Journal of Innovative Optical Health Sciences
Vol. 3, No. 1 (2010) 1–16

World Scientific
www.worldscientific.com

APPLICATIONS OF INTRANASAL LOW INTENSITY LASER THERAPY IN SPORTS MEDICINE

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Function-specific homeostasis (FSH) has been defined as a negative-feedback response of a biosystem to maintain its interior function-specific conditions so that the function is perfectly performed. There is no photobiomodulation of intranasal low intensity laser therapy (ILILT) on a function in its FSH, but ILILT could modulate a function far from its FSH. This rehabilitation has been found to be mediated by the ratio of intracellular nicotinamide adenine dinucleotide (NAD^+) and its reduced form NADH, NAD^+/NADH, and then sirtuin 1 (SIRT1). There might be FSH-specific NAD^+/NADH (FSN) and SIRT1 activity (FSA). ILILT might enhance NAD^+/NADH and SIRT1 activity until they arrive at FSN and FSA, respectively. The NAD^+/NADH and SIRT1 activity of related cells of many athletic diseases such as upper respiratory tract infection, asthma, osteoarthritis, exercise-induced muscle damage, wound, traumatic brain injury, and osteoporosis are lower than FSN and FSA, respectively. Therefore, there may be therapeutic effects of ILILT on those athletic diseases. Furthermore, many phenomena and the ILILT mechanism have been integrated to support the prophylaxis effects of ILILT on the swine-origin influenza A (H1N1).

Keywords: Photobiomodulation; homeostasis; nicotinamide adenine dinucleotide; sirtuin 1; sports medicine.

1. Introduction

Photobiomodulation (PBM) is a modulation of laser irradiation or monochromatic light (LI) on biosystems. The LI used in PBM is always low intensity LI (LIL), $\sim$10 mW/cm^2. However, moderate intensity LI (MIL), $10^{2\sim3}$ mW/cm^2, also has PBM if the radiation time is not so long to cause organelles or cells damages. The PBM of LIL and MIL are denoted as LPBM and MPBM, respectively. From 1989 on, many Russian groups have studied the therapeutic effects of intranasal LIL treatment on the local inflammation in vasomotor rhinitis[1,2] and acute and chronic maxillary sinusitis.[3] In Mainland China, intranasal LIL has been used to treat internal diseases from 1998 on and the special treatment was called intranasal low intensity laser therapy (ILILT).[4] The treatment of ILILT is local, but its therapeutic effects are global. There are four possible pathways mediating ILILT, olfactory nerve, blood cells, autonomic nervous system, and meridians in traditional Chinese medicine.[4] In this paper, its possible applications in sports medicine will be discussed.

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2. Cellular Rehabilitation

Function-specific homeostasis (FSH) has been defined as a negative-feedback response of a biosystem to maintain the function-specific conditions inside the biosystem so that the function is perfectly performed.[4] A biosystem in a FSH means the function is in its FSH so that it is perfectly performed. A biosystem far from a FSH means the function is far from its FSH so that it is dysfunctional. The LI is defined as low level LI (LLL) if there is no PBM on a function in its FSH, but there is PBM on a function far from its FSH.[4] The PBM and therapy of LLL are denoted as LLLP and LLLT, respectively. Obviously, LPBM and ILILT are a kind of LLLP or LLLT. MPBM is mediated by reactive oxygen species (ROS).[4] MPBM is also a kind of LLLP if the produced ROS level is so low that it has no effects on a function in its FSH. Intravascular low energy laser therapy (ILELT) is a kind of intravascular MPBM and also a kind of LLLT.[4]

The rehabilitation of LLLP includes anti-inflammation, anti-apoptosis, anti-oxidation, upregulating the expression of endothelial nitric-oxide synthase (eNOS) and heat shock factor 1, and so on. It has been found that after ILILT treatment serum amyloid β protein, malformation rate of erythrocytes, plasma cholecystokinin-octapeptide, the level of viscosity at lower shear rates, hematocrit, and serum lipid decreased, respectively, but melatonin (MLT) production, red cell deformability, superoxidase dismutase (SOD) activity, and β endorphin increased, respectively, circulation was improved, and immunity was regulated.[4] Su *et al.* have studied the therapeutic effects of ILILT treatment on vascular diseases.[5] Ninety old patients of average age 76.1 years with coronary heart disease or cerebral infarction were randomly divided into two groups, 60 in the treatment group and 30 in the control group. The treatment group and the control group were intranasally treated with low intensity GaInP/AlGaInP diode laser irradiation at 650 nm at 3 and 0 mW for 30 min each time once a day and ten days each session for two sessions, respectively. After the treatment, blood viscosity at high shear, plasma viscosity, red blood cell aggregation, and total cholesterol decreased, respectively, while high-density lipoprotein cholesterol increased in the treatment group, but no significant differences occurred in the control group; low-density lipoprotein cholesterol, redox viscosity at low shear and high shear decreased in the treatment group but increased in the control group, respectively; blood viscosity at low shear increased in the control group, but no significant differences occurred in the treatment group.

Maintenance of health depends on the ability to respond appropriately to environmental stressors via reciprocal interactions between the body and the brain. In this context, it is well recognized that the pineal hormone MLT plays an important role. ILILT may enhance MLT level.[4] Xu *et al.* have treated 38 patients with insomnia with low intensity He–Ne laser (LHNL) at 3.5–4.5 mW for 30 min each time, which was done once a day and ten days each session for two sessions, and found serum MLT increased.[6] Xu *et al.* have divided the objects into two groups, 47 patients with Alzheimer's disease (AD) and 22 patients with gastric ulcer, and treated the patients with LHNL at 3.5–4.5 mW for 30 min each time, which was done once every morning for 30 days. They found that MLT, score in minimental state exam and score in Wechsler memory scale for adult increased in AD group, but there was no LPBM on gastric ulcer group.[7] In terms of self-rating depression scale (SDS), Xu *et al.* divided 177 patients with stroke into two groups, 45 in pure stroke group (SDS $<$ 40) and 132 in post-stroke depression (PSD) group (SDS $>$ 40), and then treated the two groups with LHNL at 3.5–4.5 mW for 30 min each time, which were done once a day in the afternoon for 30 days, and found serum MLT increased and SDS decreased only in PSD group, but there is no such changes in pure stroke.[8] Xu *et al.* have treated 47 patients with Parkinson's disease (PD) with LHNL at 3.5–4.5 mW for 30 min each time, which was done once every morning for 20 days, and found the PD symptom improvement of 14 (29.8%), 27 (57.4%), and 6 (12.8%) patients were significant, mild and none, respectively, and SOD and MLT increased and malondialdehyde (MDA) decreased.[9] MLT preserves the expression of a longevity protein, sirtuin 1(SIRT1), in the hippocampus of total sleep-deprived rats[10] and MLT can enhance nicotinamide adenine dinucleotide (NAD^+) level[11] and SIRT1 activity.[12] SIRT1 is a NAD^+-dependent deacetylase.[13] Recently, It is widely reported that SIRT1 has been found to have beneficial effects in metabolic diseases, mediate high-density lipoprotein synthesis, and regulate endothelial nitric-oxide to protect against cardiovascular disease, and have a cardioprotective role

