

Ginkgo

Species (Family)

Ginkgo biloba L. (Ginkgoaceae)

Synonym(s)

Fossil Tree, Kew Tree, Maidenhair Tree

Part(s) Used

Leaf

Pharmacopoeial and Other Monographs

BHP 1996^(G9)

Complete German Commission E^(G3)

Martindale 32nd edition^(G43)

Mills and Bone^(G50)

PDR for Herbal Medicines 2nd edition^(G36)

Ph Eur 2002^(G28)

WHO volume 1 1999^(G63)

Legal Category (Licensed Products)

Ginkgo is not included in the GSL.^(G37)

Constituents^(1,2,G64)

Leaf

Amino acids 6-Hydroxykynurenic acid (2-carboxy-4-one-6-hydroxyquinoline), a metabolite of tryptophan.⁽³⁻⁵⁾

Flavonoids Dimeric flavones (e.g. amentoflavone, bilobetin, ginkgetin, isoginkgetin, sciadopitysin);⁽⁶⁾ flavonols (e.g. quercetin, kaempferol) and their glycosides^(3,7) and coumaroyl esters.

Proanthocyanidins

Terpenoids Sesquiterpenes (e.g. bilobalide), diterpenes (e.g. ginkgolides A, B, C, J, M, which are unique cage molecules,^(8,9,G48) and triterpenes (e.g. sterols).

Other constituents Benzoic acid, allergenic ginkgolic acids, 2-hexenal, polyprenols (e.g. di-*trans*-poly-*cis*-octadecaprenol), sugars, waxes,⁽¹⁾ a peptide.⁽¹⁰⁾

Seeds

Alkaloids Ginkgotoxin (4-O-methylpyridoxine).⁽¹¹⁾

Amino acids

Cyanogenetic glycosides Allergenic ginkgolic acids. Ginkbilobin.⁽¹²⁾

Standardised extracts of *G. biloba* leaves are standardised on the content of ginkgo flavonoid glycosides (22–27%; determined as quercetin, kaempferol and isorhamnetin), and terpene lactones (5–7%; comprising around 2.8–3.4% ginkgolides A, B and C, and 2.6–3.2% bilobalide, and less than 5 ppm ginkgolic acids).^(G3,G56)

Food Use

Ginkgo biloba is not used in foods.

Herbal Use

Ginkgo has a long history of medicinal use, dating back to 2800BC. Traditional Chinese medicine used the seeds (kernel/nuts) for therapeutic purposes. The seed is used in China as an antitussive, expectorant and anti-asthmatic, and in bladder inflammation.^(1,11,G50) In China, the leaves of *Ginkgo biloba* were also used in asthma and in cardiovascular disorders,⁽¹⁾ although the leaves have little history of traditional use in the West. Today, standardised concentrated extracts of *G. biloba* leaves are marketed in several European countries, and are used in cognitive deficiency, intermittent claudication (generally resulting from peripheral arterial occlusive disease), and vertigo and tinnitus of vascular origin (see Pharmacological Actions, Clinical studies).^(G3,G32,G56,G63)

Dosage

Cognitive deficiency

Leaf extract 120–240 mg dry extract orally in two or three divided doses.^(G3)

Peripheral arterial occlusive disease and vertigo/tinnitus

Leaf extract 120–160 mg dry extract orally in two or three divided doses.^(G3)

Clinical trials of standardised extracts of *G. biloba* leaves (EGb 761, Willmar Schwabe GmbH and LI 1370, Lichtwer Pharma GmbH) in patients with cognitive deficiency have generally used oral doses ranging from 120 to 240 mg daily, usually for 8–12 weeks, although some studies have continued treatment for up to 24 or 52 weeks.^(G56) Clinical trials in peripheral arterial occlusive disease used oral doses of 120–160 mg extract daily for 3–6 months.^(G56)

Pharmacological Actions

In vitro and animal studies

There is a vast literature describing basic scientific research relating to the effects of ginkgo. Several pharmacological activities have been documented for ginkgo leaf extracts and/or their constituents. These include effects on behaviour, learning and memory, cardiovascular activities, effects on blood flow and antioxidant activity. The most important active principles of ginkgo extract include the ginkgo flavonoid glycosides and the terpene lactones.⁽¹⁾ Ginkgo has been described as having polyvalent action, i.e. the combined activity of several of its constituents is likely to be responsible for its effects.⁽¹³⁾

The pharmacological activities of ginkgo have been reviewed,^(1,8,9,13–15) and other texts bring together several studies in specific areas, e.g. neuroprotective effects.⁽¹⁶⁾ A summary of some of the literature on the *in vitro* and *in vivo* (animals) effects of ginkgo leaf is given below.

Effects on behaviour, learning and memory The effects of a standardised extract of ginkgo leaf (EGb 761) on learning and memory, and on behaviour in relation to ageing and in recovery from brain injury, have been well studied.⁽¹³⁾ Animal models (rats and mice) designed to test aspects of learning and memory (e.g. acquisition and retention) have documented improvements in animals treated with oral, intraperitoneal or subcutaneous EGb 761, compared with controls.⁽¹³⁾ Studies involving rats reported improvements in acquisition and retention in older (24-month-old), but not younger (eight-month-old) rats. Other experiments involving rats of different ages have found that older rats (12- and 18-months old) showed improved performance in an eight-arm radial maze test following oral administration of EGb 761

30 or 60 mg/kg/day, whereas performance was stable among young rats (eight weeks old) following EGb 761 administration.⁽¹³⁾ EGb 761 200 mg/kg administered orally to rats aged more than 26 months old led to significant improvements in aspects of cognitive behaviour.⁽¹⁷⁾ *In vivo* studies have also shown that oral administration of EGb 761 (50 or 100 mg/kg/day for three weeks) to rats prevented the short-term memory-impairing effects of scopolamine administered intraperitoneally (0.125 mg/kg).⁽¹³⁾

The anxiolytic effects of a range of doses (0.01–10 mg/kg) of combination preparations containing different mixture ratios of standardised extracts of ginkgo leaf and ginger root have been tested in rats using the elevated plus-maze test.⁽¹⁸⁾ Compared with controls, rats treated with the combination preparation (mixture ratio of ginger extract to ginkgo extract, 2.5:1; 1 mg/kg, intragastrically) spent increased amounts of time in the open arms of the maze, whereas the behaviour of rats treated with preparations of a mixture ratio of 1:1 and 1:2.5 did not change.

