

Highlights of the 11th International Symposium on Ginseng (27th October to 30th October 2014, Seoul, Korea)

Evidence – based efficacy of Ginseng: An Update

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Abstract:

11th International symposium on ginseng was held at Seoul at New Millennium Hall of Konuk University, Seoul, Korea from 27th to 30th October 2014. The meeting was organized by The Korean Society of Ginseng. The symposium was organized with a mission to advance the basic and applied sciences and highlighted an advancement in the cultivation, immune modulation, particularly in the areas of cancer, neurodegeneration, infertility, diabetes and related disorders. This report discusses various aspects of ginseng and its status in diverse pathological / disease condition as well as agriculture use. This report is mix of various plenary lecture, symposia, young investigator colloquia, oral /poster presentation.

Keywords:

Introduction

11th International symposium on ginseng was held at Seoul at New Millennium Hall of Konuk University, Seoul, Korea from 27th to 30th October 2014. The meeting was organized by The Korean Society of Ginseng. The symposium was organized with a mission to advance the basic and applied sciences related to the cultivation, biology, biochemistry, pharmacology, veterinary science, and processing of ginseng for medicinal purposes and clinical studies. It also served as a platform to explore the advancement in the cultivation, immune modulation, particularly in the areas of cancer, neurodegeneration, infertility, diabetes and related disorders. Present report briefly addresses evidence based efficacy of ginseng at its *cellular and molecular aspects, recent developments and future challenges in the field of immuno modulation, cancer, diabetes and neurodegeneration.*

The meeting was opened by the speech of Dr. Si-Kwan Kim, President of the Local Organizing Committee and Dr. Dong-Kwon Rhee, Chair of the Organizing Committee. Their speech highlight the overview of the entire meeting program, that consists of 13 symposia, 2 young investigator colloquia, young scientist lecture and multiple poster sessions ranging from invitro genetic architecture to clinical studies and from immuno modulation to neurological disorders.

A total of 700 scientists from various countries attended this meeting. Present reports highlights the key issues discussed in the areas of immune modulation, cancer, diabetic complications, infertility and neurodegeneration etc.

Cancer / Immuno modulation-

Cancer is major health problem throughout the world consequent to increase longevity of the population, changing the environment and life style. Chemoprevention has emerged as a new and promising strategy against cancer burden. Ginseng is known for its various ailments in human beings. It is one of the most commonly used herbal medicines or dietary supplements in the world. When administered orally the problem with the ginseng is its bioavailability. Main problems associated with its poor bioavailability are its incomplete parent compound absorption and conversion to its metabolites in GIT. Deglycosylation reactions by intestinal microbiome are mainly responsible for the conversion of ginseng saponins to pharmacologically active ginseng compound K and protopanaxadiol available in systemic circulation. At the same time ginseng and its metabolites alters the structure of intestinal microbiome. So, understanding the two way interaction between ginseng metabolites with GIT homeostasis is very much important. Dr. Chun-su Yuan and his group from Tannng center for Herbal Medicine Research, university of Chicago, Illinois USA elucidated that using gut specific in vivo animal models they are able to detect the significant effects of ginseng metabolites on colon cancer chemoprevention. Further, oral administration studies in humans revealed that cancer chemoprevention was supported by metabolomic fingerprints analyzed by chip-based nano LC/Q-TOF-MS methods in biological fluids.

Heat processed formulation of *Panax ginseng* was shown to inhibit 12-*O*-tetradecanoylphorbol-13-acetate (TPA) induced tumors in mouse skin. Young-Joon Surh from Research Institute of Pharmaceutical Sciences, Seoul National University, Korea has shown that the antitumor promoting activity of heat processed ginseng formulation is associated with the cyclooxygenase-2, ornithine decarboxylase inhibitory property and as well as activation of NF- κ B. Further, same group has also documented that Korean Red Ginseng treatment on PC12 cell lines increases nuclear translocation, antioxidant response element binding and transcriptional activity of NF-E2 related factor (Nrf2), a master redox-sensitive transcription factor. This resulted in an increased expression and up regulation of hemoxygenase-1 (HO-1) and catalytic subunit of glutamate cysteine ligase (GCLC) there by increased the cellular defense against oxidative stress in PCB126 induced cytotoxicity in cultured PC-12 cells.

In addition, Dr. Sang-Moo Kang and his group from Center for Inflammation, Immunity & Infection and Department of Biology, Georgia State University, Atlanta, USA stated that long term oral administration of Korean red ginseng extract to mice loaded with influenza virus and respiratory syncytial virus (RSV) shown to

effective by stimulating the antiviral cytokine interferon (IFN- γ) production. It also inhibited the infiltration of the inflammatory cells in the bronchial airways leading to decreased viral loads in lungs. Clinically, also Korean red ginseng extract resulted in reduced weight loses in patients with live RSV infections, reduced IL-4 production, modulated the CD3 T cell population toward a T helper type 1 responses, there by reduced the inflammatory responses.