in heart failure, protect against neurodegenerative pathological changes, promote osteoblast differentiation, and also play a pivotal role as an anti-inflammatory mediator in chronic obstructive pulmonary disease.[14] As intracellular NAD^+ levels directly influence the histone deacetylase activity of SIRT1,[15] the higher the ratio of NAD^+ and its reduced form NADH, NAD^+/NADH, the higher the intracellular SIRT1 activity.[13] There are diverse physiological roles of SIRT1[13] so that there are diverse therapeutic effects of ILILT.[4]

ILILT may enhance NAD^+ level and SIRT1 activity by increasing MLT level. ILILT might also directly enhance NAD^+/NADH and SIRT1 activity. Karu has studied the cellular response of LIL from the viewpoint of cellular redox potential, and suggested that the cellular response is absent when the redox potential is optimal, and stronger when the redox potential of the target cell is initially shifted to a more reduced state.[16] The cellular redox potential might be represented by NAD^+/NADH.[16] A normally functioning cell in its FSH has its specific redox potential, NAD^+/NADH, and SIRT1 activity, respectively, which are referred as the FSH-specific redox potential (FSR), the FSH-specific NAD^+/NADH (FSN), and the FSH-specific SIRT1 activity (FSA), respectively.[17] A dysfunctional cell far from its FSH is initially shifted to a more reduced state with lowered NAD^+/NADH and SIRT1 activity. In terms of Karu's suggestion,[16] the magnitude of LPBM is determined by redox potential,[16] NAD^+/NADH[16] or SIRT1 activity[17] of the cell at the moment. LPBM may enhance the redox potential,[16] NAD^+/NADH,[16] and SIRT1 activity,[17] respectively, in cells far from their FSH (Fig. 1). The lower the redox potential below the FSR is, the lower the NAD^+/NADH below FSN will be, and the lower the SIRT1 activity below the FSA will then be, and the stronger the LPBM will finally be in terms of Karu's suggestion.[16] ROS can also enhance the redox potential, NAD^+/NADH, and SIRT1 activity so that LLLP of MIL shares the same SIRT1-mediated mechanism (Fig. 1). There is connexin 43 (Cx43), a NAD^+ transporter, in the cellular membrane so that there is bidirectional NAD^+ transport across cellular membrane.[18] ILILT and ILELT may enhance NAD^+ level in the irradiated blood cells, and then in the blood through Cx43, and then in the un-irradiated cells through Cx43, which increase SIRT1 activity in both the irradiated cells and the un-irradiated cells.

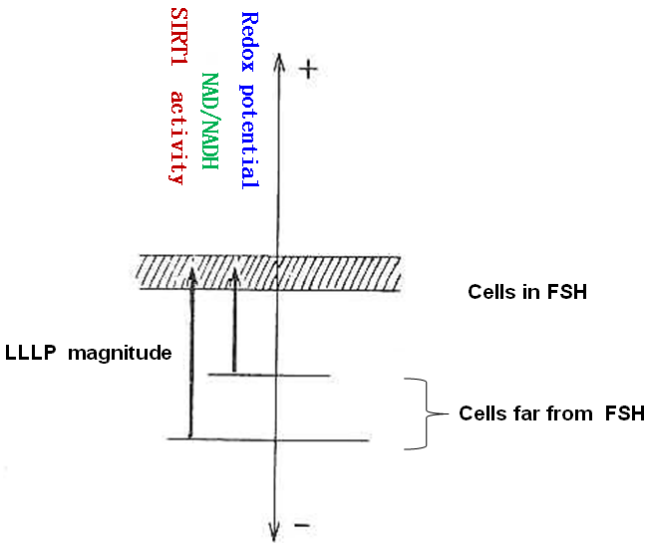

Fig. 1. Cellular rehabilitation mechanism of low level light photobiomodulation (LLLP). Photobiomodulation can enhance redox potential, the ratio of nicotinamide adenine dinucleotide (NAD^+) and its reduced form NADH (NAD^+/NADH), and sirtuin 1(SIRT1) of cells far from function-specific homeostasis (FSH). Modified from Ref. 17.

The deacetylation activity of SIRT1 can be stimulated by several polyphenolic compounds.[19] Polyphenols are a wide group of dietary compounds from plants, occurring in high amounts in fruits, vegetables, cereals, wine, and tea. Epidemiological studies suggest that a diet rich in polyphenols may protect against cardiovascular diseases, and mechanistic studies in cells and animals have shown that polyphenols have a wide range of properties that also may play a role in the prevention of other diseases, such as cancer and neurodysfunctions.[20] In the following sections, the possible applications of ILILT in sports medicine are discussed in the view of the therapeutic effects of polyphenols, MLT, LLL, and ILELT because they share the same SIRT1-mediated mechanism.

3. Upper Respiratory Tract Infection

Upper respiratory tract infection (URTI) is regarded as the most common medical condition affecting both highly trained and elite athletes, in particular those participating in endurance events.[21] The applications of ILILT in the prophylaxis and treatment of URTI will be discussed in this section.

