The anti-stress ability of Morinda Officialis extracts in mice

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Abstract: **Purpose**: To explore the abilities of Morinda officinalis of oligosaccharides (MW-97) to endure under stress in mice. **Methods**: 40 SD male mice were subjected to various stressors on a daily basis over 15-day period and the image system was used to observe the spontaneous motor activity. Meanwhile, we got the pathogenic section of adrenal glands and the WBC counts and the relative percentage in peripheral blood. Moreover, the serum levels of stress hormones were detected by radioimmunoassay. **Results:** Chronic stress results in diffuse hyperplasia of the adrenal cortex and atrophy of the adrenal medulla in mice, which suggested that stress-adaption failure of the adrenal gland occurred, while adrenal gland of the mice with MW-97(100 mg/kg, ip) prior to each stressor for 15 days did not result in any pathologic changes. Moreover, chronic stress also significantly reduced WBC counts and relative WBC percentages in the peripheral blood, including the percent of lymphocytes, monocytes and neutrophils. Furthermore, MW-97 (25 and 100 mg/kg) may reverse the above changes and raise WBC counts, along with the relative WBC percentages significantly. In the meanwhile, we found that the serum testosterone decreased and corticosterone increase apparently in chronically stressed SD mice. However, MW-97 should also significantly decline the serum corticosterone level and raise the concentration of serum testosterone level. At the same time, we found that MW-97 had no effects on the spontaneous motor activity in the stressed mice. **Conclusion**: We strongly suggested that MW-97 may enhance the immunity antistress ability under chronic stress. However, it had no any excitatory or inhibitory effects on the CNS. Therefore, oligosaccharide from Morinda officinalis could be used for an anti-stress drug which is safe for human.

[Cheng-Hui Lin, Yu-Hsiang Kuan, Chi-Ting Horng. **The anti-stress ability of Morinda Officialis extracts in mice.** *Nat Sci* 2018;16(1):101-109]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 12. doi:10.7537/marsnsj160118.12.

Keyword: Morinda officinalis, anti-stress ability

Introduction

Morinda officinalis How (family Rubiaceae) is a plant extensively used as a Yang-tonic agent for about 2000 years in ancient China. This medical plant grows in humid areas of southeast China, Korea, and Japan. It is common used in Chinese medicine to nourish “Kidney-Yang” and strength the “bone and muscle” indicated for impotence, emission, enuresis, infertility, and treat cold and Dampness syndrome such as rheumatism, pain, and fatigue〔1〕. Recently, the root of Morinda officinalis was further effectively to treat the patients with depression, short and long memory loss, osteoporosis, spermatorrhea, varicocele, Alzheimer’s diseases, irregular menstruation, menstrual disorders, diabetes mellitus (DM), rheumatoid arthritis (RA), post-traumatic stress disorder (PTSD) and even male fertility in clinic 〔2,3,4,5,6,7,8,9,10,11,12,13,14,21,22,23,58〕. Moreover, the various extracts of Morinda officinalis also has several physiological abilities, for example, cyto-protective effects, anti-conceptive and anti-inflammatory functions, anti-oxidant properties, and anti-fatigue abilities〔15,16,17,18,19,20,24,25〕.

In some previous studies, Morinda officinalis extracts were found to own the inulin-type oligosaccharides (MW-97) which could treat the patients with depression. To our knowledge, depression is one of the most prevalent and debilitating disorders worldwide that cause high social and economic burden. Currently available anti-depressants have undesirable side effects and therefore, the extract of Morinda officinalis was considered as the popular Chinese herbs for the treatment of depression which also belongs to a type of environmental factor. Furthmore, MW-97 was the mixture of several inulin-type oligosaccharides of Morinda officinalis which was the effective component. It is well known that the key character of the depression or chronic stress was hyperaction of the hypothalamo-pituitary-adrenal (HPA) axis and the main serum glucocorticoids-corticosterone (Cort) is persistently elevated, and then the neuroendocrine

immunomodulating network would be in disorders, which may be expressed with defection, sexual function, and immunity as well as learning and memory, depression, and dementia, etc.

As the key effector of the HPA axis, the compensative pathologic changes of the adrenal glands would also happen. In this study, the chronic stress models in SD mice were established at first and we wanted to know and realize the exact of anti-stress ability of MW-97 from Morinda officinalis extract.

