Paradigm Academic Press
Journal of Innovations in Medical Research
ISSN 2788-7022
DEC. 2022 VOL.1 NO.5

Analysis of Massage Treatment Mechanism of Parkinson's Disease

Long Wang[1] & Zhibin Liu[1,2]

[1] Shaanxi University of Traditional Chinese Medicine, Xianyang, Shaanxi 712046

[2] Acupuncture and Pharmaceutical Combination Innovation Research Center, Shaanxi University of Traditional Chinese Medicine, Xianyang, Shaanxi 712046

Correspondence: Zhibin Liu, Shaanxi University of Traditional Chinese Medicine, Xianyang, Shaanxi 712046, Acupuncture and Pharmaceutical Combination Innovation Research Center, Shaanxi University of Traditional Chinese Medicine, Xianyang, Shaanxi 712046.

doi:10.56397/JIMR/2022.12.05

Abstract

Parkinson's disease as a common neurological degenerative disease, there is no clear cure, now approved treatment can only alleviate symptoms, and cannot effectively prevent the further development of the disease and the emergence of side reaction, massage as complementary and alternative medical means one of the most commonly used form, its improve Parkinson's disease motor symptoms and nonmotor symptoms have a good advantage, but its potential treatment mechanism has not been further discussed. Therefore, this paper will deeply explore the potential action mechanism of massage therapy to improve the symptoms of Parkinson's disease from multiple angles, in order to provide theoretical support for the rationality of massage treatment of Parkinson's disease, so that massage therapy can be better used in clinical practice.

Keywords: massage, complementary and alternative medical methods, Parkinson's disease, mechanism of action

1. Introduction

Parkinson's disease (PD), as a chronic neurodegenerative disease, non-motor symptoms such as delay, static tremor, body stiffness, postural instability and autonomic dysfunction, the main pathological feature is the loss of dopaminergic neurons in the mesa nigra degeneration, reduced dopamine levels in the striatum and neuronal eosinophilic inclusions known as Lewy bodies (Lewy body) and α -synaptic nucleins (α -synuclein) aggregation. According to the latest epidemiology, the prevalence rate of people over 65 years old in China is as high as 1.7%. It is expected that the number of Parkinson's disease patients in China will exceed 5 million by 2030, then accounting for 50% of the global number of Parkinson's disease patients (Chen Shengdi & Chen Haibo, 2020). As the disease progresses, its motor and non-motor symptoms will become more severe, making the patient's adherence to the medication even more important, and a complex medication regimen or titration plan will also become a part of the patients' daily life. At present, most of the symptoms of PD patients can be effectively controlled by the corresponding drug treatment, but with the passage of time and the degenerative effect of the disease itself, patients will gradually appear no response to drug treatment, lead to the deterioration of symptoms, and affect the body function and daily life, therefore, more and more patients or clinicians began to focus on various complementary or alternative medical means (C AM), one of the most common means of acupuncture, massage, Chinese medicine decoction, biofeedback therapy, homeopathy and physical and mental therapy, etc.

A retrospective study noted that the No (Wang Y, Xie CL, Wang WW, et al., 2013), C AM usage is between 26% and 76% globally, while C AM usage in PD is 38.7% in England, 10.34% in Sweden, 11.25% in Argentina, 12.40% in America, Singapore, 13.61% in Korea, 14.76%, with 4.6% to 26% of P D patients choosing two CAM, and 14% to 33% of P D patients choosing three or more C AM. As one of the most commonly used forms of

complementary and alternative medical means, massage can very well ameliorate both motor and non-motor symptoms in P D patients. One study found that (Hernandez-Reif M, Field T, Largie S, et al., 2002). The 16 Patients with early Parkinson's disease without levodopa showed significant improvement in sleep disturbances at the end of the course and decreased adrenaline and norepinephrine levels at the end of the course; another study evaluating the effect of Japanese massage on P D patients also found (Donoyama N & Ohkoshi N., 2012), Massage can significantly improve the gait impairment, increase the range of shoulder movement, and reduce the V AS score. Likewise, the Juntakarn (Juntakarn C, Prasartritha T & Petrakard P., 2017) Thai massage has also found that Thai massage can relieve muscle stiffness and bradykinesia by stimulating the parasympathetic nervous system and increasing blood flow. Therefore, this paper will deeply explore the potential mechanism of massage to improve PD symptoms, in order to provide theoretical support for the rationality of massage treatment for PD treatment.

