# MHBA Research

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## Matured hop extract reduces body fat in healthy overweight humans: a randomized, double-blind, placebo-controlled parallel group study

Morimoto-Kobayashi Y, Ohara K, Ashigai H, Kanaya T, Koizumi K, Manabe F, Kaneko Y, Taniguchi Y, Katayama M, Kowatari Y, Kondo S. Matured hop extract reduces body fat in healthy overweight humans: a randomized, double-blind, placebo-controlled parallel group study.
Nutr J. 2016 Mar 9;15:25. doi: 10.1186/s12937-016-0144-2. PMID: 26960416; PMCID: PMC4784395.
https://pmc.ncbi.nlm.nih.gov/articles/PMC4784395/

**Body Fat Reduction:** A randomized, double-blind, placebo-controlled trial involving 200 healthy overweight individuals demonstrated that daily consumption of a beverage containing 35 mg of MHBA over 12 weeks led to significant reductions in visceral fat area and total fat area compared to a placebo group.

**Results:** Compared to the placebo group, a significant reduction was observed in the visceral fat area after 8 and 12 w, and in the total fat area after 12 w in the active group. There was also a concomitant decrease in body fat ratio in the active group compared to the placebo group. No adverse events related to the test beverages or clinically relevant abnormal changes in the circulatory, blood and urine parameters were observed in either group.

**Conclusions:** The present study suggests that continual ingestion of MHE safely reduces body fat, particularly the abdominal visceral fat of healthy overweight subjects.

## The relationship between the effect of matured hop extract and physical activity on reducing body fat: re-analysis of data from a randomized, double-blind, placebo-controlled parallel group study

Suzuki, S., Yamazaki, T., Takahashi, C. *et al.* The relationship between the effect of matured hop extract and physical activity on reducing body fat: re-analysis of data from a randomized, double-blind, placebo-controlled parallel group study.
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**Exercise and Fat Reduction:** A combined effect of MHE and physical activity on body fat was evaluated from previous study data to explore the relationship between the effect of MHE and walking as an index of physical activity and fat loss.

**Abstract:** We recently reported that successive ingestion of matured hop extract (MHE), produced by oxidation of hops, results in a reduction of body fat in healthy overweight participants. A combined effect of MHE and physical activity on body fat has not been investigated. Thus, we re-analyzed data from the previous study to explore the relationship between the effect of MHE and walking as an index of physical activity.

**Results:** There was a significant negative correlation between the change in VFA and daily steps taken in the active group ($r = -0.208$, $P = 0.048$). No significant correlation in TFA or SFA. Although the interaction effect in TFA was not significant, the main effect of ingestion was significant ($P = 0.045$). In contrast, the interaction effect in VFA was suggested to be synergistic ($P = 0.055$).

**Conclusion:** The results suggested that MHE ingestion combined with light intensity exercise would induce a greater reduction in VFA which would be beneficial for obese or overweight individuals in reducing obesity and obesity-related diseases.

## Supplementation with Matured Hop Bitter Acids Improves Cognitive Performance and Mood State in Healthy Older Adults with Subjective Cognitive Decline

Fukuda T, Ohnuma T, Obara K, Kondo S, Arai H, Ano Y. Supplementation with Matured Hop Bitter Acids Improves Cognitive Performance and Mood State in Healthy Older Adults with Subjective Cognitive Decline.
J Alzheimers Dis. 2020;76(1):387-398. doi: 10.3233/JAD-200229. PMID: 32474473; PMCID: PMC7369117.
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**Cognitive Function and Mood Enhancement:** A study focused on 100 healthy older adults with subjective cognitive decline. Participants who consumed MHBA supplements daily for 12 weeks showed notable improvements in divided attention, as measured by the Symbol Digit Modalities Test, and reported enhanced mood states.

**Objective:** We investigated the effects of MHBA supplementation on cognitive function and mood state in healthy older adults with perceived subjective cognitive decline.

**Methods:** Using a randomized double-blind placebo-controlled trial design, 100 subjects (aged 45-69 years) were randomly assigned into placebo (n = 50) and MHBA (n = 50) groups, and received placebo or MHBA capsules daily for 12 weeks.

**Results:** Symbol Digit Modalities Test (SDMT) score assessing divided attention at week 12 was significantly higher ($p = 0.045$) and β-endorphin at week 12 was significantly lower ($p = 0.043$) in the subjects receiving MHBA. Transthyretin in serum, a putative mild cognitive impairment marker, was significantly higher at week 12 in the MHBA group than in the placebo group ($p = 0.048$). Subgroup analysis classified by the subjective cognitive decline questionnaire revealed that in addition to improved SDMT scores, memory retrieval assessed using the standard verbal paired-associate learning tests and the Ray Verbal Learning Test at week 12 had significantly improved in the subgroup with perceived subjective cognitive decline and without requirement for medical assistance in the MHBA group compared with that in the placebo group.

**Conclusion:** This study suggested that MHBA intake improves cognitive function, attention, and mood state in older adults.

