

# Mechanism of Itranasal Low Intensity Laser Irradiation Therapy

Timon Cheng-Yi Liu <sup>\*a</sup>, Jian-Ling Jiao<sup>b</sup>, Jun Liang<sup>a</sup>, Song-Hao Liu<sup>c</sup>

a Laboratory of Laser Sports Medicine, South China Normal University, Guangzhou, GD 510631, China

b Medical College, Jinan University, Guangzhou, GD 510630, China

c School for Information Science and Optoelectronic Technology, South China Normal University, Guangzhou, GD 510631, China

## ABSTRACT

**Background and Objective:** Intranasal low intensity laser therapy (ILILT) began in China in 1998. Now in China it has been widely applied to treat hyperlipidemia, the blood-stasis syndrome of coronary heart disease and brain diseases such as Alzheimer's disease, Parkinson's disease, insomnia, poststroke depression, intractable headache, ache in head or face, cerebral thrombosis, acute ischemic cerebrovascular disease, migraine, brain lesion and mild cognitive impairment. Its mechanism was discussed in this paper. **Study Design/Materials and Methods:** ILILT was an intranasal photobiomodulation (PBM), and was discussed in terms of the cellular rehabilitation of PBM from viewpoints of three pathways mediating ILILT, blood cells, Yangming channel and autonomic nervous system (ANS). **Results:** Blood cells might mediate ILILT as is intravascular low energy laser therapy. Two unhealth acupoints of Yangming channel inside nose might mediate ILILT as is laser acupuncture. Dysfunctional ANS might be modulated and then mediate ILILT. These three pathways are integrated in ILILT so that serum amyloid  $\beta$  protein, malformation rate of erythrocytes, CCK-8, or serum lipid might decrease, and melanin production, SOD activity or  $\beta$  endorphin might increase after ELILT treatment. **Conclusions:** ILILT as a safe therapy might work in view of the previous research, but it should be supported by randomized placebo-controlled trial

**Keywords:** photobiomodulation, low intensity laser therapy, laser acupuncture

## 1. Introduction

Intranasal low intensity laser therapy (ILILT) began in 1998(Li et al 1998). It has been applied to treat hyperlipidemia (Zhang et al 2003), the blood-stasis syndrome of coronary heart disease (Xiong et al 2006) and brain diseases (Jiang et al 2001) such as insomnia (Xu et al 2001&2002a), intractable headache (Li et al 1998a), Alzheimer's disease (Xu et al 2002b), Parkinson's disease (Li et al 1999b, Xu et al 2003, Zhao et al 2003), poststroke depression (Xu et al 2002c), ache in head or face (Li et al 1998b), cerebral thrombosis (Li et al 1999a), acute ischemic cerebrovascular disease (Jie et al 1999), migraine (Chen 2003), brain lesion (Dou et al 2003) and mild cognitive impairment (Jin et al 2000&2001). The studies indicated that serum amyloid  $\beta$  protein(Jin et al 2000), malformation rate of erythrocytes (Li et al 1999a), CCK-8 (Li et al 1999b), the level of viscosity at lower shear rates and hematocrit (Jie et al 1999), and serum lipid (Dou et al 2003, Zhang et al 2003) decrease, respectively, and melanin production(Xu et al 2001-2003), SOD activity (Xu et al 2003) and  $\beta$  endorphin (Li et al 1998) increase, respectively, after ILILT. In this paper, its mechanism will be discussed.

---

\* liutcy@scnu.edu.cn

## 2. Homeostatic Regulation

Photobiomodulation (PBM) is a modulation of monochromatic light or laser irradiation (LI) on biosystems, which stimulates or inhibits biological functions but does not result in irreducible damage (Liu et al 2003&2004). The LI used in PBM is always low intensity LI (LIL),  $\sim 10$  mW/cm<sup>2</sup>. However, moderate intensity LI (MIL),  $10^2\sim 10^3$  mW/cm<sup>2</sup>, is of PBM if the radiation time is not so long that it damages organelles or cells. The PBM of LIL and MIL are called LPBM and MPBM, respectively, for short. There are two kinds of pathways mediating cellular PBM, the specific pathway which is mediated by the resonant interaction of LI with molecules such as photosensitizers or endogenous photosensitizers, the non-specific pathway which is mediated by the non-resonant interaction of LI with the proteins on the membrane of cells or organelles (Liu et al 2004). The concentration of endogenous photosensitizers is so low that LPBM is mainly mediated by the non-specific pathways, but MPBM is mainly mediated by the specific pathways, respectively. Therefore, MPBM is mainly mediated by reactive oxygen species (ROS) (Lubart et al 2005). ILILT is based on intranasal LPBM, but the intravascular low energy laser irradiation therapy (ILELT) (Jiang et al 2005, Liu et al 2006) is based on intravascular MPBM.