2. Modern Medical Research on the Pathogenesis of Parkinson's Disease

2.1 Neuroinflammation

Whitton et al (More SV, Kumar H, Kim IS, et al., 2013) the expression of the major histocompatibility complex (MHC) was significantly upregulated in the brain of PD patients, suggesting the first correlation between neuroinflammation and PD. In recent years, several studies show that the (Tansey MG & Goldberg MS., 2010), Proinflammatory factors are involved in PD and other neurodegenerative lesions. For example, through the autopsy analysis of PD patients, the expression of proinflammatory cytokines (TNF-a), interleukin-1 β (IL-1 β), interleukin-6 (IL-6), interleukin-12 (IL-12) (I L-12) and IIFN-y) were significantly upregulated, and downstream inflammatory signaling pathways were activated (Yan J, Fu Q, Cheng L, et al., 2014); Epidemiological and genetic pathology studies also suggest that inflammation can increase the susceptibility to PD. In addition, microglia (MG), as the smallest glial cells in the central nervous system, also belong to the immune cells in the brain. They can be activated under the action of various stimuli such as bacteria, viruses, toxins, pesticides, neuronal damage, etc. After activation, they release a variety of cytokines to participate in the neuroinflammatory response (Richardson JR & Hossain MM., 2013). But M G mediated neuroinflammation has two-sided, on the one hand, can produce protective effect in infection, inflammation, trauma and removal of metabolites, on the other hand, in the development of chronic neurodegenerative diseases PD, MG activation is mainly to damage, leading to increased secretion of inflammatory factors or the clearance of α -syn.

2.2 Oxidative Stress Response

Oxidative stress has been suggested as a common underlying mechanism leading to cell dysfunction and ultimately to cell death. When there is an imbalance between the production of reactive oxygen species (R OS) and cellular antioxidant activity, oxidative stress occurs, which participates in a cascade and eventually leads to the degeneration of dopamine cells. Because oxidants and superoxide radicals are produced as products of oxidative phosphorylation, mitochondria become the main site for ROS production in cells. Many sources and mechanisms of ROS have been discovered, including the metabolism of dopamine itself, mitochondrial dysfunction, iron, neuroinflammatory cells, calcium, and aging; PD gene products, including DJ-1, PINK1, parkin, α -synaptic protein, and LRRK2, which affect mitochondrial function in a complex manner, leading to increased ROS generation and susceptibility to oxidative stress. Because oxidative stress is also difficult to determine whether oxidative stress causes cell degeneration, such as, neuroinflammation, mitochondrial dysfunction, nitric oxide toxicity, etc.

