Black ginger (*Kaempferia parviflora*): a review of historical use, pharmacology, preclinical and clinical studies, and safety

By

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Contents

BLACK GINGER BACKGROUND

Research on some nutraceuticals suggests one primary benefit, while others offer multiple benefits due to their unique mechanism(s) of action. Clearly, multiple benefits are preferable from a health and wellness perspective. Black ginger (*Kaempferia parviflora*), also known as "Thai ginseng", is an herbal extract with multiple benefits as described below.

Historical use

Black ginger (*Kaempferia parviflora*), a plant in the Zingiberaceae ginger family, is a traditional herbal medicine of Thailand. It is found in tropical areas such as Malaysia, Sumatra, Borneo Island, and Thailand. Its rhizome has been used as folk medicine for many centuries. Among the Hmong hill tribe, Black ginger is widely believed to reduce perceived effort, improve physical work capacity, and prolong hill trekking.[1] Its rhizomes are used to treat a variety of gastrointestinal disorders, improve blood flow, and as a traditional treatment for inflammatory and allergic disorders. An alcoholic extract of the rhizomes is also used by communities in Northern Thailand to treat inflammation, as a spasmolytic, and to treat gastric ulcers.[2]

PHARMACOLOGY

This is consistent with number of pharmacological studies, in which black ginger has shown the following properties: antiallergenic, anti-inflammatory, antimutagenic, antidepressive, anticholinesterase, antimicrobial, anticancer, anti-peptic ulcer, cardioprotective, anti-obesity activity, and aphrodisiac.[3] Research demonstrates that black ginger polymethoxyflavones offer a range of benefits, including fat reduction[4 5], promoting physical fitness[6 7], and supporting sexual health in men[8 9].

POLYMETHOXYFLAVONES

The primary active constituents of Black ginger are its naturally occurring methoxyflavones, collectively referred to as polymethoxyflavones (PMF). One major methoxyflavone is 5,7-dimethoxyflavone[10], which has been identified as an active component in some human[11] and animal[12] research. In other research[13 14 15], it is the totality of the PMF that has been found to provide specific activity. These PMF included 5,7-dimethoxyflavone, 3,5,7-trimethoxyflavone, 5,7,4'-trimethoxyflavone, 3,5,7,4'-tetramethoxyflavone, 5,7,3',4'-tetramethoxyflavone, and 3,5,7,3',4'-pentamethoxyflavone.

PRECLINICAL RESEARCH

Preclinical research was conducted to examine the impact of black ginger on aging, benign prostate hyperplasia, fat and weight loss, muscle health, neuroprotection, osteoarthritis, physical fitness, and sexual health.

Aging

Skin aging is accompanied by an increase in the number of senescent cells, resulting in various pathological outcomes. These include inflammation, impaired barrier function, and susceptibility to skin disorders such as cancer. Black ginger has been shown to counteract inflammation, cancer, and senescence. This study[16] demonstrates that PMF purified from black ginger rhizomes suppressed cellular senescence, reactive oxygen species, and the senescence-associated secretory phenotype in primary human dermal fibroblasts. In addition, they increased tropocollagen synthesis and alleviated free radical-induced cellular and mitochondrial damage. Moreover, the compounds mitigated chronological aging in a human *ex vivo* skin model by attenuating senescence and restoring expression of essential components of the extracellular matrix, including collagen type I, fibrillin-1, and hyaluronic acid. PMF also enhanced epidermal thickness and epidermal-dermal stability, while blocking age-related inflammation in skin explants. These findings support the use of PMF from black ginger as natural anti-aging agents, highlighting their potential as active ingredients in cosmeceutical and nutraceutical products.

Intrinsic skin aging is a complex biological phenomenon mainly caused by cellular senescence and mitochondrial dysfunction. This study[17] evaluated the inhibitory effect of black ginger ethanol extract (BGE) on hydrogen peroxide-stimulated cellular senescence and mitochondrial dysfunction both *in vitro* and *in vivo*. BGE significantly increased cell growth and suppressed senescence-associated β-galactosidase activation. BGE inhibited the expression of cell-cycle inhibitors (p53, p21, p16, and pRb) and stimulated the expression of cell-cycle activators (E2F1 and E2F2). Hydrogen peroxide-induced hyperactivation of the phosphatidylinositol 3-kinase/protein kinase B (AKT) signaling pathway was suppressed by BGE through regulated expression of forkhead box O3a (FoxO3a; i.e., a transcription factor that regulates a number of cellular processes) and mammalian target of rapamycin (mTOR). BGE attenuated inflammatory mediators (interleukin-6 (IL-6), IL-8, nuclear factor kappa B (NF-κB), and cyclooxygenase-2 (COX-2) and increased the mRNA expression of PGC-1α, ERRα, NRF1, and Tfam, which modulate mitochondrial biogenesis and function. Consequently, reduced ATP levels and increased ROS level were also reversed by BGE treatment. In hairless mice, BGE inhibited wrinkle formation, skin atrophy, and loss of elasticity by increasing the collagen and elastic fibers. The results indicate that BGE prevents intrinsic aging process in hairless mice by inhibiting cellular senescence and mitochondrial dysfunction, suggesting its potential as a natural antiaging agent.

Benign prostate hyperplasia

5α-reductase (5αR) facilitates the conversion of testosterone to dihydrotestosterone (DHT), which is implicated in the development of benign prostate hyperplasia (BPH). In the present study[18], the inhibitory activities of extract from black cohosh rhizome against 5αR was investigated, and the effects of the extract in BPH was also studied using a mouse model. Preparations of extracts from the rhizomes of black ginger, *Curcuma zedoaria* and *Zingiber officinale*, and methoxyflavones isolated from black ginger was used for the 5αR inhibition assay. The BGE was administered to castrated mice for 14 days. Results were that BGE showed more potent inhibitory activity on 5αR than *C. zedoaria* and *Z. officinale* extracts. The active principles were identified as 3,5,7,3',4'-pentamethoxyflavone and 5,7,3',4'-tetramethoxyflavone. Furthermore, BGE suppressed the weights of prostates and seminal vesicles in BPH model rats

by daily administration for 14 days. In conclusion, these results indicate that BGE can be a promising agent for the treatment of BPH.