Several studies have reported that treatment with EGb 761, compared with control, aids recovery of function following brain injury, as demonstrated by behavioural tests in rats who had undergone bilateral frontal lobotomy or septohippocampal deafferentation, and in rat models of cortical hemiplegia.⁽¹³⁾

It has been suggested that the effects of EGb 761 in the experimental animal models described above may involve aspects of neuronal plasticity, e.g. neuronal regeneration.⁽¹³⁾ Studies in rats have investigated, for example, the effects of EGb 761 administration on expression of neurotrophins and apolipoprotein E, and on behavioural recovery, following entorhinal cortex lesions, and on regeneration of primary olfactory neurons following olfactory bulbectomy. Research investigating the effects of EGb 761 on neuronal plasticity has been summarised.^(1,13,19)

Cardiovascular and haemorrhological activities Studies investigating the molecular mechanisms that may contribute to the vasoregulatory (vasodilatation and vasoconstriction) effects of standardised ginkgo leaf extract (EGb 761) have been described.^(13,20) *In vitro* experiments using isolated rabbit aorta suggested that possible mechanisms include effects on cyclic-GMP phosphodiesterase, prostaglandin I₂ and nitric oxide (NO). *Ex vivo* studies using isolated guinea-pig heart showed that EGb 761 led to a concentration-dependent increase in coronary blood flow. In studies involving isolated rat heart and in anaesthetised rabbits, EGb 761 administration has been reported to protect against myocardial ischaemia-reperfusion injury; the antioxidant

and free-radical scavenging effects of EGb 761 (*see below*) may be important in this regard.⁽¹³⁾ One study using isolated rat hearts suggested that the cardio-protective effects were due to the terpenoid constituents of EGb 761, and that the mechanism was independent of direct free radical-scavenging activity.⁽²¹⁾ An *in vitro* study with endothelial cells suggested that the anti-ischaemic activity of EGb 761 may be due partly to the effects of the constituent bilobalide in protecting mitochondrial activity.⁽²²⁾

The effects of ginkgo leaf extract have been studied in normal rats and those with ischaemic brain damage with middle cerebral artery occlusion.⁽²³⁾ Oral administration of ginkgo extract 100 mg/kg was reported to increase cerebral blood flow in normal rats, but the increase was less marked in rats with cerebral artery occlusion.

In vitro studies using human blood cells have documented effects of EGb 761 on several haemorrhological parameters.⁽¹³⁾ For example, *in vitro*, EGb 761 normalised changes in erythrocyte viscosity and in the viscoelastic properties of the erythrocyte membrane induced by standard metabolic challenge (pH 6.8; 380 mosmol/L) in six human blood donors. In other *in vitro* experiments, EGb 761 protected against hydrogen peroxide-induced damage in human erythrocytes. In studies using blood from patients with circulatory disorders, incubation with EGb 761 was reported to decrease erythrocyte aggregation. *In vitro* experiments using human neutrophils have found that EGb 761 at a concentration of 10 µmol/L inhibits release of hydrogen peroxide from these cells. The effects of EGb 761 on inhibition of human platelet aggregation elicited by substances such as thrombin and collagen have been documented.⁽¹³⁾ A study using blood donated by healthy volunteers ($n=35$) reported that a standardised extract of ginkgo leaf inhibited ADP- and collagen-induced platelet aggregation in platelet-rich plasma, gel-filtered platelets and in whole blood in a concentration-dependent manner.⁽²⁴⁾

Platelet-activating factor antagonism Ginkgolides have been reported to competitively inhibit the binding of platelet-activating factor (PAF) to its membrane receptor.^(8,9,25)

Ginkgolide B antagonises thrombus formation induced by PAF and, in guinea-pigs, it also induces a rapid curative thrombolysis. A protective effect is exerted by ginkgolides on PAF-induced bronchoconstriction and airway hyperactivity in immunanaphylaxis and in antigen-induced bronchial provocation tests. Oral or intravenous injection of ginkgolide B antagonises cardiovascular impairments and

bronchoconstriction induced by PAF. Ginkgolide B does not appear to interfere with cyclooxygenase, but at an earlier step involving PAF receptors and phospholipase activation. Eosinophil infiltration occurs in asthma and in allergic reactions, the number of eosinophils increasing during late phase. Since PAF is a potent activator of eosinophil function, it has been argued that ginkgolide B may interfere with the late-phase response.⁽²⁵⁾

Pre-administration of ginkgolide B (1–5 mg/kg, intravenous) to rats has been reported to reduce PAF-induced decreases in diastolic and systolic arterial blood pressure in anaesthetised normotensive rats; this effect has also been reported in this animal model when ginkgolide B is administered shortly after PAF administration.⁽¹³⁾

Ginkgolide B has also been documented to have some beneficial effects in endotoxic shock; PAF is believed by some to be implicated in shock states. In anaesthetised guinea-pigs, intravenous administration of ginkgolide B (1 or 6 mg/kg) prior to injection of *Salmonella typhimurium* endotoxin reduced the initial rapid decrease in blood pressure, and intravenous administration of ginkgolide B during the prolonged phase of shock (1 hour after endotoxin administration) immediately and dose dependently reversed the decrease in blood pressure.⁽¹³⁾ Other studies have found that ginkgolide B reduced arterial blood pressure in the secondary, but not the early, phase following administration of *Escherichia coli* endotoxin.⁽¹³⁾

Antioxidant activity The free radical-scavenging effects and antioxidant activity of EGb 761 *in vitro* are well documented.⁽¹³⁾ EGb 761 scavenges several reactive oxygen species, including hydroxyl, superoxide and peroxy radicals.^(13,26,27) In rat cerebellar neurons and cerebellar granule cells, ginkgo extract was reported to protect against oxidative stress induced by hydrogen peroxide, another reactive oxygen species.^(28,29) In cultures of rat hippocampal cells, incubation with EGb 761 protected against cell death induced by β -amyloid, protected against toxicity induced by hydrogen peroxide, and blocked β -amyloid-induced events, such as accumulation of reactive oxygen species.⁽³⁰⁾ Bilobalide has also been documented to protect neurons against oxidative stress induced by reactive oxygen species *in vitro*.⁽³¹⁾ Experiments in gerbils have suggested that the neuroprotective effects of ginkgo extract may be due to inhibition of nitric oxide formation.⁽³²⁾