Material and Methods

Materials:

40 male Sprague-Dawley (SD) mice (the mean body weight: 170 ± 20 g) were introduced from the Taipei Animal Laboratory Center last year. They were housed in a temperature and light controlled room. The mice had free access to water and food pellets. The laboratory condition is 22 ± 2°C; 12 hours light / 12 hours dark cycle (light on at 08:00). Besides, the humidity is 40-60%. The Bajitian oligosaccharides extract (MW-97, yellow powder, purity beyond 90%) was from Botanical Chemistry of Institute of Pharmacology and Toxicology, Academy of Military Medical Science (Beijing, China). In the meantime, the concentration of despiramine (DIM) which is a type of tricyclic anti-depressant was from Sigma-Aldrich Company (Bornem, Belgium). The classic three kinds of anti-depressants all benefit for depression for several year〔26〕. Moreover, corticosterone radioimmunossay ELISA kit was from Cayman Co. (Canada). In general, the levels of corticosterone are a glucocorticoid produced by adrenal cortex in response to ACTH (corticotropic hormone) and are the precursor to aldosterone. Hence, the production of the glucorcorticoids is increased under various stress; therefore, the amount of the corticosterone can be used as the biomarker of stress〔27〕. Moreover, we gained testosterone radioimmunossay ELISA kit from Abnova Co. (USA). In clinic, the levels of testosterone are one of the most important androgens secreted into the bloodstream and synthesized from pregnenolone which is itself formed from cholesterol.

In fact, testosterone is the main androgen secreted by the Leydig cells of the testes and effects both primary and secondary sexual development such as muscle mass and sex drive. Besides, in adult humans, the testosterone will circulate in plasma predominately bound to proteins produced by Sertoli cells, including specific sex hormones binding globulins and nonspecific proteins such as the albumin. In the meantime, testosterone is needed for maintenance of the spermatogenic process and inhibition of germ cells. If complete inhibition of intra-testicular testosterone occurred, this condition may lead to complete failure of spermatogenesis. Therefore, in our study, we checked the changes of the concentrations of testosterone and coticosterone for further evaluation and intervention. At first, all the mice were acclimated to handing and allowed to adapt for a minimum of 7 days before starting the series of experiments. In medical field, there are three main kinds of classic anti-depressants in clinical practice including tricyclic anti-depressants (such as desipramine), selective reiptake inhibitors (SSRIs) (such as fluoxetine) and the monoamine inhibitors (MAOIs) (such as moclobemide). In this study, we selected the desipramine (DIM) to treat the mice under chronic stress for the purpose of being a positive control group. Then, we will compare the therapeutic effects from DIM and various doses of Monrinda officinalis extracts and the negative control group. In clinic, we observed a part of patients with depression and took the three type of anti-depression agents which own their therapeutic actions on depression; however, the associated various side effects were reported. Therefore, we try to find out other new drugs for patients' safety. So, in this experiment, we would exanimate the Monrinda officinalis extract if it was benefit for the patients with depression or chronic stress.

All 40 SD rats were randomly divided into 5 groups (8 mice in each group) according to their body weights as normal control (group 1), chronic stress control (group 2), drug treatment (group 3, 4 and 5) (DIM 15mg/kg, MW97 25 and 100 mg/kg, ip) respectively. Drugs were injected daily 30 min before each stressor and the control groups (group 1 and 2) received only water injected daily. All the experiments were performed at Medical Laboratory Center in National defense Medical Center (Taipei, Taiwan, ROC).

Chronic stress procedure in mice:

According to Li and Roth's study〔28,30〕, we modified some programs of the chronic stress regimen. Stressors were administered once per day over a period of 15 days between 8:00 am to 11:00 am. The exact order of stressors was recorded between 9:00 am to 11:00 am. The actual order of various stressors was detailed in Table 1. The spontaneous motor activity of the mice was detected between 9:00 am to 11:00 am. and the tail vein blood sample 20μL was collected between 2:00 pm to 4:00 pm on the 16th day, using the live blood cell analysis apparatus (Sysmes Co, Japan), the white blood cells (WBC) was proceeded. On 17th day, after sacrifice a trunk blood sample was collected and allowed to clot at room temperature. Furthermore, we removed the adrenal glands from all SD mice. The blood was centrifuged at 130 x *g* for 10 min, and the supernatant was removed and stored at - 20°C until radioimmunoassay of testosterone was performed.

