abort B6 grou
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 significa more effectiv the pla relievin severity nausea pregna = 0.014

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	Three spontan abortio observe ginger

Human studies – Platelet Aggregation

Author/date	Study design	Population/stud 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 aggregation– Agonist(s): A Epi;
Bordia *et al.,* 1997	No data.	No data.	No data.	No data.	Fibrinogen;
Bordia *et al.,* 1997	No data.	No data.	No data.	No data.	Fibrinolytic a

Bordia *et al.,* 1997	No data.	20	1 day. Outcomes measured at: baseline, 4 hours post-consumption	10 g single dose. Unstandardised capsules	Platelet aggr - Agonist(s): A 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) Unstandardized capsules Consumed with 25 mg dose of rac-warfarin, consumed once per study period.	Platelet aggr Agonist: AA; Plasma warfa 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 aggr - Agonist(s): A collagen, rist ADP; Bleedin Platelet coun Thromboelas

Rubin *et al.*, 2019	Case report	Female, 70 yrs	No data.	48 mg daily Chewable ginger supplement for approx. 1 month	INR - 8.0 app month after t ginger supple
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 thron B2 productio

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 aggr Agonist(s): A Epi
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 normal huma volunteers ar hypertensive patients.

In vitro studies

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

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	Chlor extra cytot = 9.0 aque muta conc agair strai prese 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 si chan contr cellu or ch total conte ginge prim embr cardi
No data.	No data.	No data.	No data.	No data.	inhib contr activ 12.5-

No data.	No data.	No data.	No data.	No data.	Chan cellu and p conte dose mann conc µM)
No data.	No data.	No data.	No data.	No data.	Signi decre cardi diffe for a conc exce in ES
No data.	No data.	No data.	No data.	No data.	Signi decre cellu and p conte cell-c cardi with 6-gin conc expo
Nakamura & Yamamoto (1982)	Escherichia coli Hs30	Not specified	Juice of ginger rhizome, 6-gingerol	Mutagenicity	ginge supre spon muta ginge muta isola

Nakamura & Yamamoto 1983	Escherichia coli Hs30	Not specified	6-shogaol, 6-gingerol	Mutagenicity	[6]-S 104 t muta conc 700u [6]-g
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- poter unalt treat ginge
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 cytot 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	muta both and T 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
Plengsuriyakarn *et al.,* 2012	OV and nitrosamine (OV/ DMN)-induced CCA hamsters	90	1000, 3000, and 5000 mg/kg bw/d	No data.	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

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.
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

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

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 conatining gingerols, shogaols, 3-dihydroshogaols, gingerdiols	Effects of ginger components on LPS-induced PGE2 production	Inhibition LPS-stimulated PGE2 productio (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		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 o COX-2 expressior

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. N effect on CYP2A6; maximum inhibition CYP2B6: IC - 22 mg/m IC50 - 122 mg/mL against CYP2C8 in the presence amodiaqu 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	Out
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 *in vitro* platelet aggregation	Inhi arac acid epir ade diph (AD colla indu plat agg
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	Red thro form from exo AA; of A epir ADP colla indu plat agg

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	Ging cons resu 37% inhi thro B2 proc (p<
Suekawa *et al.*, 1986 (abstract only)	Rat hind paw and aorta, rabbits	Unknown	Unknown	6-shogaol	Effect of 6-shogaol on arachidonic acid cascade	Inhi carr indu swe hind rats arac acid indu plat agg in ra Inhi pros 12 (rele rat a Poss caus COX inhi

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	Seru redu both leve dose sign redu seru both and non- sign redu the TXB obse whe was IP b sign diffe from grou
No data.	No data.	No data.	No data.	No data.	No data.	Sign redu leve chol rats high No s char trigl leve eith eith 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 dec blo lev nor rat hrs mg Sig dec nor BG in S 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 cor in r wit juic cor tho wit 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 abs pla life dec the rat and of me