Quercetin may increase mRNA expression of SIRT1 and then increases brain and muscle mitochondrial biogenesis and exercise tolerance.[22] Nieman *et al.* found URTI rates of athletes did not differ during the initial 21-d period between quercetin (14 mg/kg) and control groups, but they were significantly different during the 14-d period after the 3 d of intensified exercise.[23] Davis *et al.* have studied the effects of quercetin (12.5 mg/kg) feedings in mice on susceptibility to the influenza virus A/Puerto Rico/8/34 (H1N1) following stressful exercise, and found that short-term quercetin feedings may prove to be an effective strategy to lessen the impact of stressful exercise on susceptibility to respiratory infection.[24]

The causes of URTI remain unclear. Viruses such as rhinovirus, adenovirus, and para-influenza virus are frequently reported as the source of URTI. However, in a few comprehensive laboratory and epidemiological studies which reported at least a 30% incidence of URTI, no identifiable pathogens were either reported or studied. A recent, longitudinal study investigated symptomatology and pathogenic etiology in sedentary controls, recreational and elite athletes. The highest incidence of URTI occurred in elite athletes. However, only 11 out of 37 illness episodes overall had pathogenic origins, and most of the unidentified upper respiratory illnesses were shorter in duration and less severe than infectious ones. Therefore, there might be inflammation without infection in athletes' URTI.[21] Fortunately, ILILT has been used to treat local inflammation. Tulebaev *et al.* have found the ILILT treated patients with vasomotor rhinitis showed a significant increase of T-lymphocytes and a higher capacity of T-cells to form the migration inhibition factor.[1] Kruchinina *et al.* have studied therapeutic effect of ILILT on microcirculation of nasal mucosa in children with acute and chronic maxillary sinusitis, and found that laser therapy produced a positive effect on microcirculation and reduced the potential of relapses.[3] Shevrygin *et al.* have shown that ILILT is effective in correction of microcirculatory disorders and tissue mechanisms of homeostasis in children with neurovegetative vasomotor rhinitis.[2]

As discussed above, oral quercetin may increase SIRT1 activity and alleviate URTI. SIRT1 can also resist inflammation[13] since SIRT1 negatively regulates nuclear factor-κB (NF-κB) activation to decrease pro-inflammatory cytokine release.[25] ILILT may also enhance NAD^+/NADH in the blood and then intracellular SIRT1 activity in the related cells through Cx43 so that it may alleviate URTI. Chen *et al.* randomly divided 48 child patients with chronic cough associated with post-nasal drip syndrome into two groups, 24 in drugs-only group and 24 in ILILT + drugs group, and then treated ILILT + drugs group with LHNL at 20 mW for 30 min each time, which was done once a day for 10 days, and found 19 patients were improved in ILILT + drugs group, but only 13 patients were improved in drugs-only group, and the difference was very significant.[26]

4. Asthma

A high prevalence of asthma and airway hyperresponsiveness (AHR) has been reported in the athlete population. Factors potentially predisposing athletes to these conditions have not been clearly identified. Although moderate exercise has been shown to be beneficial in patients with asthma, repeated high-intensity exercise could possibly contribute to the development of asthma and AHR. The prevalence of asthma and AHR are higher in athletes than in the general population, particularly in swimmers and athletes performing sports in cold air environments.[27] The patients may receive long-term treatment with different formulas and doses of glucocorticoids (GC) which is of considerable diagnostic and therapeutic importance, but inhaled GC can cause iatrogenic adrenal cortex failure.[28] The applications of ILILT in the prophylaxis and treatment of asthma and AHR will be discussed in this section.

Resveratrol(3,4,5-trihydroxystilbene), a SIRT1-activating molecule, is a polyphenolic stilbene found in the skins of red fruits, including grapes, that may be responsible for some of the health benefits ascribed to consumption of red wine. Lee *et al.* have investigated the suppressive effects of resveratrol (intraperitoneal injection) on asthmatic parameters such as cytokine release, eosinophilia, AHR, and mucus hypersecretion, in an ovalbumin-induced allergic mouse model of asthma. They found resveratrol significantly inhibited increases in T-helper type 2 (Th2) cytokines such as interleukin (IL)-4 and IL-5 in plasma and bronchoalveolar lavage fluid, and also effectively suppressed AHR, eosinophilia, and mucus hypersecretion, in the asthmatic mouse model. These results suggest that resveratrol may have applications in the treatment of bronchial asthma (BA).[29]

Quercetin has demonstrated significant anti-inflammatory activity because of direct inhibition of several initial processes of inflammation. All patients with asthma have a specific pattern of inflammation in the airways that is characterized by degranulated mast cells, an infiltration of eosinophils, and an increased number of activated Th2 cells.[30] And recently, it was shown that T-bet and GATA-3 were master T-helper type 1 (Th1) and Th2 regulatory transcription factors. Park *et al.* have studied its anti-allergic effect in the Th1/Th2 immune response.[31] Quercetin reduced the increased levels of IL-4, Th2 cytokine production in ovalbumin-sensitized and -challenged mice. On the other side, it increased type I interferon gamma, Th1 cytokine production in quercetin administrated mice. They also examined to ascertain whether quercetin could influence eosinophil peroxidase activity. The administration of quercetin before the last airway ovalbumin challenge resulted in a significant inhibition of all asthmatic reactions. Accordingly, this study may provide evidence that quercetin plays a critical role in the amelioration of the pathogenetic process of asthma in mice.

Ostronosova has studied efficacy of LIL by changes in a histamine level in peripheral blood and external respiration function (ERF).[32] A total of 228 patients with exogenic bronchial asthma (EBA) were divided into two groups: 167 patients with nonhormone-dependent asthma (group 1) and 61 patients with hormone-dependent BA (group 2). LIL lowered a histamine level and improved ERF in both groups 1 and 2. A definite negative correlation was found between histamine content and ERF parameters. LIL alone is effective in mild EBA.

There may be therapeutic effects of ILELT on Asthma. Farkhutdinov has investigated action of ILELT on production of ROS in patients with BA.[33] The trial included 59 BA patients aged from 20 to 60 years (mean age 40.2 years). ROS generation in whole blood was registered with luminol-dependent chemiluminescence (CL). Basic therapy was given to 42 patients. ILELT was added to basic therapy in 17 patients. They found that CL of whole blood in BA patients depended on severity of inflammation. BA patients with intensive CL exposed to ILELT retained free radical oxidation defects and the disease symptoms. In low intensity of blood CL, ILELT activated ROS generation and raised treatment effectiveness.[33] Liu *et al.* have studied the effect and mechanism of ILELT of He–Ne laser irradiation at 1.5 mW for 40 min once a day for five days on the patients with BA.[34] After its integrated use with drugs, the symptoms of 13 patients were controlled or eased, the parameters of lung function were improved to some extent, the content of middle molecular substances (MMS) in plasma reduced and IgG and IgA in plasma increased significantly in comparison with drugs-used only. All these data suggested that the ILELT might be an effective method for the treatment of asthma, its mechanism might involve reduction of MMS and free radicals in plasma, enhancement of immunological function, and improvement of microcirculation.[34]

As discussed above, either resveratrol, quercetin, LIL, or ILELT may increase SIRT1 activity and alleviate asthma and AHR. ILILT may also enhance NAD^+/NADH in the blood and then intracellular SIRT1 activity in the related cells through Cx43 so that it may also alleviate asthma and AHR.