Dr. Geun-Shik Lee (form College of Veterinary Medicine, Kangwon National University, Korea) talked about the role of Korean red ginseng extracts in inflammasome activation extensively explained the inflammasome mediated activation of caspase-1. In his study using NLRP3 and AIM2 induced inflammasome activation in mouse and human macrophages, red ginseng extract treatment inhibited IL-1 β maturation and secretion as well as pathogen clearance via pyroptotic cell death by macrophages against NLRP3 and AIM2 induced inflammasome activation. Further, ginsenosides Rg1 and Rh3 were found to be the inhibitors involved in this inflammasome activation. Dr. S. Kala and his group from School of Biological Science, University of Hong Kong, Hong Kong further demonstrated that ginsenoside-Rb1, a nontoxic saponins isolated from the rhizome of *Panax quinquefolius* has anti-tumor activity with lower toxicity and side effect profile apart from its anti-angiogenic efficacy. Further, it has claimed that Rb1 is capable of targeting the tumor –initiating cells.

Dr. Tahira Fatima and their group from Department of Physiology and Pharmacology, Schulich School of Medicine, Western University, London in their study reported the cyto-protective and immuno modulatory effects of crude polysaccharide fraction of *Panax quinquefolius* on single sub-lethal dose of cyclophosphamide (300mg/kg, i.p) induced toxicity in Balb/c mice. Cyclophosphamide treatment resulted in reduction of phagocytic index, hemagglutination, splenocyte counts, bone marrow cellularity and plasma cytokine levels (IL-1, IL-6 & TNF- α). Histologically, white cell depletion in spleen, increase in mitotic index in bone marrow and reduction in germ cell layers of testicular seminiferous tubules. All these alterations were opposed by oral administration of crude polysaccharide fraction of ginseng by oral gavage for 14 days at dose levels of 50 and 100ng/kg. This study also pointed out that starting the first dose crude extract of ginseng within one hour following cyclophosphamide administration has had same effect as that obtained by the treatment started after 3 days indicating that inhibition of cyclophosphamide bio-activation is not responsible for the observed effects.

Angiogenesis, the formation of neovessels is known to play important role in tumor genesis. Dr. MH Keung and their group from Biology, Hong Kong Baptist University, Hong Kong demonstrated the role of miRNA

in Ginsenoside-Rg3 induced angiosuppression. The miRNA expression profiling analysis showed that 6 and 3 miRNAs were found to be up - or down -regulated in vascular endothelial growth factor (VEGF)-induced human umbilical vein endothelial cells (HUVECS) after Rg3 treatment, respectively. Among the miRNA candidates up-regulated miR-520h was found to target Ephrin receptor (Eph) B2 and B4 and reduced them by 20- and 2.2 fold respectively. The same was resulted in in-vitro transfection assay and zebrafish angiogenic models; showed over expressed miR-520h inhibited EphB2 and B4 protein expression, proliferation and tube formation of endothelial cells and sub intestinal vessels formation of zebrafish. Thus they have highlighted the role of miRNAs in Rg3 induced angiosuppression.

Dr. Pradeep Kumar Goyal from Radiation and Cancer Biology Laboratory, Department of Zoology, University of Rajasthan, Jaipur, India has shown anticancer and antioxidative potential of *Panax ginseng* against chemical induced skin carcinogenesis in mammals. Swiss albino mice were received single topical application of 7, 12-dimethylbenz (a) anthracene (100 µg/100µL acetone) and after 2weeks repeated application of croton oil (thrice in a week in 1% acetone) till the end of 16 weeks to induce and promote the skin tumors. Oral administration of hydro-alcoholic ginseng root extracts (25mg/kg/day) at the peri-initiation, post-initiation and peri-post initiation stages caused significant reduction in tumor incidence, cumulative number of tumors, tumor yield and tumor burden as compared to control group. Further, a significant enhancement in glutathione (GSH), superoxide dismutase (SOD), catalase, vitamin C and total proteins, significant reduction in lipid peroxidation (LPO) levels in both liver and skin were observed with ginseng root extract treatment suggesting the potential to ameliorate cancer in mammals.

Diabetes and its complication

Panax ginseng exhibits pleiotropic beneficial effects on metabolic, cardiovascular, central nervous and immune systems. The mechanism of ginseng and its active constituents is complex and demonstrated to be either modulates insulin production/secretion, glucose metabolism and uptake, triglyceride biosynthesis or inflammatory pathways in both insulin dependent and insulin independent manners. Ginseng has recently become an increasingly popular candidate for the prevention and treatment of cardiac remodeling with evidences shown both in-vitro and in-vivo for their anti-hypertrophic and anti-remodeling effects. Dr. Morris Karmazyn from University of Western Ontario, Canada in his studies using sustained coronary artery occlusion in animals with North American Ginseng (*Panax quinquefolius*) treatment shown not only prevention but also to reversal post-infarction cardiac remodeling and

heart failure. Besides its efficacy tested using isolated cardiomyocytes which were subjected to a variety of hypertrophic agonists including angiotensin-II, endothelin-I, phenylephrine as well as leptin was demonstrated to prevent hypertrophy. The mechanisms responsible for the observed effects were elucidated further. It was shown that inhibition of sodium-hydrogen exchange isoform 1 (NHE1) is primarily responsible for the observed effects. Inhibition of NHE1 lead to decreased intracellular calcium overload, calcineurin activation and other mechanisms like prevention of COX-2 activation have been reported to participate in preventing the hypertrophic response.