Other studies which have described neuroprotective effects of EGb 761 have suggested that antioxidant activity may be involved.⁽¹⁶⁾ *In vitro*, a standardised ginkgo leaf extract was found to inhibit

photo-induced formation of cholesterol oxides in a concentration-dependent manner.⁽³³⁾

Antioxidant activity has been documented for EGb 761 *in vivo*. In rats, treatment with EGb 761 increased the concentrations of circulating and cellular polyunsaturated fatty acids, and reduced erythrocyte cell lysis induced by hydrogen peroxide.⁽³⁴⁾ Also in rats, oral administration of EGb 761 was reported to increase activity of the enzymes catalase and superoxide dismutase in the hippocampus, striatum and substantia nigra.⁽³⁵⁾ Other data collected in this study suggested a decrease in lipid peroxidation in rat hippocampus in EGb 761-treated rats. In another study in rats, EGb 761 (200 mg/kg/day for four weeks) protected against carbon tetrachloride-induced (1.5 mL/kg) liver damage, as determined by malondialdehyde concentrations (a breakdown product of lipid peroxidation).⁽³⁶⁾

Other activities *In vivo* studies have suggested that EGb 761 may protect against chemically induced carcinogenesis. In mice, oral administration of EGb 761 (150 mg/kg daily for two weeks), compared with control, was reported to reduce tumour multiplicity; however, the inhibitory effect was not statistically significant.⁽³⁷⁾ It was also reported that EGb 761-treatment reduced the cardiotoxicity of doxorubicin.

EGb 761 and ginkgolide B have been shown to inhibit peripheral-type benzodiazepine receptor (PBR) expression and cell proliferation in the human breast cancer cell line MDA-231, which is known to be rich in PBR.⁽³⁸⁾ By contrast, the proliferation of MCF-7 breast cancer cells, which are low in PBR, was not affected.

In rats, oral administration of standardised ginkgo leaf extract 300 mg/kg was shown to ameliorate nephrotoxicity induced by administration of gentamicin 80 mg/kg.⁽³⁹⁾

Aqueous extracts of dried ginkgo leaves have been reported to inhibit monoamine oxidases (MAO) A and B.⁽⁴⁰⁾ A study investigating the effects of bilobalide on gamma-aminobutyric acid (GABA) concentrations and on glutamic acid decarboxylase activity in mouse brain found that GABA concentrations and glutamic acid decarboxylase activity were significantly higher in animals treated orally with bilobalide 30 mg/kg daily for four days.⁽⁴¹⁾ However, there were no differences between treated and control mice with regard to glutamate concentrations.

Several *in vivo* studies have documented adaptive effects for EGb 761.⁽²⁰⁾

A peptide isolated from the leaves of *Ginkgo biloba* has been reported to have antifungal activity against several fungi, including *Pellicularia sasakii* and *Alternaria alternata*.⁽¹⁰⁾

Three long-chain phenols, anacardic acid, bilobol and cardanol, isolated from seeds of *G. biloba* are active against Sarcoma 180 ascites in mice.⁽⁴²⁾

Clinical studies

Pharmacokinetics Data on the pharmacokinetics of standardised extracts of ginkgo leaf have been summarised.^(1,15,G18,G21) Mean bioavailabilities of ginkgolide A, ginkgolide B and bilobalide following oral administration of ginkgo extract 120 mg to fasting healthy volunteers were 80%, 88% and 79%, respectively. Food intake increased the time taken to reach peak concentration (suggesting slower absorption), but did not affect bioavailability.^(1,G18) Peak concentrations of ginkgolides A and B and bilobalide observed in fasting volunteers ranged from 16.5 to 33.3 ng/mL, and from 11.5 to 21.1 ng/mL in volunteers who had consumed food.⁽¹⁾ Urinary excretion of ginkgolides A and B, and bilobalide, is around 70%, 50% and 30%, respectively, of the dose administered orally.^(G18)

Therapeutic effects Most clinical trials of ginkgo have explored its effects in the treatment of cognitive deficiency or cerebral insufficiency,^(43,G56) a term used to describe a collection of symptoms thought to arise from an age-related reduction in cerebral blood flow. These symptoms include forgetfulness, poor concentration, poor perception, debilitation, dizziness, fatigue, sleep disturbances, listlessness, depressed mood, headache, mood swings, restlessness, tinnitus, anxiety, hearing loss and disorientation.^(43,G56) Several studies have tested the effects of standardised ginkgo leaf extracts on cognitive function in patients with Alzheimer's disease⁽⁴⁴⁾ and/or multi-infarct dementia.⁽⁴⁵⁾ Both are conditions which share several symptoms (e.g. memory impairment) with cerebral insufficiency. Several other trials have explored the effects of ginkgo extracts on cognitive ability in individuals with no history of significant cognitive impairment. A few studies have explored the effects of ginkgo on tinnitus alone.⁽⁴⁶⁾

Clinical research with ginkgo extracts has also focused on effects in improving pain-free walking distance in patients with intermittent claudication/peripheral arterial occlusive disease.^(47,G56) Other studies have explored the effects of ginkgo in patients with chronic venous insufficiency, antidepressant-related sexual dysfunction, seasonal affective disorder (SAD), and symptoms of depression.

Almost all clinical trials of ginkgo have investigated the effects of the standardised ginkgo leaf extracts EGb 761 and LI 1370.

Cognitive deficiency, dementia in Alzheimer's disease, multi-infarct dementia A review of controlled clinical trials of ginkgo in patients with cerebral insufficiency identified 40 studies.⁽⁴³⁾ Generally, trials tested oral doses of standardised extracts of ginkgo leaf of 120 mg daily administered for at least four to six weeks. Most trials reported significant results or positive (but not statistically significant) trends in favour of ginkgo, compared with control. However, it was reported that most trials were of poor methodological quality; only eight studies were considered to be well-conducted. All of these eight studies reported statistically significant results for ginkgo, compared with placebo. Nevertheless, further randomised, double-blind, controlled trials involving larger numbers of patients were deemed necessary.⁽⁴³⁾ Details of 39 controlled studies of the ginkgo extracts EGb 761 and LI 1370 have been summarised.^(G56) All but two^(48,49) of these studies were conducted before new guidelines for testing the efficacy of nootropic drugs were developed.^(G56) Details of the two studies that did meet the methodological criteria described in the guidelines are given below.