5. Osteoarthritis

Former elite athletes from most sports disciplines have lower overall morbidity risk and enjoy better self-rated health in later years compared with the general population and matched controls who were healthy at young age.[35] However, aside from a high risk of acute injury in specific sports, possible negative effects of long-standing athletic activity on the development of osteoarthritis (OA) should not be neglected.[35] The nonsteroidal anti-inflammatory drugs (NSAIDs) have been always used in the treatment of OA. The comparative overall costs of NSAIDs bears little relation to drug acquisition cost, and that the iatrogenic cost factor is one of the most important determinants of overall costs.[36] The possible applications of ILILT in treatment of OA will be discussed in this section.

Niacinamide is one of NAD^+ precursors which can increase NAD^+/NADH and then SIRT1 activity.[13] Jonas *et al.* have evaluated the effect of niacinamide, on selected parameters of OA using a double-blind, placebo-controlled study design.[37] Seventy-two patients with OA were randomized for treatment with niacinamide or an identical placebo for 12 weeks. They found global arthritis impact improved by 29% in subjects on niacinamide and worsened by 10% in placebo subjects. Pain levels did not change but those on niacinamide reduced their anti-inflammatory medications by 13%. Niacinamide reduced erythrocyte sedimentation rate by 22% and increased joint mobility by 4.5 degrees

over controls (8 degrees vs 3.5 degrees). Their study indicated that niacinamide may improve OA.

Silymarin, derived from the milk thistle plant, Silybum marianum, has been traditionally used in the treatment of liver disease. Li *et al.* found silymarin protected A375-S2 cell against ultraviolet-induced apoptosis was partially through SIRT1 pathway and modulation of the cell cycle distribution.[38] Hussain *et al.* have performed a double-blind clinical trial in which 220 patients (79 males and 141 females) with painful knee OA were randomized into five groups, treated with either silymarin (300 mg/day), piroxicam (20 mg/day), meloxicam (15 mg/day), or a combination of silymarin with piroxicam or meloxicam. They found silymarin reduces significantly serum levels of IL-1 alpha and IL-8, C3 and C4 after 8 weeks compared to the pre-treatment levels. Piroxicam showed no significant reduction in IL-1 alpha levels, while IL-8 decreased significantly, compared to pre-treatment value. Meloxicam elevates serum levels of IL-1 alpha significantly, while IL-8 did not significantly change compared to the pre-treatment value. Piroxicam or meloxicam produced slight, nonsignificant increase in serum levels of complement proteins after the 8-week treatment period. Adjunct use of silymarin with piroxicam results in significant reduction in both cytokines (IL-1 alpha and IL-8), and serum levels of C3 and C4. However, its adjunct use with, meloxicam did not reveal any significant changes in this respect. Their studies indicated silymarin reduces the elevated levels of interleukins and complement proteins, when used alone, or in combination with NSAIDs for the treatment of knee OA.[39]

Hegedus *et al.* have studied the pain-relieving effect of LLLP and possible microcirculatory changes in patients with knee OA.[40] Patients with mild or moderate knee OA were randomized to receive either LLLP or placebo LLLP. Treatments were delivered twice a week over a period of 4 weeks with a diode laser (wavelength 830 nm, continuous wave, power 50 mW) in skin contact at a dose of 6 J/point. The placebo control group was treated with an ineffective probe (power 0.5 mW) of the same appearance. In the group treated with active LLLP, a significant improvement was found in pain, circumference, pressure sensitivity, and flexion. In the placebo group, changes in joint flexion and pain were not significant. In the group treated with active LLLP, thermographic measurements showed at least a 0.5°C increase in temperature, and thus an improvement in circulation compared to the initial values. In the placebo group, these changes did not occur. Their results showed that LLLP reduces pain in knee OA and improves microcirculation in the irradiated area.

Xiao *et al.* have studied the effect of ILELT for the elderly patients with OA. Sixty patients were randomly divided into two groups: laser group (30 patients) and control group (30 patients). For consecutive 30 days, laser group was treated with ILELT of GaInP/AlGaInP diode laser irradiation at 650 nm and 2.0–3.2 mW for 60 min once a day and half dose of NSAIDs twice a day, and control group was treated with full dose of NSAIDs twice a day. They found that there was no statistical difference between laser group and control group in regarding to curative effect as indicated by the clinical manifestations such as joint stiffness and tenderness. The serum transforming growth factor $\beta 1$ (TGF$\beta 1$) and SOD levels in laser group were significantly increased as compared to those of control group. Serum MDA in laser group was decreased compared to control group. This study indicated that ILELT can improve the symptoms of the elderly patients with OA and reduce the use of NSAIDs.[41]

As discussed above, either niacinamide, silymarin, LLL, or ILELT may increase SIRT1 activity and improve OA. ILILT may also enhance NAD^+/NADH in the blood and then intracellular SIRT1 activity in the related cells through Cx43 so that it may improve OA.

6. Exercise-Induced Muscle Damage

Exercise-induced muscle damage (EIMD) is referred to the micro-damage of skeletal muscle induced by an unaccustomed, especially high-intensity and eccentric exercise. Human EIMD is also named as delayed onset muscle soreness (DOMS)[42] because the athletes with EIMD experienced DOMS after exercise. The possible applications of ILILT in treatment of DOMS will be discussed in this section.

There might be three phases of DOMS recovery, Z-line streaming, proteolysis of damaged proteins and protein synthesis for myofibril remodeling, and its key phase might be the phase 2 during which ubiquitin-proteasome pathway (UPP) should plays a key role.[43] Floyd *et al.* have studied modulation of peroxisome proliferator activated receptor gamma (PPARγ) stability and transcriptional activity in adipocytes by resveratrol.[44] They found the observed decreases in PPARγ protein levels

are associated with increased targeting of PPARγ for ubiquitin-dependent degradation as shown by the increase in PPARγ-ubiquitin conjugate formation in the presence of resveratrol. UPP function is diminished in locomotor skeletal muscle of ageing animals.[45] Li *et al.* have examined the effects of dietary restriction (DR) on the UPP in the aged rat heart.[46] They observed that DR significantly reduced age-related impairments in proteasome-mediated protein degradation, and reduced age-related increases in ubiquitinated, oxidized, and sumoylated protein in the heart. SIRT 1 level increased following caloric-restriction treatment.[13] SIRT1 might enhance proteasome-mediated protein degradation in skeletal muscle as in adipocytes or in heart so that SIRT1 might promote DOMS recovery from UPP viewpoint.

