T. K. Lim

Edible Medicinal and Non-Medicinal Plants

Volume 3, Fruits

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Contents

Introduction

This book continues as volume 3 of a multi-compendium on *Edible Medicinal and Non-Medicinal Plants.* It focuses on edible fruits/seeds used fresh, cooked or processed into other by-products, or as vegetables, spices, stimulant, edible oils and beverages. It covers species from the following families: Ginkgoaceae, Gnetaceae, Juglandaceae, Lauraceae, Lecythidaceae, Magnoliaceae, Malpighiaceae, Malvaceae, Marantaceae, Meliaceae, Moraceae, Moringaceae, Muntigiaceae, Musaceae, Myristicaceae and Myrtaceae. However, not all the edible species in these families are included for want of coloured illustrations. The edible species dealt with in this work include to a larger extent lesser-known, wild and under-utilized crops and also common and widely grown crops.

As in the preceding two volumes, topics covered include: taxonomy (botanical name and synonyms); common English and vernacular names; origin and distribution; agro-ecological requirements; edible plant part and uses; plant botany; nutritive and medicinal/pharmacological properties with up-to-date research findings, traditional medicinal uses other non-edible uses; and selected/cited references for further reading.

Ginkgoaceae is a family of temperate gymnosperms which appeared during the Mesozoic Era, of which the only extant representative and living fossil is *Ginkgo biloba*. *Gingkgo biloba* has both culinary and medicinal uses. Several thousands of scientific papers have been published on the phytochemicals and associated pharmacological and medicinal properties of the aerial plant parts of *G. biloba*. The edible seed is rich in niacin, and vitamin A, phosphorus and potassium. It is a good source of starch and protein, but is low in unsaturated or monounsaturated fats. The seed also contains vitamin B1 (thiamine), B2 (riboflavin), vitamin C and iron, sodium and calcium (USDA 2010). Important bioactive constituents reported to occur in the medicinally used Ginkgo leaves include terpene trilactones, i.e., ginkgolides A, B, C, J and bilobalide, many flavonol glycosides, biflavones, proanthocyanidins, alkylphenols, simple phenolic acids, and polyprenols (van Beek 2002).

Gnetaceae is a representative of tropical gymnosperms. *Gnetum*, a genus of about 30–35 species, is the sole genus in the family Gnetaceae and order Gnetales. They are tropical, evergreen trees, shrubs and lianas and occur in Indomalaysia, tropical parts of West Africa, Fiji and the northern regions of South America. Many *Gnetum* species including *Gnetum gnemon* are edible, with the seeds being roasted, and the foliage used as a leaf vegetable. *Gnetum gnemon* contains bioactive chemicals like flavonostilbenes and stilbenes that play a role in various pharmacological activities. *Gnetum gnemon* is found in Assam, southeast Asia, the Philippines and Papua New Guinea, Fiji, Solomon Islands and Vanuatu.

The large and economically important Juglandaceae, or the walnut and hickory family is a family of deciduous, semi-evergreen, or evergreen, monoecious (rarely dioecious) trees, rarely shrubs in the order Fagales. The family contains 9 genera and 50 or more species, which are

distributed mainly in the north temperate zone but extend through Central America along the Andes Mountains to Argentina and, in scattered stands, from temperate Asia to the highlands of Java and New Guinea. The commercially important nut-producing trees include walnut (*Juglans regia*), pecan (*Carya illinoinensis*), and hickory (*Carya* spp). Walnut, hickory, and gaulin (*Alfaroa costaricensis*) are also valuable timber trees. Both Persian walnut, *Juglans regia*, and pecan nut which are covered in this volume, have culinary, nutritive and medicinal attributes.

The Lauraceae or laurel family contains about 55 genera and over 2,000 species world-wide, mostly from warm subtropical or tropical regions, especially Southeast Asia and Brazil. Most are aromatic evergreen trees or shrubs, a few genera are deciduous, and *Cassytha* is a genus of parasitic vines. The Lauraceae are economically important as sources of medicine, timber, nutritious fruits (e.g., *Persea americana*), spices (e.g. *Cinnamomum aromaticum*, *C. verum, Laurus nobilis* covered in later volumes), and perfumes and essential oils. Avocados are important oil-rich and nutritious fruit with health and medicinal properties, that are now planted in warm climates across the world. *Litsea garciae* is another edible tropical fruit but is lesser-known and under-utilised. The hard wood of several species is a source for timber around the world.

Lecythidaceae, a tropical plant family, is indigenous to South America and Madagascar. It has about 20 genera and 250–300 species of woody plants. Neotropical Lecythidaceae comprises ecologically dominant species in the Amazonian forests and are spectacular plants with showy flowers and large woody fruits. They include the edible and economically important Brazil nut (*Bertholletia excelsa*), and the edible, lesser-known paradise nut or monkey nut (*Lecythis* spp.). Other edible but lesser-known species are the *Barringtoni*a species which are eaten in southeast Asian and the Pacific Island countries. The genus *Barringtonia* is also placed in the family, Barringtoniaceae.

Magnoliaceae comprises about 225 species in 7 genera. Magnoliaceae is better known for its ornamental species and timber species. The bark and flowers from several species are believed to possess medicinal qualities. In this family the edible fruit species that is treated in this volume is *Michelia mediocris*, a highly valued and productive indigenous Vietnamese timber species. The fruit and seeds of this species have good potential as a spice.

Malpighiaceae comprises approximately 75 genera and 1,300 species, all of which are native to the tropics and subtropics. About 80% of the genera and 90% of the species occur in the New World (the Caribbean and the southernmost United States to Argentina) and the rest in the Old World (Africa, Madagascar, and Indomalaysia to New Caledonia and the Philippines). The Malpighiaceae are shrubs, small trees, or woody lianas. Of the two edible genera *Malpighi*a and *Bunchosi*a, the former also has species with pharmacological and medicinal attributes. Acerola (*Malpighia emarginata*) has been reported to have very high vitamin C content, much higher than other fruits like pineapple, araçá (*Eugenia stipitata*), cashew, guava, kiwi, orange, lemon, and strawberry. Acerola has also reported to have carotenoids and bioflavonoids which contribute to its high antioxidant capacity and provide important nutritive and pharmacological values.

The Marantaceae or arrowroot or prayer plant family, is a family of flowering, herbaceous plants under the order Zingiberales. Based on nucleotide sequence variation, 59 species (21 genera) formed the ingroup, and 12 species (12 genera) of other Zingiberales formed the outgroup (Andersson and Chase 2001). There is no support for the traditional subdivision of Marantaceae into a triovulate and a uniovulate tribe or the informal groups previously proposed (Andersson 1981). Based on phylogeny it is concluded that Africa where early diversification of the family took place, in spite of being much poorer in species, is the most likely ancestral area of Marantaceae. The family is found in the lowland tropics of Asia and Africa, mainly (80%) in American tropics, occasionally subtropics, southern United States to northern Argentina. The family is known for its large starchy rhizomes and house-hold ornamental plants. The most significant food plant is *Maranta arundinacea*, cultivated in tropical regions

worldwide for arrowroot starch. However, one species, *Thaumatococcus daniellii* produces fruit with edible aril which furnished a natural source of thuamatin, an intensely sweet protein which is about 100,000 times sweeter than sugar on a molar basis and 3,000 times on a weight basis. Thaumatin is used as a sweetener and flavour enhancer for food, desserts, confectionary and beverages.