In a randomised, double-blind, placebo-controlled trial, after a four-week placebo run-in period, 216 patients with mild-to-moderate primary degenerative dementia of the Alzheimer type, or multi-infarct dementia, received standardised ginkgo leaf extract (EGb 761) 120 mg orally twice daily, or placebo, for 24 weeks.⁽⁴⁸⁾ At the end of the study, data for 156 patients were eligible for analysis. There were significantly more responders to treatment (defined as a response to at least two of the three primary outcome measures – a psychopathological assessment, an assessment of cognitive performance and a behavioural assessment of activities of daily life) in the ginkgo group, compared with the placebo group (28% versus 10% of ginkgo and placebo recipients, respectively; $p=0.005$). The difference was also statistically significant in an intention-to-treat analysis (23% versus 10% of ginkgo and placebo recipients, respectively; $p=0.005$).

A randomised, double-blind, placebo-controlled study involved 327 patients with mild-to-severe dementia related to Alzheimer's disease or multi-infarct dementia.⁽⁴⁹⁾ Participants received standardised ginkgo leaf extract (EGb 761) 40 mg orally three times daily ($n=166$), or placebo ($n=161$), for 52 weeks, and underwent a battery of assessments at 12, 26 and 52 weeks. The primary outcome measures were the Alzheimer's Disease Assessment Scale Cognitive Subscale (Adas-Cog), the Geriatric Evaluation by Relative's Rating Instrument (GERRI) and the Clinical Global Impression of Change (CGIC). In

an intention-to-treat analysis ($n=309$), ginkgo recipients scored significantly better than did placebo recipients on the Adas-Cog and the GERRI ($p=0.04$ and $p=0.004$, respectively). A slight worsening on the CGIC was observed for both groups. The average end-points for the intention-to-treat analysis were 38.6 and 34.6 weeks for the ginkgo and placebo groups, respectively.

A systematic review of randomised, double-blind, placebo-controlled trials assessing the effects of standardised ginkgo leaf extracts on cognitive function in patients with Alzheimer's disease, characterised according to recognised criteria, included four studies.⁽⁴⁴⁾ These involved oral administration of ginkgo extract 120 or 240 mg daily for 12–26 weeks, and involved a total of 212 patients each in the ginkgo and placebo groups. A meta-analysis of the results of the four studies indicated a modest effect for ginkgo, compared with placebo (difference of 3% on the Adas-Cog).

Another systematic review included nine randomised, double-blind, placebo-controlled trials of standardised ginkgo leaf extracts in patients with dementia of the Alzheimer type and/or multi-infarct dementia.⁽⁴⁵⁾ The review included two studies described above.^(48,49) Studies generally involved the administration of oral doses of ginkgo extract 120 or 240 mg daily for 6–12 weeks, although two studies involved a 24-week⁽⁴⁸⁾ or 52-week⁽⁴⁹⁾ administration period. One study involved the administration of intravenous infusions of ginkgo extract 200 mg four times per week for four weeks. It was reported that, overall, the studies provided evidence to support the efficacy of standardised ginkgo leaf extracts in the symptomatic treatment of dementia. However, methodological limitations of several of the included studies (e.g. poorly defined inclusion and exclusion criteria and method of randomisation, treatment period less than six months, small sample sizes) were also emphasised. It was concluded that further studies are required to establish the benefits of ginkgo in dementia.⁽⁴⁵⁾

In a randomised, double-blind, placebo-controlled study, 60 elderly volunteers with mild-to-moderate, age-related cognitive dysfunction received oral ginkgo extract (GB-8; no further details provided) 40 mg, 80 mg or placebo, three times daily for three months.⁽⁵⁰⁾ At the end of the study, for the 54 patients who completed, it was reported that memory function (as assessed by the Wechsler Memory Scale) improved significantly in the low-dose ginkgo group, compared with baseline values ($p=0.016$), but that there was no significant improvement in the placebo or high-dose ginkgo groups, compared with baseline values. A significant decrease in diastolic

blood pressure, compared with baseline values, was also reported for the low-dose ginkgo group ($p = 0.04$). This study, however, had methodological limitations (e.g. small sample size), and the report of the study did not include statistical analyses between groups.

A more methodologically rigorous randomised, double-blind, placebo-controlled trial involving patients with age-related impairment of memory and/or concentration assessed the effects of an alcohol/water extract of fresh leaves of ginkgo (drug extract ratio 1:4; total flavonoid glycosides 0.20 mg/mL, total ginkgolides 0.34 mg/mL).⁽⁵¹⁾ Participants received undiluted ginkgo extract ($n = 77$), diluted ginkgo extract (1:1 with placebo) ($n = 82$), or placebo ($n = 82$), 40 drops (1.9 mL) three times daily for 24 weeks. At the end of the treatment period, a check for blinding indicated that participants were unable to identify the treatment they received. There were no statistically significant differences between the three groups in subjective perceptions of memory and concentration, and in the following objective measures: the Expended Mental Control Test (a measure of attention and concentration), and Rey test parts 1 and 2 (which measure short-term memory and learning curve, and long-term memory and recognition, respectively). However, a significant difference between groups was observed in the Benton test of visual retention-revised (a measure of short-term visual memory) – increases in baseline scores of 18, 26 and 11% were recorded for the high-dose ginkgo, low-dose ginkgo and placebo groups, respectively ($p = 0.0076$).⁽⁵¹⁾

In an open study, 18 elderly patients with 'possible or probable' Alzheimer's disease were randomised to receive a single oral dose of tacrine 40 mg or a standardised extract of ginkgo leaf (SeGb; no further details provided) 240 mg in two separate sessions within three- to seven-day intervals.⁽⁵²⁾ It was reported that both interventions induced pharmacological effects in the central nervous system (CNS), as assessed by quantitative pharmaco-electroencephalogram measurements. It should be noted that this was an uncontrolled study.

Cognitive enhancement in healthy volunteers Ginkgo has been tested for its cognitive enhancing effects in healthy (i.e. cognitively intact) individuals in addition to investigations into its effects in patients with cognitive deficiency.

In a double-blind, placebo-controlled, cross-over study, 20 healthy volunteers aged 19–24 years received a standardised extract of ginkgo leaf (GK501) at doses of 120 mg, 240 mg and 360 mg.⁽⁵³⁾ A battery of tests used to assess cognitive

performance was carried out immediately before and at 1, 2.5, 4 and 6 hours after ginkgo administration. It was reported that with doses of ginkgo extract of 240 and 360 mg, there was a statistically significant improvement in 'speed of attention' (a measure of reaction time) from 2.5 hours up to 6 hours (the last measurement point) after ginkgo administration.