## Hop Bitter Acids Increase Hippocampal Dopaminergic Activity in a Mouse Model of Social Defeat Stress

Ano, Y.; Kitaoka, S.; Ohya, R.; Kondo, K.; Furuyashiki, T. Hop Bitter Acids Increase Hippocampal Dopaminergic Activity in a Mouse Model of Social Defeat Stress.
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**Stress Resilience and Dopaminergic Activity:** Animal studies have indicated that chronic administration of hop bitter acids can increase dopaminergic activity in the hippocampus and medial prefrontal cortex, areas associated with emotional regulation. This heightened activity was linked to improved stress resilience and reduced depression-like behaviors in mice.

**Abstract:** As daily lifestyle is closely associated with mental illnesses, diet-based preventive approaches are receiving attention. Supplementation with hop bitter acids such as iso-α-acids (IAA) and mature hop bitter acids (MHBA) improves mood states in healthy older adults. However, the underlying mechanism remains unknown. Since acute oral consumption with IAA increases dopamine levels in hippocampus and improves memory impairment via vagal nerve activation, here we investigated the effects of chronic administration of hop bitter acids on the dopaminergic activity associated with emotional disturbance in a mouse model of repeated social defeat stress (R-SDS). Chronic administration of IAA and MHBA significantly increased dopaminergic activity based on the dopamine metabolite to dopamine ratio in the hippocampus and medial prefrontal cortex following R-SDS. Hippocampal dopaminergic activity was inversely correlated with the level of R-SDS-induced social avoidance with or without IAA administration. Therefore, chronic treatment with hop bitter acids enhances stress resilience-related hippocampal dopaminergic activity.

**Results:** We measured the IAA effects on dopaminergic activity in several dopaminoceptive brain areas with or without R-SDS using HPLC-ECD. Since dopamine is rapidly metabolized to its metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 3-methoxytyramine (3-MT) upon dopamine release, the ratio of dopamine metabolites to dopamine reflects the biochemical index of dopaminergic activity. Mice were fed regular chow containing IAAs for 14 days and were subjected to R-SDS.

In defeated mice, IAA administration increased the hippocampal ratios of (DOPAC + HVA)/dopamine ($p < 0.05$, dopamine factor and stress factor main effects and dopamine × stress interaction, two-way ANOVA; $p = 0.040$, designated comparison, Tukey-Kramer post-hoc test) and DOPAC/dopamine ($p < 0.05$, dopamine × stress interaction, two-way ANOVA; $p = 0.042$, designated comparison, Tukey-Kramer post-hoc test. It also increased the ratio of mPFC DOPAC/dopamine in the defeated group ($p < 0.05$, dopamine × stress interaction, two-way ANOVA; $p = 0.039$, designated comparison, Tukey-Kramer post-hoc test. R-SDS alone did not significantly alter these ratios in these brain areas. Moreover, the dopamine, DOPAC, HVA and 3-MT levels were not significantly altered in these brain areas, nor did they contribute to the IAA-induced dopaminergic activity increase. Contrarily, in the defeated mice, neither the NAc nor CPu exhibited IAA effects on dopaminergic activity. These results show that chronic IAA administration enhances dopaminergic activity in the hippocampus and mPFC after R-SDS.

## Matured Hop Bitter Acids in Beer Improve Lipopolysaccharide-Induced Depression-Like Behavior

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**Anti-Inflammatory and Antidepressant Effects:** Research has also shown that MHBA consumption can suppress inflammation-induced depression-like behavior in mice. The mechanism involves increased norepinephrine secretion and reduced production of inflammatory cytokines in the brain, contributing to improved mood and cognitive function.

**Abstract:** Recent studies have demonstrated a close association between neural inflammation and development of mental illnesses, such as depression. Clinical trials have reported that treatment with non-steroidal anti-inflammatory drugs is associated with reduced risk of depression. Moreover, nutritional approaches for the prevention and management of depression have garnered significant attention in recent years. We have previously demonstrated that iso-α-acids (IAAs) – the bitter components in beer – suppress hippocampal microglial inflammation, thereby improving cognitive decline. However, effects of hop-derived components other than IAAs on inflammation have not been elucidated. In the present study, we demonstrated that consumption of matured hop bitter acids (MHBAs) generated from α- and β-acids, which show a high similarity with the chemical structure of IAAs, suppress lipopolysaccharide (LPS)-induced cytokine productions in the brain. MHBAs administration increased norepinephrine (NE) secretion and reduced immobility time which represents depression-like behavior in the tail suspension test. Moreover, MHBAs components, including hydroxyallohumulinones and hydroxyalloisohumulones, reduced LPS-induced immobility time. Although further researches are needed to clarify the underlying mechanisms, these findings suggest that MHBAs reduce inflammatory cytokine productions and increase NE secretion, thereby improving depression-like behavior. Similarly, inoculation with LPS induced loss of dendritic spines, which was improved upon MHBAs administration. Additionally, vagotomized mice showed attenuated improvement of immobility time, increase in NE level, and improvement of dendrite spine density following MHBAs administration. Therefore, MHBAs activate the vagus nerve and suppress neuronal damage and depression-like behavior induced by inflammation.