Homeostasis is a negative-feedback response of a biosystem to maintain the constant conditions inside the biosystem (Murphy et al 1983), and can be represented by the metabonomics/metabolomics of the biosystems (Dumas et al 2005). There are two kinds of homeostatic processes in the internal environment and external environment of a biosystem, the pathogenic processes which disrupt the old homeostasis, and the sanogenetic processes (Kryzhanovsky 2004) which restore the old homeostasis or establish a new homeostasis. MPBM might be a pathogenic process if the ROS level is so high that it disrupts the old homeostasis as Shefer et al (2001) have found for MPBM (177 mW/cm<sup>2</sup>, 3s) on i28 myoblasts after 36h fetal calf serum deprivation that the MPBM specifically activates ROS mediated mitogen-activated protein kinase/extracellular signal-regulated protein kinase (MAPK/ERK) pathway. LPBM might be a sanogenetic process as Karu (1998) has pointed there is no effects of LIL on the cell which redox potential is so that the cell normally functions, and the lower the redox potential of a cell comparing with the normal redox potential, the stronger the effects of LIL. MPBM might be also a sanogenetic process if the ROS level is not so high that it disrupts the old homeostasis as Liu et al (2006) have pointed that there is no PBM on health blood for ILELT. At this point, PBM can be classified as pathogenic PBM which can disrupt a homeostasis, and sanogenetic PBM which can modulate the pathogenic factor induced disruption of a homeostasis until the homeostasis has been restored or a new homeostasis has been established, but can not change homeostatic processes from one to another one. In other words, sanogenetic PBM is just a homeostatic regulation(Liu et al 2007).

Obviously, ILILT, as an intranasal LPBM, is just a homeostatic regulation so that it only modulates dysfunctional biosystems. Tulebaev et al (1989) have found the LPBM 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. Kruchinina et al (1991) have studied therapeutic effect of He-Ne laser 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. Shevrygin et al (2000) have shown that LPBM is effective in correction of microcirculatory disorders and tissue mechanisms of homeostasis in children with neurovegetative vasomotor rhinitis. Except these ILILT on the local inflammation, there are four possible pathways mediating the ILILT, olfactory nerve, blood cells, Yangming channel and autonomic nervous system. The olfactory nerves are healthy in the diseases mentioned in the introduction so that it might not play a role in ILILT. The other three pathways will be discussed in next sections.

### 3. Laser Hemotherapy

Laser hemotherapy was mentioned in discussing ILELT (Tsvettsikh et al 1999), and will be discussed in this section as the blood cells in the diseases mentioned in the introduction are always far from homeostasis so that there might be LPBM on their functions.