Fat and weight loss

This this study[19] investigated whether BGE alleviates both obesity in ob/ob mice. Wild-type C57BL/6J and ob/ob mice were provided with a normal diet ad libitum, and ob/ob mice were orally given KPE at a dose of 100 mg/kg/day or 200 mg/kg/day for eight weeks. BGE significantly decreased body weight, fat volume, and fat weight without affecting appetite. It inhibited the expression of adipogenic transcription factors and lipogenic enzymes by upregulating AMP-activated protein kinase (AMPK) in epididymal fat. BGE could be a promising material to alleviate obesity by inhibiting adipogenesis and lipogenesis.

This study[20] investigated the anti-obesity effects of BGE using feeding experiments (low dose: 0.5% BGE, high dose: 1.0% BGE) in mice. For both 0.5% BGE and 1.0% BGE, 7 weeks' feeding of BGE contained in a high-fat diet (HFD) significantly decreased body weight gain, intraabdominal fat accumulation, and plasma triglyceride and leptin levels. Concurrently, BGE administration increased oxygen consumption in mice fed on a HFD. We also found that 1.0% BGE feeding significantly increased the uncoupling protein 1 (UCP1) expression in brown adipose tissue (BAT). Moreover, BGE administration increased urinary noradrenaline secretion levels. These results demonstrate that BGE promotes energy metabolism by activation of BAT, at both doses and up-regulation of UCP1 protein at a high dose. The present study demonstrated that BGE suppresses HFD-induced obesity through increased energy metabolism.

The purpose of this study[21] was to explore the visceral fat reduction mechanism of black ginger (BG) in C57BL/6J male mice. The mice were fed for 8 weeks with test food limited to 3 g/day/mouse. We divided the mice into 4 groups as follows: 1) normal diet group (controls), 2) high fat diet group (HFD), 3) high fat diet + 0.5% BGE group (HFD + BGE 0.5%), and 4) high fat diet + BGE 1.0% group (HFD + BGE 1.0%). At the end of the 8th week, the visceral fat of the mice was collected and weighed and the expression levels of adiponectin, leptin, IL-6, and IL-1β in adipose tissues were measured by RT-PCR. Leptin and IL-6 expressions were decreased with a significant difference between group 4 and group 2. Adiponectin expression was significantly higher in group 4 than in group 2. The present study indicated that the anti-obesity effect of BGE in vivo normalizes the function of leptin by suppressing its resistance upon ingestion of high-fat meals and inhibits fat accumulation by thermogenesis in brown adipocytes.

Muscle

The extracts from black ginger rhizomes contain at least ten methoxyflavone derivatives that exhibit enhancing effects on ATP production and glucose uptake in skeletal muscle cells. The present study[22] investigated the effects of ten black ginger-derived methoxyflavone derivatives (six 5,7-dimethoxyflavone (DMF) derivatives and four 5-hydroxy-7-methoxyflavone (HMF) derivatives) on skeletal muscle hypertrophy. Murine C2C12 myotubes and senescence-accelerated mouse-prone 1 (SAMP1) mice treated with methoxyflavones were used as experimental models to determine the effects of HMF derivatives on myotube diameter and size and muscle mass. The four HMF derivatives, but not the six DMF derivatives, increased myotube diameter. Dietary administration of the mixture composed of the four HMF derivatives resulted in an increase in the soleus muscle size and mass in SAMP1 mice. HMF derivatives also

promoted protein synthesis in myotubes, and treatment with the intracellular Ca2+ chelator BAPTA-AM, which depletes intracellular Ca2+ levels, inhibited this promotion. Furthermore, BAPTA-AM inhibited HMF-promoted protein synthesis even when myotubes were incubated in Ca2+-free medium. These results indicate that HMF derivatives induce myotube hypertrophy and that both the 5-hydroxyl group and the 7-methoxy group in the flavones are necessary for myotube hypertrophy.

This study[23] investigated whether BGE alleviates muscle atrophy using ob/ob mice. Wild-type C57BL/6J and ob/ob mice were provided with a normal diet ad libitum, and ob/ob mice were orally given BGE at a dose of 100 mg/kg/day or 200 mg/kg/day for eight weeks. Results were that BGE markedly increased the muscle fiber size, muscle volume, and muscle mass, resulting in the enhancement of muscle function, such as exercise endurance and grip strength. On the molecular level, it activated the phosphatidylinositol 3 kinase (PI3K)/Akt pathway, a key regulator in protein synthesis in skeletal muscle. BGE could be a promising material to alleviate muscle atrophy.

Neuroprotection

This study[24] investigated whether and how BGE and *Myristica fragrans* volatile oil could influence the levels of neurotransmitters and the whole proteomic profile in the hippocampus of Sprague Dawley (SD) rats. The effects of BGE and *M. fragrans* on protein changes were analyzed by two-dimensional gel electrophoresis (2D-gel), and proteins were identified by liquid chromatography tandem mass spectrometry (LC-MS/MS). The target proteins were then confirmed by Western blot. The levels of neurotransmitters were evaluated by reversed-phase high-performance liquid chromatography (RP-HPLC). The results showed that BGE, *M. fragrans* and fluoxetine (the control drug for this study) increased serotonin, norepinephrine and dopamine in the rat hippocampus compared to that of the vehicle-treated group. Our proteomic data showed that 37 proteins in the black ginger group were up-regulated, while 14 were down-regulated, and 27 proteins in the *M. fragrans* group were up-regulated, while 16 were down-regulated. In the fluoxetine treatment group, we found 29 proteins up-regulated, whereas 14 proteins were down-regulated. In line with the proteomic data, the levels of GFAP, PDIA3, DPYSL2 and p-DPYSL2 were modified in the SD rat groups treated with BGE, *M. fragrans* and fluoxetine as confirmed by Western blot. BGE and *M. fragrans* mediated not only the levels of monoamine neurotransmitters but also the proteomic profiles in the rat hippocampus, thus shedding light on the mechanisms targeting neurodegenerative diseases.

