Journal of Applied Pharmaceutical Science Vol. 4 (03), pp. 096-103, March, 2014
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2014.40319
ISSN 2231-3354

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.

ARTICLE INFO

Article history:
Received on: 19/11/2013
Revised on: 02/12/2013
Accepted on: 01/01/2014
Available online: 30/03/2014

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

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.

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). Ultrastucture 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-demethyldiazepam (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 cardiospirin, 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; Keheyan *et al.,* 2011). GBE decreased mitochondrial membrane potential and stimulated pyruvate-malate-dependent State 2 respiration of the heart mitochondria (Baliutyte *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 cardiomycetes 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 choriocarcinoma 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.,* 2013). 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 nitrosodiethylamine (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 antioxidant ability, and increased blood glucose levels, lipid profile and lipid peroxidation observed in streptozotocin-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 A_2 ($cPLA_2$) (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 acetylcholine (ACh) levels in rat medial prefontal 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 ginkgolide B and quercetin 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 adenine 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 malonyladehyde (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; Dante and Facchinetti, 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 for it the consideration as one the primary treatments for dementing conditions such Alzheimer's disease and other neuropsychiatric problems.

Its antiproliferative 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.

REFERENCES

Abdel-Wahab BA, Abd El-Aziz SM. *Ginkgo biloba* protects against intermittent hypoxia-induced memory deficits and hippocampal DNA damage in rats. Phytomedicine, 2012; 19(5):444–450.

Aleixo LCM, Moreno SRF, Freitas RS, Thomaz H, Santos-Filho SD, Bernardo-Filho M. *Ginkgo biloba* extract alters the binding of the sodium [^{123}I] iodide ($Na^{123}I$) on blood constituents. Appl Radiat Isot, 2012; 70(1):59–62.

Amin A, Abraham C, Hamza AA, Abdalla ZA, Al-Shamsi SB, Harethi SS, Daoud S. A Standardized extract of *Ginkgo biloba* neutralizes cisplatin-mediated reproductive toxicity in rats. J Biomed Biotechnol, 2012; 2012:1-11.

An HM, Tan YL, Shi J, Wang ZR, Li J, Wang YC, Kosten TR, Zhou DF, Yang FD, Zhang XY. Extract of *Ginkgo biloba* is equivalent to vitamin E in attenuating and preventing vacuous chewing movements in a rat model of tardive dyskinesia. Behav Pharmacol, In Press.

Augustine S, Rimbach G, Augustin K, Schliebs R, Wolfframa S, Cermak R. Effect of a short- and long-term treatment with *Ginkgo biloba* extract on amyloid precursor protein levels in a transgenic mouse model relevant to Alzheimer's disease. Arch Biochem Biophys, 2009; 481(2):177–182.

Baliutyte G, Baniene R, Trumbeckaite S, Borutaite V, Toleikis A. Effects of *Ginkgo biloba* extract on heart and liver mitochondrial functions: mechanism(s) of action. J Bioenerg Biomembr, 2010; 42(2):165-172.

Bao YM, Liu AH, Zhang ZX, Li Y, Wang XY. Effects of *Ginkgo biloba* extract 50 preconditioning on contents of inflammation-related cytokines in myocardium of rats with ischemiareperfusion injury. Zhong Xi Yi Jie He Xue Bao, 2010; 8(4):373-378.

Bauer K, Grauvogel-Stamm L, Kustatscher E, Krings M. Fossil ginkgophyte seedlings from the Triassic of France resemble modern *Ginkgo biloba.* BMC Evolut Biol, 2013; 13:177-184.

Barton DL, Burger K, Novotny PJ, Fitch TR, Kohli S, Soori G, Wilwerding MB, Sloan J A, Kottschade LA, Rowland Jr., KM, Dakhil SR, Nikcevich DA, Loprinzi CL.The use of *Ginkgo biloba* for the prevention of chemotherapy-related cognitive dysfunction in women receiving adjuvant treatment for breast cancer, N00C9. Support Care Cancer, 2013; 21(4):1185-1192.