The adrenal gland was put in 10% formalin solution for fixation and pathologic section was prepared carefully with regular method including dehydration, transparency, embedment, slicing, and H & E stain. Finally, the pathologic changes were observed and taken picture with microscopy. Besides, some serum sample from mice was prepared and stored at - 20°C for radioimmunoassay of corticosterone. In other articles, the anti-stress or anti-fatigue function was measured by using the tested animals under forced swimming test (FST) or treadmill exercise of running which is the similar as our design for testing the maximal endurance of the exercised animals〔39,40〕.

Table 1. Chronic stress regime of mice

Day	Treatment	Duration
1.	Cold swimming (12°C)	6 min
2.	Food deprivation	24 h.
3.	Food shock (1mA, 1 sec duration, average I shock/min)	30 min
4.	Over hang (2-3cm apart from surface of water)	30 min
5.	Water deprivation	24 h.
6.	Tail pinch (1cm apart from the end of the tail	1 min
7.	Overhang	1 h.
8.	Food shock	45 min
9.	Cold swimming	6 min
10.	Water deprivation	24h
11.	Overhang	1.5 h
12.	Food deprivation	24 h
13.	Tail pinch	2 min
14.	Food shock	1 h
15.	Cole swimming	6 min

Spontaneous motor activity

Thirty minutes after drug injections, stressed mice were plunged individually into an open field (40cm x 30cm x 20cm) fitted with a black rubber floor. 4 mice were always performed in one period. The Video scene was shown by computer display unit and image pattern analytic instrument (Columbus Co, USA) was operated and controlled by the computer. After the subjects were placed in the open filed, allowed to habituate to the environment for 10 min, subsequently the Video system would automatically display and record their spontaneous movement in later 10 min. We would record four parameters included travelling distance, ambulatory time, resting time and average speed,

Statistics

All the experimental values are presented in means ± standard deviation (SD). Each group of SD mice is compared with one-way ANOVA internally. Then we used the Duncan method to compare significance between every group. If the difference were apparently, the *p* value may be defined as lower 0.05 ($P < 0.05$).

Results

1. Pathologic change of adrenal gland in stressed mice

We found that the pathologic section of adrenal glands in normal control mice showed normal configuration. In chronically stressed mice, it was shown that cortex of the adrenal gland was diffuse hyperplasia and the medulla was atrophic which may be caused by excessive secretion of corticosterone in cortex and depletion of adrenalin vesicles in medulla. It is interesting to be found that while adrenal glands of stressed mice treated with DIM 15 mg/kg was improved apparently, even returned to normal condition. However, the adrenal glands of mice treated with MW-97 100 mg did not display any pathologic changes. Therefore, we proposed that the usage of DIM and MW-97 had the ability to fight with the overwhelming stress without dangerous concern.

2. The WBC counts in stressed mice

One of the characters of stress or depression was immunity detection which was mediated by higher blood level of corticosterone. In our studies, we demonstrated that the counts of total WBC, lymphocytes, monocytes, and neutrophils were all decreased significantly. However, MW-97 at the dose of 25 and 100 mg/kg should improved immunosuppressive states induced by corticosterone (Table 2). Hence, all these results supported that MW-97 had stronger anti-stress effect.

3. Modulation of MW-97 on serum testosterone and corticosterone in stressed mice

Compared with the normal group, the weight of testicle of chronically stressed mice showed decreased tendency, but there was no remarkable difference. Besides, we found that serum level of testosterone in stressed mice decreased. At the same time, treatment of MW-97 at the doses of 25 and 100 mg/kg may

enhance the increase of corticosterone (Table 3) and decrease of corticosterone in chronically stressed mice (Table 4). Several studies had ever reported that Morinda officinalis extract have been shown to reduce immobility in the forced swimming test and enhance the anti-stress abilities which is the similar to ours 〔54,55〕.

Table 2. Effect of MW-97 on WBC counts in stressed mice.