AMPkinase signaling pathway is a key molecule to sense the cellular energy. Once activated, it switches on catabolic pathways generating ATP, while switching off biosynthetic pathways consuming ATP. Pharmacological activation of AMPK by metformin holds a therapeutic potential to reverse the metabolic abnormalities such as type 2 Diabetes mellitus and non-alcoholic fatty liver disease. Dr Do Woon Kim and their group from Department of Pharmacology and Clinical pharmacy, College of Pharmacy, Kyung Hee University, Seoul, Korea in their studies using invitro, animal models and human clinical trials have shown that ginseng and ginsenosides have diverse molecular targets in these diseases, particularly on AMP kinase signaling pathway. Further, Dr. Hae-Mi Cho and their group from Department of Biomedical Sciences, Cell dysfunction Research Center, Seoul, Korea has shown that *Panax red ginseng* extract prevents high fat diet (HFD) induced obesity by regulating lipid mobilization in adipose tissues. It has inhibited the lipogenesis pathway in white adipose tissue through activation of the 5' AMP-activated protein kinase pathway. Further, it has been shown that *Panax red ginseng* extracts strongly activated Hormone-Specific Lipase (HSL) via protein kinase A. Since activation of HSL induces lipolysis in white adipose tissue and fatty acid oxidation in brown adipose tissue, *Panax red ginseng* may find its place for treatment in obesity as it has prevented the high fat diet induced obesity by regulating lipid mobilization and energy expenditures.

Dr. Oran Kwon from Department of Nutritional Science and Food Management, Ewha Womans University, Seoul, Korea described the potency of *Panax ginseng* extract rich in protopanaxatriol on endothelium dependent relaxation in spontaneously hypertensive rats and humans. In human umbilical vein endothelial cells they have tested wide variety of ginseng extract namely, crude extract, CE, protopanaxatriol-enriched extract, TE; protopanaxadiol-enriched extract, DE and individual ginsenosides (RgI, Re and Rb1). Among these, TE treatment resulted in rapid activation of intracellular signaling pathways, immediate linear rise of NO, and increased eNOS activation, followed by CE, DE and

Rg1. Further, TE induced activation of eNOS was abolished by pretreatment with wortmannin (inhibitor of PI3-Akt), compound -C (inhibitor of AMPK), or L-NAME (Inhibitor of NOS), whereas Rg1-induced eNOS phosphorylation was only partially attenuated. Further, in their analysis it is revealed that TE, but not Rg1 resulted in AMPK phosphorylation at Thr172. Then to confirm the physiological relevance of *in vitro* studies they examined the effects of TE on endothelium dependent relaxation in spontaneously hypertensive rats (SHRs). TE administration stimulated nongenomic Akt-mediated eNOS activation, enhanced NO production, improved vessel wall thickening and alleviated hypertension in SHRs, thus supported the physiological relevance of *in vitro* studies with TE. Besides, they also investigated the effects of low (100mg) and high (300mg) doses of TE on blood pressure in adults over 20 years old with a systolic BP (SBP) between 120 and 159 mm of Hg or a diastolic BP (DBP) between 80-99mm of Hg along with placebo controls (n=90). Drug treatment was started after 2 weeks of washout period and continued up to 8 weeks. They observed that at high dose levels of TE, there was some significant decrease in BP from baseline ($p < 0.05$), but this effect was not maintained over 8 weeks.

Dr. Gabriel Hoi-huen Chan from Department of Biology, Hong Kong Baptist University, Hong Kong and their group demonstrated that both PPT and PPD type ginsenosides can restore the diabetes induced impaired vascular relaxation and can reduce serum triglyceride but not cholesterol levels in the diabetic rats. From the results, they have concluded that the ginseng extract can down regulate the atherosclerosis related genes and alters the expression of lipid related genes thus helping to restore normal endothelial functions.

Dr.Kyung_Mi Lee from Department of Biochemistry and Molecular Biology, Korea University College of Medicine, Seoul, Korea in his experiments on C57/BL6 mice demonstrated the prophylactic potential of Korean red ginseng (KRG) extract against STZ induced diabetes model. KRG extract was fed for 2 weeks prior to the administration of STZ. KRG extracts significantly reduced blood glucose levels to an average of 250-350 mg/dL. Histo-logically STZ induced destruction of pancreatic tissue was prevented by prophylactic treatment with KRG along with restoration of insulin secretion through the restoration of lymphoid organs in secondary lymphoid organs. Further, immuno compartments of diabetic mice were found to be preserved in KRG treated mice suggesting that KRG may benefit type-1 diabetic patients not only for its hypoglycemic action but also for its immuno-modulatory effects.