There is LPBM on erythrocytes, such as its protecting human erythrocytes from hypotonic hemolysis (Iijima et al 1991), its improving the deformability of stored human erythrocytes (Iijima et al 1993, Yokoyama et al 2003), its producing AchEase activity changes (Kujawa et al 2003) and its inducing long-term conformational transitions of erythrocytic membrane which were related to the changes in the structural states of both erythrocyte membrane proteins and lipid bilayer and which manifested themselves as changes in fluorescent parameters of erythrocyte membranes and lipid bilayer fluidity so that there was the modulation of membrane functional properties: changes in the activity of membrane ion pumps and, thus, changes in membrane ion flows (Kujawa et al 2004). Luo et al (2005) have studied the role of membrane aquaporin-1 (APQ-1) in the LPBM on erythrocytic deformability with human echinocytes and APQ-1 inhibitor, HgCl<sub>2</sub>. Human echinocytes were irradiated by He-Ne laser irradiation at 1-5 mW and 5-30 min, respectively. They found that the He-Ne laser irradiation optimum dose promoting echinocyte deformability is  $1.3 \times 10^4 \text{ J/m}^2$  at  $4 \text{ mW/cm}^2$ , but the effect is significantly inhibited by  $0.2 \mu\text{M}$  HgCl<sub>2</sub>, which showed AQP-1 might mediate the effect of low intensity He-Ne laser irradiation on erythrocytic deformability. There were so many LPBM studies on erythrocytes, but a few of LPBM studies on platelets (Olban et al 1998), which provides the foundation for ILILT on the rheological properties of blood so that serum amyloid  $\beta$  protein (Jin et al 2000), malformation rate of erythrocyte (Li et al 1999a), the level of viscosity at lower shear rates and hematocrit (Jie et al 1999), and serum lipid (Dou et al 2003, Zhang et al 2003) decreased, respectively, and SOD activity increased (Xu et al 2003) after ILILT.

There is also LPBM on leukocytes, such as its stimulating lymphocytes to produce factor(s) that can modulate endothelial cell proliferation in vitro (Agaiby et al 2000), its attenuating ROS production by human polymorphonuclear neutrophils (PMNs) (Fujimaki et al 2003), its modulating nitric oxide and cytokines production by leukocytes (Klebanov et al 2002). Here is the only one signal transduction research on ILILT. Duan et al (2001) have probed signal transduction pathways of respiratory burst of bovine PMNs which were induced by He-Ne laser irradiation at a dose of  $300 \text{ J/m}^2$  by using the protein tyrosine kinases (PTKs) inhibitor, genistein, the phospholipase C (PLC) inhibitor, U-73122, and the protein kinase C (PKC) inhibitor, calphostin C, respectively, and found the inhibitor of PTKs can completely inhibit the He-Ne laser-induced respiratory burst of PMNs, and PLC and PKC inhibitors can obviously reduce it, but not fully inhibit it. These results suggest that PTKs play a key role in the He-Ne laser-induced respiratory burst of PMNs and [PTK-PLC-PKC-NADPH oxidase] signal transduction pathways may be involved in this process. These cellular LPBM studies provide the foundation for ILILT on immunological functions so that the CD3/CD8 increased and CD4/CD8 decreased after ILILT (Zhou et al 2005)

### 4. Laser Acupuncture

Laser acupuncture as an alternative, noninvasive, painless and cost-effective therapy has been widely used for acute and chronic pain, nausea, circulatory functions, mood-related behavioral disorders and so forth (Jiao et al 2003). It might mediated ILILT since there are two unhealthy acupoints of Yangming channel inside human nose.

Laser acupuncture devices were cleared for marketing by FDA through the Premarket Notification/510(k) process as adjunctive devices for the temporary relief of pain (FDA 2002). The research on the effects of laser acupuncture on pain has shown that laser acupuncture can improve the expression of  $\beta$  endorphin (Chen KZ et al 2004), which has been also found for ILILT (Li et al

1998a&b). Zhang (2005) found therapeutic effect of acupuncture at acupoints along the Hand and Foot-Yangming Channels on trigeminal neuralgia, which has been also found for ILILT (Li et al 1998a&b). In this way, it is easily understood that there might be therapeutic effects of ILILT on intractable headache (Li Q et al 1998a), ache in head or face (Li Q et al 1998b) and migraine (Chen S 2003).