2.3 Mitochondrial Dysfunction

Mitochondrial organelles, as highly dynamic organelles, have a variety of functions. Besides their participation in energy metabolism, they also participate in various cellular processes, such as stress response, cell apoptosis and the regulation of calcium homeostasis. Several studies have shown that mitochondria dysfunction plays a key role in P D pathogenesis. In the autopsy of P D patients, mitochondrial respiratory chain complex I activity was significantly reduced in the substantia black a (R. H. Haas, F. Nasirian, K. Nakano, D. Ward, M. Pay, R. Hill & C. W. Shults, 1995). A subsequent 30% reduction in the mitochondrial respiratory chain complex I activity was also detected in the mitochondria of the frontal cortex (W. D. Parker Jr., J. K. Parks & R. H. Swerdlow, 2008). With mitochondrial impaired electron flux in complex I, A TP production decreases, while the production of reactive oxygen and nitrogen species increases, ultimately leading to neuronal cell death. In addition, mitochondria as an important source of reactive oxygen species, if increased mitochondrial R OS formation and / or R OS clearance system defects, will lead to mitochondrial (mt) D NA, proteins and lipid oxidation damage, and the oxidation of mt DNA may damage the respiratory chain subunit encoded by mt RNA, thus establishing a vicious cycle of oxidative stress and bioenergetic exhaustion (A. W. Linnane, S. Marzuki, T. Ozawa & M. Tanaka, 1989). Moreover, many endogenous and exogenous inhibitors that affect mitochondrial function can induce PD-like symptoms (Litim N, Morissette M & Di Paolo T. 2017). It also further indicates that mitochondrial dysfunction is closely related to Parkinson's disease. In addition, mutations in various genes (such

as D J-1 gene, Parkin gene, P INK1 gene and L RRK2 gene) can also cause mitochondrial dysfunction and then lead to the onset or deterioration of P D.

2.4 Protein Overexpression and Aggregation

α -Syn is a small protein encoded by the SNCA gene that is expressed abundantly in the presynaptic terminals of the CNS. Under normal conditions, native α -Syn exists in a dynamic equilibrium between unfolded monomer and α -helical folded tetramers with a low aggregation tendency, and the aggregation process of α -Syn involves conformational changes (Lashuel, H. A., Overk, C. R., Oueslati, A. & Masliah, E., 2013). As a plastic protein with a significant conformation, α -Syn can adopt a variety of structural conformations (Deleersnijder, A., Gerard, M., Debyser, Z. & Baekelandt, V., 2013); and each α -Syn conformation shows different properties in terms of neurotoxicity, stability, and seeding and reproductive ability. It has been shown that α -Syn aggregates can induce neuronal toxicity leading to neuronal death through a variety of mechanisms, including mitochondrial dysfunction, lysosomal damage, membrane disorders, ER stress, and synaptic dysfunction. It is well known that the pathological aggregation of α -Syn is a common feature of multiple neurodegenerative diseases, including PD, Lewy body dementia (DLB), and multisystem atrophy (MSA), collectively known as synaptic nucleolopathies. And pathological α -Syn has prion-like properties and can spread throughout the brain through cell-to-cell transport mechanisms (Ma J, Gao J, Wang J, et al., 2019). The neuropathological hallmark of PD is the abnormal accumulation and aggregation of the α -synaptic nuclear protein (α -Syn) in the form of Lewy bodies and Lewy axons. In the course of PD pathogenesis, the soluble and abnormal accumulation of α -syn monomers in neurons to form oligomers, which then aggregate into fibrils and eventually form fibrillary tangles to produce neuronal toxic effects, leading to the development of PD (Tran, H. T. et al., 2014; Besong-Agbo, D. et al., 2013; Xuan Q. et al., 2011) . In addition, misfolded α -Syn can activate microglia; similarly, activated microglia can enhance the aggregation and spread of α -Syn, forming a positive feedback loop between inflammation and α -Syn aggregation, and this interaction also plays a key role in the pathogenesis of PD (Olanow, C.W., Savolainen, M., Chu, Y., Halliday, G.M. & Kordower, J. H., 2019). Alternatively, lysosomal dysfunction impairs the ability to remove toxic aggregates, thereby increasing the possibility of α -Syn aggregation and diffusion, which can be degraded by lysosomes under physiological conditions, and so that changes in lysosomal function must affect α -Syn levels (Martinez-Vicente, M., Talloczy, Z., Kaushik, S., Massey, A.C., Mazzulli, J., Mosharov, E.V., et al., 2008). Similarly, α -Syn aggregates may impair autophagy-lysosome pathway function and establish interrelationships (Xilouri, M., Brekk, O.R. & Stefanis, L., 2013a).