Molecular Pharmacology

Dr. Cuong Thach Nguyen and their group from School of Pharmacy, Sungkyunkwan University, Su-Won,

Korea in their study using neuroblastoma cells evaluated the effect of Korean Red Ginseng (KRG) on oxidative stress induced apoptosis. They found that apoptosis inhibition was mediated by ER- β up regulation via the PI3K/AKT signaling pathway. The up regulation of PI3K/AKT signaling inhibited apoptotic signals by decreasing p-p53 and caspase-3 expression but increasing BCL2 expression.

Whereas Dr. Qian Mao and their group from Department of Pharmaceutical Analysis & Metabolomics, Jiangsu Province Academy of Traditional Chinese Medicine, China in their study with gastric carcinoma cells further elucidated the anti-cancer mechanism of ginsenoside F2 using gastric carcinoma cells (SGC7901 cells). In SGC7901 gastric carcinoma cells, ginsenoside F2 induced ROS accumulation followed by decreased mitochondrial trans-membrane potential (MTP), and cytochrome C release. Further, they have elucidated that modulation of ASK-1/JNK pathway is responsible for the observed apoptosis.

Dr. Kwang-Soo Baek and their group from Department of Genetic Engineering, Sungkyunkwan University, Suwon, Korea, described the protective effects of KRG derived components (KRG-dC) using *in vivo* gastritis and peritonitis models. This KRG-dC ameliorated the EtoH/HCl induced gastritis and down-regulated the peritoneal exudates derived NO production from lipopolysaccharide injected mice. This inhibitory effect was regulated through the suppression of p38, JNK and TANK-binding kinase 1 (TBK1), thereby subsequent inhibition of activating transcription factor (ATF)-2, CREB and IRF-3 activation. These results have been shown that highest inhibitory potency ginsenosides of G-Rc type on IRF-3 mediated luciferase activity.

Dr. Dong-Yoon Lim from Department of Pharmacology, School of Medicine, Chionsan University Gwangju, Korea further described the mechanisms involved in the effect of ginsenosides-Rb2 (Rb2) on the secretion of catecholamines (CA) in the rat perfused model of adrenal medulla. Rb2 (3-30 μ M) perfused in to the adrenal vein for 90 min inhibited the Ach (5.32nM) evoked CA secretion in dose and time dependent fashion. Rb2 (10 μ M) time dependently inhibited the CA secretion evoked by DMPP (100 μ M, a selective neuronal nicotinic receptor agonist) and high K^+ (56mM, a direct membrane depolarizer). Rb2 itself does not affected the basal CA secretion, but in the presence of Rb2(10 μ M), the secretory responses of CA evoked by veratidine (a selective Na^+ channel activator (50 μ M), Bay-K-8644 (an L-Type dihydropyridine Ca^{2+} channel activator, 10 μ M) and cyclopiazonic acid (a cytoplasmic Ca^{2+} -ATPase inhibitor, 10 μ M) were significantly reduced. Interestingly, in the presence of L-NAME (an inhibitor of NO synthase, 30 μ M) the inhibitory responses of Rb2 (10 μ M) on Ach evoked CA secretory

response was considerably recovered to the extent of the corresponding control secretion compared with the inhibitory effect of Rb2 alone. Also there was increase in the level of NO release from the adrenal medulla after Rb2 (10 μ M) treatment compared to basal release level. Thus the author concluded that the RB2 inhibits the CA secretory responses evoked by nicotinic stimulation as well as by direct membrane stimulation from the isolated perfused rat adrenal medulla. Further, the inhibitory effect was mediated by inhibiting both the influx of Ca^{2+} and Na^{+} into the adreno-medullary chromaffin cells and also by suppressing the release of Ca^{2+} from the cytoplasmic calcium stores.

Dr Man Hee Rhee from Laboratory of Veterinary Physiology and Cell Signaling, Kyungpook National University, Korea described the protective effect of Korean Red Ginseng extract on atherosclerosis and the underlying mechanisms involved. Low density lipoprotein (LDL) receptor deficient mice were fed with Western Diet (WD) and ginseng treatment for 13 weeks. Increased plasma glucose levels of WD fed group was reversed by ginseng. Serum levels of total cholesterol, LDH, and triglycerides (TG) were also markedly reduced. The level of high density lipoprotein (HDL) relative to total cholesterol was decreased in WD group, which is restored at low dose and enhanced at higher dose, where as increased LDH level of WD group was reduced by ginseng treatment. In addition AST and ALT plasma levels were inhibited in a dose dependent manner. However, plasma levels of GGT were not affected. There is also reduced transcriptional activity of TNF- α , IL-6, leptin and adiponectin in adipose tissue implying the inflammatory gene mediated anti atherosclerotic effect of ginseng.