Laser acupuncture and then ILILT on cerebrovascular diseases should be in view of acupuncture at Yangming channel points (Jiang et al 2005). Zhang et al (1990) observed the effect of acupuncture at points of hand-yangming meridian was bigger than that of foot-yangming meridian on the facial temperature of the patients with facial nerve paralysis. Wu et al (1996) have adopted the principle of clearing Yangming and nourishing the kidney and heart in the treatment of 156 cases of Gilles de la Tourette's Syndrome with acupuncture, and they found the pathological waves in 54 disappeared or ameliorated after the treatment among 84 cases with abnormal EEG. Zhang et al (1999) have found one of the mechanisms governing acupuncture treatment of apoplexy acupuncture at Yangming channel points as main points was that acupuncture could produce therapeutic effects by adjusting the imbalance of important vaso-active substances, endothelin level in plasma, TXB2 and 6-Keto-PGF1 alpha levels in urine. Wang et al (2005) found the acupuncture therapy of "mother-son" reinforcing-reducing method of five Shu points of The Hand-Yangming and Foot-Yangming Channels based on differentiation of yin, yang and deficiency and excess of channels by Cunkou and Renying Vessel methods can increase clinical therapeutic effect on stroke at restoration stage. Therefore, there might be therapeutic effects of ILILT on brain diseases (Jiang et al 2001) such as Alzheimer's disease (Xu et al 2002b), Parkinson's disease (Li et al 1999b, Xu et al 2003, Zhao et al 2003), insomnia (Xu et al 2001&2002a), poststroke depression (Xu et al 2002c), cerebral thrombosis (Li et al 1999a), acute ischemic cerebrovascular disease (Jie et al 1999), brain lesion (Dou et al 2003) and mild cognitive impairment (Jin et al 2000&2001).

## 5. Autonomic Nervous System Mediated Pathways

The autonomic nervous system inside human nose might be dysfunctional so that it might mediate ILILT. It might be also one of the pathways mediating acupuncture and laser acupuncture (Jiao et al 2003). Autonomic dysfunction is responsible for much of the morbidity associated with frequently encountered neurological disorders, such as Parkinson's disease, multiple sclerosis, cerebrovascular disease, and peripheral neuropathies, as well as with the rarer primary autonomic nervous system degenerations (Freeman et al 1993) so that there might be therapeutic effects of ILILT on brain diseases (Jiang M et al 2001) such as Alzheimer's disease (Xu et al 2002b), Parkinson's disease (Li et al 1999b, Xu et al 2003, Zhao et al 2003), insomnia (Xu et al 2001&2002a), poststroke depression (Xu et al 2002c), cerebral thrombosis (Li et al 1999a), acute ischemic cerebrovascular disease (Jie et al 1999), brain lesion (Dou et al 2003) and mild cognitive impairment (Jin et al 2000&2001). For example, melanin production can be improved in ILILT (Xu et al 2001-2003) since the activation of sympathetic subsystem can enhance melatonin production (Tang et al 2002).

## 6. Discussion

LPBM is a safe modality for clinical use (Wolbarsht 1994, Logan et al 1995) so that ILILT is also a safe modality for clinical use. Complete laser hatching of human embryos using the Zona infrared laser optical system does not have an adverse effect on subsequent development (Wong et al 2003). There is no cytotoxic and genotoxic potential of low intensity laser irradiation (660 nm, 12 mW, 5 kHz, 2 and 20 J/cm<sup>2</sup>) on mammalian cells (Logan et al 1995). The induction of cell-cycle delay of visible-light irradiation at 660 nm is not initiated by DNA strand breaks (Joyce et al 1999).

Following the doses of IR-A (700-2000 nm) that induced ferritin levels, there was no alteration seen for nuclear DNA type damage, oxidative stress proteins or proteases involved in the degradation of skin (Applegate et al 2002).

As a safe modality for clinical use, ILILT might be integratedly mediated by blood cells, Yangming channel and autonomic nervous system as discussed above. The mechanism can be used to extend its clinic applications. For example, ILILT might be used to promote the antimicrobial effects. There have been in vivo antimicrobial effects of LPBM (Wang et al 1998, Neimark et al 2000, Gizinger et al 2006, Dolgushin et al 2006) and ILELT (Karniushina et al 1989, Neimark et al 2000), which might be due to cellular rehabilitation of sanogenetic PBM on the induction and formation of neutrophil extracellular traps (NETs). PMNs undergo a ROS-triggered death that allows microbial killing by the formation of NETs (Fuchs et al 2007). The ILELT induced ROS level in PMNs might rehabilitate NET induction and formation but not induced PMN apoptosis or necrosis. LIL might also rehabilitate NET induction and formation since PMN number has been found to decrease in antimicrobial effects of LIL in vivo (Wang et al 1998).