Groups	Dose	Total WBC	Lymphocytes	Monocytes	Neutrophils
Normal	—	7.4 ± 0.5	6.2 ± 0.8	0.30 ± 0.11	1.6 ± 0.3
Stress	—	5.1 ± 1.1^{c}	3.8 ± 1.8^{c}	0.17 ± 0.10^{a}	1.0 ± 0.4^{a}
DIM	15	7.0 ± 2.5^{b}	5.7 ± 2.5^{b}	0.32 ± 0.11^{b}	1.4 ± 0.4
MW-97	100	7.9 ± 2.0^{b}	5.9 ± 0.8^{b}	0.28 ± 0.17^{b}	1.9 ± 0.3^{b}
	25	7.2 ± 1.9^{b}	5.2 ± 0.8^{b}	0.20 ± 0.11	1.9 ± 0.3^{b}

The unit of dose is /mg*kg^{-1} The unit of WBC is x 10^{-9}/L^{-1}

1. 8 SD mice were enrolled in each group 2. $P^{a} < 0.05$ vs stress control 3. $P^{b} < 0.05$, $P^{c} < 0.01$ vs normal control.

Table 3. Modulation of MW-97 on serum testosterone concentration in stressed mice

Groups	Dose	Testosterone
Normal	—	295 ± 78
Stress	—	42 ± 78^{a}
DIM	15	278 ± 49^{b}
MW-97	100	193 ± 48^{b}
	25	354 ± 68^{c}

The unit of dose is /mg*kg^{-1} The unit of testosterone is /ng*L^{-1}

1. 8 SD mice were enrolled in each group 2. $P^{a} < 0.05$ vs stress control 3. $P^{b} < 0.05$, $P^{c} < 0.01$ vs normal control.

4. Spontaneous motor activity in stressed mice

In our design, the spontaneous activities of mice included walking, scratching, washing face, licking, and smelling, etc. However, all types of the parameters of activities between stressed and normal mice were no significant difference. Moreover, the travelling distance, ambulatory time, and average speed of the stressed mice were all shorted and the resting time was prolonged after the DIM treatment. Therefore, we concluded that DIM had a sedative effect in stressed mice. In addition, the spontaneous motor activities of the mice did not show any apparent change in our experiment. Therefore, we further persisted on that MW-97 did not own the excitatory or sedative functions (Table 5).

Table 4 Table 3 Modulation of MW-97 on serum corticosterone concentration in stressed mice

Groups	Dose	Corticosterone
Normal	—	60 ± 23
Stress	—	200 ± 45^{b}
MW-97	100	130 ± 33^{a}
	25	120 ± 45^{a}

The unit of dose is /mg*kg^{-1} The unit of corticosterone is /μg*L^{-1}

1. 8 SD mice were enrolled in each group 2. $P^{a} < 0.0$ 1 vs stress control 3. $P^{b} < 0.01$ vs normal control.

Table 5. Effect of MW-97 on spontaneous movement in stressed mice

Groups	Dose	Distance	Ambulatory time	Resting time	Speed
Normal	—	1735 ± 125	352 ± 22	245 ± 52	5.5 ± 1.5
Stress	—	1685 ± 225	366 ± 101	239 ± 47	4.9 ± 1.2
DIM	15	1122 ± 322^{a}	263 ± 52^{a}	300 ± 29^{a}	3.4 ± 1.5^{a}
MW-97	100	1599 ± 212	344 ± 84	255 ± 69	4.8 ± 2.9
	25	1543 ± 111	346 ± 55	248 ± 46	4.9 ± 3.8

The unit of dose is /mg*kg^{-1}, The unit of distance is cm The unit of ambulatory time is /sec^{1}, The unit of resting time is /sec The unit of speed is /cm*Sec^{-1}