In a randomised, double-blind, placebo-controlled, crossover study, eight healthy female volunteers (mean age 32 years) were given a standardised extract of *G. biloba* leaf at doses of 120, 240 and 600 mg.⁽⁵⁴⁾ One hour after treatment, volunteers undertook a series of psychological tests. Memory was found to be significantly improved with *G. biloba* leaf 600 mg, compared with placebo.

A randomised, double-blind, placebo-controlled, crossover trial involving 31 volunteers aged 30–59 years tested the effects of a standardised extract of ginkgo leaf (LI 1370) 50 mg three times daily, 100 mg three times daily, 120 mg each morning, 240 mg each morning, and placebo, each taken for two days followed by a washout period of at least five days.⁽⁵⁵⁾ A battery of tests to assess memory and cognitive and psychomotor performance was carried out 30 minutes before ginkgo administration and then hourly for 12 hours. It was reported that there was a 'marginally significant' effect of treatment, compared with placebo, in a test assessing short-term memory, although the p -value given for this was greater than 0.05 ($p = 0.053$). Post-hoc analyses suggested that ginkgo extract 120 mg each morning was associated with better performance in this test than other doses of ginkgo extract (including ginkgo extract 50 mg three times daily) and placebo. There were no statistically significant effects of treatment on immediate and delayed word recall and choice reaction time.

Other studies have assessed the cognitive-enhancing effects of ginkgo extracts in older volunteers. In a randomised, double-blind, placebo-controlled trial, 48 cognitively intact individuals aged over 55 years received a standardised ginkgo leaf extract (EGb 761) 60 mg three times daily, or placebo, for six weeks.⁽⁵⁶⁾ A battery of neuropsychological tests was carried out before treatment and at the end of the study. Ginkgo extract recipients experienced a significant improvement in tests assessing speed of processing abilities, compared with placebo recipients ($p < 0.03$). However, no statistically significant differences between the ginkgo extract and placebo groups were evident for tests assessing memory.

In a questionnaire survey, the effects of administration of a standardised ginkgo leaf extract (LI 1370) 120 mg daily for four months on the activities of daily living were assessed in volunteers aged 32–97

years (mean (SD) 68.9 (8.4) years).⁽⁵⁷⁾ Volunteers were recruited via editorial in a magazine. Of 8557 initial respondents, 5028 were eligible for the survey. In total, 1000 volunteers (who were not currently using any ginkgo products) were said to be randomly allocated to receive ginkgo extract; all other respondents were allocated to the no-treatment control group, unless they had stated that they only wished to receive ginkgo. It was reported that ginkgo extract recipients achieved significantly better scores than the control group on a scale assessing ability to perform activities of daily living, self-assessment of ability to cope, and visual analogue scales for mood and sleep. However, for several reasons, the results of this study should be interpreted cautiously. For example, the study was carried out by post, therefore investigators did not meet participants at any time, the study was not truly randomised, the study was open, the control group did not receive placebo tablets, and there was no check on compliance.

Tinnitus and hearing loss Tinnitus and hearing loss are two of the symptoms of dementia.^(G56) Several studies have assessed the effects of ginkgo on these conditions alone.

A systematic review of randomised, controlled trials of ginkgo extracts in tinnitus included five studies – four studies compared ginkgo extracts with placebo, and one study compared ginkgo extract with conventional drugs. Three trials tested the standardised ginkgo leaf extract EGb 761; full details of other extracts tested in the other studies are not given in the review. The review concluded that, overall, the studies identified provided evidence to support ginkgo extracts as a treatment for tinnitus, but that further investigation was required to fully establish the benefits. Typically, at least two of the studies had methodological flaws.⁽⁴⁶⁾

A double-blind, controlled trial, published since the systematic review, tested the effects of a standardised ginkgo leaf extract (LI 1370) 50 mg, or placebo, three times daily for 12 weeks in 1121 individuals, aged 18–70 years, with tinnitus who were otherwise healthy.⁽⁵⁸⁾ Participants were recruited via advertisements placed in the UK national press and in a British Tinnitus Association's publication. The main outcome measure was participants' self-assessment of tinnitus (loudness and 'how troublesome') before, during and after treatment, carried out via postal questionnaires and telephone calls. Participants were paired where possible (489 pairs, i.e. 978 of 1121 participants were matched) and then randomly allocated to active or placebo. At the end of the study, the results indicated that ginkgo extract (LI 1370) 50 mg three times daily was 'no more effective than

placebo in treating tinnitus'.⁽⁵⁸⁾ The design of this study has been criticised. For example, participants did not have face-to-face contact with an investigator at any time during the study.⁽⁵⁹⁾

In a randomised, controlled trial, 28 patients with untreated sudden loss of hearing received intravenous infusions of 6% hydroxyethyl starch (HES), or intravenous and oral ginkgo extract, for 10 days.⁽⁶⁰⁾ There were no statistically significant differences between the two groups in improvements in hearing. Further studies involving larger numbers of participants are required.⁽⁶⁰⁾

Peripheral arterial occlusive disease/intermittent claudication The effects of standardised extracts of ginkgo have been investigated in patients with Fontaine stage II peripheral arterial occlusive disease. This condition is characterised by the onset of pain, as a result of oxygen deficit in the leg muscles, on walking distances greater than around 30–300 metres.^(G56) The rationale for using ginkgo in this condition is for its effects in improving blood flow.