ILILT might work in view of the previous research, but it should be supported by randomized placebo-controlled trial. Up to date, there has been only one clinical research according to the principle of random, single blind and parallel controlled trial (Xiong et al 2006). Xiong et al (2006) have observed the therapeutic effects of intranasal diode 650 nm laser irradiation on patients suffering from the blood-stasis syndrome of coronary heart disease, and found there was significant therapeutic effects of the ILILT on the blood-stasis syndrome of coronary heart disease, which improved some traditional Chinese medicine symptoms such as fatigue and feebleness.

#### Acknowledgement

It is supported by National Science Foundation of China (60478048, 60178003 and 6027812) and Key Project (20011480) and General project (20031526) of Guangdong Science Foundation of China.

#### References

- Agaiby AD, Ghali LR, Wilson R, Dyson M. 2000. Laser modulation of angiogenic factor production by T-lymphocytes. *Lasers Surg Med.* 2000;26(4):357-63.
- Applegate LA, Scaletta C, Panizzon R, Frenk E, Hohlfeld P, Schwarzkopf S. 2000. Induction of the putative protective protein ferritin by infrared radiation: Implications in skin repair. *Int J Mol Med* 5 (3): 247-251 MAR 2000.
- Chen KZ, Liu TCY, Jiao JL, Li Z, Li ZR, Deng SX and Liu SH. 2004. Low intensity laser acupuncture effects on pain relief. *Lasers Surg Med.* 34(S16): 41
- Chen S. 2003. Therapeutic observation and nursing for endonasal low intensity laser treatment of migraine. *Shanghai Nursing.* 3(1): 27-28 (in Chinese).
- Dou Z, Hu X and Zhu H. 2003. The effects of two kinds of laser irradiation on patients with brain lesion. *Chin J Phys Med Rehabil.* 25(2): 86-88 (in Chinese).
- Dolgushin II, Gizinger OA, Telesheva LF. 2006. [Immunological and microbiological aspects of low intensity laser effect on the factors of local immunity of the reproductive tract in women with chlamydia infection] *Zh Mikrobiol Epidemiol Immunobiol.* 2006 Jul-Aug;(4):105-9.
- Duan R, Liu TC-Y, Li Y, Guo H, and Yao L-B. 2001. Signal transduction pathway involved in low intensity He-Ne laser-induced respiratory burst in bovine neutrophils: a potential mechanism of low intensity laser biostimulation. *Lasers Surg. Med.* 29(2): 174-178
- Dumas ME, Canlet C, Vercauteren J, Andre F, Paris A. 2005. Homeostatic signature of anabolic steroids in cattle using 1H-13C HMBC NMR metabonomics. *J Proteome Res.* 2005 Sep-Oct;4(5):1493-502.

