Ginkgo biloba: A ‘living fossil’ with modern day phytomedicinal applications

Abdulmumin A. Nuhu
Department of Chemistry, Ahmadu Bello University, P.M.B. 1069, Zaria, Kaduna, Nigeria.

ABSTRACT

Ginkgo biloba has survived for over 200 million years now. With other members of this gymnosperm extinct, it is considered as a ‘living fossil’. Yinxing, as it is called in Chinese, is very popular in East Asia as a remedy for lung congestion, ischemia and asthma. In modern day medical practice, growing consideration is given to the extract from this tree as a line of treatment in many cancer conditions partly due to the side effects of conventional drugs of therapy. The extract has also anti-diabetic, anti-inflammatory and cardio- and hepatoprotective roles. These and other numerous recent applications of this important botanical drug are discussed in this review.

Key words: Ginkgo biloba, EGb 761, Phytomedicinal applications, Botanical drug.

INTRODUCTION

Ginkgo biloba L. belongs to the family Ginkgoaceae and the order Ginkgoales. The tree, which can live up to 1000 years, grows to a height of 30 m, and is indigenous to East Asia (Trease and Evans, 1983). Having survived for many million years, Yinxing (Chinese) is the oldest known gymnosperm species alive and is, therefore, considered a ‘living fossil’ (Pandey et al., 2011; Galian et al., 2012). Findings from investigations of G. biloba fossil records have suggested the persistence of the wild species in the Dalou Mountains of southwestern China (Tang et al., 2012). Ulstracture of stomatal development in this species have been studied (Rudall et al., 2012). Bauer et al. (2013) have found significant resemblance between modern day G. biloba and fossil ginkgophyte seedlings from the Triassic of France. Products from this species can now be found in various forms, including tea, bars, tablets, capsules and extracts. Standardized leaf extract of Ginkgo, EGb 761®, which may contain about 24% flavones and 6% terpenes, is the result of the early research work conducted in Europe in the 1960s, with Germany and France playing very crucial roles in its development into modern herbal medicinal product (Lang et al., 2013). This extract is now one of the best-selling and popular botanical drug preparations in the world. A regimen of 40-80 mg, three times daily, is the recommended dosage.

Important proteins with functional properties have been isolated from G. biloba seeds (Deng et al., 2011). The Chinese have used these seeds for thousands of years for the treatment and management of many ailments including ischemia, lung congestion and asthma. In modern day, this phytomedicine is put into use in the treatment of sexual dysfunction, premenstrual syndrome, dementia, and cognitive impairment in many parts of the world, especially, China, Germany and France (Evans, 2013). These and other phytomedicinal functions of this important plant are discussed in the present review.

PHARMACOKINETIC & PHARMACODYNAMIC ROLES

Because of the increasing interest in G. biloba as herbal remedy for many ailments, regulatory authorities are now requesting for information on the pharmacokinetic and pharmacodynamic effects on drugs that can be co-administered with G. biloba extract (GBE). GBE can present with contradicting effects depending on several factors such as dose, time, subject or target cells, and whether in vivo or in vitro.

* Corresponding Author
Abdulmumin A. Nuhu:
E-mail: aanuhu@abu.edu.GSM: +2348022699193
When the normally prescribed dose is taken over a period of 4 weeks, GBE did not affect the pharmacokinetics of diazepam or excretion of its metabolite N-demethyl Diazepam (Zuo et al., 2010). Its co-administration with cilostazol did not show any significant effect on either pharmacodynamics or pharmacokinetics of the drug in human subjects (Kim et al., 2013). In ApoE null mice that were fed a high fat diet, however, this co-treatment led to synergistic decrease in reactive oxygen species (ROS) and resulted in a more potent anti-atherosclerotic effect of cilostazol (Jung et al., 2012).

The extract did slightly decrease plasma concentration of atorvastin but had no significant effect on its cholesterol-lowering efficacy (Guo et al., 2012). It also has no significant effect on in vivo activity of major CYP enzymes (Zadoyan et al., 2012). However, Guo et al. (2010) have earlier reported that GBE may alter the expression of genes coding for drug metabolizing enzymes and disrupt Nrf-2 mediated oxidative stress response pathway, and Myc gene-centered network.