Hydrogen sulfide (H_2S) mediates the vasoactivity of garlic.[47] One cellular activity of H_2S is to increase the activity of SIR-2.1, the SIRT1 homologue.[48] Allicin (diallyl thiosulfinate), the main organosulfur compound, is produced from the amino acid alliin by action of the enzyme alliinase when garlic is crushed. Su *et al.* have investigate the effects of allicin supplementation on EIMD, IL-6, and anti-oxidative capacity through a double-blinded, placebo-controlled study in well-trained athletes.[49] Subjects were randomly assigned to an allicin supplementation group (AS group) and a control group, and received either allicin or placebo for 14 days before and 2 days after a downhill treadmill run. Plasma creatine kinase (CK), muscle-specific CK (CK-MM), lactate dehydrogenase (LDH), IL-6, SOD, total anti-oxidative capacity (TAC), and perceived muscle soreness were measured pre- and post-exercise. AS group had significantly lower plasma levels of CK, CK-MM, and IL-6, and reduced perceived muscle soreness after exercise, when compared with the control group. AS group also demonstrated a trend toward reducing plasma concentration of LDH after exercise, although not statistically significant. Allicin supplementation induced a higher value of TAC at rest, and this higher value was maintained 48 h after exercise; however, there was no difference in SOD values after exercise between the two groups. The results suggested that allicin might be a potential agent to reduce EIMD.

The intake of dietary polyphenols from curcumin (Cur) or grape seed extract could reduce genomic instability events in a transgenic mouse model for AD.[50] Davis *et al.* have examined the effects of Cur on inflammation and recovery of running performance following downhill running in mice. Male mice were assigned to downhill placebo (Down-Plac), downhill Cur (Down-Cur), uphill placebo (Up-Plac), or uphill Cur (Up-Cur) groups and run on a treadmill at 22 m/min at -14% or $+14\%$ grade, for 150 min. At 48 h or 72 h after the up/downhill run, mice (experiment 1) underwent a treadmill performance run to fatigue. Another subset of mice was placed in voluntary activity wheel cages following the up/downhill run (experiment 2) and their voluntary activity (distance, time, and peak speed) was recorded. Additional mice (experiment 3) were killed at 24 h and 48 h following the up/downhill run. Downhill running decreased both treadmill run time to fatigue (48 h and 72 h) and voluntary activity (24 h), and Cur feedings offset these effects on running performance. Downhill running was also associated with an increase in inflammatory cytokines (24 h and 48 h) and CK (24 h) that were blunted by Cur feedings. These results support the hypothesis that Cur can reduce inflammation and offset some of the performance deficits associated with eccentric EIMD.[51]

Liu and co-workers have studied LIL on rat muscle injury after eccentric exercise.[52] Seventy-two Sprague-Dawley rats were randomly divided into five groups: one sedentary control group, and four exercise groups: one exercise control group and three exercise + LIL groups. The exercise is a bout of downhill running (gradient at -16 degree, speed at 16 m/min) to exhaustion. The LIL irradiation was done immediately, 18 h and 42 h after exercise on the middle bellies of bilateral gastrocnemius muscles with LIL at 20, 46 and 71 mW/cm^2 for 10 min, respectively. At both 24 h and 48 h after exercise, LIL at 71 mW/cm^2 reduced muscular inflammation, inhibited serum CK activity, lowered muscular MDA level and enhanced muscular SOD activity and eNOS activity as compared to the exercise control group, but there were no significant differences in the serum CK activity and muscular MDA level as compared to the sedentary control group. LIL at 20 or 46 mW/cm^2 reduced muscular inflammation and inhibited serum CK activity at 48 h after exercise. These studies indicated that LIL may simultaneously inhibit inflammation and oxidation and enhance muscular SOD activity and eNOS activity. His further discussion indicated that the multicomponent roles of LIL might be mediated by SIRT1.

As discussed above, either resveratrol, allicin, Cur, or LIL may increase SIRT1 activity and promote DOMS recovery. ILILT may also enhance NAD^+/NADH in the blood and then intracellular SIRT1 activity in the related cells through Cx34 so that it may promote DOMS recovery.

7. Wound

Wound healing occurs in "phases."[53] The main phases of wound healing include coagulation, which begins immediately after injury; inflammation, which initiates shortly thereafter; a migratory and proliferative process, which begins within days and includes the major processes of healing; and a remodeling process, which may last for up to a year and is responsible for scar tissue formation and development of new skin. As research techniques in wound care management improve, treatment protocols for the care of wounds must also change to ensure safe and optimal healing. Goldenberg have surveyed current practices of athletic trainers regarding the care of athletic wounds and compared the findings to current literature. Wet-to-dry, irrigation, and soaks were the three most common methods used to debride and cleanse a wound. Povidone-iodine (Betadine) and hydrogen peroxide were the two most popular cleansing agents. Conventional gauze was the primary dressing used by 67% of the athletic trainers, while 20% of those surveyed used occlusive dressings. Although povidone-iodine and hydrogen peroxide are commonly used, both are toxic to cells involved in the wound-healing process and delay healing. Research indicates that the best method of cleansing and debriding a wound is to irrigate it with saline. Occlusive dressings have a lower infection rate, are viral barriers, and are associated with faster wound healing and less pain than gauze dressings.[54] The possible applications of ILILT in treatment of wound will be discussed in this section.

Proanthocyanidins or condensed tannins, a group of biologically active polyphenolic bioflavonoids that are synthesized by many plants, are known to facilitate wound healing. Grape seed proanthocyanidin extract (GSPE) facilitated vascular endothelial growth factor (VEGF) expression in keratinocytes. Pretreatment of HaCaT keratinocytes with GSPE up-regulated VEGF expression and release. The herbal extract influenced the transcriptional control of inducible VEGF expression. In a murine model of dermal excisional wound, a combination of grape seed extract and 5000 ppm resveratrol markedly accelerated wound contraction and healing.[53]

Soybir *et al.* have studied the effects of MLT hormone on angiogenesis in wound healing on 100 Wistar-Albino rats. The rats were divided into two groups. MLT dissolved in 0.9% NaCl was administered to the study group in a dose of 0.4 mg/kg/rat per day (0.25 cc/rat per day), and 0.9% NaCl to the control group in a dose of 0.25 cc/rat per day. Incisions 5 cm in length were made on the back skin of the rats and the wounds were closed with a skin stapler. They found the commencement of neovascularization and a significant increase in the number of vessels were observed at all stages of the study group but not in the control group. The tissue hydroxyproline levels were also higher in the study group than in the control group. This study indicated MLT may have a positive effect on both angiogenesis and wound healing.[55]

