

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 difference between 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 11 abortions.
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; pregnancy = 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 thromboxane B2 production
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Young <i>et al.</i> , 2006	Not specified.	20	72 days.	1 g ginger (+ 10 mg nifedipine).	Synergistic effect of ginger and nifedipine on anti-platelet aggregation in human volunteers 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 2 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): and Epi
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In vitro studies

Author	Test System	Exposure	Characterisation of test substance	Main outcome measure	Out
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 agai 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 ch tota cont ging prim emb card
NA	NA	NA	NA	NA	inhib cont activ 12.5

NA

NA

NA

NA

NA

Char
cellu
and
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dose
man
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μM).

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Sign
decr
cellu
and
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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 $\mu\text{g}/\text{m}$
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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 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 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 <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, 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 (IC₅₀ -
-
221.5 mg/ml)
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.	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 arachidonic acid (AA) and epinephrine-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; Inhibits AA-induced epinephrine and ADP-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
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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 c-
No sig-
chang-
trigly-
levels
eithe-
eithe-
or IP.

Okonta
et al.,
2008

Rabbits
(3F, 2M).⁵

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