Malvaceae has been circumscribed to embrace the non-monophyletic families, Bombacaceae, Tiliaceae, and Sterculiaceae, which have always been considered very close to the traditional Malvaceae *sensu stricto,* a very homogeneous and cladistically monophyletic group. Following this circumscription which is based on newer techniques, Malvaceae *sensu lato* now include all of these families so as to have a monophyletic group. The circumscription of the Malvaceae is still controversial. A close relationship between Bombacaceae and Malvaceae has long been recognized but until recently the families have been kept separate in most classification systems, and continue to be separated in many recent references, including the reference work in classification of flowering plants by Heywood et al. (2007) and Takhtajan (2009). However, the Angiosperm Phylogeny Group (2003, 2009) have lumped them together into a larger family Malvaceae *sensu lato*. Heywood et al. (2007) assert "although closely related to Malvaceae, molecular data supports their separation. Only pollen and habit seem to provide a morphological basis for the separation." Contrariwise they say: "One approach is to lump them (the families in the core Malvales, including Bombacaceae) all into a 'super' Malvaceae, recognizing them as subfamilies. The other, taken here, is to recognize each of these ten groups as families". Members of the Bombacaceae have been covered in volume 1. In this volume, members of Sterculiaceae (e.g. kola, cacao, cupuassu) are included together with species belonging to the traditional Malavaceae *sensu stricto* which comprises the mallows, abutilons, cotton, okra, hibiscuses and related plants. Species of Malvaceae *sensu lato* provide sources of fibre, food and beverages, medicines, timber, and in horticulture (ornamental). Also some members are deemed as weeds or invasive species. The species with edible fruits/seeds and medicinal properties covered in this volume include *Grewia asiatica, Abelmoschus esculentus, Scaphium macropodum, Sterculia foetida, Sterculia monosperma and Sterculia parviflora, Theobroma bicolour, T. cacao* and *T. grandiflorum.* Due to their high concentration of catechins and procyanidins, bioactive compounds with distinct properties, cocoa and chocolate products may have beneficial health effects against oxidative stress and chronic inflammation, risk factors for cancer and other chronic diseases (Maskarinec 2009).

The Meliaceae or mahogany family comprises about 50 genera and 550 species, with a pantropical distribution but a weak penetration into the temperate zone. One genus (*Toona*) extends north into temperate China and south into southeast Australia, and another (*Melia*) nearly as far north. The species are evergreen or deciduous trees or tree-lets and rarely shrubs; the bark sometimes with a milky latex. Meliaceae species are very common trees in the understory of lowland primary forest throughout Malesia. Various species are used for vegetable oil, soap-making, insecticides, and highly prized wood mahogany (*Swietenia* spp. and *Aglai*a spp.). Species that provide edible fruits are mainly tropical and include various *Aglaia* spp., the duku, langsat, lonkong (*Lansium domesticum*) and the santol (*Sandoricum koetjape*). The latter two species are popular and widely eaten fruits in southeast Asia and also have several pharmacological properties; various plant have been used in traditional folkloric medicine.

The Moraceae family comprises between 37 and 43 genera and 1,100–1,400 species, widespread in tropical and subtropical areas but less common in temperate areas. They comprise trees, shrubs, vines, frequently with milky or watery latex. Flowers occur usually in heads and are unisexual; ovule is anatropous or campylotropous and united into a more or less fleshy compound fruits. Economically, the most important species are those of *Morus* and *Maclura* associated with the production of silk. Some species in *Broussonetia*, *Maclura*, and *Morus* are important for paper making. Some *Artocarpus* and *Broussonetia* species are used for furniture or timber.

Some species in *Artocarpus*, *Ficus*, *Prainea*, *Treculia* and *Morus* have edible fruit. The common edible tropical *Artocarpus* species include the bread fruit *A. altilis*, the breadnut *A. camansi*, jackfruit *A. heterophyllus*, chempedak *A. integer* and the marang or terap *A. odratissimus*. Many of the edible *Artocapus s*pecies contain bioactive compounds such as the prenylated flavonoids or stilbenoids, and lectins which have significant pharmacological activities. The edible *Ficus* species include the common and popular fig *Ficus carica* and other lesser-known fig trees like the elephant ear fig tree, *F. auricalata*, cluster fig, *F. racemosa*, the creeping ivy fig, *F. pumila* and dinner plate fig tree *F. dammaropsis*. Many of the *Ficus* species have medicinal attributes. *Prainea limpato* is a rare species with unusual stellate, grosteques looking fruit which is edible. The edible *Morus* species include the red (*M. rubra*), white (*M. alba*) and black (*M. nigra*) mulberries, the plant parts of which have bioactive chemicals with pharmacological activities.

Moringaceae or horseradish tree family comprise only one genus with 12 species, found mainly in tropical and subtropical climates. The most widely known species is *Moringa oleifera*, a multi-purpose tree native to the foothills of the Himalayas in north-western India and cultivated pan-tropically. *M. stenopetala*, an African species, is also widely cultivated, but to a much lesser extent than *M. oleifera*. *Moringa oleifera* (horseradish or drumstick tree) has edible fruits and leaves. The seeds provide "ben oil" used in perfumery and light lubricants and the seeds are also used to purify water and removal of industrial pollutants and heavy metals. *Moringa oleifera* oil was found to have potential as acceptable feedstock for biodiesel. The leaves made highly nutritious cattle feed and the roots are also a source of edible condiment. The tree's bark, roots, fruit, flowers, leaves, seeds, and gum are also used medicinally.

Muntigiaceae is indigenous to the neotropics. The small family includes the monotypic genera, *Muntingi*a, *Dicraspidia* and *Neotessmania*. They were previously included in Elaeocarpaceae, Tiliaceae or Flacourtiaceae. Muntigiaceae is closely related to the rosid order Mavales (Sterculiaceae, Tiliaceae, Bombaceae and Malvaceae) and several other families but the relationships are still obscure and unresolved. *Muntingia calabura,* the type species, has edible fruits and contains phytochemicals with pharmacological properties.

The genus *Musa* in the family Musaceae is divided into four sections, including members of both seeded and non-seeded (parthenocarpic) types. Two of the sections contain species with a chromosome number of 2n = 20 (*Callimusa* and *Australimusa*) while the other two sections (*Eumusa* and *Rhodochlamys*) have species with a basic chromosome number of 11 (2n = 22). The majority of cultivated bananas arises from the *Eumusa* group of species. This section is the biggest in the genus and the most geographically widespread, with species being found from India, throughout South East Asia to the Pacific Islands.

Linnaeus first classified banana (*Musa*) into two species based on their culinary use, *Musa sapientum* for dessert bananas and *Musa paradisiaca* for plantains. This distinction is entirely semantic and artificial with no botanical basis and no consistent culinary basis. In 1948, Cheesman found that *Musa sapientum* and *Musa paradisiaca*, described by Linnaeus, were actually cultivars and intra and interspecific hybridizations of two wild and seedy species, *Musa acuminata* and *Musa balbisiana,* each contributing the A and B genomes respectively. The identification of *Musa* cultivars has traditionally been based upon various combinations of morphological, phenological and floral criteria. The preponderance of cultivars magnified the taxonomic problems of classifying *Musa* until Simmonds and Shepherd (1955) devised a scoring system based on 15 diagnostic morphological characters to differentiate *M. acuminata* cultivars from *M. balbisiana* cultivars and their hybrids into six genome groups. Generally, modern classifications of banana cultivars follow Simmonds' and Shepherd's system. The accepted names for bananas are *Musa acuminata*, *Musa balbisiana* or *Musa acuminata* × *balbisiana*, depending on their ancestral genome. Examples of the new classification scheme adopted include: *Musa acuminata* (AA group) 'Lakatan', *Musa acuminata* (AAA Group) 'Gros

Michel', *Musa acuminata x balbisiana* (AAB Group) 'Horn Plantain', *Musa acuminata x balbisiana* (AAB Group) 'Pisang Raja' *Musa acuminata x balbisiana* (ABB Group) 'Bluggoe'. Other edible Muss spp covered in this volume are *Musa troglodytarum* (Fei bananas), *Musa velutina* and *Musa zebrina*.