Hopkins *et al.* have used a randomized, triple-blind, placebo-controlled design with two within-subjects factors (wound and time) and one between-subjects factor (group). Two standardized 1.27 cm^2 abrasions were induced on the anterior forearm of 22 healthy subjects, respectively. After wound cleaning, each subject then received LLLT (8 J/cm^2; treatment time = 125 s; pulse rate = 700 Hz) to 1 of the 2 randomly chosen wounds from either a laser or a sham 46-diode cluster head. At days 6, 8, and 10, follow-up testing revealed that the laser group had smaller wounds than the sham group for both the treated and the untreated wounds. The LLLT resulted in enhanced healing as measured by wound contraction. The untreated wounds in subjects treated with LLLT contracted more than the wounds in the sham group, so LLLT may produce an indirect healing effect on surrounding tissues. These data indicate that LLLT is an effective modality to facilitate wound contraction of partial-thickness wounds.[56]

There may be therapeutic effects of ILELT on wound. Kravchenko-Berezhnaia *et al.* have provided evidence for that it is expedient to perform multistage ILELT in patients with severe mechanical trauma and massive blood loss in the early posttraumatic period. The use of He–Ne laser radiation at 1.5–2.0 mW for 30 min as part of complex therapy in this group of patients promotes the increase of plasma albumin transport ability and the general stimulation of natural detoxifixation mechanisms.[57] Luo *et al.* have studied the effect of ILELT on

skin flap survival after orthotopic transplantation in avulsion injury. Fifty-eight cases suffered avulsion injury were treated by debridement and orthotopic transplantation of avulsed flap within 6 h, 31 of them were received ILELT of He–Ne laser irradiation at 4.8 mW for 60 min once a day for 15 days and routine treatment, and 27 of them were received routine treatment only as control group. They found that the survival area and quality of avulsed flap in the experimental group were superior to that of control group after 15 days of operation, and the hemorheological items were markedly changed at 5 days after operation. This study indicated that the better flap survival after orthotopic transplantation in avulsion injury can be improved by ILELT through changed SOD activity and hemorheological items in optimal irradiation intensity.[58]

As discussed above, either GSPE, resveratrol, MLT, LIL, or ILELT may increase SIRT1 activity and promote wound healing. ILILT may also enhance MLT level and NAD^+/NADH in the blood and then intracellular SIRT1 activity in the related cells so that it may also promote wound healing.

8. Traumatic brain injury

Research in the area of sport-related concussion has provided the athletic training and medical professions with valuable new knowledge in recent years. Recurrent concussions to several high-profile athletes, some of whom were forced into retirement as a result, have increased awareness among sports medicine personnel and the general public. All football players — or other people subjected to repeated blows to the head — may be susceptible to chronic traumatic encephalopathy (CTE). The possible applications of ILILT in the prophylaxis and treatment of CTE will be discussed in this section.

Schültke *et al.*[59] have studied the neuroprotective effect of quercetin in an animal model of traumatic brain injury (TBI). Twenty-six adult male Sprague-Dawley rats were submitted to moderate fluid percussion injury (FPI) in the anterior midline position. Animals were divided into two experimental groups: one group received 25 mumol/kg quercetin starting 1 h after injury, while animals in the second group received saline vehicle (n = 13 per group). Eight animals were used as uninjured healthy controls. Eight animals in each experimental group were sacrificed at 24 h, while five animals per group were allowed to recover for 72 h following injury. Compound action potential amplitudes (CAPAs) were recorded on 400-microm vibrotome sections of the corpus callosum superfused with oxygenated artificial cerebrospinal fluid (CSF) (n = 3 per animal) in 20 experimental animals and five healthy controls. Three brains from animals in each experimental group and healthy controls were used for histological, immunocytochemical, and biochemical analysis after sacrifice at 24 h. CAPAs in uninjured animals had a mean of 1.12 mV. This decreased to 0.55 mV in saline vehicle-treated injured animals by 24 h and changed little over the next 3 days. CAPAs were significantly better at 0.82 mV at 24 h and 0.76 mV at 3 days in quercetin-treated injured animals when compared to injured saline vehicle controls. Quercetin significantly prevented decrease of glutathione levels and decreased myeloperoxidase activity. They concluded that this dietary flavonoid has therapeutic potential following brain trauma.[59]

Wang *et al.* used an in vitro ischemic model of oxygen-glucose deprivation followed by reperfusion (OGD-R) and an in vivo ischemic model of middle cerebral artery occlusion (MCAO) to investigate the neuroprotective effects of TSG (2,3,5,4′-tetrahydroxystilbene-2-O-beta-D-glucoside, an active component of the rhizome extract from Polygonum multiflorum) on ischemia/reperfusion brain injury and the related mechanisms. They demonstrated that OGD-R-induced neuronal injury, intracellular ROS generation, and mitochondrial membrane potential dissipation were reversed by TSG. The elevation of H_2O_2-induced $[Ca^{2+}]$i was also attenuated by TSG. Inhibition of the c-Jun N-terminal kinase (JNK) and Bcl-2 family-related apoptotic signaling pathway was involved in the neuroprotection afforded by TSG. Meanwhile, TSG inhibited inducible NO synthase(iNOS) mRNA expression induced by OGD-R. And to explore the mechanisms underlying the inhibitory effect of iNOS gene expression by TSG after OGD-R, NF-κB activity was analyzed by indirect immunofluorescence assay using confocal microscopy. They found exposure to OGD-R caused the majority of intracellular p65(the p65 subunit of NF-κB) translocation from the cytoplasm to the nucleus, and this translocation was greatly inhibited by pretreatment with 25 μM TSG. Then they measured whether the activation of SIRT1 was involved in the regulation of the NF-κB signaling pathway and the inhibition of iNOS gene expression after OGD-R by TSG. When cells were treated with the SIRT1 inhibitor nicotinamide, the inhibitory effect of TSG

on OGD-R-induced NF-κB activation could be partially attenuated, and the inhibitory effect of TSG on iNOS gene expression during OGD-R was partially relieved. They also found that the levels of SIRT1 were elevated after the normal cells were incubated for 3 days with TSG at the concentration of 25 or 50 μM. These results suggest that TSG inhibited iNOS gene expression induced by OGD-R, which may be partially mediated by the activation of SIRT1 and thereby inhibition of NF-κB activation. In vivo studies further demonstrated that TSG significantly reduced the brain infarct volume and the number of positive cells by transferase-mediated dUTP nick end labeling (TUNEL) staining in the cerebral cortex compared to the MCAO group. Their study indicates that TSG protects against cerebral ischemia/reperfusion injury through multifunctional cytoprotective pathways.[60]