Neuroprotection

Neuroprotection is a promising strategy in treatment of various neurological disorders associated with brain damage and neurodegeneration. Though the exact mechanism of action of ginseng has not been well described, there have been many evidences that showing the efficacy of ginseng against Alzheimer's disease (AD), Huntington's, Parkinson's Diseases and other neurodegenerative disorders. Evidence from animal studies suggests that *Panax ginseng* extracts can modulate the functioning of the mammalian central nervous system. With regards humans, whilst evidence of improved psychological well being following ginseng remains equivocal, a number of controlled trials have demonstrated improved cognitive function in terms of memory, attention and executive function. Animal studies have suggested the diverse mechanism of action of ginseng in AD. Some ginsenosides such as Rb1 and Rg1 appeared to potentiate cholinergic system in the central nervous system. Choline-acetyl transferase levels were shown to be increased by Rb1 and Rg1.

Ginsenosides Rb1 and M1 recovered the amyloid induced axonal atrophy and synaptic loss.

Dr. Yeonju Lee and their group from Molecular Medicine, School of Medicine, Ewha Womans University, Korea determined the memory enhancing effect of red ginseng (RG) using C57BL/6 mice (21 month old, male). These mice were fed with 0.12% red ginseng extract mixed in experimental diet pellets for 3 months. RG treatment suppressed the production of age-processed iNOS, COX-2, TNF- α , IL-1 β expressions. They also reported that RG treatment also shown antioxidative effects on aged mice by increasing the suppressed GSH, Nrf2 and HO-1 levels as compared to young mice of 4 month old. Status epilepticus is a dangerous disorder when prolonged seizures can lead to neuron death. Moreover an initial brain injury caused by SE can induce neurodegeneration and reorganization of neuronal circuits thus resulting in progressive brain damage, memory and cognitive impairment and epileptogenesis. Dr Elena Suleymanova from Laboratory of General Physiology of Temporary connections, Institute of Higher nervous activity of RAS, Russian Federation in their study using lithium-pilocarpine SE model in rats demonstrated the effect of ginseng extract on progression of brain damage and behaviour impairment. Administration of ginseng extract attenuated the early changes in hippocampus after SE, and hippocampal volume also preserved after a month of SE. Locomotor activity and rearing was decreased in ginseng treated rats when compared to saline treated groups.

Dr. Ik-Hyun Cho from Department of Convergence Medical Sciences, College of Korean Medicine and Institute of Korean Medicine, Kyung Hee University, Seoul, Korea has demonstrated the protective effects of Korean red ginseng extract (KRGE) in HD and PD animal models. KRGE (50, 100 and 250 mg/kg/day, p.o) pretreatment for 10 days before the 3-nitropropionic acid (3-NP) injection significantly decreased the neurological impairment, lethality, lesion area in striatum and neuronal loss by 3-NP injection. KRGE pretreatment also shown to attenuate microglial activation, phosphorylation of MAPK and NF- κ B signaling in striatum after 3-NP injection. KRGE further reduced the mRNA expression of TNF- α , IL-1 β , IL-6, iNOS and OX-42 in striatum after 3-NP injection. Whereas, KRGE (50, 100, 200 mg/kg/day, p.o) pretreatment for 7 days before MPTP injection showed to significantly decreased neurological impairment, tyrosine hydroxylase immuno reactive cells, glial cell activation and inflammatory mediators in the substantia nigra. These studies revealed the therapeutic potential of KRGE in suppressing the HD and PD like symptoms.

Infertility

Ginseng has been regarded as a tonic and aphrodisiac in the Orient from the ancient past, without any reported

complications. Experimental data have demonstrated that ginsenosides promote nitric oxide release and subsequent smooth muscle relaxation. Dr. Mi-Kyung Pyo and their group from Natural Products Development Lab, International Ginseng and Herb Research Institute, Korea in their study using alcohol induced erectile dysfunction (ED) revealed the effects of ginseng. They have used ginsenoside Re enriched fraction (GS-F3K1, ginsenoside Re 10% w/w) at a dose levels of 0.1, 0.25 and 0.5 g/kg along with one normal group and one positive control group (red ginseng extracts 0.5g/kg). ED was induced by oral administration of 20% ethanol for 5 weeks. The erectile response of the penile corpus cavernosum of the rats was restored by GS-F3K1 to a level similar to the normal group. There also observe the increase in NO and cAMP levels in the corpus cavernosum of GSF3K1 administered male rats.

Dr Tommaso Cai and their group from Department of Urology, Santa Chira Hospital, Trento, Italy in their study on patients suffering with chronic prostatitis (CP) due to Chlamydia trachomatis (Ct) infection, revealed the beneficial effects of ginseng extracts (fertimev). 206 patients with proven Ct general infection and oligoasthenoterazoospermia were enrolled in a prospective, randomized and controlled study. Prulifloxacin (600mg) was administered daily for 14 days and then the patients were divided in to 2 groups; group A: antibiotic therapy alone (n=109); and group B: antibiotic therapy and additional therapy with FERTIMEV (1 vial daily for 6 months) (n=97). Microbiological and semen parameter analysis were performed both at enrollment and after 6 months and no differences were reported with regard to laboratory, clinical and instrumental data. Six months treatment, statistically significant differences were demonstrated between both the groups in terms of sperm concentration (21.3 ± 13.2 millions/mL vs 11.5 ± 13.2 millions/mL, $p,0.001$) and percentage of motile sperm ($42.4 \% \pm 5.2\%$ vs $29.3\% \pm 11.0 \%$, $p<0.001$).