As described above, most banana cultivars are derived from two species, *Musa acuminata* (A genome) and *Musa balbisiana* (B genome). However, Shepherd and Ferreira (1982) found cultivars derived from hybridizations with *M. schizocarpa* (S genome), which was subsequently confirmed by Carreel et al. (1993). Several landraces containing the two genomes *acuminata* and species from the Australimusa section (T genome) and two landraces containing the three genomes, A, B and T have been found in Papua New Guinea and a Philippine clone (Butuhan) is considered to be the result of an ancient hybridization between *M. balbisiana* and *M. textilis* (T genome) (Carreel et al. 1993).

Myristicaceae, the nutmeg family comprises about 20 genera and approximately 500 species of evergreen trees and shrubs found in tropical Asia to the Pacific islands and also in Africa and tropical America. The most well known and widely cultivated species is the spice, *Myristica fragrans*, the nutmeg or mace. Nutmeg has culinary and medicinal uses. Two other edible species covered in this volume are *Myristica fatua Myrtaceae*, and *Horsfeldia australiana.*

Myrtaceae , the myrtle family, placed within the order Myrtales comprises at least 133 genera and 3,800 species of woody shrubs to tall trees. It has centers of diversity in Australia, southeast Asia, and tropical to southern temperate America, but has little representation in Africa. The family is distinguished by a combination of the following features: entire aromatic leaves containing oil glands, flower parts in multiples of four or five, ovary half inferior to inferior, numerous brightly coloured and conspicuous stamens, internal phloem, and vestured pits on the xylem vessels. Until relatively recently, the family has been considered to be naturally divisible into two subfamilies, the fleshy-fruited Myrtoideae and the capsular-fruited Leptospermoideae. This was seriously challenged by Johnson and Briggs (1984) who concluded, from a cladistic analysis based on morphological and anatomical characters, that these subfamilies must be abandoned. Species of the myrtle family provide many valuable products, including timber (e.g. *Eucalyptus*), essential oils and spices (e.g. allspice, cloves), and horticultural plants (e.g. ornamentals such as *Verticordia*, *Callistemon, Leptospermum*) and edible fruits such as the common guava, strawberry guava, other *Psidium* spp., Feijoa, myrtle, rose myrtle, jaboticaba*, Eugenia* spp*. Myrciaria* spp. *and Syzygium* spp. Many of these myrtaceous plants also have medicinal properties.

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Ginkgo biloba

Scientific Name

***Ginkgo biloba* L.**

Synonyms

Ginkgo biloba Siebold & Zucc., *Ginkyo biloba* Mayr, *Pterophyllus salisburiensis* Nelson, *Saliburya biloba* Hoffmanns., *Saliburya biloba* Hoffmansegg, *Salisburia adiantifolia* Sm., *Salisburia biloba* (L.) Hoffsgg.

Family

Ginkgoceae

Common/English Names

Common Ginkgo, Duck's Foot Tree, Gingko, Gingko Biloba, Gingko Nuts, Golden Fossil Tree, Kew Tree, Maidenhair Tree

Vernacular Names

Afrikaans: Vrekboom Ginkyo;
Arabic: Gingko, Ginkgoes, Ginkgos, Mabad Ag;
Bohemian: Ginko, Jinan Dvoulaločný;
Brazil: Guincos, Nogueira-Do-Japão;
Chinese: Ginnan, Icho, Paikua Su, Pakgor, Bai Guo, Su, Ya-Chiao;
Croatian: Ginko;
Czech: Jinan Dvoulalocný;
Dutch: Chinese tempelboom, Ginkgo, Japanse Notenboom, Japanse tempelboom, Tempelboom, Waaierboom;
Danish: Ginkgo,Tempeltrć;
Dutch: Chinese Tempelboom, Gingko, Ginkgo Biloba, Japanse Notenboom, Japanse Tempelboom.
Eastonian: Hõlmikpuu;
Finnish: Neidonhiuspuu, Neidonhiuspuut, Temppelipuu;
French: Arbre Aux Mille Écus, Arbre Aux Quarante Écus, Arbre Fossile, Arbre Sacré Des Temples D'asie, Noyer Du Japon Arbre À Noix, Arbre Aux Quarante Ecus, Arbre Des Pagodes, Noyer Du Japon;
German: Fächerblattbaum, Ginkgobaum, Ginko, Goldfruchtbaum, Japanbaum, Japanischer Nussbaum, Mädchenhaarbaum, Silberaprikose, Tempelbaum, Chinesischer Tempelbaum, Elefantenohrbaum, Entenfußbaum, Fächerbaum, Fächerblattbaum, Frauenhaarbaum, Goethebaum, Großvater-Enkel-Baum, Japanischer Nußbaum, Japanischer Tempelbaum, Mädchenhaarbaum, Silberaprikose, Silberpflaume, Tempelbaum, Weiße Frucht;
Greek: Gigko, Gingko, Gkingko;
Hungarian: Ginkgófa, Páfrányfenyő;
Icelandic: Musteristré, Musterisviður;
India: Balkuwari (Hindu);
Italian: Ginko;
Japanese: Ichou, Ginkyo, Ginnan;
Korean: Apgaksu, Baekgwamok, Gongsonsu, Eun-Hang-Na-Moo, Haeng-Ja-Mok, Okgwamok;

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Nepali: Bal Kumari;
Norwegian: Ginkgo, Tempeltre;
Polish: Chiński, Miłorząb Dwudzielny, Miłorząb Dwuklapowy, Miłorząb Japoński;
Portuguese: Ginkgo, Nogueira-Do-Japão;
Russian: Ginkgo;
Singapore: Pakgor Su;
Slovašcina: Ginko Dvokrpi;
Slovencina: Ginko Dvojlaločné;
South Africa: Vrekboom;
Spanish: Arbol Sagrado, Árbol De Oro, Árbol De Las Pagodas, Árbol De Los Cuarenta Escudos, Árbol De Los Escudos, Gingo, Ginkgo;
Swedish: Gingko, Kinesiskt Tempelträd, Tempelträd;
Taiwan: Yin Xing;
Thailand: Pae Guay;
Turkish: Fosil Ağacı, Gingko Ağacının, Japon Eriği, Japon Eriği Olarak Bilinir, Mabet Ağacı;
Vietnamese: Bạch Quả, Cây Bạch Quả, Cây lá quat.

Origin/Distribution

Ginkgo is native to Far East Asia – China, Japan and Korea. It is commonly planted in Buddhist and Taoist temples in East Asia. It has been introduced to other temperate areas in both hemispheres.