Biggs ML, Sorkin BC, Nahin RL, Kuller LH, Fitzpatrick A. *Ginkgo biloba* and risk of cancer: Secondary analysis of the Ginkgo evaluation of memory (GEM) study. Pharmacoepidemiol Drug Saf, 2011; 19(7): 694–698.

Brinkley TE, Lovato JF, Arnold AM, Furberg CD, Kuller LH, Burke GL, Nahin RL, Lopez OL, Yasar S, Willimason JD. Effect of *Ginkgo biloba* on blood pressure and incidence of hypertension in elderly men and women. Am J Hypertens, 2010; 23(5):528–533.

Chen J-S, Chen Y-H, Huang P-H, Tsai H-Y, Chen Y-L, Lin S-J, Chen J-W. *Ginkgo biloba* extract reduces high-glucoseinduced endothelial adhesion by inhibiting the redox-dependent interleukin-6 pathways. Cardiovasc Diabetol, 2012; 11:49-59.

Chen X-H, Miao Y-X, Wang X-J, Yu Z, Geng M-Y, Han Y-T, Wang L-X. Effec ts of *Ginkgo biloba* Extract EGb761 on human colon adenocarcinoma cells. Cell Physiol Biochem, 2011; 27:227–232.

Cheng B, Wang W, Lin L, Li F, Wang X. The change of the spinal cord ischemia–reperfusion injury in mitochondrial passway and the effect of the *Ginkgo biloba* extract's preconditioning intervention. Cell Mol Neurobiol, 2011; 31(3):415-420.

Cheng DC, Liang B, Li Y.Antihyperglycemic effect of *Ginkgo biloba* extract in streptozotocin-induced diabetes in rats. BioMed Res Int, 2013; 2013:1-7.

Cybulska AK, Mozaffarieh M, Flammer J. *Ginkgo biloba*: An adjuvant therapy for progressive normal and high tension glaucoma. Mol Vis, 2012; 18:390-402.

Dante G, Facchinetti F. Herbal treatments for alleviating premenstrual symptoms: a systematic review. J Psychosom Obstet Gynecol, 2011; 32(1):42-51.

Deng Q, Wang L, Wei F, Xie B, Huang F-H, Huang W, Shi J, Huang Q, Tian B, Xue S. Functional properties of protein isolates, globulin and albumin extracted from *Ginkgo biloba* seeds. Food Chem, 2011; 124(4):1458–1465.

Dias MC, Furtado KS, Rodrigues MAM, Barbisan, LF. Effects of *Ginkgo biloba* on chemicallyinduced mammary tumors in rats receiving tamoxifen. BMC Compl Alt Med, 2013, DOI: 10.1186/1472-6882-13-93.

Di Pierro F, Rinaldi F, Lucarelli M, Rossoni G. Interaction between ticlopidine or warfarin or cardioaspirin with a highly standardized deterpened *Ginkgo biloba* extract (VR456) in rat and human. Acta Biomed, 2010; 81(3):196-203.

El Mesallamy HO, Metwally NS, Soliman MS, Ahmed KA, Abdel Moaty MM. The chemopreventive effect *of Ginkgo biloba* and *Silybum marianum* extracts on hepatocarcinogenesis in rats. Cancer Cell Int, 2011; 11:38-49.

Evans JR. *Ginkgo biloba* extract for age-related macular degeneration. The Cochrane Collaboration, 2013, DOI: 10.1002/14651858.CD001775.pub2.

Fan L, Mao X-Q, Tao G-Y, Wang G, Jiang F, Chen Y, Li Q, Zhang W, Lei H-P, Hu D-L, Huang Y-F, Wang D, Zhou H-H. Effect of *Schisandra chinensis* extract and *Ginkgo biloba* extract on the pharmacokinetics of talinolol in healthy volunteers. Xenobiotica, 2009; 39(3):249-254.

Fehske CJ, Leuner K, Muller WE. *Ginkgo biloba* extract (EGb761®) influences monoaminergic neurotransmission via inhibition of NE uptake, but not MAO activity after chronic treatment. Pharmacol Res, 2009; 60(1):68–73.