Dr. Si-Kwan Kim and their group from Department of Biomedical Chemistry, College of Biomedical & Health Science, Konkuk University, Chungju, Korea reported an improvement of spermatogenesis and sperm quality in diversified testicular malfunctions with Korean red ginseng water extract (KRG-WE) treatment in guinea pigs and rats. KRG-WE (100 and 200 mg/kg) significantly increased sperm quality in 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD, 1 μ g/kg) exposed guinea pigs. TCDD exposed animals died within 18days where as 40-70% KRG-WE treated groups survived until at the 40th week with all being fertile regardless of TCDD exposure. In aged rats and doxorubicin exposed rats, KRG-WE treatment significantly attenuated the ROS induced cellular damage, and restored the decreased expression levels of steroid hormone receptors (AR, LHR, FSHR) and spermatogenesis associated

molecules (nectin, inhibin, C/REB).

Ginseng is popular herbal medicine that has been used for over 2000 years in oriental countries without having a systematic characterization of their estrogenic action and mechanism on reproductive tissues.

Dr Ying Xu and their group from Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing, China in their study on immature mice and ovariectomized (OVX) mice described the estrogenic efficacy of ginseng on reproductive tissues. Intragastric daily treatment of ginseng at a dose of 12, 18 and 24 g/kg (n=10 per group) for 7 days and 4 weeks in immature mice and ovariectomized mice respectively resulted in development of uterus and vagina in immature mice and restoration of estrus cycle and reversal of atrophy of uterus and vagina in ovariectomized mice. Further, ginseng treatment resulted in up regulation of estrogen receptors (both α and β , former being stronger) at protein and mRNA level in the reproductive tissues in immature and ovariectomized mice. There is also significant increase in adrenal gland weight, serum estradiol, and decrease in weight gain caused by ovariectomy. All these effects of ginseng were clearly opposed by simultaneous administration of estrogen receptor antagonist Veratrum nigrum (0.045 g/kg).

Dr. Man-Sau Wong from Department of Applied Biology and Chemical Technology, the Hongkong Polytechnic University, Hong Kong along with their group reported the estrogen like effects of ginsenoside Rg1, one of the active ingredients of ginseng root using human breast cancer (MCF-7) cells. In their studies they had shown that actions in MCF-7 cells are due to cross talk between estrogen receptor (ER)- α and insulin growth factor I receptor (IGF-IR) dependent pathways. The stimulation of IGF-IR expression and the activation of IRS-1 phosphorylation by Rg1 are both ER-dependent. Rg1 preferentially activates ER- α via phosphorylation of AF-1 domain in MCF-7 cells via MAPK pathway. Recent studies the same group revealed that Rg1 exerts potent estrogenic effects in endometrial cells in vitro as well as in heart and brain tissues in vivo. However, it does not exert any estrogenic effects on reproductive tissues in vivo nor did it stimulate bone tissues in vivo or in vitro. At cellular levels, Rg1 induces rapid translocation of ER α from the cytoplasm to the nucleus and increases total ER α phosphorylation at Ser 118 in MCF-7 cells in a similar manner to that of 17 β -estradiol. However, differences in sub cellular level distribution of phosphorylated ER α in MCF-7 cells in response to Rg1 and 17 β -estradiol. With these results they have concluded that Rg1 rapidly induces ER α phosphorylation at Ser 118 principally in the cytoplasm while 17 β -estradiol induces the same in cytoplasm and in nucleus.

Further, Dr. Janardhan Prasad Bhattarai and his group in their study using patch clamp technique in Gonadotropin releasing hormone neurons (GnRH), revealed the mechanism of action of Korean red ginseng. In this when they have applied KRGE (3 μ g/ μ L) under whole cell patch resulted in reproducible, concentration dependant, remarkable inward currents and depolarization in GnRH neurons. These inward currents and depolarization are not opposed by the presence of voltage gated Na⁺-channel blocker Tetrodotoxin (TTX). In gramicidin perforated patch, application of KRGE induced depolarization and inward currents are partially blocked by 6-cyano-7-nitroquinoxaline-2,3-dione, (CNQX) (non-NMDA glutamate receptor antagonist, 10 μ M) or picrotoxin (GABA_A receptor antagonist, 50 μ M) and almost blocked by picrotoxin and CNQX mixture, suggesting the possible GABA_A and non-NMDA glutamate receptors mediated activation in GnRH neurons.