- FDA. 2002. <http://www.fda.gov/cdrh/consumer/laserfacts.html>
- Freeman R, Miyawaki E. 1993. The treatment of autonomic dysfunction. *J Clin Neurophysiol.* 1993 Jan;10(1):61-82.
- Fuchs TA, Abed U, Goosmann C, Hurwitz R, Schulze I, Wahn V, Weinrauch Y, Brinkmann V, Zychlinsky A. 2007. Novel cell death program leads to neutrophil extracellular traps. *J Cell Biol.* 2007 Jan 15;176(2):231-41.
- Fujimaki Y, Shimoyama T, Liu Q, Umeda T, Nakaji S, Sugawara K. 2003. Low-level laser irradiation attenuates production of reactive oxygen species by human neutrophils. *J Clin Laser Med Surg.* 2003 Jun;21(3):165-70.
- Gizinger OA, Dolgushin II. 2006. [Low-intensity laser effects on local immunity of female reproductive system affected with chlamidia infection] *Vopr Kurortol Fizioter Lech Fiz Kult.* 2006 Sep-Oct;(5):20-3.
- Iijima K, Shimoyama N, Shimoyama M, Mizuguchi T. 1991. Red and green low-powered He-Ne lasers protect human erythrocytes from hypotonic hemolysis. *J Clin Laser Med Surg.* 1991 Oct;9(5):385-9.
- Iijima K, Shimoyama N, Shimoyama M, Mizuguchi T. 1993. Effect of low-power He-Ne laser on deformability of stored human erythrocytes. *J Clin Laser Med Surg* 1993, 11(4):185-9.
- Jiang JF, Wang LL. 2005. [Study on acupuncture and moxibustion treatment of cerebrovascular diseases based on the theory of collaterals] *Zhongguo Zhen Jiu.* 2005 Sep;25(9):659-62.
- Jiang M and Yang A. 2001. Observation of endonasal low energy He-Ne laser treatment of 105 cases of brain disease. *Laser Journal.* 22(4): 17(in Chinese).
- Jiao JL, Liu TCY, Li CZ, Liu SH. 2003. Information biology of laser acupuncture. *P Soc Photo-Opt Ins* 5254: 131-138 2003.
- Jie J, Cao Q and Xu J. 1999. Effects of laser irradiation therapy through nasal cavity on viscosity at lower shear rates and hematocrit in patients with acute ischemic cerebrovascular disease. *J Binzhou Medical College.* 22(6): 533-534(in Chinese).
- Jin L, Shi B and Zhou C. 2000. The effect on serum amyloid protein of patients with mild cognitive impairment after semiconductor laser therapy. *Acta Academiae medicinae Qingdao Universitatis.* 36(3): 175-176(in Chinese).
- Jin L and Shi B. 2001. Effect of low intensity semiconductor laser irradiation on EEG power spectrum and P3 PL in cognitive disorder patients. *Chin J Phys Ther.* 24(4): 197-199(in Chinese).
- Joyce KM, Downes CS, Hannigan BM. 1999. Cell-cycle delay is induced in cells of a U937 promonocytic cell line by low-intensity light irradiation at 660 nm. *J Photoch Photobio B* 52 (1-3): 117-122 SEP-OCT 1999.
- Karniushina NL, Veniaminov LK, Inozemtseva OV, Vorob'eva LN, Grigorev EG. 1989. [Intravascular laser irradiation of the blood in the treatment of patients with surgical infection]. *Vestn Khir Im I I Grek.* 1989 Sep;143(9):48-51.
- Klebanov GI, Poltanov EA, Dolgina EN, Nikankina LA, Anokhina EB, Gancovskaya LV, Kreinina MV, Vladimirov YA. 2002. Investigation of action of low power laser irradiation on nitric oxide and cytokines production by leukocytes. *Biol Membrany* 19 (5): 391-402 SEP-OCT 2002.
- Kruchinina I, Feniksova LV, Rybalkin SV, Pekli FF. 1991. Therapeutic effect of helium-neon laser on microcirculation of nasal mucosa in children with acute and chronic maxillary sinusitis as measured by conjunctival biomicroscopy. *Vestn Otorinolaringol.* 1991 May-Jun;(3):26-30.
- Kryzhanovskiy GN. 2004. Some categories of general pathology and biology: health, disease, homeostasis, sanogenesis, adaptation, immunity New approaches and notions. *Pathophysiology.* 11(3):135-138.
- Kujawa J, Zavodnik L, Zavodnik I, Bryszewska M. 2003. Low-intensity near-infrared laser radiation-induced changes of acetylcholinesterase activity of human erythrocytes. *J Clin Laser Med Surg* 21 (6): 351-355 DEC 2003.