Agroecology

Ginkgo is a cool temperate species but does not tolerate extreme frost. It grows in lowland broad-leaved forests and valleys up to 2,000 m altitude. It tolerates a range of soil types but thrives on acidic, well-watered, well-drained, (pH = 5–5.5), yellow loess. It thrives best in full sun.

Edible Plant Parts and Uses

Peeled nuts (endosperms) are eaten roasted, baked, boiled in soups, porridge, stews, or fried in dishes with meat or other vegetables. Ginkgo endosperms are popular in congee or herbal sweet-dessert soups, commonly serves at birthdays, weddings and the lunar New year as part of the famous vegetarian dish called Buddha's Delight. Japanese used the endosperm in dishes such as *Chawanmushi* and in other dishes. The endosperms are available dried or canned whence it is sold as "White nuts" in many Asian grocery stores. Roasted endosperms are relished in China and Japan and marketed widely in East Asia. They are also used as spice especially for fish dishes. A report says that the seed can be eaten raw whilst another says that large quantities of the seed are toxic. It needs to be heated or cooked before being eaten in order to destroy a mildly acrimonious compound. An edible oil is obtained from the seed.

Botany

A deciduous, resinous, dioecious branched tree, to 40 m tall with light grey or greyish brown bark that is longitudinally fissured especially on old trees and with trunk diameter reaching 1.5 m in old trees (Plates 1 and 2). Male trees show an upright and irregular form, female trees are low and spreading. Branches are stiff, covered with elliptic leaf scars and dimorphic, the elongated bearing alternate leaves and the abbreviated terminated with whorl of leaves surrounding a bud (Plates 1, 2 and 4). Leaves (Plates 2, 3, 4 and 5) are borne on 3–10 cm long petioles which are channelled on the adaxial surface, lamina is

Plate 1 Habit of old Ginkgo tree

Plate 2 Lush foliage of Ginkgo tree

Plate 3 *Ginkgo* leaves

Plate 4 Fruiting Ginkgo branch

Plate 5 Close-up Ginkgo leave and fruit

Plate 6 Hard-shelled Ginkgo seeds

fan-shaped, to 13×8–15 cm, mostly 1.5 times wider than long, glossy pale green (resembling those of the maidenhair fern or *Adiantum*), turning bright yellow in Autumn, with irregularly toothed or notched upper margins and dichotomously veined. Trees flower after 20–35 years, females exhibiting an abundance of ovules in pairs on stalks each containing an egg cell, initially very green, but later turning greenish-yellow, then orange and brown. The male flowers are ivory-coloured, catkin-like pollen cones (microsporangia), 3–6 on each short shoot containing boat-shaped pollen sacs with widely gaping slit. A single naked ovule ripens into a elliptic, narrowly obovoid, or ovoid, 2.5–3.5×1.6–2.2 cm green fruit (Plates 4 and 5). Seed with yellow, or orange-yellow, glaucous, sarcotesta with acrid, rancid odour when ripe; sclerotesta white, with 2 or 3 longitudinal ridges; endotesta pale reddish brown (Plates 6 and 7). The fleshy-coated seeds are frequently incorrectly designated as fruits or nuts.

Plate 7 Ginkgo seeds intact and de-shelled

Nutritive/Medicinal Properties

The nutrient composition (per 100 g edible portion) of raw ginkgo nuts (exclude 24% shell refuse) was reported as water 55.20 g, energy 182 kcal (761 kJ), protein 4.32 g, total lipid 1.68 g, ash 1.20 g, carbohydrates 37.60 g, Ca 2 mg, Fe 1.00 mg, Mg 27 mg, P 124 mg, K 510 mg, Na 7 mg, Zn 0.34 mg, Cu 0.274 mg, Mn 0.113 mg, vitamin C 15 mg, thiamine 0.220 mg, riboflavin 0.090 mg, niacin 6.00 mg, pantothenic acid 0.160 mg, vitamin B-6 0.328 mg, total folate 54 μg, vitamin A RAE 28 μg, vitamin A 558 IU, total saturated fatty acids 0.319 g, 14:0 (myristic acid) 0.006 g, 16:0 (palmitic acid) 0.288 g, 18:0 (stearic acid) 0.016 g; total monounsaturated fatty acids 0.619 g, 16:1 undifferentiated (palmitoleic acid) 0.079 g, 18:1 undifferentiated (oleic acid) 0.512 g, 20:1 (gadoleic acid) 0.010 g; total polyunsaturated fatty acids 0.618 g, 18:2 undifferentiated (linoleic acid) 0.578 g, 18:3 undifferentiated (linolenic acid) 0.021 g; tryptophan 0.071 g, threonine 0.268 g, isoleucine 0.209 g, leucine 0.316 g, lysine 0.206 g, methionine 0.055 g, cystine 0.023 g, phenylalanine 0.171 g, tyrosine 0.061 g, valine 0.283 g, arginine 0.420 g, histidine 0.102 g, alanine 0.247 g, aspartic acid 0.543 g, glutamic acid 0.836 g, glycine 0.232 g, proline 0.347 g and serine 290 g (U.S. Department of Agriculture and Agricultural Research Service 2010).

The seed is rich in niacin, and vitamin A, phosphorus and potassium. It is a good source of starch and protein, but is low in fats. These fats are mostly unsaturated or monounsaturated. The seed also contain vitamin B1 (thiamine), B2 (riboflavin), vitamin C and iron, sodium and calcium.

Other Phytochemicals

Important bioactive constituents reported to occur in the medicinally used *Ginkgo* leaves include terpene trilactones, i.e., ginkgolides A, B, C, J and bilobalide, many flavonol glycosides, biflavones, proanthocyanidins, alkylphenols, simple phenolic acids, 6-hydroxykynurenic acid, 4-O-methylpyridoxine and polyprenols (van Beek 2002). However, in the commercially important Ginkgo extracts some of these compound classes may not be present. Since 2001 over 3,000 papers on *Ginkgo biloba* had been published, and about 400 of them pertain to chemical analysis in a broad sense and in the same period over 2,500 patents were filed on *Ginkgo* and the very few related to analysis were mentioned as well (van Beek and Montoro 2009). A sharp contrast to the plethora of papers on terpene trilactones, flavonol glycosides, and ginkgolic acids forms the low number of papers on biflavones, proanthocyanidins, simple phenolics, simple acids, and other constituents that make up the remaining 70% of Ginkgo standardised extracts.

Five terpene lactones were determined in ginkgo dry extract (Ekman et al. 2009). The content of bilobalide was found to be in the range of 2.6–3.4% in all samples, whereas the sum of ginkgolides A, B and C was found to be in the range of 3.0–3.6%. Ginkgolide J was found in the range of 0.3–0.6%.

Six flavonoid constituents (quercetin, isorhamnetin, kaempferol, bilobetin, ginkgetin and sciadopitysin) were isolated from *Ginkgo biloba* leaves (Chi et al. 1997) and also the flavonoid, 5, 7, 4′-trihydroxy-flavone from the leaves (Chi and Xu 1998). Wang et al. (2007a) identified and purified genistein from the hydrolysate of *G. biloba* leaf extract. Eight flavonoid compounds, namely rutin, myricetin, quercitrin, quercetin, luteolin, kaempferol, apigenin, and isorhamnetin were determined in *G. biloba* (Tang et al. 2010).