3. Potential Mechanism by Which Manipulation Affects P D

3.1 Promoting Neurotrophic Factor Production

Massage for improving symptoms in PD patients may benefit from its increased production of growth factors that affect synaptic plasticity. Studies have found that (Wen Z, Zeng W, Dai J, et al., 2012), Paraspinal fascial massage for neonatal rats for 15 consecutive days significantly increased insulin-like growth factor 1 (IGF-1) expression and cell proliferation in the lateral ventricular and hippocampal dentate gyrus, suggesting that paravertebral fascial massage could promote brain development in neonatal rats by upregulating the I GF-1 pathway. Similarly, I GF-1 was also significantly increased in the blood of the infants after massage treatment. It has been proved that (Russo VC, Gluckman PD, Feldman EL & Werther GA., 2005; Fernandez AM & Torres-Alemán I., 2012) I GF-1 receptors are highly dense in the black matter of the brain, which are protective against black matter dopaminergic neurons, and I GF-1 levels are dependent on increased dopaminergic neurons and black matter neuron cells. Furthermore, a study of the relationship between maternal behavior and hippocampal development showed (Liu D, Diorio J, Day JC, Francis DD & Meaney MJ., 2000) touch stimulation provided in female mice can increase brain-derived neurotrophic factor (BDNF) mRNA expression, enhance spatial learning and memory capacity, and increase cholinergic innervation and hippocampal synapse plasticity. And a growing number of studies show that the (Mercado NM, Collier TJ, Sortwell CE & Steece-Collier K., 2017) BDNF is closely associated with pathological changes in substantia of PD patients, and B DNF not only protects dopaminergic neurons from neurotoxin damage, but also promotes maturation and functional expression of these neurons. Based on the underlying relationship between I GF-1 and B DNF and the development of PD, the mechanism of massage to improve Parkinson's symptoms may be related to promote the production of neurotrophic factors, but further studies are also needed to test this hypothesis.

3.2 Adjust the Hypothalamic-Pituitary-Adrenal Axis (Soares, N.M., Pereira, G.M., Altmann, V. et al., 2019)

Patients with Parkinson's disease have a dysregulation of the hypothalamic-pituitary-adrenal axis (H PA), and this dysregulation may be closely related to the development and development of the disease. Higher cortisol level in P D patients is the result of H PA axis dysregulation, and cortisol can inhibit BDNF expression in the rat hippocampus. A study including 25 people found that the No (Wu JJ, Cui Y, Yang YS, et al., 2014) after 4 weeks of massage treatment, control cortisol levels were significantly reduced, but the effect was shorter and plasma B

DNF was significantly increased; this finding was also associated with Tornhage (Törnhage, CJ., Skogar, Ö., Borg, A.et al., 2013). The results are consistent. Another study of the effects of scalp massage on stress hormones, blood pressure and heart rate in healthy women also found (Kim IH, Kim TY & Ko YW., 2016), scalp site massage reduces the levels of norepinephrine and cortisol, as well as blood pressure in healthy women. In addition, the Field T (Field T., 2016) it was also found that moderate massage stress subsequently reduced cortisol levels by enhancing vagal activity.