1. 8 SD mice were enrolled in each group 2. $P^{a} < 0.0$ 1 vs stress control

Discussion

Morinda officinalis How (Bajitian), a traditional tonic herbal medicine, has been used as natural nutrient and healthy food, and ingredients (enhancing the sexual function) in Chinese medicine for thousands years. Besides, the medical plant should nourish the kidneys, strengthen the tendons and bones, and relieve rheumatism. Furthermore, studies showed that Morinda officinalis roots can promote bone formation, inhibition bone reabsorbing in vivo, and may exert certain favourable effects on preventing and treating bone loss- -related diseases. In the meanwhile, it is considered as the drug which could decrease sperm deformity rate, promote the growth of the testis and increase the production of sperm from the testis 〔45,46〕. Moreover, Morinda officinalis is mostly cultivated in Guangdong and Fujian provinces in China〔15〕. The root of Morinda officinalis is cylinder-shaped (with round circumference of the section) and slightly curved. Moreover, the surface is yellowish-grey or dark grey. It is used to support the entire body treating a wide range of symptoms including patients with poor digestion, high blood pressure (hypertension), respiratory problems, and immune deficiencies in China since ancient times. Until now, more and more studies showed that total polysaccharides or crude polysaccharides from the medical root of Morinda officinalis had multifarious biological activity for many diseases, including anti-mite ability, protective effect on bone loss, relieving constipation, atherosclerosis, age-induced bone degeneration, anti-fatigue, antioxidant, hypoglycemic and immunomodulation agents. Therefore, Ren Jie indicated that Morinda officinalis had significantly higher immunity-stimulating activity which is good for anti-stress conditions 〔29,50〕.

Chronically stressed condition may simulate the symptoms of depression, for instance, chronic stress could induce the atrophy of hippocampus and denaturation of neurons in CA3 pyramidal neurons 〔31,32〕. Moreover, it is reported that hippocampal volume is decreased in patients suffering from depression or post-traumatic stress disorder (PTSD) compared to the healthy control group, which may be caused by the hyper-action of hypothalamic-pituitary-adrenal (HPA) axis and, thereby the higher blood concentration of glucocorticoid (GCs)〔33〕. Hyperaction of HPA axis in major depressive patients has been well demonstrated and anti-glucocorticoid therapies in major depression and associated various stress are very satisfying, indicating the CGs play a key role in the occurrence of depression and its associated stress 〔31,32,33〕. Therefore, in rat brain, the region with the richest GCs receptors is hippocampus, where is also a major site for emotional processes. Hales et al also reported that stressed-induced HPA axis hyperaction would inhibit the activity of hypothalamus-pituitary-gonad (HPG) axis. The level of corticosterone could decrease synthesis from testicles〔36〕. Bingama and his co-workers further reported that testosterone could also inhibit the release of corticotropion-releasing factor from the hypothalamus and the activity of HPA axis 〔37〕. Therefore, the relationship between corticosterone and testosterone was reversing cascade〔38〕. The elevation of serum testosterone after treatment with MW-97 may be one of the important basis for improving of the immune activity.

Moreover, this study provided further evidence of the antagonism of WM-97 on chronic stress. The HPA axis of WM-97 on chronically stressed mice was hyperactive and the corticosterone secreted from cortex of adrenal gland was excessive, naturally, the cortex was hyper-plastic and plump compensationally. On the contrary, a high concentration of corticosterone could induce medulla pheochromcytes to release catecholamine exhaustively, ultimately, the medulla became atrophic. In fact, the hyperplasia of cortex and atrophy of medulla were all compensational pathological changes induced by stress and they were related with each other, which represented the synergetic the synergetic effect between HPA axis and sympathetic adrenal medulla system. Treatment with MW-97 made these two systems balanced and protected adrenal gland from the pathologic change, this evidence further supported with MW-97's anti-stress and anti-depressant effects.

In many research, the depressive disorder may be closely related to the excessive /long-lasting plasma CG-induced lesion in hippocampus. In addition, chronic stress may also induce the lesion or apoptosis of lymphocytes and neutrophils in mice and the series of changes were mediated by a higher concentration of serum corticosterone induced by stress〔34,35〕. In our study.

Chronic stressed situation would induce the increase of serum corticosterone and decrease of immune cell count (WBC) in these mice. We found that MW-97 at the doses of 100 and 25 mg/kg reversed the changes which supported its anti-stress effects. In other studies, the repeated administration of Morinda officinalis extract at three doses levels (150, 600, and 2400 mg/kg po once per day) for 13 consecutive weeks, the rats of either sex have not shown any apparent toxicological signs. Hence, we firmly suggested that the extract of Morinda officinalis is possibly non-toxic to human which is

also benefit for any types of depression Therefore, it possesses the anti-depressant effect and muscle power reinforcement in clinic〔16〕.