Feng X, Zhang L, Zhu H. Comparative anticancer and antioxidant activities of different ingredients of *Ginkgo biloba* extract (EGb 761). Planta Med, 2009; 75(8): 792-796.

Galian JA, Rosato M, Rossello JA. Early evolutionary colocalization of the nuclear ribosomal 5S and 45S gene families in seed plants: evidence from the living fossil gymnosperm *Ginkgo biloba*. Heredity, 2012; 108: 640–646.

Guo C-X, Pei Q, Yin J-Y, Peng X-D, Zhou B-T, Zhao Y-C, Wu L-X, Meng X-G, Wang G, Li Q, Ouyang D-S, Liu Z-Q, Zhang W, Zhou H-H. Effects of *Ginkgo biloba* extracts on pharmacokinetics and efficacy of atorvastatin based on plasma indices. Anim Pharmacokinet Met, 2012; 42(8):784-790.

Guo L, Mei N, Liao W, Chan P-C, Fu PP. *Ginkgo biloba* extract induces gene expression changes in xenobiotics metabolism and the Myc-centered network. OMICS A J Integr Biol, 2010; 14(1): 75-90.

Haines DD, Varga B, Bak I, Juhasz B, Mahmoud FF, Kalantari H, Gesztelyi R, Lekli I, Czompa A, Tosaki A. Summative interaction between astaxanthin, *Ginkgo biloba* extract (EGb761) and vitamin C in suppression of respiratory inflammation: a comparison with ibuprofen. Phytother Res, 2011; 25:128–136.

Huang C-H, Yang M-L, Tsai C-H, Li Y-C, Lin Y-J, Kuan Y-H. *Ginkgo biloba* leaves extract (EGb 761) attenuates lipopolysaccharide-induced acute lung injury via inhibition of oxidative stress and NF-κB-dependent matrix metalloproteinase-9 pathway. Phytomedicine, 2013; 20:303– 309.

Ihl R, Bachinskaya N, Korczyn AD, Vakhapova V, Tribanek M, Hoerr R, Napryeyenko, O. Efficacy and safety of a once-daily formulation of *Ginkgo biloba* extract EGb 761 in dementia with neuropsychiatric features: a randomized controlled trial. Int J Geriat Psychiatry, 2011; 26:1186–1194.

Ihl R, Tribanek M, Bachinskaya N. Baseline neuropsychiatric symptoms are effect modifiers in *Ginkgo biloba* extract (EGb 761®) treatment of dementia with neuropsychiatric features. Retrospective data analyses of a randomized controlled trial. J Neurol Sci, 2010; 299(1–2):184–187.

Ji L, Yin X-X, Wu Z-M, Wang J-Y, Lu Q, Gao Y-Y. *Ginkgo biloba* extract prevents glucose-induced accumulation of ECM in rat mesangial cells. Phytother Res, 2009; 23:477–485.

Jung I-H, Lee Y-H, Yoo J-Y, Jeong S-J, Sonn SK, Park J-G, Ryu KH, Lee BY, Han HY, Lee SY, Kim D-Y, Lee H, Oh GT. *Ginkgo biloba* extract (GbE) enhances the anti-atherogenic effect of cilostazol by inhibiting ROS generation. Exp Mol Med, 2012; 44: 311-318.

Kang JW, Kim JH, Song K, Kim SH, Yoon J-H, Kim K-S. Kaempferol and quercetin, components of *Ginkgo biloba* extract (EGb 761), induce caspase-3-dependent apoptosis in oral cavity cancer cells. Phytother Res, 2010; 24:S77–S82.

Kasper S, Schubert H. *Ginkgo biloba* extract EGb 761® in the treatment of dementia: Evidence of efficacy and tolerability.Fortschritte der Neurologie, Psychiatrie, 2009; 77(09):494-506.

Keheyan G, Dunn LA, Hall WL. Acute effects of *Ginkgo biloba* extract on vascular function and blood pressure. Plant Food Hum Nutr, 2011; 66(3):209-211.