A meta-analysis of randomised, double-blind, placebo-controlled trials of ginkgo extract for the treatment of intermittent claudication included eight studies that assessed effects on walking distance.⁽⁶¹⁾ The trials involved a total of 415 patients who received a standardised extract of ginkgo leaf at doses of 120 or 160 mg daily, or placebo, for 6, 12 (one trial each) or 24 weeks. The pooled results from all trials indicated a statistically significant increase in pain-free walking distance for ginkgo-treated patients, compared with placebo recipients (weighted mean difference (WMD): 34 metres; 95% confidence intervals (CI): 26–43 metres). A similar result was obtained when results for the six studies of good methodological quality were pooled (WMD: 37 metres; 95% CI: 26–47 metres). It is questionable whether the extent of these increases in pain-free walking distance is clinically relevant.⁽⁶¹⁾

Chronic venous insufficiency and venous ulcers A randomised, double-blind, placebo-controlled trial assessed the protective effects of a combination preparation (Ginkgor Forte) containing a standardised extract of ginkgo (2.3%), troxerutine (48.85%) and heptaminol (48.85%) against venous wall injury in 48 female patients with chronic venous insufficiency.⁽⁶²⁾ Ginkgor Forte 625 mg daily, or placebo, was given for four weeks. In total, 42 patients completed the study, but only 28 were included in the final analysis because of protocol violations. Circulating endothelial cell (CEC) count was used as a measure of injury to the vascular endothelium (CEC counts are raised in patients

with chronic venous insufficiency.⁽⁶²⁾ After four weeks' treatment, CEC counts decreased significantly in both the treatment and placebo groups (by 14.5% and 8.4%, respectively), compared with baseline values ($p = 0.0021$ and $p = 0.0146$, respectively). The mean change in CEC count after four weeks' treatment was reported to be significantly greater for the treatment group, compared with the placebo group ($p = 0.039$).

In another double-blind trial, 213 patients with chronic venous or mixed ulcers located at the malleolus (rounded protuberance on ankle joint) received ginkgo extract 160 mg daily, or placebo, together with standard care (elastic stockings, local dressings and cleansing of ulcers) for 12 weeks.⁽¹⁾ At the end of the study, ginkgo extract recipients, compared with placebo recipients, showed a significant reduction in ulcer area.

Asthma, PAF antagonism Intradermal injections of PAF induce a biphasic inflammatory response similar to that observed in sensitised individuals subjected to moderate doses of allergen. A single dose of a mixture of ginkgolides has been reported to antagonise this response.⁽⁶³⁾ Oral administration of ginkgolides resulted in a reduction of eosinophil infiltration in atopic patients given intracutaneous injections of PAF.⁽⁶³⁾

In a randomised, double-blind, crossover study, 80 and 120 mg capsules containing a standardised mixture of ginkgolides A, B and C (ratio of 40:40:20) were given as a single oral dose 2 hours before challenge by intradermal PAF/histamine. Both dose ranges inhibited flare which was maximal after 5 minutes. Within 15–30 minutes wheal volume was reduced, with the greatest effect being observed for the higher dose treatments. The protection was still present 8 hours after oral dosing.⁽⁸⁾ Similar inhibition of PAF was observed for platelet aggregation with single oral doses of 80 and 120 mg extract which were given 2 hours before blood withdrawal. The ginkgolide mixture given orally also blocked PAF-induced airway hyper-responsiveness.

Antagonism of the effects of PAF by a standardised mixture of ginkgolides was assessed in a double-blind, placebo-controlled crossover study in six healthy subjects aged 25–35 years.⁽⁶⁴⁾ Wheal and flare responses to PAF examined 2 hours after ingestion of 80 mg and 120 mg of ginkgolide mixture were inhibited in a dose-related manner. Both doses significantly inhibited PAF-induced platelet aggregation in platelet-rich plasma.⁽⁶⁴⁾

A randomised, double-blind, crossover study involved patients with atopic asthma who were challenged with their specific dust or pollen anti-

gen.⁽⁸⁾ After 6.5 hours, participants were subjected to a provocation test with acetylcholine so that the treatment of later stages of an asthma attack could be assessed. Mixed ginkgolide standardised extract, 40 mg three times daily, or placebo, were given during the three days before the test and a final single dose of 120 mg of extract was given 2 hours before the challenge. The results suggested that ginkgolides were effective in both the early phase and the late phase of airway hyperactivity.⁽⁸⁾

A study involving six patients with a history of exercise-induced asthma assessed the effects of a specific PAF antagonist (BN 52063, a standardised mixture of ginkgolides A, B and C, ratio of 40:40:20) on the response to isocapnic hyperventilation with dry cold air.⁽⁶⁵⁾ Participants were randomised to receive BN 52063 240 mg orally 2 hours before cold air challenge, 2.4 mg by metered dose inhaler 30 minutes before cold air challenge, or placebo. It was reported that oral BN 52063 did not reduce bronchoconstriction during challenge. A significant increase in airways resistance was observed after inhalation of BN 52063. In another study, six patients with a history of exercise-induced asthma received BN 52063 120 mg orally twice daily, 1 mg by spinhaler three times daily, or placebo, for three days, then, on the test day, 240 mg orally 3 hours before exercise challenge, 5 mg by spinhaler 1 hour before challenge, or placebo, respectively. With oral treatment, the prolonged reduction in peak expiratory flow was significantly attenuated ($p < 0.05$).⁽⁶⁵⁾

Antidepressant-related sexual dysfunction Two open, uncontrolled studies have explored the effects of ginkgo extract in sexual dysfunction associated with treatment with antidepressant drugs.^(66,67) One of these studies involved 63 men and women who were receiving treatment with selective serotonin reuptake inhibitors (SSRIs), venlafaxine, nefazodone, bupropion, phenelzine or protriptyline, and experiencing sexual dysfunction, including decreased libido, erectile difficulties, delayed or inhibited orgasm and/or ejaculatory failure.⁽⁶⁶⁾ All participants received ginkgo extract 40 or 60 mg twice daily, titrated up to a maximum of 120 mg twice daily (average daily dose 207 mg), for four weeks. It was reported that sexual dysfunction was relieved, as assessed by clinical interview and self-report, in 91% and 76% of female and male participants, respectively. An open, prospective pilot study involved 14 patients with sexual dysfunction (severe or complete loss of libido, with or without inability to achieve or maintain erection, failure or delay in ejaculation, anorgasmia) associated with current

treatment with antidepressant drugs, mainly SSRIs, but also hypericum (St. John's wort) extract, amitriptyline and clomipramine.⁽⁶⁷⁾ Participants received a standardised extract of ginkgo 240 mg daily for six weeks. Assessment included an eight-item 'sexual stress' score, 'sleep problems' score, and the Hamilton Anxiety and Depression Scale scores. Among the 12 individuals who completed the study statistically significant improvements in scores were observed for anxiety at week 6 ($p < 0.05$) and sexual stress at weeks 3 and 6 ($p < 0.01$ for both), all compared with baseline values.

One of these studies⁽⁶⁶⁾ has been criticised for its methodological limitations and poor quality of the report.⁽⁶⁸⁾ Owing to their open, uncontrolled designs, neither study provides reliable evidence of the effects of ginkgo extract in antidepressant-related sexual dysfunction, as the observed effects cannot be reliably attributed to treatment with ginkgo.