GBE inhibited P-glycoprotein in humans. Hence, co-administration of this extract with drugs, such as talinol, that are primarily transported by P-glycoprotein, may require a necessary dose adjustment (Fan et al., 2009). While co-administration of GBE with anticoagulant drugs such as cardioparin, warfarin and ticlopidine may not lead to prolonged bleeding time in human subjects (Kim et al., 2010), this effect was observed in rats and is associated with terpenoid content of the undeterpened extract (Di Pierro et al., 2010).

**ANTI-INFLAMMATORY ROLES**

Heat, redness, swelling and pains are some of the ways by which a living tissue can express its reaction to irritation, injury or infection. These reactions can range from mild to severe, and in many times very discomforting. The extracts of Ginkgo have shown many positive results in alleviating these conditions. Several mechanisms are involved, but interleukin (IL) regulation appears to play a key role in the anti-inflammatory functions of GBE. Results from treatment of rats with medium dose of GBE 50 indicated that it can alleviate inflammatory reactions after ischemia-reperfusion injury by promoting the activity of IL-4, an anti-inflammatory cytokine, and inhibiting the activity of IL-6, an inflammatory cytokine (Bao et al., 2010). By acting both at the site of inflammation and at the spinal cord level, EGB 761 inhibited inflammation in rat carrageenan model (Thorpe et al., 2011). Inflammatory processes resulting from oxidized low density lipoproteins (oxLDL)-induced oxidative stress in vascular endothelial cells were ameliorated by the administration of GBE (Ou et al., 2009). This extract also reduced high-glucose-induced production of IL-6, ROS and endothelial adhesiveness to monocyte, among the many inflammatory reactions that may accompany atherosclerosis (Chen et al., 2012). Suppression of monocyte activation via inhibition of nitric oxide and tristetraprolin-mediated toll-like receptor 4 expression is another way by which GBE regulates systemic inflammation (Lee et al., 2011). Activated keratinocytes produce vascular endothelial growth factor and IL-8, both of which play important roles in skin inflammation. Trompezinski et al. (2011) explained that GBE exerted a strong inhibitory activity on these inflammation promoters. In the oral chronic inflammatory disease periodontitis, G. biloba plays an anti-inflammatory role by up-regulating heme oxygenase 1 (HO-1) and Nrf-2 levels in the nucleus (Ryu et al., 2012). Results of pre-treatment of NCI-H292 cells with 40 µM each of kaempferol and quercetin indicate that these constituents in GBE might be responsible for the suppression of IL-1β-induced MUC5AC gene expression in human airway epithelial cells (Kwon et al., 2009). Haines et al. (2011) showed that EGB 761, astaxanthin and vitamin C interact synergistically to suppress respiratory inflammation in asthmatic guinea pigs.

**CARDIOVASCULAR AND HEPATOPROTECTIVE ROLES**

Although Kuller et al. (2010) have reported lack of evidence to support reduced risk of cardiovascular events, other reports have shown beneficial effects of GBE against cardiovascular and hepatic conditions. It has been shown to have vasodilatory and antihypertensive properties (Brinkley et al., 2010; Keheyen et al., 2011). GBE decreased mitochondrial membrane potential and stimulated pyruvate-malate-dependent State 2 respiration of the heart mitochondria (Baliyte et al., 2010). Depending on the target cells and on dosage used, either apoptotic or anti-apoptotic activities can be observed following administration of GBE. On one hand, prevention of atherosclerosis in a rat model of type 2 diabetes was influenced by reduced proliferation of vascular smooth muscle cells (VSMC) through the increased apoptotic activity of caspase-3 (Lim et al., 2011). On the other hand, components of EGB 761 have protected hypoxia-reoxygenated cardiomyocytes against apoptosis by inhibiting mitochondria-dependent caspase pathway, leading to reduced release of cytochrome c from mitochondria and attenuated cleavage activities of caspases (Shen et al., 2011).

Bioactive constituents of GBE, i.e. terpenoids and flavonoids, facilitate drug metabolism in liver by the selective activation of pregnane X receptor, constitutive adrostane receptor and aryl hydrocarbon receptor (AhR) (Li et al., 2009). Following carbon tetrachloride-induced hepatic injury, significant dose-dependent reversal in the levels of biochemical indicators of cell damage was observed in Sprague-Dawley rats as result of treatment with GBE (Yang et al., 2011).