Kehr J, Yoshitake S, Ijiri S, Koch E, Noldner M, Yoshitake T. *Ginkgo biloba* leaf extract (EG b 761®) and its specific acylated flavonol constituents increase dopamine and acetylcholine levels in the rat medial prefrontal cortex : possible implications for the cognitive enhancing properties of EGb 761®. Int Psychogeriatr, 2012; 24(S1):S25-S34.

Kim B-H, Kim K-P, Lim KS, Kim J-R, Yoon SH, Cho J-Y, Lee Y-O, Lee K-H, Jang I-J, Shin S-G, Yu K-S. Influence of *Ginkgo biloba* extract on the pharmacodynamic effects and pharmacokinetic properties of ticlopidine: An open-label, randomized, two-period, two-treatment, two-sequence, single-dose crossover study in healthy Korean male volunteers. Clin Ther, 2010; 32(2):380–390.

Kim H-S, Kim G-Y, Yeo C-W, Oh M, Ghim J-L, Shon J-H, Kim E-Y, Kim D-H, Shin J-G. The effect of *Ginkgo biloba* extracts on the pharmacokinetics and pharmacodynamics of cilostazol and its active metabolites in healthy Korean subjects. Brit J Clin Pharmacol, 2013, DOI: 10.1111/bcp.12236

Kim MJ, Park YJ, Chung KH, Oh SM. The Inhibitory effects of the standardized extracts of *Ginkgo biloba* on aromatase activity in JEG-3 human choriocarcinoma cells. Phytother Res, 2013; Doi: 10.1002/ptr.4927.

Koh P-O. *Gingko biloba* extract (EGb 761) prevents cerebral ischemia-induced p70S6 kinase and S6 phosphorylation. Am. J. Chin. Med., 2010; 38(4):727-734.

Kuller LH, Ives DG, Fitzpatrick AL, Carlson MC, Mercado C, Lopez OL, Burke GL, Furberg CD, DeKosky ST. Does *Ginkgo biloba* reduce the risk of cardiovascular events? Circ Cardiovasc Qual Outcomes, 2010; 3:41-47.

Kwon SH, Nam JI, Kim SH, Kim JH, Yoon J-H, Kim K-S. Kaempferol and quercetin, essential ingredients in *Ginkgo biloba* extract, inhibit interleukin-1β-induced MUC5AC gene expression in human airway epithelial cells. Phytother Res, 2009; 23:1708–1712.

Lang F, Hoerr R, Noeldner M, Koch E, 2013. *Ginkgo biloba* Extract EGb 761®: From an ancient Asian plant to a modern European herbal medicinal product. In: Evidence and rational based research on Chinese drugs. Springer: Vienna, pp.431-470.

Leadbetter G, Keyes LE, Maakestad KM, Olson S, Patot MCT, Hackett PH. *Ginkgo biloba* does—and does not—prevent acute mountain sickness. Wild Environ Med, 2009; 20(1):66–71.

Lee Y-W, Lin J-A, Chang C-C, Chen Y-H, Liu P-L, Lee A-W, Tsai J-C, Li C-Y, Tsai C-S, Chen T-L, Lin F-Y. *Ginkgo biloba* extract suppresses endotoxin-mediated monocyte activation by inhibiting nitric oxide- and tristetraprolin-mediated toll-like receptor 4 expression. J Nutr Biochem, 2011; 22:351–359.

Li L, Stanton JD, Tolson AH, Luo Y, Wang H. Bioactive terpenoids and flavonoids from *Ginkgo biloba* extract induce the expression of hepatic drug-metabolizing enzymes through pregnane X receptor, constitutive androstane receptor, and aryl hydrocarbon receptor-mediated pathways. Pharm Res, 2009; 26(4):872–882.

Li X, Hu Y, Fu Y, Ying Y, Chen G. Effect of *Ginkgo biloba* extract on glucose uptake of diaphragm in diabetic rats. Zhongguo Zhong Yao Za Zhi, 2010; 35(3):356-359.

Li X, Ji ., Fu Y, Ying Y, Hu Y. Effects of *Ginkgo biloba* extract on cellular cholesterol content and CD36 expression of macrophages from diabetic rats. Biomedical Engineering and Biotechnology (iCBEB), 2012 International Conference, 28-30 May, 2012, Macau, Macao, p221-223.