Osteoarthritis

A search was conducted for the effects black ginger and the active components of BGE on osteoarthritis (OA) as well as its mechanism of action. Results from a study of BGE using the monoiodoacetic acid rat OA model revealed that BGE reduced the pain threshold and severity of osteoarthritic cartilage lesions. The mechanism of action and active components were then investigated using IL-1β-treated human knee-derived chondrocytes. BGE, as well as 5,7-dimethoxyflavone and 5,7,4'-trimethoxyflavone, which are key constituents of KPE and highly absorbable into the body, reduced the expression of matrix metalloproteinases (MMPs), which are the main extracellular matrix enzymes that degrade collagen within cartilage. In conclusion, BGE acted to suppress OA and 5,7-dimethoxyflavone and 5,7,4'-trimethoxyflavone were shown to be involved as part of BGE’s mechanism that inhibits MMPs.[25]

Physical fitness

This study[26] evaluated the effects of BGE on physical fitness performance and muscular endurance in mice. Male mice were orally administered BGE for 4 weeks, and then forced swimming test, open-field test, inclined plane test, and wire hanging test were performed. BGE significantly increased the swimming time, motility after swimming, and grip strength. IL-6 and TNF-α mRNA expression levels were decreased in the soleus muscle, whereas peroxisome proliferator-activated receptor γ coactivator (PGC)-1α and glycogen synthase mRNA expression levels, mitochondrial number, and glycogen content were increased. These results were in agreement with those obtained for BGE and PMFs in C2C12. Therefore, the activation of AMPK by PMFs may be one of the mechanisms by which BGE improves physical fitness performance and muscular endurance.

Sexual health

This study[27] aimed to investigate the efficacy of black ginger (BG) on sexual behavior and sperm parameter in streptozotocin (STZ)-induced diabetic male rats. Diabetes was induced in twenty male rats by STZ and divided into four groups: diabetic control group, and 3 treatment groups where BG was dose at 140, 280 and 420 mg/kg orally once a day for 6 weeks. Five normal control rats were treated with vehicle. The body weight, blood glucose, food intake, epididymal sperm parameter, sexual behavior and serum testosterone level was evaluated. The results showed that BG treatment had a significant increase in sperm density in diabetic rats ($p < 0.05$) at highest dose of BG. Furthermore, BG treatment demonstrated a significant recovery of sexual behavior and serum testosterone levels in diabetic rats. These results confirm that BG exhibits aphrodisiac properties that improve the sperm density, testosterone level and sexual performance of STZ-induced diabetic rats.

HUMAN CLINICAL RESEARCH

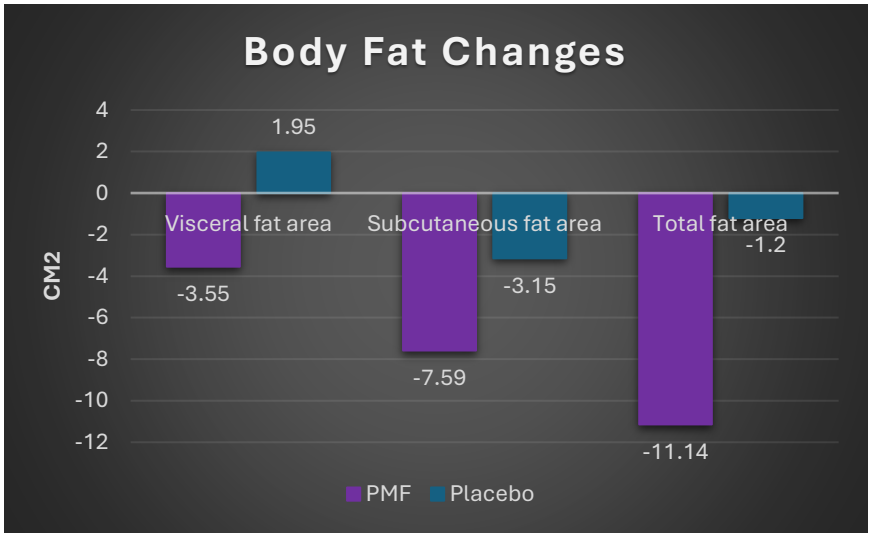
Human clinical trials have been conducted on BGE, examining its impact on body fat/weight loss, physical fitness, and sexual health.

Fat and Weight Loss

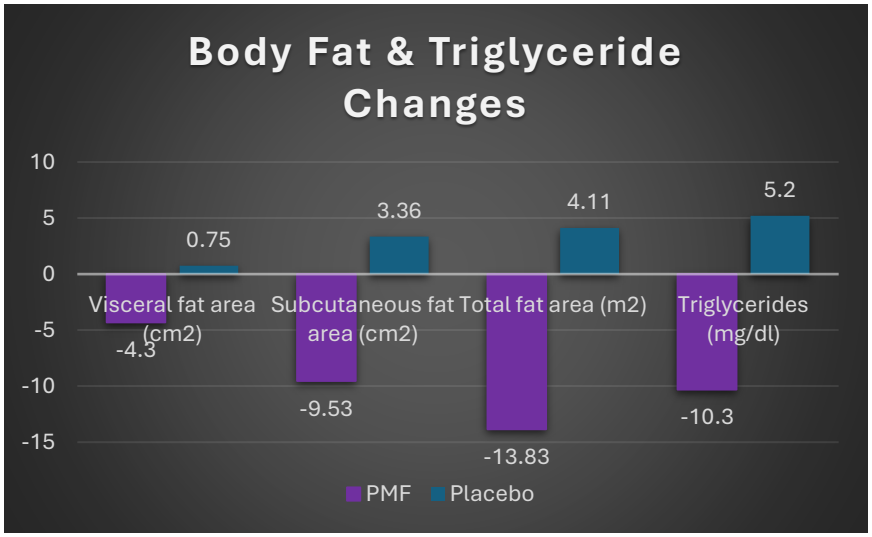
Let's start with a discussion on the mechanism of action. A 7-week, randomized, single-blind, placebo-controlled, crossover study[28] was conducted to examine the acute effects of BGE ingestion on energy expenditure (EE, aka, fat burning) in 20 healthy male subjects (21-29 years) and to analyze its relation to the activity of brown adipose tissue (BAT). Results were that after an oral ingestion BGE (providing 10.48 mg of PMF), EE increased significantly, showing a maximal increase of 229±69 kJ/d at 60 min, while it did not change after placebo ingestion. The results suggest that a single oral ingestion of the BGE can potentially increase EE through the activation of BAT in healthy men.