3.3 Affects Dopamine, Serotonin and Substance P

Increasing evidence affecting dopamine, serotonin, and substance P suggests that the evolution of non-motor symptoms of PD may stem from the disruption of both the dopaminergic and non-dopaminergic systems, and from the involvement of different structures outside of the nigrostriatal system. In addition to dopamine, the noradrenergic system of the locus coeruleus, the serotonergic system of the dorsal raphe nucleus, and the cholinergic system of the Meynert basal nucleus have been suggested to be involved in the pathogenesis of PD (Qamar, M.A., Sauerbier, A., Politis, M., Carr, H., Loehrer, P. & Chaudhuri, K.R., 2017). While substance P, widely found in substantia black a, can aggravate the degeneration loss of dopaminergic neurons through neurokinin-1 receptor-independent activation of N ADPH oxidase in microglia (Wang Q, Chu CH, Qian L, et al., 2014). A study showed that (Field T, Diego M, Cullen C, et al., 2002), massage reduces substance P levels in fibromyalgia patients and increases sleep duration when compared to some simple relaxation. In addition, some studies have been found (Field T, Hernandez-Reif M, Diego M, Schanberg S & Kuhn C., 2005) massage therapy can not only effectively reduce cortisol levels, but also increase serotonin and dopamine levels. This finding also fits with Hernandez, who found that long-term massage improves anxiety and depression mood in breast cancer patients and also increased urinary dopamine, serotonin, N K cells, and lymphocytes.

3.4 Immunomodulation

In recent years, increasing studies have suggested that neurological inflammation may be involved in P D progression, and Watson et al have first demonstrated the existence of early and persistent microglia-mediated congenital inflammation prior to the damage of the nigrostriatum. In addition, they also observed the spread of inflammation from the striatum to substantinoigra. This study suggests that early inflammation may be key to causing progressive pathological changes in the nigrostriatum in PD, although the initiating factors that trigger the inflammatory response remain difficult to define. A retrospective study showed that the study No (Jiang, S., Gao, H., Luo, Q.et al., 2017) the decreased number of C D3 +, C D4 + lymphocyte subsets and increased number of natural killer cells, the CD8 + lymphocyte subsets decreased in PD, and the higher the H-Y score, the fewer C D3 +, C D4 + and CD8 + lymphocytes. Therefore, it can be speculated that when microglia-mediated chronic neuroinflammation occurs, C D3 +, C D4 + and CD8 + T lymphocyte subsets may be affected by the neuroendocrine immunomodulation network of the central nervous system, and with the course of PD, the effect of inhibition becomes more obvious; while the increase of N K cells may be mediated by the A DCC effect of K cells. A study of 29 homosexual patients (20 H IV +, 9 H IV- -) treated with a one-month massage was found that the study (Ironson G, Field T, Scafifidi F, et al., 1996), after massage therapy, patients showed decreased cortisol and a significant increase in C D8 + lymphocytes and NK cells. In parallel, Green et al (Green VL, Alexandropoulou A, Walker MB, et al., 2010), it was also found that massage could change the patient's immune balance in a potential way. Thus, massage may ameliorate parkinsonian symptoms by influencing the immune changes mediated by the NK and T cell subsets as another potential mechanism.

Summarize the traditional Chinese medicine massage therapy as a common medical treatment in the process of P D treatment, not only for PD patients' movement symptoms have obvious improvement, and for non-sports symptoms, such as sleep disorders, pain, anxiety, depression and constipation can also be improved by different massage techniques, in general, most massage therapy can continue to improve the quality of life of P D patients. However, the current research on massage treatment for Parkinson's disease is very limited, which may be related to the inherent difficulty of assessing the efficacy of massage treatment. Although the possible potential mechanism of action is discussed, further research is still needed to confirm these results. The efficacy of massage treatment is relatively mild, and since there are no serious side effects, we also encourage clinical practice to combine massage and massage treatment with traditional standard treatment while developing personalized programs for P D patients.

Fund Project

National Natural Science Foundation of China (Project No. 81873388).

References

Chen Shengdi, Chen Haibo, (2020). Chinese Guidelines for the Treatment of Parkinson's Disease (Fourth edition). *Chinese Neurology Journal*, (12), 973-986.

Wang Y, Xie CL, Wang WW, et al. (2013, August). Epidemiology of complementary and alternative medicine use in patients with Parkinson's disease. *Journal of Clinical Neuroscience: Official Journal of the Neurosurgical Society of Australasia, 20*(8), 1062-1067.