There are some chemical components in Morinda officialis extract including anthraquinone, organic acid, flavones glycosides, iridoids glycosides (such as monotropein and deacetylasperulosidic acid), oligosaccharides, and polysaccharides with carbohydrates constituting about 49.8-58.2% of dry weight 〔52,53〕. The different extracts own various functions. For example, iridoid glycosides are the major bioactive components of Morinda oficinalis could be responsible for the anti-nocieptive and anti-inflammatory effects. Polysaccharides could ameliorate the dextran sulfate sodium-induced colitis in mice by NF-κB inactivation〔56〕. Besides, polysaccharides extract could own anti-fatigue ability, anti-inflammatory function, and antioxidant activity (reverse the accumulation of ROS and MDA) 〔18,25,56,57〕. However, oligosaccharides extract could improve the Alzheimer's disease, male infertility, sexual function, depression, cyto-protective effect and osteoporosis〔6,7,11,13,16,51,56〕. Anthraquinone compounds were associated with bone disorders and treated patients with DM〔59,60〕. Specifically, the benzaldehyde derivate may be used as the anti-mite agent〔52〕.

The main constituents of oligosaccharides of Morinda officialis extracts are inulin-type oligosaccharides (ranging from 40% to 75%) which include nystose, 1F-fructofuranosylnystose, inulin-type hexasaccharide (IHS) and inulin-type heptosaccharide, etc. The quantitative analysis of 7 inulin-type oligosaccharides in Morinda officinalis 〔51〕. In Zhang's study, the anti-depressant activity improved after bioassay directed fraction and that the pharmacological effect of Morinda officinalis extract may be ascribe to inulin-type oligosaccharide〔41〕. Recently, some clinical trial showed that the inulin-type of oligosaccharides from Morinda officinalis would have the anti-depressant activities. For instance, Liang et al. reported that it should improve the symptoms of patients with mild to moderate depression〔42〕and that this product was remarkably safe, devoid of major side effects typical for tricyclic anti-depressant (TCA) (for example, DIM) or for the specific serotonin reuptake inhibitors (SSRI) 〔43,44〕. The generally good tolerability of Morinda officinalis is benefit for the patients and the immunological function seems to be abnormal in some sub-types of depression〔45〕. Unfortunately, the mechanisms by which Morinda officinalis extract produced antidepressant effect still remain unclear. It is well known that three kinds of classic anti-depressants all can protect the primary cultured rat hippocampal neurons from the lesion induced by corticosterone, while antipsychotic drug chlorpromazine or anxiolytic diazepam have no such effect〔46〕. Li et al. suggested that chronic administration of oligosaccharide extracted from Morindo officinalis or DIM for 21 days may upregulate the activity of Gpp (NH)-p stimulated adenylated cyclase on the synaptic membrane of the frontal cortex, hippocampus or hypothalamus in rat study. In the meanwhile, upregulate the nerve growth factor or brain derived neurotropic factor mRNA level in frontal cortex and hippocampus〔47〕. Li and his coworkers also demonstrated that oligosaccharide from Baijitian mixture or nerve growth factor also inhibit the corticosterone-induced lesion in PC12 cells (adrenal gland cells)〔48〕Therefore, many researchers suggested that the expression of neurotrophic factors is an important base for the cyto-protective and anti-depressant of IHS. Indeed, HIS has been demonstrated to increase mineral absorption, improve immune response and prevent from colorectal cancer in clinic〔49〕. Xu and his colleges reported that oligosaccharides of Morinda officinalis exhibited resilience to chronic unpredictable stress, accompanied by the increases in the expression of the brain-derived neurotrophic factor (BDNF), phosphorylated-Ser9-glycogen synthase, kinase-3β, and β-catenin in the medial pre-frontal cortex which could show the anti-stress and anti-depressant activities〔23〕. However, the true mechanisms need further evaluation in the future.

Conclusion

Morinda officinalis oligosaccharides have been detected as the active ingredient and benefit for the human for many diseases in clinic〔22〕. In series of studies, we found that the inulin-type extracted oligosaccharide from tonic traditional medicine Bajitian could enhance significantly the improvement of the stressful condition and did not have excitatory or inhibitory effects on CNS. Furthermore, it had little toxicity and now could be taken orally in treating the associated disorders〔58〕. All of the completed results revealed that Morinda officinalis may be used as an antistress and antidepressants for patients which could enhance physical performance in daily activities.

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12/24/2017