**ANTITUMOR AND ANTI-PROLIFERATION ROLES**

Research into the possible roles of GBE as antitumor and anti-proliferative herbal drug has gained a lot of interest partly due to many side effects of current cancer therapeutics. Although Biggs et al. (2010) did not find a significant positive correlation between regular use of GBE and reduced risk of cancer, especially breast and colorectal types, in a randomized, double-blind, placebo-controlled clinical trial of Ginkgo supplementation, several other research findings have shown beneficial effect of this extract against different cancer cell lines. Wu et al. (2011) have
isolated, purified and tested the in vitro antitumor activities of polysaccharides from G. biloba sarcotesta with positive results. Apoptosis of oral cavity cancer cells was induced by kaempferol and quercetin constituents of EGb 761 (Kang et al., 2010). When mammary epithelial cells, MCF-10A, were challenged with benzo[a]pyrene, both kaempferol and isorhamnetin of GBE antagonized the activation of AhR signaling pathway by which the bioactivation of procarcinogens are catalyzed (Rajaraman et al., 2009). However, Zhao et al. (2013) have demonstrated that antiproliferative effect of GBE on estrogen receptor (ER)-negative breast cancer cells was accompanied by the enhancement of cytochrome P450 1B1 (CYP 1B1), an indication that a pathway different from that of AhR may be responsible.

Aromatase inhibitors block the synthesis of estrogen and are considered as first-line hormonal therapy for breast cancer. GBE has demonstrated this functionality in JEG-3 human chorionicarcinoma cells and in recombinant CYP 19 microsomes, an approach that may present with lesser side effects than the increased bone loss and musculoskeletal complaints associated with current line of therapy with tamoxifen (Kim et al., 2011). When compared with tamoxifen (100 mg/kg), treatment with GBE (100 mg/kg) for 4 weeks significantly increased the proportions of degenerative areas (72.9%), and lowered the proportions of live (24.8%) and necrotic (2.9%) areas in mammary tumors in Sprague-Dawley rats (Dias et al., 2013). Antiproliferative and apoptosis-inducing activities of GBE were also expressed in ER-negative human breast cancer line MDA-MB-231 by significantly activating caspase-3 and altering mRNA levels of bcl-2 and bax genes (Park et al., 2013). Previously, down-regulation of bcl-2 genes and up-regulation of p53 and enhancement of caspase-3 activities inhibited the progression of human colon cancer cell HT-29 in a time-dose dependent way (Chen et al., 2011).

Chemopreventive roles of G. biloba against hepatocarcinogenesis induced by nitrosodimethylamine (NDEA) may be executed through its antioxidant, antiangiogenic and antigenotoxic activities as demonstrated by decreased levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyltransferase (GGT), and decreased comet assay parameters and improved liver architecture (El Mesallamy et al., 2011). GBE inhibits proliferation in sarcoma and leukemia cell lines by increasing the levels of free radical scavenging enzymes, and this activity is enhanced by increasing the concentration of aglycone portion of the constituent flavonoid glycosides (Feng et al., 2009). Aglycones have stronger inhibitory effect on CYP 1A1 enzyme than 3-O-rutinosides of kaempferol and quercetin in the presence of benzo[a]pyrene (Ribonnet et al., 2011).

**ANTI-DIABETIC ROLES**

There are growing evidences to support the viability of GBE in regulating many pathological states associated with high blood glucose levels. In vitro models have shown the potential of this extract in the management of hyperglycemia and hypertension (Pinto et al., 2009). Hypertension resulting from the clipping of the renal artery was normalized in 2K, IC rats (Mansour et al., 2011). In normal conditions, glucose uptake is repressed by GBE (Zhou et al., 2011), while in diabetic rats glucose tolerance is enhanced by increasing the expression of glucose transporter 4 (GLT4) mRNA and glucose uptake rate (Li et al., 2010). Recently, Cheng et al. (2013) have found that decreased body weight and antioxidative ability, and increased blood glucose levels, lipid profile and lipid peroxidation observed in streptoztocin-induced diabetes were all reversed following oral treatment with GBE (100, 200, and 300 mg/kg) once daily for 30 days. According to Li et al. (2012), atherosclerotic effects of diabetes can be reversed by GBE via modulation of cellular cholesterol content and CD36 expression in macrophages.

