

# Annex B - Summary of Studies

## In this guide

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## Human Studies

<b>Author/Date</b>	<b>Study type</b>	<b>Study size/No. of Patients at End</b>	<b>Exposure (ginger dose/day)</b>	<b>Study period</b>	<b>Length of Treatment (days)</b>	<b>Main outcome measures</b>	<b>Main results</b>
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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 significantly more effective relieving than vit B6 (p <
Ensiyeh <i>et al.</i> , 2005	Double-blind randomised controlled trial.	70/69	Ginger powder capsules (500 mg 2x/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 spontaneous abortions ginger 1 in B6 no congenital anomalies observed 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 subjects
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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).	<p>Three malformations were reported in the control group, ventricular septal defect (VSD), lung abnormality, and kidney abnormality (pelvic).</p> <p>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.</p>
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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 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 <sup>4</sup>	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/stud 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 aggr - Agonist(s): 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 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): collagen, rist ADP; Bleedin Platelet coun Thromboelas

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 throm B2 productio
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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**

<b>Author</b>	<b>Test System</b>	<b>Exposure</b>	<b>Characterisation of test substance</b>	<b>Main outcome measure</b>	<b>Outc</b>
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No data.

No data.

No data.

No data.

No data.

Char  
cellu  
and p  
cont  
dose  
man  
conc  
μM)

No data.

No data.

No data.

No data.

No data.

Signi  
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for a  
conc  
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No data.

No data.

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No data.

No data.

Signi  
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cellu  
and p  
cont  
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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 <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 $\mu\text{g}/\text{m}$
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### ***In vivo studies***

<b>Author</b>	<b>Test System</b>	<b>Study size</b>	<b>Exposure</b>	<b>Characterisation of test substance</b>	<b>Duration</b>
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 *et al.*,  
2011

Wistar rat

30

Oral: 100, 250,  
and 500 mg/kg Ginger essential  
per day once oil  
daily

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)	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 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.
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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 $\mu$ M	[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 6 $\mu$ M

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 = 0.08 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 5.1u g/ml CYP2C9 IC50 (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 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 (IC<sub>50</sub> -  
-  
221.5 mg/  
by ginger  
extract. No  
effect on  
CYP2A6;  
maximum  
inhibition of  
CYP2B6: IC<sub>50</sub> -  
- 22 mg/ml  
IC<sub>50</sub> - 122  
mg/mL  
against  
CYP2C8  
in the  
presence of  
amodiaquin  
IC<sub>50</sub> - 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	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 <i>in vitro</i> platelet aggregation	Inhibi 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% 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	Inhil carn indu swe hinc rats arac acid indu plat agg in ra Inhil pros 12 ( rele rat a Poss caus COX inhil

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

No data.

No data.

No data.

No data.

No data.

No data.

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dose  
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eith  
or IP

## Herb-drug interactions

Author	Test System	Study size	Exposure of test substance	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; normoglycemic rats showed 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  
anc  
of  
me