Hernandez-Reif M, Field T, Largie S, et al. (2002). Parkinson's disease symptoms are differentially affected by massage therapy vs. progressive muscle relaxation: a pilot study. *J Bodyw Mov Ther., 6*, 177–182.

Donoyama N, Ohkoshi N. (2012). Effects of traditional Japanese massage therapy on various symptoms in patients with Parkinson's disease: A case-series study. *J Altern Complement Med*, 18, 294-299.

Juntakarn C, Prasartritha T, Petrakard P. (2017). The effectiveness of thai massage and joint mobilization. *Int J Ther Massage Bodywork, 10*, 3-8.

More SV, Kumar H, Kim IS, et al. (2013). Cellular and molecular mediators of neuroinflammation in the pathogenesis of Parkinson's disease. *Mediators Inflamm*, *23*(8), 952-958.

Tansey MG, Goldberg MS. (2010). Neuroinflammation in Parkinson's disease: Its role in neuronal death and implications for therapeutic intervention. *Neurobiol Dis, 37*(3), 510-518.

Yan J, Fu Q, Cheng L, et al. (2014). Inflammatory response in Parkinson's disease. *Mol Med Rep, 10*, 2223-2233.

Richardson JR, Hossain MM. (2013). Microglial ion channels as potential targets for neuroprotection in Parkinson's disease. *Neural Plast, 2013*, 587418.

R. H. Haas, F. Nasirian, K. Nakano, D. Ward, M. Pay, R. Hill, C. W. Shults, (1995). Low platelet mitochondrial complex I and complex I/II activity in early untreated Parkinson's disease, *Ann. Neurol., 37*, 714-722.

W. D. Parker Jr., J. K. Parks, R. H. Swerdlow, (2008). Complex I deficiency in Parkinson's disease frontal cortex, *Brain Res.,1189*(1) 215-218.

A. W. Linnane, S. Marzuki, T. Ozawa, M. Tanaka, (1989). Mitochondrial DNA, mutations as an important contributor to ageing and degenerative diseases, *Lancet, 1*(8639), 642 -645.

Litim N, Morissette M, Di Paolo T. (2017). Effects of progesterone administered after MPTP on dopaminergic neurons of male mice. *Neuropharmacology, 117*, 209-218.

Lashuel, H. A., Overk, C. R., Oueslati, A., Masliah, E. (2013). The many faces of α-synuclein: From structure and toxicity to therapeutic target. *Nat. Rev. Neurosci. 14*(1), 38-48.

Deleersnijder, A., Gerard, M., Debyser, Z., Baekelandt, V. (2013). The remarkable conformational plasticity of alpha-synuclein: Blessing or curse? *Trends Mol. Med., 19*(6), 368-377.

Ma J, Gao J, Wang J, et al. (2019). Prion-like mechanisms in Parkinson's disease. *Frontiers in Neuroscience, 13*, 552.

Tran, H. T. et al. (2014). α Synuclein immunotherapy blocks uptake and templated propagation of misfolded α-synuclein and neurodegeneration. *Cell Rep., 7*, 2054-2065.

Besong-Agbo, D.et al. (2013). Naturally occurring α-synuclein autoantibody levels are lower in patients with Parkinson disease. *Neurology, 80*, 169-175.

Xuan Q. et al. (2011). Increase expression of a-synuclein in aged human brain associated with neuromelanin accumulation. *J. Neural. Transm., 118*, 1575-1583.

Olanow, C.W., Savolainen, M., Chu, Y., Halliday, G.M., Kordower, J. H. (2019). Temporal evolution of microglia and α-synuclein accumulation following foetal grafting in Parkinson's disease. *Brain: A J. Neurol, 142*(6), 1690-1700.

Martinez-Vicente, M., Talloczy, Z., Kaushik, S., Massey, A.C., Mazzulli, J., Mosharov, E.V., et al. (2008). Dopamine-modified α-synuclein blocks chaperone-mediated autophagy. *J. Clin. Invest., 118*(2), 777-788.