High-glucose-induced pathological changes in lens epithelial cells and lens opacity were ameliorated by GBE, thus protecting against diabetes-influenced cataract (Lu et al., 2013). By up-regulating HO-1 expression, GBE has reduced high-glucose-induced ROS and endothelial adhesion in a dose-time dependent manner (Tsai et al., 2013). The extract has also protected against glucose-induced accumulation of extracellular matrix (ECM) in rat mesangial cells through inhibition of the synthesis of ECM as well as promotion of its degradation (Ji et al., 2009). This anti-nephropathic role was enhanced by combination therapy with either captopril or valsartan (Zhai et al., 2010).

**COGNITIVE AND NEUROPSYCHIATRIC ROLES**

One of the most interesting roles of GBE involves its ability to alleviate neuropsychiatric conditions and to boost cognitive functions. It produces anti-depressant effect (Rojas et al., 2011), and protects against neuronal damage by inhibiting the activity of cytosolic phospholipase A2 (cPLA2) (Zhao et al., 2011). The extract potentiates nerve growth factor (NFG) and plays a beneficial role in the expression of neurofilaments (Xu et al., 2012). These functions are more noticeable in brainstem and cerebellum (Martin et al., 2011).

**Ischemia**

Ischemia is a condition characterized by deficient blood supply to parts of the body. It is implicated in many neuropsychiatric conditions, and GBE has found use in alleviating these conditions partly due to its function in increasing cerebral blood flow. This has been noticed in the left occipital white matter of elderly human subjects given 60 mg of GBE twice daily for 4 weeks (Mashayekh et al., 2011). Evidence has been presented on the ability of GBE to protect against apoptosis after ischemia-reperfusion through both caspase-dependent and caspase-independent pathways of the mitochondria (Cheng et al., 2011). This extract uses its preventive role against injury-derived decrease in p70S6 kinase and S6 phosphorylation to protect neuronal cells in adult male rats (Koh, 2010). EGb 761 can be a good therapeutic agent against ischemic stroke by enhancing the activation of Akt, cAMP response element binding protein.
(CREB) and the expression of brain-derived neurotrophic factor (BDNF) (Zhang et al., 2012). Shah et al. (2011) have suggested that this role against ischemic stroke may follow, in part, the HO-1 pathway.

Dementia

Several studies have been carried out in search of answers regarding the question of whether or not Ginkgo has any significant implication on cognition deficit and dementia. The answer can only be provided on case-by-case analysis. While some studies have found no significant influence of GBE on cognition deficit or dementia, many others are positive regarding the applicability of this botanical drug in alleviating neuropsychiatric conditions. For instance, results from administration of 60 mg twice daily did not support the ability of GBE in preventing cognitive deficit in patients receiving chemotherapy for cancer (Barton et al., 2013). In the same line, 120 mg twice daily also did not result in less cognition decline in older adults presenting with normal cognition or having mild cognitive impairment (Snitz et al., 2009). In children and adolescent having attention-deficit/hyperactive disorder (ADHD), administration of GBE was less effective than methylphenidate (Salehi et al., 2010).

On the positive side, however, systematic search of literature of all randomized, placebo-controlled clinical trials combined with standard meta-analysis methods have found GBE to be effective in improving cognition functions in dementia during a treatment period of 6 months (Wang et al., 2010). Other findings in support of this assertion have been presented (Ihl et al., 2011; Weinmann et al., 2010). Two Ginkgo-specific acylated flavonol glycosides Q-ag and K-ag have increased dopamine (DA) and acetylcarnosine (ACh) levels in rat medial prefrontal cortex (mPFC), a positive indication for the role of Ginkgo in the improvement of cognitive function (Kehr et al., 2012). Another constituent of this extract, cardanol (ginkgol) enhances the growth of NSC-34 immortalized motor neuron-like cells and improves working memory-related learning ability in young rats on chronic administration (Tobinaga et al., 2012).

GBE enhances dopaminergic neurotransmission in animal models (Fehske et al., 2009), and improved neuropsychiatric inventory (NPI) scores (Preuss et al., 2013; Ihl et al., 2010). Post-ischemic oral administration of EGB 761 led to significant recovery of spatial memory in a model of vascular dementia in gerbils, as assessed by object location test (OLT) (Rocher et al., 2011). It was found that this extract protects against intermittent memory deficits resulting from oxidative stress, and protects against hippocampal damage in rats (Abdel-Wahab and Abd El-Aziz, 2012).

