

# 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 results
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 in relieving symptoms than v 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 spontaneous abortions ginger 1 in B no con anomaly observ 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 elective adverse effects observ 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).	<p>Three malformations were noted in the study group, ventricular septal defect (VSD), lung abnormality, and kidney abnormality (pelvic).</p> <p>One infant with idiopathic congenital precocious puberty age 2. No significant differences between two groups: term 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 in ginger group; 9 abortions in 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 in pregnancy. P = 0.01.

## Human studies - Platelet Aggregation

Author/date	Study design	Population/study size	Study Duration	Exposure	Outcome
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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 aggr Agonist(s): A Epi;
Bordia <i>et al.</i> , 1997	NA	NA	NA	NA	Fibrinogen;
Bordia <i>et al.</i> , 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 throm- B2 production
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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 ni- on anti-plate- aggregation i- human volun- hypertensive
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## In vitro studies

Author	Test System	Exposure	Characterisation of test substance	Main outcome measure	Outcome
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## In vivo studies

Author	Test System	Study size	Exposure	Characterisation of test substance	Duration	Main outcome measure	Outcome
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.	Embryonic loss in treated groups 2x that of controls. Exposed fetuses found to be significantly heavier than control. gross structural malformations observed.

### Effect on CYPs and prostaglandin activity

Author	Test System	Exposure	Characterisation of test substance	Main outcome measure	Outcome
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### Effect on Platelet Aggregation

Author	Test System	Study size	Exposure	Characterisation of test substance	Main outcome measure	Outcome
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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.	Ginger consumption resulted in a 37% inhibition of thromboxan B2 production (p<0.01).
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## Herb-drug interactions

Author	Test System	Study size	Characterisation Exposure of test substance	Duration	Main outcome measure	Outcome
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## 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
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Laekman et al., 2021	Observational study, clinical 51/44. trial.		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
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Bordia <i>et al.</i> , 1997	NA	20	1 day. Outcomes measured at: baseline, 4 hours post- consumption.	10 g single dose. Unstandardised capsules.	Platelet aggregation Agonist(s): and 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) ginger extract Unstandardized capsules Consumed with 25 mg dose of rac-warfarin, consumed once per study period.	Platelet aggregation Agonist: AA Plasma war enantiomer protein binding & warfarin enantiomer concentrat Urinary S- 7- hydroxywar

Rubin <i>et al.</i> , 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
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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 aggregation Agonist(s): Adp and Epi
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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>Out</b>
Abudayyak <i>et al.</i> , 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 again stra pres mix.
Mohammed <i>et al.</i> , 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

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NA

NA

NA

Sign  
decr  
card  
diffe  
for a  
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exce  
in ES

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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  
spor  
mut  
ging  
mut  
isola

Nakamura & Yamamoto 1983	Escherichia coli Hs30.	Not specified.	6-shogaol, 6-gingerol.	Mutagenicity.	[6]-9 104 mut conc 700 ging
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 pote unab trea ging
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 cyto 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.	mut 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/ml
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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 abortifacient 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.
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 $\beta$ -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 <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.

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
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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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**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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 2010;	Human CYP3A4 and CYP2C9 microsomes.	Not specified.	NA	Inhibitory effect on CYP3A4 and CYP2C9 activity.	significant inhibition of CYP3A4 IC50 5.1u g/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

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/ml)  
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	Outcomes
Srivivas, 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 <i>in vitro</i> platelet aggregation.	Inhibits release of arachidonic acid (AA) and epinephrine-induced adenosine diphosphate (ADP) and collagen-induced platelet aggregation.
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.	Reduces thromboxane formation from exogenous AA; Inhibition of AA-induced epinephrine and ADP-induced collagen-induced platelet aggregation.

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  
swell  
hind p  
rats a  
arach  
acid (C  
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.

Serum  
reduced  
both  
levels  
dose  
signifi-  
reduced  
serum  
both  
and IP  
non-  
signifi-  
reduced  
the le-  
TXB2  
observed  
when  
was i-  
IP but  
signifi-  
differ-  
from  
group

NA

NA

NA

NA

NA

NA

signifi-  
reduced  
levels  
chole-  
rats g-  
high  
No sig-  
chang-  
trigly-  
levels  
eithe-  
eithe-  
or IP.



Okonta  
*et al.*,  
2008

Rabbits  
(3F, 2M).<sup>5</sup>

1 ml/kg,  
orally.

Ginger extract.

3 days.

Effect of ginger on  
the  
pharmacokinetics  
of metronidazole.

Sign  
inc  
ab  
pla  
life  
de  
the  
rat  
an  
of  
me