Lim S, Yoon JW, Kang SM, Choi SH, Cho BJ, Kim M, Park HS, Cho HJ, Shin H, Kim Y-B, Kim HS, Jang HC, Park KS. EGb761, a *Ginkgo biloba* extract, is effective against atherosclerosis in vitro, and in a rat model of type 2 diabetes. PLoS ONE, 2011; 6(6): e20301, DOI: 10.1371/journal.pone.0020301.

Lu Q, Yang T, Zhang M, Du L, Liu L, Zhang N, Guo H, Zhang F, Hu G, Yin X. Preventative effects of *Ginkgo biloba* extract (EGb761) on high glucose-cultured opacity of rat lens. Phytother Res, 2013, Doi: 10.1002/ptr.5060.

Ma K, Xu L, Zhang H, Zhang S, Pu M, Jonas JB. The effect of *Ginkgo biloba* on the rat retinal ganglion cell survival in the optic nerve crush model. Acta Ophthalmol, 2009; 88:553–557.

Mansour SM, Bahgat AK, El-Khatib AS, Khayyal MT. *Ginkgo biloba* extract (EGb 761) normalizes hypertension in 2K, 1C hypertensive rats: Role of antioxidant mechanisms, ACE inhibiting activity and improvement of endothelial dysfunction. Phytomedicine, 2011; 18(8–9):641–647.

Martin R, Mozet C, Martin H, Welt K, Engel C, Fitzl G.The effect of *Ginkgo biloba* extract (EGb 761) on parameters of oxidative stress in different regions of aging rat brains after acute hypoxia. Aging Clin Exp Res, 2011; 23(4):255-63.

Mashayekh A, Pham DL, Yousem DM, Dizon M, Barker PB, Lin DDM. Effects of *Ginkgo biloba* on cerebral blood flow assessed by quantitative MR perfusion imaging: a pilot study. Neuroradiology, 2011; 53(3):185–191.

Okuyan B, Izzettin FV, Bingol-Ozakpinar O, Turan P, Ozdemir ZN, Sancar M, Cirakli Z, Clark PM, Ercan F. The effects of *Ginkgo biloba* on nephrotoxicity induced by cisplatin-based chemotherapy protocols in rats. IUFS J Biol, 2012; 71(2):103-111.

Ou H-C, Lee W-J, Lee I-T, Chiu T-H, Tsai K-L, Lin C-Y, Sheu WH-Y. *Ginkgo biloba* extract attenuates oxLDLinduced oxidative

functional damages in endothelial cells. J App Physiol, 2009; 106(5):1674-1685.

Ozgoli G, Selselei E, Mojab F, Majd HA. A randomized, placebo-controlled trial of *Ginkgo biloba* L. in treatment of premenstrual syndrome. J Alt Compl Med, 2009; 15(8):845-851.

Pandey A, Tamta S, Giri D. Role of auxin on adventitious root formation and subsequent growth of cutting raised plantlets of *Ginkgo biloba* L. Int J Biodivers and Conserv, 2011; 3(4):142-146.

Park YJ, Kim MJ, Kim HR, Yi MS, Chung KH, Oh SM. Chemopreventive effects of *Ginkgo biloba* extract in estrogen-negative human breast cancer cells. Arch Pharmacal Res, 2013; 36(1):102-108.

Pinto MDS, Kwon Y-I, Apostolidis E, Lajolo FM, Genovese MI, Shetty K. Potential of *Ginkgo biloba* L. leaves in the management of hyperglycemia and hypertension using in vitro models. Bioresour Technol, 2009; 100(24):6599–6609.

Preuss UW, Bachinskaya N, Kaschel R, Wong JW, Hoerr R, Gavrilova SI. 1689 – *Ginkgo biloba* extract EGb 761 in mild cognitive impairment with neuropsychiatric symptoms: a randomized placebo-controlled trial. Eur Psychiatry, 2013; 28(S1):1

Rajaraman G, Yang G, Chen J, Chang TKH. Modulation of CYP1B1 and CYP1A1 gene expression and activation of aryl hydrocarbon receptor by *Ginkgo biloba* extract in MCF-10A human mammary epithelial cells. Can J Physiol Pharmacol, 2009; 87(9):674-683.