Alzheimer’s disease

Alzheimer’s disease (AD) is a type of dementia that presents with specific abnormalities in the brain. Commentary and review on the impacts of GBE on this disease have been compiled (Shi et al., 2010; Tian et al., 2010). In one study, the extract was able to reduce energy deficiency and mitochondrial defects in patients suffering from this degenerative disease (Rhein et al., 2010). Mechanism (s) of these actions can be studied through the evaluations of effects of ginkgolis B and queretin on beta amyloid (Aβ) peptides (Shi et al., 2009). It has been suggested that combination therapy using GBE and donepezil is more effective and has lesser side effects than mono-therapy in the treatment of AD (Yancheva et al., 2009; Kasper et al., 2009).

Long-term (16 months) treatment of transgenic mice carrying genes for human amyloid precursor protein (APP) with GBE has led to 50% reductions in APP levels in the cortex as compared to control (Augustine et al., 2009). This did not, however, lead to reduced risk of progression to AD in human subjects (Vellas et al., 2012).

MISCELLANEOUS ROLES

Several other roles have been attributed to extracts and components of G. biloba. Shi et al. (2010) have found that EGB 761 can protect SAMP8 mice against aging-associated mitochondrial dysfunctions such as decreased activity of cytochrome c oxidase, and decreased adenosine triphosphate (ATP) and glutathione (GSH) contents in platelets and hippocampi. It protects against nephrotoxicity induced by antineoplastic agents, such as cisplatin, by normalizing serum creatine and kidney malondialdehyde (MDA) levels, and improving the levels of kidney GSH depleted during the course of treatment with such agents (Okuyan et al., 2012). GBE has yielded higher survival rate in retinal ganglion cells (Ma et al., 2009). The extract can be beneficial to glaucoma patients having normal or normalized intraocular pressure (Cybulska et al., 2012). Through antagonism of platelet activating factor, increased blood flow and prevention against free-radical associated membrane damage, GBE plays important roles in thrombosis (Ryu et al., 2009) and in the pathology of age-related macular degeneration (AMD) (Evans, 2013). Results from studies of the interaction of G. biloba and radiolabelled constituents of blood indicate potential usefulness of the constituents of GBE in diagnostic nuclear medicine (Aleixo et al., 2012).

By inhibiting oxidative stress and NF-κB-dependent matrix metalloproteinase-9 pathway, EGB can protect against lipopolysaccharide-induced acute lung injury (Huang et al., 2013). Gentamicin ototoxicity can lead to permanent damage to the inner ear. Treatment with GBE has protected cochlear hair cells against this effect through reduction in ROS and in nitric oxide-related apoptosis (Yang et al., 2010). The extract has also found use in alleviating reproductive problems (Amin et al., 2012). It reduces pre-menstrual syndrome (PMS) (Ozgoli et al., 2009; Danti and Facchini, 2011), suppresses doxorubicin-induced oxidative stress and apoptosis in rat testes (Yeh et al., 2009), and significantly facilitated copulation by improving contact erection in male rats (Yeh et al., 2010). EGB is a potential therapeutic agent in the treatment of the common hypopigmentation disorder vitiligo vulgaris (Szczurko et al., 2011). Its effectiveness against vacuous...
chewing movement in rats is comparable to that of vitamin E, a promising finding towards the management of tardive dyskinesia (An et al., 2013). Source and composition of GBE determine whether or not the plant can be effective in alleviating the severity of acute mountain sickness as a result of rapid ascent to high altitude (Leadbetter et al., 2009).

CONCLUSIONS

Ginkgo biloba is the oldest gymnosperm species alive and has been used by the Chinese as a traditional cure for different ailments. Owing to the presence of many bioactive constituents, such as kaempferol, quercetin, ginkgol and the acylated flavonol glycosides Q-ag and K-ag, the extract from this plant has been put to modern uses as anti-diabetic, and cardio- and hepatoprotective drug. One of its main functions is its ability to boost cognition which has earned it the consideration as one the primary treatments for dementing conditions such Alzheimer’s disease and other neuropsychiatric problems.

Its anti proliferative and chemo-preventive roles have found applications in the control and management of different types of cancer. Results of pharmacokinetic studies of its interaction with other drugs indicate that, in many instances, co-administration of this extract with conventional drugs is more effective than mono-therapy. It is believed that as interest in research on this plant continues to grow and clinical trials are conducted, positive results will ultimately boost the acceptance of this botanical drug as a first line of treatment for many pathological conditions.

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