Other conditions A Cochrane review of the effects of ginkgo extract in age-related macular degeneration identified one randomised, controlled trial involving 20 patients.⁽⁶⁹⁾ The study design did not include blinding of the assessment of outcome. The review concluded that the effects of ginkgo extract in preventing progression of age-related macular degeneration had not yet been adequately assessed.

In a randomised, double-blind, controlled trial, 27 patients with seasonal affective disorder (SAD) received standardised extract of ginkgo leaf (Bio-Biloba, containing flavone glycosides 24 mg and terpene lactones 6 mg) one tablet twice daily ($n = 15$), or placebo ($n = 12$), for 10 weeks or until development of depression requiring treatment.⁽⁷⁰⁾ All participants began the trial during October to December; assessments were carried out at baseline and on termination of study medication. Six of the 15 ginkgo recipients and two of the 12 placebo recipients terminated the study treatment because of emerging symptoms of SAD ('winter depression'). It was reported that this difference between groups was not statistically significant, according to Fisher's exact test. Also, there were no statistically significant differences between groups on the Montgomery-Asberg Depression Rating Scale, the ATYP scale (for symptoms of hypersomnia, hyperphagia and carbohydrate craving) and on self-assessed symptoms (energy, tiredness, appetite, carbohydrate craving, depressed mood). The results of this study cannot be considered definitive because of the small sample size of the study and other limitations.⁽⁷⁰⁾

An open pilot study explored the effects of a standardised dried extract of ginkgo leaf (LI 1370) on cognitive performance in patients with major

depression who were receiving trimipramine 200 mg daily.⁽⁷¹⁾ Eight participants received trimipramine for six weeks, and ginkgo extract 120 mg twice daily from day 8 to day 35 of the study. The data for these individuals were compared with those for eight age- and sex-matched controls who received trimipramine only for six weeks. At the end of the study, there was a significantly higher response rate (determined by a reduction of 50% or more in baseline Hamilton Depression Rating Scale scores) among patients who received trimipramine only, compared with those who received trimipramine plus ginkgo extract ($p \leq 0.05$). However, duration of illness before enrolment in the study was reported to be significantly longer for ginkgo extract recipients than for controls ($p \leq 0.05$). It was claimed that the ginkgo extract group, compared with the control group (trimipramine only), had improved sleep efficiency and augmented non-REM (random eye movement) sleep, although p -values were not given. Furthermore, by contrast, sleep time was found to be significantly prolonged in participants receiving trimipramine only. The design of the study, together with conflicting results, do not allow any definitive conclusions regarding the effects on sleep of ginkgo extract in addition to trimipramine treatment.

A placebo-controlled trial involving 165 women with premenstrual syndrome explored the effects of standardised ginkgo leaf extract (EGb 761) 160 mg daily, or placebo, taken from day 16 of the menstrual cycle to day 5 of the following cycle, for two cycles.⁽⁷²⁾ Both groups experienced improvements in symptoms, compared with baseline values, although ginkgo recipients, compared with placebo recipients, were reported to experience significantly greater improvements in breast tenderness (as evaluated by the physician).

The effects of ginkgo extract have been explored in patients with schizophrenia. The rationale for this is based on the theory that excess free radical formation may occur in patients with schizophrenia, since superoxide dismutase (SOD) concentrations have been reported to be higher in certain tissues in such patients. (SOD is an enzyme that detoxifies superoxide radicals.) In a double-blind, placebo-controlled trial, 82 inpatients with chronic schizophrenia (illness for at least five years) were 'divided randomly' to receive haloperidol 0.25 mg/kg daily, with or without ginkgo extract 360 mg daily, for 12 weeks.⁽⁷³⁾ At the end of the study, mean SOD concentrations (expressed as ng/mL haemoglobin) were reported to be significantly lower, compared with baseline values, for ginkgo recipients (mean (SD): 815.8 (697.8) and 596.7 (148.3), respectively; $p = 0.021$). In participants who received haloperidol only, mean

(SD) SOD concentrations fell from 780.4 (605.4) at baseline to 617.6 (189.7) at the end of the study, although this decrease was reported to be statistically non-significant. A between-group comparison was not reported. Mean (SD) SOD concentrations in a group of 30 age- and sex-matched healthy volunteers were 515.8 (70.4).⁽⁷³⁾

The effects of a preparation comprising *Ginkgo biloba* dimeric flavonoids in a 1:2 complex with phosphatidylcholine (GBDF-Phytosome) on the microcirculation of the skin have been investigated using various techniques including, infrared photo-pulse plethysmography, laser doppler flowmetry, high-performance contact thermography and computerised videothermography.⁽⁷⁴⁾ In a controlled study, small numbers of healthy individuals and volunteers with acrocyanosis or cellulitis were treated with 0.5 mL of a cream (oil-in-water emulsion) containing 3% GBDF-Phytosome or an oil-in-water emulsion of 2% phosphatidylcholine (control). Participants who received the GBDF-Phytosome preparation were reported to experience significant increases in capillary blood flow and skin temperature, compared with baseline values, whereas no significant changes were observed for the control group. No between-group comparisons were reported.⁽⁷⁴⁾ These preliminary findings suggest that the effects of this preparation on skin microcirculation may deserve further investigation.

A phase II (open, uncontrolled) study explored the effects of standardised ginkgo leaf extract (EGb 761) given in combination with 5-fluorouracil (5-FU) in 44 patients with advanced progressive colorectal cancer who had previously received 5-FU.⁽⁷⁵⁾ The rationale for including ginkgo extract in the regimen was based on its reputed ability to increase local blood flow. Thus, it was hypothesised that ginkgo extract might 'enhance local tumour blood flow and thus improve the distribution of 5-FU'. In the study, participants received ginkgo extract 350 mg in 250 mL saline intravenously over 30 minutes on days 1–6, and 5-FU 500 mg/m² in 250 mL saline intravenously over 30 minutes on days 2–6. The regimen was repeated every three weeks until recurrence of tumour progression. Data from 32 patients who had received at least two courses of treatment were eligible for analysis. Of these patients, 69% experienced progression of disease, 25% experienced no change, and 6.3% ($n=2$) were in partial remission.⁽⁷⁵⁾