Before describing the following studies, it should be noted that visceral fat is belly fat found deep within the abdominal cavity. It surrounds important organs, including your stomach, liver and intestines. Research suggests that if a person has a potbelly—or are more "apple-shaped" than "pear-shaped"—they may have more visceral fat.

A 12-week, randomized, double-blind, placebo-controlled parallel group study[29] was conducted in 80 overweight adults investigating the effects of BGE on visceral fat. Subjects received either BGE (12 mg PMF/day) or placebo. The primary outcome was a reduction in visceral fat area (VFA), while the secondary outcome was a reduction in subcutaneous fat area (SFA) and total fat area (TFA). Results showed that VFA, SFA and TFA was significantly reduced in the BGE group compared to placebo:



Another 12-week, single-center, randomized, double-blind, placebo-controlled clinical trial[30] was conducted to examine the effects of BGE in reducing abdominal fat in 76 overweight and preobese Japanese subjects. Once again, the subjects in each group ingested one capsule of placebo or BGE (12 mg PMF/day) once daily for 12 weeks. Also once again, the primary outcome was reduction in visceral fat area, with the key secondary outcomes as reductions in subcutaneous fat area and total fat area. Results were, compared with the placebo group, the BGE group exhibited significant reduction in abdominal fat area (visceral, subcutaneous, and total fat) and triglyceride levels after 12 weeks:

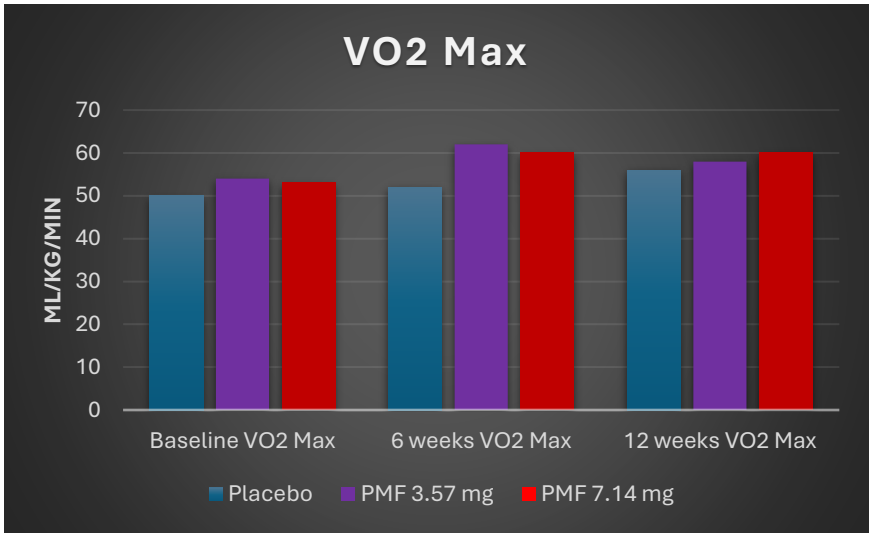


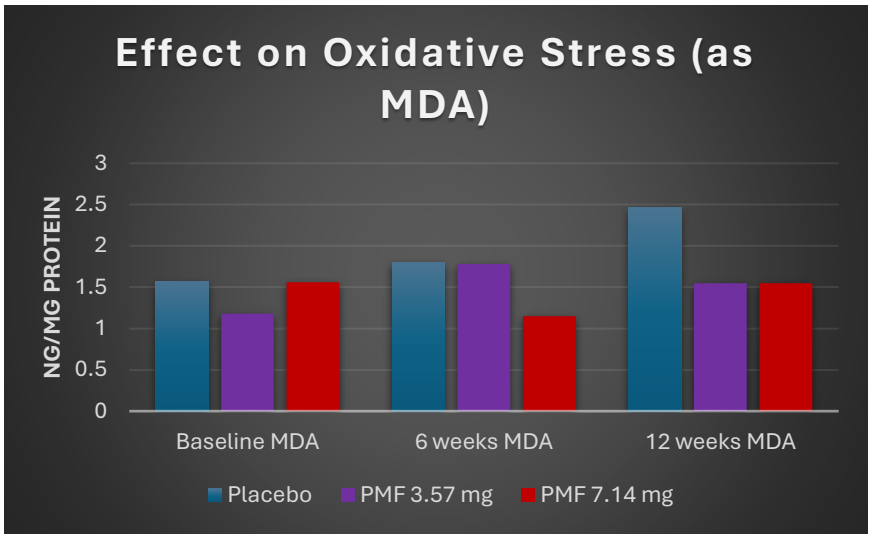
Physical Fitness

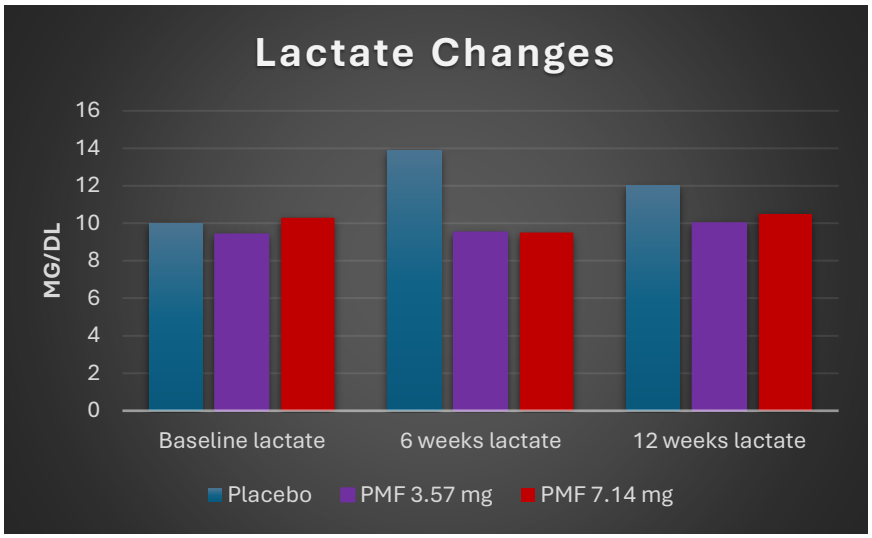
There were three human trials relating to physical fitness, with populations including healthy adults, adolescents, and soccer players.

Physical fitness in healthy adults

This 12-week, 3-arm randomized, double-blind, placebo-controlled, parallel group study[31] examined the effect of a functional drink containing BGE on the physical fitness of healthy adult male and female volunteers (19-60 years old). Subjects were randomly divided into placebo, or two BGE groups. All the subjects were directed to consume a drink containing placebo or BGE at doses yielding 3.57 mg PMF and 7.14 mg PMF per serving per 80 mL, respectively. Endpoints of the study included various parameters of physical fitness which were assessed before the intervention, and at 6 and 12 weeks of intervention. Results were that subjects who consumed both doses of the drink had significantly increased VO_2 max ($p<0.05$) at 6 weeks. Subjects consuming the higher dose displayed improved performance in both the timed shuttle run test and 5 min distance run ($p<0.05$) at 12 weeks. At 6 weeks, subjects who consumed both doses of the drink significantly increased the activities of the antioxidant enzymes SOD and catalase compared to the placebo group ($p< 0.05$). The significant reduction in the MDA level (i.e., an oxidative marker) after 6 weeks of consumption was observed only in the subjects who consumed the high dose of the drink compared to the placebo group ($p< 0.05$). When the consumption was prolonged to 8 weeks, it was found that the subjects who consumed the functional drink at both doses had a decreased MDA level compared to the placebo group ($p< 0.01$). At six weeks, both doses also significantly reduced serum lactate levels compared to the placebo group ($p< 0.05$). In conclusion, BGE can be successfully used to improve cardiorespiratory fitness and physical performance by improving oxidative stress and lactate.