Xilouri, M., Brekk, O.R., Stefanis, L. (2013a). α-Synuclein and protein degradation systems: a reciprocal relationship. *Mol. Neurobiol., 47*(2), 537–551.

Qamar, M.A., Sauerbier, A., Politis, M., Carr, H., Loehrer, P., Chaudhuri, K.R. (2017). Presynaptic dopaminergic terminal imaging & non-motor symptoms assessment of Parkinson's disease: Evidence for dopaminergic basis? *Parkinson's Dis., 3*, 5.

Wen Z, Zeng W, Dai J, et al. (2012, May). Paravertebral fascial massage promotes brain development of neonatal rats via the insulin-like growth factor 1 pathway. *Neural Regeneration Research, 7*(15), 1185-1191.

Russo VC, Gluckman PD, Feldman EL, Werther GA. (2005). The insulin-like growth factor system and its

pleiotropic functions in brain. *Endocr Rev. United States, 26*, 916-943.

Fernandez AM, Torres-Alemán I. (2012). The many faces of insulin-like peptide signalling in the brain. *Nat Rev Neurosci., 13*, 225-239, Nature Publishing Group.

Liu D, Diorio J, Day JC, Francis DD, Meaney MJ. (2000, August). Maternal care, hippocampal synaptogenesis and cognitive development in rats. *Nature Neuroscience, 3*(8), 799-806.

Mercado NM, Collier TJ, Sortwell CE, Steece-Collier K. (2017). BDNF in the Aged Brain: Translational Implications for Parkinson's Disease. *Austin Neurology & Neurosciences, 2*(2).

Soares, N.M., Pereira, G.M., Altmann, V.et al. (2019). Cortisol levels, motor, cognitive and behavioral symptoms in Parkinson's disease: a systematic review. *J Neural Transm, 126*, 219-232.

Wu JJ, Cui Y, Yang YS, et al. (2014). Modulatory effects of aromatherapy massage intervention on electroencephalogram, psychological assessments, salivary cortisol and plasma brain-derived neurotrophic factor. *Complement Ther Med, 2*, 456-462.

Törnhage, CJ., Skogar, Ö., Borg, A.et al. (2013). Short and long-term effects of tactile massage on salivary cortisol concentrations in Parkinson's disease: a randomised controlled pilot study. *BMC Complement Altern Med, 13*, 357.

Kim IH, Kim TY, Ko YW. (2016). The effect of a scalp massage on stress hormone, blood pressure, and heart rate of healthy female. *J Phys Ther Sci., 8*, 2703-2707.

Field T. (2016). Massage therapy research review. *Complement Ther Clin Pract., 24*, 19-31.

Wang Q, Chu CH, Qian L, et al. (2014, September). Substance P exacerbates dopaminergic neurodegeneration through neurokinin-1 receptor-independent activation of microglial NADPH oxidase. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 34*(37), 12490-12503.

Field T, Diego M, Cullen C, et al. (2002). Fibromyalgia pain and substance P decrease and sleep improves after massage therapy. *J Clin Rheumatol, 8*, 72-76.

Field T, Hernandez-Reif M, Diego M, Schanberg S, Kuhn C. (2005). Cortisol decreases and serotonin and dopamine increase following massage therapy. *Int J Neurosci., 115*, 1397-1413.

Jiang, S., Gao, H., Luo, Q.et al. (2017). The correlation of lymphocyte subsets, natural killer cell, and Parkinson's disease: a meta-analysis. *Neurol Sci., 38*, 1373-1380.

Ironson G, Field T, Scafifidi F, et al. (1996). Massage therapy is associated with enhancement of the immune system's cytotoxic capacity. *Int J Neurosci., 84*, 205-217.

Green VL, Alexandropoulou A, Walker MB, et al. (2010). Alterations in the Th1/Th2 balance in breast cancer patients using reflexology and scalp massage. *Exp Ther Med, 1*, 97-108.