TBI is followed by an energy crisis that compromises the capacity of the brain to cope with challenges, and often reduces cognitive ability. New research indicates that events that regulate energy homeostasis crucially impact synaptic function and this can compromise the capacity of the brain to respond to challenges during the acute and chronic phases of TBI. Sharma *et al.* have studied the influence of the phenolic yellow curry pigment Cur on molecular systems involved with the monitoring, balance, and transduction of cellular energy, in the hippocampus of animals exposed to mild FPI. Young adult rats were exposed to a regular diet (RD) without or with 500 ppm Cur for four weeks, before an FPI was performed. The rats were assigned to four groups: RD/Sham, Cur/Sham, RD/FPI, and Cur/FPI. They found that FPI decreased the levels of AMP-activated protein kinase (AMPK), ubiquitous mitochondrial creatine kinase (uMtCK) and cytochrome c oxidase II (COX-II) in RD/FPI rats as compared to the RD/sham rats. The Cur diet counteracted the effects of FPI and elevated the levels of AMPK, uMtCK, COX-II in Cur/FPI rats as compared to RD/sham rats. In addition, in the Cur/sham rats, AMPK and uMtCK increased compared to the RD/sham. Results show the potential of Cur to regulate molecules involved in energy homeostasis following TBI.[61]

The pineal hormone MLT has been shown to exert neuroprotective activity in a variety of experimental neuropathologies in which free radicals are involved. This neuroprotective effect has been attributed to the anti-oxidant properties of MLT. Considering that free radicals also play a deleterious role in TBI, Mésenge *et al.* have studied the beneficial effect of MLT in this pathology. Head injury was induced in mice. In this model, MLT (1.25 mg/kg, i.p.) given 5 min and repeated at 1, 2, and 3 h after head trauma significantly reduced the neurological deficit. This beneficial effect was not due to MLT-induced hypothermia since repeated treatment with MLT did not modify the colonic temperature of mice. This study shows that MLT exerts a beneficial effect on the neurological deficit induced by TBI in mice.[62]

Following TBI in mice, Oron *et al.* have assessed the hypothesis that LLLT might have a beneficial effect on their neurobehavioral and histological outcome. TBI was induced by a weight-drop device, and motor function was assessed 1 h post-trauma using a neurological severity score (NSS). Mice were then divided into three groups of eight mice each: one control group that received a sham LLLT procedure and was not irradiated; and two groups that received LLLT at two different doses (10 and 20 mW/cm^2) transcranially. An 808-nm Ga-As diode laser was employed transcranially 4 h post-trauma to illuminate the entire cortex of the brain. Motor function was assessed up to 4 weeks, and lesion volume was measured. There were no significant changes in NSS at 24 and 48 h between the laser-treated and nontreated mice. Yet, from 5 days and up to 28 days, the NSS of the laser-treated mice were significantly lower ($p < 0.05$) than the traumatized control mice that were not treated with the laser. The lesion volume of the laser-treated mice was significantly lower (1.4%) than the nontreated group (12.1%). Their data suggest that a noninvasive transcranial application of LLLT given 4 h following TBI provides a significant long-term functional neurological benefit.[63]

As discussed above, either quercetin, TSG, Cur, MLT, or LIL may increase SIRT1 activity and could be used for prophylaxis and treatment of CTE. ILILT may also enhance MLT level and NAD^+/NADH in the blood and then intracellular SIRT1 activity in the related cells so that it may also could be used for prophylaxis and treatment of CTE.

9. Osteoporosis

The number of women participating in organized sports has increased dramatically. The female athlete triad is a condition seen with increasing

frequency in young athletes and is characterized by the triad of amenorrhea, disordered eating, and osteoporosis.[64] The triad is caused by an imbalance between energy intake and energy expenditure and can be associated with significant medical morbidity. It occurs most frequently in sports emphasizing a lean appearance. Early recognition and intervention are essential. In an adolescent athlete, amenorrhea should be considered an indicator of a potential problem and should not simply be attributed to a consequence of training. The athlete should be evaluated for an underlying eating disorder and tested for osteoporosis. The possible applications of ILILT in the prophylaxis and treatment of osteoporosis will be discussed in this section.

Mori *et al.* have examined whether the supplementation of isoflavones (ISO) exerts beneficial effects on the bone mineral density (BMD). Eighty-one healthy Japanese pre- and post-menopausal women were randomly assigned to the following two groups taking either ISO (100 mg) tablets (ISO group) or placebo tablets (P group) containing vitamins C (25 mg) and E (5 mg) daily for 24 weeks in a double-blind placebo-controlled parallel design. Seventy women completed the intervention study (34 on ISO, 36 on P), only ISO group was proven to increase significantly BMD and to significantly decrease body fat measured, while body mass index (BMI) was maintained in ISO group despite significant BMI increase in P group. Thus, percent changes in BMI were significantly different between ISO and P groups 24 weeks after the intervention. This prospective study confirmed a long-term ISO supplementation, 100 mg/day could not only prevent menopausal bone resorption but also increase BMD and decrease body fat concomitantly with BMI reduction. Enough ISO supplementation may contribute to the risk reduction of osteoporosis and obesity and, thus to overall health promotion in menopausal women.[65]

Uslu *et al.* have analyzed histomorphometric, densitometric, and biochemical effects of MLT on osteoporosis in ovariectomized rats. Wistar rats were divided into six groups. Group C: control; Group I: bilateral ovariectomy (OVX); Group II: OVX + vehicle; Group III: OVX + 10 mg/kg/day MLT; Group IV: OVX + 30 mg/kg/day MLT; Group V: sham + 10 mg/kg/day MLT. They found that trabecular thickness and trabecular area of vertebra and femur and cortical thickness of femur showed remarkable decrease after OVX, but increased after MLT treatment in the OVX + MLT groups. Following OVX, no statistically significant difference was found in number of osteoblasts or osteoclasts, trabecular number or levels of hydroxyproline after treatment with MLT. OVX caused significant decrease in BMD, but treatment with MLT was unable to reverse this effect. This study indicated that MLT may trigger microscopic changes in bone, and time of application is critical for clinical recovery.[66]

Inhibiting adipocyte formation and promoting osteoblast differentiation to enhance bone formation is a promising therapy for osteoporosis.[67] Bäckesjö *et al.* have studied the effect of activation of SIRT1 on adipocyte formation during osteoblast differentiation of mesenchymal stem cells, and found that resveratrol and isonicotinamide markedly inhibited adipocyte and promoted osteoblast differentiation, it means that activation of SIRT1 in mesenchymal stem cells can decrease adipocyte and increase osteoblast differentiation.[68]

Xu *et al.* have investigated the effect of LIL on mRNA expression of receptor activator of NF-kappaB ligand (RANKL) and osteoprotegerin (OPG) in rat calvarial cells. They found that LIL may directly promote osteoblast proliferation and differentiation, and indirectly inhibit osteoclast differentiation, by downregulating the RANKL: OPG mRNA ratio in osteoblasts.[69] Thus, LIL may play an important role in bone remodeling, and should be valuable for the treatment of bone diseases such as osteoporosis.