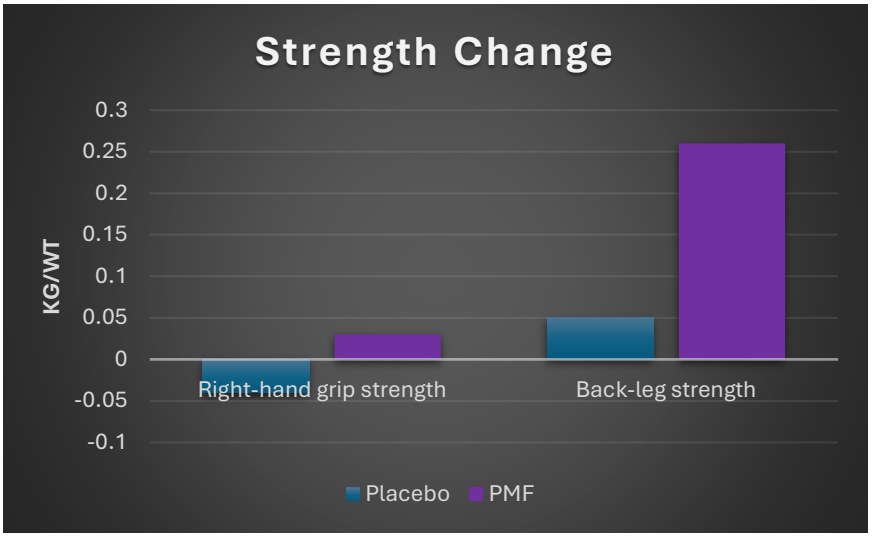


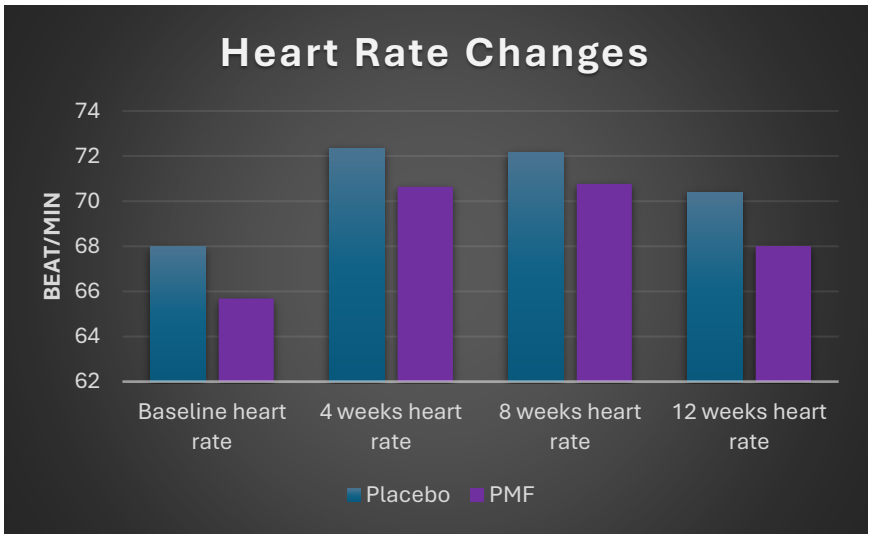


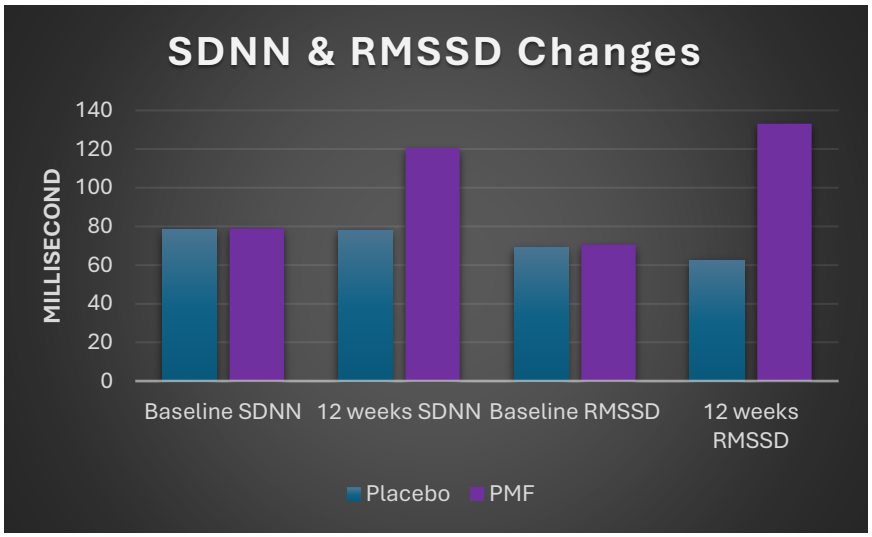
Physical fitness in adolescents

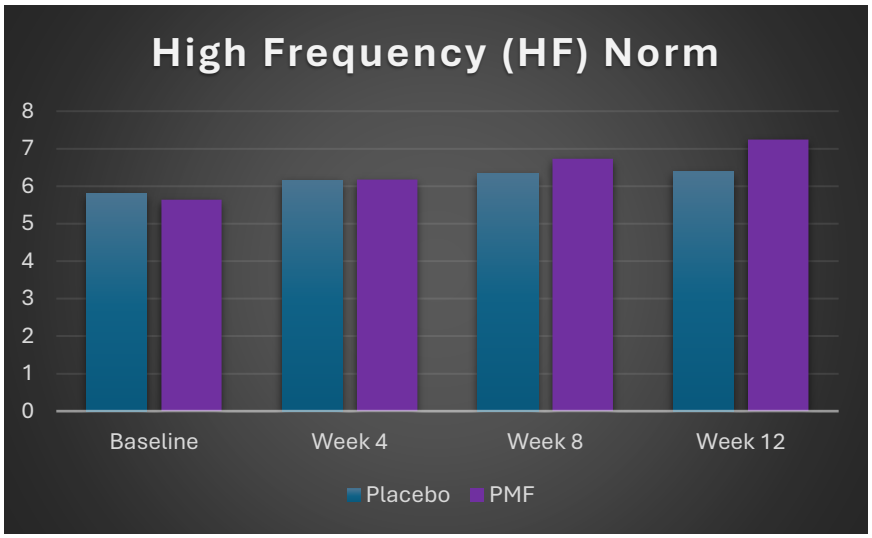
This randomized double-blind controlled study[32] aimed to investigate the effects of a standardized BGE on the physical fitness and heart rate variability (HRV) parameters in adolescent sport school students. 194 male students were recruited and randomized into two groups (n = 97), matched by age and sports. The BGE-treated group received BGE extract capsules at a dose yielding 125.46 mg PMF and the control group received placebo capsules, continuously for 12 weeks. Physical fitness performance and HRV parameters were monitored with blood biochemical analysis for product safety. Results were that BGE significantly ($p<0.05$) increased the right-hand grip strength, the back-leg strength and maximal oxygen consumption (VO_2 max) and decreased the time used for 50-meter sprint test without changing the sit-and-reach test and the 40-yard technical test. For HRV parameters, BGE significantly ($p<0.05$) increased physiological resilience against stress (measured by standard deviation of normal-to-normal intervals [SDNN]), improved parasympathetic nervous system impact on heart rate (measured by square root of the mean of square of successive normal to normal interval differences [RMSSD]) and increased parasympathetic nervous system increase on the heart via

the vagus nerve (measured by high frequency [HF] norm), without changing low frequency (LF) norm and LF/HF ratio. The increase in stress resistance and decrease in stress index were found in the BGE-treated group, without changing the autonomic nervous system (ANS) activity and balance. Blood biochemical analysis showed normal values of all participants. This data indicates the safety and positive effects of BGE on muscle strength, endurance and speed. The modulatory effects of BGE on HRV parameters suggest its anti-stress effects and would encourage the application in sport training and exercise.