Five types of ginkgolic acid (C13:0, C15:1, C17:2, C15:0 and C17:1) were determined in *Ginkgo biloba* leaves (Yang et al. 2002). The relative percentage content of ginkgolic acids C15:1 and C17:1 was about 85%. Ginkgolic acid C17:2 had not been reported in China. The content of ginkgolic acids in the leaves of *Ginkgo biloba* collected in April, May and June was 1.48%, 1.19% and 1.11% respectively. The average recovery of *Ginkgo biloba* leaves collected in June was 97.0%. Six kinds of ginkgolic acid (C13:0, C15:1, C17:2, C15:0, C17:1 and an unknown compound C17:3 tentatively) were determined in the *Ginkgo biloba* extract (Wu et al. 2003). The relative percentage concentration of ginkgolic acids C13:0, C15:1 and C17:1 was above 94%. The content of ginkgolic acids in one type of *Ginkgo biloba* extract preparations (tablet) was 49.2 μg/g. The average recovery was 98.2%.

An antifungal protein ginkbilobin-2 (Gnk2) was isolated from *Ginkgo biloba* seeds (Miyakawa et al. 2007). It did not exhibit homology to other pathogenesis-related proteins, but did displayed homology to the extracellular domain of plant cysteine-rich receptor-like kinases. *G. biloba* 11S seed storage protein, ginnacin, was purified by sequential anion-exchange and gel-filtration chromatography (Jin et al. 2008). *G. biloba* also contained allergenic and toxic compounds such as ginkgotoxin (Leistner and Drewke 2010).

A number of secondary metabolites comprising terpenoids, polyphenols, allyl phenols, organic acids, carbohydrates, fatty acids and lipids, inorganic salts and amino acids had been isolated from the plant. However, the main bioactive constituents found were terpene trilactones and flavonoid glycosides, considered responsible for the pharmacological activities of its standardized leaf extract (Singh et al. 2008). Leaf extract of *Ginkgo biloba* (GBE) was reported to be increasingly used as an herbal medicine for the treatment of neurodegenerative, cardiovascular and cerebrovascular diseases (Gu et al. 2009). Extracts from the leaves of *Ginkgo biloba* had been used in Chinese medicine for thousands of years (He et al. 2009). To-date, various standardized preparations from *G. biloba* leaf extract had been developed. Products prepared from *Ginkgo biloba* are leading botanical dietary supplements in the United States and top-selling phytopharmaceuticals especially in Europe and (Leistner and Drewke 2010). In European medicine, *G. biloba* medications are employed to improve memory, to treat neuronal disorders such as tinnitus or intermittent claudication, and to ameliorate brain metabolism and peripheral blood flow. During the past 20 years, an estimated two billion daily doses (120 mg) of *Ginkgo biloba* (GB) had been sold (Pérez 2009). French and German agencies consider it to be effective for the treatment of several diseases. *Ginkgo biloba* (EGb 761) extract had been reported to be the most prescribed phytomedicine in Europe for the treatment of cerebral insufficiency and vascular diseases (Vilar et al. 2009). European Regulation 1924/2006 states that all health claims made on foods need to be substantiated scientifically. After evaluation of 35 human intervention studies, the three health claims, namely improvement of blood circulation, improvement of symptoms of old age and improvement of memory of herbal products with *G. biloba* could not be substantiated because of the lack of evidence (Fransen et al. 2010).

Ginkgo biloba leaves were found to contain two major bioactive constituents, flavonoid glycosides (24%) and terpene lactones (6%), along with less than 5 ppm of the allergenic component, ginkgolic acid (Mahadevan and Park 2008). The *Ginkgo* leaf extract had been reported to have neuroprotective, anticancer, cardioprotective, stress alleviating, and memory enhancing effects and possible effects on tinnitus, geriatric complaints, and psychiatric disorders. The therapeutic mechanisms of action of the Ginkgo leaf extract had been suggested to be through its antioxidant, antiplatelet, antihypoxic, antiedemic, hemorrheologic, and microcirculatory actions, where the flavonoid and the terpenoid constituents may act in a complementary manner. Toxicity studies showed Ginkgo leaf extract to be relatively safe for consumption, although a few side effects had been reported, that is, intracerebral hemorrhage, gastrointestinal disturbances, headaches, dizziness, and allergic skin reactions. The use of Ginkgo leaf extract may be promising for

treatment of certain conditions, although its long-term use still needs to be evaluated.

A plethora of papers running into several thousands have been published on the phytochemicals and associated pharmacological and medicinal properties, some of which are highlighted below.

Antioxidant Activity

Flavonoids of *Ginkgo biloba* were shown to have some protective effects on the damage of antioxidizing system of mice induced by acute alcohol administration (Yao et al. 2005). The *G. biloba* supplement prevented the rise of malondialdehyde level and the decrease of glutathione, glutathione peroxidase and superoxide dismutase caused by acute alcohol intakes. The findings of studies by Brunetti et al. (2006) showed that *Ginkgo biloba* extract containing 24.1% flavonoids and 181% terpene lactones bilobalide (0.542%), ginkgolide A (0.570%), ginkgolide B (0.293%), ginkgolide C (0.263%), and ginkgolide J (0.138%) pretreatment completely reversed both basal and hydrogen peroxide-stimulated isoprostane production. Isoprostanes are prostaglandin (PG) isomers generated from oxygen radical peroxidation of arachidonic acid, which are reliable markers of membrane oxidative damage. Amyloid beta-peptide-induced isoprostane production was also inhibited, both in young and aged rats. This suggested that the oxygen radical scavenging properties of the *Ginkgo biloba* extract were fully effective in young, as well as in old rats, with a greater inhibition of isoprostane production in the latter.

A novel polysaccharide (GBP50S2) with high antioxidant activity was isolated from *Ginkgo biloba* (Yuan et al. 2010). The backbone of GBP50S2 was composed of (1 → 4)-linked α-d-mannopyranosyl residues which branched at O-3. The three branches consisted of β-l-rhamnopyranosyl residues, (1 → 4)-linked α-d-galactopyranosyl terminated with β-l-rhamnopyranosyl residues, and (1 → 3,4)-linked α-d-mannopyranosyl terminated with β-l-rhamnopyranosyl residues, respectively. In the in-vitro antioxidant assay, GBP50S2 was found to possess DPPH (2,2-diphenyl-1-picrylhydrazyl) radical-scavenging activity and hydroxyl radical-scavenging activity with IC_{50} values of 0.412 mg/ml and 0.482 mg/ml, respectively.

The results of studies by Qa'dan et al. (2011) showed that all the isolated compounds from the tannin fraction of *G. biloba* leaves, namely the new trimeric prodelphinidin, epigallocatechin-(4β → 8)-epigallocatechin-(4β → 8)-catechin, catechin, epigallocatechin, gallocatechin, and three dimeric proanthocyanidins exhibited potent free radical scavenging activities which were higher than that of BHT (butylated hydroxytoluene) (IC_{50} = 15.5 μg/ml). This suggested that the condensed tannins from *G. biloba* leaves strongly contributed to the overall antioxidant effects. The dimeric prodelphinidin epigallocatechin-(4β → 8)-epigallocatechin exhibited the strongest DPPH radical scavenging activity with IC_{50} value of 1.7 μg/ml followed by the trimeric prodelphinidin, epigallocatechin-(4β → 8)-epigallocatechin-(4β → 8)-catechin (IC_{50} = 2.1 μg/ml). The crude leaf extract exhibited high DPPH radical scavenging activity with IC_{50} of 15.5 μg/ml comparable with that of BHT. Polymeric proanthocyanidins were eluted after the fractions of flavonol glycosides and biflavone glycosides from an extract from *Ginkgo biloba* leaves (Qaâdan et al. 2010). A purified proanthocyanidin polymer accounted for 86.6% of the total proanthocyanidins, and for 37.7% of the total antioxidant activity of the leaf extract.