Poster sessions

Several posters sessions were organized in the areas of cancer, diabetic complications, and neurodegeneration –

Mechanism of anti-cancer effects: Ginsenoside Rh2 (G-Rh2) induces the activation of two imitator caspases (caspase 8 and 9) in human cancer cells. Dr. Yang Li and his group from Key laboratory for molecular enzymology and engineering of the ministry of education, college of life sciences, Jilin University, China elucidated the mechanism of action of G-Rh2 stimulated activation of caspase 8 and 9 using HeLa cells. G-Rh2 treatment up regulated the membrane death receptors Fas and TNFR1. However, the induced expression of Fas has been contributed to apoptosis process. P53-mediated Fas expression and subsequent caspase-8 activation as well as p53 independent caspase9 activation contribute to the activation of downstream effector caspas-3/7 leading to tumor cell death.

Dr. Nak Yoon Sung and their group from department of genetic engineering, Sungkyunkwan University, Suwon, Korea discussed the anti-proliferative and proapoptotic activities of ginsenoside Rp1 (G-Rp1). G-Rp1 dose dependently suppressed the proliferation of colorectal cancer LoVo cells and increased their apoptosis. It has markedly upregulated the protein levels of apolipoprotein (Apo)A1 in LoVo, SNU-407, DLD-1, SNU-638, AGS, KPL-4 and SK-BR-3 cells. Knock down of Apo-A1 increased the levels of cleaved poly (ADP-Ribose) polymerase and p53 and reduced the proliferation of LoVo cells. Thus he concluded that G-Rp1 may act as anticancer agent by strongly inhibiting cell proliferation and enhancing the apoptosis through Apo-A1. The same group in their other poster discussed the anticancer effect of red ginseng using xenograft cancer model. They elaborated that induction of apoptosis (caspase 8 and 3) is the mode of action for

observed anti cancer effects of red ginseng in urine RMA lymphoma cells injected c57BL/6 xenograft cancer model. Dr. Wonchung Lim and their team from Bioscience and Biotechnology, Sejong University, Korea explained about COX-2/PGE2 pathway in hypoxic cancer cells and its importance in inflammation and tumorigenesis. In human distal lung epithelial A549 cells hypoxia lead to induction of COX-2 protein and is suppressed by KRG. This suppression was shown to be mediated through Sirt1. This effect of KRG was not antagonized by glucocorticoid receptor antagonist but by PPAR gamma agonist, estrogen receptor antagonist. Dr. Jaemoo chun and his group from College of Pharmacy, Natural products research institute, Seoul National University, Korea has discussed the novel roles of Ginsenoside Rg3 (Rg3) in cancer cells lines. In human lung adenocarcinoma cells Rg3 treatment led to the cancer cell death not only through apoptosis but also by down regulation of epidermal growth factor receptor (EGFR). Rg3 treatment inhibited the EGFR dimerization by EGF stimulation and caused EGFR internalization from the cell membrane. Rg3 increased the phosphorylation of tyrosine 1045 (pY1045) and serine 1046/1047 (pS1046/1047) for EGFR degradation and attenuated pY1173 and pY1068 for MAPK activity. 40% decrease in tumor volume was observed with Rg3 30mg/kg treatment compared to control.

Mechanism of anti-diabetic effects: Dr Dong-Hyuk Jung along with their group from Department of Family Medicine, Yonsei University College of Medicine, Korea performed the randomized, placebo controlled double blind study on 80 subjects with metabolic syndrome to reveal the effect of red ginseng. Significant improvement in mitochondrial function, increase in total testosterone and IGF- 1 levels were observed with the red ginseng treatment. Dr. Shree Priya Ponnuraj and her team from Department of Oriental Medicinal Material and Processing, Korea discussed the diabetic associated colon cancer and the effect of ginsenoside Rk1+Rg5 complex in HT-29 cells. Rk1+Rg5 complex treatment was found to induce the CHOP mediated apoptotic pathway. At 100 μ M concentration of this Rk1+Rg5 complex treatment, the expression levels of CHOP, a proapoptotic gene was increased in colorectal cancer cells. There is also increased expression of Bax and caspase 12 genes were observed. Dr. Hana Yang and their group from Department of Microbiology, School of Medicine, Kyung Hee University, Seoul, Korea has elaborated the antidiabetic effects of Korean Red ginseng by genome wide analysis. Using microarray gene expression data of in diabetic rat retina discovered the target genes responsible for the effects of KRG. Dr. Paulrayer from College of Veterinary Medicine, Biosafety Research Institute, Chonbuk National University, Jeonju Citym Korea described the relationship between the anti-diabetic effects of KRG

and heart gene expression profiles in db/db mice. KRG treatment reduced the levels of apoptosis related genes such as Cideb, Bdnf, Myc, Cd74, Inhbb, Lcn2, Cyfip2, Aen, Prune2, Sppl, Gadd45b, and Sphk1 genes. However, KRG treatment increased Gas1, Angptl4, Fn1, Tpx2, Egfr, Snai2, Sfrp2, Lpar1 genes which are associated with the abnormal physiology via diabetes.