Rhein V, Giese M, Baysang G, Meier F, Rao S, Schulz KL, Hamburger M, Eckert A. *Ginkgo biloba* extract ameliorates oxidative phosphorylation performance and rescues Aβ-induced failure. PLoS ONE, 2010; 5(8): e12359.

Ribonnet L, Callebaut A, Nobels I, Scippod M-L, Schneider Y-J, De Saegere S, Pussemier L, Larondelle Y. Modulation of CYP1A1 activity by a *Ginkgo biloba* extract in the human intestinal Caco-2 cells. Toxicol Lett, 2011; 202(3):193–202.

Rocher M-N, Carre D, Spinnewyn B, Schulz J, Delaflotte S, Pignol B, Chabrier P-E, Auguet M. Long-term treatment with standardized *Ginkgo biloba* Extract (EGb 761) attenuates cognitive deficits and hippocampal neuron loss in a gerbil model of vascular dementia. Fitoterapia, 2011; 82:1075–1080.

Rojas P, Serrano-Garcia N, Medina-Campos ON, Pedraza-Chaverri J, Ogren SO, Rojas C. Antidepressant-like effect of a *Ginkgo biloba* extract (EGb761) in the mouse forced swimming test: Role of oxidative stress. Neurochem Int, 2011; 59(5):628–636.

Rudall P, Rowland A, Bateman RM. Ultrastructure of stomatal development in *Ginkgo biloba*. Int. J. Plant Sci., 2012; 173(8):849–860.

Ryu EY, Park AJ, Park SY, Park SH, Eom HW, Kim YH, Park G, Lee S-J. Inhibitory effects of *Ginkgo biloba* extract on inflammatory mediator production by *Porphyromonas gingivalis* lipopolysaccharide in murine macrophages via Nrf-2 mediated heme oxygenase-1 signaling pathways. Inflammation, 2012; 35(4):1477-1486.

Ryu KH, Han HY, Lee SY, Jeon SD, Ima G-J, Lee BY, Kim K, Lim K-M, Chung J-H. *Ginkgo biloba* extract enhances antiplatelet and antithrombotic effects of cilostazol without prolongation of bleeding time. Thromb Res, 2009; 124(3):328–334.

Salehi B, Imani R, Mohammadi MR, Fallah J, Mohammadi M, Ghanizadeh A, Tasviechi AK, Vossoughi A, Rezazadeh S-A, Akhondzadeh S. Ginkgo biloba for Attention-Deficit/Hyperactivity Disorder in children and adolescents: A double blind, randomized controlled trial. Prog Neuropsychopharmacol Biol Psychiatry, 2010; 34:76–80.

Shah ZA, Nada SE, Dore S. Heme oxygenase 1, beneficial role in permanent ischemic stroke and in *Gingko biloba* (EGb 761) neuroprotection. Neuroscience, 2011; 180:248–255.

Shen J, Lee W, Gu Y, Tong Y, Fung PCW, Tong L. *Ginkgo biloba* extract (EGb761) inhibits mitochondria-dependent caspase pathway and prevents apoptosis in hypoxia-reoxygenated cardiomyocytes. Chin Med, 2011; 6:8-16.

Shi C, Liu J, Wu F, Yew DT. *Ginkgo biloba* extract in Alzheimer's disease: From action mechanisms to medical practice. Int J Mol Sci, 2010; 11:107-123.

Shi C, Xiao S, Liu J, Guo K, Wu F, Yew, DT. Xu J. *Ginkgo biloba* extract EGb761 protects against aging-associated mitochondrial dysfunction in platelets and hippocampi of SAMP8 mice. Platelets, 2010; 21(5):373-379.

Shi C, Zhao L, Zhu B, Li Q, Yew DT, Yao Z, Xu J. Protective effects of *Ginkgo biloba* extract (EGb761) and its constituents quercetin and ginkgolide B against β-amyloid peptide-induced toxicity in SH-SY5Y cells. Chem Biol Interact, 2009; 181(1):115–123.