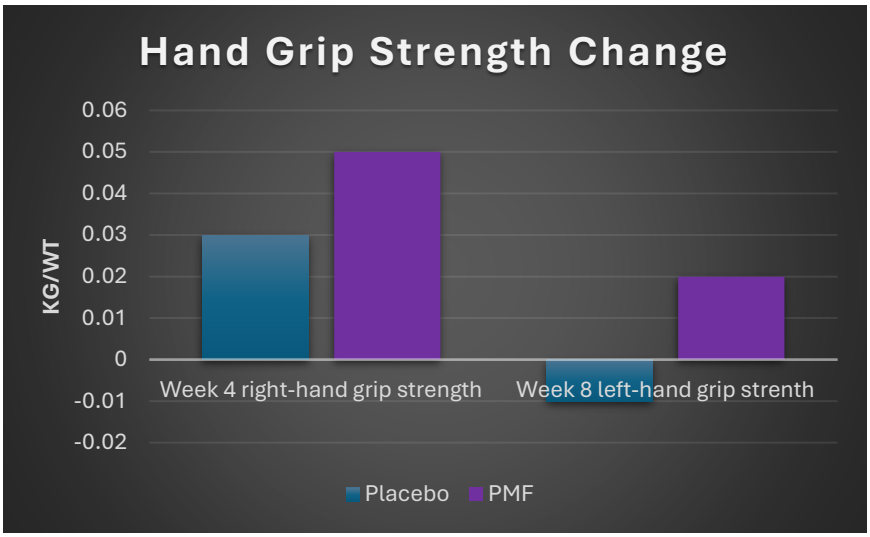






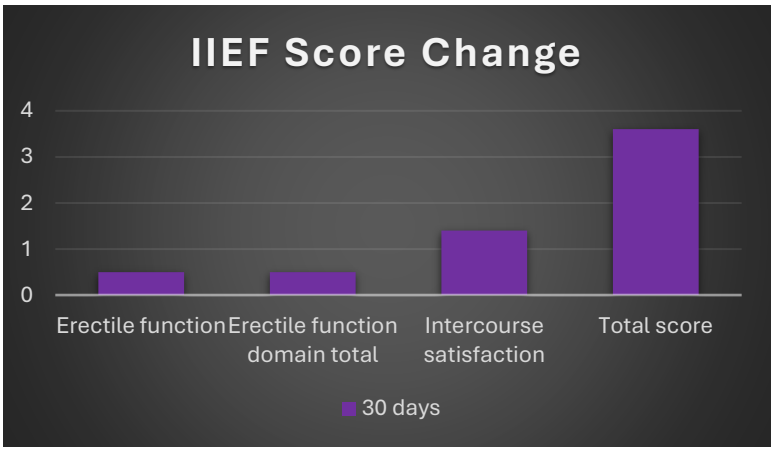
Physical fitness in soccer players

This 12-week, randomized, double-blind, placebo-controlled trial[33] examined the effect of placebo and BGE at a dose yielding 13.5 mg PMF on the physical fitness of 60 soccer players. Baseline data were collected using the following 6 tests of physical performance: a sit-and-reach test, a hand grip strength test, a back-and-leg strength test, a 40-yard technical test, a 50-metre sprint test, and a cardiorespiratory fitness test. All of the tests were performed every 4 weeks throughout the 12-week study period. Results were that treatment with BGE significantly increased right-hand grip strength at weeks 4, 8, and 12. The left-hand grip strength was significantly increased at week 8. In conclusion, supplementation with BGE 12 weeks may significantly enhance some physical fitness components in soccer players.



Sexual Health

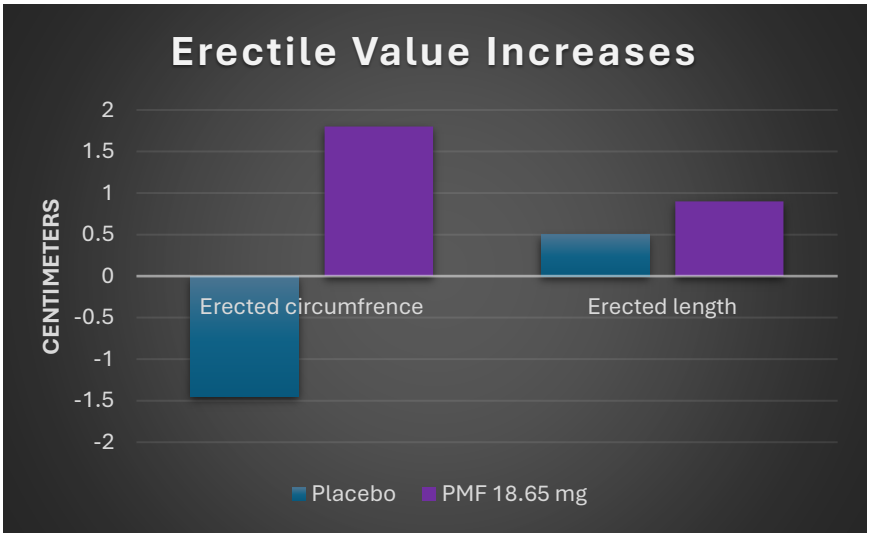
Sexual health positively correlates with overall wellbeing. Existing therapeutics to enhance male sexual health are limited by factors that include responsiveness, adherence and adverse effects. As the population ages, safe and effective interventions that preserve male sexual function are needed. Research suggests that various preparations of black ginger may be able to help ameliorate erectile function.



The aim of this open-label, one-arm, pilot study[34] was to examine the effects of BGE on erectile function in 14 generally healthy middle-aged and older men (50-68 years) with self-reported mild erectile dysfunction, who were not using prescription treatments. Participants took BGE daily (yielding 5 mg 5,7-dimethoxyflavone) for 30 days. Evaluations were conducted at baseline and on the final study assessment. Primary efficacy analyses included the International Index of Erectile Function (IIEF); secondary efficacy analyses included the Global Assessment Question about erectile function. Results were that 13 participants completed the 30-day study. Supplementation with BGE resulted in statistically significant improvements in erectile function, intercourse satisfaction and total scores on the IIEF questionnaire. BGE was well tolerated and exhibited an excellent safety profile. In conclusion, BGE may improve erectile function in healthy middle-aged and older men. While the effects were not as pronounced as what might be seen with prescription medication, most participants found them satisfactory.