In a comparative in-vitro antioxidative study of the fluid extract from maidenhair tree (*Ginkgo biloba*), motherwort (*Leonurus cardiaca*) and hawthorn (*Crataegus monogyna*), the radical scavenging capacity in the DPPH* reaction system determined was in the following order: hawthorn (70.37%) < the fluid extract of maidenhair tree (82.63%) < the fluid extract of motherwort (84.89%), while in the ABTS* + (2,2′-azinobis(3-ethylbenzthiazoline-6-sulphonic acid)) reaction system, the manifestation of the radical scavenging capacity was in the following order: the fluid extract of hawthorn (87.09%) < the fluid extract of motherwort (88.28%) < the fluid extract of maidenhair tree (88.39%) (Bernatoniene et al. 2009). The results showed that in the DPPH* reaction system, fluid extract of motherwort

manifested higher antioxidant activity, compared to the fluid extracts of maidenhair tree and hawthorn. By contrast, in the ABTS*+reaction system, higher antioxidant activity was found in the fluid extract of maidenhair tree, compared to the fluid extracts of motherwort and hawthorn. This would suggest that preparations manufactured from these herbal raw materials could be used as effective preventive means and valuable additional remedies in the treatment of diseases caused by oxidative stress.

Studies conducted by Erdogan et al. (2006) found that bleomycin induced oxidative stress in rats could be prevented by *Ginkgo biloba* treatment via high plasma anti-oxidant enzyme (superoxide dismutase, glutathione peroxidase) activities together with decreased radical production from xanthine oxidase. Bleomycin is an antineoplastic agent and its clinical usage is limited by its toxicity in inducing plasma oxidative stress injury. Studies by Liu et al. (2009c) showed that extract of *Ginkgo biloba* (EGb) had stronger antioxidant activities than flavonoids, but terpenoids did not show antioxidant activity. EGb and flavonoids but not terpenoids were demonstrated to significantly induce the antioxidant enzyme glutamate cysteine ligase catalytic subunit (GCLC), directly scavenged O^{2-}, OH^{-} and inhibited rat erythrocyte hemolysis and lipid peroxidation of rat liver homogenate. The antioxidant activities of the flavonoids were weaker than those of EGb containing similar dose of flavonoids.

Neuroprotective/Alzheimer's Disease/Dementia Activity

Ginkgo biloba extract, EGb 761, had been therapeutically used for several decades to increase peripheral and cerebral blood flow as well as for the treatment of dementia. EGb 761 is currently used as symptomatic treatment for cerebral insufficiency that occurs during normal ageing or which may be due to degenerative dementia, vascular dementia or mixed forms of both, and for neurosensory disturbances (Ahlemeyer and Krieglstein 2003a). EGb 761 was found to be a complex mixture containing flavonoid glycosides, terpene lactones (non-flavone fraction) and various other constituents believed to contribute to its neuroprotective and vasotropic effects (Ahlemeyer and Krieglstein 2003a, b). A profusion of basic and clinical studies, conducted both in-vitro and in-vivo, had shown *Ginkgo biloba* extract EGb 761 to have neuroprotective and "anti-stress" properties.

DeFeudis and Drieu (2000), Ahlemeyer and Krieglstein (2003a) elucidated that EGb 761 had several major actions: cognition enhancement, improvement of blood rheology and tissue metabolism, and counteracting the detrimental effects of ischaemia. Several mechanisms of action were found to be useful in explaining how EGb 761 benefited patients with Alzheimer's disease and other age-related, neurodegenerative disorders. In animals, EGb 761 was found to possess antioxidant and free radical-scavenging activities, it reversed age-related losses in brain alpha 1-adrenergic, 5-HT1A and muscarinic receptors, protected against ischaemic neuronal death, preserved the function of the hippocampal mossy fiber system, increased hippocampal high-affinity choline uptake, suppressed the down-regulation of hippocampal glucocorticoid receptors, enhanced neuronal plasticity, and counteracted the cognitive deficits that follow stress or traumatic brain injury. Identified chemical constituents of EGb 761 had been associated with certain actions. Both flavonoid and ginkgolide constituents were involved in the free radical-scavenging and antioxidant effects of EGb 761 which decreased tissue levels of reactive oxygen species (ROS) and inhibited membrane lipid peroxidation. Regarding EGb 761-induced regulation of cerebral glucose utilization, bilobalide was found to increase the respiratory control ratio of mitochondria by protecting against uncoupling of oxidative phosphorylation, thereby increasing ATP levels, a result supported by the finding that bilobalide increased the expression of the mitochondrial DNA-encoded COX III subunit of cytochrome oxidase. With regard to its "anti-stress" effect, EGb 761 was reported to act via its ginkgolide constituents to decrease the expression of the peripheral benzodiazepine receptor (PBR) of the adrenal cortex.

In-vitro studies

Results of in-vitro studies on hippocampal primary cultured cells suggested that neuroprotective effects of *Ginkgo biloba* extract (EGb 761) were partly associated with its antioxidant properties (Bastianetto et al. 2000a). Co-treatment with EGb 761 dose-dependently (10–100 μg/ml) protected hippocampal neurons against toxicity induced by Abeta fragments, with a maximal and complete protection at the highest concentration tested. EGb 761 (100 μg/ml) was even able to protect hippocampal cells from a pre-exposure to Abeta 25–35 and Abeta 1–40. EGb 761 was also able to both protect and rescue hippocampal cells from toxicity induced by H_2O_2 (50–150 μM), a major peroxide possibly involved in mediating Abeta toxicity. Moreover, EGb 761 (10–100 μg/ml), completely blocked Abeta-induced events, e.g. reactive oxygen species accumulation and apoptosis. An excess of the free radical nitric oxide (NO) was viewed as a deleterious factor involved in various CNS disorders. Results of studies conducted by Bastianetto et al. (2000b) suggested that the protective and rescuing abilities of EGb 761 were not only attributable to the antioxidant properties of its flavonoid constituents but also via their ability as a No scavenger in inhibiting NO-stimulated protein kinase C activity. The terpenoid constituents of EGb 761, known as bilobalide and ginkgolide B, as well as inhibitors of phospholipases A [3-[(4-octadecyl) benzoyl] acrylic acid (OBAA)] and C (U-73122), failed to display any significant effects. The results also highlighted its possible effectiveness in neurodegenerative diseases, e.g. Alzheimer's disease via the inhibition of Abeta-induced toxicity and apoptosis. *Ginkgo biloba* extract EGb 761 exhibited neuroprotective abilities against dysfunction and death of neurons caused by Abeta deposits (Bastianetto and Quirion 2002). Beta-amyloid (Abeta) deposition had been postulated to play a causal role in the lesions that occur in Alzheimer's disease. A co-treatment with EGb 761 dose-dependently protected hippocampal cells against toxicity induced by Abeta fragments. EGb 761, also completely blocked Abeta-induced events, such as reactive oxygen species accumulation and apoptosis. Shi et al. (2009) found that EGb 761 was able to prevent Abeta (1–42)-induced cell apoptosis, reactive oxygen species (ROS) accumulation, mitochondrial dysfunction and activation of c-jun N-terminal kinase (JNK), extracellular signal-regulated kinase 1/2 (ERK1/2) and Akt signalling pathways. Both quercetin and ginkgolide B may be involved in the inhibitory effects of EGb 761 on JNK, ERK1/2 and Akt signalling pathways. Ginkgolide B also ameliorated mitochondrial functions but quercetin failed to show this effect. Additional experiments suggested that the protective effects of EGb 761 against Abeta toxicity may be associated with its antioxidant and platelet activating factor (PAF) antagonist activities. Quercetin but not ginkgolide B was one of the constituents responsible for the antioxidant action of EGb 761. Both quercetin and ginkgolide B may be involved in the PAF antagonist activity of EGb 761.