**Results:** To evaluate the effects of MHBAs on depression-like behavior induced by inflammation, we conducted TST using mice that were intracerebroventricularly inoculated with LPS. TST test revealed that immobility time in LPS-treated mice was significantly longer than that in sham-treated mice, indicating LPS-induced depression-like behavior in mice. In contrast, the immobility time in LPS-inoculated mice treated with MHBAs at 10 or 50 mg/kg was significantly shorter than that in LPS-inoculated sham-treated mice. Locomotor activities, as evaluated by OFT, did not differ among the groups. These results indicate that MHBAs improved LPS-induced depression-like behavior. Moreover, we measured interleukin (IL)-1β levels in the hippocampus to evaluate inflammation level. IL-1β level in the hippocampus of LPS-inoculated mice was significantly increased compared with that in the hippocampus of sham-treated mice but significantly decreased in the hippocampus of LPS-inoculated mice treated with either 1 or 10 mg/kg MHBAs. These results suggest that MHBAs prevent inflammation in the hippocampus. Previous studies have shown that NE might play important roles in depression-like behavior. Thus, we quantified NE level in the hippocampus of mice using HPLC. NE levels in the hippocampus of mice treated with 10 and 50 mg/kg MHBAs were significantly increased. IL-1β ($r = 0.26$, $P = 0.052$) and NE ($r = -0.35$, $P = 0.009$) levels in the hippocampus of mice were weakly correlated with immobility time observed in TST.

**Matured hop bitter acids constitute both α- and β-acid oxidants with β-tricarbonyl structures.** Effects of three major constituents (HAH, HAIH, and TCOIHA) of MHBAs on depression-like behavior were examined in TST. Immobility time in mice treated with 1 mg/kg HAH and HAIH was significantly lower than that in the sham-treated mice and was equivalent to the effect of MHBAs at 10 mg/kg. Moreover, mice treated with 1 mg/kg TCOIHA showed a reduced immobility time ($P = 0.068$). These results indicate that major compounds in MHBAs contribute to the suppression of the concomitant depression-like behavior in TST induced by inflammation.

**Involvement of the Vagus Nerve in Effects of MHBAs on Depression-Like Behavior**
To elucidate whether MHBAs act through the blood–brain barrier (BBB) or through the vagus nerve, vagotomized or sham-treated mice were administered oral MHBAs and subjected to TST. Immobility time in LPS-inoculated vagotomized mice was significantly longer than that in saline-inoculated vagotomized mice. In contrast, immobility time remained unchanged in vagotomized mice administered MHBAs or DW. Locomotor activities in OFT remained unchanged among all vagotomized groups. These results indicate that the vagus nerve was involved in effects of MHBAs on the improvement of LPS-induced depression-like behavior.

**Conclusion:** MHBAs administration suppressed neural inflammatory responses, increased hippocampal NE levels, and attenuated LPS-induced depression-like behavior. Furthermore, these effects of MHBAs were mediated by VNS. However, detailed mechanisms underlying anti-depressant effects of MHBAs warrant further research. Activation of the vagus nerves through specific diet, which can in turn improve depression-like behavior, is a safe and novel approach for treating depression.

## Brown adipose tissue is associated with cardiometabolic health

Becher T, Palanisamy S, Kramer DJ, Eljalby M, Marx SJ, Wibmer AG, Butler SD, Jiang CS, Vaughan R, Schöder H, Mark A, Cohen P. *Nat Med*. 2021 Jan;27(1):58-65. doi: 10.1038/s41591-020-1126-7. Epub 2021 Jan 4. PMID: 33398160.
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**The lack of measurable brown adipose tissue is cause for alarm of cardiocirculatory issues:** Too much white fat, a characteristic of obesity, has been shown to increase the risk of type 2 diabetes, high blood pressure, and other diseases. A less common type of fat, called brown fat, uses blood sugar and fat molecules to create heat and help maintain body temperature. Studies suggest it may have beneficial health effects.

**Abstract:** White fat stores excess energy, whereas brown and beige fat are thermogenic and dissipate energy as heat. Thermogenic adipose tissues markedly improve glucose and lipid homeostasis in mouse models, although the extent to which brown adipose tissue (BAT) influences metabolic and cardiovascular disease in humans is unclear[1,2]. Here we retrospectively categorized 134,529 $^{18}$F-fluorodeoxyglucose positron emission

tomography-computed tomography scans from 52,487 patients, by presence or absence of BAT, and used propensity score matching to assemble a study cohort. Scans in the study population were initially conducted for indications related to cancer diagnosis, treatment or surveillance, without previous stimulation. We report that individuals with BAT had lower prevalences of cardiometabolic diseases, and the presence of BAT was independently correlated with lower odds of type 2 diabetes, dyslipidemia, coronary artery disease, cerebrovascular disease, congestive heart failure and hypertension. These findings were supported by improved blood glucose, triglyceride and high-density lipoprotein values. The beneficial effects of BAT were more pronounced in individuals with overweight or obesity, indicating that BAT might play a role in mitigating the deleterious effects of obesity. Taken together, our findings highlight a potential role for BAT in promoting cardiometabolic health.