As discussed above, either ISO, MLT, or LIL may increase SIRT1 activity and inhibit osteoporosis. ILILT may also enhance MLT level and NAD^+/NADH in the blood and then intracellular SIRT1 activity in the related cells so that it may also be of use in the prophylaxis and treatment of osteoporosis.

10. Discussion

For ILILT, there are many health care applications in hyperlipidemia, blood hyperviscosity, insomnia, and high blood coagulation status in healthy pregnant women at term, and many clinic applications in mild cognitive impairment, AD, PD, schizophrenia, pain relief, stroke, depression, inflammation, coronary heart disease, myocardial infarction and cerebral palsy, and many possible applications in hypertension, vascular dementia, cancer, diabetes, ageing, olfactory dysfunction, withdrawal symptoms, renal failure, and health promotion.[4] In this

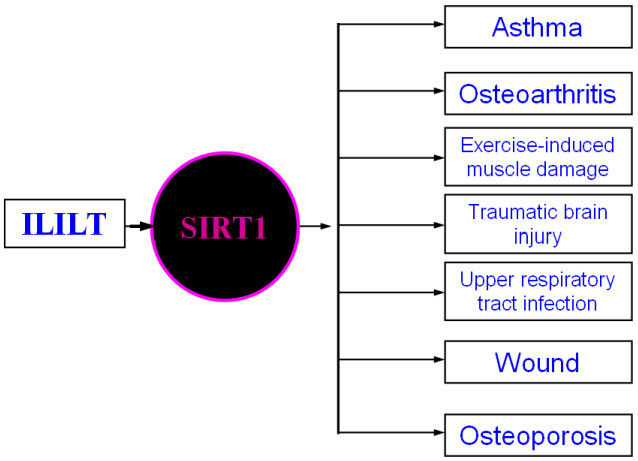

Fig. 2. Sirtuin 1 (SIRT1) mediated therapeutic effects of intranasal low intensity laser therapy (ILILT).

paper, the possible applications of ILILT in treating URTI, asthma, OA, EIMD or DOMS, wound, TBI, and osteoporosis have been discussed in the view of polyphenols, MLT, LIL, and ILELT (Fig. 2). All these applications of ILILT may play important roles in medical treatments in sports medicine and athletic health care since there are no side effects.

There may be possible prophylaxis effects of ILILT treatment on the flu since its possible application in treating URTI. There is now a pandemic of a swine-origin influenza A (H1N1) virus (S-OIV). An international team of scientists working at breakneck speed has provided the most detailed description yet of the origins of the S-OIV now causing a global outbreak.[70] Their report explained that this novel H1N1 has two genes from avian influenza that entered Eurasian swine in 1979, three from the old-fashioned H1N1 in North American swine, two from the triple reassortants in North American swine, and the final one from humans transmitted to us from birds in 1968. That head-spinning mix has never been seen before, and given its genetic distance between known strains. The virus was likely lurking around somewhere long before it jumped into humans. The encouraging news for vaccine development is that the many isolates of the new viruses analyzed in this report showed little variation, much less than typical seasonal influenza viruses. This makes it much easier to make a vaccine. Early on, Centers for Disease Control and Prevention in USA began to brew a "seed" strain for a possible vaccine against the virus, and by 27 April the World Health Organization in Geneva, Switzerland, was already talking to vaccine manufacturers. One key problem is that the world's influenza vaccine production capacity — which still relies on growing the vaccine virus in chicken eggs — is limited to some 400 million vaccine doses a year and is impossible to expand quickly. For now, the virus is treatable with the influenza drugs oseltamivir (Tamiflu) and zanamivir (Relenza). But the drug's complex manufacturing process makes it too pricey for many poor nations. There are insufficient data available at this point on the S-OIV infection. At this time, the same situation for seasonal influenza complications should also be considered for the swine-origin influenza complications. As infection results from immunodeficiency and there may be therapeutic potential of MLT in immunodeficiency states and viral diseases,[71] the possible rehabilitation effects of ILILT treatment on dysfunctional immunity might be of very importance for the prophylaxis of swine-origin influenza and cost much less money.

Therapeutic effects of polyphenols, MLT and LLLP such as ILELT and ILILT share the same SIRT1-mediated mechanism. However, there may be significant difference between the drugs and LLLP. There is no PBM of LLLP on a function in its FSH, but polyphenons or MLT can destroy a FSH and establish a new FSH. Dudley *et al.* have studied the dose-dependent effects of resveratrol on the ischemia–reperfusion injury. Rats were randomly fed for 14 days by gavaging any of the four doses of resveratrol −2.5, 5.0, 25, or 50 mg/kg — while vehicle-fed animals served as placebo control. After 14 days, isolated working hearts were prepared from both experimental and control animals, and the hearts were subjected to 30-min global ischemia followed by 2 h of reperfusion. They found that resveratrol exerts survival signal by up-regulating anti-apoptotic and redox proteins protein kinase B and Bcl-2 at lower doses (2.5 or 5 mg/kg), while it potentiates a death signal by down-regulating redox proteins and up-regulating pro-apoptotic proteins at higher doses ($>$ 25 mg/kg).[72] Adriaens *et al.* have studied the dose-dependent effects of MLT on oocyte maturation capacity, and found there is no effects of MLT at the concentration lower than 1 mM, but 1 mM negatively influenced oocyte maturation capacity and 2 mM is toxic.[73]

Iatrogenic-related morbidity and mortality rates are difficult to determine. Certain estimations have suggested that drug-related accidents alone could account for 5–10% of all acute hospitalizations.[74] Independent of the human aspect, health care expenditures related to

iatrogenic accidents are substantial. Although the cost/benefit ratio remains highly positive, statistically speaking one cannot ignore the high cost of severe accidents. Almost all effective medicines, like all surgical procedures, carry a risk. However, LLLP is an exception. There is zero risk for LLLP.[4] Therefore, ILILT is suggested to be widely used especially in sports medicine.

Acknowledgment

This work was supported by National Science Foundation of China (60878061, 60478048, 6017800, and 6027812).

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