Results of studies by Luo et al. (2002) suggested that neuronal damage in Alzheimer's disease might be due to two factors: a direct Abeta toxicity and the apoptosis initiated by the mitochondria. The results also indicted that multiple cellular and molecular neuroprotective mechanisms, including attenuation of apoptosis and direct inhibition of Abeta aggregation, underpinned the neuroprotective effects of EGb 761. EGb 761 significantly mitigated mitochondrion-initiated apoptosis and reduced the activity of caspase 3, a key enzyme in the apoptosis cell-signalling cascade. The results of in-vitro studies by Lee et al. (2004) suggested that ginkgolide B but not ginkgolide A may elicit its anti-amnesic effect by minimizing the inhibitory effect of beta-amyloid peptides on cholinergic transmission in hippocampal brain slices. Treatment with EGb 761 and ginkgolide B could protect the rat neurons against glutamate-induced injury (Xu et al. 2010). EGb 761 and ginkgolide B increased cell viability, reduced apoptosis rate and decreased LDH leakage in varying degree. The protective effect of ginkgolide B was superior to EGb 761.

Ahlemeyer and Krieglstein (2003b) examined the neuroprotective and anti-apoptotic ability of the main constituents of the non-flavone fraction, the ginkgolides A, B, C, J and bilobalide. In focal cerebral ischemia models, pre-treatment of

bilobalide before ischemia, dose-dependently reduced infarct area and infarct volume in mouse brain. Pre-treatment with ginkgolide A and ginkgolide B reduced the infarct area in the mouse model of focal ischemia. In primary cultures of hippocampal neurons and astrocytes from neonatal rats, ginkgolide B (1 μM) and bilobalide (10 μM) protected the neurons against damage caused by glutamate. Bilobalide (0.1 μM) was able to increase the viability of cultured neurons from chick embryo telencepalon when exposed to cyanide. In addition, bilobalide (100 μM) protected cultured rat hippocampal neurons from apoptosis caused by serum deprivation (24h), whereas ginkgolide B (100 μM) and bilobalide (100 μM) reduced apoptotic damage induced by staurosporine (300 nM). Ginkgolide A failed to affect apoptotic damage neither in serum-deprived nor in staurosporine-treated neurons. The results suggested that some of the components of the non-flavone fraction of EGb 761 possessed neuroprotective and anti-apoptotic capacity, and that bilobalide was the most potent one. Contrariwise, ginkgolic acids (100–500 μM) produced neuronal death, but these constituents were removed from EGb 761 below an amount of 0.0005%. Their findings provided experimental evidence for a neuroprotective effect of EGb 761 that agreed with clinical studies showing the efficacy of an oral treatment in patients with mild and moderate dementia.

Studies by Yao et al. (2001) demonstrated that *Ginkgo biloba* leaf extract (EGb 761) dose-dependently inhibited the formation of beta-amyloid-derived diffusible neurotoxic soluble ligands (ADDLs), suggested to be involved in the pathogenesis of Alzheimer's disease. The results indicated that the terpenoid and flavonoid constituents of EGb 761, were responsible for rescuing the neuronal PC12 cells from Abeta-induced apoptosis and cell death; their mechanism of action being distinct of their antioxidant properties. Bilobalide, a terpene extracted from *G. biloba* leaves, protected neuronal PC12 cells from beta-amyloid peptide fragment 25–35 (A beta 25–35)-induced cytotoxicity (Zhou et al. 2000). Bilobalide also inhibited A-beta 25-induced elevation of lipid peroxidation and decline of antioxidant enzyme activities. Accumulation of amyloid beta (Abeta) in form of senile plaques was postulated to play a central role in the pathogenesis of Alzheimer's disease mediated by oxidative stress and increasing evidence showed that Abeta generates free radicals in-vitro, which mediated the toxicity of this peptide (Eckert et al. 2003). In their study in PC12 cells they found that EGb 761 protected mitochondria from the attack of hydrogen peroxide, antimycin and Abeta. In addition, they found that EGb 761 reduced ROS levels and ROS-induced apoptosis in lymphocytes from aged mice treated orally with EGb 761 for 2 weeks. Their data further emphasized neuroprotective properties of EGb 761, such as protection against Abeta-toxicity, and antiapoptotic properties, which they postulated were probably due to its preventive effects on mitochondria. One of the components of *Ginkgo biloba* leaf extract, ginkgolide B, a potent platelet-activating factor (PAF) antagonist was found to exhibit neuroprotective property (Smith et al. 1996). The neuroprotective activity was postulated to be attributable to the terpene fraction of *Ginkgo biloba*, which contained the ginkgolides, as well as the flavonoid free radical scavengers.

Longpré et al. (2006) demonstrated that EGb 761 could prevent the activation of NF-kappaB, ERK1/2, and JNK pathways induced by Abeta and could also activate SIRT1 on neuroblastoma cell line N2a. EGb 761 and its flavonoid fraction (CP 205) could also prevent the Abeta fibril (fAbeta) formation in-vitro. They showed that Abeta was less toxic to N2a neuroblastoma cells when the peptide was previously incubated with the flavonoid fraction or EGb 761 during the fibril formation period. *Ginkgo biloba* leaf extract, EGb 50, was found to be capable of enhancing the proliferation of Schwann cells cultured in-vitro, which may be one of the important mechanisms to promote peripheral nerve regeneration (Lin et al. 2008).

Results of studies suggested that EGb 761 promoted clearance of Abeta from the brain by regulating the expression of RAGE and LRP-1 during brain ischemia (Yan et al. 2008). EGb 761 significantly reversed chronic hypoxic and hypoglycemic-induced upregulation of RAGE (receptor

for advanced end glycation products) expression and downregulation of LRP-1 (low-density lipoprotein receptor-related protein-1) expression. In-vitro studies highlighted the beneficial effect of *G. biloba* extract on the performance of cellular oxidative phosphorylation system and restoration of Abeta-induced mitochondrial dysfunction in energy metabolism (Rhein et al. 2010). Studies in isolated rat hippocampal neurons indicated that the modulatory effects of GBE on N-methyl-D-aspartate (NMDA)-activated currents may contribute to the neuroprotective effects of GBE and the modulatory effect of nanometer GBE on NMDA-activated current was greater than that of mGBE (Li et al. 2011).