This 8-week, double-blind, placebo-controlled, randomized trial[35] investigated the effect of supplementation with BGE administration on erectile response of male elderly volunteers. A total

45 male healthy elderly volunteers were divided into 3 groups: placebo, BGE yielding about 5.18 mg PMF and BGE yielding about 18.65 mg PMF, once daily at a period of 2 months. The erectile function tests were assessed after single administration, 1 and 2 months of treatment, and included the response latency time to visual erotic stimuli, size and length of penis both in flaccid and erection states. Testosterone, FSH and LH concentrations were also measured. Results were that BGE at a dose providing 18.65 mg PMF/day exhibited a significant enhanced all parameters after 1 and 2 months of treatment—although there were no significant changes for hormone concentrations. Moreover, the penile length at erection states and the response latency to sexual erotic stimuli showed significant changes during the delay period. In conclusion, this study clearly demonstrates that BGE has potential for the treatment of aged related male erectile dysfunction.



Meta-analysis

In addition to the aforementioned research, a meta-analysis[36] was conducted to test the hypothesis that administration of BGE and its PMF in-vivo could improve metabolic syndrome, erectile dysfunction, and related outcomes in in vivo. Studies from 4 databases (i.e., PubMed, Scopus, Embase, and Cochrane Library) were searched from inception up to December 2022. It included animal studies and randomized controlled trials comparing BGE to a placebo control. The effect estimate was presented as the standardized mean difference along with its 95% confidence interval (CI). Of 664 articles, a total of 57 articles met the prespecified criteria. Results demonstrated that BGE significantly decreased fasting blood glucose in both animal and human studies with standardized mean difference of -0.88 and -0.51, respectively. Furthermore, BGE also markedly improved sexual function and physical performance. In conclusion, BGE was shown to have beneficial effects for metabolic syndrome, erectile dysfunction, and physical performance.

Future research

Research on BGE is still ongoing. A new BGE called Actiz!ng™ (from Nutraland USA) provides a relatively high potency of PMF (32%) and 5,7-dimethoxyflavone (5,7-DMF)(20%). Since current commercially available extracts provide a maximum of 15% PMG and 5% 5,7-

DMF, the significance of this higher potency is that a lower quantity of BGE from Actiz!ng™ would be required to yield a clinically relevant dose of PMF and 5,7-DMF.

I am now coordinating a 56-day, open-label, human clinical pilot study with 12 adults aged 30-65 to test the effectiveness of Actiz!ng™ BGE (providing 12 mg PMF/day) on changes in body fat and body composition via dual-energy X-ray absorptiometry (DEXA) scans and Bioelectrical impedance analysis to examine fat mass, lean mass and visceral adipose tissue. In addition, the study will also utilize subjective methods of assessment. This includes Quality of Life Questionnaire (SF-36), Sexual Quality of Life Questionnaire (SQOL), and a Visual Analogue Scale for physical and metal energy, as well as vitality. Indices of safety and cardio-metabolic health (clinical chemistry panel, lipid panel, CBC) as well as vital signs and Adverse Events will also be monitored. This study should be completed during the second or third quarter of 2025 and will contribute to the existing body of research on BGE and its PMF.

SAFETY

With regard to toxicological evaluation, a study[37] was conducted to investigate the safety profile of standardized BGE via mutagenicity and sub-chronic toxicity evaluations using in vitro and in vivo techniques. The in-vitro mutagenicity of BGE was assessed via reverse mutation tests using *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537, and Escherichia coli WP2 uvrA. The sub-chronic toxicity profile was evaluated after daily oral administration of KP extract to Sprague-Dawley rats for 90 days. Reverse mutation tests revealed that BGE did not induce gene mutations at any of the concentrations tested. In the sub-chronic toxicity test, a few changes were observed, including increased salivation in the animals administered high-dose BGE (249 mg/kg body weight (bw)/day). No toxicologically relevant changes were observed in the biochemical analysis. Sub-chronic administration of BGE increased platelet levels in animals administered low-dose BGE (25 mg/kg bw/day). However, the hematological and biochemical parameters remained within normal physiological ranges for the animal species. No toxicological changes were observed in the macroscopic and histopathological analyses performed in this study. These results demonstrate that BGE is not genotoxic and that 90-day oral administration of the doses tested did not result in toxicity. Therefore, BGE has a high safety margin for daily use.

With regard to safety and adverse events, A randomized double-blind placebo-controlled study[38] was conducted with 52 recruited healthy Japanese subjects to evaluate the safety of daily consumption of BGE. Each subject received five BGE tablets providing 12-18 mg PMF/tablet or placebo daily for 4 weeks. There were no adverse events related to BGE intake or any abnormalities compared with placebo group in anthropometric, cardiovascular, blood, and urine parameters during the course of the study. Thus, daily BGE ingestion was found to be safe in healthy Japanese men and women. Likewise, a systematic review[39] of 7 clinical studies found no adverse events when up to 1.35 g/day of BGE was used.

CONCLUSION

BGE has been used as traditional herbal medicine of Thailand and other cultures for centuries to improve physical work capacity and for other purposes. It provides a broad range of pharmacological properties including, but not limited to, antiallergenic, anti-inflammatory,

antimutagenic, antidepressive, anticholinesterase, antimicrobial, anticancer, anti-peptic ulcer, cardioprotective, antiobesity activity, and aphrodisiac. The primary active components in BGE are total PMF and 5,7-DMF.

Preclinical research has demonstrated the effectiveness of BGE in addressing aspects of aging, BPH, fat and weight loss, muscle health, neuroprotection, osteoarthritis, physical fitness, and sexual health. Human clinical trials have been conducted on black ginger extract, examining its impact on body fat/weight loss, physical fitness, and sexual health. In addition, a meta-analysis on BGE and its PMF found that it had beneficial effects for metabolic syndrome, erectile dysfunction, and physical performance. Furthermore, a new pilot study is underway which will examine the effects of a BGE (Actiz!ng™) on fat mass, lean mass, visceral adipose tissue, quality of life, sexual quality of life, physical and mental energy, vitality and indices of safety, cardio-metabolic health, as well as vital signs and adverse events.

Consideration of BGE's historical use, together with modern preclinical and human clinical research, suggest that this herb has a promising future in addressing human health and wellness concerns.

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