- Kujawa J, Zavodnik L, Zavodnik I, Buko V, Lapshyna A, Bryszewska M. 2004. Effect of low-intensity (3.75-25J/cm<sup>2</sup>) near-infrared (810 nm) laser radiation on red blood cell ATPase activities and membrane structure. *J Clin Laser Med Sur.* 22 (2): 111-117 APR 2004.
- Li Q, Guo K, Kang J and Jiang B. 1998a. Clinic analysis of endonasal low energy He-Ne laser treatment of 39 cases of intractable headache. *Acta Academiae medicinae Qingdao Universitatis.* (1): 53(in Chinese).
- Li Q, Guo K, Kang J, Jiang B and Wang Y. 1998b.  $\beta$  endorphin research for endonasal low energy He-Ne laser treatment of ache in head or face. *Chin J Neurol.* 31(2): 91(in Chinese).
- Li Q, Kang J, Song Y, Shen L, Liu Z and Tan J. 1999a. Electron microscope observation of erythrocytes of cerebral thrombosis treated by endonasal low energy He-Ne laser. *Shandong Med & Pharm.* 39(2): 3-4(in Chinese).
- Li Q, Song L, Guo K, Yu Y, Ma S and Shen L. 1999b. The effect of endonasal low energy He-Ne laser treatment of Parkinson's disease on CCK-8 content in blood. *Chin J Neurol.* 32(6): 364(in Chinese).
- Liu TCY, Jiao JL, Duan R, Li Yan, Yeung YY and Liu SH. 2003. Membrane mechanism of low intensity laser biostimulation on a cell. Simunovic Z (ED). *Lasers in Medicine, Surgery and Dentistry.* Croatia: European Medical Laser Association. 2003. 83-105.
- Liu TCY, Jiao JL, Xu XY, Liu XG, Deng SX and Liu SH. 2004. Photobiomodulation: Phenomenology and its Mechanism. *Progress in Biomedical Optics and Imagine.* 5(33): 185-191.
- Liu TCY, Duan R, Wang SX, Liu J, Cui LP, Jin H, Liu SH. 2006. Basic studies on intravascular low intensity laser therapy. *Progress in Biomedical Optics and Imaging - Proceedings of SPIE, v 6047 II, Fourth International Conference on Photonics and Imaging in Biology and Medicine, 2006, p 60473R.*
- Liu TCY, Li JH, Wang YF, Xu XY and Liu SH. 2007. Homeostatic photobiomodulation. *Lasers Surg Med.* 39(S19) : 69
- Logan ID, Mckenna PG, Barnett YA. 1995. An investigation of the cytotoxic and mutagenic potential of low-intensity laser irradiation in friend-erythro leukemia cells. *Mutat Res Lett* 347 (2): 67-71 JUL 1995.
- Lubart R, Eichler M, Lavi R, Friedman H, Shainberg A. 2005. Low-energy laser irradiation promotes cellular redox activity. *Photomed Laser Surg.* 2005 Feb;23(1):3-9.
- Luo GY, Huang CY, Liu TCY, Zhao YP and Liu SH. 2005. Membranotropic photobiomodulation on red blood cell deformability. *Lasers Surg Med.* 36(17S): 60.
- Murphy EA, Trojak JE. 1983. The dynamics of quantifiable homeostasis. I. The individual. *Am J Med Genet.* 1983 Jun; 15(2):275-90.
- Neimark AI, Muzalevskaia NI. 2000. [Low-intensity laser radiation in preoperative preparation of patients with benign prostatic hyperplasia] *Urologiia.* 2000 Jan-Feb;(1):11-5.
- Olban M, Wachowicz B, Koter M, Bryszewska M. 1998. The biostimulatory effect of red laser irradiation on pig blood platelet function. *Cell Biol Int* 22 (3): 245-248 1998
- Shefer G, Oron U, Irintchev A, Wernig A, Halevy O. 2001. Skeletal muscle cell activation by low-energy laser irradiation: a role for the MAPK/ERK pathway. *J Cell Physiol.* 2001 Apr;187(1):73-80.
- Shevrygin BV, Rybalkin SV, Pekli FF, Feniksova LV. 2000. [Correction of microcirculatory disorders with low-energy laser radiation in children with vasomotor rhinitis] *Vestn Otorinolaringol.* 2000;(2):31-3.
- Tang M, Liu TCY, Li Y. 2002. Color indirect effects on melatonin regulation. *Proc SPIE.* 4536: 127-129.
- Tsvettsikh VE, Sultanbaev VR, Berdichevskii BA, Kazeko NI, Ovchinnikov AA, Sultanbaev RA, Murychev AV. 1999. [Endovascular Helium-Neon laser irradiation of the blood in the treatment of chronic pyelonephritis]. *Urologiia.* 1999 Nov-Dec;(6):13-5.
- Tulebaev RK, Sadykov ShB, Romanov VA, Khalitova GK. [Indicators of the activity of the