Snitz BE, O'Meara ES, Carlson MC, Arnold AM, Ives DG, Rapp SR, Saxton J, Lopez, OL, Dunn LO, Sink KM, DeKosky ST. *Ginkgo biloba* for preventing cognitive decline in older adults: A randomized trial. JAMA, 2009; 302(24):2663-2670.

Szczurko O, Shear N, Taddio A, Boon H. *Ginkgo biloba* for the treatment of vitilgo vulgaris: an open label pilot clinical trial. BMC Complemet Alternat Med, 2011; 11:21-26.

Tang CQ, Yang Y, Ohsawa M, Yi S-R, Momohara A, Su W-H, Wang H-C, Zhang Z-Y, Peng M-C, Wu Z-L. Evidence for the persistence of wild *Ginkgo biloba* (Ginkgoaceae) populations in the Dalou Mountains, southwestern China. Am J Bot., 2012; 99(8):1408-1414.

Thorpe LB, Goldie M, Dolan S. Central and local administration of *Gingko biloba* extract EGb 761 inhibits thermal hyperalgesia and inflammation in the rat Carrageenan model. Anesth Analg, 2011; 112:1226–1231.

Tian J, Shi J, Zhang X, Wang Y. Herbal therapy: a new pathway for the treatment of Alzheimer's disease. Alzheimers Res Ther, 2010; 2:30-33.

Tobinaga S, Hashimoto M, Utsunomiya I, Taguchi K, Nakamura M, Tsunematsu T. Chronic administration of cardanol (ginkgol) extracted from *Ginkgo biloba* leaves and cashew nutshell liquid improves working memory-related learning in rats. Biol Pharm Bull, 2012; 35(1):127-129.

Trease GE, Evans WC, 1983. Pharmacognosy, Ballière Tindall: Eastbourne.

Trompezinski S, Bonneville M, Pernet I, Denis A, Schmitt D, Viac J. *Gingko biloba* extract reduces VEGF and CXCL-8/IL-8 levels in keratinocytes with cumulative effect with epigallocatechin-3-gallate. Arch Dermatol Res, 2010; 302(3):183-189.

Tsai H-Y, Huang P-H, Lin F-Y, Chen J-S, Lin S-J, Chen J-W. *Ginkgo biloba* extract reduces high-glucose-induced endothelial reactive oxygen species generation and cell adhesion molecule expression by enhancing HO-1 expression via Akt/eNOS and p38 MAP kinase pathways. Eur J. Pharm Sci, 2013; 48(4–5):803–811.

Vellas B, Coley N, Ousset P-J, Berrut G, Dartigues J-F, Dubois B, Grandjean H, Pasquier F, Piette F, Robert P, Touchon J, Garnier P, Mathiex-Fortunet H, Andrieu S. Long-term use of standardised *Ginkgo biloba* extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial. Lancet Neurol, 2012;11(10):851-859.

Wang B-S, Wang H, Song Y-Y, Qi H, Rong Z-X, Wang B-S, Zhang L, Chen H-Z. Effectiveness of standardized *Ginkgo biloba* extract on cognitive symptoms of dementia with a six-month treatment: A bivariate random effect meta-analysis. Pharmacopsychiatry, 2010; 43(3):86-91.

Weinmann S, Roll S, Schwarzbach C,Vauth C, Willich SN. Effects of *Ginkgo biloba* in dementia: systematic review and meta-analysis. BMC Geriatrics, 2010; 10:14-21.

Wu X, Mao G, Zhao T, Zhao J, Li F, Liang L,Yang L. Isolation, purification and in vitro anti-tumor activity of polysaccharide from *Ginkgo biloba* sarcotesta. Carbohyd Polym, 2011; 86(2):1073–1076.

Xu SL, Choi RCY, Zhu KY, Leung K-W, Guo A JY, Bi D, Xu H, Lau DTW, Dong TTX, Tsim KWK. Isorhamnetin, a flavonol aglycone from *Ginkgo biloba* L., induces neuronal differentiation of cultured PC12 cells: Potentiating the effect of nerve growth factor. Evid-Based Compl Alt, 2012; 2012:1-11.