Side-effects, Toxicity

The safety and toxicity of ginkgo have been reviewed.^(G18,G21) Available data indicate that stan-

dardised extracts of ginkgo leaf are well tolerated when used at recommended doses.^(43,G21) Adverse effects are uncommon. A postmarketing surveillance study involving 10 815 patients who received a standardised extract (LI 1370) of ginkgo leaf reported that the frequency of adverse effects was 1.7%.^(G56) Adverse effects reported with standardised extracts of ginkgo leaf are generally mild, and include nausea, headache, gastrointestinal upset and diarrhoea; allergic skin reactions occur rarely.^(76,G21,G56)

A systematic review of nine randomised, double-blind, placebo-controlled trials of standardised ginkgo leaf extracts in patients with dementia of the Alzheimer type and/or multi-infarct dementia concluded that, overall, the frequency of adverse effects reported for ginkgo was not markedly different than that for placebo.⁽⁴⁵⁾ The largest trial included in this review involved 327 patients with mild-to-severe dementia related to Alzheimer's disease or multi-infarct dementia who received standardised ginkgo leaf extract (EGb 761) 40 mg orally three times daily ($n=166$), or placebo ($n=161$), for 52 weeks.⁽⁴⁹⁾ It was reported that there was no statistically significant differences between ginkgo and placebo in the number of participants reporting adverse events, or in the frequency and severity of adverse events. Of 188 adverse events reported during the study, 97 were reported by ginkgo recipients and 91 by placebo recipients. However, clinical trials generally only have the statistical power to detect common, acute adverse effects. Similar findings were reported in another systematic review/meta-analysis which included eight randomised, double-blind, placebo-controlled trials of ginkgo extract for the treatment of intermittent claudication, involving a total of 415 patients who received standardised extract of ginkgo leaf at doses of 120 or 160 mg daily, or placebo, for up to 24 weeks.⁽⁴⁷⁾ Five of the eight studies included reported (rarely) mild, transient adverse events occurring in ginkgo recipients; the remaining three studies, comprising almost 50% of the total number of patients, did not report any adverse events.

There are isolated reports of bleeding associated with ingestion of *Ginkgo biloba* extract. One report describes a 70-year-old man who experienced spontaneous bleeding from the iris into the anterior chamber of the eye one week after he began taking standardised ginkgo extract 80 mg daily.⁽⁷⁷⁾ A 61-year-old man who had taken ginkgo extract 120 mg or 160 mg daily for six months experienced a subarachnoid haemorrhage.⁽⁷⁸⁾ Another report describes a 33-year-old woman who began experiencing increasingly severe headaches, as well as double vision and nausea and vomiting, over sev-

eral months.⁽⁷⁹⁾ During the course of investigations, it was revealed that she had been consuming standardised ginkgo extract 120 mg daily for two years. Her symptoms improved, although her headaches were not entirely relieved, after evacuation of bilateral subdural haematomas which were identified following an MRI scan. On stopping ginkgo extract, her prolonged bleeding time was reduced, and on follow-up she was symptom-free. A causal relationship between ginkgo ingestion and bleeding in these cases has not been definitively established.

There is a report of acute myoglobinuria in a 29-year-old man who was a regular weight-trainer and who had been taking a combination preparation containing extracts of ginkgo (200 mg), guarana (*Paullinia cupana*, 500 mg) and kava (*Piper methysticum*, 100 mg).⁽⁸⁰⁾ The man was admitted to an intensive care unit with severe muscle pain and blood creatine kinase and myoglobin concentrations of 100 500 IU/L (normal values: 0–195) and 10 000 ng/mL (normal values: 0–90), respectively. Signs and symptoms subsided within six weeks. The relevance, if any, of ginkgo ingestion to the man's condition, is unclear.

Contact or ingestion of the fruit pulp has produced severe allergic reactions including erythema, oedema, blisters and itching.⁽⁶³⁾ The seed contains the toxin 4-O-methylpyridoxine which is reported to be responsible for 'gin-nan' food poisoning in Japan and China.⁽¹¹⁾ The main symptoms are convulsion and loss of consciousness and lethality is estimated in about 27% of cases in Japan, infants being particularly vulnerable.

Contra-indications, Warnings

The fruit pulp has produced severe allergic reactions and should not be handled or ingested. The seed causes severe adverse effects when ingested.

Ginkgo extract should only be used with caution in patients taking anticoagulant or antiplatelet agents.

Pregnancy and lactation No studies appear to have been reported on the effects of *G. biloba* leaf extracts or ginkgolides in pregnant or lactating women. In view of the many pharmacological actions documented and the lack of toxicity data, use of ginkgo during pregnancy and lactation should be avoided.

Pharmaceutical Comment

There is a vast scientific literature describing the pharmacological effects of ginkgo leaf extracts and their constituents.⁽⁸¹⁾ These data provide

some supporting evidence for the modern clinical uses of standardised ginkgo leaf extracts.^(1,2,8,13,14,16,19,20,76,82,83)

Also, standardised ginkgo leaf extracts are among the herbal preparations that have undergone most extensive clinical investigation. The effects of ginkgo extracts in dementia have been tested clinically mostly in trials involving patients with cognitive deficiency, Alzheimer's disease⁽⁴⁴⁾ and/or multi-infarct dementia. Some high-quality studies involving patients with dementia have reported significant beneficial effects for standardised ginkgo leaf extracts.^(48,49) However, systematic reviews/meta-analysis of all relevant randomised, double-blind, placebo-controlled trials have reported modest effects for ginkgo extract, compared with placebo,⁽⁴⁴⁾ and have concluded that further high-quality studies are required to establish the benefits of ginkgo in dementia.⁽⁴⁵⁾ Small randomised, double-blind, placebo-controlled trials investigating the cognitive enhancing effects of ginkgo extracts in healthy volunteers have reported conflicting results. Further study is required to determine whether ginkgo extracts are of value in cognitively intact individuals. The effects of ginkgo extract in patients with tinnitus have not been definitively established by trials carried out to date. A meta-analysis of trials of standardised ginkgo leaf extract in peripheral arterial occlusive disease found that ginkgo significantly improved pain-free walking distance, although the clinical relevance of the extent of improvement is questionable.⁽⁴⁷⁾

Generally, the intended uses of ginkgo are not suitable for self-medication.

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See also General References G3, G5, G18, G21, G29, G31, G32, G36, G43, G50, G54, G56, G63 and G64.

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