A new *Ginkgo biloba* extract P8A (TTL), 70% enriched with terpene trilactones, hindered A beta (1–42) induced inhibition of long-term potentiation in the CA1 region of mouse hippocampal slices (Vitolo et al. 2009). This neuroprotective effect was attributed largely to ginkgolide J that completely replicated the effect of the extract. Ginkgolide J was also capable of inhibiting apoptosis of rodent hippocampal neurons caused by A-beta (1–42). This beneficial and multi-faceted mode of action of the ginkgolide makes it a new and promising lead in designing therapies against Alzheimer's disease. Using human SH-SY5Y neuroblastoma cells and primary hippocampal neurons, Shi et al. (2010b) found that bilobalide prevented Abeta 1–42-, H(2)O(2)- and serum deprivation-induced apoptosis. Bilobalide dose-dependently increased PI3K activity and levels of phosphorylated Akt. The results further suggested that the PI3K/Akt pathway might be involved in the protective effects of bilobalide. Since modern technology allows production of purified bilobalide with high bioavailability, bilobalide may be useful in developing therapy for diseases involving age-associated neurodegeneration.

Studies by Zhao et al. (2011) confirmed that the neuroprotective effect of *Ginkgo biloba* extract EGb 761 was mediated in part by inhibition of cytosolic phospholipase A_2 ($cPLA_2$), an enzyme that is known to play a key role in mediating secondary pathogenesis after acute spinal cord injury. EGb 761 administration significantly reversed the elevated expression of phosphorylated $cPLA_2$ ($p\text{-}cPLA_2$), a marker of $cPLA_2$ activation, and neuronal death caused by insults with glutamate and hydrogen peroxide. They demonstrated that the extracellular signal-regulated kinase 1/2 signaling pathway was involved in EGb 761's modulation of $cPLA_2$ phosphorylation.

In-vivo studies

Smith and Luo (2003), Luo (2006) found that treatment of neuroblastoma cells or transgenic *Caenorhabditis elegans* both expressing accumulation of Abeta, with *Ginkgo biloba* extract EGb 761 significantly attenuated the basal as well as the induced levels of hydrogen peroxide-related reactive oxygen species (ROS). Further, EGb 761 eased its toxicity in the transgenic *C. elegans.* Wu et al. (2006) found that EGb 761 and one of its components, ginkgolide A, alleviated Abeta-induced pathological behaviors, including paralysis, and reduced chemotaxis behavior and 5-HT hypersensitivity in a transgenic *Caenorhabditis elegans* (Wu et al. 2006). The findings suggested that (1) EGb 761 suppressed Abeta-related pathological behaviors, (2) the protection against Abeta toxicity by EGb 761 was mediated primarily by modulating Abeta oligomeric species, and (3) ginkgolide A had therapeutic potential for prevention and treatment of AD.

The results of focal cerebral ischemia model studies conducted by Ahlemeyer and Krieglstein (2003b) suggested that some of the constituents of the non-flavone fraction of *Ginkgo biloba* extract EGb 761 exhibited neuroprotective and anti-apoptotic capacity, and that bilobalide (5–20 mg/kg, s. c.) was the most potent one. In contrast, ginkgolic acids (100–500 μM) induced neuronal death, which showed features of apoptosis as well as of necrosis, but these constituents were removed from EGb 761 below an amount of 0.0005%. The data provided experimental evidence for a neuroprotective effect of EGb 761 that agreed with clinical studies showing the efficacy of an oral treatment in patients with mild and moderate dementia. Results of separate animal studies indicated that long-term pre-treatment of EGb 761 administered either alone or in combination with drugs such as $MgSO_4$, FK506, or

MK-801 exerted significantly effective neuroprotection on infarct volume in gerbil ischemic brains (Chung et al. 2006). Standardized *Ginkgo biloba* extract EGb 761 was found to exhibit potential beneficial effects to patients with Alzheimer's disease (AD) using a mouse model (Tchantchou et al. 2007). EGb 761 significantly and dose-dependently increased cell proliferation in the hippocampus of both young (6 months) and old (22 months) transgenic mice, and the total number of neuronal precursor cells in-vitro. Administration of EGb 761 reduced Abeta oligomers and restored cAMP response element binding protein (CREB) phosphorylation in the hippocampus of these mice. The present findings suggested that (1) enhanced neurogenesis by EGb 761 may be mediated by activation of CREB, (2) stimulation of neurogenesis by EGb 761 may contribute to its beneficial effects in AD patients and improved cognitive functions in the mouse model of AD, and (3) EGb 761 had therapeutic potential for the prevention and improved treatment of AD.

Studies indicated that orally administered *Ginkgo biloba* extract can protect the brain against beta-amyloid from changes leading to memory deficit through its effect on the cholinergic system in rats (Tang et al. 2002). The extract reversed the decrease in choline actyltransferase activities in the hippocampus. Yao et al. (2004) found *Ginkgo biloba* extract (EGb 761) could improve cognitive function in patients with Alzheimer's disease. In aging rats, EGb 761 treatment decreased free circulating cholesterol and suppressed the production of brain beta-amyloid precursor protein and amyloid beta-peptide. Augustin et al. (2009) in studies with mice transgenic for human APP (Tg2576) found that the potential neuroprotective properties of EGb 761 may partly be related to its amyloid precursor protein lowering activity. Amyloid precursor protein appeared to be an important molecular target of EGb 761 in relation to the duration of the *Ginkgo biloba* treatment and/or the age of the animals.

The results of animal studies by Saleem et al. (2008) demonstrated that EGb 761 could be used as a preventive or therapeutic agent in cerebral ischemia and suggest that heme oxygenase 1 contributed, at least in part, to its neuroprotective effect. Results of animal studies suggested that administration of EGb761, Selenium and its combination with EGb761 exerted significant neuroprotective effects on ischemia/reperfusion (I/R) injury in a rat model of transient global cerebral I/R via suppression of oxidative stress (Erbil et al. 2008). A standardized extract of *Ginkgo biloba*, EGb 761, was shown to exert a neuroprotective effect against permanent and transient focal cerebral ischemia in rats (Koh 2009). EGb 761 decreased the elevated Bad and Bcl-X(L) interaction caused by Ischemic brain injury Ischemic brain injury. The results of animal studies by Koh (2010) confirmed that EGb 761 protected neuronal cells against ischemic brain injury by preventing injury-induced decreases in p70S6 kinase and S6 phosphorylation.

Oral administration of *Ginkgo biloba* extract (EGb 761) to a mouse model of Alzheimer's disease was confirmed to enhance hippocampal neurogenesis (Tchantchou et al. 2009). Bilobalide and quercetin, two of its components, were also found to enhance in a dose-dependent manner, neurogenesis and synaptogenesis in mice brains suggesting a common final signalling pathway mediated by phosphorylation of cyclic-AMP Response Element Binding Protein (CREB) in the hippocampal neurons. Synaptogenesis and neurogenesis in adulthood could serve as a therapeutic target for the prevention and treatment of Alzheimer's disease. Studies showed that EGb761 treatment could accelerate recovery of the pathological synaptic plasticity in vascular dementia model rats with apparent and long-lasting dysfunction of learning and memory (Zhang and Wang 2008). The results suggested that EGb 761 played an important and improving role on learning and memory dysfunction of vascular dementia.

EGb 761, a standardized extract of *Ginkgo biloba* was found to exert protective effects against ischemic brain injury (Cho et al. 2009). The study in adult male rats suggested that EGb 761 prevented cell death due to brain injury and that EGb 761 protection was effected by preventing the injury-induce decrease of Akt phosphorylation. Additionally, EGb 761 inhibited the