Yancheva S, Ihl R, Nikolova G, Panayotov P, Schlaefke S, Hoerr R. *Ginkgo biloba* extract EGb 761®, donepezil or both combined in the treatment of Alzheimer's disease with neuropsychiatric features: A randomised, double-blind, exploratory trial. Aging Ment Health, 2009; 13(2): 183-190.

Yang L, Wang C-Z, Ye J-Z, Li H-T. Hepatoprotective effects of polyprenols from *Ginkgo biloba* L. leaves on CCl_4-induced hepatotoxicity in rats. Fitoterapia, 2011; 82(6):834–840.

Yang TH, Young YH, Liu SH. EGb 761 (*Ginkgo biloba*) protects cochlear hair cells against ototoxicity induced by gentamicin via reducing reactive oxygen species and nitric oxide-related apoptosis. J Nutr Biochem, 2010; 22(9):886-894.

Yeh K-Y, Liu Y-Z, Tai M-Y, Tsai Y-F. *Ginkgo biloba* extract treatment increases noncontact erections and central dopamine levels in rats: role of the bed nucleus of the stria terminalis and the medial preoptic area. Psychopharmacology, 2010; 210(4):585-590.

Yeh Y-C, Liu T-J, Wang L-C, Lee H-W, Ting C-T, Lee W-L, Hung C-J, Wang K-Y, Lai H-C, Lai H-C. A standardized extract of *Ginkgo biloba* suppresses doxorubicin-induced oxidative stress and p53-mediated mitochondrial apoptosis in rat testes. Brit J Pharmacol, 2009; 156:48–61.

Zadoyan G, Rokitta D, Klement S, Dienel A, Hoerr R, Gramatte T, Fuhr U. Effect of *Ginkgo biloba* special extract EGb761® on human cytochrome P450 activity: a cocktail interaction study in healthy volunteers. Eur J Clin Pharmacol, 2012; 68(5): 553-560.

Zhai Y, Pang X, Cheng Q, Liu L, Jin Y, Lu Q, Yin X. Effects of monotherapy and combination therapy of *Ginkgo biloba* extract,captopril,valsartan on high glucose-induced proliferation and hypertrophy of rat mesangial cells. Acta Academiae Medicinae Xuzhou, 2010; 6:004.

Zhang Z, Peng D, Zhu H, Wang X. Experimental evidence of *Ginkgo biloba* extract EGB as a neuroprotective agent in ischemia stroke rats. Brain Res Bull, 2012; 87(2–3):193–198.

Zhao X-D, Dong N, Man H-T, Fu Z-L, Zhang M-H, Kou S, Ma S-L. Antiproliferative effect of the *Ginkgo biloba* extract is associated with the enhancement of cytochrome P450 1B1 expression in estrogen receptor-negative breast cancer cells. Biomed Rep, 2013; 1(5):797-801.

Zhao Z, Liu N, Huang J, Lu P-H, Hu X-M. Inhibition of $cPLA_2$ activation by *Ginkgo biloba* extract protects spinal cord neurons from glutamate excitotoxicity and oxidative stress-induced cell death. J Neurochem, 2011; 116:1057–1065.

Zhou L, Meng Q, Qian T, Yang Z. *Ginkgo biloba* extract enhances glucose tolerance in hyperinsulinism-induced hepatic cells. J Nat Med, 2011; 65(1):50-56.

Zuo X-C, Zhang B-K, Jia S-J, Liu S-K, Zhou L-Y, Li J, Zhang J, Dai L-L, Chen B-M, Yang G-P, Yuan H. Effects of *Ginkgo biloba* extracts on diazepam metabolism: a pharmacokinetic study in healthy Chinese male subjects. Eur J Clin Pharmacol, 2010; 66(5):503-509.

How to cite this article:

Abdulmumin A. Nuhu., *Ginkgo biloba*: A 'living fossil' with modern day phytomedicinal applications. J App Pharm Sci. 2014; 4 (03): 096-103.