Mechanism of neuroprotection: Dr. Yu Young Lee from Molecular Medicine, Ehwa Womans University Medical School, Korea reported the antiinflammatory effects of ginseng saponins metabolite Rh3 in LPS induced microglia by modulating the AMPK signaling pathway. They also reported that ginsenoside Rh3 inhibits the expressions of iNOS, TNF α , IL-6 at mRNA and protein level, enhanced hemeoxygenase-1 (HO-1) expression. There is also increased inhibition of transcription factor for NF-kB and enhanced activity of NRF2 DNA binding. Further, Rh3 treatment is also shown to be associated with the enhancement of LPS induced phosphorylation of AMPK which was further confirmed by AMPK siRNA studies. Dr Aravinthan Adithan and his group from college of veterinary medicine, bio safety research institute, Chonbuk National University, Jeonju city, Korea discussed the neuroprotective effects of ginsenosides in 3-nitropropionic acid induced striatal degeneration. Pretreatment with ginsenosides, before the 3-NP treatment reduced striatal lesion volume and significantly increased the survival rate even in aged rats also.

Dr. Jing-Gang Hou and their group from Food Science and Technology, Chungnam National University, Korea, in their poster discussed the effect of selective ginsenosides on trimethyltin (TMT) induced hippocampal neurotoxicity. They concluded that two week treatment with individual ginsenosides (Rd, Rg3 and Rh2, 10mg/kg, o.p) before 3 consecutive doses of TMT (2mg/kg) showed better score than that of negative control mice in tremor/seizure severity tests. All the ginsenosides ameliorated the hippocampal damage, reduced the GFAP positive cells than the negative control groups. Further, they also elaborated the TMT induced dementia and role of red ginseng extract in mice. AchE activity and MDA levels were found to increase in the brains of mice treated with TMT alone. However RG extract pretreatment for two weeks (100 and 300 mg/kg, i.p) inhibited the oxidative stress and increased the antioxidant enzyme levels (GPx, TAOC). Dr. Da Hye Jeong and their team from Laboratory of Veterinary Physiology and Cell Signaling, Kyungpook National University, Korea described the ant-inflammatory effect of low temperature black ginseng extract (LT-BGE) and black ginseng extract (BGE) in LPS stimulated BV2 microglia. There was significant suppression of LPS induced nitrite production in BV2 microglia was observed with two black ginseng treatments.

LPS induced expression of iNOS, COX2 and cytokines (IL-6, IL-1 β and TNF- α) was highly suppressed by BGE than LT-BGE. But equivocal suppression of PGE2 was observed with both the treatments. Phosphorylated MAPK was increased by LPS treatment which was significantly suppressed by both the treatments there by decreased the NF-kB activation.

Dr. Vu Thuy Hong and his team from Department of Food Science and Technology, Chungnam National University, Korea, discussed the neuroprotective effects of black ginseng against aluminum induced neurotoxicity. Aluminum content in the brains of black ginseng treatment groups were significantly reduced compared with aluminum alone treated groups. The formation of neuro fibrillary tangles was corresponded to the regions of Al-rich cytoplasm. Dr Yea-Hyun Leem from Department of Molecular Medicine, Ehwa Womans University described how the cerebroventricular infusion of ginsenoside Rc and Rg altered the G protein α -subunit mRNA in rat brain. 7 days continuous infusion of ginsenoside Rc and Rg1 (10 μ g/10 μ L/hr, i.c.v) does not altered the G α s mRNA levels, but the levels of G α i mRNA was significantly elevated in frontal cortex and hippocampus. However, the levels of G α i mRNA was significantly decreased in parts of hippocampus and cerebellum after ginsenoside Rg1 treatment revealing that ginsenosides are associated with the region specific effect on G protein α subunit mRNA. Further, the same team in the same above model has reported the alterations of mRNA levels of the family of NMDA receptor subtypes (NR1, NR2A, 2B, 2C) in rat brain. They reported that NR1 mRNA is significantly increased in temporal cortex, caudate putamen, hippocampus, and granule layer of cerebellum with Rg1 infusion. The levels of NR2 mRNA were elevated in frontal cortex, decreased in CA1 region of hippocampus in Rg1 treated rats. No significant changes were observed with Rc infusion either in NR1 and NR2 mRNA levels. The levels of NR2B mRNA are elevated in cortex, caudate putamen and thalamus in both Rc and Rg infused rats. Whereas NR2B level is decreased in CA3 in Rg1 infused rats. The level of NR2C mRNA is increased in the granule layer of cerebellum in only Rg1 but not Rc infused rats.

Miscellaneous events- Besides, poster presentations, workshop, young investigator colloquia, young investigator lectures and on diverse areas of immune/cancer related disorders was also organized during the conference.

Concluding Remarks- The present report discusses various updates in immune modulation, cancer therapy, neuroprotection, infertility and diabetic associated disorders.