- immune system during laser therapy of vasomotor rhinitis]. *Vestn Otorinolaringol.* 1989 Jan-Feb;(1):46-9.
- Wang L, Wang Y, Cheng D, He Y, An M and Luo L. 1998. Therapeutic effects of ultrashortwave and He-Ne laser on experimental infection in skin flaps of rabbits. *Chinese Journal of Reparative and Reconstructive Surgery.* 12(1): 55-57 (in Chinese).
- Wang L, Yan DY. 2005. [Observation on clinical therapeutic effect of "mother-son" reinforcing-reducing method on stroke at restoration stage]. *Zhongguo Zhen Jiu.* 2005 May;25(5):309-11(in Chinese).
- Wolbarsht ML. 1994. Low-level laser therapy (lllt) and safety considerations. *J Laser Appl* 6 (3): 170-172 SEP 1994.
- Wong BC, Boyd CA, Lanzendorf SE. 2003. Randomized controlled study of human zona pellucida dissection using the Zona Infrared Laser Optical System: evaluation of blastomere damage, embryo development, and subsequent hatching. *Fertil Steril* 80 (5): 1249-1254 NOV 2003.
- Wu L, Li H, Kang L. 1996. 156 cases of Gilles de la Tourette's syndrome treated by acupuncture. *J Tradit Chin Med.* 1996 Sep;16(3):211-3.
- Xiong H, Sun LJ, Jia LQ, Zhao YQ, Zheng XK, Zhang XL, Wang RH. 2006. Semi-conductor laser for coronary heart disease of blood-stasis syndrome: A randomized, blind and parallel control study. *Chinese Journal of Clinical Rehabilitation.* 10(39): 36-38.
- Xu C, Wang L, Liu J, Tan Y and Li Q. 2001. Endonasal low energy He-Ne laser treatment of insomnia. *Qian Wei J Med & Pharm.* 18(5): 337-338 (in Chinese).
- Xu C, Wu Z, Wang L, Shang X and Li Q. 2002a. The effects of endonasal low energy He-Ne laser treatment of insomnia on Sleep EEG. *Prac J Med & Pharm.* 19(6): 407-408(in Chinese).
- Xu C, Wang L, Shang X and Li Q. 2002b. Endonasal low energy He-Ne laser treatment of Alzheimer's disease. *Prac J Med & Pharm.* 19(9): 647-648(in Chinese).
- Xu C, Wang L and Lu C. 2002c. Endonasal low energy He-Ne laser treatment of poststroke depression. *Prac J Med & Pharm* 19(11): 893(in Chinese).
- Xu C, Lu C, Wang L and Li Q. 2003. The effects of endonasal low energy He-Ne laser therapy on antioxydation of Parkinson's disease. *Prac J Med & Pharm.* 20(11): 816-817(in Chinese).
- Yokoyama K, Sugiyama K. 2003. Influence of linearly polarized near-infrared irradiation on deformability of human stored erythrocytes. *J Clin Laser Med Surg.* 2003 Feb;21(1):19-22.
- Zhang D, Wen B, Wei Z, Gao H, Peng Y, Meng J. 1990. [The comparison of changes of the facial temperature after acupuncturing point of hand and foot-yangming meridians by the thermography]. *Zhen Ci Yan Jiu.* 1990;15(3):191-3(in Chinese).
- Zhang S, Ye X, Shan Q, Zhang W, Ye L, Cui Y. 1999. Effects of acupuncture on the levels of endothelin, TXB2, and 6-keto-PGF1 alpha in apoplexy patients. *J Tradit Chin Med.* 1999 Mar;19(1):39-43.
- Zhang X and Chen C. 2003. The effects of endonasal low energy He-Ne laser therapy on serum lipid level. *Zhejiang J ITCWM.* 13(10):633-634(in Chinese).
- Zhang XY. 2005. [Therapeutic effect of deep acupuncture at local acupoints on trigeminal neuralgia] *Zhongguo Zhen Jiu.* 2005 Aug;25(8):549-50(in Chinese).
- Zhao G, Guo K and Dan J. 2003. 36 case analysis of Parkinson's disease treated by endonasal low energy He-Ne laser. *Acta Academiae medicinae Qingdao Universitatis.* 39: 398(in Chinese).
- Zhou Y, Zhu W. 2005. Influence of laser therapy via nasal cavity on the CD antigen of peripheral lymphocytes in patients with cerebral embolism. *Journal of Binzhou Medical College.* 28(2): 95-96 (in Chinese).